Understanding the Assessment of Spatial Neglect and its Treatment Using Prism Adaptation Training

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Contents

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List of Abbreviations

BI = Barthel Index

BIT = Behavioural Inattention Test

CBS = Catherine Bergego Scale

CVS = Caloric Vestibular Stimulation

FIM = Functional Independence Measure

fMRI= Functional Magnetic Resonance Imaging

KF-NAP = Kessler Foundation Neglect Assessment Process

LAT = Limb Activation Treatment

MRI = Magnetic Resonance Imaging

NHS = National Health Service

NIHSS = National Institutes of Health Stroke Scale

OCS = Oxford Cognitive Screen

OT = Occupational Therapy

OTs = Occupational Therapists

PAT = Prism Adaptation Training

SAT = Sustained Attention Training

SN = Spatial Neglect

tACS = Transcranial Alternating Current Stimulation

TAPAT = Tonic and Phasic Alertness Training

tDCS = Transcranial Direct Current Stimulation

tES = Transcranial Electrical Stimulation

TMS = Transcranial Magnetic Stimulation

VAS = Visual Analogue Scale

VSA = Visual Scanning Activity

VST = Visual Scanning Training

Abstract

Spatial neglect is a syndrome that is most frequently associated with damage to the right hemisphere, although damage to the left hemisphere can also result in signs of spatial neglect. It is characterised by absent or deficient awareness of the contralesional side of space. The screening and diagnosis of spatial neglect lacks a universal gold standard, but is usually achieved by using various modes of assessment. Spatial neglect is also difficult to treat, although prism adaptation training (PAT) has in the past showed some promise.

Study one aimed to first identify the spatial neglect assessments used the most by clinicians as a first step to reaching a universal consensus. This online survey attracted 454 responses from clinicians in 33 countries. In identifying and quantifying the selection of spatial neglect assessments (and reasons for their use), the survey found tentative signs of emerging consensus - in line with previous research. This survey also found that professionals worldwide express a desire for harmonisation, citing the varied range of assessments available to them.

Study two was designed to ascertain whether PAT could enhance engagement in occupational therapy for stroke - an established intervention for stroke survivors. This study video-recorded patients (n=43) and therapists taking part in a visual search activity. These videos were later rated by an expert occupational therapist, finding that PAT did not significantly enhance engagement in occupational therapy by our operationalisation. This work highlights the need for a universal definition of engagement in therapy, and the potential need for interventions to enhance engagement and, by extension, outcomes after discharge.

Study three aimed to uncover whether PAT has any efficacy (i.e. in the short term) in treating spatial neglect, specifically on cognitive and open-loop pointing outcomes. This aim was formulated following previous reviews of PAT effectiveness which were inconclusive (at best). This systematic-review and meta-analysis of eight eligible studies (N=216) found no evidence to suggest that PAT is efficacious in resolving the signs of spatial neglect within one month post-intervention. The use of PAT to treat spatial neglect lacks a clear evidence base, and more work is required to identify its mechanism(s) of action and how well it can resolve signs of spatial neglect.

These studies highlight that the care of stroke and brain injury survivors with spatial neglect could be better-informed; the current literature provides a varied account of the assessment of, and interventions for, spatial neglect. There are promising signs of an appetite for harmonisation of assessment. For PAT, this thesis highlights that further work may be required to fully appreciate the limits of its usefulness in the clinical setting.

Declaration of Originality

I hereby confirm that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Copyright Statement

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Authorship & Collaboration

Matthew Checketts was responsible for the planning, data collection, data analysis, and write-up of all research presented within this thesis, with support and feedback from PhD supervisors Prof Audrey Bowen and Prof Andy Vail and co-authors of individual studies. Additionally, local clinicians, stroke survivors, and undergraduate and postgraduate placement students provided invaluable time, assistance and guidance during data collection for the proof-of-concept study in Chapter 3.

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Chapter 1

Introduction: Spatial Neglect and Prism Adaptation Training

1.1 Overview of the Thesis

This chapter will begin with a brief description of stroke and spatial neglect, followed by a description of the cognitive and functional impact of spatial neglect on stroke patients, leading to a discussion of assessments and interventions used in spatial neglect. This review will then focus on the literature surrounding the clinical application of prism adaptation to treat spatial neglect, including some insight into the mechanisms by which prism adaptation might improve patients' spatial awareness and participation in therapy. The term 'spatial neglect' is used throughout this thesis, although there is a focus predominantly on neglect in the visual domain, since this is the mechanism of action of prism adaptation training, and the most predominantly discussed and studied neglect subtype (Williams et al., 2021).

This introductory chapter is intended to provide an overall background to this thesis, which will incorporate in subsequent chapters: a survey study of stroke professionals regarding their screening and diagnostic test choices for spatial neglect; a proof-of-concept study investigating the effect of prism adaptation training on engagement in recommended occupational therapy for stroke (including a statistical comparison of methods we developed to measure engagement), and; a systematic review of the efficacy of prism adaptation training. The scope of chapter one may give rise to necessary repetition in the component chapters of the thesis, which were written in a style suitable for publication in peer-reviewed journals. These chapters will inform the scope for comprehensive service provision to enhance participation in and efficacy of rehabilitation for neglect patients - rehabilitation which, according to a Cochrane review from Longley et al. (2021), is currently deficient.

1.2 Spatial Neglect

1.2.1 Overview

In the United Kingdom, stroke is the third commonest cause of death, and the single most common cause of adult disability (Office for National Statistics, 2011; Stroke Association, 2018). In the global context, stroke represents a leading cause of adult disability, with an estimated 80 million stroke survivors around the world who may be suffering from residual disabilities that impact quality of life and independent functioning (Johnson et al., 2019). These disabilities can include hemiparesis or other motor difficulties, aphasia, dysarthria, executive dysfunction, mood disorders, visual disturbances, and distressing and debilitating attentional difficulties such as spatial neglect.

Spatial neglect is a relatively common syndrome that occurs in a large proportion of stroke survivors, and to some extent in other types of traumatic or degenerative injury (Andrade et al., 2010; Bender, 2011; Gilad et al., 2006; Lunven & Bartolomeo, 2017; Shinoura et al., 2009; Silveri et al., 2011). Spatial neglect typically manifests as a reduced or absent awareness of contralesional space. Estimates of incidence of post-stroke spatial neglect often vary between 12% and 95%, depending on neglect definitions and assessments used (Halligan & Robertson, 2014). Chen et al. (2015) pooled the demographics of eight studies to highlight the proportion of stroke survivors exhibiting signs of spatial neglect. They found that in patients who sustained right hemisphere damage (n=881), the prevalence of spatial neglect was 51%, and in patients who sustained left hemisphere damage (n=918), the prevalence of spatial neglect was 29%. In the case of posterior cortical atrophy, as an example of non-stroke pathology, a study of 24 patients revealed that 16 exhibited signs of spatial neglect (Andrade et al., 2010). These results suggest that spatial neglect manifests in a large proportion of stroke survivors, and to some extent in survivors of other brain injury, however it is extremely important to note that the individual studies pooled in this analysis all used different assessment methods for identifying spatial neglect. The proportion of individuals with spatial neglect that one might identify by using a standard set of assessments is likely to differ (see section 1.3 and chapter 2 for more on assessments, and the original text of Chen et al. (2015) for an interesting breakdown of individual studies). The varying definition and assessment of spatial neglect, and different estimates of how common it is, makes the prediction of required clinical care for incoming patients difficult. Such variability in definitions and assessment tools also makes it difficult to compare between different studies concerning spatial neglect.

Hammerbeck et al. (2019) found that neglect prevalence among inpatients (who had stayed in hospital for at least 3 days) was more recently estimated in the UK at 30%, based on a positive screen for spatial neglect on the National Institutes of Health Stroke Scale (Brott et al., 1989). However, it is important to note here that the inattention subscale of the NIHSS is designed as a screening test (as opposed to a diagnostic test) for neglect and has the potential to mask subtle signs early after stroke, hence the true prevalence may be somewhat higher. The presence of spatial neglect is a significant predictor of length of hospital stay - increasing in some cases by a factor of up to 2.7 - and can limit the degree of functional recovery (Gialanella & Ferlucci, 2010; Hammerbeck et al., 2019; Jehkonen et al., 2006). In addition, patients in UK rehabilitation settings do not always receive therapy at the recommended frequency or intensity (Clarke et al., 2018), and those with spatial neglect are likely to experience difficulties in engaging and participating fully in their therapy sessions (Kringle et al., 2018) - see chapter 3. Despite these findings, a universally-agreed gold standard for the definition, diagnosis and treatment of spatial neglect remains to be defined, although consensus work is ongoing (see chapter 2).

A 2013 longitudinal cohort study reports that whilst spontaneous recovery of spatial neglect is possible, and most likely in the first 12 to 14 weeks post-stroke, this phenomenon is not universally observed - an estimated 30% to 40% of patients still exhibit signs of spatial neglect 1 year post-stroke (Nijboer et al., 2013). Spatial neglect is most often associated with right parietal damage (Halligan & Robertson, 2014) (as highlighted in 1.2.4), and/or lesions in subcortical regions such as the basal ganglia or the thalamus (Karnath, Rennig, Johannsen, & Rorden, 2011). Spatial neglect appears to be most likely after an infarct of the middle cerebral artery, which supplies a large proportion of cerebral cortex 'downstream' (Li & Malhotra, 2015; Verdon et al., 2010). Hence, patients who present with symptoms of spatial neglect also tend to sustain damage to temporal and frontal areas (Li & Malhotra, 2015), and this is likely to exacerbate functional and cognitive impairments that can prolong recovery time by precluding full participation in standardised rehabilitative care. Indeed, Katz et al. (1999) found that spatial neglect was associated with poorer performance on measures of activities of daily living and a slower, attenuated recovery trajectory (as compared to right hemisphere stroke patients without spatial neglect). Moreover, there is evidence that different neglect subtypes (section 1.2.3) are associated with different recovery trajectories. For example, Spaccavento et al. (2017) found that stroke survivors with peripersonal or extrapersonal neglect exhibited poorer recovery (as measured by the functional independence measure; Keith et al., 1987) than stroke survivors with personal neglect. Although this association does not confirm cause and effect between spatial neglect and poor outcome, differentiated recovery trajectories and reduced functional independence in some stroke survivors with spatial neglect is of great concern regarding the effective rehabilitation of attentional impairments post-stroke.

A systematic review found that of 126 variables (i.e. signs and symptoms), 8 of these were able to adequately explain, using multivariate modelling, functional (in)dependence of stroke survivors post-rehabilitation (Meyer et al., 2014). These variables included executive dysfunction, previous stroke event, and spatial neglect. Other researchers regard spatial neglect as one of the best predictors of poor functional outcome post-stroke, indexed by length of hospital stay and defined by researchers as post-discharge functionality in daily living (Jehkonen et al., 2006; Oh-Park et al., 2014). For instance, patients with spatial neglect are likely to struggle with tasks such as dressing, eating, navigating, or searching for personal belongings around them. Hence, research into effective diagnosis and treatment of spatial neglect is crucial not only for patients' recovery and quality of life post-stroke, but also to help in alleviating the burden of post-stroke care on patients' informal carers and on the state.

1.2.2 Co-morbid Anosognosia

Anosognosia is often associated with spatial neglect and is frequently reported as a significant co-morbidity. Anosognosia refers to a patient's inability to recognise the presence of their illness or disorder; in the case of spatial neglect this may present as a denial of extreme spatial re-orientation (Gallagher et al., 2013; Grattan et al., 2017). Ongoing work suggests that anosognosia is present at both explicit and implicit levels, as measured by visual analogue scales and recording of physiological markers (including skin conductance response and electroencephalography), and is applicable to lateralised spatial judgement tasks and non-lateralised tasks (Ronchi, 2020).

The presence of anosognosia, and absence of patients' awareness, makes assessment and treatment of spatial neglect all the more challenging. For assessment, clinicians rely on and often select paper-and-pencil tests or functional assessments to detect and quantify the presence and severity of spatial neglect and its impact on activities of daily living (Eschenbeck et al., 2010), without gaining the additional benefit of patients' insights. For treatment, evidence suggests that anosognosia is an important factor that predicts poorer performance in standardised assessments of activities of daily living (Vossel et al., 2013) and, as discussed in chapter 3, can preclude evaluation of treatment success. However, the picture may be more nuanced than a dichotomous 'anosognosia' versus 'no anosognosia' comparison. Qualitative evidence indicates that patients with spatial neglect initially express no awareness of their deficits but may regain awareness as rehabilitation progresses (Chen & Toglia, 2019; Tobler-Ammann et al., 2020). The potential benefit in rehabilitation of capitalising on emergent awareness of spatial neglect remains to be seen, but may be achieved by techniques that can increase arousal or general attention. Altogether, it is clear that anosognosia is a barrier to engagement in rehabilitation (e.g., if patients do not recognise spatial neglect-related deficits, they may be less motivated to remedy them), and work to elucidate alternative means of enhancing engagement is necessary (see chapter 3).

1.2.3 Classification of Spatial Neglect

Some clinicians and researchers highlight distinctions between 'subtypes' of spatial neglect, usually depending on the sensory modality or the spatial frame in which neglect signs manifest. For example, Vallar (1998) proposed a comprehensive taxonomy of spatial neglect to dissociate subtypes based on how the signs manifest. Vallar's (1998) taxonomy includes sensory modality, but also spatial reference frame (near/far and high/low, relative to the observer) and processing domain (e.g. neglect dyslexia in reading, or neglect in facial processing). Vallar (1998) also included the concept of 'hyperattention', which refers to magnetic attraction to objects or events in the non-neglected space. Rode et al. (2017) classified spatial neglect subtypes according to sensory modality (e.g. visual, auditory), spatial reference frame (e.g. extrapersonal), and associated lesion patterns. These definitions are discussed in more detail in Chapter 6. Rode et al. (2017) also provide differential diagnoses (e.g. hemianopia, deafness, hemiplegia), although it is important to note here that some differential diagnoses may also be co-morbidities requiring a different approach to assessment and treatment (Gallagher et al., 2013).

In terms of spatial reference frames, a study of 130 stroke survivors with left spatial neglect found that on neuropsychological and functional measures, 68% of patients had extrapersonal neglect (spatial neglect in the space outside of a patient's reach), 69% had peri-personal neglect (space within a patient's arm's length), and 46% had personal neglect (space on or very close to the patient's body) (Spaccavento et al., 2017). These subtypes are not necessarily mutually-exclusive; the percentages reported above represent patients exhibiting signs of those subtypes regardless of whether other subtypes are present. The authors found that 11% of patients had only extrapersonal neglect, 17% only peripersonal neglect, and 12% only personal neglect.

These findings contrast with those of Demeyere and Gillebert (2019), who found a minority of approximately 25% (out of 176) of patients exhibited both egocentric and allocentric neglect. Egocentric neglect refers to neglect relative to the body midline, and allocentric neglect refers to neglect relative to the midline of external objects.. It is important to note key differences in the approaches of the two studies: Spaccavento et al. (2017) used the personal/peripersonal/extrapersonal distinction, whereas Demeyere and Gillebert (2019) use the ego/allocentric distinction. This difference is complicated by the fact that neuropsychological assessments (particularly paper-and-pencil tests) may be good, in some cases, at dissociating allo- and ego-centric neglect, but they are typically conducted in patients' peri-personal space and thus provide no information about this alternative distinction regarding spatial reference frames. Regardless, these findings suggest that subtypes of neglect based on spatial reference frame can co-occur as well as occurring in isolation, which further complicates the processes of assessment and treatment. Clinicians therefore require clear guidelines on which particular assessments to select, since various tests can identify different subtype features.

Chapter 2 begins to address the issue of assessment selection, however work to identify tests sensitive to spatial neglect subtypes will take place in the future. Given the frequent co-occurrence of different neglect subtypes, clinicians may be able to use these to selectively target treatments based on which reference frame or domain that the symptoms persist in. Some evidence suggests that patients with different neglect subtypes follow different recovery trajectories, given that they are dissociable. Spaccavento et al. (2017) and Iosa et al. (2016) found that patients with extrapersonal and peri-personal (but not personal) neglect experienced poorer outcomes after rehabilitation, suggesting a distinct recovery process for personal neglect. However, it is not clear whether co-occurrence of personal neglect and extra- or peri-personal neglect can improve the otherwise attenuated recovery trajectories of these two non-personal forms. It is also not certain what the different recovery trajectories, if any, are for neglect occurring in different sensory modalities (e.g. visual, auditory, somatosensory).

Instead of targeting spatial reference frames e.g. egocentric or allocentric neglect, treatments for spatial neglect may target different sensory subtypes with crossover to other modalities. For example, some evidence suggests that the treatment of spatial neglect using prism adaptation (in the visual/proprioceptive domains) transfers to improvement in auditory neglect, suggesting the possibility effects on the supramodal representation of space (Jacquin-Courtois et al., 2010a; Tissieres et al., 2018) via a bottom-up pathway; that is, the modulation of space representation by targeting afferent inputs (vision, in this case). Likewise, Van Vleet and DeGutis (2013) demonstrated that auditory sustained attention training can improve performance in visual neglect tests, suggesting that these supramodal effects of neglect treatments may also come from top-down influences. Whilst it is possible that auditory and visual neglect may share some key cognitive processes to allow for cross-modal treatment effects (Rode et al., 2017), and that these may simultaneously recover over time without specific intervention, these findings suggest that it may be possible to develop interventions that are useful for more than one neglect subtype. However, it would be desirable to first achieve consensus on how these subtypes are best defined (exemplified in the comparison of Spaccavento et al. (2017) and Demeyere & Gillebert (2019)) and assessed.

1.2.4 An Overview of Postulated Models of Impaired Visual Attention

The difference in prevalence between left and right neglect (Chen et al., 2015) can potentially be explained using neuroanatomical models of attention and spatial neglect. On the whole, these models suggest that the large degree of right hemisphere lateralisation of spatial processing, and a lack of a functional homologue in the left hemisphere, makes attention vulnerable to right brain damage (Oh-Park et al., 2014). In the healthy brain, the right hemisphere is thought to be dominant in the control of attention. Spagna et al. (2020) demonstrated an advantage for right hemisphere processing (particularly for attention orienting and disengagement from stimuli) in a lateralised attention network test designed to measure inter-hemispheric differences in the executive control of attention. A large history of research supports this hemispheric dominance theory in spatial neglect, whereby the right hemisphere is dominant in the processing of attention, and subserves the processing of left space, and some of right space, whereas the left hemisphere subserves the processing of right space only (Benwell et al., 2014; Heilman & Abell, 1980; Hilgetag et al., 1999). This model of right hemispheric dominance is supported by anatomical evidence; De Schotten et al. (2012), using magnetic resonance imaging, identified a front-parietal white matter tract (specifically, the second branch of the superior longitudinal fasciculus) that is anatomically larger in the right hemispheres of healthy subjects. The degree of enlargement of this structure, relative to its homologue in the left hemisphere, also correlated with performance on a spatial attention task.

Other models of spatial processing can also serve to explain the anatomical basis of left and right spatial neglect. One such example is the activating-orienting hypothesis of attention, first proposed by Reuter-Lorenz, Kinsbourne and Moscovitch (1990), which proposes that the allocation of attention is directed contralaterally to the activated hemisphere. During rest, each hemisphere exerts an inhibitory influence on the another. When this balance is disrupted by the onset of a stimulus in one hemispace, the activated contralateral hemisphere exerts a relatively larger inhibitory influence on the non-activated ipsilateral hemisphere. In the case of spatial neglect, damage of the right hemisphere would allow for its greater inhibition by the left hemisphere at rest (Koch et al., 2013). Likewise, in the case of right neglect, this model would refer to the excessive inhibition of the left hemisphere by the intact right hemisphere, thus accounting for the patient's re-orientation leftwards. Emerging evidence suggests that it is not only the dominant or activated hemisphere that plays a role in directing attention - the dominant eye can also exert an influence on the allocation of attention. Schintu et al. (2020) examined the allocation of attention in a group of 40 healthy adults, who typically exhibit ’pseudoneglect’ - a subtle leftward bias resulting from right hemispheric dominance - under normal viewing conditions. Half of this sample were reported to have a dominant right eye, and the other half a dominant left eye. Schintu et al. (2020) found that individuals with a dominant right eye, exerting an influence on the ipsilateral hemisphere, exhibited pseudoneglect on the Landmark task, whereas individuals with a dominant left eye exhibited a markedly reduced, non-significant leftward bias under the same conditions. Whilst this clearly has theoretical implications for how we might define spatial neglect neurologically, there is not yet any information on the role of eye dominance in patients with spatial neglect.

The neurocognitive profile of spatial neglect is still debated in the literature, not least owing to its heterogeneous manifestation between patients, and indirect correlational evidence - predominantly from MRI - supporting anatomical models of spatial neglect (Karnath & Rorden, 2012; Verdon et al., 2010; Vuilleumier, 2013). Karnath and Rorden (2012), in their review of the literature, argue that spatial neglect may be used as an umbrella term for patients exhibiting various perceptual and attentional deficits post-stroke, including classic or ‘traditional’ signs of neglect, such as gaze deviation and inattention to events occurring centrally or on their left side. This may lead to the erroneous assumption that spatial neglect is either a widely heterogeneous disorder, or that it is a clinically irrelevant entity. Indeed, when all subtypes of neglect are considered, it may be difficult to prescribe a particular treatment plan for a particular patient without considering their profile of signs and symptoms in a more robust and useful framework. Karnath & Rorden propose that spatial neglect can be conceptualised in terms of ‘core’ deficits (such as biased gaze orientation and biased search patterns, sometimes with anosognosia) accompanied by a combination of dissociable ‘satellite’ deficits (such as neglect of limbs, neglect of objects in near space, and neglect of objects and events in extrapersonal space), thereby providing a framework for useful diagnosis and treatment of spatial neglect symptoms. However, it remains unclear what should constitute a core versus a satellite deficit, and in real terms whether this framework has clinical utility, or indeed if such deficits dissociate anatomically from the core deficit(s). Moreover, the presence of multiple cognitive models of spatial neglect may only serve to confuse clinicians who will want to try to select the correct assessments and prescribe the correct interventions - if multiple therapeutic targets are presented, a consensus on the gold standard of assessment and treatment is more difficult to obtain. Work is currently ongoing to establish consensus in definition, assessment (see chapter 2), and treatment.

1.2.5 Non-Spatial Aspects of Spatial Neglect

Spatial neglect also presents with a number of non-spatial attentional deficits in some patients, which can contribute to impaired post-stroke cognition and daily functioning. In the experimental setting, this may manifest as an overall increase in reaction time to target stimuli (Samuelsson et al., 1998), coupled with exaggerated electrophysiological response to stimuli in the non-neglected side and a deficient response to stimuli on the neglected side (Lasaponara et al., 2018), or an increased execution time in re-orienting attention (Posner et al., 1987). In the clinical setting, patients may be unable to switch attention between tasks (Petersen & Posner, 2012), or may exhibit a reduced visual or spatial working memory capacity, manifesting as recursive visual inspection of items on a cognitive screen, for example (Mannan et al., 2005; Wansard et al., 2014). Deficiencies in non-spatial attention are a potential therapeutic target for treatment of the spatial neglect syndrome; interventions reducing excessive cognitive load (the threshold for which may well be lower in stroke survivors) could create greater processing capacity for interventions that target spatial neglect directly. A review of clinical and neuroimaging literature by Corbetta and Shulman (2011) implicates non-spatial attention in the persistence of neglect symptomatology, with one explanation being the shared functional correlates between spatial attention (i.e. the observed symptoms of spatial neglect) and non-spatial attention, which are both postulated to be right hemisphere functions (see section 1.2.4).

A specific example of non-spatial attentional impairment is in auditory sustained attention - the acquisition and maintenance of attention towards auditory stimuli. Robertson et al. (1997) recruited 30 right hemisphere stroke patients (15 with spatial neglect, matched on lesion location/extent with the remaining 15 without spatial neglect) to undergo a tone counting task. Robertson et al. found that the presence of spatial neglect was associated with impaired performance on overall tone counting abilities as compared to their matched controls, and that this apparent deficiency in sustained attention did not vary with lesion location or extent.

More recent studies have elucidated the association between non-spatial cognition and the manifestation of spatial neglect. For example, Ricci et al. (2016), in a study of 8 spatial neglect patients, found that increased non-spatial perceptual or cognitive load in classic visual search tasks had the effect of worsening visual search performance – effectively exacerbating the symptoms of spatial neglect – as compared to right hemisphere stroke patients without neglect, and healthy controls. Posner's models of the attentional system are parsimonious in explaining this finding. Indeed, therapies that target sustained attention have shown some efficacy based on these models, although these will be discussed in section 1.4. Posner and colleagues (Petersen & Posner, 2012; Posner & Petersen, 1990) outline three separate neural systems that subserve attention. These are the posterior systems of orienting and selection, and the anterior alerting or sustained attention system. The computations of the latter are largely undertaken by the right parietal cortex, which projects onto posterior systems. Hence, the systems of orienting and selection (perhaps the most qualitatively obvious impairments in spatial neglect patients) receive considerable modulation from the sustained attention system – elements of which appear to be deficient in right hemisphere stroke patients in general (above). However, it is unclear if these are true associations, or if these are artifactual findings resulting from larger strokes that are typically seen in this population (Li & Malhotra, 2015). These findings have been used to inform behavioural interventions of spatial neglect, which feature in section 1.4.

1.3 Assessing Spatial Neglect

The assessment of spatial neglect can be undertaken through two primary approaches: cognitive/neuropsychological assessment, and functional assessment. These two approaches have distinct advantages and disadvantages in their own right, and are reported by clinicians to work well together in a comprehensive approach to profiling the neglect profile of patients, although there still exists a need for harmonisation and a universal gold standard for assessment - this is discussed in chapter 2.

1.3.1 Neuropsychological Approaches

The assessment and diagnosis of spatial neglect is often carried out using behavioural and cognitive assessment tools. These are used initially to establish the direction and degree of attentional bias, and later to establish the severity of neglect. Tests for neglect traditionally utilise paper-and-pencil tests or test batteries that incorporate some kind of symmetry judgement. A popular and widely-used example is the Behavioural Inattention Test battery (BIT) (Wilson et al., 1987). The BIT is a collection of visual search and bisection subtests, along with some tests of everyday activities. Indeed, current UK guidelines recommend the BIT be used to confirm suspected cases of spatial neglect (Intercollegiate Stroke Working Party, 2016). Another example is the Oxford Cognitive Screen (OCS; Demeyere et al., 2015) and one of its component parts, the broken hearts test, which is a cancellation test made up of heart shapes. Some of these heart shapes have gaps, which can aid the dissociation of egocentric neglect (relative to bodily midline) and allocentric neglect (relative to objects’ midlines, in this case those of the heart shapes). In the initial development study from Demeyere et al. (2015), 88 acute stroke patients underwent the hearts test, which produced a reported sensitivity and specificity of neglect detection of 94.12% and 69.01% respectively. This was a comparison with performance on the star cancellation subtest of the gold-standard BIT, with a reported correlation between these two tests of 0.645. Whilst this may not seem particularly useful in light of the successful application of the BIT previously, the overarching benefit of the OCS as applied to stroke patients is its accessibility (it is reported to be both aphasia and neglect friendly), and its comprehensiveness. The OCS includes tests of other cognitive functions, such as language, executive function, memory, calculation, et cetera. Previously, clinicians would have relied on other cognitive screens, such as the Montreal Cognitive Assessment, which may not always be accessible to every stroke patient, and may ignore the presence of spatial neglect altogether (Demeyere et al., 2015). The utility of the OCS as applied to stroke patients is its ability to screen individual cognitive abilities of stroke patients whilst minimising confounds from cognitive impairments that are not the subject of a particular subtest, thereby allowing the potential for personalised interventions to specifically target patients' cognitive deficits – another recommendation from the Intercollegiate Stroke Working Party (2016).

The broken hearts test, and the related apple cancellation test, are also useful for dissociating 'egocentric' and 'allocentric' subtypes of neglect. These tests contain an array of larger and smaller simple heart or apple shapes - some of which are complete, and others have gaps taken out of either the left or right upper quadrants of the heart, and the patient is instructed to cross out, with a pen, only the complete shapes. An apparent inability of a patient with right hemisphere damage (for instance) to cancel complete shapes on the left-hand side of the page corresponds to left egocentric neglect, and a large number of false-positives on the left side of shapes (that is, where patients have cancelled a majority of hearts with gaps in their left upper quadrant) corresponds to left allocentric neglect. This dissociation is particularly important in the clinical setting, where different neglect subtypes may predict differential recovery trajectories (Bickerton et al., 2011).

The above test batteries are just two examples of what clinicians may opt to use to assess spatial neglect. In light of the subtypes of neglect mentioned earlier, and considering the negative impact of spatial neglect on daily functioning (Jehkonen et al., 2006; Meyer et al., 2014; Oh-Park et al., 2014), it is not surprising that each test assesses neglect in only one domain, and not in the others – leaving the potential for spatial neglect to remain undetected, or inadequately documented. The BIT, for example, detects spatial neglect in the egocentric domain, and then only at the level of cognitive impairment and visuomotor activity (Menon & Korner-Bitensky, 2004). The OCS assesses spatial neglect similarly (although is sensitive to ego- as well as allocentric neglect), but also incorporates other subtests that involve the use of language, numbers, and memory – so is arguably more functionally informative, albeit with a limited subtest for neglect.

1.3.2 Functional Approaches

One assessment battery does, however, assess neglect in personal, peripersonal, and extrapersonal/allocentric spatial reference frames, through assessment of activities of daily living – the Catherine Bergego Scale (CBS) (Bergego et al., 1995; Chen et al., 2012; Menon-Nair et al., 2007; Menon & Korner-Bitensky, 2004). The CBS assesses patients' functional capabilities by the observation of everyday activities, such as dressing, eating, moving around, awareness of limbs, et cetera. Naturally, particular functional capacities may be tested according to the patient's stage of stroke recovery. For example, it may be worth testing limb awareness, grooming activities, eating food, et cetera whilst the patient is bed-restricted, and testing of dressing, navigation, writing et cetera are likely to become more relevant as the patient improves sufficiently. Here there is already a clear advantage of the CBS, in that it follows a more ecologically valid procedure for assessing the functional impact of neglect, as opposed to other more rigid testing batteries that require a patient to follow instructions to perform tasks that they would not necessarily perform in their daily lives. Additionally, the CBS is argued to be superior to other commonly used measures of activities of daily living due to its direct observation of the impact of spatial neglect on patients' functioning, as compared to other impaired functions (Chen et al., 2012).

Chen et al. (2015) developed the Kessler Foundation Neglect Assessment Process (KF-NAP), which itself is based on the CBS. Not only is the KF-NAP able to quantify the symptoms of spatial neglect through assessment of daily activities, it does so with a specific emphasis on spatial neglect-related difficulties than two alternative measures – the functional independence measure and the Barthel index (Mahoney & Barthel, 1965). However, the comprehensiveness of the CBS and KF-NAP notwithstanding, it is easy to forget to consider how and when these assessments are used. In the clinical research domain, it is perhaps negligent to only consider spatial neglect in terms of visuospatial impairment and recovery, without considering impact in terms of functional recovery. On the other hand, in practical clinical terms, these different tests are highly valid tools of assessment – the timing of their deployment is the crucial difference. Specifically, the BIT can be useful for initial testing for neglect upon (or soon after) admission, although it can be inaccessible to some very unwell patients. For this reason, individual BIT subtests are often used as rapid initial screens before more comprehensive assessments can be administered. The use of more functionally-oriented tests such as the CBS and KF-NAP are best saved until later, when rehabilitation of post-stroke activity limitations becomes the focus of the clinical team.

Overall, it is clear that a range of assessment options is available for clinicians to identify and quantify the presence and severity of spatial neglect in the cognitive and functional domains. Decision-making remains unclear for clinicians trying to identify and treat spatial neglect; the studies above shed light on the utility of these tests, but their selection and utilisation in clinical practice is poorly understood, and is addressed in chapter 2.

1.4 Rehabilitation of Spatial Neglect

Rehabilitation of spatial neglect often focuses on cognition and function, and can be delivered via routine occupational therapy as the medium for intervention, with meta-analyses supporting the beneficial effect of regular occupational therapy interaction (Lincoln et al., 2011). In the rehabilitation of stroke, cognitive rehabilitation with a patient-centred, interdisciplinary approach promoting functional and cognitive training (capitalising on the theorised latent plasticity of cerebral cortex) is often associated with improved outcomes following discharge – a finding from a review conducted by Langhorne and colleagues (Langhorne et al., 2011). Within the cognitive rehabilitation paradigm, there are two approaches, which differ greatly but can often be combined: top-down, which utilises patients' cognitive abilities and awareness of an impairment to consciously alter impaired behaviour; and bottom-up, which does not necessarily require awareness of an impairment, and aims to retrain maladaptive functionality without conscious effort of the patient (Bowen et al., 2013; Gallagher et al., 2013; Grattan et al., 2017). These two approaches will inform the structure of this section of this literature review, since many current and experimental therapies used to treat spatial neglect can be categorised into one or the other.

Before appraisal of specific therapies for spatial neglect, it may be useful to first discuss the concept of cognitive rehabilitation more broadly. Cognitive rehabilitation is an umbrella term for a number of therapies that are designed to either restore deficient cognitive functioning (also known as restitutive), or to otherwise compensate for impairments using learnable strategies (also known as compensatory). Cognitive rehabilitation has been found to be clinically beneficial for patients with acquired brain injury – including those with stroke – in a series of systematic reviews from Cicerone and colleagues, utilising data from the years 1998 to 2008 (Cicerone et al., 2005, 2011). Cicerone and colleagues, through their evaluation of 370 intervention studies in total to date, advocate the use of cognitive rehabilitation in those patients with language, memory, executive function, and attentional problems, although these reviews do not compare the relative efficacy of individual treatment programmes. Instead, a rather sweeping recommendation is made whereby all right hemisphere stroke patients are recommended to undergo visual scanning training for spatial neglect, despite no supporting evidence from their literature search. Indeed, not every right hemisphere stroke patient exhibits spatial neglect (see introduction), nor does every patient with spatial neglect respond optimally to visual scanning training. The authors do note, however, that patient characteristics should be of concern to clinicians, citing an example of the relationship between memory remediation and severity of memory impairment. Similarly, in spatial neglect, the presence of particular subtypes of neglect may inform treatment selection – but again, this will be considered below when individual interventions are discussed. An important conclusion from the Cicerone reviews is that cognitive rehabilitation may be maximally effective following the acute period – that is, even when impairment is chronic (Cicerone et al., 2011) - and it is important to bear this in mind, since many clinical studies recruit patients at different time points or mixed time points, thus limiting our ability to translate these findings into practice.

1.4.1 Top-Down Approaches

Historically, the approach to treating cognitive deficits following stroke was largely based on the experience of individual clinicians, although recent contributions of cognitive neuroscience have contributed to the relatively rapid development of theory-based approaches designed to treat specific impairments (Clarke et al., 2015). As mentioned previously, cognitive rehabilitation interventions can be divided into two approaches: top-down, and bottom-up. To reiterate, top-down interventions refer to interventions that require a certain amount of volition and conscious awareness from the patient, whereas bottom-up interventions refer to interventions that target afferent (sensory) pathways to the brain, and require little or no volitional effort from the patient. This review will first focus on top-down interventions, and then move on to bottom-up interventions, the latter being the applicable description of prism adaptation training, which will follow in section 1.5.

One example of a top-down approach is sustained attention training (SAT), which was devised by Robertson and colleagues (1995) as a means to improve neglect patients' deficient orienting and target selection abilities (i.e. the posterior system) via the modulation of the anterior sustained attention system (Petersen & Posner, 2012; Posner & Petersen, 1990). Robertson et al. proposed that training neglect patients to gain conscious control of their intact sustained attention could improve neglect via the sustained attention system's modulatory influence on the posterior system. This procedure is readily applied in the context of an everyday task, such as coin sorting or reading, with the patient trained to self-instruct with loud verbal commands to "Attend!". In the original study, Robertson et al. reported small but significant improvements in at least two out of four measures of neglect in neglect patients in sustained attention and neglect measures in which they had not been trained, with treatment effects persisting in the range of 24 hours to 14 days. Similarly, Van Vleet and DeGutis (2013) updated SAT into what is now known as tonic and phasic alertness training (TAPAT), which aims to improve neglect patients' phasic alertness (which fluctuates over the course of minutes or hours) which itself is implicated in deficient operations of orientation and selection. Previous studies have targeted phasic alertness from a bottom-up approach, although such modulations lasted in the order of seconds (Robertson et al., 1998; Vleet & Robertson, 2006). Van Vleet and DeGutis hypothesised that top-down modulation of phasic alertness would be able to improve spatial neglect patients' performance on non-spatial and spatial attention tasks across modalities for longer – similar to SAT. The authors found that all patients showed small improvements in several untrained spatial and non-spatial visual attention tests and also demonstrated a reduced rightward bias. Whilst, like SAT, there is expansion to untrained tasks in another modality, the modest benefit here was reported to have disappeared 13 days later.

Whilst there is an expansion of the therapeutic effects of SAT and TAPAT to more general tasks (unlike the majority of VST papers), robust evidence for the longevity of these improvements is absent, and there is no supporting evidence for top-up sessions of SAT that can improve the long-term efficacy of this intervention. Moreover, the existence of differing protocols (and the way in which these may be applied to patients) means that if applied universally, the benefit of this intervention to patients is unclear without larger-scale randomised controlled trials. Similarly, there is not much known about the type of patient (with a specific neurocognitive profile) that can maximally benefit from a given intervention, given that different interventions are based on different cognitive targets. Whilst it was mentioned earlier that the presence of neglect is not a precursor for the presence of impaired sustained attention, this does not mean that every patient with spatial neglect will have problems in sustained attention, thus application of SAT/TAPAT universally may not be a sensible approach to treatment, and more work is required to elucidate the nature of sustained attention impairments in spatial neglect patients. Indeed, validation studies and subsequent updates (e.g. the original Robertson paper and the Van Vleet et al. paper) used very small sample sizes that are unlikely to capture the full range of neglect subtypes – 8 and 14 respectively. SAT as an intervention may require more validation work in terms of which patients will gain maximum benefit from modulation of a non-spatial attentional system.

The top-down approach to rehabilitation focuses on the hierarchical organisation of cognitive networks, and the deployment of conscious strategies to activate a descending stream of processing to activate defective, lower-order cognitive processes. An issue with this approach to treating neglect is the problem of sustained attention and patients' unawareness of their extreme re-orientation in the spatial domain. Many patients with spatial neglect have anosognosia and thus may forget how and when to deploy these top-down compensatory strategies outside of the therapeutic setting, or may even disengage from therapy sessions that may be seen as irrelevant or dull, or impractical to use in everyday settings (e.g., self-instructing to "attend!"). Moreover, the existence of several procedures used to deploy top-down therapies leads to some variation between studies, and between practitioners, and thus some heterogeneity in the limited evidence supporting improved outcomes.

1.4.2 Bottom-Up Approaches

The bottom-up approach to rehabilitation takes a contrary theoretical starting point to that of the top-down approach. Bottom-up methods of rehabilitating spatial neglect still rely on some kind of hierarchical structure to cognitive mechanisms, however they target afferent inputs to the brain (e.g. from limbs or peripheral musculature) in order to modulate impaired higher-order processes (Bowen et al., 2013), such as how the brain allocates attention. In this way, bottom-up approaches avoid the necessity of voluntary, conscious effort in the rehabilitation process, and by extension the prohibitive influence of anosognosia.

Some bottom-up approaches, an example of which is caloric vestibular stimulation (CVS), operate on equilibrioception - the sense that combines multisensory input from the visual system, the vestibular system, and the proprioceptive system (arising from afferent input from skeletal muscles and joints) to create the sensation of (mis)balance (Bottini, 2001). CVS works by flooding the auditory canals with water: cold water (i.e. slightly below core body temperature) is introduced in the right auditory canal, and/or warm water (usually around 44°C) is introduced in the left auditory canal, thereby invoking a vestibulo-ocular reflex, manifesting as leftward slow-phase nystagmus (Miller & Ngo, 2007). In the case of neglect, this mechanism is exploited to encourage transient leftward eye movements, with patients subsequently exhibiting a typical left-to-right visual search pattern instead of their usual right-to-left pattern that is characteristic of spatial neglect (Rubens, 1985; Sturt & Punt, 2013). Moreover, there is case study evidence to suggest that CVS is potentially effective in reducing the degree of anosognosia in spatial neglect patients, by making the degree of their neglect-related attentional bias transiently clearer during related motor tasks (Ronchi et al., 2013). However, improvement in neglect symptoms following this intervention appears to be short-term, with studies either not following up patients at all, or doing so with very short time periods following CVS (Miller & Ngo, 2007). The therapeutic effects of CVS may also be offset by the side-effects of vertigo and nausea, and the impracticality of routine irrigation of the auditory canals (Wilkinson et al., 2014). It could also be the case that the irrigation of auditory canals produces an increase in arousal - an extraneous factor in this paradigm that could contribute to transient amelioration of neglect symptoms, via similar processes that are outlined in relation to SAT.

Another example of a bottom-up approach is limb activation treatment (LAT). The rationale behind LAT is concerned with laterality - that is, in a large proportion of severe spatial neglect patients, there exists a degree of motor paralysis on the left side, with the right hand side of the body used to complete tasks (including diagnostic paper-and-pencil tests). The use of the right hand, for example, activates the left hemisphere to a point where there may be a stronger attentional re-orientation rightwards, as postulated by Reuter-Lorenz and colleagues (Reuter-Lorenz et al., 1990) in their activating-orienting hypothesis of attention, and by Rizzolatti and Camarda (1987) in the premotor theory of spatial attention. Alternatively, the cueing procedure that the use of the left hand represents may also encourage the patient to attend relatively leftwards (Jewell and McCourt, 2000). In either case, the paralysed left side of the body is used as a 'perceptual anchor' to encourage patients to scan leftwards.

LAT may be used in these cases to encourage use of the left side of the body wherever possible. This activates the right hemisphere via afferent input and activation of right motor cortex and thereby 'tempts' patients' attentional spotlight leftwards (Eskes et al., 2003; P W Halligan & Robertson, 1999). Case studies documenting the performance of neglect patients on the BIT shows that line bisection and cancellation performance was more accurate with the use of the left hand compared to when they used their right hand (Peter W. Halligan & Marshall, 1989). One way of deploying LAT is via the use of a limb activation device, which is equipped with a buzzer (timed to go off at certain intervals) and a button, which is to be pressed by the patient using their left arm to cancel the buzzing. This participation is not contingent on awareness of a deficit, but does depend on the patient being physically able to push a button and cognitively able to remember when, how, and why they need to press the button. However, the bottom-up principle of using afferent neural signals to divert the spotlight of attention is maintained here, with the resulting activation of the right hemisphere contributing to leftward scanning - not volitional efforts of the patient to consciously scan leftwards (Priftis et al., 2013).

A similar approach may be taken in the haptic feedback received from a limb. Visuomotor feedback training can be implemented using lightweight rods that extend into left and right space. When patients with neglect are asked to grasp rods in their centre, the sensation of misbalance when patients with neglect inevitably mis-bisect rods towards the right of veridical centre causes their attentional bias to become consciously apparent. Through this sensation of misbalance, patients are able to correct their grasping point until the veridical centre of the rod is in their grasp (Harvey et al., 2003). Rod grasping, when administered daily in the clinical setting and in the community, can significantly reduce attentional bias in neglect on neuropsychological tests (Harvey et al., 2003; Rossit et al., 2019).

There is evidence to suggest that a combined approach to rehabilitating spatial neglect provides greater functional outcomes than the use of a single treatment approach. For example, a case study by Pitteri et al. (2013) compared the use of LAT on its own with the combination of LAT and contralateral arm vibration - another bottom-up approach with a similar attentional cueing mechanism - as applied to spatial neglect patients. The authors found that particular aspects of spatial neglect were more amenable to the combination of treatments, possibly through the additive effects of the two treatments that operate on slightly different attentional mechanisms, or by the addition of an extra dose of bottom-up attentional modulation in the form of an adjunctive therapy. However, this was not the case for all aspects of spatial neglect, suggesting that combinations of treatments require some degree of personalisation according to the clinical presentation of neglect, and the specific needs of the patient.

1.5 Prism Adaptation Training

Prism adaptation training (PAT) is a bottom-up intervention for spatial neglect. PAT is thought to focus on the perception of visual space itself and aims to recalibrate how attention is allocated by the damaged right hemisphere through alteration of visual perception and subsequent adaptation via the use of motor tasks and proprioceptive feedback. PAT may work by fitting left-neglecting patients with optical prisms that shift the visual image a certain degree rightwards in the horizontal plane. This shift in the visual image prompts the visuomotor system to recalibrate to new spatial co-ordinates. Whilst the prisms are worn, patients are given a pointing task (e.g. pointing to targets) in order to help the visuomotor system adapt; initially, patients over-reach rightwards relative to pointing targets. As pointing movements continue, patients begin to perform motor corrections leftwards to compensate for the prism-induced error, until they eventually reach the target. At this point, prismatic adaptation is achieved. Please see Appendix A for a description of how PAT was administered in study two of this thesis. When the prisms are removed, patients exhibit leftward over-reaching, which is known as the prism after-effect. The prism after-effect may be measured by asking the subject to point straight ahead with prisms removed either with eyes closed (also known as the subjective straight ahead), by looking and pointing at targets, with the hand concealed (visual open-loop pointing), or by comparing performance on paper-and-pencil tasks before and after the adaptation period. The prism after-effect decays over time without top-up sessions (Turton et al., 2010), however there are variable reports of the longevity and extension of prism after-effects in the literature in terms of paper-and-pencil tasks and activities of daily living (Priftis et al., 2013; Rossetti et al., 1998).

1.5.1 Clinical Evidence

A comprehensive discussion of the clinical utility of PAT is provided in chapters 3 and 4; an outline is provided here. As a bottom-up approach to rehabilitation, PAT is thought to work through recalibration of visuomotor coordination, which can in turn affect the organisation of higher-level spatial representation, and appears to generalise to both arms and to non-trained tasks, such as an auditory task (Jacquin-Courtois et al., 2010b) and untrained motor behaviours such as posture and wheelchair driving (Watanabe & Amimoto, 2010). However, a major flaw in studies such as these is the use of neuropsychological test batteries to index recovery from stroke. Whilst there is indeed improvement in scores on these batteries, functional recovery is not always taken into account, even though clinical research in spatial neglect is moving towards a consensus on the importance of functional assessment along with neuropsychological assessment (Longley et al., 2021).

However, some clinical studies have utilised randomised designs with functional measures of improvement to investigate the potential therapeutic benefits of PAT. Turton, O'Leary, Gabb, Woodward and Gilchrist (2011) recruited 16 spatial neglect patients to participate in a programme of PAT, using prisms with a 6° shift. Turton et al. found that despite PAT-related leftward biases in pointing exercises, there was no overall effect of PAT on CBS scores following intervention, as compared to a group of 18 patients receiving non-deviating prisms.

Ten Brink et al. (2017) also conducted a randomised controlled trial of PAT with 70 spatial neglect patients in the subacute phase poststroke using prisms with an optical shift of 10°. PAT was given to 34 of these patients, with the remaining 35 receiving sham adaptation. The authors assessed whether PAT applied in this poststroke phase could ameliorate symptoms of spatial neglect in the domain of activities of daily living (ADL), again using the CBS as a scale to measure functional benefits of PAT. Despite an increased optical shift compared to the 6° prisms utilised by Turton et al. (2011), Ten Brink et al. reported that there was no beneficial effect of PAT on CBS scores, although there was a time-dependent improvement of patients' functional abilities over the 14 week study. This suggests that PAT has no therapeutic effect on functional measures, even when subanalyses considered patients with severe symptoms of spatial neglect. Owing to heterogeneity amongst spatial neglect patients, it is possible that group-level analyses obscured beneficial effects of PAT, however small. This, in combination with theories of neural plasticity and recovery and individual effects of standard treatments, does not entirely write off the possibility of PAT being of some benefit – if not in measures of functional independence and of spatial (in)attention, then in the enhancement of engagement in standard therapies.

Interestingly, Mancuso et al. (2012), in another randomised controlled trial with a similar number of participants, were able to demonstrate effects in patients who were treated with 10° prisms. Previously, Mancuso et al. employed 5° prisms in a separate treatment group, who exhibited no clinical gains whatsoever. Hence, there is evidence to suggest that PAT may only be efficacious in the rehabilitation of spatial neglect when prismatic shift is around 10° or higher – potentially explaining the lack of agreement between studies using different doses of prisms. This idea of optimal dosing in PAT is supported by experimental evidence using healthy subjects. A study by McIntosh, Brown & Young (2019) reported a dose-response relationship between prism adaptation and visuomotor adaptation as indexed by spatial bias on a bisection task (the Landmark task (Harvey et al., 1995)) and visual open-loop pointing. The authors concluded that use of laterally deviating prisms with a shift of at least 15° and 250 or more pointing movements are adequate to induce prism after-effects in neurologically healthy individuals (McIntosh et al., 2019). However, this relationship between prism strength and exposure and prism after-effects in the clinical population so far remains unknown (see chapter 4).

The mixed success of PAT in treating spatial neglect may also be explained by the selectivity of PAT's effects on the attentional system, and thus may require even further titration (alongside dose and intensity) to achieve the desired effects in patient subgroups. A case study (Mancuso et al., 2018) and a literature review (Striemer & Danckert, 2010) both raise the possibility that PAT exerts an influence on attentional control in the egocentric spatial reference frame. Egocentric spatial neglect is not universal (see section 1.2.3), hence these findings suggest an additional limiting factor in the utility of PAT for patients with spatial neglect.

Regarding our current state of knowledge regarding the mechanisms of PAT as well as optimal dosing of the prisms themselves, PAT may not be ready for large-scale, standardised clinical application; information regarding feasibility and dosing of PAT as applied to spatial neglect inpatients is particularly pertinent to this thesis, and has the potential to inform larger future randomised clinical trials that can assess patient candidacy for long-term clinical and functional gains.

1.5.2 Hypothesised Mechanism of Action

PAT may be different to other bottom-up approaches that act as more basic modulators of afferent signals to produce transient effects. PAT may be thought of as a stimulator of active processes related to space representation across different modalities, and may therefore facilitate functional reorganisation of attentional processing in the damaged hemisphere (Rossetti et al., 1998; Tissieres et al., 2018). In other words, the visual shift induced by prisms may stimulate processes that map visual space to recalibrate in the direction opposite to the visual shift, thus reversing the bias induced by post-stroke spatial neglect.

Functional neuroimaging studies implicate several brain areas that are activated during prism adaptation that are frequently associated with normal visuospatial output (Luauté et al., 2006; Jacques Luauté et al., 2009). These areas include the cerebellum, which is often associated with hand-eye coordination and visual guidance and multisensory integration of motor behaviours via the thalamus (and could be integral to computing the corrective behaviours and thus adaptation to prisms), and the anterior cingulate and anterior intraparietal cortices (Clarke & Crottaz-Herbette, 2016). It may be via the cerebellum and the thalamus that the bottom-up effects of PAT manifest . Luauté et al. (2006) also note a gradual decrease in activation in the right posterior parietal lobe, which could reflect an adaptation-related increase in the efficiency of visuospatial computations in this area, which is known to be dominant in intact visuospatial processing (Longo et al., 2015; Luauté et al., 2009). This increased efficiency could be due to the bottom-up effects of re-calibration, mediated by the cerebellum and the thalamus, with a subsequent focusing of the attentional spotlight during visuomotor tasks. Another explanation for the after-effects observed in PAT in neglect patients could be that these patients do not exhibit sufficiently strong disparity signals with their neglect-induced disorganisation of spatial representation. The visual-proprioceptive disparity induced by prism exposure and reaching tasks could be a key factor in up-regulating signals that can be useful in stimulating the correction of neglect-induced rightward biases, which may stimulate natural recovery processes in spatial representations (Rossetti et al., 1998).

1.6 Summary, Component Studies, and Thesis Aims

PAT is increasingly becoming an accessible and widely-used method in several experimental and clinical studies, and was pitched to be one of the most effective interventions for spatial neglect (Priftis et al., 2013). However, some debate remains regarding how PAT works, what the optimal dosing of PAT may be, whether it can be feasibly incorporated into a spatial neglect patient's routine care regimen (to enhance engagement, for instance), if particular subgroups of patients benefit more from PAT, and finally how outcomes should be collected (i.e. neglect subtests alone or combined with assessment activities of daily living (Bowen et al., 2013)). Hence, the calls for PAT to become the new standard treatment for spatial neglect are not yet justified based on our current knowledge of PAT. The overall aims of the research projects that form this thesis are intended to address some of the issues highlighted in this introductory chapter. Chapter 2 reports a survey study distributed to clinicians worldwide working in stroke rehabilitation which aimed to find out which screening and diagnostic assessments are commonly used in spatial neglect, with a view to recommending a core assessment set after future studies. Chapter 3 details a proof-of-concept study within a larger phase II feasibility randomised controlled trial of PAT which aims to identify what effect, if any, PAT has on engagement in NHS occupational therapy, and also discusses the operationalisation of patient engagement for empirical study. Finally, chapter 4 contains a systematic review of the efficacy of PAT for spatial neglect, and discusses why reviews of effectiveness previously report little benefit of PAT. Taken together, these studies narrate a storyline from diagnosis of spatial neglect in the acute setting, how spatial neglect may be ameliorated through the use of prisms, and how the use of prisms may have benefits beyond their sensorimotor mechanism of action when used as an adjunct to existing recommended NHS stroke rehabilitation.

The aim of this thesis is to contribute to progress in the assessment of spatial neglect (particularly regarding an international, multidisciplinary consensus) and, in light of the various treatment options with mixed support, to investigate the extent of the effects of prism adaptation on signs of spatial neglect and on patient engagement in recommended occupational therapy. A brief overview of the component studies presented in this thesis is provided below.

Study One (Chapter 2)

Title: Current clinical practice in the screening and diagnosis of spatial neglect: findings from a multidisciplinary international survey. Objective: To identify which assessments are used for the screening and for the diagnosis of spatial neglect, by which professionals, in which countries, and for what reason (professional choice versus institutional policy). Methods: An online survey distributed to clinicians via professional bodies and via professional networks. The survey asked participants which assessments, from a list, they prefer to use for the screening and for the diagnosis of spatial neglect, and whether this selection is based on professional autonomy or institutional policy. Free-text boxes were also provided. Multi-factorial logistic regression was used to assess the independent associations of 'profession' and 'country' after adjustment for potentially confounding influences of professional experience, research activity, and clinical setting.

Study Two (Chapter 3)

Title: One session of prism adaptation training does not increase immediate engagement in occupational therapy in people with spatial neglect early after stroke. Objective: To investigate whether PAT can have an immediate effect on engagement in occupational therapy early after stroke, beyond PAT's effects on spatial neglect. Methods: Video-recording of patients carrying out a standardised activity in their first occupational therapy session post-recruitment before and after PAT (or a control activity). Engagement was scored by a blinded video rater experienced in occupational therapy for stroke, who used a 100mm visual analogue scale anchored by 'No Engagement' at 0, and 'Full Engagement' at 100. Treating therapists also provided their unblinded impressions of whether engagement changed after PAT (or a control activity) on a 3-point Likert scale.

Study Three (Chapter 4)

Title: Efficacy of prism adaptation training for spatial neglect following adult brain injury: A systematic review. Objective: To assess the efficacy of PAT for alleviating the symptoms of spatial neglect, with a view to identifying some of the conditions that may be necessary to fully capture the potential benefits of PAT for spatial neglect. Methods: A systematic search and meta-analysis of randomised controlled trials investigating the effects of PAT on spatial neglect, as compared to usual care, sham PAT, attention control or another intervention.

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Chapter 2

Current Clinical Practice in the Screening and Diagnosis of Spatial Neglect Post-Stroke

Findings from a Multidisciplinary International Survey

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Abstract

Spatial neglect has profound implications for quality of life after stroke, yet we lack consensus for screening/diagnosing this heterogeneous syndrome. Our first step in a multi-stage research programme aimed to determine which neglect tests are used (within four categories: cognitive, functional, neurological and neuroimaging/neuromodulation), by which stroke clinicians, in which countries, and whether choice is by professional autonomy or institutional policy. Clinicians (n=454) responded to an online survey: 12 professions from 33 countries e.g. occupational therapists (39%), from the UK (38%). Multifactorial logistic regression suggested inter-professional differences but fewer differences between countries (Italy was an outlier). Cognitive tests were used by 82% (particularly by psychologists, cancellation and drawing were most popular); 80% used functional assessments (physiotherapists were most likely). Surprisingly 20% (mainly physicians, from Italy) used neuroimaging/ neuromodulation. Professionals largely reported clinical autonomy in their choices. Respondents agreed on the need for a combined approach to screening and further training. This study raises awareness of the translation gap between theory and practice. These findings lay an important foundation to subsequent collaborative action between clinicians, researchers and stroke survivors to reach consensus on screening and diagnostic measures. The immediate next step is a review of the measures' psychometric properties.

2.1 Introduction and Objectives

Spatial neglect is a multifaceted and disabling cognitive syndrome that commonly follows stroke and other brain injury or neurodegenerative disease (Andrade et al., 2010; Bender, 2011). It is clinically characterised as no or insufficient attention especially towards contralesional space, and manifests in many stroke survivors – particularly those with right hemisphere damage (Corbetta & Shulman, 2011; Rode et al., 2017). The academic literature provides distinctions between 'subtypes' of spatial neglect, usually depending on the domain and/or the spatial frame(s) in which symptoms manifest (although it is not obvious that this knowledge has translated into routine clinical practice of screening for neglect). One example of subtypes of neglect is a study of 166 inpatients and outpatients with right hemisphere stroke, Buxbaum et al., 2004 which found that 86 acute patients had spatial neglect. Most of the 86 showed egocentric neglect e.g. one exhibited signs of personal (i.e. bodily reference frame) neglect, 23 of peripersonal (i.e. visual space within an arm's reach) neglect, 12 motor neglect. A further 15 showed perceptual (i.e. allocentric) neglect and the rest had more than one subtype.

Halligan & Robertson (1999) note that the incidence of neglect varies widely across studies, between 12% and 95%. Of course incidence will depend on the operational definition of neglect used, along with the assessment or combination of assessments to identify neglect and, the marked heterogeneity of neglect presentation (Ting, Pollock, Dutton, Doubal, Ting, Thompson, & Dhillon, 2011).

Identifying spatial neglect and separating it into different subtypes might help clinicians and researchers to target treatment approaches. For example, we know that egocentric and allocentric neglect have a different impact on functional independence and recovery pathways (Bickerton et al., 2012; Chechlacz et al., 2010, 2012). The presence of post-stroke neglect is associated with longer stays in hospital and poorer functional outcomes (Bultitude et al., 2013; Chen, Hreha, et al., 2015; Nijboer et al., 2013). Data from 88,000 UK hospital stroke admissions suggested that those with neglect had a greatly increased length of stay (27 vs. 10 days) and on discharge were 'dependent' (76% vs. 57%) according to the modified Rankin scale (Hammerbeck et al., 2019). Although neglect impedes active participation in stroke rehabilitation, decreases independence in activities of daily living (ADLs), and has an adverse impact on quality of life there is no compelling evidence for specific interventions that improve life after stroke (Bowen et al., 2013). Evidence also suggests that neglect is a potential safety hazard with respect to falls (Chen et al., 2015; Wee & Hopman, 2008).

Many national clinical guidelines recommend the comprehensive and timely screening and diagnosis of neglect as an essential part of post-stroke clinical care planning e.g. the Royal College of Physicians London (Intercollegiate Stroke Working Party, 2016), the Canadian Stroke Association (Hebert, Lindsay, McIntyre, Kirton, Rumney, Bagg, et al., 2016), the American Heart Association (Winstein, Stein, Arena, Bates, Cherney, Cramer, et al., 2016), and the National Stroke Foundation of Australia's clinical guidelines for stroke management (National Stroke Foundation, 2019). However, these lack specific guidance on which of the many neglect tests to choose, for which subtypes of neglect and at which timepoints.

Various standardised assessments of neglect, or of functions that could be affected by neglect, are available. Anecdotally we know that those chosen by clinicians mostly fall into four broad but unequal categories: cognitive/neuropsychological assessment, functional assessment, neurological assessment, and (in some countries) neuroimaging/neuromodulation. Cognitive assessment is the measurement of abilities and processes such as attention and memory by means of standardised assessments. An example of a cognitive assessment for neglect is The Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), comprising 15 subtests involving target cancellation, drawing, line bisection, text reading, clock reading, and visual description - all assessing neglect in peri-personal space. Functional assessment is the structured appraisal of a patient's ability to perform everyday tasks, such as dressing or making a hot drink. The Catherine Bergego Scale (CBS; Bergego, Azouvi, Samuel, Marchal, Louis-Dreyfus, Jokic, et al., 1995) is a 10 item structured functional assessment, and focuses on personal space and performance of activities of daily living (ADLs) in extra-personal space. Each item is scored by direct observation from 0-3, giving a maximum possible score of 30. There is also a self-evaluation and anosognosia scale, which mirrors the functional assessment checklist and provides a self-awareness score between 0-30. (An anosognosia score can be obtained by calculating the difference between the observer's and the patient's scores.) Neurological assessment is the clinical examination of signs and symptoms including, but not specific to, those indicative of neglect. The National Institutes of Health Stroke Scale (NIHSS; Brott, Adams, Olinger, Marler, Barsan, Biller, et al., 1989) is primarily used in the acute phase post-stroke to inform immediate treatment and subsequent rehabilitation. Certain NIHSS subscales are used to screen for neglect e.g. horizontal gaze, sensation, and extinction/neglect subscales. Neuroimaging is another important approach in the acute phase to initially detect lesion location and extent and guide assessment. Some professionals use neuroimaging findings to associate cognitive and functional deficits with lesion location and/or damage to distributed neural networks (Vuilleumier, 2013) although it is not known whether neuroimaging is commonly used in clinical practice for screening or diagnosis.

Currently it is unknown how different clinical professional groups screen, assess, or diagnose neglect and whether they use any or all of these four categories. Previous attempts to understand the selection of neglect assessments focused on identifying the gap between best and current practice within a profession, rather than similarities or differences between professional groups or countries. For example, a survey of 253 Canadian occupational therapists conducted by Menon-Nair, Korner-Bitensky & Ogourtsova (2007) found that while identification of neglect-related problems was high, the use of evidence-based, standardised assessments was less than optimal. This is consistent with a previous retrospective study of medical records, that found standardised neglect assessment was not standard clinical practice amongst participating hospitals in Canada (Menon-Nair et al., 2006). Furthermore, it is not uncommon for clinicians to assess neglect informally – that is, without use of standardised tests (Halligan & Robertson, 1999). The selection of neglect assessments varies widely across research studies (Chen et al., 2015) due to the varied operational definition of the syndrome and its symptom presentations (Verdon et al., 2010). Reflecting the wide range of assessments available, a Cochrane review of cognitive rehabilitation for stroke acknowledged that there was no one neglect assessment that was common across included studies (Bowen et al., 2013).

The various approaches to measuring neglect require clarification for clinicians and researchers alike, with the ultimate goal of forming a consensus on the best approaches to use. We acknowledge there is also a considerable psychometric literature comparing the sensitivity and specificity of cognitive versus functional tests of neglect and comparing tests within a category (e.g. cancelling bells or stars versus cancelling apples (Basagni et al., 2017; Bickerton et al., 2011)). Before exploring the psychometric literature we aimed to take the first of several steps in an international, multidisciplinary, multi-stage consensus process beginning by scoping clinical practice across a range of professionals, countries and clinical settings. We hypothesised that selection of neglect assessments differs according to professional background, role in a multidisciplinary team, and/or local and national policies.

We designed this study to answer the following research questions:

1. Which assessments of neglect after stroke are used by which clinical professionals, and in which countries? 2. Are assessments selected on the basis of professional choice

or institutional policy? 3. Are there assessments not listed in the study that are deemed to be useful?

2.2 Methods

2.2.1 Participants

Respondents were recruited by email invitations via professional organisations or key individuals worldwide, and opportunity sampling on Twitter. This study was approved by an ethics review committee (The University of Manchester, 2018-3901-7379) and hosted on the online platform SelectSurvey. The survey was open from 19th November 2018 to 24th February 2019.

2.2.2 Survey Development

The list of assessments was collaboratively developed through iterative discussion amongst the authors, and in consultation with local stroke clinicians otherwise not involved with the study design process. Assessments were included if they were informally appraised to be either specific to the detection of spatial neglect, or non-specific to spatial neglect detection but potentially used during routine examination and assessment as more general neurocognitive or functional probes. The survey was developed in a 4-stage sequential, multimethod approach. At stage 1, authors held initial in-person meetings followed by video conferences and email communications to determine the objectives and research questions. At stage two, the first author (MC) created the first draft of the survey to collect comments and suggestions on its design from the other authors. After multiple iterations the survey was converted into online format and at stage 3, co-authors and local research collaborators pilot-tested the functionality of the survey and the utility of the format in which data were rendered by the survey software. At this stage, the survey reached its current format of four assessment categories (cognitive, functional, neurological, and neuroimaging/neuromodulation), where the first three contained a non-exhaustive list of assessments with three response options each: ‘Use – Professional Choice’, ‘Use – Institutional Policy’, and ‘Do Not Use’, with only one option available per assessment. The neuroimaging/neuromodulation section contained free text options for respondents to indicate their choice of assessment(s). Stage 4 consisted of final tweaking of the online survey design as well as the compilation of target organisations and email addresses before distribution of the survey advertisement (survey content is provided as supplementary material).

The main rationale for including a non-exhaustive list of assessments in the main body of the survey was to avoid over-burdening respondents, to maximise the response rate and accuracy of responses. For the same reason we did not ask respondents to repeat the questions for each neglect subtype (e.g. egocentric, allocentric), severity or setting/timescale (e.g. in acute phase and chronic phases). Instead, at the end of the questions we included the opportunity to respond with free choice, narrative data. The main rationale for not including a list of neuroimaging/neuromodulation techniques was our assumption that the technologies used between professional groups and countries would not vary (e.g. MRI and CT use is prolific in the diagnosis of stroke). Rather, we sought to uncover more specifically which, if any, aspects of these scanning procedures or sequences are used to screen and diagnose neglect (e.g., diffusion tensor imaging, T2-weighted imaging, or VBLM – all in the case of MRI), by which professionals and in which countries. Inclusion of items was not a recommendation. We sought to find out what is being done in clinical practice not what should be done. We focused this initial work on clinicians, mindful that clinical and research practice may be very different.

2.2.3 Procedures

2.2.3.1 Demographic Questions

Those clinicians not currently practising (i.e. treating patients with neglect in the preceding 12 months) were ineligible and removed from the survey. Other demographic questions collected information on country of practice, profession/discipline, practice setting (e.g. inpatient, outpatient), length of service in stroke medicine/rehabilitation, and whether or not respondents were active in neglect research (either as an investigator or assisting in recruiting for someone else's research). The survey did not collect any health information, internet protocol addresses, or other data that would potentially be personally identifiable.

2.2.3.2 Assessments for Neglect

After answering preliminary questions, participants responded to questions on the screening and diagnosis of neglect organised into the four categories described above. The flowchart (Figure 2.1) depicts a respondent's passage through the survey. For each individual assessment, respondents indicated whether or not they use it for the screening or diagnosis of neglect. Respondents could select only one of the following: Use – Institutional Policy, Use – Professional Choice, Do Not Use. There was no limit to the number of assessments a respondent could select. If respondents' most frequently used assessment(s) did not appear in the list, they were asked to provide the name(s) of such assessments in a comment box underneath the original question. At the end of the four categories, there was a final page of three open questions. Here we asked what respondents would use, given a free choice, as (i) a screening assessment, (ii) as a diagnostic assessment, and finally (iii) asked if they had any further comments.

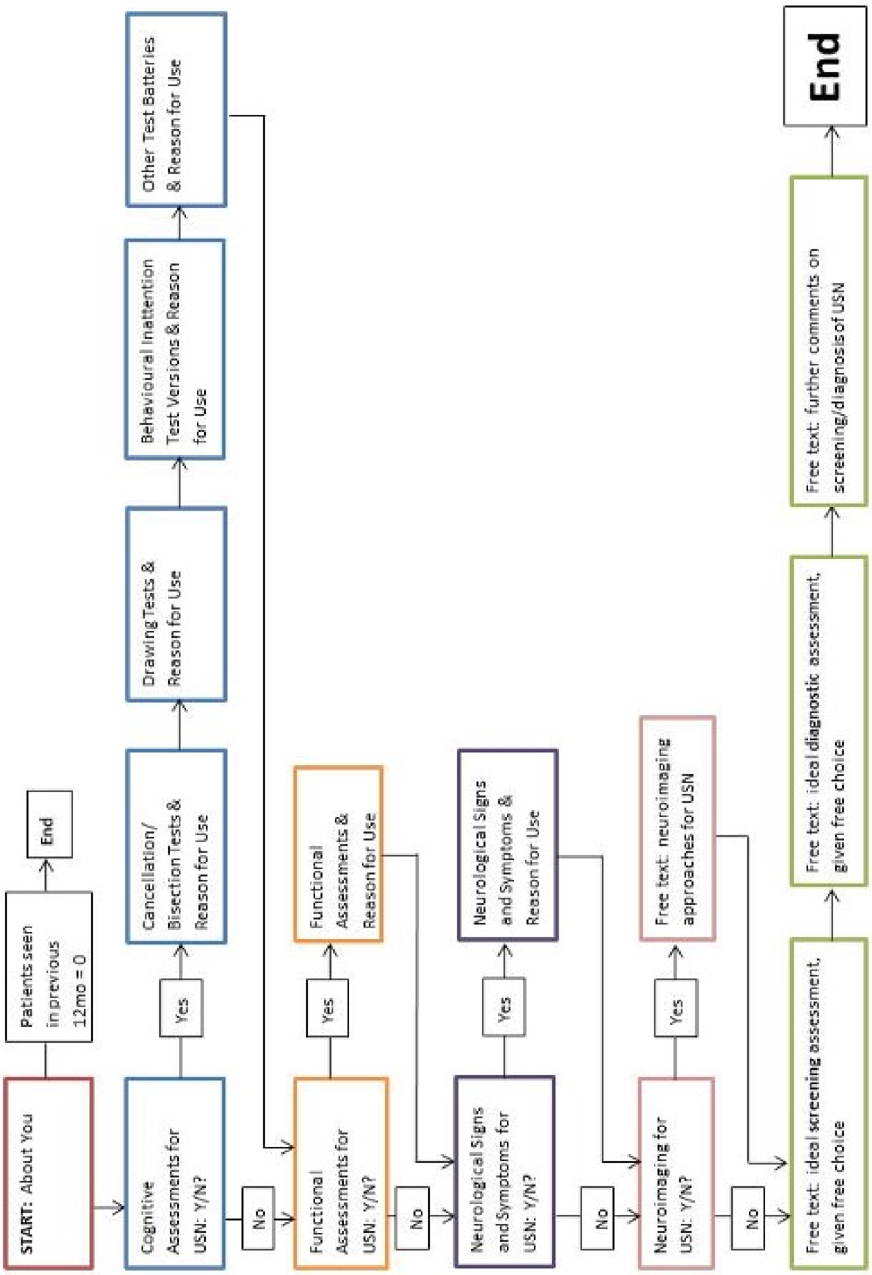

Figure 2.1: Flowchart depicting respondents' pathway through the survey.

2.2.4 Analysis

Raw, fully anonymised data were downloaded in Excel format from the SelectSurvey platform in March 2019. Participant characteristics and relationships with assessment tools were analysed with descriptive and frequency statistics. After visualising the data, a multi-factorial logistic regression model was designed to assess the independent associations of ‘profession’ and ‘country’ after adjustment for the potentially confounding influences of experience, research activity, and clinical setting (question one). These regression analyses allowed us to calculate which professional group, or which country of practice, made it more likely for a particular assessment category to be selected. For clinical setting, respondents could choose more than one of these three options, which were handled in regression models as individual factors in their own right rather than as levels within one factor. The first level, usually the most prevalent, served as the reference for each categorical factor with odds ratio (OR) = 1.0 by definition (with the exception of clinical setting). For example, OTs serve as the reference for ‘profession’ with the other professional categories shown relative to OTs (see Table 2.1; the reference categories are underlined).

Further multifactorial logistic regression was undertaken to answer question two, limited to respondents who used each specific assessment. For all analyses 95% confidence intervals (CIs) are given and statistical significance was concluded using the threshold of $p \leq 0.05$. We also summarised the most popular individual assessments within the categories.

2.3 Results

2.3.1 Participant Characteristics

Out of a total number of 476 responses, we excluded 22 that indicated no experience in treating patients with neglect in the preceding 12 months. Therefore, after meeting the criteria, 454 responses were included in the study (see Table 2.1).

Table 2.1 presents the numbers of respondents according to their profession, geographical location, months of experience, number of patients with neglect seen in the past twelve months, clinical setting, and research involvement. Occupational therapists (OTs) represent the most frequent professional group within this survey (39%), followed by psychologists (19%), medical doctors/physicians (15%), and physiotherapists (12%). For the purpose of analysis, the small number of respondents from speech & language therapists, orthoptists, and other self-reported professional backgrounds form a single ‘other’ category (15%). The greatest number of respondents was from the United Kingdom (UK, 38%), followed by the United States of America (USA, 22%) and Italy

Table 2.1: Characteristics of respondents. NB: one respondent from the psychology group, one from the medicine group, and one from the 'other' group did not provide months of experience. For clinical setting, respondents were allowed to select more than one response. Underlined categorical groups served as reference categories for logistic regression analyses.

Demographics (N=454)	Occupational Therapy (n=179, 39%)	Psychology (n=84, 19%)	Medicine (n=70, 15%)	Physiotherapy (n=55, 12%)	Other (n=66, 15%)	Total
Country						
○ **UK**	63	21	19	27	42	172 (38%)
○ **USA**	71	1	5	11	11	99 (22%)
○ **Italy**	11	47	14	0	4	76 (17%)
○ **Other Europe**	10	15	23	7	3	58 (13%)
○ **Other Non-Europe, Non-USA**	24	0	9	10	6	49 (11%)
Median Months of Experience (Min, Max)	96 (1-408)	120 (12-420)	204 (25-600)	125 (4-406)	120 (6-420)	120 (1-600)
Patients with neglect in past 12mo						
○ **1 to 6**	62	27	14	25	22	150
○ **7+**	117	57	56	30	44	304
Clinical Setting						
○ **Inpatient**	138	62	63	41	54	358
○ **Not Inpatient**	41	22	7	14	12	96
○ **Outpatient**	41	47	43	13	42	186
○ **Not Outpatient**	138	37	27	42	24	268
○ **Community**	26	13	3	9	15	66
○ **Not Community**	153	71	67	46	51	388
Research Involvement						
○ **None**	140	37	34	47	50	308
○ **Investigator**	14	36	26	6	7	89
○ **Recruitment**	25	11	10	2	9	57

(17%). Similarly, for the purpose of analysis, responses from other European countries (including Denmark, France, Germany, Luxembourg, Sweden, and Switzerland) and responses from other countries excluding Europe and the USA (including Australia, Canada, Japan, and South Korea) were combined to form ‘Other Europe’ (13%) and ‘Other Non-Europe, Non-USA’ (11%) groups respectively. The majority of respondents reported spending time with seven or more patients with symptoms of neglect in the preceding twelve months (67%), and the overall median length of clinical experience was ten years.

2.3.2 Assessment Categories

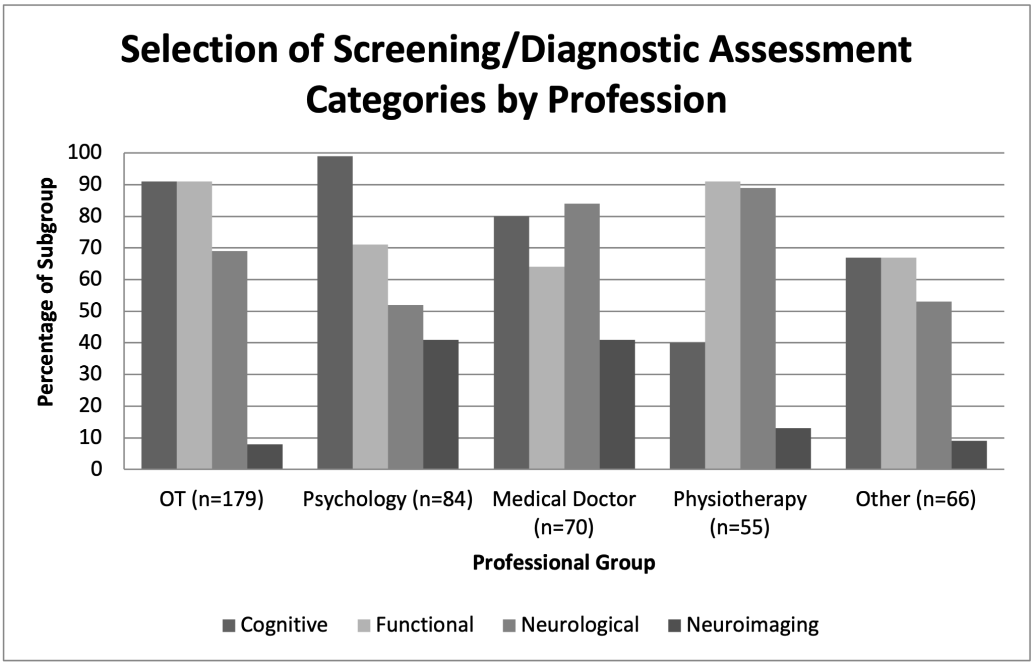

Figure 2.2: Percentage of respondents from each professional group who use each category of neglect assessment.

Figure 2.2 represents the percentage of respondents within each professional group who indicated their use of the four potential assessment categories – cognitive assessments, functional assessments, neurological assessments, and neuroimaging/neuromodulation techniques. There is variation between professional groups. For example, similar proportions of occupational therapists report using both cognitive and functional assessments. In contrast, psychologists predominantly select cognitive assessments, followed by functional assessments, and no more than 50% use neurological assessment and neuroimaging/neuromodulation techniques. Physicians and physiotherapists select assessments that reflect their training and practice, with physicians using cognitive and neurological assessments more than other categories, and physiotherapists more often selecting assessments from the functional and neurological categories.

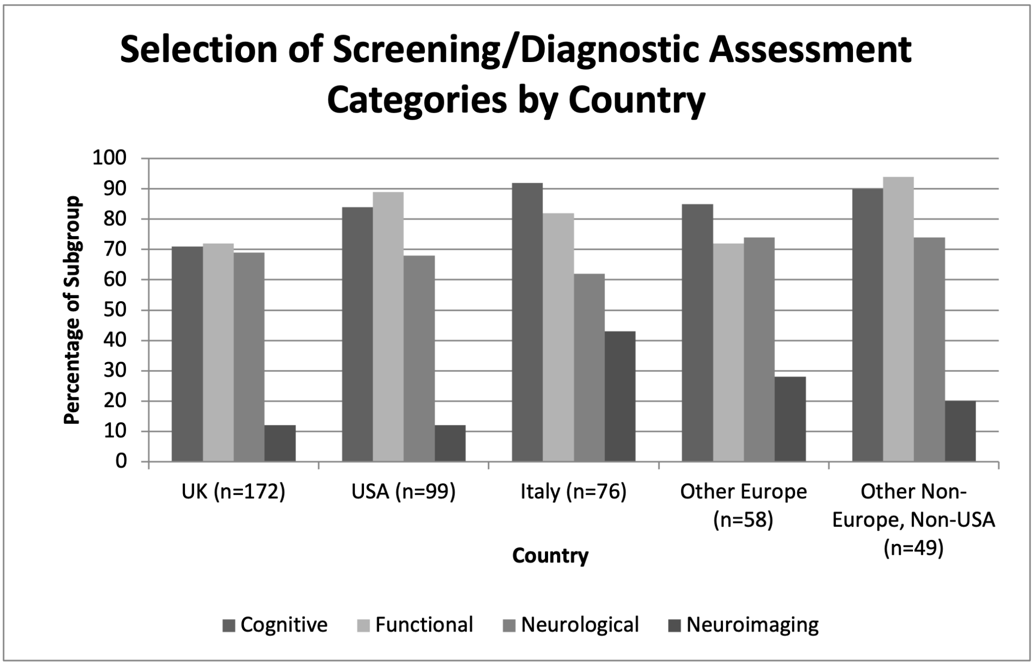

Figure 2.3: Number of respondents from each country who indicate their use of each category of neglect assessment.

Figure 2.3 represents the proportion of respondents from each country or country category per assessment category. There is comparatively little variation between different countries with the possible exception of Italy. Respondents from each country exhibit similar patterns, with cognitive and functional assessments the most popular and neuroimaging/neuromodulation the least.

Three hundred and sixty-eight (82%) respondents reported use of cognitive assessments to identify neglect. Psychologists were most likely to use these, OR (95% CI) = 7.2 (0.90 to 60). Other professionals were significantly less likely to use cognitive assessments: physicians, OR (95% CI) = 0.2 (0.10 to 0.70), physiotherapists, OR (95% CI) = 0.05 (0.02 to 0.10), and 'others', OR (95% CI) = 0.2 (0.10, 0.50). Respondents outside of Europe and the USA were significantly more likely to use cognitive assessments: OR (95% CI) = 4.4 (1.40 to 14). Respondents active in research were also more likely to use cognitive tools: OR (95% CI) = 5.04 (1.60 to 16).

Three hundred and sixty-one (80%) respondents reported use of functional assessments to identify neglect. Physiotherapists were more likely than all others: OR (95% CI) = 1.1 (0.40 to 3.2), and psychologists, OR (95% CI) = 0.14 (0.06 to 0.34), physicians, OR (95% CI) = 0.1 (0.04 to 0.23), and 'other' professions, (95% CI) = 0.16 (0.07 to 0.37), were significantly less likely. Respondents outside of Europe and the USA were the most likely: OR (95% CI) = 4.9 (1.3 to 18), followed by those in Italy: OR (95% CI) = 2.8 (1.2 to 6.6).

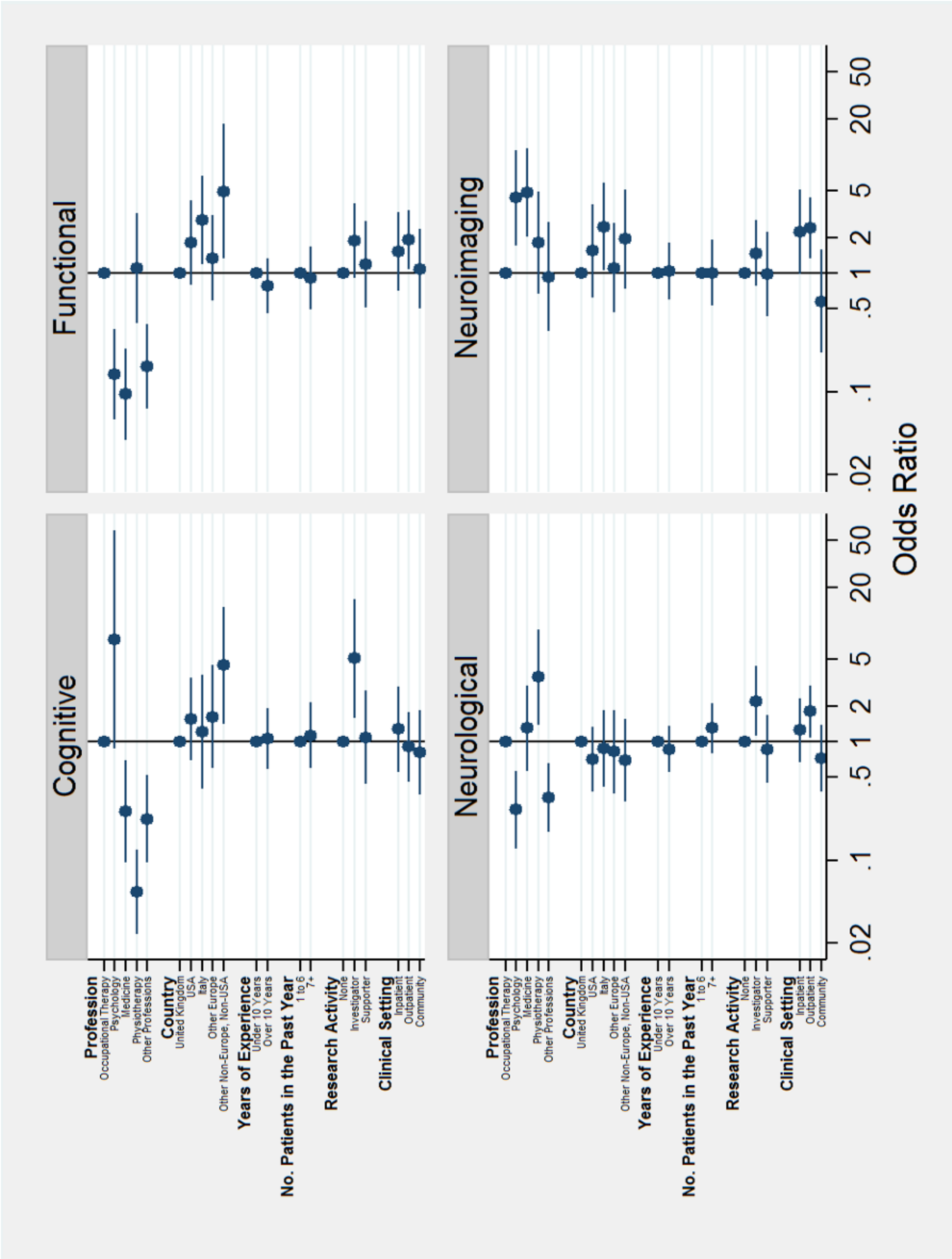

Figure 2.4: Forest plots depicting logistic regression results for selection of each assessment category. Note: x-axes are on a logarithmic scale. Logistic regression results are presented as odds ratios with 95% confidence intervals.

Three hundred and eleven (69%) respondents reported use of neurological signs and symptoms to identify neglect symptoms. Physiotherapists were the most likely, recording OR (95% CI) = 3.5 (1.4 to 8.8). Psychologists and 'other' professionals were less likely to use neurological signs and symptoms, recording OR (95% CI) = 0.27 (0.13 to 0.56) and OR (95% CI) = 0.34 (0.17 to 0.65) respectively. Clinicians working in the outpatient setting were also significantly more likely to use neurological signs and symptoms: OR (95% CI) = 1.8 (1.1 to 3.0), as were clinicians involved in research: OR (95% CI) = 2.2 (1.1 to 4.3).

Finally, 91 respondents (20%) reported using neuroimaging/neuromodulation techniques. Physicians were most likely, recording OR (95% CI) = 4.8 (2.0 to 11.2), followed by psychologists, recording OR (95% CI) = 4.3 (1.7 to 10). Use was also significantly higher in Italy: OR (95% CI) = 2.5 (1.1 to 5.8). Clinicians working in the outpatient setting were also significantly more likely to use neuroimaging/neuromodulation: OR (95% CI) = 2.4 (1.3 to 4.3).

2.3.3 Selection of Specific Assessments

As well as asking what categories of assessment stroke clinicians use, we also wanted to find out which individual assessments are most frequently used. The ultimate goal in our research programme, of which this is stage one, is an international, multi-professional consensus on the best approach to screen and diagnose neglect, where frequency and feasibility of assessment use are two of potentially several influencing factors along with psychometric properties that will be investigated in stage two. Figures 2.5 to 2.8 display the percentage of selections per professional group for individual screening/diagnostic assessments for neglect. Each figure is sub-divided into profession and country.

2.3.3.1 Cognitive Assessments

Figure 2.5 shows the percentage of respondents who reported use of each individual screening/diagnostic cognitive assessment, categorised by profession (5A) and country (5B).

The most popular cognitive assessment selected by 292 clinicians was the line cancellation test (Albert, 1973). Six assessments – line cancellation, clock drawing, star cancellation, letter cancellation, figure drawing and figure copying – were reported by at least 60% of OTs and 70% of psychologists. Line bisection was similarly popular amongst psychologists but not OTs. No other assessment was used by more than 40% of any professional group.

Figure 5B suggests that a greater proportion of respondents from Italy select specific cognitive assessments, compared to their colleagues from other countries. For example, greater proportions of clinicians from Italy select line, star, and letter cancellation tests, as well as figure copying and drawing, and all presented versions of the BIT.

At the end of each cognitive assessment sub-category, respondents were asked about any other cognitive assessments that weren’t provided in the survey list. One hundred additional assessments, including 39 cancellation and bisection tests, 26 drawing tests, and 35 test batteries, were reported by participants. Only the Bells Test

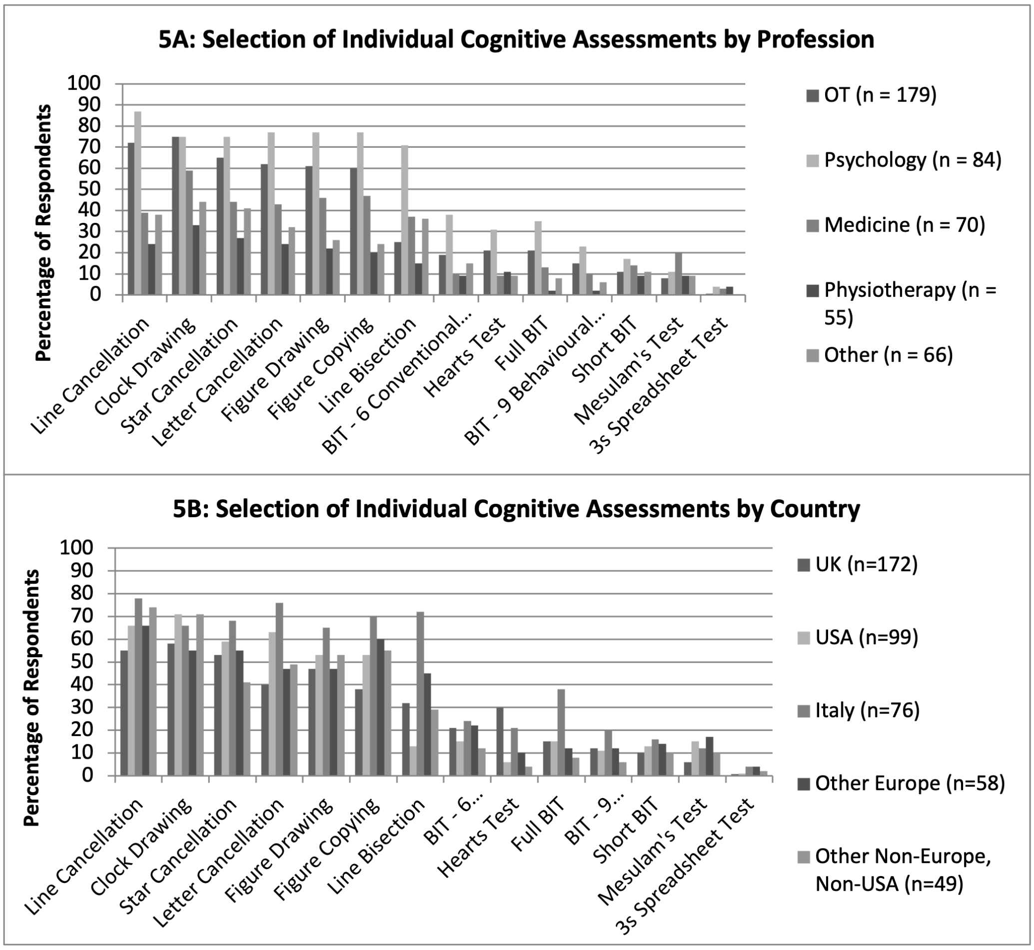

Figure 2.5: Cognitive assessment selections by professional group (5A) and by country (5B).

(Gauthier et al., 1989) was more popular than one test included in the survey question - the 3s spreadsheet test (Chen et al., 2017) with 38 versus 8 responses respectively.

2.3.3.2 Functional Assessments

Observation (clinical, unstructured) was the most commonly selected assessment from the functional category, with 309 positive responses. The distribution for functional assessments (Figure 6A) is comparatively more varied. The two most popular assessments – observation and interview - are selected by the majority of OTs compared to other professional groups, however standardised generic (non-neglect specific) approaches such as the functional independence measure (FIM; Keith, Granger, Hamilton, & Sherwin, 1987), the Barthel index (BI; Mahoney & Barthel, 1965) and the instrumental activities of daily living scale (IADL; Lawton & Brody, 1969) are selected by greater proportions of psychologists (e.g., FIM) and physicians (e.g., BI and IADL). Neglect-specific approaches based on observation of functional activities such as the Catherine Bergego Scale (CBS) and the Kessler Foundation Neglect Assessment Process (KF-NAP; Chen, Hreha, Fortis, Goedert, & Barrett, 2012) are selected by greater proportions of OTs.

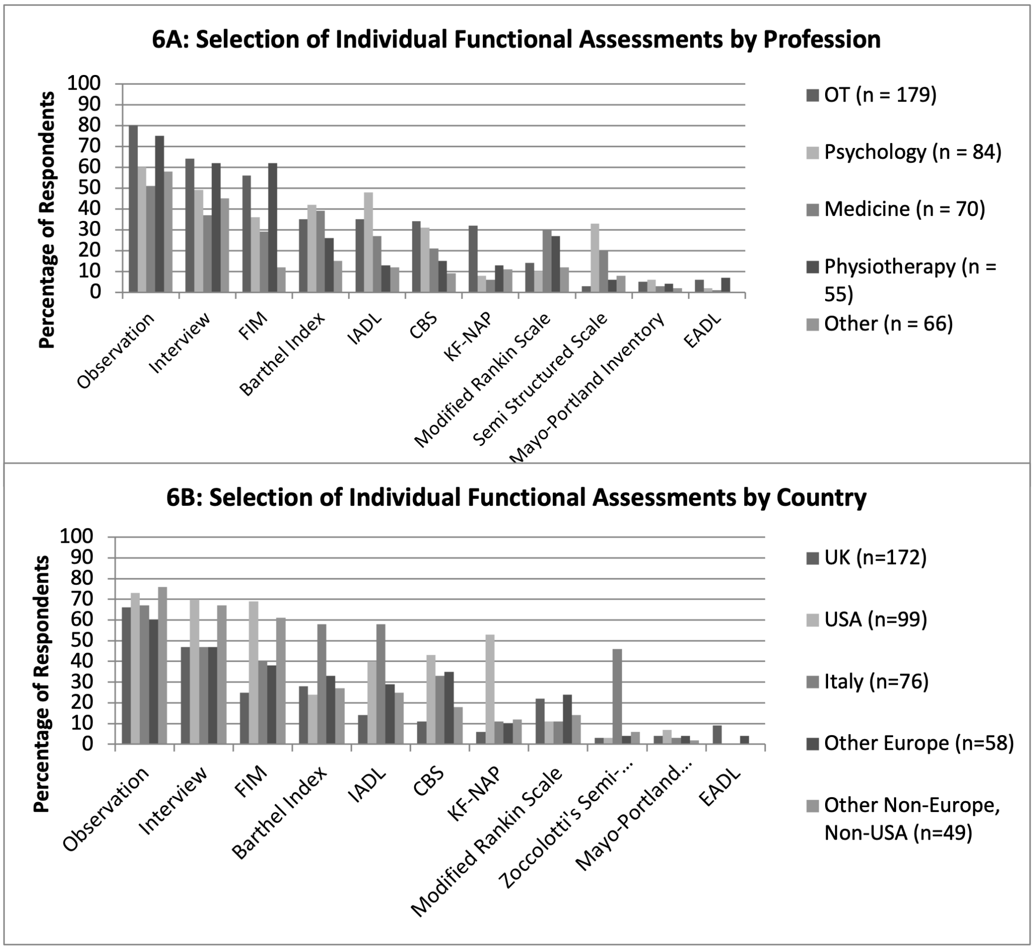

Figure 2.6: Functional assessment selections by professional group (6A) and by country (6B).

Figure 6B suggests that a greater proportion of USA clinicians favour interviews, the FIM, the CBS and the KF-NAP. Clinicians from Italy appear to more frequently use the BI, the IADL and Zoccolotti's semi-structured scale for the functional evaluation of hemi-inattention in personal space (Zoccolotti et al., 1992). The most popular functional assessment, i.e. observation, was selected by a greater proportion of respondents from 'other worldwide' countries.

When asked if they wished to outline any other functional assessments that were not listed, respondents reported 60 additional assessments, but none were as popular as those listed in the survey.

2.3.3.3 Neurological Assessments, Neuroimaging and Neuromodulation

For the third category (neurological/clinical examination), observation (unstructured) was the most popular assessment choice, with 293 positive responses. In the case of neurological assessments (Figure 7A), the majority of these are favoured by greater proportions of physiotherapists, except in the case of screening for visual field loss, extinction, anosognosia, and somatoparaphrenia, which were favoured by physicians.

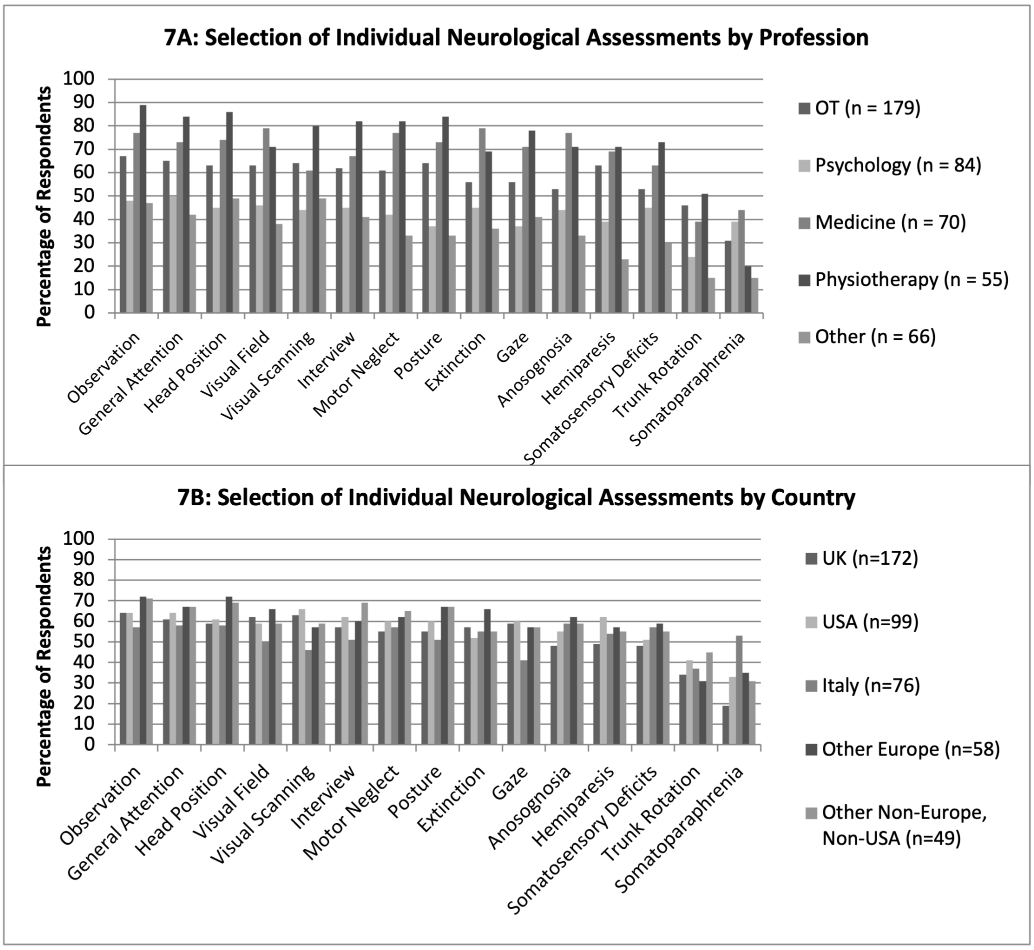

Figure 2.7: Neurological assessment selections by professional group (7A) and by country (7B).

Figure 7B suggests that there appears to be fewer differences in the proportions of respondents from country subgroups in terms of assessment selection. The greatest agreement between countries seems to be in the selection of examination of general attention, motor neglect, and somatosensory deficits. However, the least agreement is in the selection of screening for somatoparaphrenia, which is clearly favoured by clinicians from Italy.

When asked if they would like to provide additional information about other neurological approaches unlisted within the survey 25 additional assessments were reported, none of which were as popular as those already included in the survey.

Finally, of the 91 (20%) respondents who indicated their preferred neuroimaging/neuromodulation technique, 78 respondents provided further detail. The responses are summarised in figure 2.8.

Neuroimaging/neuromodulation was most popular amongst psychologists (n=31) and physicians (n=27), and clinicians based in Italy (n=30) but far less so in the UK. The most frequently reported neuroimaging assessment was use of magnetic resonance imaging (MRI) with 61 occurrences in-text, followed by computerised tomography (CT)

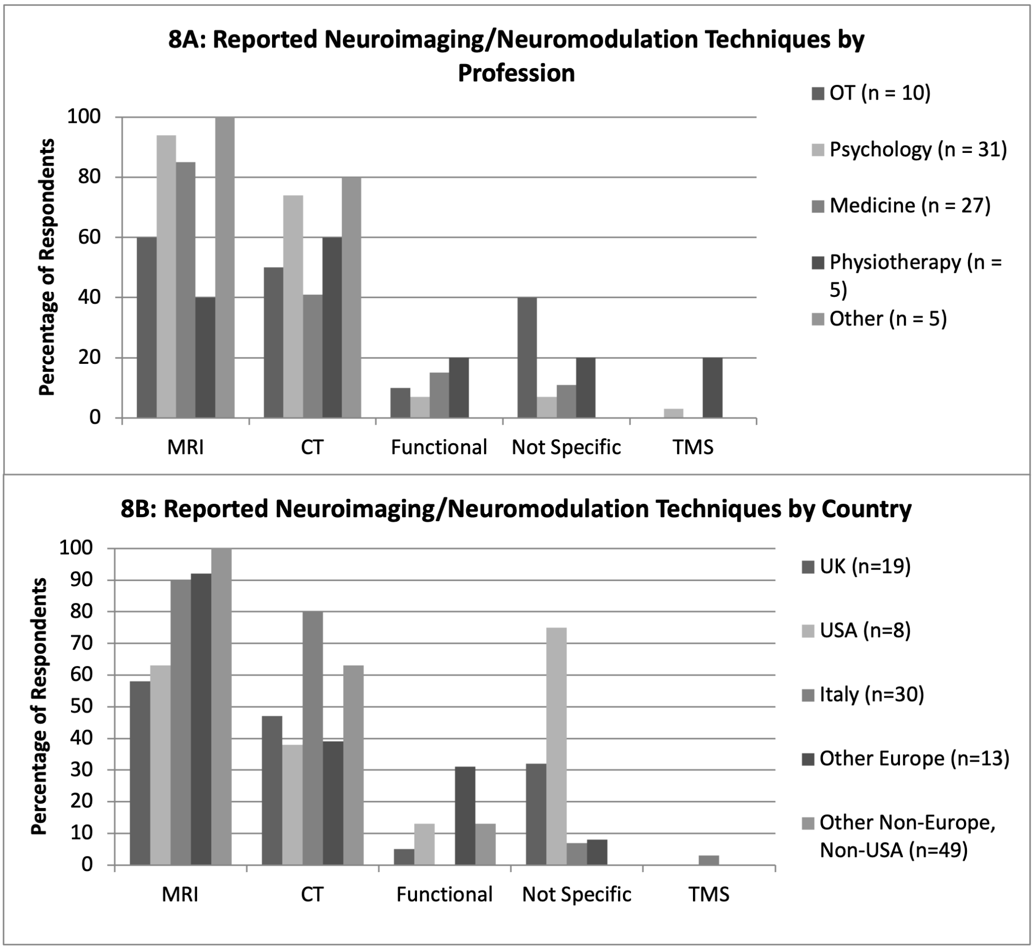

Figure 2.8: Reported neuroimaging/neuromodulation techniques by professional group (8A) and by country (8B).

with 42. Other functional techniques were reported (primarily electroencephalography and functional MRI [fMRI]), as were neuromodulation paradigms such as transcranial magnetic stimulation (TMS). Figures 8A and 8B suggest that conventional structural scanning is the most popular tool used by clinicians in the identification of neglect. The 'non-specific' category incorporates responses that do not explicitly mention a particular technique but refer to concepts such as 'structural scans', or 'lesion mapping'.

Within the free-text data, there appeared to be a distinction between some respondents depending on whether neuroimaging/neuromodulation is used to deduce the presence of neglect by lesion location (for example, "[I] look at the location of the stroke to see if the areas are consistent with areas of the brain that are more common to have neglect after a stroke"), or whether it is used in differential diagnosis (for example, "I would use imaging results to guide my thoughts over whether I was looking for a neglect or a hemianopia, or if a patient that looked like they had neglect had brain damage consistent with neglect"). Some respondents also employ more specific neuroimaging procedures, particularly in the case of MRI; these include diffusion tensor imaging (DTI) for the visualisation of white matter tracts and/or visualisation of vascular tissue, and voxel-based lesion mapping to visualise the extent of lesions. Few respondents selected functional neuroimaging approaches (e.g., functional MRI, EEG, MEG) or transcranial magnetic stimulation (TMS); however, more often than not, these approaches appeared in combination with structural scanning procedures. Several respondents made the distinction between the use of neuroimaging as a standalone diagnostic assessment and the use of neuroimaging as one source of additional information, which is combined with other approaches to inform tailored rehabilitation programmes for patients.

2.3.4 Reasons for Using Screening/Diagnostic Assessments

Figure 2.9 presents the relative proportions of the two ‘reasons for use’ responses for individual assessments – professional choice versus institutional policy.

Figure 2.9 suggests that for cognitive assessments (9A), approximately 20% to 40% of assessment selections are driven by institutional policy. In the functional assessment category (9B), there is greater variation between specific assessments in terms of reasons for their selection: between 20% and 70% of selections of specific tools here are made on the basis of institutional policy. Figure 9B suggests that assessments not specific to neglect but that are used for multiple different purposes (e.g. the FIM, BI, and mRS) are selected the most based on institutional policy, with neglect-specific assessments (e.g. the CBS and KF-NAP) exhibiting the inverse pattern. For neurological assessments (9C), approximately 30% to 40% of assessment selections are driven by institutional policy.

2.3.5 Narrative Data

2.3.5.1 Screening Assessments - Free Choice

One hundred and ninety-eight (44%) respondents commented on their ideal screening assessment, given free choice. Of these 198 respondents, 36% were OTs, 21% were psychologists, 34% were physicians, 9% were physiotherapists, and 7% were ‘others’.

Table 2.2 displays examples of screening assessments as chosen by clinicians in their ‘ideal’ scenario. The most common theme arising was with regard to cognitive assessments, yielding 75 references among respondents. The reasons for these selections were either: the rapid nature of cognitive screening (e.g., paper-and-pencil tests) or the respondent only being aware of the particular assessments they suggested. Only one respondent mentioned the screening of spatial neglect subtypes, without any detail on specific assessments.

Table 2.2: Self-reported 'ideal' screening assessments as reported by 176 respondents. Column 1 shows themes emerging from free-text responses, column 2 shows the number of respondents contributing to each theme, and column 3 shows examples of each theme.

Theme	No. of Respondents	Examples
Cognitive Assessments	75	- BIT - Cancellation Tests - Hearts test (from OCS) - OCS
Combinatorial Approaches	41	- Cognitive plus functional assessments - Custom combinations based on individual cases - Custom approaches based on individual cases requiring particular intervention (e.g. cancellation tasks and visual scanning training) - Custom combinations of individual assessments taken from batteries that are easier to administer
Functional Assessments	32	- CBS - CBS via the KF-NAP - Functional observation - ADL performance
Neurological Assessments	18	- Neurological examination with a focus on contralesional function - NIHSS - Extinction tests - Visual field testing - fMRI
Desire for Further Information	12	- Responses focus primarily on uncertainty surrounding range of available screening assessments - Some report use of non-standardised assessments if free/accessible assessments aren't available
Sources Other Than The Patient	8	- Information gathering from family members - Information gathering from other clinicians involved in patient's care

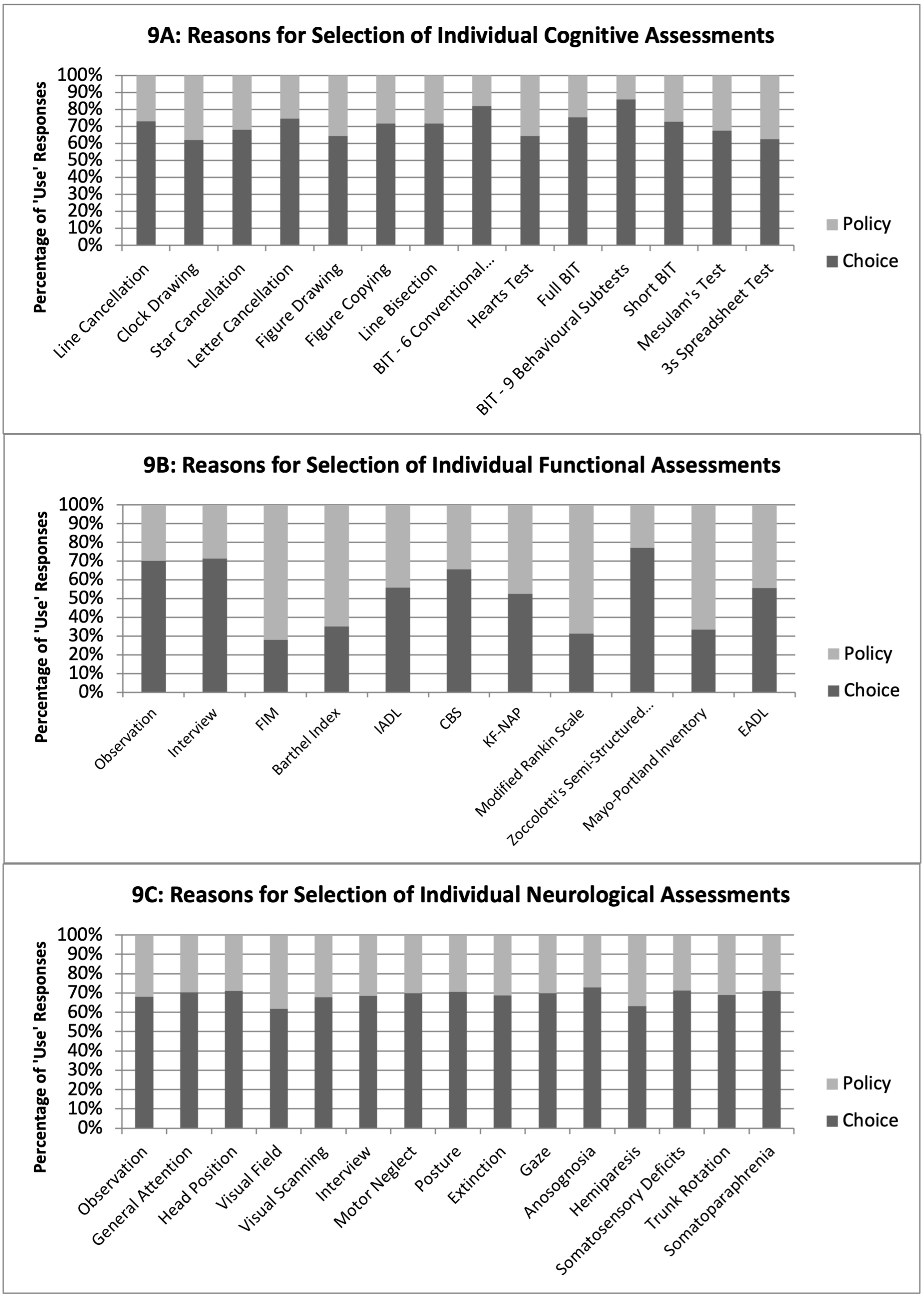

Figure 2.9: Proportions of ‘use’ responses according to reason for selection – institutional policy or professional choice.

2.3.5.2 Diagnostic Assessments - Free Choice

One hundred and seventy six (39%) respondents commented on their ideal diagnostic assessment, given free choice. Of these 176 respondents, 31% were OTs, 25% were psychologists, 17% were physicians, 14% were physiotherapists, and 13% were ‘others’.

Table 2.3: Self-reported 'ideal' diagnostic assessments as reported by 176 respondents.

Theme	No. of Respondents	Examples
Combinatorial Approaches	43	- 31 responses contained at least one cognitive element: usually combinations of cognitive assessment - Cancellation/bisection/symmetry judgement combined with tests of representational neglect - Cognitive and functional assessment - Cognitive assessment and neuroimaging reports - Cognitive and functional assessment with neuroimaging reports - Cognitive assessment and reaction time measurement
Functional Assessments	35	- CBS - CBS via the KF-NAP - Functional observation - ADL performance
Neurological Assessments	20	- Neurological examination - MRI - Visual scanning - Visual acuity
Desire for Further Information	26	- Any best-practice assessment as stipulated by best-practice guidelines - Desire to integrate comprehensive diagnostic assessment if staffing and financial resource allowed - Expertise of multidisciplinary team - Several responses contained a single word: "unknown"

2.3.5.3 Respondents' Further Comments

One hundred (22%) respondents provided further comments at the end of their participation in the survey. Of these 100 respondents, 31% were OTs, 16% were psychologists, 17% were physicians, 15% were physiotherapists, and 21% were 'others'.

Table 2.4: Additional comments on the screening and diagnosis of neglect as provided by 100 respondents.

Theme	No. of Respondents	Examples
Desire for Further Training	27	- Little to no training in neglect screening/diagnosis at degree level - Professional differences in amount of neglect-specific training - Increased awareness of impact of neglect in order to generate resources for more comprehensive screening/diagnosis
Under-Use of Existing Assessments	21	- Limited understanding of how to score cognitive assessments appropriately - Subjectivity in assessment scoring and interpretation fosters invalidity of assessments - Dislike of large test batteries that can take too much time and are less acceptable to patients (desire for research into new, short comprehensive batteries linked to this) - Lack of any assessment with clinicians' ideal psychometric properties (high sensitivity and specificity) - Incorrect combinations of assessments may also be sub-optimal
Clinician Factors	26	- Different clinicians prefer different approaches; beauty of a multidisciplinary team - Some clinicians more dynamic in their approach than others (e.g. tailoring assessment to neglect presentation) - Some clinicians experience scarcer resources than others – impact on time spent with neglect patients - Pooling of neglect-specific and non-specific assessment results from different professionals within multidisciplinary team

Table 2.4 displays the results of the final question in the survey, which asked clinicians for their general comments on the screening and diagnosis of neglect. The

most common theme identified was that of a desire for further training (27 respondents). Other themes were tangentially related in that they allude to information-gathering from various sources to inform good clinical practice in the screening and diagnosis of neglect. Four respondents here mentioned the assessment of spatial neglect subtypes. Of these, two respondents mentioned the utility of functional assessments (including the KF-NAP) in addressing “types and sequelae” of spatial neglect, one respondent advocated combined cognitive and motor assessment to dissociate motor neglect from other subtypes, and one respondent commented on a lack of education provided on various subtypes of spatial neglect.

2.4 Discussion

Before we can build consensus on the approaches that should be used for the screening and diagnosis of spatial neglect, this study identified which assessments are being used in clinical practice, by which professional groups and in which countries, whether these selections are determined by professional choice or institutional policy, and whether clinical professionals suggest alternative methods. This preparatory study raises awareness of the translational gap between academic theory in neglect research and application into clinical practice, and suggests the next steps to bridge that gap, including a review of psychometric properties of tests and consensus-building activities such as Delphi and an expert panel. The study also highlights positive signs of an emerging consensus within clinical professional groups and, to an extent, between countries. Less surprising is the evidence of inter-professional differences. The latter raise the interesting possibility that these differences are not a limitation but cue the need for contributions from the multidisciplinary stroke team, with formulation led by the psychologist or occupational therapist.

There was strong interest in this topic, attracting 454 responses over three months, from 12 healthcare professional groups from 33 countries, and it was encouraging to see the greatest response was from occupational therapists and psychologists as expected. The number and type of respondents supports the external validity of this study. The findings provide a rich data source on current clinical practice per professional groupings, and at a higher level reveal inter-professional differences in assessment category selection and individual assessment selection. There are also modest differences between countries. We found that individual neglect-specific assessments are more often than not selected on the basis of professional choice rather than institutional policy whereas the reverse was true for generic functional assessments which may be more multipurpose across stroke care e.g. FIM. We did not ask respondents to distinguish between specific and non-specific assessments, choosing to keep the survey neutral to capture what is actually happening in clinical practice. Free text responses indicated clinicians' willingness to combine assessments and adopt a multidisciplinary approach to screening and diagnosis of neglect; this is a particular strength of current clinical practice and allows for the tailoring of assessment selection based on the patient's profile, and what they can be realistically expected to perform. There is a need for training in understanding neglect and how to screen for and diagnose it, especially given differences in the initial training of different members of multidisciplinary healthcare teams e.g. psychologists, physicians and therapists. Naturally, this leads to differences in neglect assessment approaches employed within stroke teams, which must be knitted together for patient-centred care. Overall, whilst the anticipated diversity in current practice is an issue, given the huge number of assessments in use it is encouraging to see the appetite for harmonisation, which supports our plan to proceed to the next stage of consensus-building including Delphi exercises and an expert panel. These latter activities are more appropriate than this survey for examining the important issues of screening and diagnosis of neglect subtypes, severity and chronicity. However our immediate next step must be an examination of the psychometric and other properties of assessments such as their cost (financial and time required) as these will inform their feasibility and acceptability.

2.4.1 Cognitive Assessments

Cognitive assessments were the most frequently used by psychologists and OTs (>90%) but only 40% of physiotherapists reported using these. The selection of cognitive assessments is slightly modulated by country, with those from other countries worldwide (non-Europe, non-USA) being more likely to select cognitive assessments. Respondents who reported being active in research as an investigator were also more likely to select cognitive assessments.

A previous review of patient notes by Menon-Nair et al. (2006) highlighted that cognitive assessments are popular selections in the Canadian stroke inpatient setting. A subsequent survey found that cognitive assessments are a very popular selection amongst Canadian OTs, particularly assessments that are not specific to neglect, including the OSOT perceptual evaluation (Boys et al., 1988), the Motor-Free Visual Perception Test (MVPT, Colarusso & Hammill, 2003; Colarusso & Hammill, 1972), the Chessington Occupational Therapy Neurological Assessment Battery (COTNAB, (Tyerman et al., 1986), and non-standardised visual perception testing (Menon-Nair et al., 2007). The Canadian authors found that assessments that are specific to neglect are also used, albeit to a lesser extent e.g. Bells test and clock drawing test. The use of standardised assessment batteries was particularly low amongst these OTs. However the present study concluded that cognitive assessments are highly popular among OTs worldwide, both standardised and non-standardised assessments.

The present survey found that selection of cognitive tests that include cancellation, bisection, or drawing are highly popular among OTs but rarely used by physiotherapists. Standardised batteries are more likely to be used by psychologists than therapists. The differences in research involvement and in professional training may help to explain this professional difference, together with specificities and goals of each of these activities (e.g. diagnostic evaluation versus delivering therapy). The majority of OTs in the present study reported no involvement in research, whereas the majority of psychologists reported some. The clinical training of psychologists, which advocates a brain-behaviour approach to defining and measuring neuropsychological syndromes, and their exposure to clinical research, which often uses cognitive test batteries such as the BIT and OCS, may predispose psychologists to using batteries. Conversely, those OTs who report no involvement in research may be more inclined to select individual tests that are used routinely on stroke wards. This is corroborated by free-text responses, where an emergent theme from clinician responses was a need for enhanced training in neglect aetiology and how to use screening and diagnostic assessments more comprehensively. Data in Figure 2.6 also suggests that selection of assessments is down to clinical and professional experience, with most individual cognitive assessments selected on the basis of professional choice, rather than some institutional policy.

Similarly, respondents often reported that subtests of batteries are generally found to be easier to administer than complete batteries, which were often felt to require too much time. A potential outcome from this finding regarding cognitive assessments is also reflected in the free-text responses. Respondents suggested further research is needed to either update or develop comprehensive cognitive assessments to generate results with potential clinical impact. However, given the number of individual assessments and batteries that already exist, further research might identify the most optimal combinations of these. Indeed, in free text responses detailing the ‘ideal’ scenario for neglect assessment, several respondents highlighted the combinatorial approach taken. This is a key strength of current clinical practice and complies with the current UK national clinical guideline for stroke (see 4.3.7.1 (B)) which advocates use of a standardised test battery and related effects on activities of daily living and mobility (Intercollegiate Stroke Working Party, 2016).

2.4.2 Functional Assessments

OTs and physiotherapists most often selected the functional assessment category compared to physicians and psychologists. Respondents from other worldwide (non-

Europe, non-USA) countries and from Italy were significantly more likely to select functional assessments, as were those working in outpatient settings.

The use of functional assessments was high in Menon-Nair et al.'s 2006 review of clinical notes from Canadian inpatient settings. Indeed, the prevalence of use of assessments such as observation (during clinical care, examination, or ADL assessment) was relatively high at 48%, 57%, and 46% respectively. This is in line with our findings, where functional observation, interview, and the generic Functional Independence Measure (FIM) were extremely popular. Observation and interview approaches were particularly favoured by OTs, whereas the FIM was overall selected by a greater proportion of physiotherapists. The FIM is the exception within this trio whereby it was generally selected as a result of institutional policy rather than professional choice; indeed, the use of the FIM in isolation to identify neglect is not usually recommended, since various neglect-specific assessments have been developed that identify the presence and severity of neglect in different domains (Chen et al., 2015; Gialanella Ferlucci, 2010; Luukkainen-Markkula, Tarkka, Pitkänen, Sivenius, & Hämäläinen, 2011). It is not surprising that OTs and physiotherapists are more inclined to select observational and/or interview approaches as they are feasible to integrate into routine clinical care, particularly if assessments are conducted away from inpatient wards. However, the common co-occurrence of anosognosia potentially results in an interview that does not identify the presence of neglect. Similarly, training for OTs and physiotherapists tends to focus on functional recovery and supporting activity, whereas physicians and psychologists are likely to be trained in terms of neurological and/or cognitive impairments at the neural level.

There was greater variation between functional assessments in terms of reasons for their selection, compared to responses generated for the cognitive and neurological categories. The individual assessments selected due to institutional policy in the functional category were generally not neglect-specific, and are used as general assessments to quantify stroke severity and outcome in the acute and post-acute settings (i.e. the FIM, MPI, mRS and BI). Whilst these assessments are undoubtedly useful in planning clinical care for stroke patients with neglect, these measures in isolation do not adequately capture the profile of the neglect syndrome for individual patients. Respondents selected a number of neglect-specific tools above, and it seems likely that institutionally-dictated assessment choices such as the FIM, MPI, mRS and BI are part of routine assessment upon admission and continued inpatient care, and are applied in conjunction with neglect-specific assessments as and when required. As mentioned, use of these broader functional assessments in isolation to identify neglect is not usually recommended. Institutions must be made aware that they risk not providing the best care for people with neglect if they do not mandate specific measures.

The results from Menon-Nair et al’s (2007) study of Canadian OTs differ from those of the present survey study. The 2007 survey found that use of standardised assessment that incorporates assessment of function was extremely low compared to standardised cognitive assessments, regardless of whether these are specific or non-specific to neglect. The focus of OT respondents to the 2007 survey appears to be heavily skewed in the direction of cognition and perception, with only the A1- Árnadóttir neurobehavioural evaluation (Árnadóttir, 1990) representing any assessment of function in the screening and diagnosis of USN. However, for our study, and specific to OTs, our results demonstrate that function is a major consideration for neglect identification. This was demonstrated by the proportion of OTs selecting functional assessments, as well as the free-text responses that emphasise incorporating functional assessment in neglect detection. This either represents a paradigm shift within the OT profession in the past twelve years, or could be due to the present survey offering assessment options divided by category of assessment, rather than allowing a series of open-ended responses based on case vignettes as previously. In either case, current screening and diagnosis by international OTs clearly has a focus on functional assessments.

2.4.3 Neurological Assessments and Neuroimaging/Neuromodulation

Neurological assessments/clinical examination were popular amongst all countries, with between 60% and 75% of respondents indicating their use of these. They were most popular amongst physicians and physiotherapists, with psychologists and ‘other’ professional groups significantly less likely to select this category. In terms of individual neurological assessments, there is a highly consistent pattern between them in terms of which professionals (and from which countries) select them. Selection of visual scanning and trunk rotation are exceptions to this general rule, which OTs are slightly more likely than physicians to use. Another exception is somatoparaphrenia, which physiotherapists rarely screen for. Physiotherapists were more likely to select all but four of the individual neurological assessments provided within the survey. The physiotherapists’ assessments mostly used observation, general attention, head position, motor neglect, trunk rotation, and posture.

Given the marked heterogeneity in the clinical presentation of neglect (Ting et al., 2011; Verdon et al., 2010), clinicians may be of the view that a number of different neurological signs are necessary to provide adequate neurocognitive profiling of the syndrome. Relatedly, neglect may manifest alongside various co-morbidities e.g.

neglect and visual field loss often co-occur, as can hemiplegia (Gallagher et al., 2013), delirium (Boukrina / Barrett, 2017), and anosognosia (Bisiach, Vallar, Perani, Papagno, / Berti, 1986; Chen / Toglia, 2019; Vocat, Staub, Stroppini, / Vuilleumier, 2010). The use of neurological assessments that are not specific to neglect could be a useful approach for the detection of co-morbidities. We do not recommend profiling using only assessments that have not been developed for identification of neglect. We were curious to discover whether neuroimaging/neuromodulation played a role in screening and diagnosing neglect and found they were selected the most by psychologists and physicians, although not by a majority in either category. Neuroimaging/neuromodulation were also selected by a greater proportion of respondents from Italy and other Non-Europe, Non-USA, but this is a small proportion of the overall sample. Neuroimaging is standard for newly admitted stroke patients for hyperacute treatments. However, reading neuroimaging reports is not within the scope of practice by therapy staff (e.g. OTs, PTs, and speech therapists) in many countries, including the UK and USA.

We found that magnetic resonance imaging (MRI) is particularly popular amongst this sample. The benefit of this technology is its extremely good spatial resolution of cortical and subcortical structures, which lends itself naturally to voxel-based lesion mapping (VBLM), which appeared in free-text responses to the neuroimaging question in the survey. VBLM is used to assess the extent of lesions to predict likely cognitive and functional impairments. Importantly, several respondents clarified that this was not used as a primary method for neglect detection. MRI and other neuroimaging methods were reported to be used alongside other neurological assessments, as well as cognitive and functional assessments. Other techniques such as electroencephalography (EEG) may be easier and cheaper to apply, but are rarely used, and come with their own methodological challenges (including limited spatial resolution and acceptability to patients).

2.4.4 Limitations

Despite its many strengths in laying a foundation for subsequent collaborative action towards consensus the study’s limitations should be acknowledged. We sought to identify the most commonly used neglect assessments by stroke clinicians worldwide. To do this, a non-exhaustive list of assessments was categorised into cognitive, functional, and neurological approaches. Whilst this list allowed us to more easily quantify their use (and for which reason), the free-text responses after each category highlighted more assessments that could have been included in the main quantitative analyses. Similarly, to avoid overburdening respondents and elicit high quality data we did not ask whether clinicians differentiated between neglect subtypes (e.g. personal vs peripersonal, allocentric vs egocentric), severity or setting nor whether they considered the sensitivity and specificity of measures although respondents had opportunities to include these issues in their free text responses. The category least likely to be used (neuroimaging/neuromodulation category) was left entirely as a free-text response, instead of providing neuroimaging techniques that respondents could select as per the other categories.

The reported use of the non-neglect specific measures such as the FIM and BI raise the possibility that survey respondents misread the survey question as being about screening for stroke disability in general. We don't think it is very likely that there was a widespread failing across the large sample given that the participant information sheet specified that the study was about screening for neglect, we carefully avoided overburdening respondents with too many questions and laid them out clearly and the respondents' free text answers suggested this focus on neglect had been communicated. Instead, reported use of these measures seemed to be mandated by institutional policy. Although we are too early in the consensus-making process to make recommendations about what should be used we can and do say above that we do not believe these general measures adequately capture the profile of the neglect syndrome for individual patients.

There is a possible limitation related to the wording of our response options to uncover reasons for assessment use. We asked participants to indicate whether they used an assessment based on institutional policy or professional choice. The former term was not defined and might have served as a catch-all categorisation that encompassed clinical guidelines, insurance requirements, local or national policy in stroke. However, the inclusion of this wording against the alternative 'professional choice' is, we feel, intuitive for the clinicians we targeted, and has revealed interesting differences between free choice and policy, even if the specific reasons for policy are not known.

A methodological consideration for this study was the use of an online, rather than paper, platform to host the survey. Whilst this approach brings many benefits in terms of convenience for both respondents and researchers, there is always the issue of accessibility. We did not have any information regarding the potential size of our target population (i.e. international stroke clinicians of different specialities), and thus cannot comment on response rate. Our approach of targeting clinicians online via professional bodies, organisations, and personal networks may not have reached some clinicians. Similarly, some clinicians may not have been able to access the SelectSurvey platform – due to institutional restrictions on external web access, or the device they were using. Balanced against this is that we elicited the participation of 454 valid, clinically-active respondents from a large number of countries and from the key professional groups, strengthening the external validity of our findings. The magnitude of interest supports our view that there is a clinical need and will to move forward in the next stage of reaching consensus.

A final consideration is that this survey was written in English. The rationale for not seeking professional translation was the assumption that most international clinicians will have working knowledge of written English to consume clinical research, receive and/or undertake clinical training, and attend conferences. The existence of the survey only in English could have limited the sample. Although online translation tools are readily available, low and middle income countries may have had less opportunities to participate.

2.4.5 Conclusion

This study, designed by our interdisciplinary and international collaboration, confirms and quantifies the large number of methods that healthcare professionals use to screen for and diagnose spatial neglect after stroke. Whilst there are interesting differences in the approaches chosen by key professional groups such as occupational therapy and psychology, there is intra-professional consistency and less variability between countries. Despite the differences, there are tentative signs of an emerging consensus, an identified need for a combined approach to screening and diagnosis, and for further training. Although it is too early in our research programme to say what should be used, healthcare professionals can use these initial findings as a benchmark against which to evaluate their own practice. As professionals largely reported that they have clinical autonomy in choice of approaches rather than being bound by institutional policy, there is potential to engage in a collaborative action to finalise consensus for a core screening set and ultimately a core outcome set. We welcome interest from clinicians, researchers and stroke survivors in participating in the next steps towards reaching consensus. Several projects are in progress or in planning. These include an ongoing review using PRISMA-Scr guidelines, led by Lindy Williams in Adelaide, of the psychometric properties of screening and diagnostic methods, including sensitivity and specificity. We will also seek differentiation e.g. for neglect subtypes, severities and settings. This work along with the findings from the present survey will feed into consensus-building activities such as Delphi and an expert panel of key stakeholders, moving us from what is used in clinical practice to agreeing what should be used in practice and research.

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Chapter 3

Prism Adaptation Training for Enhancing Engagement in Occupational Therapy: A Proof-of-Concept Study

One session of prism adaptation training does not increase immediate engagement in occupational therapy in people with spatial inattention/neglect early after stroke

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Abstract

Objectives

Spatial neglect is a debilitating, cognitive syndrome and predictor of poor functional outcome. Spatial neglect affects attention and awareness and may impede participation in therapy. In a proof-of-concept study, nested within a phase II RCT, we investigated whether prism adaptation training (PAT) had an immediate effect on engagement in occupational therapy early after stroke.

Methods

We video-recorded patients carrying out a standardised activity in their first trial occupational therapy session, before and after PAT (or a control therapy activity). Engagement was later scored by a video rater, experienced in therapy, blind to arm allocation (intervention/control) and whether videos were recorded pre- or post-therapy. The rater recorded engagement scores on a 100mm visual analogue scale. Treating therapists also reported, on a 3-point Likert scale, whether or not engagement changed.

Results

49 of the trial's 53 patients were recruited (37 PAT, 12 control), 43 of whom consented to be video-recorded. Regression analysis revealed no evidence of improvement in engagement following one session of PAT from the blinded expert video scoring method: mean difference (95% CI) = -0.5 (-7.4 to 6.4) mm; p=0.89). Similarly, post-hoc re-rating of engagement scores, when the video rater viewed paired pre- and post-therapy recordings but remained blind to arm allocation, excluded any material difference in engagement following PAT: mean difference (95% CI) = 1.2 (-2.5 to 4.9) mm; p=.52). Impressions of engagement provided by the treating occupational therapists also found no evidence of change: OR (95% CI) = 1.3 (0.13 to 13); p=0.81).

Conclusions

We are confident in our conclusion that a single session of PAT did not enhance immediate engagement in occupational therapy in this population with spatial neglect early after stroke. Our study does not address the alternative definition of engagement as a longitudinal, rapport-building process.

3.1 Introduction

Spatial neglect is a common and multifaceted syndrome following stroke that has a profound impact on quality of life. The manifestation of spatial neglect can vary between people in terms of the area of space and types of stimuli of which the person is unaware. Spatial neglect is most common after right brain damage. Estimates vary wildly but a recent study of 88,000 UK stroke survivors estimated acute incidence at around 30% (Hammerbeck et al., 2019).

Spatial neglect is clinically characterised as deficient attention, particularly for contralesional space, and is often accompanied by broader, global attentional dysfunction (Corbetta & Shulman, 2011; Halligan & Robertson, 1999; Rode et al., 2017; Ting et al., 2011). Patients with spatial neglect are likely to experience longer hospital stays and poorer functional outcomes compared to patients without spatial neglect (Chen et al., 2015; Hammerbeck et al., 2019; Jehkonen et al., 2006; Nijboer et al., 2013). We hypothesised that one factor may be the disruptive effect of the syndrome on full participation in recommended rehabilitation for stroke, regardless of severity or responsiveness to established treatments (Chen et al., 2015; Jehkonen et al., 2006).

Patient engagement in therapy is a key driver of success (Brett et al., 2017). Although therapists routinely appraise engagement informally in clinical practice (Bright et al., 2015; Kortte et al., 2007; Lawton et al., 2016; Lequerica & Kortte, 2010) there is no universally agreed definition. A 2009 survey of occupational therapists in the USA used the following operational definition of engagement: “a deliberate effort and commitment to working toward the goals of rehabilitation therapy, typically demonstrated through active participation and cooperation”, p.753 (Lequerica et al., 2009). The concepts of collaboration in goal-setting and therapy work were also highlighted in a review by Bright et al. (2015) who produced a multi-factorial concept of patient engagement, emphasising both the process of engagement and state of engagement. The latter engagement state may vary over time due to internal and external influences and is a potential target for improvement via interventions.

Prism adaptation training (Rossetti et al., 1998) is a straightforward intervention that aims to remediate spatial neglect by way of visuomotor adaptation. Anecdotal reports from therapists suggest that it is well-tolerated by many stroke survivors with spatial neglect. PAT has been reported to improve performance on common cognitive and functional tests for spatial neglect (Lavery & Rowe, 2015; Nys et al., 2008; Priftis et al., 2013; Serino et al., 2009; Shiraishi et al., 2010), although longer-term effectiveness is yet to be robustly established. Given the difficulties experienced in activities of daily living by stroke survivors post-discharge (Hammerbeck et al., 2019), it is important to identify ways of augmenting what therapy stroke survivors currently receive, so that they can gain engage in and benefit maximally from their routine therapy. To our knowledge there are no studies that investigate whether PAT enhances engagement in therapy.

The present study, a proof of concept study nested within a randomised controlled feasibility trial (SPATIAL), aimed to measure the immediate effect of PAT on patient engagement in an established therapy for stroke and neglect - occupational therapy. We conceptualised engagement as when a patient is both actively involved in a therapy activity and socially interacting with the therapist, and we were interested in the immediate influence of PAT on engagement within a single therapy session. This is because effects of PAT reported previously have generated aftereffects rapidly (e.g. Rossetti et al., 1998), and also because a longitudinal design may have been contaminated by the effects of other routine therapy received by stroke survivors.

3.2 Method

3.2.1 Recruitment of Participants to the Proof of Concept Study

All procedures were approved by a UK NHS research ethics committee (18/YH/0480). The design, conduct and dissemination of the SPATIAL study was enhanced by active patient involvement from our advisory group at the level of collaboration as defined by NIHR INVOLVE (National Institute for Health Research, 2020).

For this proof of concept study, we aimed to recruit at least 60 patients, allowing 90% power at the 5% significance level to detect a standardised difference of 1.0 standard deviations. The decision to include a difference of this magnitude was a clinical one, and is appropriate because PAT can only obtain the postulated ‘downstream’ clinical benefits by making a clear difference to immediate engagement with therapy. Moreover, there is a lack of knowledge related to how engagement may be defined, and how PAT may influence it. It was also considered potentially unethical to randomise patients without ensuring sufficient power to detect group differences. Participants for the present study were recruited contemporaneously from the 53 stroke service in-patients with neglect who were randomised, with a 3:1 allocation ratio, to the intervention or control arms of SPATIAL; a multicentre, feasibility, randomised controlled trial across the NW of England (paper in preparation).

All participants in SPATIAL received occupational therapy but only the intervention group received PAT, and this was delivered at the start of each therapy session. For the RCT methods and full inclusion and exclusion criteria, see the SPATIAL feasibility trial register (ISRCTN88395268). At the time of consenting to the trial participants were offered the option of also consenting to the present, proof of concept, study which involved agreeing to have the start of their first research therapy session (intervention or control) with their occupational therapist video-recorded.

3.2.2 Prism Adaptation Training in SPATIAL

For the present study, we standardised a typical therapy activity (visual scanning - see below) to be performed once before and once after PAT (or a control activity) during the first occupational therapy session following randomisation. The PAT intervention involved up to ninety pointing movements to targets presented in three lateral positions whilst all but the terminal part of the arm movement were concealed by an open-ended box (otherwise known as terminal exposure). We opted to use terminal exposure in our protocol in line with several previous studies of PAT in this population (e.g. Turton et al., 2010). The targets were brightly-coloured lollipop sticks held up in one of three lateral positions at the distal side of the box by the treating therapist, who was positioned opposite the patient. The position of the target for each trial was altered in a non-random sequence by the therapist. Pointing movements were performed while 25 prism dioptre (12.5°) prism glasses were worn, with black cardboard blinkers (h=150mm, w=55mm) attached to the sides of the frames to reduce interference from peripheral vision and prevent ambient light from distorting the altered foveal image. We selected 12.5°prism glasses because our colleagues previously found no evidence of benefit in a pilot randomised controlled trial using 6°prisms (Turton et al., 2010), and some researchers have proposed that prism after-effects are more likely with higher prism strengths (Mancuso et al., 2012). Prism direction was determined by neglect side, where patients with neglect of the left side were provided with right-deviating prisms, and patients with neglect of the right side were provided with left-deviating prisms. Full details of PAT in SPATIAL are available in Appendix A using the TIDieR checklist (Hoffmann et al., 2014).

3.2.3 Capturing Engagement: The Visual Scanning Activity

For the purposes of operationalising engagement to measure instant changes, we standardised a clinically valid therapy activity for spatial neglect that was a composite of patient behaviours and patient-therapist interactions. This therapy activity and associated engagement scoring sheet was custom-designed for the SPATIAL study and is not intended as a universal research tool to elicit engagement behaviours. These activities were reviewed by our dedicated patient advisory team and local clinicians to ascertain face validity for engagement. Existing measures of engagement are based on self-report and frequent therapeutic interactions between the patient and the same therapist. We were looking for an immediate rather than a longitudinal effect to avoid the possibility of contamination by the effects of other therapies or patient-therapist interactions which may have varying effects on engagement generally. The issue with self-report with neglect is the common comorbidity of anosognosia, a lack of insight or awareness of difficulties (Grattan et al., 2017). The present study was conducted in a UK National Health Service setting, where different occupational therapy activities are provided by different occupational therapists during the course of the patient's stay. For this proof of concept study we opted to use a common single activity that could be video-recorded before and after (PAT or control), and later rated.

Our 'visual scanning activity' was designed to simulate a search task similar to typical process activities used by OTs to help patients to develop strategies to improve their spatial awareness. This activity was selected based on the frequent use of visual scanning in therapy for spatial neglect (Chen et al., 2018). The search activity was not used as an assessment. Instead our intention was that the therapist interacted with the patient, encouraging them, giving suggestions and feedback on performance. The activity consisted of a large sheet of paper designed to fit standard-issue adjustable height tables. This sheet of paper contained images scattered across it - the images were large enough to see when positioned normally in a chair. Images containing six categories of real-life objects were used, where each category had six exemplars within it. Therapists worked with patients to either search for all six of one object category (e.g. "find all the coins"), or a specific exemplar from within a category (e.g. "find the red mug") on the large sheet of paper (see Figure 3.1) which was secured in the patient's midline. Two versions of the visual scanning activity were developed where objects appeared in different locations between versions in order to prevent any learning effects between the two time points (before and after PAT (or a control activity)). The presentation order of the two versions of the visual scanning activities was randomised using a random number generator.

The visual scanning activity was performed once before and once after 5 minutes of PAT (or a 5 minute standard OT activity in the control arm, e.g. upper limb training). Each visual scanning activity session (including briefing, activity, and debrief) was video recorded for each patient; the PAT session, or control intervention session, was not video recorded. Each patient therefore provided two video clips which were organised into compilations for viewing, after they were individually edited to ensure rater blinding. Videos were recorded on a password-protected and fully encrypted Apple iPad.

The videos were later viewed by a blinded expert rater experienced in OT for stroke, who was guided by a scoring sheet (see Appendix B) containing prompts for observable indicators of engagement, and rated engagement on a 100mm visual analogue scale where 0 = judged as no engagement and 100 = judged as best engagement. The scoring sheet, including prompts, was custom-designed for the SPATIAL study and is not intended as a universal research tool for recording patient engagement in therapy. If patients did not give explicit consent to video recording, an unblinded member of the research team observed the therapy session and completed an identical form.

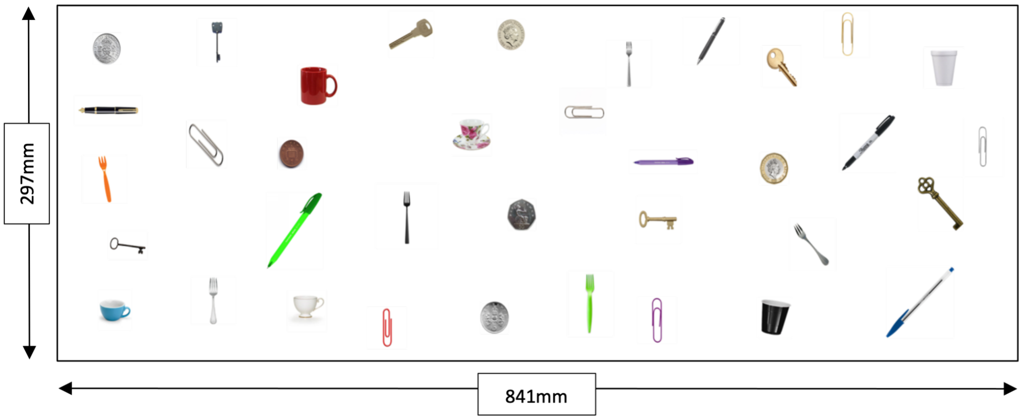

Figure 3.1: A visual scanning activity developed specifically to simulate an occupational therapy-like interaction, sized to fit on a standard issue adjustable height table. Performance of this activity was video-recorded.

3.2.4 Video Scoring: Blinded Unpaired Viewing

To ensure the video rater was blinded, our a priori plan was that videos were randomly organised into compilations of approximately 20 'unpaired' videos e.g. compilations contained either a pre-PAT (or control activity) or a post-PAT (or control activity) video from each patient. Videos were separated by a five second interval, allowing the rater to complete the visual analogue scale. The position of the rater's lines was measured after all the scores within a compilation were collected and recorded in millimetres from 0. This blinded unpaired viewing method was the primary outcome of this study.

3.2.5 Video Scoring: Blinded Paired Viewing

During the study we decided post-hoc to compare ratings of engagement, using our purpose-designed scoring method under a second 'paired' condition. This arose because the video rater (and the treating OTs) noted difficulty in separating 'engagement' from performance (e.g. accuracy, speed, scanning ability) in the visual scanning activity. The 'paired' method began only after completion of the unpaired video viewing.

For paired viewing, each compilation of videos contained a pre-PAT (or control activity) and a post-PAT (or control activity) video from each patient randomised into the compilation by the trial statistician. The pre- and post-PAT/control video from each patient was presented one after the other ('pre-' followed by 'post-' therapy) to allow within-patient comparison and a patient-specific baseline of therapeutic engagement. Patient videos were separated by a five second interval, allowing the blinded rater to complete the visual analogue scale for each of the pre- and post-therapy videos.

3.2.6 Treating Occupational Therapists: Unblinded Scoring

At the treatment session, all patients also received a live single unblinded rating of engagement from their treating occupational therapist (30 in total across all sites), who received the same prompts as the video rater regarding observable indicators of engagement (see Appendix C). The therapists scored a single tick box from three options: poorer engagement, similar engagement, or improved engagement in the post-PAT (or control) activity compared to the pre-PAT activity. The reason for not using the same visual analogue scale for the treating therapists is because the therapists were always engaged in the therapy session with their patients. Asking for two ratings would have disrupted the occupational therapy session and may have had a negative influence on patient engagement.

Figures depicting the level of agreement between the treating therapists and the blinded video rater (a scatterplot; for unpaired and paired scoring) and the level of agreement between the video rater's unpaired and paired scores (a Bland-Altman plot) are provided in Appendixes D and E.

3.3 Results

3.3.1 Participant Characteristics

Forty-nine (out of 53) patient participants from the SPATIAL feasibility RCT consented to take part in the proof-of-concept study. Due to the 3:1 randomisation ratio, 37 were from the intervention arm, and 12 from the controls. Of these 49, 43 consented to video recording, and 6 (5 intervention, 1 control) to observation by a researcher who completed the same visual analogue scale used for video rating. However following preliminary data exploration (but before analysis of main effects), we decided to only analyse data from the 43 video-consenting patients rated by a single expert rather than to introduce potential noise by adding in the six ratings from different observing researchers. Characteristics of the final pool of 43 patient participants are summarised in Table 3.1.

Proof of concept participants had a median age of 70, were predominantly male (58%), and of white British ethnicity (95%). They mainly had an ischaemic stroke (79%), on average three weeks previously, affecting their right hemisphere (86%), with a median total stroke severity score (NIHSS; Brott et al., 1989) of 13 on admission,

Table 3.1: Characteristics of SPATIAL patient participants who provided video-recorded proof-of-concept data. NB: The SPATIAL study, where the present proof-of-concept study is embedded, did not routinely collect information on co-morbidities such as cognitive impairment or anosognosia.

	Intervention n=32	Control n=11	Whole Cohort N=43
Sex			
Male n(%)	19 (59%)	6 (55%)	25 (58%)
Female n(%)	13 (41%)	5 (45%)	18 (42%)
Missing n(%)	-	-	-
Age at consent			
Mean(SD)	71 (13.1)	68 (9.9)	70 (12.3)
Min, Max	33, 89	49, 80	33, 89
Missing n(%)	-	-	-
Days Post-Stroke on Date of Video Recording			
Mean (SD)	20.4 (14.2)	22.3 (9.6)	20.9 (13.1)
Min, Max	9, 83	8, 42	8, 83
Missing n(%)	-	-	-
Total NIHSS on Admission			
Median	13	11	13
IQR	8.5, 17.0	2.0, 16.0	7.0, 17.0
Min, Max	3, 24	0, 27	0, 27
Missing n(%)	2 (6%)	2 (18%)	4 (9%)
Inattention Side			
Left n(%)	28 (88%)	9 (82%)	37 (86%)
Right n(%)	4 (13%)	2 (18%)	6 (14%)
Missing n(%)	-	-	-
Inattention Severity at Baseline - OCS Hearts			
Number Attempted n(%)	30 (94%)	6 (55%)	36 (84%)
Median Score	17	9.5	16
Min, Max	3, 47	2, 43	2, 47

resulting in neglect most often of the left side (86%). Several baseline measures of severity of neglect were taken e.g. cancellation tasks (the broken hearts test (Demeyere et al., 2015) or star cancellation (Wilson et al., 1987)), text reading and a standardised functional assessment of neglect (KF-NAP; Chen et al., 2015). For neglect severity on the broken hearts test, participants were scored between 0 (very severe) and 50 (no neglect). Predictably, the proportions rated with mild, moderate and severe neglect varied by test, and were possibly worse on hearts cancellation although only 36/43 (84%) could attempt that test. Of the 36 patients who attempted the hearts cancellation test, 30 exhibited signs of egocentric neglect. Overall assessment of neglect severity, by treating occupational therapists based on test scores and clinical observation, was 23% mild, 36% moderate and 40% severe.

3.3.2 Video Ratings: Paired and Unpaired

The ladderplots in Figure 3.2 compare the ’pre’ and ’post’ scores from the blinded video rater per participant according to study arm and mode of video viewing. These suggest there is less variability in scoring for the paired viewing, compared to the unpaired and that the video rater’s change scores were very small, particularly for paired viewing.

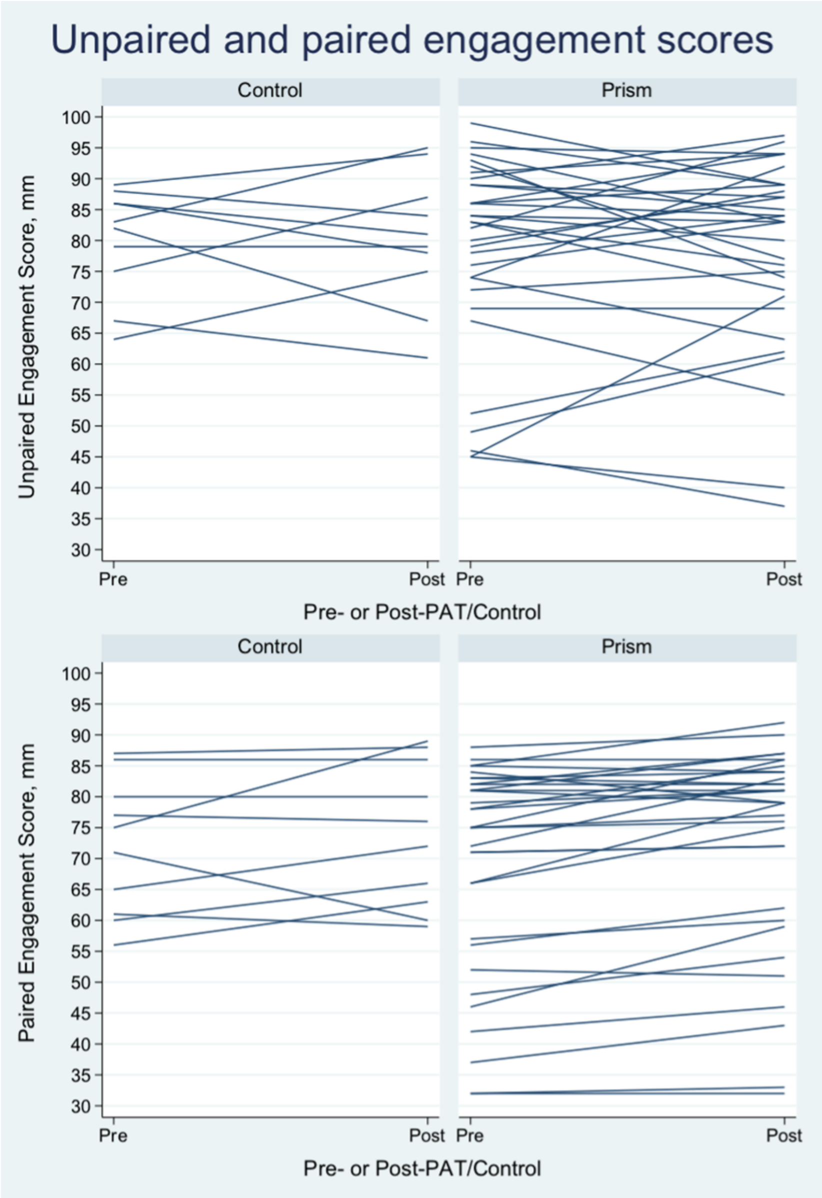

Figure 3.2: Ladderplots displaying the pre- and post-therapy engagement scores from the blinded video rater, by arm, for the unpaired viewing (top) and paired viewing (bottom).

Mean blinded unpaired engagement scores on a 100mm visual analogue scale are summarised in Table 3.2. Participants in the prism arm were rated as having a slightly smaller engagement change scores on average than control participants, although the variability is large within each group. Linear regression analysis of the unpaired 'pre' and 'post' engagement scores found no evidence of improvement in engagement following prism adaptation training, recording a mean difference (95% CI) of -0.5 (-7.4 to 6.4) mm; p=0.89 with quite a wide confidence interval.

Mean blinded paired engagement scores on a 100mm visual analogue scale are summarised in Table 3.3. As anticipated, paired video viewing reduced the variation (SD) of the change scores. Participants in the prism arm on average were rated to have larger change scores than those in the control arm, but these differences were small, i.e.

Table 3.2: Blinded unpaired video engagement scores in millimetres (100mm visual analogue scale). *Due to corrupted video data, one control patient did not receive a 'post' therapy engagement score and was thus removed.

Arm	Unpaired 'Pre' (mean, SD)	Unpaired 'Post' (mean, SD)	Unpaired Change (mean, SD)
PRISM (n=32)	78.4 (15.7)	78.5 (15.1)	0.1 (10.2)
CONTROL (n=10)*	79.9 (8.7)	80.1 (10.8)	0.2 (9.4)

a few millimetres. Linear regression of the paired 'pre' and 'post' engagement scores found no evidence of improvement in engagement after prism adaptation training, recording a mean difference (95% CI) of 1.2 (-2.5 to 4.9) mm; p=0.52. The reduced variation led to a tighter confidence interval, ruling out a true difference of 5mm or more between arms.

Table 3.3: Blinded paired video engagement scores in millimetres (100mm visual analogue scale). *Due to spoiled video data, one control patient did not receive a 'post' therapy engagement score and was thus removed.

Arm	Paired 'Pre' (mean, SD)	Paired 'Post' (mean, SD)	Paired Change (mean, SD)
PRISM (n=32)	69.0 (17.1)	72.5 (16.7)	3.4 (4.4)
CONTROL (n=10)*	71.8 (11.0)	73.9 (11.6)	2.1 (6.8)

Figure 3.3 displays the unblinded therapist ratings by arm. Three participants were rated as having poorer engagement after therapy compared to before (two in the prism arm, one in the control arm). Forty-one participants were rated as exhibiting no change in engagement (31 in the prism arm, 10 in the control arm) and 5 participants were rated as exhibiting improved engagement (4 in the prism arm, 1 in the control arm). Binary logistic regression analysis revealed no evidence of improvement in engagement following PAT, recording an odds ratio (95% CI) of 1.3 (0.1 to 13.2); p=0.81. These findings are consistent with those generated by the video viewing procedures, above.

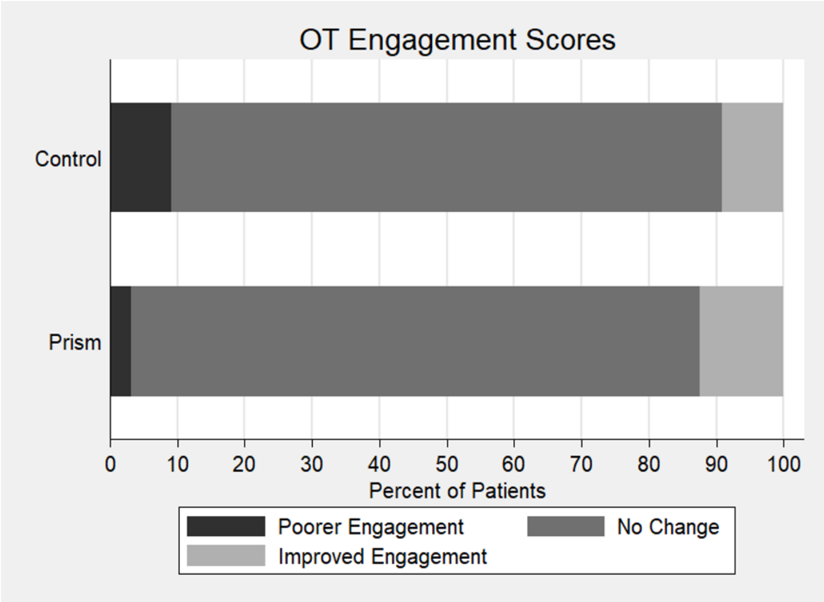

Figure 3.3: Unblinded treating therapist engagement ratings by arm.

3.4 Discussion

3.4.1 Summary of Results

By nesting a proof of concept study within a feasibility randomised controlled trial we explored whether a single dose of PAT for spatial neglect immediately improves patient engagement within one session of occupational therapy. Our novel method to objectively measure immediate engagement, created specifically for this study rather than as a standalone measure of the broader concept of therapeutic engagement, found that immediate engagement was not improved within one occupational therapy session incorporating PAT. Indeed, the study was sufficiently powered to rule out what may be considered a minimally important difference of 1cm (10mm) on the VAS. This finding is consistent across both unpaired and paired video viewing methods (from a blinded single rater, thereby removing concerns about inter-rater reliability) and concurs with ecologically valid ratings of no change in engagement from unblinded treating occupational therapists. However before concluding there is no effect of PAT on engagement it is important to consider alternative explanations for this consistent finding and the strengths and limitations of our study.

3.4.2 Measuring Immediate Engagement: How Good was our Novel Method?

Key strengths of the study were the enhanced validity through patient involvement as research partners and input from occupational therapists, and our efforts to reduce bias during analysis. We also feel that the novelty of our methods in devising an operationalised definition of engagement in therapy will be beneficial in identifying intervention candidates in future work. Furthermore, all of our results (blinded paired, unpaired, and unblinded therapists' scores) simultaneously suggest that one session of PAT does not enhance engagement immediately. The initial unpaired video scoring method (a standardised visual scanning activity) was designed to ensure full blinding of the video rater with respect to allocation (intervention/control) and time point (pre- or post-therapy). According to the rater, the concealment was maintained throughout unpaired viewing. An unforeseen consequence was that this made it difficult to separate 'engagement' from pure 'performance' on the visual search task (e.g., accuracy, speed, scanning ability). Returning to conceptualisations of engagement, Bright et al. (Bright et al., 2015) highlight the 'state' of engagement, which we attempted to capture in video recordings, but also the longitudinal 'process' of engagement. It could be argued that the process of establishing engagement could occur in parts of the task not always captured on video, e.g. during task set-up and instructions, which occasionally contained dialogue that would unblind the video rater and was thus eliminated on a case-by-case basis from the processed videos. Whilst no patient was rated at 100% ('full engagement') on the visual analogue scales, some of the pre- therapy scores are above the 50% and even the 75% level particularly in the blinded unpaired condition. Whilst these levels of engagement do indeed leave room for improvement, it is possible that this patient group with neglect does not have the severest impairments of engagement that we were anticipating.

The paired video scoring method was added to the study following scoring of the unpaired videos and feedback from the rater (and treating therapists) but before analyses were conducted. In paired viewing, the pre- and post-therapy videos of each patient were presented together allowing for a within-patient comparison of engagement change (although importantly the rater was still blinded to allocation to PAT/control). This method, according to the video rater, made it easier to rate the state of engagement independently, without any performance confound. This is reflected in our results, where the variability for paired scoring is markedly less than in unpaired viewing. As with the unpaired viewing the rater did not use the maximum value of 100% engagement on the visual analogue scale, although it is clear that any change in engagement score is minute when the millimetre scale of the visual analogue scale is taken into account. Compared to the unpaired pre-therapy scores, the paired scores recorded for the pre-therapy videos tended to be lower. One potential explanation for this is that the rater had an expectation of poor engagement pre-therapy, and of response to therapy, which is exactly why we initially designed the study to examine unpaired blinded data and why these remain our primary analysis. Nonetheless the paired data provide a useful sensitivity analysis and show consistency in our finding that one session of PAT does not immediately enhance engagement in OT.

The videos were all recorded in the first OT session within the SPATIAL feasibility RCT. One might question whether patients who were on average only three weeks post stroke would exhibit changes in engagement observable on video by a rater not involved in their care. There may be an optimal later time point post-stroke where patients possess sufficient cognitive resources to engage in therapy or for this to be observable based on a short viewing. Conversely, it could also be the case that patients who met the inclusion criteria for SPATIAL were those with enough cognitive capacity to participate in occupational therapy (and a feasibility trial), and those with the most impaired engagement may have been excluded. With the support of our patient advisory group we encouraged the therapists to be as inclusive as possible and people with severe stroke and severe neglect were included, including those requiring tilt-in-space chairs. We will explore further the issue of who was excluded within our feasibility trial paper which also explores outcome measures after up to three weeks of PAT. The focus of the current paper is the proof of concept study nested within the trial to explore whether the mechanism underlying a putative therapeutic benefit of PAT might be an immediate change in engagement in that therapy session.

3.4.3 How Useful was the Inclusion of Engagement Ratings from the Treating Occupational Therapists?

Another strength of the study was the triangulation of data. In addition to the objective blinded (unpaired and paired) video ratings the NHS occupational therapists delivering the interventions were also asked about their impressions of their patients' engagement immediately after the first OT session. The treating therapists were given three choices: poorer engagement, similar engagement, or better engagement - in the post-therapy visual scanning activity session compared with the pre-therapy visual scanning activity session. The majority of scores obtained in this way indicated no change in engagement which concurs with the findings from the blinded video scoring methods. Of course one could argue against our conceptualisation of engagement, which we freely accept took a snapshot approach, and suggest that the 'process' of engagement development between patient and therapist and the resulting 'state' of engagement should be considered over a period of time and with more naturalistic observation or qualitative interview. The downside of these alternative approaches would be that factors such as variability in the interpersonal skills of different therapists would make it difficult to measure the effects of PAT. Notwithstanding possible limitations of our methods they had many strengths and in our experience we would have expected to see some indication of an increase in engagement had it been present. In fact the limitation is that we succeeded in focusing objectively on immediate engagement in a standardised task and it remains to be established whether the much broader concept of therapeutic engagement is affected by PAT, if indeed that broader concept could be reliably captured.

3.4.4 Is one Session of PAT an Insufficient Dose?

Several studies have suggested PAT rapidly ameliorates spatial neglect in stroke patients. A recent case study conducted by Abdou et al. (Abdou et al., 2020) claimed that a single PAT session significantly improved sitting balance as measured by electromyography of the patient's trunk muscles and a pressure mat. In terms of neural mechanisms of PAT effects, Crottaz-Herbette et al. (2017) reported that a single exposure to prisms in patients with spatial neglect significantly enhanced compensatory mechanisms situated in the intact left hemisphere and rapidly improved neglect behaviours. These findings require testing in adequately powered randomised controlled trials but justify our decision to look for an immediate effect on engagement following the first dose of PAT.

There is some evidence to suggest that PAT effects extend beyond trained visuomotor and spatial attention tasks to wheelchair driving, navigation, visuo-verbal tasks, and even beyond the visual domain in tactile or haptic tasks, and in auditory extinction (Jacquin-Courtois et al., 2013). Whilst this is encouraging in terms of potential expansion to engagement in therapy, there is no strong evidence that these effects are elicited after a single exposure to PAT. The findings of the present study suggest that PAT did not increase engagement, and we cannot say whether a series of PAT sessions would have had a greater effect. Indeed, a Cochrane review Longley et al. (2021) found that trials of several interventions for spatial neglect (including PAT, but several other non-pharmacological interventions) produce very uncertain evidence for the beneficial effects of therapy on outcomes measuring activities of daily living. These findings are corroborated by the findings of a previous Cochrane review by Loetscher et al. (2019), who concluded that there is currently no evidence to support cognitive rehabilitation as a treatment for attentional disorders post-stroke, despite detecting some signal for very short-term beneficial effects that decay rapidly. Furthermore, in our separate feasibility trial paper we report an absence of any benefits on a range of outcome measures after three weeks of PAT, consistent with the findings in the current paper. Unfortunately, the above pattern also emerges with respect to broader cognitive and physical difficulties post-stroke. A Cochrane review by Elsner et al. (2020) concluded that there is little-to-no evidence supporting the use of transcranial direct current stimulation (another bottom-up intervention - see section 1.4.2) as an intervention to improve arm function, leg function, muscle strength, or general cognitive abilities after stroke. There is a significant need for studies of PAT and other interventions for stroke survivors to be preceded by early-phase research to define appropriate dose (e.g. Dalton et al., 2022) and appropriate patient subgroups (e.g. Saj et al., 2019).

Moreover, some evidence suggests that PAT is more specific in terms of neural adaptation than previously claimed, and thus may not be a useful intervention for the broader cognitive and emotional processes likely to be involved in therapeutic engagement. There is emerging evidence that the effects of PAT are more likely to be seen in certain subgroups of patients, for example those with specific neglect subtypes (Mancuso et al., 2018) or those with very specific patterns of cortical damage (e.g. Goedert et al., 2020; Saj et al., 2019). Milner and Goodale (Goodale Milner, 1992; Milner Goodale, 2012) proposed that visuospatial processing is composed of two routes: the allocentric ventral stream, coding for the recognition and identification of objects in space and located in the ventral temporal cortex, and the egocentric dorsal stream, coding for object location and visually guided behaviours that help to physically locate these objects and located in the superior parietal lobule and inferior parietal sulcus. A case study by Mancuso et al. (Mancuso et al., 2018) reported that PAT reduced symptoms of egocentric neglect (i.e. neglect relative to bodily midline), but not allocentric neglect (i.e. neglect relative to the midline of individual objects). Furthermore, a review by Striemer Danckert (Striemer Danckert, 2010) concluded that the beneficial effects of PAT are a result of direct modulation of the dorsal stream (and thereby egocentric processing). These beneficial effects of PAT may also rely on successful neural communication between the dorsal and ventral streams, which is precluded by lesions of the inferior parietal lobe and/or the temporal gyrus, areas which are usually damaged in patients with spatial neglect (Corbetta Shulman, 2011; Mort et al., 2003). It is noteworthy here that 30 of the patients in the present study exhibited signs of egocentric neglect on the hearts cancellation test and still did not appear to benefit from PAT, contradicting a case report from Mancuso et al. (2018) who found that PAT may work better in patients with egocentric neglect. The possible specificity of PAT effects may weaken the chances of enhanced engagement which may draw on broader neural modulation than is considered in relation to PAT.

3.4.5 Does our Conceptualisation of Engagement Affect how we Study it?

Engagement in therapy, for example in occupational therapy, is a factor considered likely to enhance or impede recovery from stroke. Engagement has a broad conceptualisation that presents challenges for empirical investigations (Brett et al., 2017; Kennedy Davis, 2017). For example, the definition of engagement from Bright et al. (Bright et al., 2015) encompassed the quality of the relationship between the patient and therapist/service, perceived usefulness of treatment, co-construction of rapport, as well as some ’observable’ constructs such as willingness to participate, persistence and determination, and assertion of personal identity. Lawton et al.’s concept of therapeutic alliance extends some of these factors to factors outside of the therapy setting, including ’optimal’ involvement of friends and family in recovery, and more tangible system drivers that include organisational and financial constraints (Lawton et al., 2016). The approach taken by Lequerica et al. (Lequerica et al., 2009) further expands the focus of ’engagement in therapy’. The authors identified several barriers (e.g. depressed mood, working memory impairment, aversion to correction, confusion, decreased alertness) and facilitators (e.g. support for meaningful activities, rapport, patient control, flexibility) related to patient engagement. Whilst these findings may have validity in the population they recruited from, they don’t fit our conceptualisation or inform our measurement of patient engagement as an immediate outcome of PAT. We acknowledge that we focused on a robust investigation of just one aspect of engagement, although we suggest our findings provide novel evidence that warrants caution about PAT for neglect early after stroke. These findings, and the absence of benefit from the outcomes measured in our feasibility trial elsewhere, have been sufficient to halt our plans to proceed to a definitive trial of early PAT and have sent us in search of alternative interventions for this patient population.

We consider the probable range of cognitive impairments present in our sample of stroke survivors to be a particular strength of the larger SPATIAL study, given that these patients are often overlooked in clinical research. However, it has been consistently reported that stroke survivors who have spatial neglect often present with a mixed neurocognitive profile (Ting et al., 2011), possibly resulting from large lesions that disrupt several cognitive processes (Verdon et al., 2010) which may hinder engagement in therapy. These different profiles may result in different requirements for measuring and improving engagement. As mentioned previously, some measures of therapeutic engagement exist, although we consider these to be inappropriate for the present study because they rely on self-report (Kortte et al., 2007; Lenze et al., 2004), or because they have been developed for use in different clinical populations (e.g. dementia (Cohen-Mansfield et al., 2011), mental health (Hall et al., 2001)), or in different therapies (e.g. Speech and Language Therapy (Simmons-Mackie Damico, 2009) or group therapy (Roy et al., 2012)).

Finally, previous studies that sought to define the concept of engagement tended to utilise qualitative rather than quantitative methodology. This has ramifications for clinical research and ultimately practice, since interventions cannot be developed or tested without a set of definitions and outcomes to guide researchers. Efforts should be made to synthesise the qualitative data available with a view to transferring this rich knowledge to quantitative investigation to further investigate the effect of interventions on engagement and ultimately on outcomes.

3.4.6 Strengths and Limitations

In addition to its strengths this study has limitations. First, we took care in our attempt to measure the immediate effect of PAT on engagement in occupational therapy, a process aided by a dedicated SPATIAL advisory group of stroke survivors. However, we did not measure the immediate effect of PAT on established neuropsychological and functional measures of spatial neglect, nor did we measure whether individual patients adapted to the prisms post-treatment. We did not check for adaptation effects because a previous pilot randomised controlled trial (Turton et al., 2010) reported that all randomised patient participants adapted to the prisms, so we did not feel this a necessary addition to our protocol. Moreover, our feasibility trial outcomes suggested good adherence to the intervention protocol, which was designed to be broad enough to allow all patient participants to adapt to prisms. Specifically, we stipulated a minimum amount of PAT that patients should receive, set at either 5 minutes or 90 pointing movements with prisms on (whichever is earliest). Future studies should include a check for adaptation following PAT, because there is emerging evidence that different subgroups of patients may respond differently to prisms (e.g. Goedert et al., 2020; Saj et al., 2019).

Secondly, this proof of concept study was nested within a randomised controlled trial study and benefited from the reduction of bias however there was a difference in inter-video activities between the two study arms. The participants in the prism arm received five minutes of PAT, whereas the control group received five minutes of a "control intervention". We deliberately did not stipulate what the control activities could be as we wanted it to be usual occupational therapy e.g. some patients received upper limb training, additional visual scanning tasks, and formal neuropsychological testing. It could be the case that patients in the control arm received stronger social primers for ’engagement’, particularly given that PAT is generally a silent activity, and OT interventions are not. Several trials of PAT have previously used sham PAT (with neutral lenses) as a control intervention (e.g.Mancuso et al., 2012; Nys et al., 2008; Rode et al., 2015; Ten Brink et al., 2017; Turton et al., 2010). Whilst sham controls can be useful in intervention trials, we opted not to include them because there was no expectation that they would enhance our findings. A lack of an effective control (sham prisms, in this case) should serve to exaggerate differences between treatment groups; therefore our findings have ruled out any meaningful effect of prisms. In other words, if sham prisms were included as part of the control intervention, our conclusions would be unchanged. In the future, single-case analysis of patients undergoing routine therapy for spatial neglect post-stroke may be interesting to explore, since engagement in therapy (and the content of personalised therapeutic regimens) is likely to be a highly personalised construct. Use of a series of single-case designs would avoid intervention effects on engagement being obscured by heterogenous, group-level data. However, such designs may come with the caveat that this may not be enough to recommend single interventions for all patients as part of clinical guidelines.

Thirdly, the activity we designed to simulate OT for the purposes of video recording may not have elicited engagement behaviours as we intended. The visual scanning activity was designed to be a collaborative and active therapy task, whereas in reality some patients and therapists may have treated it more like an assessment of cognition and function. Indeed, the video rater noted that some therapists were silent during the visual scanning activity and may not have provided patients with the opportunity to demonstrate their engagement.

Fourthly, we did not systematically capture which co-interventions individual patients might have been receiving. In the UK, stroke patients are usually offered physiotherapy, nursing and medical care and to a lesser extent speech and language therapy and psychology. Differential combinations of input from these services may have influenced the state of engagement. However, the randomisation procedure stratified by site should have minimised this. Additionally, whilst a strength of the SPATIAL study was that we recruited from a large range of sites increasing generalisability of our findings, the between site differences in service provision might be viewed as a limitation.

Finally, individual differences may be a confound in this study such as different stroke aetiologies (lesion location and extent, single or multiple strokes, left or right neglect) or co-morbidities (e.g. visual field defects) influencing engagement behaviours and the effects of PAT. However the randomisation should have balanced these between the prism and control arms. Likewise, individual patient characteristics may make it difficult to objectively rate engagement. For example, some patients may use humour at different rates or for different reasons, or may have physical impairments such as postural instability that make them appear less engaged. We decided not to ask individual patients about their own engagement, because some may have had anosognosia and may not have been able to provide insight about their engagement in therapy. However, we recognise that not all patients with spatial neglect have anosognosia, so future work could include this qualitative element when studying engagement in therapy. Indeed, a fully mixed-methods approach may be a very informative future approach when developing an operational definition of engagement and investigating candidate interventions to up-regulate it.

3.4.7 Conclusions

There is no evidence that a single session of PAT enhanced immediate engagement in occupational therapy, in fact our proof of concept study ruled out any meaningful effect on engagement (as defined by us). This conclusion is strengthened by triangulating different measurements: blinded (unpaired) ratings of videos of a study-specific standardised therapy activity, ratings of paired videos, and the perceptions of the therapists providing the interventions However, a broader conceptualisation of engagement, as a longitudinal, rapport-building process involving interaction with both the therapist and the therapy activity, might not be captured using our snapshot method, and may not be a straightforward target for the PAT intervention. Questions remain regarding whether a larger dose of PAT could increase engagement, or whether PAT needs to be delivered at a later time post stroke or in a more specific subset of patients with neglect, and whether the broadest conceptualisation of engagement in therapy can be quantified and manipulated for improving outcomes in rehabilitation research.

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The authors declare no conflicts of interest.

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Chapter 4

A Systematic Review and Meta-Analysis of the Efficacy of Prism Adaptation Training for Spatial Neglect

Efficacy of Prism Adaptation Training for Spatial Neglect Following Adult Brain Injury: A Systematic Review and Meta-Analysis

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This chapter has been written in a format suitable for publication.

Abstract

Background and Objectives

Spatial neglect is an attentional disorder that commonly follows brain damage. Prism adaptation training (PAT) is increasingly being used as a means of treating spatial neglect, although reports of its effects are mixed. The aim of this systematic review was to identify randomised controlled trials and ascertain the short-term effects of PAT (i.e. PAT efficacy) immediately after a treatment regimen. We also aimed to find out whether a dose-response effect, with regards to PAT dose and magnitude of prism after-effects, was present in cognitive outcomes or open-loop pointing measures within one month post-intervention.

Data Sources

We searched the CENTRAL, MEDLINE, EMBASE, CINAHL, APA PsycInfo, CRD/DARE, NIHR-HTA, Scopus, and OpenGrey databases covering the period from 1946 to November 2020.

Eligibility Criteria

We included identified studies if they were RCTs comparing PAT using wedge prisms with a control group (receiving no intervention, treatment as usual, PAT with placebo or sham prisms, attention control, or an alternative treatment). RCTs were eligible for inclusion if participants were adult patients with stroke, neurodegenerative disease, or other brain injury. Furthermore, studies were eligible if they included our primary outcome of cognitive measurements of spatial neglect, preferably using cancellation tasks.

Study Appraisal and Data Synthesis

We extracted patient demographics, cognitive outcomes, and open-loop pointing outcomes from studies where these data were readily available or made available on request. All studies were assessed for risk of bias (Cochrane) and quality of the overall evidence was summarised (GRADE) by at least two authors. Data were synthesised for meta-analysis of each outcome separately using standardised mean differences.

Results

We included eight small studies (n=216). PAT was compared with sham adaptation (in addition to usual care) in five of the included studies. One additional study compared PAT with usual care alone, and two other studies compared PAT with other neglect interventions delivered alongside usual care. High risk of bias was identified in two out of four studies contributing to meta-analysis and the overall quality of evidence was

assessed to be ‘very low’. The evidence is uncertain about the overall efficacy of PAT in the short term on: cognitive measures (four studies, 63 participants: SMD -0.26, 95% CI -0.70 to 0.17), and direct visuomotor effects measured by open-loop pointing (one study, 18 participants: SMD 0.34, 95% CI -0.59 to 1.28). The findings from planned subgroup and sensitivity analyses were limited by the sparse data.

Conclusions

Overall, firm conclusions regarding the efficacy of PAT are limited by high risk of bias and the low quantity and quality of evidence available. We did not find evidence to indicate an immediate visuomotor after-effect or any short-term clinical benefit of PAT in reducing cognitive difficulties associated with spatial neglect. Our meta-analyses are limited by the sparsity of summary data available from RCTs, thus the possibility of an effect in either direction cannot be ruled out. Any future studies should be well-designed, should incorporate careful steps to reduce bias (including preregistration) and steps to improve reporting of outcome measures if the effects of PAT, if any, are to be understood.

4.1 Introduction

Spatial neglect, sometimes also known as 'inattention', is a disorder of attention which commonly follows brain injury. Spatial neglect is most frequently associated with stroke, although other pathological processes are also associated, including trauma and neurodegenerative disease where spatial neglect signs are extremely similar to those widely reported in stroke survivors (Andrade et al., 2010; Bender, 2011; Gilad et al., 2006; Lunven & Bartolomeo, 2017; Shinoura et al., 2009; Silveri et al., 2011).

Spatial neglect presents in stroke survivors and other populations as an insufficient or absent awareness of space. Insufficient or absent awareness is more likely in the contralesional space, although this is sometimes evident to a lesser extent in ipsilesional space (Halligan & Robertson, 1999). Estimates of incidence of post-stroke spatial neglect vary between 12% and 95%, often depending on definitions and assessments used, and time points post-stroke tested (Bowen et al., 1999; Chen et al., 2015; Halligan & Robertson, 1999). The prevalence of spatial neglect among stroke admissions in a one year period in England, Wales and Northern Ireland was recently estimated at around 30% (Hammerbeck et al., 2019), and was identified in 67% of a sample of 24 patients with posterior cortical atrophy (Andrade et al., 2010). The impact of spatial neglect on patients' functioning, quality of life, and length of recovery is substantial. In the case of stroke, the presence of spatial neglect can more than double the length of hospital stay and often limits the degree of functional recovery (Gialanella & Ferlucci, 2010; Hammerbeck et al., 2019; Jehkonen et al., 2006).

Prism adaptation training (PAT) is a brief procedure designed to alleviate spatial neglect. In the case of left-sided spatial neglect, it is thought to work by fitting left-neglecting patients with optical prisms that shift the visual image a certain degree horizontally rightwards. The visual deviation of the prisms (measured in degrees or dioptres) can differ between studies. This shift in the visual image is thought to prompt the attentional system to recalibrate in the opposite direction of the prismatic shift according to new spatial co-ordinates, possibly by recruiting cortical areas in the left hemisphere (Clarke & Crottaz-Herbette, 2016; Jacquin-Courtois et al., 2013), thus resulting in a bias in the opposite direction to the prismatic shift. There is no consensus on how to deliver PAT, but a general procedure for one session is as follows: whilst the prisms are worn, patients are given a motor task (e.g. pointing to targets) in order to encourage the visuomotor system to adapt. Initially, left-neglecting patients wearing right-deviating prisms over-reach rightwards relative to the targets. When the initial part of the pointing movement is concealed (with patients only able to see the point of contact between their finger and the target, known as terminal exposure), patients perform motor corrections leftwards to compensate for the prism-induced error, until they eventually reach the target. Adaptation is achieved when patients exhibit leftward over-reaching after the prisms are removed - this is known as the prism after-effect (Jacquin-Courtois et al., 2013). Different patients may require different prism exposure times to reach adaptation, which is why PAT protocols may stipulate a pre-set number of pointing movements or a pre-set length of prism exposure time (in the order of minutes) in a ’one size fits all’ approach. However, there are no universally-agreed minima for the number of pointing movements or the duration of prism exposure.

We identified several previous reviews of cognitive rehabilitation either including PAT or focusing solely on PAT for spatial neglect (see Appendix G). The majority of these reviews focused on post-stroke spatial neglect, with only two including other brain injury in its inclusion criteria (Longley et al., 2021; Riggs et al., 2007). The most recently published review (Longley et al., 2021) focused on PAT effectiveness, finding no clear evidence of an effect in either direction. The present review has a focus on efficacy (immediate outcomes), in order to identify if there are any short-lived beneficial effects of PAT upon which other therapies may capitalise. Four out of five PAT-specific reviews explicitly emphasise the short-term clinical benefits (i.e. efficacy) of PAT in stroke patients which may be a result of some specific aetiology of cortical damage or the use of different measurements of post-adaptation effects (Barrett et al., 2012; Champod et al., 2018; Lavery & Rowe, 2015; Luaute, et al., 2006b). The remaining review concluded that PAT has a facilitative effect for patients with neglect conducting visual search, however the authors presented no evidence for more complex tasks such as activities of daily living (ADLs) (De Wit et al., 2018).

Three reviews of cognitive rehabilitation following stroke reported limited and low-quality evidence supporting PAT as a useful therapy for the rehabilitation of spatial neglect, with improvements in cognitive outcome measures immediately following the adaptation period (Luaute et al., 2006a; Riggs et al., 2007; Yang et al., 2013). Eight reviews included non-randomised designs (sometimes alongside RCTs) in their syntheses; inclusion of non-randomised designs reduces the confidence in these conclusions due to the possibility of lower-quality data in the original studies (Barrett et al., 2012; Champod et al., 2018; De Wit et al., 2018; Lavery & Rowe, 2015; Luauté et al., 2006a; Luaute et al., 2006b; Riggs et al., 2007; Yang et al., 2013). A Cochrane review of cognitive rehabilitation for stroke (Bowen et al., 2013), recently updated and expanded to a wider brain injury population by Longley et al. (2021), did not find evidence to support PAT as one of several interventions for spatial neglect, concluding that there is continued uncertainty about the benefit or risk of PAT and recommending high-quality definitive studies.

There is an important distinction between previous reviews and the present review. Previous reviews have a focus on clinical effectiveness trials, which are usually designed to be pragmatic and to determine whether an intervention confers benefit under 'real world' clinical conditions (Gartlehner et al., 2006; Godwin et al., 2003); these reviews usually extract outcome measurements several days or weeks post-intervention (e.g. Longley et al., 2021), and tend to enrol very heterogenous samples (Gartlehner et al., 2006). The present review has a focus on the efficacy of PAT in clinical trials; efficacy is defined as whether an intervention works to confer some benefit in 'ideal' conditions (Gartlehner et al., 2006; Godwin et al., 2003). Therefore, the present review diverges from previous reviews in its focus on a specific and short term measurement timepoint (within one month post-intervention), albeit using data extracted from trials designed to investigate effectiveness, in order to answer the question 'can PAT work?'. All of the identified previous reviews claim that the long-term effects of PAT are at best promising and not supported by high-quality evidence. The majority of reviews also agree that even short-term benefits of PAT lack a robust enough evidence base to indicate a rollout of PAT to stroke and brain injury patients with spatial neglect. As with some of the other broader reviews, these conclusions are partially based on synthesis of results from small, underpowered, non-randomised designs, which can introduce bias (particularly regarding participant selection or PAT protocol non-compliance) into the totality of RCT evidence examining PAT efficacy.

Given our current state of knowledge regarding the optimal application of PAT, it is not ready for large-scale, standardised clinical application as a therapy. Previous reviews state the need for exploratory trials of efficacy, pragmatic trials of effectiveness, as well as research detailing the underlying mechanisms of PAT and the potential for dose-response approaches to tailored treatment of spatial neglect (Facchini et al., 2011). The most recently published review (Longley et al., 2021) focused on clinical effectiveness; this review aims to contribute to these authors' findings by focusing on scientific efficacy. The next-most-recent review of PAT for the treatment of spatial neglect was conducted in 2018 (De Wit et al., 2018), although this review had a specific focus on visual search task measures, and not visuomotor after-effects produced by prismatic adaptation. Another previous review examining PAT for the treatment of spatial neglect was conducted in 2012 (Barrett et al., 2012), which highlighted the need for dose-response information. An investigation of prism strength is included in the present review alongside consideration of the short-term effects of PAT.

An additional perspective on the efficacy of PAT, in a broader brain injury population, is required to uncover whether PAT can elicit short-term improvements in the signs of spatial neglect, upon which established interventions can capitalise. For this review, ’efficacy’ is defined as the immediate effects of PAT on immediate outcomes on standardised assessments of spatial neglect (e.g. star cancellation) and on visuomotor after-effect (as measured by post-adaptation pointing bias). In other words, can PAT relieve classical manifestations of spatial neglect, or produce a prism after-effect, and under what conditions? Our interest in efficacy is based on the translational gap between conflicting PAT findings in small pilot studies and the lack of evidence to support wider implementation to improve longer-term outcomes. Findings in highly controlled explanatory trials of interventions like PAT may not necessarily reflect the effects that will be seen in everyday clinical practice. Likewise, results of pragmatic trials do not always allow for controlled, detailed examination of the optimal conditions under which PAT can be useful in clinical practice (Glasgow et al., 2003).

Our objective for this review is to assess the efficacy of PAT for alleviating spatial neglect, with a view to identifying some of the optimal treatment conditions (e.g. prism strength) that may be necessary to capture the postulated effects of PAT for spatial neglect. The results of this review of PAT efficacy will complement reviews of effectiveness (e.g. Longley et al., 2021), with a new focus on short-term outcomes and immediate visuomotor after-effects of PAT. We were interested in spatial neglect following stroke, brain injury, or neurodegenerative disease given similar anatomical correlates and clinical signs of spatial neglect across these populations. To that end, our main research questions are:

1. What is the efficacy of PAT for reducing spatial neglect severity or for reducing spatial neglect-related pointing bias? 2. Is there a relationship between prism strength, or frequency or intensity of PAT sessions, and reduction of spatial neglect severity/reduction of spatial neglect-related pointing bias?

4.2 Methods

4.2.1 Protocol and Registration

The review protocol was registered on PROSPERO (CRD42020123750) in advance of data collection.

4.2.2 Eligibility Criteria

Studies of prism adaptation training were included if they were randomised controlled trials (RCTs) comparing PAT (using wedge prisms of any strength) for spatial neglect with the following: no intervention; treatment as usual; PAT with placebo or sham prisms; attention control; an alternative treatment. Our primary outcome measure is the severity of signs of spatial neglect as measured by single cognitive assessments (see below). RCTs were eligible for inclusion if participants were adult patients with stroke, neurodegenerative disease, or other brain injury. Furthermore, RCTs were eligible for inclusion if they assessed neglect severity using established, standardised cognitive assessments, including: the star cancellation subtest from the Behavioural Inattention Test (BIT; Wilson et al., 1987), the hearts test from the Oxford Cognitive Screen (OCS; Demeyere et al., 2015), the line cancellation subtest from the BIT (Wilson et al., 1987), the letter cancellation subtest from the BIT (Wilson et al., 1987), the line bisection test (Schenkenberg et al., 1980), or the balloons test (Edgeworth et al., 1998).

4.2.3 Information Sources

The following electronic databases were searched for published trials: CENTRAL (Cochrane Central Register of Controlled Trials); MEDLINE; EMBASE; CINAHL; APA PsycInfo; CRD/DARE; NIHR-HTA; Scopus, all covering the period from 1946 to 25th November 2020. Grey literature was searched using the OpenGrey resource to uncover any unpublished findings, for example from doctoral theses. The search strategy for Ovid MEDLINE, which was used as the template for other databases, is provided in Appendix H.

4.2.4 Study Selection

For study selection, two authors (MC and GF) independently screened identified articles (title and abstract only) against our inclusion criteria. After checking consistency in screening, these authors then assessed full articles included at this stage for eligibility. Each stage in the study selection and data extraction process underwent a pilot test with four to six example papers and checks for consistency after completion. Following consistency checking, any apparent disagreements were resolved by discussion.

4.2.5 Data Collection

Two authors (MC and GF) independently extracted the following information for analysis from each included study where available:

- Number of patients randomised
- Cognitive outcomes at baseline and first follow-up session post-treatment
- Visual open-loop pointing effects (to assess immediate prism aftereffect)

4.2.6 Risk of Bias in Individual Studies

All included studies were evaluated for risk of bias at the time of data extraction using the Cochrane risk of bias tool (Higgins et al., 2011). This evaluation was carried out independently by MC and GF, with input from AV. Studies were rated to have low, high, or unclear risk of bias on the following items:

1. Random sequence generation - low risk of bias if:
    - allocation sequence was explained and demonstrated to be random
    - baseline differences between intervention groups did not suggest an issue with the randomisation process
    - An example of high risk of bias in this domain is evidence that the authors used a predictable sequence to allocate patient participants, e.g. based on date of stroke, or birth dates.
2. Allocation concealment - low risk of bias if the allocation sequence was adequately concealed. An example of high risk of bias in this domain is evidence that the authors did not use a consistent protocol to allocate patient participants, therefore risking selection bias according to demographic factors (e.g. ability, disease severity).
3. Blinding of participants and personnel - low risk of bias if:
    - study participants were blind to their group allocation
    - investigators (not providing interventions) were blind to group allocation
    - An example of high risk of bias in this domain is evidence that the authors, therapy providers or the patient participants were aware of their group allocation, although we recognise that this is largely impractical for PAT.
4. Blinding of outcome assessment - low risk of bias if personnel conducting outcome measurements were blind to group allocation. An example of high risk of bias in this domain is evidence that staff collecting outcome assessments were aware of which intervention patient participants received. For example, if staff delivering interventions also collected outcome measures.
5. Incomplete outcome data - low risk of bias if data for a given outcome were available for all randomised participants, or missingness was comparable in each study group and not related to withdrawal due to worsening of participants' health. An example of high risk of bias in this domain is evidence that one intervention group experienced a higher attrition rate than the other groups; particularly if this group received the intervention under study.
6. Selective reporting - low risk of bias if:

- descriptive or summary statistics were provided in adequate detail for all of the reported outcome measures
- results were reported to allow comparison of PAT vs. control outcomes
- An example of high risk of bias in this domain is if there was a lack of outcome data for certain outcome measures, or for certain groups, or for certain timepoints, despite these reported to have been measured in the trial in the published report or in a pre-registered protocol.

7. Other sources of bias (e.g. inclusion of interim analyses without pre-specified plans for adjustment)

4.2.7 Summary Measures

We aimed to collect cognitive outcome measurements and open-loop pointing measurements (mean and standard deviation) from each study at baseline (T0) and the first follow-up session following intervention (T1). We originally planned to extract outcomes of functional assessments too but decided that these were more relevant to, and reported in, the Cochrane effectiveness review (Longley et al., 2021) than our efficacy review. Where change scores or other statistics were reported, a request was made to corresponding authors to obtain mean and standard deviation of outcome values. Where this was not possible, we sought to impute values borrowed from other included studies (e.g., an imputed standard deviation was borrowed from a comparable study with the highest available value). Sensitivity analysis was undertaken to assess the influence of any imputation undertaken.

4.2.8 Synthesis of Results and Quality of Included Evidence

Available outcome data were entered into RevMan5 for fixed-effect meta-analysis using standardised mean differences as it was anticipated that different measurement scales would be reported for each outcome. An Excel spreadsheet was used to store narrative information about study outcomes and whether data were available for meta-analysis. Quality of evidence of included studies was assessed using GRADE (Schünemann et al., 2013). GRADE assessment was carried out on the assumption that RCT evidence is of high quality, and subsequently downgraded one or more levels according to the following criteria:

- Risk of bias: downgraded one level if RoB outcomes included some unclear or some high RoB; downgraded two levels if RoB outcomes included several instances of high RoB.
- Inconsistency: downgraded one level if studies generated some concerning mixed effects of PAT; downgraded two levels if study results were incompatible.

- Indirectness: downgraded by one level if PAT (or comparator interventions) were delivered in a different way to what is normally prescribed (e.g. self-administered interventions); downgraded by one level if our primary outcomes were not measured by study authors within one month post-intervention (given our focus on efficacy). Other indirectness elements of the GRADE approach (indirectness in populations, use of surrogate outcomes, and indirect comparisons) were mitigated in advance by our inclusion criteria.

- Imprecision: downgraded one level if our confidence in reported effects was reduced by inadequate sample size or the reported CI crossed the point of no effect; downgraded two levels if the reported CI crossed the point of no effect and the sample size was severely limited, particularly where few data points were included due to unavailability of data.

4.2.9 Additional Analyses

We planned to undertake subgroup analyses stratified by population (e.g. stroke, TBI), intervention (e.g. dose), and type of control group. Sensitivity analyses were planned to include omission of studies at high or unclear risk of bias in the allocation process, and low risk in all other domains (with the exception of blinding of participants and personnel, which we considered to be impractical in this context). We also planned to subject any imputation to sensitivity analysis.

4.3 Results

4.3.1 Study Inclusion

The original search was conducted in October 2019 and updated in November 2020. After removal of duplicates from the search results, 549 records were identified, of which seven met the inclusion criteria. One additional RCT was identified in the updated search in November 2020 (see Figure 4.1), bringing the number of included studies to eight. Seventeen articles were excluded: seven were not RCTs, two did not use wedge prisms, three did not include a useful comparison group (i.e. all groups received PAT at the same dose and intensity), one did not report eligible outcomes (i.e. cognitive assessments for spatial neglect (our primary outcome) or open-loop pointing), three were still reported as ongoing, and one was published in German and a translation could not be sought. See Appendix I for the full list of included and excluded articles.

4.3.2 Summary of Individual Studies

All of the included studies were very small randomised controlled trials (RCTs), with an average total sample size of 27 stroke survivors (range 17 to 67, total = 216). The

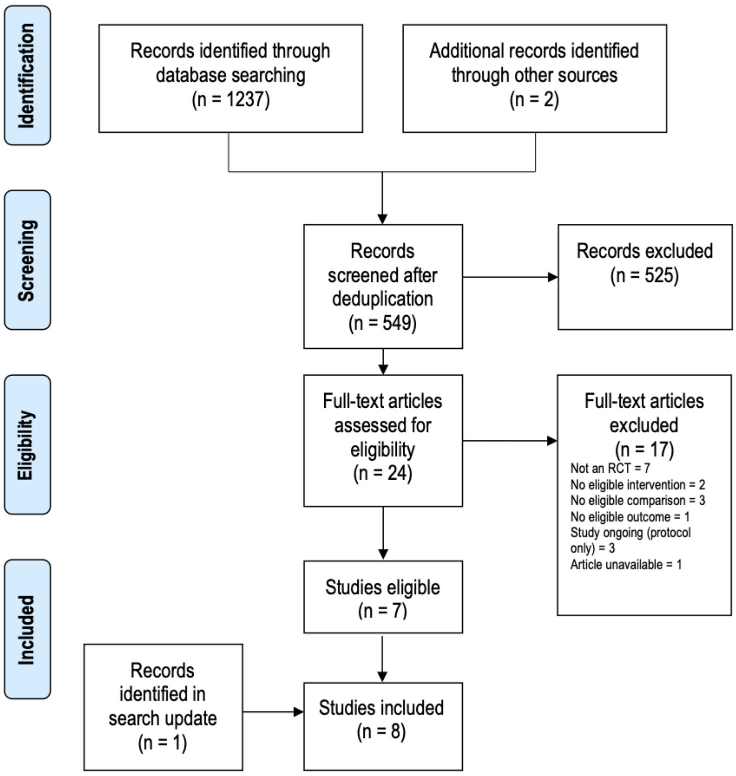

Figure 4.1: PRISMA flow chart showing how many papers were selected or excluded at each stage.

included studies recruited stroke survivors at varying time points post-stroke, ranging from 10 days to 1140 days (individual patient values).

Three out of the eight included (Nys 2008; Turton 2010; Zigiotto 2020) reported themselves as either ’pilot’ or ’feasibility’ studies. The remaining five papers, whilst described as RCTs, were extremely small with sample sizes around, or below, the recommended sample size for pilot studies of at least 30 participants (Lancaster et al., 2002). It is possible that these five RCTs were precursor pilot or feasibility studies related to future, larger RCTs, however the latter have as yet not been published. Only two studies (Ten Brink et al., 2017; Turton et al., 2010) were of a sample size compatible with Lancaster et al.'s (2002) recommendation.

Despite our wider inclusion criteria all participants in the included studies were stroke survivors. Most studies (five of those included) compared PAT with training using sham lenses (i.e. with no visual shift) in addition to usual care, one compared PAT with usual care, and two compared PAT with other spatial neglect interventions (functional electrical stimulation with usual care and multisensory stimulation in patients at varied times post-injury).

In terms of cognitive outcomes, four studies used cancellation subtests from the BIT, one used a custom-designed shape cancellation test, two used the full BIT (which includes some functional assessment), and one used the conventional BIT (neuropsychological tests only). Only three studies reported measuring pointing bias post-adaptation, two of which did not provide these data (Goedert 2020; Mancuso 2012). None of the eligible studies compared PAT protocols (e.g. different prism strengths, different intensities) between groups.

The characteristics of individual studies are summarised in Table 4.1.

Table 4.1: Characteristics of Included Studies

Study ID	Design[1]		Intervention (prismatic shift)	Control	Patients at Follow-Up		Mean (SD) Days Post Injury[4]		PAT Duration	Cognitive Outcomes
	Type	Randomisation Intvn : Ctrl			Intvn	Ctrl	Intvn	Ctrl		
Choi 2019	RCT	1:1:1[2]	PAT[2] (15°)	FES	10	10	Up to 3 months	Up to 3 months	5 days per week, maximum 15 sessions	Line Cancellation
Goedert 2020	RCT	1:1	PAT (20°)	Usual care	8	9	36.6 (5.04)	51.6 (13.3)	Once daily for 10 days	Behavioural Inattention Test
Mancuso 2012	RCT	1:1[3]	PAT (5°)	Sham PAT	13	9	180.2 (301.5)	129.0 (132.8)	Once daily for 5 days	Line Cancellation (left side)
Nys 2008	Feasibility RCT	Unclear	PAT (10°)	Sham PAT	10	6	8.8 (5.3)	11.2 (6.4)	Once daily for 4 days	Star Cancellation
Rode 2015	RCT	1:1, further stratified by SN severity	PAT (10°)	Sham PAT	10	10	51.0 (17.4)	52.2 (19.3)	Once weekly for 4 weeks	Behavioural Inattention Test
Ten Brink 2017	RCT	1:1	PAT (10°)	Sham PAT	32	35	Median (IQR) = 41.5 (39.0)	Median (IQR) = 37.0 (37.0)	Once daily for 2 weeks	Cancellation[5]
Turton 2010	Pilot RCT	4:1	PAT (6°)	Sham PAT	16	18	47.0 (39.0)	45.0 (23.0)	Once daily for 2 weeks	Behavioural Inattention Test (Conventional)
Zigiotto 2020	Pilot RCT	1:1	PAT (10°)	Multisensory stimulation	10	10	1.1 to 34.9 months	1 to 17.3 months	Once daily for 2 weeks	Star Cancellation

Notes:
[1] As reported/claimed in the article.
[2] This study included a third group who received FES alone (not included).
[3] The authors reported misbalanced groups at follow-up.
[4] Mean (standard deviation) days post-injury, unless otherwise stated.
[5] This study used a "shape cancellation task". Unlike all of the other studies this was not taken from the BIT.

In terms of design, all studies employed a parallel-groups design, with six studies randomising in a 1:1 ratio and one (Turton 2010) in a 4:1 ratio. One study stratified randomisation by spatial neglect severity (Rode 2015).

The included studies used wedge prisms with visual shifts ranging from 5 to 20 degrees; seven used prisms with at least 10 degrees of visual shift. PAT dosing in terms of frequency also varied: all but one study offered PAT once per day, with one offering PAT at a maximum of twice per day. Studies ranged from a single PAT session to a maximum of 15 sessions over three weeks.

4.3.3 Risk of Bias and Quality of Included Evidence

Between the included studies, risk of bias elements were mixed. The risk of bias judgements are summarised in Figure 4.2.

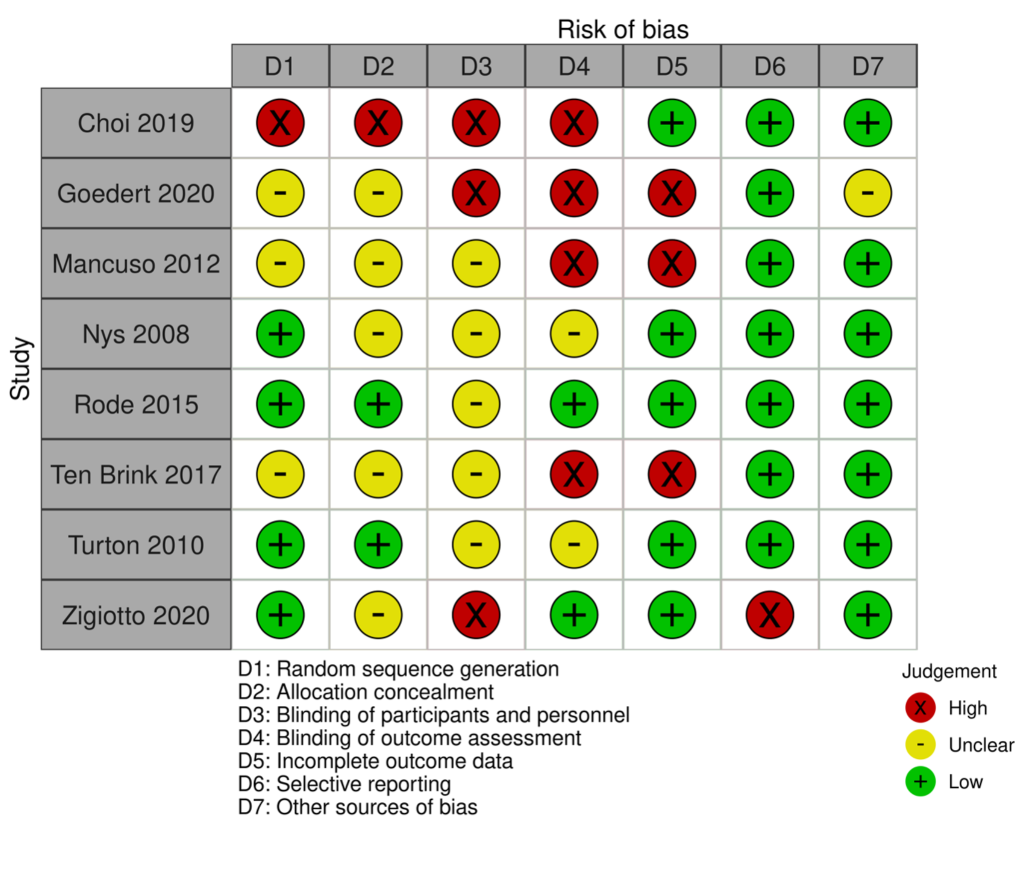

Figure 4.2: Matrix of risk of bias generated by robvis. 'Other sources of bias' include unclear risk of bias due to data-driven analysis (Goedert 2020, Rode 2015, Zigiotto 2020).

4.3.3.1 Random sequence generation

Four of the included studies were assessed to be at low risk of bias in domain one, and reported using appropriate approaches to generate random allocation sequences (Nys 2008; Rode 2015; Turton 2010; Zigiotto 2020). Three of the included studies were judged to be at unclear risk of bias (Goedert 2020; Mancuso 2012; Ten Brink 2017) where a judgement of low or high risk of bias could not be ascertained. Goedert

(2020) generated 4 distinct randomisation lists, one of which was randomly selected by an administrator - the procedure for random selection was not reported. Mancuso (2012) used a random allocation process governed by an independent centre, which intervened to address baseline imbalances in numbers allocated per group to maintain within-group homogeneity - the procedure for this was not reported. Ten Brink (2017) used a sealed envelope approach, however the order in which envelopes were opened was not reported. Finally, one study was judged to be at high risk of bias (Choi 2019), which provided no detail regarding random sequence generation.

4.3.3.2 Allocation concealment

Two of the included studies (Rode 2015; Turton 2010) were judged to be at low risk of bias in domain two, because the authors of both studies used an independent person to administer the allocation process. Five included studies were judged to be at unclear risk of bias (Goedert 2020; Mancuso 2012; Nys 2008; Ten Brink 2017; Zigiotto 2020) because there was insufficient detail to justify a judgement of low or high risk of bias. One included study (Choi 2019) was judged to be at high risk of bias. Choi (2019) did not report whether allocation was concealed from research staff.

4.3.3.3 Blinding of participants and personnel

For all of the included studies it was assumed that blinding of staff administering PAT would be impractical. None of the included studies were judged to be at low risk of bias for domain three. Five of the included studies were judged to be at unclear risk of bias (Mancuso 2012; Nys 2009; Rode 2015; Ten Brink 2017; Turton 2010). Authors of these studies reported that patient participants remained blind to their allocation through the use of sham prisms, although the effectiveness of this process was not discussed, and remains unclear given the visual shift which ought to be apparent to the wearer of prismatic lenses, but may not be obvious to a first-time wearer.

The remaining three studies were judged to be at high risk of bias (Choi 2019; Goedert 2020; Zigiotto 2020). Choi (2019) and Goedert (2020) did not use any sham interventions, and Zigiotto (2020) provided two different treatments for comparison, so it was assumed that patients were aware of which intervention they were receiving (as were the providers).

4.3.3.4 Blinding of outcome assessment

Two studies were judged to be at low risk of bias in domain four (Rode 2015; Zigiotto 2020), where a blinded investigator conducted outcome assessments. Two included studies were judged to be at unclear risk of bias (Nys 2008; Turton 2010). Nys (2008) reported some outcomes being scored retrospectively by blinded assessors, with other rolling or follow-up assessments carried out by unblinded assessors. Turton (2010) reported that the assessors for cognitive outcomes remained blind, but those measuring prism after-effects were unblinded. The remaining four included studies were judged to be at high risk of bias (Choi 2019; Goedert 2020; Mancuso 2012; Ten Brink 2017), where all of the outcomes of interest to the present review were conducted by unblinded assessors.

4.3.3.5 Incomplete outcome data

Five of the included studies were judged to be at low risk of bias for domain five (Choi 2019; Nys 2008; Rode 2015; Turton 2010; Zigiotto 2020). Rode (2015) and Turton (2010) reported two patients lost at the first follow-up, however this was one patient per study arm. The remaining low risk of bias studies reported all data for all randomised patients. The remaining three included studies were judged to be at high risk of bias (Goedert 2020; Mancuso 2012; Ten Brink 2017). Mancuso (2012) reported six drop-outs resulting in a misbalanced randomisation, but was not clear in reporting whether this was before or after the intervention period. Goedert (2020) omitted outliers following preliminary analysis without a pre-specified plan. Ten Brink (2017) reported four drop-outs, all from the intervention group.

4.3.3.6 Selective reporting

All but one of the included studies were judged to be at low risk of bias in domain six. Zigiotto (2020) was judged to be at high risk of bias because all of the outcomes were reported graphically and with basic ANOVA outputs, without presentation of descriptive statistics.

4.3.3.7 Other sources of bias

One study (Goedert 2020) was judged to be at unclear risk of bias due to concerns about data-driven decisions for analysis and omission of statistical outliers without citing a pre-specified plan. All of the remaining included studies were judged to be at low risk of bias from other sources.

4.3.3.8 Quality of Included Evidence

Using the GRADE assessment, the included evidence was rated as being very low quality, primarily due to serious concerns regarding imprecision as a result of the extremely small sample sizes recruited in each study. Full GRADE results for the quality of included studies are included in Appendices D and E for cognitive and open-loop pointing outcomes.

4.3.4 Meta-Analysis of Results: Does PAT reduce the severity of SN signs or reduce SN-related pointing bias?

The results of meta-analyses for cognitive and open-loop pointing effects are provided below. Studies not yielding usable data for meta-analysis are included in Figures 4.3 to 4.7 to highlight the amount of missing efficacy data.

4.3.4.1 Cognitive Outcomes

Four studies (92 patient participants) had all of the necessary outcome data available for meta-analysis of cognitive outcomes. One study had only reported mean values without standard deviations (Mancuso 2012; standard deviations were imputed). The meta-analysis of cognitive outcomes is summarised in Figure 4.3.

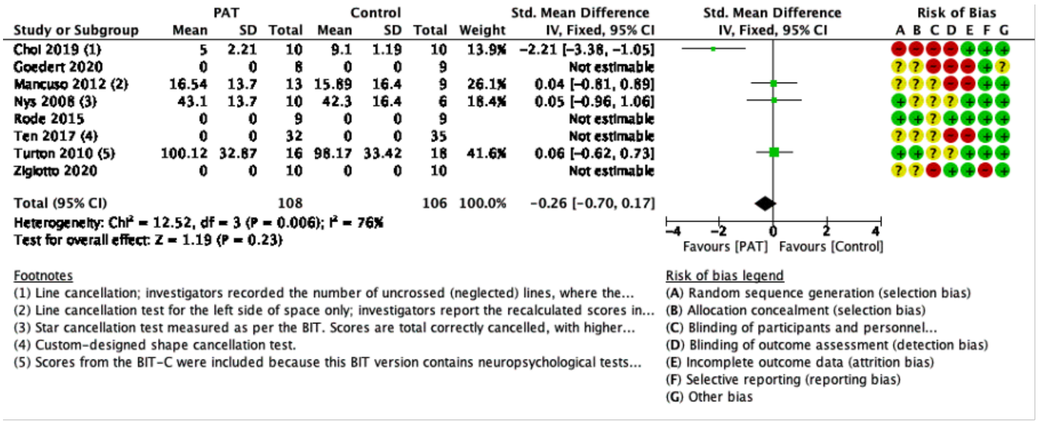

Figure 4.3: Meta-Analysis of Cognitive Outcomes

The results were substantially heterogenous (I2 = 76%) and do not provide evidence for the scientific efficacy of PAT in either direction (SMD = -0.26, 95% CI = -0.70 to 0.17), with very low associated quality (see GRADE - Appendix J).

Four of the included studies did not provide useable data for meta-analysis, however their reported findings are presented here. Goedert (2020) found that BIT scores were improved over the course of their study but did not provide any information on immediate (within one month) outcomes on the BIT. Rode (2015) identified improvements on the BIT at six months but also did not provide any information on BIT measurements within one month post-intervention. Ten Brink (2017) did not use any standardised cognitive assessments of spatial neglect, but using a custom-designed shape cancellation test the authors concluded that there were no differences between their PAT group and control group immediately post-intervention ($F(1,105) = 0.19$, $p = .661$). Rode (2015) found no evidence of PAT effects on cancellation tests (our preferred outcome), or on full versions of bisection tests (reporting an effect in centrally-presented stimuli only). Finally, Zigiotto (2020) compared PAT with multisensory stimulation, finding no evidence of effect on star cancellation, but with a modest effect size (partial eta squared = 0.39), and with a further finding suggesting that PAT did not improve personal neglect so well as multisensory stimulation.

4.3.4.2 Subgroup Analysis: Cognitive Outcomes and Prism Strength

We were originally interested in whether increasing prism strength is associated with better cognitive outcomes immediately post-intervention. Cognitive outcomes stratified by prism strength (measured in degrees) are summarised in Figure 4.4.

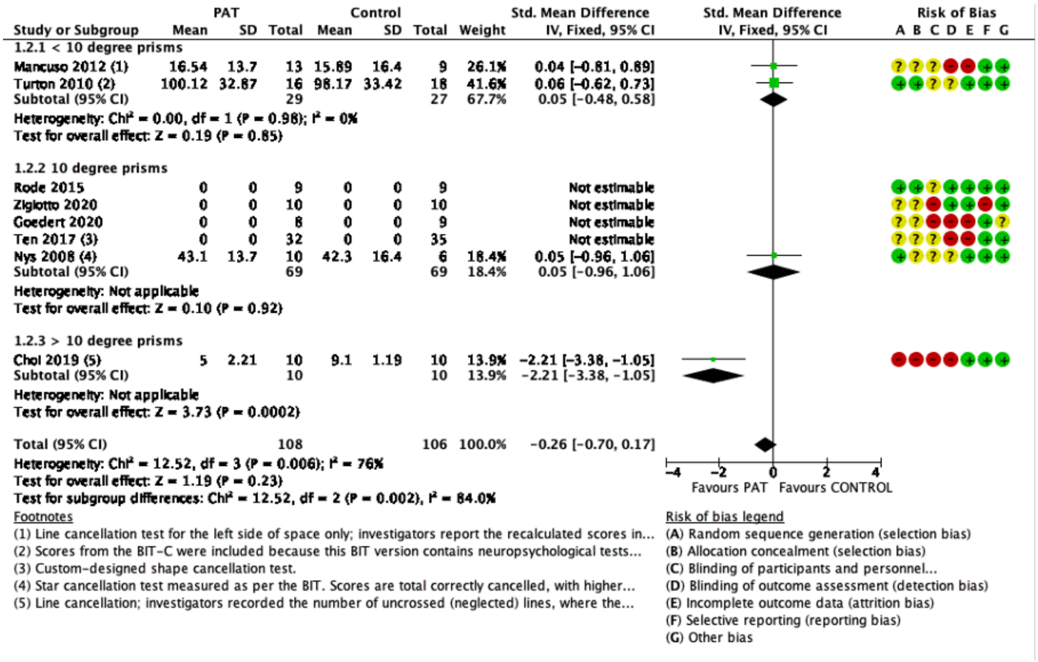

Figure 4.4: Cognitive outcomes stratified by prism strength

The stratification by strength of the prisms used revealed no convincing evidence of a dose-response relationship between prism strength and improvement on cognitive outcomes. The study with the strongest prisms (Choi 2019) superficially shows an effect, but this one small study of 20 participants is limited by its high risk of bias.

4.3.4.3 Subgroup Analysis: Cognitive Outcomes and Total Number of PAT Sessions

We were also interested in whether greater exposure to prisms would lead to better performance on cognitive assessments. A stratified analysis (by total number of PAT sessions) is summarised in Figure 4.5.

This stratification also revealed no strong evidence of a relationship between the total number of PAT sessions per patient and performance on cognitive outcomes. One small study with a higher number of PAT sessions (15; Choi 2019) superficially shows an effect, but again this study is limited by its high risk of bias. As noted in the previous section, Choi 2019 also used stronger prisms.

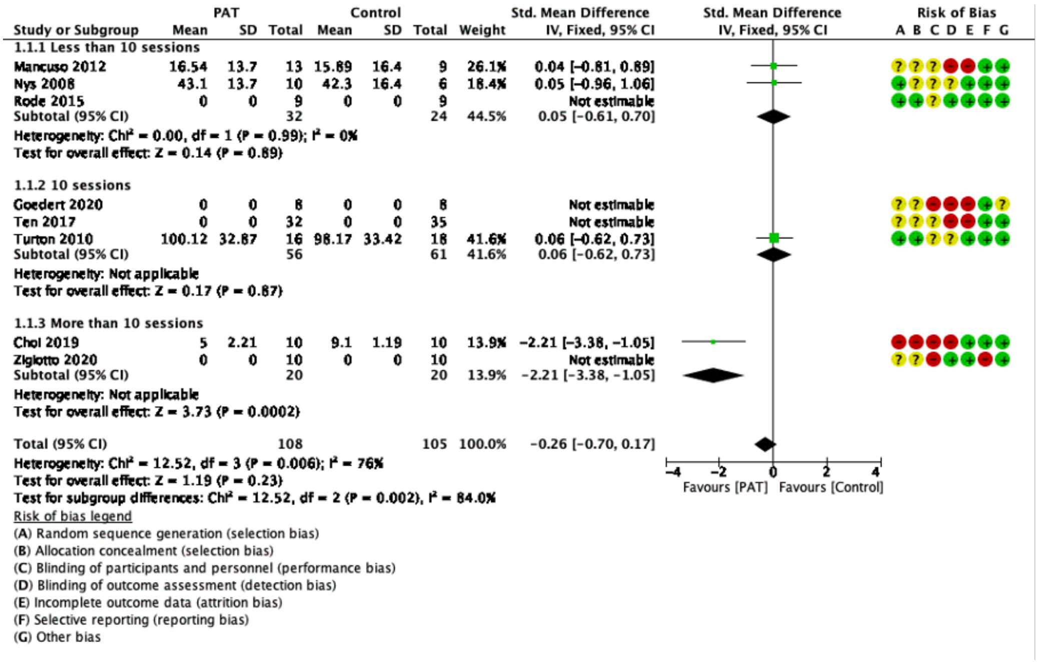

Figure 4.5: Cognitive outcomes stratified by total number of PAT sessions

4.3.4.4 Subgroup Analysis: Cognitive Outcomes and Session Duration

We were interested in whether the intensity (defined here as session duration in minutes) of individual PAT sessions is related to performance on cognitive outcome measures. Two studies (Ten Brink 2017; Turton 2010) did not report the planned duration of PAT sessions, but are included for completeness. Figure 4.6 summarises this stratified analysis.

Another way of evaluating PAT intensity is by considering the prescribed duration of individual sessions. As with the other subgroup analyses of cognitive outcomes, stratification by prescribed duration of PAT (in minutes) does not reveal any convincing relationship between intensity and performance on cognitive outcomes. One small study appears to show an effect with 20 PAT sessions (Choi 2019), but this should not be interpreted as an optimal number of PAT sessions because this study is limited by its high risk of bias.

4.3.4.5 Subgroup Analysis: Cognitive Outcomes and Comparator

The majority of included studies used sham PAT (with neutral lenses) as a comparison, however two did not (Choi 2019; Goedert 2020). Choi 2019 compared PAT plus occupational therapy plus functional electrical stimulation versus occupational therapy and functional electrical stimulation without PAT. Choi (2019) also included a third group who received PAT plus occupational therapy – these data were not extracted, allowing us

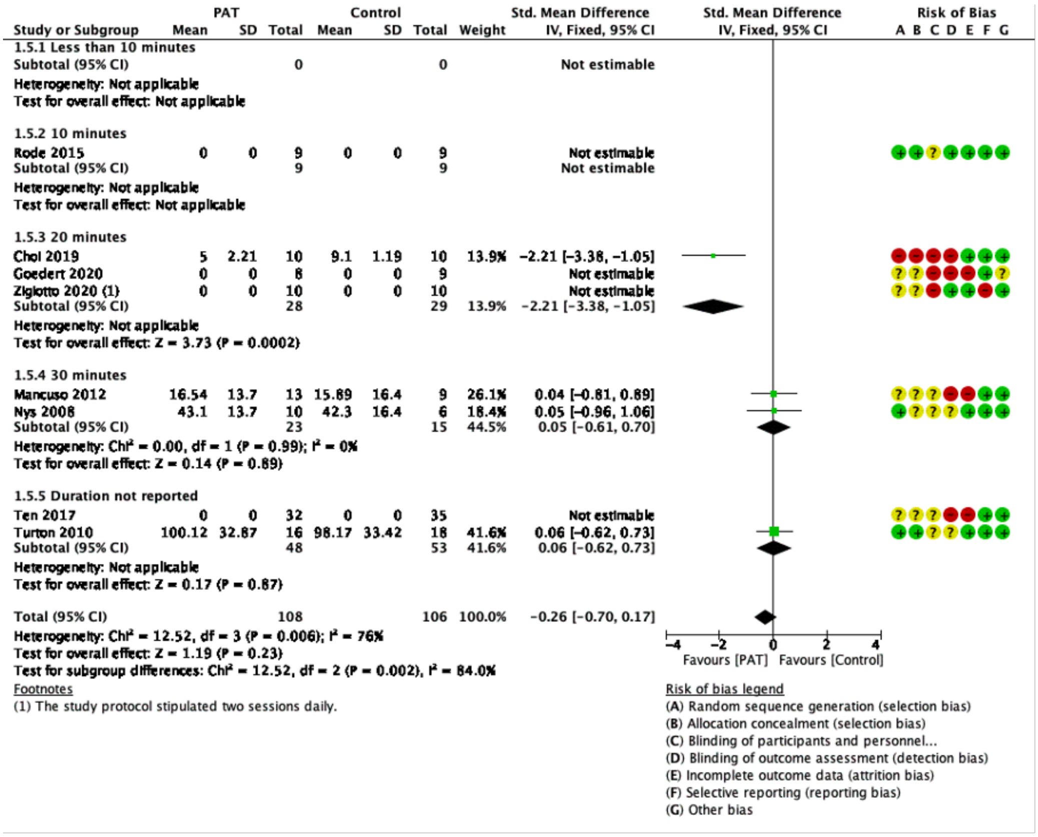

Figure 4.6: Cognitive outcomes stratified by PAT session duration

examine whether or not PAT added anything on top functional electrical stimulation and occupational therapy. Goedert 2020 compared PAT plus standard care with standard care alone. We conducted another stratified analysis - Figure 4.7 summarises the cognitive outcomes stratified by type of comparator.

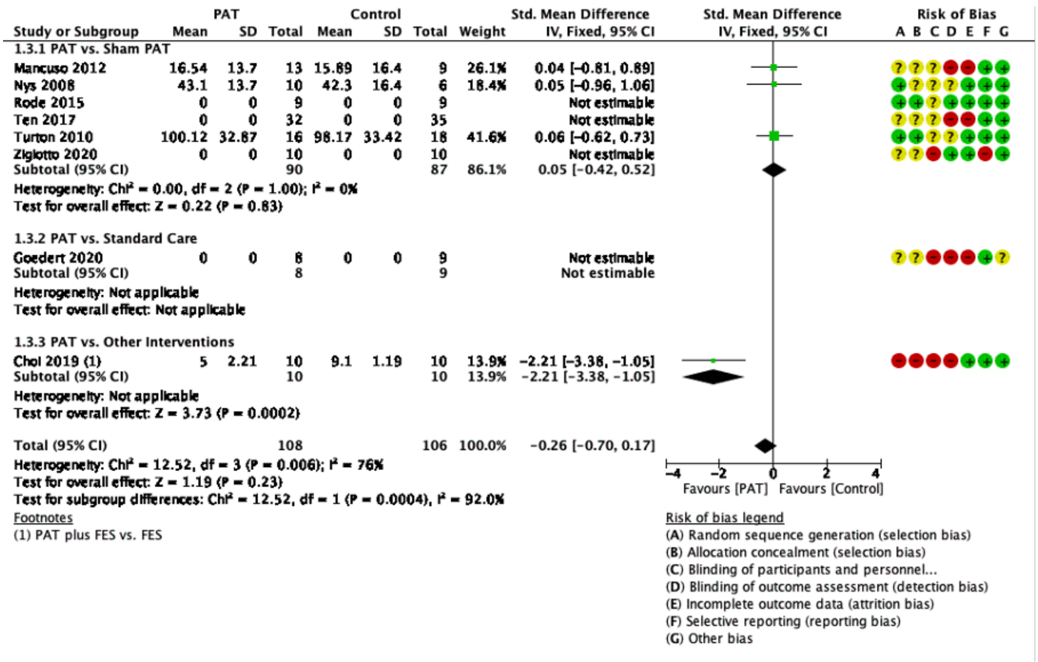

Figure 4.7: Cognitive outcomes stratified by type of comparator

Comparison of PAT with a sham PAT protocol was the most common type of comparison. There is no convincing effect of type of comparison on the results of cognitive outcomes - bearing in mind that Choi (2019) is a clear outlier, but is limited by its high risk of bias.

4.3.4.6 Subgroup Analysis: Cognitive Outcomes and Population

We had planned to undertake subgroup analysis of cognitive outcomes stratified by population type (e.g. stroke, TBI) however this was not possible because all of the recruited patients were stroke survivors.

4.3.4.7 Open-Loop Pointing Outcomes

Only one study included data for meta-analysis of open-loop pointing measuring the prismatic adaptation effect immediately post-intervention (Rode 2015 - see Figure 4.8). Rode 2015 recruited stroke survivors to undergo PAT using 10°prisms for four sessions in total (using sham PAT as a comparison). Based on this, the standardised mean difference does not favour either PAT or control interventions in terms of PAT efficacy (SMD = 0.34, 95% CI -0.59 to 1.28), with very low associated certainty (see GRADE - Appendix K).

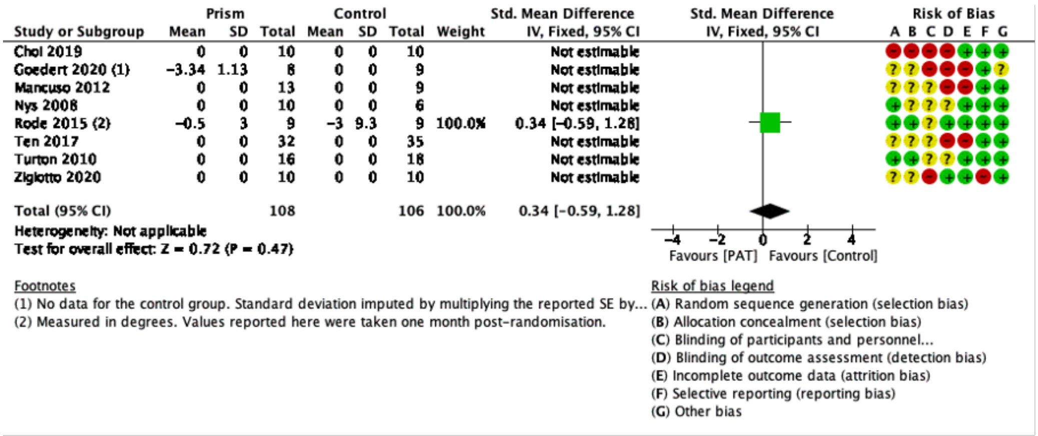

Figure 4.8: Meta-Analysis of Open-Loop Pointing Outcomes

We planned to undertake subgroup analysis of open-loop pointing measurements stratified by intervention (e.g. dose, duration), type of control group, and population (e.g. stroke, TBI). However, this was not possible because only one study presented results of open-loop pointing measurements.

4.3.4.8 Sensitivity Analyses

We had planned to omit studies at high or unclear risk of bias relating to allocation concealment (domain 2; see section 4.4.3), but at low risk of bias in all other domains (with the exception of blinding of participants and personnel, domain 3). For cognitive outcomes, only two studies met this criterion for sensitivity analysis (Rode 2015; Turton 2010). Rode (2015) did not provide usable data for meta-analysis of cognitive outcomes, thus leaving Turton (2010). Exclusion of all other studies in this meta-analysis leaves Turton (2010)'s data remaining, which is insufficient for meaningful sensitivity analysis. Rode (2015) and was the only study to provide usable open-loop pointing measurements, therefore sensitivity analysis of open-loop pointing outcomes was also not possible.

We also planned to subject any imputation to sensitivity analysis. We imputed the standard deviations for Mancuso (2012) by using the standard deviations reported by Nys (2008) - a study of comparable size and design. Omitting Mancuso (2012) from the overall analysis increased heterogeneity (I2 = 82%, up from 76%) and did not change our overall conclusion (sensitivity SMD = -0.37, 95% CI = -0.88 to 0.13). We did not impute any values for the single contributing study (Rode 2015) in the analysis of open-loop pointing measurements.

4.4 Discussion

4.4.1 Discussion of Findings

The primary outcome of this review of scientific efficacy of PAT was performance on cognitive assessments for spatial neglect, and the secondary outcome was measurement of immediate visuomotor after-effects (open-loop pointing). From eight small RCTs we found very low certainty evidence and nothing indicating whether PAT is of benefit or harm for patients with spatial neglect on cognitive assessments one month post-intervention. The only study that purported to show any benefit of PAT (Choi 2019) on cognitive outcomes was the only study at high risk of allocation bias (domains one and two); moreover Choi et al.'s (2019) estimated PAT effect size was implausibly large (two standard deviations), and the associated confidence intervals barely overlap with any other study. Subgroup analyses also revealed no convincing relationship between performance on cognitive outcomes and all of the following: prism strength (deviation); total number of PAT sessions; prescribed duration of PAT sessions; type of comparison. Planned subgroup analysis stratified by population type was not possible since all of the included patient participants were stroke survivors. Of the three studies which reported measuring prism after-effects with open-loop pointing, the one (Rode 2015) that provided data does not suggest that PAT leads to immediate visuomotor after-effects.

This robust systematic review revealed there is no strong evidence underpinning the scientific efficacy of PAT for spatial neglect. A surprisingly small number of RCTs (eight) exist, they are exclusively in stroke and they are not yet of sufficient quality or low risk of bias to determine the possible benefits or harm from PAT with any certainty. Remarkably there is virtually no randomised controlled trial evidence on the mechanism thought to underlie PAT: visuomotor adaptation as measured by open-loop pointing. Since PAT's effects are anecdotally most pronounced by testing open-loop pointing immediately after a session, it is imperative that future mechanistic studies include this procedure in their protocols so that we can be sure that PAT is working to influence the visuomotor system as expected. Further research is required to identify the precise neurological underpinnings of PAT, and its potential scientific efficacy, before better-designed and adequately-powered studies seek to investigate its clinical effectiveness.

Previous research has suggested that PAT works to facilitate functional reorganisation of attentional processing in the damaged (usually right) hemisphere (Rossetti et al., 1998; Tissieres et al., 2018), although the populations reported in the studies included in the present review did not specify neuroimaging subtypes. Functional neuroimaging studies implicate several brain areas that are activated during prism adaptation that are frequently associated with normal visuospatial output (Luauté et al., 2006c, 2009). These areas include the cerebellum, which is often associated with hand-eye coordination and visual guidance and multisensory integration of motor behaviours via the thalamus (and could be integral to computing corrective pointing behaviours and thus adaptation to prisms), and the anterior cingulate and anterior intraparietal cortices (Clarke & Crottaz-Herbette, 2016). Whilst some neuroimaging findings shed light on the possible neural underpinnings of PAT, it is difficult in practice to apply them to clinical populations because stroke survivors tend to vary in their exact aetiologies – the pattern of cortical damage and cortical sparing can be unpredictable. In addition, recent research suggests that any beneficial effects of PAT are more likely to be seen in patients with more selective damage to frontal regions and selective sparing of occipital, medial temporal cortical areas and the cerebellum (Chen et al., 2014; Goedert et al., 2020; Saj et al., 2013, 2018). Coupled with the brain's propensity to reorganise itself after damage, the application of PAT to induce adaptation might not work for everybody. There is the potential to screen patients to identify areas of cortical damage and sparing, however this would need to be justified by robust research designed to identify whether subgroups of patients with specific aetiologies would benefit maximally from a visuomotor intervention like PAT. As it stands, however, with RCTs recruiting individuals with very mixed aetiologies, there is no convincing evidence to indicate the efficacy of PAT.

All of the RCTs included in this review recruited stroke survivors with mixed lesion patterns and at different times post-injury. The shortest time post-injury reported was 10 days, and the longest was 1140 days. In terms of time post-stroke, research on the optimal time to intervene is inconclusive (Coleman et al., 2017). It may be the case that the longer the time post-injury, the more time stroke survivors have with rehabilitation services. This is undoubtedly beneficial to patients, however this does introduce heterogeneity in the evidence base for PAT, since these individuals may have been taught compensatory strategies that alleviate the impacts of spatial neglect on functioning, thus impacting the measured efficacy of PAT within trials.

PAT as an intervention was generally adequately described in the trials included in this review, and revealed interesting differences between studies regarding prism strength, session duration, and total session number. Despite PAT's presence in clinical research for over 20 years, there is still no established consensus on how it should be implemented in trials. Our planned subgroup analyses of prism strength, session duration, total session number and type of comparator found no convincing evidence of dose-response patterns amongst included RCTs. This is despite speculation that higher prism strengths may lead to greater magnitude of after-effects, and greater improvement of performance on cognitive assessments for spatial neglect. For example, Mancuso et al. (2012) and Turton et al. (2010) both used prisms generating 5°or 6°of visual shift respectively, concluding that these prism strengths may have been insufficient to generate meaningful improvement on outcome measures of spatial neglect. A pair of experiments and a meta-analysis of studies recruiting healthy adults to undergo PAT found that effect sizes on post-adaptation measures (rightward shifts on open-loop pointing and symmetry judgement tasks) exhibited small proportional increases with each 1º incremental increase in prism strength (McIntosh et al., 2019), suggesting that there may be a dose-response effect present in neurologically healthy subjects, but whether this translates to stroke survivors with spatial neglect remains unclear. One recent non-randomised study with stroke survivors with spatial neglect has indicated a correlation between the size of the prism after-effect (using 10° prisms) and the improvement on neuropsychological tests requiring motor responses (Gutierrez-Herrera et al., 2018). If the prism after-effect can be further modulated by prism strength (and other elements of the PAT protocol) then it may be reasonable to expect greater improvements on certain cognitive outcomes. Further research into the neural basis of PAT is required to fully understand its possible mechanism of action.

In terms of the methodology of included RCTs, we judged the quality of available evidence using the GRADE approach and each RCT's risk of bias in several domains using the Cochrane risk of bias tool (Higgins et al., 2011). The evidence base was judged to be of very low quality, with concerns in all of the GRADE criteria. All of the included studies were judged to be at high or unclear risk of bias in three or more of: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome measures (see section 4.4.3). All of the included RCTs were also extremely small (maximum number randomised = 35), and only four provided useful data for meta-analysis, resulting in a judgement of very low quality based on the potential for imprecision. In order to generate useful knowledge surrounding PAT as an intervention, any future studies should be rigorously designed to answer the basic questions outlined above: whether PAT works to induce an after-effect, whether this effect is selective for certain aetiologies, and whether these after-effects translate to long-term benefit for individuals with spatial neglect.

We did not identify any serious concerns regarding the indirectness of the included evidence. Although we were interested in spatial neglect after all types of brain injury, we only identified and included studies recruiting stroke survivors. This has not resulted in downgrading based on indirectness because the signs of spatial neglect are likely to be identical across all brain injury survivors who have spatial neglect. There was some variation in the time post-stroke (see above) and inclusion/exclusion criteria. However, given the real-world heterogeneity of this patient population (Li & Malhotra, 2015) these factors were not judged to have a significant influence on evidence quality. In terms of PAT as an intervention, the studies included in meta-analysis differed in terms of prism strength and the number of PAT sessions (and to a lesser extent the duration of individual PAT sessions), however these differences were of particular interest to the present review and thus were not judged to have an influence on evidence quality. Likewise, there were few differences in the outcome measures of the four studies included in meta-analysis. Three of the four studies used cancellation tasks, and one used the conventional subtest of the BIT (which contains cancellation tests among other pencil-and-paper tests, but not functional assessments). Therefore, authors' use of outcome measures did not influence our judgement of study quality.

Overall, the judgement of evidence quality was judged to be very low, which by extension lowered our judgements of confidence in the available data. This was primarily due to several of the included studies being judged to be at high or unclear risk of bias in several domains, and because of our concerns regarding imprecision. Future research should seek to be robust in design (to mitigate against risk of bias), should take advantage of opportunities to preregister work (and be forthcoming about these records), to be clear in its intended study phase (e.g. pilot/feasibility or definitive work) and should be adequately powered to draw conclusions regarding PAT.

Previous reviews either focused solely on PAT for spatial neglect, or included PAT for spatial neglect alongside other interventions (see Appendix G). Most of these reviews included only stroke survivors; two previous reviews (Longley et al., 2021; Riggs et al.,

2007) included other types of brain injury, but found very few RCTs of interventions that included participants from these populations, like the present review. Unlike the present review, previous reviews focused on the clinical effectiveness of PAT, and did not take into account factors such as prism strength, session number/duration, or measurement of after-effects. This review provides an additional perspective with a focus on the scientific efficacy of PAT, in light of the fact that previous reviews of clinical effectiveness generally conclude that evidence for PAT is unclear, with a call for further research to be conducted.

The majority of previous PAT-specific reviews emphasised the short-term clinical benefits of PAT in stroke patients (Barrett et al., 2012; Champod et al., 2018; Lavery Rowe, 2015; Luaute, et al., 2006b), despite not extracting information on scientific efficacy (e.g. PAT after-effects). The remaining review concluded that PAT has a facilitative effect for patients with neglect conducting visual search, however the authors presented no evidence for more complex tasks such as activities of daily living (ADLs) (De Wit et al., 2018). The findings of the present review differ from these conclusions. However, all of the previous PAT-specific reviews included studies of any design (not just RCTs), which has the potential to attribute benefits to PAT where they do not exist. Additionally, these reviews did not specify any specific efficacy outcomes (e.g. open-loop pointing, or time-limited cognitive assessments) whereas the present review did. Furthermore, only one of the PAT-specific reviews reported using a systematic process to identify and appraise literature, which may explain why the authors of these reviews identified some kind of PAT effect.

Three reviews including PAT for spatial neglect amongst other interventions reported limited and low-quality evidence supporting PAT as a useful therapy for the rehabilitation of spatial neglect, with improvements in cognitive outcome measures immediately following the adaptation period (Luaute et al., 2006a; Riggs et al., 2007; Yang et al., 2013). Luaute et al. (2006a) and Riggs et al. (2007) both included any study design in their reviews, which again risks generating an inaccurate profile of PAT with the inclusion of non-RCT data and the potential introduction of selection bias. Indeed, it is noteworthy that in the present review, the one study that purports to show an effect of PAT (Choi 2019) was judged to be at high risk of selection bias (see section 4.4.3). Yang et al.'s (2013) review selectively included RCT evidence, concluding that there is modest evidence for the reduction of spatial neglect signs by PAT. However, Yang et al. (2013) covered the period between January 1997 and June 2012, identifying only two of the studies included in the present review (Nys 2008; Turton 2010); the inclusion of newer studies in the present review may help explain our differences in conclusions.

Moreover, whilst these effect sizes reported by Yang et al. (2013) were large they were not statistically significant, which does not justify concluding that there is a beneficial effect of PAT. The findings of the present review of the scientific efficacy of PAT cast doubt on the conclusions of previous reviews, as it has not been robustly established that PAT works as intended in the short-term post-intervention. Our findings converge with and complement those from a Cochrane review by Longley et al. (2021), who did not find evidence to support PAT as one of several interventions for spatial neglect, although it should be noted that Longley et al. (2021) had a focus on effectiveness (longer term functional outcomes).

4.4.2 Strengths and Limitations

This review is unique in its focus on efficacy, rather than effectiveness, of PAT. This approach has provided an important additional perspective on the utility of PAT in the clinical setting, by attempting to answer the question of whether PAT works at a basic level. This approach was taken in the knowledge that published articles cite PAT as an effective or promising intervention (e.g. “a first among equals”, (Luauté et al., 2006d); “the most promising rehabilitation procedure for hemi-neglect” (Nys et al., 2008); “highly promising” (Goedert et al., 2020)), despite current reviews of effectiveness not supporting these claims. We therefore feel that a major strength of this review is in providing this additional perspective on the quality of the evidence that exists into whether or not PAT works.

Additionally, to our knowledge, this review is the first to consider the effects of PAT on visuomotor pointing responses - the immediate PAT after-effect, which appears to be underreported in studies of PAT. Our search strategy (Appendix H) was designed to be sensitive enough to identify all published RCTs of PAT for spatial neglect by including several of the alternative names that are used for PAT and for spatial neglect (e.g. "prismatic" adaptation, or "hemineglect"). Our search results initially contained 1237 articles and we are confident that these results contained all of the published work on PAT for spatial neglect up to November 2020. However, it is possible that more recent work has been published since our last search of the databases. Additionally, as discussed above, several of the studies that were eligible and included in this review did not have usable data for meta-analysis; study authors were contacted for these data, however only one responded.

Nonetheless, whilst our findings may not contribute directly to clinical practice, they offer an important insight into the limitations of our current knowledge of how PAT works to treat spatial neglect. We found that current trials of PAT for spatial neglect are on a small scale, are often at high or unclear risk of bias, vary in their approaches to administering PAT, and do not routinely measure PAT after-effects at the visuomotor level. Ultimately, the literature does not help our progress in generating unbiased conclusive evidence and identifying an effective means of treating spatial neglect.

We also acknowledge that the studies we included differed in their choice of outcome measurements. Our primary outcome of interest was performance on standardised cognitive assessments for spatial neglect, justified by findings from an international survey of stroke clinicians, those of whom who used neuropsychological assessment for spatial neglect tended to opt for cancellation tests (Checketts et al., 2020). We originally anticipated that a large proportion of the studies would use the star cancellation subtest from the BIT or make it available as supplementary information (or available on request). Of the four studies included in the meta-analysis of cognitive outcomes, three used cancellation tests and one used the conventional subtest of the BIT; our selection of standardised mean difference allowed adjustment for differences in measurement scales. We are aware that these are not the only means of assessing spatial neglect - other standardised assessments for spatial neglect that consider patients' abilities in activities of daily living are available (e.g. the Catherine Bergego Scale). However, our primary focus on cognitive outcomes is more appropriate for studying scientific efficacy as soon as possible post-intervention. Overall we feel that we have extracted similar measurements of cognitive performance from these different studies in this meta-analysis of PAT's scientific efficacy.

Our secondary outcome of interest was measurement of post-adaptation open-loop pointing, in order to identify any immediate visuomotor (but not cognitive) effects of PAT. Three of the included studies reported conducting these measurements, with only one providing the data for the intervention and control groups. Since open-loop pointing is the quickest and most direct means of assessing whether or not a patient has successfully adapted to prisms, it is essential that research includes this in the future; before assessing patients on cognitive outcomes, it seems logical to first ensure that they have successfully adapted to prisms during PAT.

Another limitation is the absence of data that we anticipated would be more readily available as means and standard deviations. In addition, all of the included studies recruited small samples (despite some purporting to be definitive RCTs, further limiting our ability to generalise to this population. For our cognitive outcomes, four studies did not report results in terms of means and standard deviations. Of these four, one reported results of mixed linear modelling and one reported only ANOVA results, one did not report outcomes immediately post-intervention, one reported only change scores and one reported absolute asymmetry scores. For open-loop pointing outcomes, only three of our studies measured these with open-loop pointing (of which one reported means and standard deviations). Whilst this clearly limits our review, this may also serve as a prompt for researchers to include open-loop pointing measurements when reporting outcomes of PAT; it may be useful for researchers to identify and generate a protocol for an appropriate way to routinely assess PAT after-effects.

An additional possible limitation of our review is the potential for a language bias, in that one study (n=18) identified for possible inclusion was only available as a full report in German, and a formal translation could not be sought. We do not anticipate this having a large bearing on our conclusions, though feel it should be noted.

Finally, some of the studies that we included cited sham PAT as a control intervention, but none clearly reported the other routine co-interventions that inpatients are likely to receive, such as differing levels of input from physicians and rehabilitation therapists (this was termed 'usual care' but may vary greatly). It is likely that these interventions will have a beneficial effect independent of (and possibly greater than) PAT over the course of an intervention period. These therapeutic effects should be more fully reported in conjunction with PAT so that researchers and clinicians can fully appreciate the extent to which PAT may or may not have an effect on patients with spatial neglect in the inpatient rehabilitation setting.

4.4.3 Concluding Remarks

We have found that RCTs of PAT for spatial neglect provide evidence of very low quality and no indication of efficacy. The low certainty does not rule out beneficial or detrimental effects either overall or for specific patient subgroups.

4.4.3.1 Clinical Implications

In terms of cognitive effects, there is a very low quality evidence base containing little information regarding benefit or harm of PAT for patients with spatial neglect. There has been speculation that the dose of PAT (manipulated e.g. by prism strength, number of PAT sessions, duration of PAT sessions) has a relationship with outcomes (whether linear, step-change, or curvilinear). The available data do not allow us to make any conclusions regarding dose and scientific efficacy. There is not enough evidence to recommend any version of PAT for clinical practice, therefore patients should continue to receive their recommended care as decided by their clinicians, and should be offered participation in future clinical trials (whether of PAT or of other interventions).

In terms of adaptation effects, there is an even poorer evidence base. In order to assess whether PAT improves performance on clinical measures of spatial neglect, it is logical to first assess whether it works at a basic visuomotor level, e.g. by open-loop pointing. This is because if the patient does not adapt to the prisms at any point during the intervention period, then it is unlikely that there will be any effect on clinical measures of spatial neglect. If PAT is still used by clinicians with patients with spatial neglect, it is recommended that clinicians conduct simple measurements to assess whether their patients are successfully adapting to the prisms, as this is currently the only means of ensuring that higher-order effects identified in some previous, low-quality work can manifest.

4.4.3.2 Research Implications

Any future research needs to satisfy current standards for conduct and reporting of random sequence generation; allocation concealment; blinding of outcome assessments; statistical size justification; and statistical analysis. Whilst we acknowledge that well-designed trials can be perceived as difficult, time-consuming and expensive, there is an ethical duty to ensure that any studies are robust, properly analysed and properly reported to allow clinicians and researchers to come to sound judgements regarding the efficacy (and, ultimately, the effectiveness) of PAT for SN. By extension, there is also an ethical duty for researchers to identify effective rehabilitation methods for spatial neglect in order to reduce the personal suffering and economic cost that comes with stroke survivors with chronic SN.

There are questions that remain after this review of the scientific efficacy of PAT. Although we found no evidence in favour of PAT, the question of whether PAT can be optimally dosed to generate meaningful effects on cognitive assessments for spatial neglect is an interesting one, and may warrant future research that is carefully-designed and appropriately reported. Well-designed pre-clinical studies with neurologically healthy adults may provide a useful proof-of-concept exploration to investigate the effects of different PAT protocols (e.g. prism strength, intensity) on the magnitude and duration of visuomotor pointing effects, before patient participants are recruited. This approach may shed some light on: whether the brain is susceptible to prismatic adaptation at all; whether any effect is maintained for any period of time beyond a training period; and whether the effects of PAT can be modulated by factors such as the PAT protocol or by co-interventions. These data may also inform clinicians about absolute minimum requirements for PAT protocols in order to sustain therapeutic effects in patients with spatial neglect. Future clinical research must also include methods to measure post-adaptation visuomotor after-effects, to allow assessment of whether PAT is working as intended, since this appears to be missing in published reports.

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Chapter 5

Discussion

The studies in this thesis have been presented in a format suitable for publication, and discussion of individual studies has been included in their respective chapters. This general discussion chapter integrates the overall findings from this related body of work into spatial neglect, providing a high level summary, the strengths, limitations, and implications of the findings, and key areas for future research. The overall aim of the thesis was to identify and begin to address gaps in the knowledge of the assessment of spatial neglect and its treatment using PAT, given that both spatial neglect and PAT appear in the literature with different operational definitions and recommendations. This aim was pursued with three studies: a survey of clinicians on their preferred methods of screening for and diagnosing spatial neglect (chapter 2), a 'proof-of-concept' study investigating whether PAT can enhance patients' engagement in NHS occupational therapy for neglect early post-stroke (chapter 3), and a systematic review to assess the efficacy of PAT for people with spatial neglect (chapter 4). Before this PhD, it was known that a wide variety of assessments and treatments were available to clinicians based on different operational definitions of the syndrome (Ting et al., 2011); the lack of consensus among clinicians is evident throughout this thesis. Many national clinical guidelines recommend the use of cognitive and functional assessment of spatial neglect for screening and diagnosis and certain interventions to reduce severity, but they do not always specify exactly which ones are best (Hebert et al., 2016; Intercollegiate Stroke Working Party, 2016; National Stroke Foundation, 2019; Winstein et al., 2016). The effects of this lack of consensus are threefold: clinicians responsible for patient care are left in doubt regarding which tests and interventions are most suitable for their patients, researchers continue to produce findings that are less comparable between studies, and patients do not benefit from a universally-agreed gold standard for timely diagnosis and effective treatment. It has been consistently reported that patients with spatial neglect experience poorer outcomes (e.g. longer length of stay, cognitive impairment, functional disability) than their peers without spatial neglect (Chen et al., 2015; Gialanella & Ferlucci, 2010; Hammerbeck et al., 2019; Jehkonen et al., 2006), and so the need for consensus among clinicians and researchers is particularly urgent if these differences in patients' outcomes are to be addressed. In addition to shortcomings in comprehensive spatial neglect assessment, reports of the utility of PAT in resolving spatial neglect have been mixed. Several small pilot studies have claimed that PAT is an effective means of rehabilitating spatial neglect, but this has so far failed to translate into routine practice, perhaps because the claims have not been substantiated by adequately designed trials. There is now an emerging picture that PAT is not useful in reducing the signs of spatial neglect in all patients, who have mixed aetiologies (Clarke & Crottaz-Herbette, 2016; Goedert et al., 2020; Saj et al., 2018; Thomas & Caulfield, 2018). In short, prior to this PhD the clinical guidelines recommending acceptable means of assessing and treating spatial neglect were unclear, hence the three projects taken together are intended to serve as a starting point for seeking consensus and resetting the direction of intervention research - focusing on the pathway from the initial identification of spatial neglect and through treatment up to discharge.

5.1 Overall Summary of Findings

The findings within this thesis have identified several areas in spatial neglect where we can collectively begin to work towards consensus. In screening and diagnosis, the survey has identified clinicians' preferences for cognitive, functional, and neurological assessments; in interventions, the proof-of-concept study and the systematic review have identified the potential limitations of using PAT with stroke survivors with spatial neglect. The survey study (chapter 2) on the identification and quantification of clinicians' use of spatial neglect screening and diagnostic tools recruited a large number of international clinicians and helped to provide a comprehensive overview of current clinical practice across professional groups. Such a broad scope is also a novel addition to the field; previous surveys had reported assessment or treatment preferences within one profession (e.g. occupational therapy - see Menon-Nair et al. (2007)), within one country (e.g. Denmark, see Evald et al. (2020)), or through the use of vignettes (e.g. Chen et al. (2017)). This work is the first in a programme of future international projects which will be designed to address the lack of consensus in: definitions of spatial neglect, the adequate use of assessments to capture the neurocognitive profile of these patients, and regarding the best ways to reduce signs of spatial neglect. This study serves as the starting point for identifying which assessment tools are currently being used so that future work can lead to an international consensus, thus ensuring high quality care for stroke survivors with spatial neglect.

This survey study found a high level of intra-professional consistency and interesting differences between professional groups in the selection of spatial neglect assessments. Specifically, clinicians with a focus on cognitive recovery (e.g. psychologists) tend to select neuropsychological test batteries (like the BIT; Wilson et al., 1987) or subtests that are taken from them (especially cancellation); other clinicians specialising in functional recovery tend to select unstructured means of assessment like clinical observation. More often than not, clinicians reported having clinical autonomy in their choices. Related to this, the systematic review (chapter 4) suggested that the picture is somewhat different in clinical research, which seems to favour neuropsychological tests (particularly cancellation), and tends to avoid functional outcome measures, despite clear guidance supporting the use of functional outcomes (e.g. Longley et al., 2021). These findings suggest a need to review the psychometric properties of the most frequently used assessments and place the field in a better position to provide evidence-based recommendations for screening and diagnosis. Other practical uses of the survey findings include clinicians' reports of inadequate instruction in spatial neglect during their initial training, which provides another (as yet unexplored) means of improving consensus between professional groups across the globe.

Regarding PAT, it was previously known that PAT has some limited short-term effects in small groups of patients with neglect, but the absence of high-quality evidence supporting its use across the entire spectrum of patients with spatial neglect was, and remains, very unclear. This PhD addressed this absence with two studies of PAT - the proof-of-concept study (chapter 3) and a systematic review of PAT efficacy (chapter 4). The proof-of-concept study (chapter 3) attempted to reframe the utility of PAT in the clinical setting by advancing the focus beyond whether it works to resolve the signs of spatial neglect to investigating whether it can enhance engagement in occupational therapy. The latter is widely offered to stroke survivors and appears to work in this population (Legg et al., 2017). The PhD's proof-of-concept study was nested within a larger study - SPATIAL feasibility - and ran within a randomised controlled trial and alongside a process evaluation. It was the first study to attempt to operationalise the concept of 'patient engagement' in occupational therapy so that PAT effects could be quantified, with the use of an expert observer. The operationalisation of engagement was based on previous work which has sought to define patient engagement phenomenologically through interviews with patients and clinicians (Bright et al., 2015; Kennedy & Davis, 2017; Lawton et al., 2016; Lequerica et al., 2009; Lequerica & Kortte, 2010). This PhD study found no evidence that PAT enhances engagement in occupational therapy, and suggested two alternative explanations for this: that PAT has no effect on engagement , and that our operational definition did not capture patients' engagement in occupational therapy. We achieved our aim of ensuring good internal validity through our use of a single video rater; however, the external validity of our concept of patient engagement is less certain.

Whether PAT has any effect on the representation of space in these patients is addressed by the third project - a systematic review and meta-analysis of the immediate effects of PAT on visuomotor behaviour and clinical outcomes (chapter 4). This systematic review found that, despite individual reports to the contrary, there is no strong evidence that PAT has an immediate effect on signs of spatial neglect, or on visuomotor aftereffects. Taken together, the proof-of-concept study and the systematic review raise considerable doubts regarding the postulated benefits of PAT in a population of patients exhibiting heterogenous signs of spatial neglect - either on engagement in recommended therapy or on clinical measures. These results do, however, leave open the possibility of PAT having an effect on 'patient engagement' that has not yet been adequately operationalised for quantitative study, or an effect on clinical measures of spatial neglect in certain subgroups possessing particular lesion patterns. There is currently little RCT evidence to support the hypothesis that particular lesion patterns can influence susceptibility to PAT. For example, Goedert et al. (2020) is the only RCT to find that frontal lesions can predict response to PAT on functional outcome measures (the KF-NAP). Some other RCTs have provided some information on lesion aetiology (including location and extent: Nys et al., 2008; Rode et al., 2015; Zigiotto et al., 2020), however further RCTs designed to detect effects of lesion location are required to test hypotheses (see section 5.2.3) suggesting that specific patterns of cortical damage/sparing have an influence on the effectiveness of PAT.

Taken as a compilation of studies addressing key issues regarding spatial neglect from identification to treatment, this thesis highlights a lack of high-quality evidence and a lack of inter-disciplinary consensus supporting the use of particular assessments and treatments for individuals with spatial neglect. Moreover, as discussed in the PhD's survey study (chapter 2), there is a clear translational gap between theoretical and applied work in spatial neglect, particularly between the hypothesised mechanism of action of PAT and how it works in the clinical setting (see section 5.2.2 and 5.2.3). It is important to note that this PhD has a particular focus on PAT, and not on the several other non-pharmacological interventions for spatial neglect (see chapter 1 for examples). The common findings across these PhD studies are that the assessments and treatments we have for spatial neglect are varied, depend on different definitions of spatial neglect, depend on the support of low-quality evidence; ultimately, clinicians require better evidence in order to convince them to change practice.

5.2 Comparisons with the Wider Literature

5.2.1 Assessment of Spatial Neglect

In line with previous surveys of clinicians who screen for and diagnose spatial neglect, we uncovered a vast range of assessments, both specific and non-specific to spatial neglect, that are selected. For example, Menon-Nair et al. (2007) found that OTs responding to vignettes of patients selected 20 different assessments to assess spatial neglect, seven of which were specific for spatial neglect (compared to our 40, with approximately 20 spatial neglect-specific). There are, however, key differences between our survey approaches. Menon Nair et al. (2007) used case vignettes, which are a useful tool to contextualise the utility of spatial neglect assessment, but are potentially open to interpretation without strict control and therefore may exaggerate or obscure aspects of spatial neglect that can, in 'real life', impact clinical management. Our work has advanced this knowledge by broadening the focus in highlighting the preferred means of assessment amongst a wider range of professional groups. Secondly, Menon-Nair et al. (2007) did not provide clinicians with a list of assessments to select from, which may more accurately reflect the decision-making processes used by clinicians without a selection of assessments to choose from. On the other hand, this approach may not consider the full range of preferred assessment options (particularly if clinicians opt for a different approach to assessment with unique clinical presentations); we attempted to take a hybrid approach by providing a list of assessments and an opportunity for respondents to highlight any approaches that we did not include. Unlike our survey, Menon-Nair et al.'s (2007) definition of 'best practice' was derived from a systematic review, conducted by the same authors (Menon & Korner-Bitensky, 2004). The use of a systematic review enhanced the validity of the authors' definition of 'best practice' according to factors such as ease of administration and reported psychometric properties of spatial neglect assessments. The 2004 review found that 16% of the sample were following 'best practice' by this previous definition. Identification of best practice will be part of a future programme of research following on from the survey study in this thesis (chapter 2), including a systematic review which will include psychometric properties of preferred assessments, to be conducted by external colleagues in Adelaide. Thirdly, the Menon-Nair et al. (2007) survey study focused only on Canada-based OTs; the present survey significantly builds on these findings by including other healthcare professionals in different countries and goes further by asking why clinicians select particular assessments.

A more recent survey study of Denmark-based healthcare professionals investigated the selection of assessment and observation methods for spatial neglect, and also surveyed clinicians' perceptions on spatial neglect prevalence, subtypes, and differential diagnoses - reflecting a comprehensive, albeit uni-national, approach. Evald et al. (2020) found strikingly similar assessment preferences to our survey. Specifically, OTs, psychologists, physicians and physiotherapists were the most likely professionals to be involved in assessment, almost all of the respondents reported using observation methods to assess neglect, and less than half reported undertaking systematic ADL observation.

It must be noted that Evald et al. (2020), like Menon-Nair et al. (2007), did not provide a list of specific assessments to choose from - instead relying on broader categorisations such as "paper'n'pencil tests" and "personal/colleagues'/relatives' observations". There is a particular issue with the broad categorisation of paper-and-pencil tests because different tests measure slightly different abilities. For example, as discussed in section 1.3.1, the star cancellation test (Wilson et al., 1987) is not sensitive to ego- or allocentric spatial neglect, whereas the hlbroken hearts test (Demeyere et al., 2015) is. Similarly, these cancellation tests are different in nature to drawing tests, or bisection tests, which require the patient to make different judgements. Full appreciation of the different tests and their properties are necessary in order to reach consensus.

However, Evald et al. (2020) went further than we did in quantifying which professional groups assess for spatial neglect subtypes, finding that speech therapists, physicians, and nurses were all the least likely professional groups to make subtype distinctions, although the authors did not specify how this was done. This would have been a useful viewpoint to gather in the present survey, although this would have come at the cost of overburdening our respondents. One aspect not considered by Evald et al. is the quantification of why particular assessments are used - institutional choice or professional autonomy. Underlying reasons for why clinicians select particular assessments represent an additional part of identifying the 'preferred' assessment selections of clinicians, and may provide assurance that recommendations based on the present findings would be less likely to be limited by institutional factors (insurance requirements, funding, etc.).

It has been shown in this thesis and in previous studies that several professional groups are involved, to differing extents and with different preferences, in the assessment of spatial neglect via the use of assessment methods; such methods are either specific (e.g., neuropsychological test batteries) or non-specific (e.g., measures of functional dependence) to the features of spatial neglect. Reports of small proportions of clinicians following 'best practice' (Menon Nair et al., 2007) and reports from clinicians on the need for more comprehensive education on spatial neglect (e.g. Checketts et al. (2020) in chapter 2, and in Evald et al. (2020)) suggest that defining clear clinical guidelines for appropriate assessment of spatial neglect is a priority; clearer means of spatial neglect screening and diagnosis (and at what point in the stroke pathway) may allow for earlier and more targeted rehabilitation of this disabling syndrome.

5.2.2 Engagement in Therapy: Measurement and Intervention

The proof-of-concept study (chapter 3) explored whether PAT immediately enhanced engagement in NHS occupational therapy within a single session. The results of this study fit with previous experimental findings suggesting that the aftereffects of PAT are evident rapidly after the first administration of PAT - in patients with spatial neglect and in healthy controls (Clarke & Crottaz-Herbette, 2016; Crottaz-Herbette et al., 2017), and that this can extend, similarly rapidly, to enhanced performance on untrained cognitive and functional tasks in healthy controls (Michel, 2015) and in patients with spatial neglect (Glize et al., 2017; Jacquin-Courtois et al., 2013). Engagement is recognised as a significant driver in therapeutic success (Brett et al., 2017), and is thought to be a requirement to fully participate in occupational therapy (Kennedy & Davis, 2017). Therefore, a lack of engagement in recommended therapy may limit the degree of recovery of patients with spatial neglect.

Our novel measure of engagement was operationalised using a 100mm visual analogue scale, which was used by an expert video rater to record judgements of patients' engagement before and after a therapy session. The scale was used in conjunction with an innovative 'engagement composite' (see Appendices B and C), which we designed specifically for the purposes of operationally defining engagement for SPATIAL feasibility and for priming the expert video rater. The engagement composite contained evidence-based examples of observable behaviours for the video rater to look out for during the custom-designed visual scanning activity; these observable behaviours were compiled from previous research in stroke rehabilitation, and other services and disciplines, mainly qualitative work with patients and clinicians.

Previous research suggests that engagement in the context of stroke rehabilitation involves the building and maintenance of a successful patient-therapist relationship, which itself must include productive collaboration in goal-setting and patient participation (Lawton et al., 2016). A 2015 literature review provides some additional information regarding the time course of engagement in rehabilitation, whereby engagement may be conceptualised in two related ways: the gradual process of relationship building, and the flexible state of being engaged (Bright et al., 2015). Other qualitative studies have sought to operationally define engagement in therapy. Lequerica et al. (2009) and Lequerica and Kortte (2010) suggest that engagement in rehabilitation can be defined as deliberate effort in working towards committed goals for rehabilitation therapy, and they make a clear qualitative distinction between engagement in therapy and performance (e.g., ability, time taken) during a rehabilitation activity. Performance should be regarded as a distinct entity, since a high level of performance (i.e. success) in an easy task may not reflect a high level of engagement, and poor performance in a complex task may mask a high level of engagement. Bearing this distinction in mind when evaluating therapeutic engagement helps to remove the potential confound of better or worse performance, particularly in stroke survivors who may have a range of needs that can make objective performance more difficult.

Qualitative research (Bright et al., 2015; Lequerica et al., 2009; Lequerica and Kortte, 2010) has informed the development of the engagement composite used in the proof-of-concept study. It is important to note that this composite was not intended to be an exhaustive list of engagement-related behaviours that can be observed, nor was it intended to be applicable across different studies and different populations. The observable behaviours included items concerned with the patient-therapy interaction and included body position, effort in participation (Matthews et al., 2002), sustained attention in activities (Kennedy and Davis, 2017; Lequerica et al., 2009), continuation despite errors (Kennedy & Davis, 2017; Matthews et al., 2002), and apparent interest and receptiveness to feedback (Kennedy and Davis, 2017; Lequerica et al., 2009). The composite also included items concerned with the patient-therapist interaction, reflecting the defined role of the patient-therapist dyad in therapeutic engagement (Lawton et al., 2016), and highlighted the importance of receptiveness to prompts and feedback and engaging in discussion with the therapist (Bright et al., 2015; Kennedy and Davis, 2017; Lequerica et al., 2009) on their performance during the therapy tasks. This approach has a particular strength regarding its basis in rich qualitative findings from practising rehabilitation therapists, combined with the expertise of the video rater who was an experienced stroke OT. However, the measurement of engagement within one session of OT could be an insufficient period of time to allow engagement to build to observable levels. This was the first attempt to quantify the concept of engagement in stroke rehabilitation before and after an experimental intervention, therefore there is no baseline with which to directly compare the findings.

There are some existing tools that aim to measure engagement in the rehabilitation setting. For example, the Rehabilitation Therapy Engagement Scale (RTES, Lequerica et al. (2006)), the Motivation for Traumatic Brain Injury Rehabilitation Questionnaire (MOT-Q, Chervinsky et al. (1998)), the Brain Injury Rehabilitation Trust Motivation Questionnaire (Self (BMQ-S) and Relative (BMQ-R), Oddy et al. (2008)), and the Hopkins

Rehabilitation Engagement Rating Scale (HRERS, Kortte et al. (2007)) all seek to measure engagement in or motivation for rehabilitation therapy over a period of time. There are several issues that precluded the use of these tools in the proof-of-concept study. Firstly, we predicted that any lack of engagement in occupational therapy would be due to underlying attentional impairments as a result of stroke, rather than low motivation or rapport with therapists, or other reasons for disengagement in occupational therapy. Our concern was that these measurements were not designed specifically for this population, or to detect immediate changes following an intervention like PAT. Secondly, self-reported scales (the BMQ-S and MOT-Q) are designed to measure levels of motivation, rather than engagement in a specific therapy, and are potentially confounded by co-morbid anosognosia in patients with spatial neglect. Thirdly, clinician-rated scales (such as the RTES, BMQ-R, and HRERS) are useful for the measurement of engagement or motivation over a series of therapy sessions with a dedicated therapist and would not be useful for a snapshot of engagement before and after PAT - particularly in the case of video viewing of one OT session. Moreover, the HRERS has only one item relevant to within-session engagement, which measures the need for verbal prompts to maintain attention in an activity. Our measure removed the confound of self-report and attempted to minimise bias through blinding (of the video rater) and the use of a standard set of engagement behaviours (rather than motivation or performance behaviours) to prime the video rater before scoring (Appendix B). The final reason for not selecting these existing measurements is that we wanted to investigate the immediate effects of PAT on engagement in OT with before and after snapshot measurements on a single timepoint - had we taken a series of engagement ratings, we might have seen some contamination by other therapies (e.g., speech and language therapy, physiotherapy), the quantity and effects of which we did not have the capacity to measure. This potential contamination could have further weakened any evidence to support PAT as an engagement primer for OT.

The selection of PAT as a means to improve engagement had not been attempted before. Other interventions have been proposed to enhance engagement following brain injury by targeting hypothesised 'mechanisms of action' such as motivation, apathy and awareness (Brett et al., 2017). Brett et al.'s (2017) systematic review uncovered 15 studies investigating various means of enhancing engagement, which tended to focus on rewarding participation (e.g. praise, verbally or via a token system), preventing attrition in a series of therapy sessions, goal setting, feedback on progress, self-regulation, or motivational interviewing. The effectiveness of these interventions may be hindered by the unawareness of some patients with spatial neglect and anosognosia of their deficits in engagement; the selection of PAT as a bottom-up treatment would overcome this, however the present findings do not support its use as a means to improve engagement. Moreover, the proof-of-concept study's focus on a single session is more appropriate for PAT, since the effects are sometimes seen relatively quickly compared to the effects of a reward system, goal setting, or motivational interviewing, which are more likely to have a cumulative effect over time on underlying meta-cognitive factors influencing engagement in therapy.

5.2.3 PAT: Is it fit for purpose?

The systematic review was designed to assess the short term effects (i.e. efficacy) of PAT for the general population of stroke survivors with spatial neglect, given that reviews of effectiveness, and individual RCTs and observation studies, seem to report different findings and conflicting recommendations for practice. These findings also align with those of the proof-of-concept study, where there was no evidence that PAT could immediately improve patient engagement. The systematic review attempted to identify whether PAT provides any short-term benefits in visuomotor pointing and cognitive outcomes, with a view to recommending PAT as a short-term therapy to generate benefits upon which other therapies could capitalise. The systematic review found no evidence to support the use of PAT even for short term outcomes, and found that any evidence for visuomotor aftereffects is extremely sparse. It may be noteworthy that some evidence suggests that the processing and correction of visuomotor pointing may be delayed in patients with spatial neglect, which may explain why some are unlikely to respond to prisms in a short period of adaptation (Rossit et al., 2012). Importantly, included studies did not always contain data that could be used in meta-analysis, highlighting a need for improved reporting of summary statistics in clinical trials of PAT. The main finding from the systematic review is in agreement with the proof-of-concept study in chapter 3, which found no evidence that PAT can enhance engagement in recommended therapy, which might have the potential to improve neglect outcomes following other interventions.

Several reviews have been conducted to investigate the likely effectiveness of PAT for spatial neglect. However, many of these reviews are limited by their design. In some cases, higher-quality RCT evidence was combined with other less controlled designs (Barrett et al., 2012; Champod et al., 2018; De Wit et al., 2018; Lavery and Rowe, 2015; Luauté et al., 2006a; Luauté et al., 2006b; Riggs et al., 2007; Yang et al., 2013). Moreover, several reviews (Barrett et al., 2012; Luauté et al., 2006b; Lavery and Rowe, 2015) were not reported to be systematic (i.e. not systematic in their search strategies or inclusion criteria), suggesting that some findings relevant to PAT were potentially overlooked or omitted.

Additionally, not all of these reviews looked at the immediate effects of PAT on clinical outcomes (i.e. efficacy), focusing on longer-term outcomes (i.e. effectiveness) where the effects of PAT may be expected to decay once the intervention period has passed (e.g. as observed in Turton et al.'s (2010) pilot RCT). Had these reviews coupled their focus on long-term effectiveness with short-term efficacy, these decaying effects might have been taken into consideration. The systematic review and meta-analysis presented in this thesis is the first to include the totality of RCT evidence (up to November 2020) to quantify the scientific efficacy of PAT for spatial neglect. With careful steps to reduce the possibility of bias, the present systematic review and meta-analysis agree found no evidence that PAT has any effect on cognitive or functional measures of spatial neglect, or the adaptation effect, although evidence for the latter is severely limited in terms of quantity (only four studies provided cognitive outcome data, and only one provided open-loop pointing data) and quality (see section 4.4.3).

It is important to note that while this systematic review may rule out the use of PAT in the general population of stroke survivors with spatial neglect, it does not address some evidence suggesting PAT effects in specific subgroups of patients. For example, a non-systematic literature review by Clarke and Crottaz-Herbette (2016) postulated the recalibration of attentional processing following PAT in patients with spatial neglect. Clarke and Crottaz-Herbette proposed that following rightward PAT in patients with spatial neglect of the right side, hemispheric dominance in attentional processing is shifted from the dominant right to the non-dominant left hemisphere, and projected to the dorsal processing stream in order to ameliorate spatial neglect-related bias. This would suggest that in patients with spatial neglect, structures in the left hemisphere that can subserve similar attentional tasks to structures in the right hemisphere (functional homologues) would need to be individually intact, or at least possess requisite residual function, alongside intact cortico-cortical connections within the left hemisphere for the control and processing of visual attention to be maintained.

If Clarke and Crottaz-Herbette (2016) are correct, then in the clinical setting, the selection of patients who may respond optimally to PAT may depend on adequate screening for the integrity of left hemisphere functional homologues, which is possible using neuroimaging, and seems to be favoured by a minority of clinicians in the survey study (chapter 2). However, this is likely to be impractical given the time and financial costs associated with neuroimaging procedures on top of what is already conducted routinely on admission. Another issue here is that, despite the availability of stroke survivor's neuroimaging results from admission, clinical trials do not consistently report lesion data for patients, including location (in terms of laterality, and brain area), time post-lesion (which can often be allowed to vary considerably and may have an influence on these postulated patterns of activation during and after PAT), and subtype of neglect (each of which may respond differently to a visuomotor intervention). Hence, even if it were practical and justifiable to routinely offer additional neuroimaging procedures to stroke survivors (beyond what is required for a stroke diagnosis), it would be difficult to protocolise and justify this given the paucity of lesion data in trials of PAT.

To summarise, the work in this thesis points towards a distinct lack of clarity surrounding the diagnosis and treatment of spatial neglect. The survey (chapter 2) points towards a set of screening and diagnostic assessments that are not yet universally agreed-upon. This lack of consensus may have the potential to create confusion among clinicians and researchers, and the possibility for under- or misdiagnosis of spatial neglect in stroke survivors. As far as intervention with PAT is concerned, the proof-of-concept study (chapter 3) and the systematic review (chapter 4) both suggest that PAT has significant shortcomings in terms of the quantity and quality of the evidence of its supposed effects on the signs of spatial neglect in the clinical setting, and its potential in enhancing established therapies such as occupational therapy.

5.3 Strengths and Limitations

This thesis has several strengths in identifying and helping to close knowledge gaps, providing examples of new ways to approach research in stroke rehabilitation by minimising bias and enhancing validity, and providing the field with future topics of research to continue progress towards a comprehensive means of identifying and treating spatial neglect.

5.3.1 Knowledge Gaps

The survey study in chapter 2, despite early reservations about the likely response rate, generated a large quantity of data on assessment selection among 454 clinicians across 33 different countries, thereby strengthening the external validity of the findings. The demographics of the survey respondents (e.g. professional group) were in line with what we would anecdotally expect from the stroke rehabilitation setting (i.e. mostly OTs and psychologists), strengthening the internal validity of the findings, although our opportunity sampling method did not allow us to calculate precise response rates e.g. by profession, by country, or by years of experience. Nonetheless, the findings of this survey were useful in confirming and quantifying the vast range of assessment tools that are used to identify the presence and severity of spatial neglect, highlighting that there is emerging consensus on an intra-professional level (and, to an extent, an international and inter-professional level).

The volume of responses from the survey demonstrates an appetite for the harmonisation of spatial neglect assessment, and suggests that a consensus is feasible - especially given that the majority of responses indicated the existence of professional autonomy in assessment selection, as opposed to institutional policies which would be harder to influence. The survey has also provided the groundwork for new projects to identify and appraise the psychometric properties of favoured assessment tools (conducted by colleagues in Australia), and to continue the theme of consensus building in the context of interventions to ameliorate the signs of spatial neglect (conducted by colleagues in the United States of America).

The proof-of-concept study and systematic review also addressed a knowledge gap related to the postulated effects of PAT on visuomotor pointing behaviours and cognitive measures of spatial neglect – with both studies suggesting that PAT is of no appreciable benefit or harm to patients with spatial neglect. The present systematic review was conducted because previous systematic reviews of effectiveness (see Appendix G) all seem to reach similar conclusions despite being replicated several times: that PAT has unclear effectiveness, hence the present systematic review which aimed to take a 'step back' to identify short-term efficacy that may translate to lasting effectiveness. The findings from the systematic review may be limited by the paucity of data available for meta-analysis. Whilst the limitations of the data are not attributable to shortcomings in data collection for this thesis, they open new lines of enquiry in highlighting an absolute requirement for an improvement in research design and reporting of findings. Indeed, a recommendation from the systematic review in chapter 4 and related work conducted by colleagues (Longley et al., 2021) is that the quality of research investigating PAT requires a wholesale improvement in order to be useful.

5.3.2 Validity

The studies included in this thesis have greatly benefited from a range of stakeholder input. In particular, the proof-of-concept study was influenced in many ways by a dedicated group of stroke survivors, who have contributed to the broader SPATIAL feasibility study as experts by experience. The proof-of-concept study incorporated elements which, in my mind, may have been uncomfortable or inconvenient to patient participants had it not been for the evaluation by the PCPI team. For example, it was important to clarify whether the video recording aspect of the proof-of-concept study might have been uncomfortable or intrusive for the patients; likewise, the visual scanning activity may have been physically or cognitively difficult for some stroke survivors to do as part of a research study. The PCPI members reviewed the process for video recording and the materials and procedures associated with this study, and provided invaluable feedback which ultimately confirmed that these processes were appropriate. The PCPI group and some of the treating occupational therapists and therapy assistants from each site were also consulted about the conceptualisation of engagement in occupational therapy during the study design phase, and provided feedback which confirmed the face validity of our approach to measuring engagement in this population, further strengthening our findings.

The proof-of-concept study incorporated a further benefit related to the triangulation of engagement scores. The primary outcome was the blinded, unpaired method of video scoring by our expert occupational therapist. This outcome was augmented by a partially unblinded (i.e. unblinded regarding the ’pre’ or ’post’-therapy status of each video, but remaining blinded to study arm allocation) set of video engagement rating by the same rater, and data from unblinded treating occupational therapists measuring pre-to-post-therapy engagement change (please see chapter 3). All of these findings point towards the same answer: that PAT has no appreciable benefit on patient engagement in occupational therapy. Moreover, the PCPI input to the proof-of-concept study also contributed to enhancing validity because these group members gave their impressions of the perceived difficulty of the visual scanning activity - the standardised OT-like activity used to elicit engagement. In the view of the PCPI group, the activity was not too easy or too difficult, and provided a stimulating and realistic simulation of the OT they received as patients. There is a potential limitation in that our custom-designed measure of engagement (a standardised OT task and observer-rated engagement scores) lacked any normative data and psychometric data upon which to score and rank patients in this study. However, despite the absence of these data, it remains the case that the benefits of this bespoke approach outweigh the limitations - specifically, this approach obviates the influence of anosognosia (a common co-morbidity) which would confound the currently available self-reported engagement scores. Moreover, whilst this approach to measuring patient engagement was not intended to be a universal measure of engagement in therapy, it was designed to be internally valid, and future research may be able to adopt similar approaches in the future. However, this would need to be approached differently depending on both the mode of therapy and the way patients engage in different therapy tasks. For mode of therapy, the simulated activity may need to be changed from a ’visual scanning activity’ to some kind of reading activity (for speech and language therapy), some physical exercise (for physiotherapy), or other activities of daily living (for other occupational therapy interventions). Likewise, the ’engagement composite’ may need to be tweaked depending on how patients are expected to engage with different therapy modalities. To summarise, the overall conclusion of the proof-of-concept study is likely to be valid, supported by three analyses of patient engagement, strengthening the internal validity of this study, and designed and conducted with support from local clinicians and our dedicated PCPI group.

The survey similarly benefitted from involvement by local clinicians, including speech and language therapists, physiotherapists, orthoptists, psychologists, occupational therapists, and neurologists. The online survey was piloted extensively during the development phase, and local clinicians provided their impressions of whether the survey was accessible and could be completed by busy respondents, and whether the questions incorporated the correct amount of assessments to choose from. These local clinicians also confirmed that opportunities for free-text responses were both appropriate (for those respondents who wished to expand or provide insights) and realistic to expect from respondents. In addition, the survey study was collaboratively designed and conducted with international clinical academics from a range of countries and backgrounds. Co-designing professional groups included psychologists, occupational therapists, neurologists and a statistician, based in the United Kingdom, the United States of America, Canada, Sweden, Italy, and Switzerland. The matching of clinical expertise and geographical location between the research team and the respondents further strengthens the validity of this particular study, and sets a strong framework upon which we can all proceed towards forming an international, multidisciplinary consensus. Finally, the survey respondents themselves confirmed in the demographics section of the survey that they were currently practising stroke or rehabilitation clinicians with a range of experience, and importantly all reported having seen a patient with spatial neglect within the previous 12months. The up-to-date clinical knowledge of the survey participants further strengthens the external validity of the survey’s findings.

5.3.3 Minimising Bias

Each of the studies in this thesis also benefitted from a range of design elements that contributed to a reduced risk of bias. The survey study was designed with as many multiple-choice responses as possible to allow for coding and statistical analysis of the results; the free text responses provided useful additional qualitative data to help explain our core findings. The survey was also piloted extensively by local clinicians and modified at each stage of the design process so that it could generate reliable and clinically-valid results.

Similarly, the proof-of-concept study was well-controlled in terms of bias. We invited one expert video rater to score engagement in patient videos, and included sensitivity analyses to ensure that the results (i.e. that PAT does not enhance engagement after a single treatment session) were reliable and not influenced by observer bias. One sensitivity analysis was to ask the video rater to re-score all of the videos again, whilst unblinded to whether the video was before or after PAT (or a control therapy) - the confidence intervals generated by this method were narrower and led us to the same conclusion. These two scoring methods used the same 100mm visual analogue scale, which is well-accepted for its reliability. We also asked the unblinded treating occupational therapists to judge whether their patients had poorer, similar, or improved engagement (using a three-point scale) after their PAT or control therapy session. The majority of patients in each treatment arm were rated as having 'similar' engagement after therapy compared to before, thus strengthening our overall conclusion. However, despite limiting bias in the proof-of-concept study, it is possible that bias was introduced at the identification and recruitment of patient participants stage. Patients who have spatial neglect tend to have longer hospital stays and poorer functional outcomes than those without spatial neglect (Hammerbeck et al., 2019). This means that those patients with the most difficulty engaging might have been excluded at the recruitment phase of the study because they were medically unfit to participate in the trial. The decisions made at first approach and recruitment were made by clinical research network (CRN) or NHS trust research staff; we did not recruit patients ourselves, thus there may also be inconsistency between NHS sites in who was approached based on their health at the time. The inclusion of patients who are 'doing better', medically speaking, might have biased our measurement of engagement, hence these results should be regarded cautiously.

The rationale for the systematic review's focus on PAT efficacy was based on the observation that other systematic reviews of effectiveness tend to come to the same conclusion - that evidence surrounding PAT is limited and therefore PAT cannot be recommended as an effective treatment for spatial neglect - hence the need to investigate whether PAT has any benefit whatsoever in the short-term, upon which therapeutic gains could be built. The present review's focus on shorter-term efficacy was intended to identify any of the characteristics of PAT and spatial neglect measurement that could be targeted in future definitive trials, and was furthermore intended as a means to highlight the need for future well-designed definitive trials. Moreover, the methods of the present systematic review limited the effect of bias in its own findings through: 1) the use of several authors to extract and cross-check data extraction, 2) the use of Cochrane risk of bias tools (which are accepted and well-used in systematic reviews and meta-analyses, albeit for effectiveness), and 3) the statistical decision to compute standardised mean differences (see chapter 2).

Overall, the strengths of this thesis are threefold. First, all of the projects contribute to closing certain knowledge gaps in the identification and treatment of spatial neglect, and simultaneously illuminate new lines of enquiry for rehabilitation researchers. Secondly, the three projects all incorporated steps to enhance the validity of the findings (e.g. through PCPI and collaborations with multiprofessional international colleagues). Thirdly, the studies also included particular design elements to limit the risk of bias in each of the findings, and (in the case of the systematic review in particular) may provide a groundwork upon which future studies can build in limits to risk of bias. The limitations of the studies included in this thesis revolve around the lack of consensus in the definition, assessment, and treatment of spatial neglect and of the operational definition of patient engagement in occupational therapy. Whilst the studies in this thesis filled certain knowledge gaps, they raise more questions related to the need for an agreement of appropriate definitions, the need for the identification of, and training in, appropriate assessments, and appropriate research methodology to investigate sensible treatments.

5.4 Clinical and Research Implications

The work presented in this thesis has important clinical implications for the screening and diagnosis of spatial neglect, and the issue of using PAT in its treatment. Likewise, there are numerous research implications including the optimal use of assessment tools for spatial neglect, and whether it is justifiable to continue investigating the use of PAT for spatial neglect. Overall, it appears that there is a lack of consensus regarding the optimal screening and diagnosis of spatial neglect, which may be based on a lack of consensus on how best to define and measure spatial neglect in the first place. Likewise, there is no consistency in the use of PAT in terms of prism strength, training intensity, frequency and duration, and if and how to measure whether patients successfully adapt. This has led to a diverse mix of research designs and PAT protocols that have not been helpful in informing clinicians on how to treat this debilitating syndrome.

The themes that have been identified in relation to PAT are not unique, and apply to other experimental or candidate interventions for spatial neglect and other deficits post-brain injury. For instance, a very recent Cochrane review (Longley et al., 2021) found that there is no single non-pharmacological intervention that has a robust evidence base to indicate its rollout to all stroke survivors with spatial neglect. Longley et al. (2021) cite the lack of adequately-powered, high-quality definitive randomised controlled trials. Longley et al.'s (2021) assertion is supported by the Stroke Recovery and Rehabilitation

Roundtable (Bernhardt et al., 2019) which proposed that trials of complex interventions (including those for spatial neglect) may fail to account for spontaneous neurological recovery. This means that trials may include misbalanced treatment groups, in terms of prognosis, resulting in trial designs that are underpowered, and may explain why several intervetions for post-brain injury deficits lack robust evidence bases. Relatedly, a systematic scoping review (Dalton et al., 2022) found that trials of interventions to promote motor recovery post-stroke lack information about appropriate dose - a point raised throughout chapter 4. Future work studying interventions for all deficits following brain injury, including PAT for spatial neglect, would benefit from early-phase research to establish appropriate dose (Dalton et al., 2022) and appropriate recruitment of patients with specific aetiologies to respond optimally to interventions (Bernhardt et al., 2016; Saj et al., 2019) before phase III definitive randomised controlled trials can be properly designed.

5.4.1 Definition, screening and diagnosis of spatial neglect

It is clear that the screening and diagnosis of spatial neglect lack consensus, although there are early signs of agreement and a clear desire of clinicians for harmonisation. There are plans to conduct a systematic review, based on the survey study in chapter 2, to collate the psychometric properties of the assessment tools used by clinicians worldwide. In addition, future work should seek to uncover more detailed reasons why assessment tools are selected the most frequently. The survey study in chapter 2 made the distinction between professional choice and institutional policy; future work should explore professional choice in more detail. For example, professional choice could refer to what clinicians have learned to use through professional training, or it might be based on clinicians' research activities. The exploration of reasons for assessment selection may have implications for delivering training to clinicians in the identification of spatial neglect.

As previously discussed, the assessment tools currently available to screen for and diagnose spatial neglect may be based on different operational definitions of the syndrome, thus future work should also endeavour to reach consensus on how spatial neglect is best defined so that the field can advance on the same understanding of spatial neglect.

5.4.2 Rehabilitation of spatial neglect and engagement in therapy

Spatial neglect remains a difficult syndrome to treat effectively – a recent Cochrane review identified 65 trials of 8 nonpharmacological interventions for spatial neglect and found no clear frontrunner for effective treatment (Longley et al., 2021). The proof of concept study (chapter 3) and the systematic review (chapter 4) did not find evidence to support PAT as a standalone intervention - either as a standalone to resolve the signs of spatial neglect directly, or as a primer to OT to enhance engagement in established therapy. There may be a benefit in future work investigating whether subtypes of neglect, or subtypes of patients with varying aetiologies, respond optimally to PAT. This line of work may be promising, given some limited evidence suggesting that the effects of PAT (a visuomotor intervention) can transfer to other domains, such as reducing the signs of auditory neglect and extinction (Jacquin-Courtois et al., 2010). This is balanced against a case study by Ptak (2017) who found that their patient with neglect dyslexia did not experience improvement in reading ability after PAT. It could be the case that primary sensory domains where neglect manifests (e.g. visual, auditory) respond better to PAT than information-processing domains affected by PAT, such as reading (see Vallar, 1998). Moreover, as discussed above, emerging evidence points towards highly specific patterns of neural damage (Clarke & Crottaz-Herbette, 2016) - whilst this may be straightforward to implement from a research perspective, the translation to clinical practice may be practically challenging.

On the subject of engagement in therapy, the measurement of engagement and interventions to enhance engagement may be useful in other therapy modalities (e.g. psychological interventions for mental health, speech and language therapy) for different groups of patients (e.g. those with mental health issues, those with impairments in language production or comprehension). However, the nature and role of engagement in therapies for stroke remains unclear. Future research may be able to generate an operational definition of engagement for stroke survivors, who have unique physical and cognitive needs, in order to ascertain whether engagement indeed does have a bearing on cognitive and functional recovery from spatial neglect (or indeed from stroke-related impairments more generally).

5.5 Summary of future research questions

1 Which assessment tools for spatial neglect, reported to be used frequently by clinicians, have the most favourable psychometric properties for deployment in the clinical setting?

2 Is there any utility in screening stroke survivors with spatial neglect for particular patterns of neural damage, or (a) specific subtype(s) of neglect who may respond optimally to intervention with prisms?

3 Does the application of prisms in a training regimen elicit robust, long term visuomotor and attentional aftereffects in healthy subjects? If so, what precludes the same effect taking place in stroke survivors with spatial neglect?

4 How might spatial neglect be better conceptualised and defined for clinical practice and for useful research definitions?

5.6 Concluding Remarks

This thesis contains a series of studies that sought to advance our knowledge in the assessment of spatial neglect and its treatment using PAT. Spatial neglect remains a common and debilitating syndrome for survivors of stroke and brain injury worldwide. In terms of assessment, there is a large variety of assessments that clinicians can use (because of several different definitions of spatial neglect), and that these selections seem to depend on clinicians' professional background, and to a lesser extent the country they work in. There is now a need to generate consensus on a universal definition of spatial neglect and its subtypes, so that we can go on to identify the most clinically useful tests and to harmonise assessment use. In terms of treatment, there is still an urgent need to identify an effective rehabilitation intervention that works for the majority of people with spatial neglect. The results of the present thesis suggest that there is not enough evidence for PAT's efficacy (for engagement or for after-effects and clinical outcomes) for everybody with spatial neglect, and currently there is not strong evidence to support its effectiveness. There is some potential for future, robust and well-reported studies to identify a use for PAT (e.g. for particular subtypes of spatial neglect); there is even more potential for clinical research to generate robust and replicable findings for other intervention approaches for spatial neglect.

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Chapter 6

Appendix

A Full Details of PAT in SPATIAL (TIDieR Checklist)

B Video Rater Engagement Scoring Sheet (Unpaired)

C Treating Therapist Engagement Scoring Sheet

D Video Rater Engagement Change Scores (100mm VAS) vs. Treating Therapist Engagement Change Scores (3-Point Scale)

E Bland-Altman Plot of ’Pre-Therapy’ and ’Post-Therapy’ Video Engagement Scores

F CONSORT Diagram: Proof-of-Concept Study

G Previous Reviews Including PAT for Spatial Neglect

H Ovid MEDLINE Systematic Review Search Strategy

I Full List of Included and Excluded Studies Following Full-Text Screening

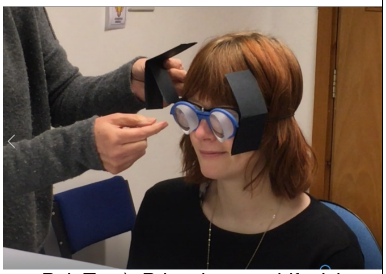
J GRADE Quality of Evidence: Cognitive Outcomes

K GRADE Quality of Evidence: Open-Loop Pointing

Appendix A: Full Details of PAT in SPATIAL (TIDieR Checklist)

TIDiER for Prism Adaptation Training, from SPATIAL feasibility

1. NAME	A feasibility Study of Prisms And Therapy In Attention Loss after stroke: SPATIAL feasibility
2. WHY Describe any rationale, theory, or goal of the elements essential to the intervention	Prism adaptation training (PAT) is a straightforward intervention that aims to remediate spatial inattention by way of visuomotor adaptation.[1] SPATIAL explores PAT as a means to enable people to participate in recommended NHS Occupational Therapy early after stroke. PAT is a simple visuo-motor procedure which requires little cognition and so is likely to be able to be used with severely affected stroke patients. However, patients need enough cognitive resources to follow task instructions. Essentially, the participant performs pointing movements to a target for a few minutes while wearing glasses fitted with wedge prisms. The prisms shift the view of the target laterally towards the neglected side and initially this causes the participant to miss the targets. However, with repeated pointing the participant adapts and adjusts their pointing to achieve accurate movements. Once the glasses are removed the adaptation has a short-term after-effect in shifting the person's representation of space further into the neglected side of space. After prism adaptation patients with spatial inattention have shown long lasting higher order effects with improved performance on neuropsychological tests of spatial attention and some functional tasks. [2] It is thought that the treatment triggers a realignment of the egocentric coordinate system that is responsible for the localisation of the body in space and of object position in relation to the body. [3] Adding PAT to the beginning of OT sessions might enable people with unilateral spatial inattention to engage in and benefit from recommended OT.

3. MATERIALS Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	• Prism glasses: (12.5°, 25 diopter, VTE Vision Training   Equipment Stress PoinTest). Prism lenses shift vision laterally by the same amount in each eye. This model of prism glasses allows the prisms to be rotated to have their thick base on the left (for patients with inattention to the left) or to the right (for those with inattention to the right). Once correctly aligned with a mark on the glasses frame a central screw is tightened to keep the lenses in place. Glasses were set up by a member of the research team for each individual participant to ensure that the prisms were correctly orientated. Once set up the glasses were used only for that one participant. • Glasses case for individual use for the period of the patient's intervention. Cases were labelled with participants' identification number and initials. • Pairs of blinkers for fitting to the prism glasses to prevent conflicting peripheral view. These were made from black card (picture). Additional pairs of blinkers were supplied for each participant. It was recommended that blinkers were replaced weekly, or more frequently as required. • Table and chairs for the patient and therapist to sit opposite one another. Ideally an adjustable height table should be used. The patient may require special

	seating or supports to ensure optimal upright seated posture. • Wipe clean A5 box files and foamboard lid/screen to create a prism therapy "box". Dimensions: 720mm wide; with depth from 180mm at the sides to 340mm at the centre (designed to fit on a standard hospital cantilever table).The participants are asked to point underneath the lid which is used to occlude the patient's vision of their pointing trajectory until nearing the target (this is called terminal exposure). All prism therapy equipment is stored inside the box files. • Target (coloured lolly stick) • Log sheet to record session set up, timing and number of pointing movements and use of equipment. • Timer for maximum pointing duration of five minutes. • Clicker counter to record the number of pointing actions (maximum 90). • Post-it notes. A coloured post it note is used to identify the start position of the participant's unaffected hand. The participant is asked to return their hand to the position after each pointing movement.
4. WHAT PROCEDURES Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	**Prism Adaptation Training** Two different methods for administering prism adaptation have been commonly reported in the literature. These differ in the amount of the pointing movement that the participant can see. One method allows the participant to see a large part of the movement as the finger approaches the target and is termed concurrent exposure. The other methods allows only the last few centimetres of the pointing movement to be seen. This is termed terminal exposure. No significant difference between the two methods in effects on either sensorimotor outcomes or neuropsychological outcome measures have been found. [4] For the SPATIAL study we used the terminal exposure method. This method was chosen as experience in a previous trial had shown that all participants showed after-effects in their pointing after PAT. [5] Before the session materials are collected together and the table is set up with the prism adaptation box and chairs for therapist and for the individual participant, bearing in mind any pillows, specialist seating or equipment that may be needed to support the individual in an upright sitting posture. The participant is seated close up to the table, with the PAT box in front of them. The boxes could be placed in 'portrait' or 'landscape' orientation to suit the height of the participant/ table. The therapist explains to the participant that they will be required to do repeated pointing movements to a target (lolly stick) on the other side of the box using the hand contralateral to the side of the inattention. They are shown the target and start position (post-it note) on which to place the pointing hand. The start position was under the box lid, at a comfortable point close to the participant's body in midline.

	Sitting opposite the participant, the therapist shows the participant how they will present the target and that they will be reaching under the screen and that their finger will be visible to them only at the end of the movement as it appears on the other side of the screen. They explain that the participant should return their pointing hand to the start position after touching the target and that the therapist will move the target and then the participant can reach again. A number of practice trials are completed without the prism glasses to make sure the participant understands and can carry out the task and to encourage them to move their arm quickly. The therapist explains that the pointing will be carried out while wearing prism glasses and shows them the glasses; explaining that the prisms will not affect their ability to see, but that they may find that they have to adjust their pointing a little while they are wearing the prisms for the pointing task. The therapist fits the glasses to the participant and fits the blinkers to the sides so that the participant's vision is only through the prisms and they cannot see around the edges of them. The therapist checks that the participant can still see the target. For wearers of prescription glasses the prism glasses and blinkers were fitted over the top of the prescription glasses.
	
	The therapist prepares the participant to start the pointing task and tells them that they can rest if they become fatigued. The targets are presented in three different places (centre, left and right) in a random order. The total number of pointing actions is tallied using the clicker counter. The therapist can prompt the person to scan to the affected side to find the target, or move the target if the participant is unable to see it. Reminders are given to return their hand to the start position and to make the pointing movements to touch the target fairly quickly. A maximum of 90 pointing movements are carried out, but the task is stopped, and the prism glasses are removed after five minutes even if the 90 movements are not achieved. The date, time taken and number of pointing movements are recorded on the PAT log sheet.
5. WHO PROVIDES For each category of intervention provider (e.g. psychologist,	PAT was provided by Occupational Therapists or their support staff. For practical reasons the intervention did not have to be delivered by the same member of staff at each session. All occupational therapy staff involved in the study received face to face training on the research process and PAT from one of the research Occupational Therapists. PAT was demonstrated and

nursing assistant), describe their expertise, background and any specific training given.	therapy staff all had an opportunity to trial the prism glasses and practice providing PAT. Staff were all provided with their own study handbook which included detailed PAT instructions with images of PAT set up and PAT being performed. Staff were also provided with a link to a video showing PAT being set up and carried out. The first PAT session for each participant was attended by a member of the research team who supported therapy staff by responding to queries and provided feedback on how to perform PAT.
6. HOW Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	PAT was carried out face to face with individual participants. Standardised OT was carried out face to face in both one to one and group sessions.
7. WHERE Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	In the hospital/ rehabilitation unit or in the participant's home including care home setting. A quiet room was the preferred choice, but sometimes nowhere quiet was available and then PAT was carried out at the bedside. All participants commenced PAT in hospital/ in-patient rehabilitation unit. Two participants received some of their PAT sessions at home, and one received PAT in a care home setting.
8. WHEN AND HOW MUCH Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	The aim was to complete PAT once a day, up to 5 times a week for a maximum of 3 weeks. PAT was provided immediately prior to standard OT. When more than one OT session was scheduled in a day the therapist was asked to provide PAT prior to the session most likely to be affected by spatial inattention or at the earlier session if possible. If participants were discharged during the three-week intervention period PAT could be continued in the community at some sites if PAT trained community staff were available.
9. TAILORING If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Due to the range of physical, cognitive and visual impairment across the study population, the therapists were advised to personalise some aspects of the intervention. Participants with severe seating posture difficulties were enabled to participate using specialist seating and/or pillows to support them to achieve an upright sitting posture; instructions were modified when necessary so that they could be understood by patients with communication or cognitive problems; participants who struggled to notice the targets were given additional prompts to help them to find it. Therapists were also

	advised that if the participant was unable to locate the target on the inattentive side then the target could be moved closer to the midline
10. MODIFICATIONS If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	No modifications were made to the intervention during the study.
11. HOW WELL Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Staff in the study sites were trained initially and were observed at each participant's first session. They were not observed after that. However the therapy staff were asked to record details of each PAT session on a log sheets to include: • If blinkers were fitted to the prism glasses • The orientation of the sides of the prism box (landscape or portrait) • How patient was seated (wheelchair/ chair) • If adjustable height table was used • Total number of pointing movements • Length of time for PAT to be completed • If there was a delay of more than 15 minutes before the commencement of the standard OT.

12. Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	• Of the 322 PAT sessions completed by 38 participants (median number of sessions 8 IQR 5,12) PAT was typically carried out for up to 5 minutes or a maximum of 90 pointing movements:
	  ◦ There were PAT 21 (7%) sessions, affecting 6 (16%) participants, where more than 90 pointing movements were completed, of which the median number was 103 (IQR: 96, 107) and ranged from 91 to 133.
	  ◦ 2 PAT sessions (less than 1%), affecting 2 (5%) participants lasted longer than 5 minutes. Neither was more than 10 seconds beyond the required 5 minutes.
	  ◦ 10 PAT sessions (3%) affecting 6 (16%) of participants did not complete a minimum of 90 pointing movements or 5 minutes of PAT.
	• 1 (3%) participant had 2 sessions of PAT recorded on one day
	• 7 (18%) participants received PAT over a period of more than 3 weeks

	• Blinkers were used with the prism glasses in all but 1 session (<1%) for one participant.

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2. Jacquin-Courtois, S., O'Shea, J., Luaute, J., Pisella, L., Revol, P., Mizuno, K., & Rode, G. Rehabilitation of spatial neglect by prism adaptation. A peculiar expansion of sensorimotor after-effects to spatial cognition. Neuroscience and Biobehavioral Reviews, 2013; 37(4), 594–609. https://doi.org/http://dx.doi.org/10.1016/j.neubiorev.2013.02.007
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Appendix B: Proof-of-Concept Video Rater Scoring Sheet

Video Rater Engagement Scoring Sheet (Unpaired)

Engagement Video Scoring Sheet: SPATIAL Feasibility

Date of Rating:
Name of Rater:

Video ID:

Office use only
Site ID:

Participant ID:

Session ID:

There are several behavioural and interactional observations that may be available when rating the video sessions. Of particular importance are the behaviours exhibited by the patient participant during the activity set up and briefing, during the activity, and during debrief when the activity concludes. Also of interest are the interactions between the patient participant and the therapist during these times. The following table lists some examples of these observations:

Engagement in Therapy	Engagement with Therapist
Body position (e.g. leaning forward to perform task) denoting **interest** and initial engagement	**Nonverbal language** (e.g. pointing to activity, gesturing towards therapist)
Participation in activity (NB: the more **active/effortful**, the better the engagement)	**Receptiveness and response to prompts** and encouragement/**asking** for help if required
Sustained attention in the activity (denotes **stable state** of engagement)	Engaging in conversation with therapist **about the activity** (i.e. no disruptive or distracting conversation); tone of voice
Continuation of activity in spite of errors in performance/**determination**	
Apparent interest in task purpose and completion	

Please use the scale to indicate your impression of the level of patient engagement. Using a pen, place a single vertical line at the point along the scale which represents your impression of patient engagement.

Engagement Rating

0 —————————————— **10**

No Engagement　　　　　　Full Engagement

Appendix C: Proof-of-Concept Treating Therapist Scoring Sheet

Treating Therapist Engagement Scoring Sheet

Engagement Therapist Scoring Sheet: SPATIAL Feasibility

Date of Rating:
Name of Rater:

Office use only
Site ID:

Participant ID:

Session ID:

There are several behavioural and interactional observations that may be important to you as a therapist when appraising the level of therapeutic engagement exhibited by a patient. Of particular importance might be the behaviours exhibited by the patient participant during the activity set up and briefing, during the activity, and during debrief when the activity concludes. Similarly, the interactions between the patient participant and the therapist during these times may also be important. The following table lists some examples of these observations:

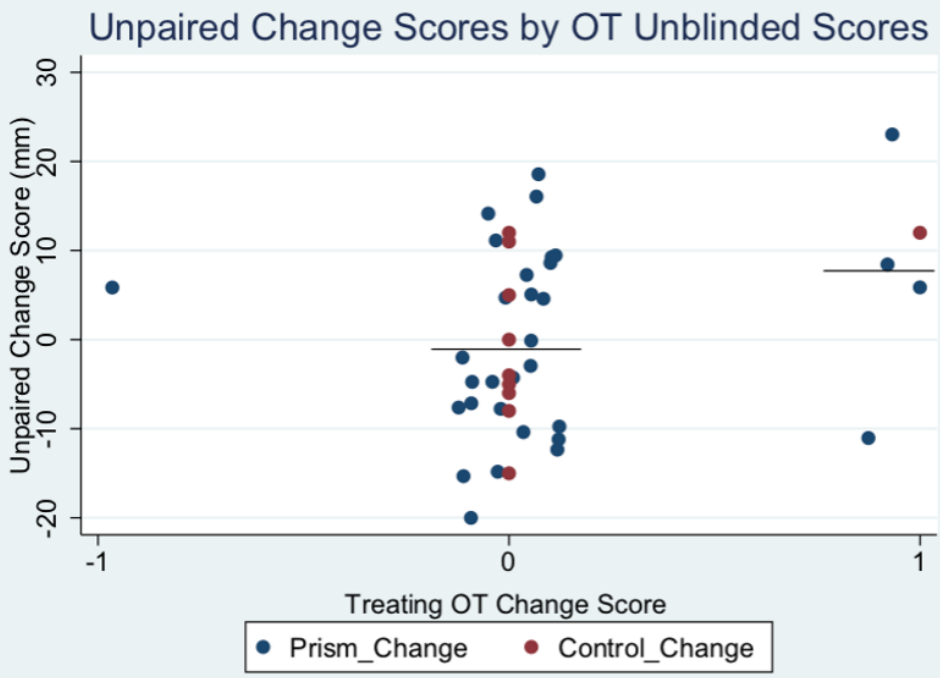
Engagement in Therapy	**Engagement with Therapist**
Body position (e.g. leaning forward to perform task) denoting **interest** and initial engagement	**Nonverbal language** (e.g. pointing to activity, gesturing towards therapist)
Participation in activity (NB: the more **active/effortful**, the better the engagement)	**Receptiveness and response to prompts** and encouragement/**asking** for help if required
Sustained attention in the activity (denotes **stable state** of engagement)	Engaging in conversation with therapist **about the activity** (i.e. no disruptive or distracting conversation); tone of voice
Continuation of activity in spite of errors in performance/**determination**	
Apparent interest in task purpose and completion	

Comparing the behaviours of the patient during therapy **before** and **after** prism adaptation training (or the control, non-PAT activity), please tick one box below to indicate whether engagement **seemed the same**, **improved**, or **worsened** between the two visual search sessions:

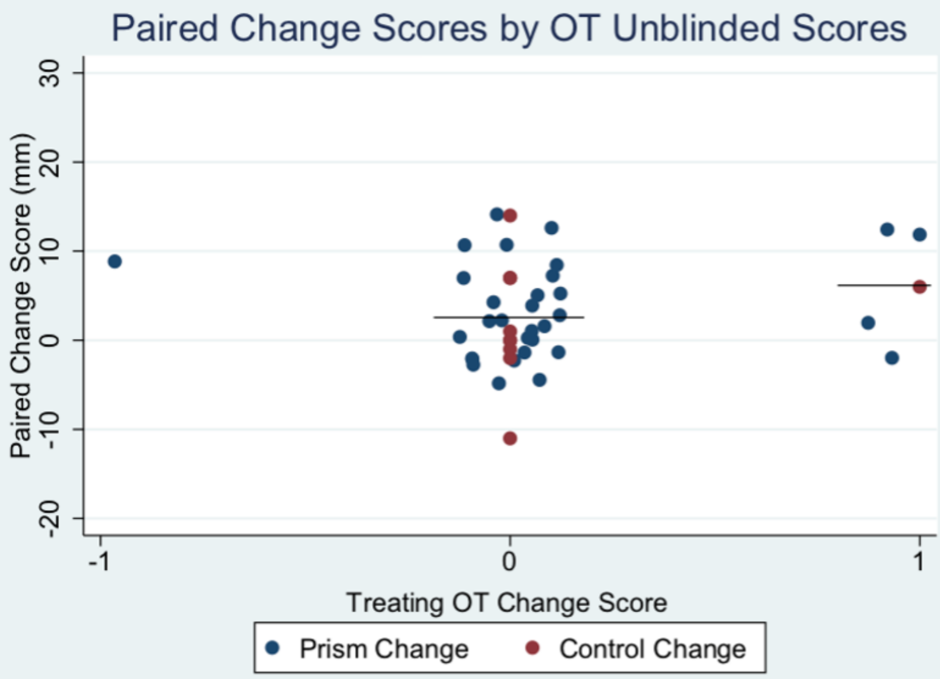
Poorer Engagement ☐ **Similar** Engagement ☐ **Improved** Engagement ☐

Appendix D: Proof-of-Concept Scatterplot of Video Rater and Therapist Engagement Scores

Scatterplots displaying the video rater's engagement change scores (100mm visual analogue scale) on the y-axis, grouped by each patient's corresponding treating OT score (-1, 0, 1) on the x-axis.



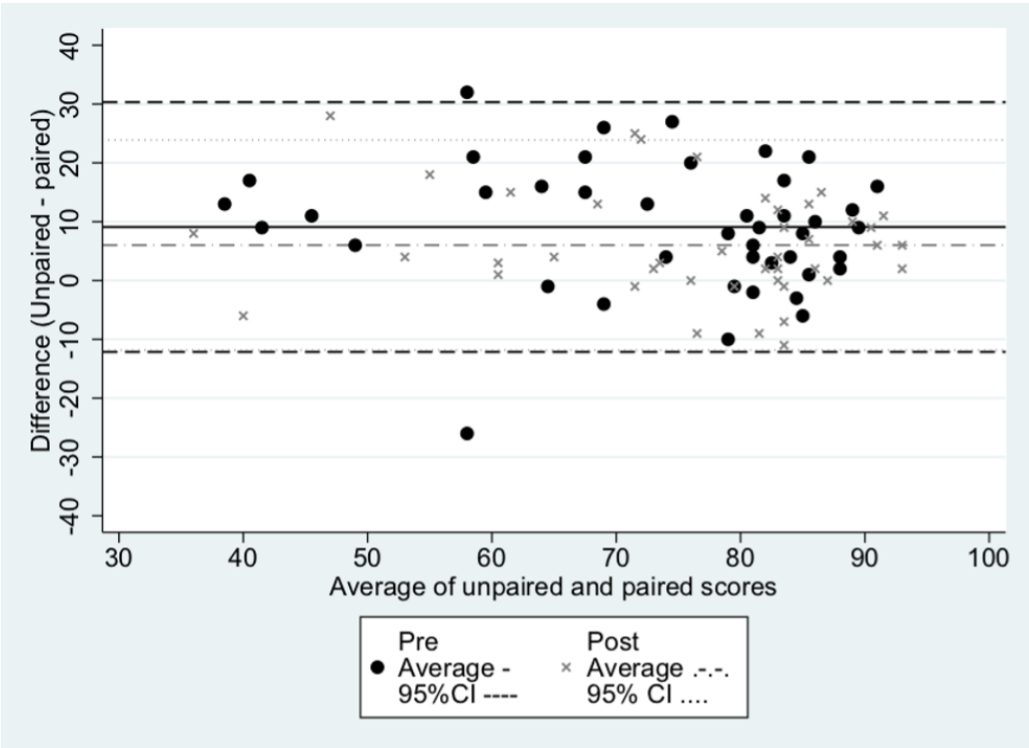
Unpaired Change Scores by OT Unblinded Scores
Unpaired Change Score (mm)
-20
-10
0
10
20
30
-1
0
1
Treating OT Change Score
Prism_Change
Control_Change



Paired Change Scores by OT Unblinded Scores
Paired Change Score (mm)
-20
-10
0
10
20
30
-1
0
1
Treating OT Change Score
Prism Change
Control Change

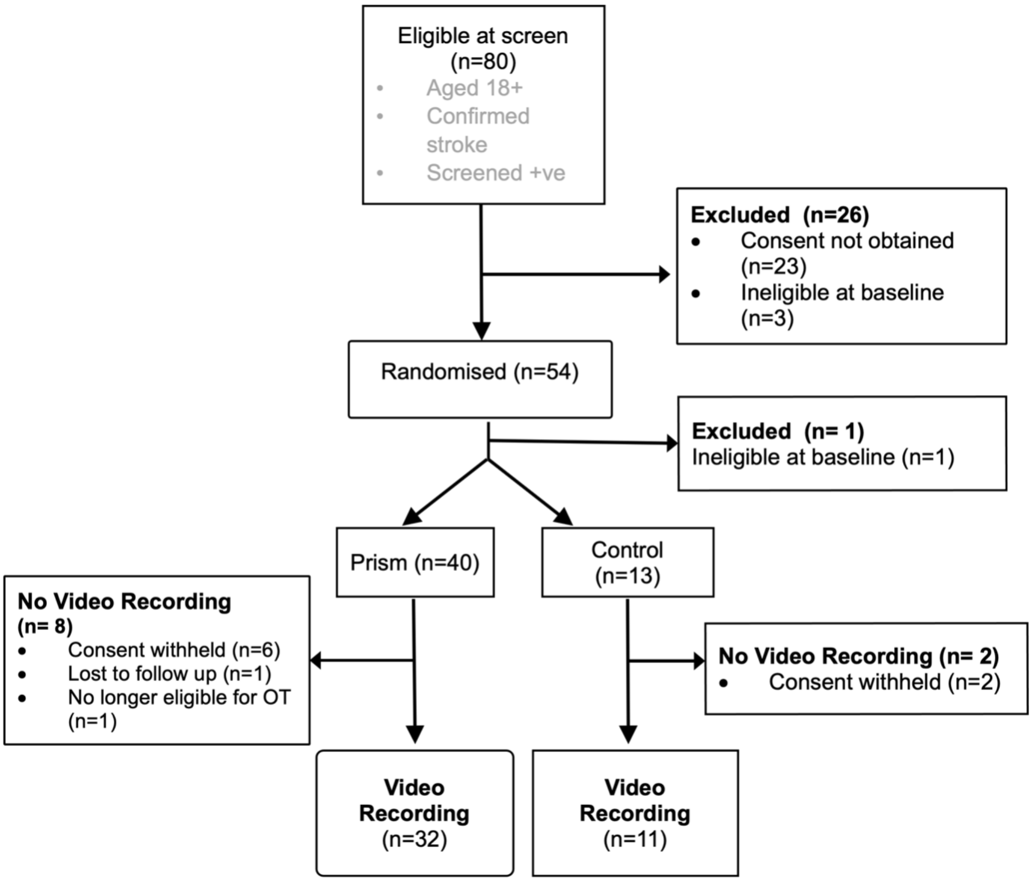
Appendix E: Bland-Altman Plot of ’Pre-’ and ’Post-Therapy’ Video Engagement Scores

Bland-Altman plot combining the ’pre’ scores (unpaired - paired) and the ’post’ scores (unpaired-paired). ’Pre’ scores are represented in black and denoted by solid circles, with the average difference (unpaired-paired) denoted by a solid line, and 95% limits of agreement denoted by dashed lines. The ’post’ scores are represented in grey, with the average difference denoted by a ’dotdash’ line, and 95% limits of agreement denoted by dotted lines.



Appendix F: Proof-of-Concept CONSORT Diagram

CONSORT Diagram for the Proof-of-Concept Study



Appendix G: Previous Reviews of PAT for Spatial Neglect

Previous Reviews Including PAT for Spatial Neglect

Citation	Approach	Disorder	Pop^{n}	SN Intervention	Designs	Total Papers	PAT Evidence
Bowen et al. (2013)	S	SN	Stroke	Any	RCTs	23	Unclear in either direction
Longley et al. (2021)	S	SN	Stroke, brain injury	Any	RCTs	65	Unclear in either direction
Luaute et al. (2006a)	S	SN	Stroke	Any	Orig	54	Limited (short-term and some long-term improvements in small studies; no meta-analysis)
Yang et al. (2013)	S	SN	Stroke	Any	RCTs & "pseudo-RCTs" *	12	Limited (short-term effects only)
Riggs et al. (2007)	S	Visual attention deficits	Stroke, brain injury	Any	All	30	Limited (short-term effects only)
Barrett et al. (2012)	N	SN	Stroke	PAT	Orig	48	Limited (short-term only in some subgroups; no meta-analysis)
Luauté et al. (2006b)	N	Left SN	Stroke	PAT	Orig	21	Limited (control trials and single cases)
De Wit et al. (2018)	S	SN	Stroke	PAT	Orig (English)	30	Limited (visual search only; no meta-analysis)
Lavery & Rowe (2015)	N	SN	Stroke	PAT	Orig (English)	9	Limited (low-quality, short-term; no meta-analysis)
Champod et al. (2018)	S	SN	Stroke	PAT	Orig	26	Limited (immediate functional outcomes; no meta-analysis)

Appendix H: Ovid MEDLINE Systematic Review Search Strategy

Ovid MEDLINE Search Strategy

1. prism*.ab,ti. 2. (prism* and shift).ab,ti. 3. (prism* and adapt*).ab,ti. 4. (prism* and train*).ab,ti. 5. (prism* and therap*).ab,ti. 6. (prism* and point*).ab,ti. 7. neglect.ab,ti. 8. hemineglect.ab,ti. 9. inattention.ab,ti. 10. hemi-inattention.ab,ti. 11. hemiinattention.ab,ti. 12. spatial neglect.ab,ti. 13. unilateral neglect.ab,ti. 14. hemispatial neglect.ab,ti. 15. visual neglect.ab,ti. 16. visuo-spatial neglect.ab,ti. 17. visuospatial neglect.ab,ti. 18. personal neglect.ab,ti. 19. peri-personal neglect.ab,ti. 20. peripersonal neglect.ab,ti. 21. extra-personal neglect.ab,ti. 22. extrapersonal neglect.ab,ti. 23. representational neglect.ab,ti. 24. motor neglect.ab,ti. 25. Perceptual Disorders/ 26. 1 or 2 or 3 or 4 or 5 or 6 27. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 28. 26 and 27

Appendix I: Systematic Review: List of Included and Excluded Studies

Full list of included and excluded studies following the full-text screening phase

Included

Choi, H.-S., Kim, D.-J., & Yang, Y.-A. (2019). The Effect of a Complex Intervention Program for Unilateral Neglect in Patients with Acute-Phase Stroke: A Randomized Controlled Trial. Osong Public Health and Research Perspectives, 10(5), 265–273. https://doi.org/https://dx.doi.org/10.24171/j.phrp.2019.10.5.02

Goedert, K. M., Chen, P., & Foundas, A. L. (2020). Frontal lesions predict response to prism adaptation treatment in spatial neglect: A randomised controlled study. Neuropsychological Rehabilitation, 30(1), 32–53. https://doi.org/http://dx.doi.org/10.1080/09602011.2018.1448287

Mancuso, M., Pacini, M., Gemignani, P., Bartalini, B., Agostini, B., Ferroni, L., Caputo, M., Capitam, D., Mondin, E., & Cantagallo, A. (2012). Clinical application of prismatic lenses in the rehabilitation of neglect patients. A randomized controlled trial. European Journal of Physical and Rehabilitation Medicine, 48(2), 197–208.

Nys, G. M. S., De Haan, E. H. ., Kunneman, A., & De Kort, P. L. M. (2008). Acute neglect rehabilitation using repetitive prism adaptation: A randomized placebo-controlled trial. Restorative Neurology and Neuroscience, 26(1), 1–12.

Rode, G., Lacour, S., Jacquin-Courtois, S., Pisella, L., Revol, P., & Luaute, J. (2014). A once-weekly regime of prism adaptation reduces only sensori-motor biases of neglect. A double-blind RCT essay. Annals of Physical and Rehabilitation Medicine, 57(SUPPL. 1), e140. https://doi.org/http://dx.doi.org/10.1016/j.rehab.2014.03.1579

Ten Brink, A. F., Visser-Meily, J. M. A., Schut, M. J., Kouwenhoven, M., Eijsackers, A. L. H., & Nijboer, T. C. W. (2017). Prism Adaptation in Rehabilitation? No Additional Effects of Prism Adaptation on Neglect Recovery in the Subacute Phase Poststroke: A Randomized Controlled Trial. Neurorehabilitation and Neural Repair, 31(12), 1017–1028. https://doi.org/https://dx.doi.org/10.1177/1545968317744277

Turton, A. J., O'Leary, K., Gabb, J., Woodward, R., & Gilchrist Ailie J. (2010). A single blinded randomised controlled pilot trial of prism adaptation for improving self-care in stroke patients with neglect. Neuropsychological Rehabilitation, 20(2), 180–196. https://doi.org/http://dx.doi.org/10.1080/09602010903040683

Vaes, N., Nys, G., Lafosse, C., Dereymaeker, L., Oostra, K., Hemelsoet, D., & Vingerhoets, G. (2018). Rehabilitation of visuospatial neglect by prism adaptation: Effects of a mild treatment regime. A randomised controlled trial. Neuropsychological Rehabilitation, 28(6), 899–918. https://doi.org/http://dx.doi.org/10.1080/09602011.2016.1208617

Zigiotto, L., Damora, A., Albini, F., Casati, C., Scrocco, G., Mancuso, M., Tesio, L., Vallar, G., & Bolognini, N. (2020). Multisensory stimulation for the rehabilitation of unilateral spatial neglect. Neuropsychological Rehabilitation, DOI: https://doi.org/10.1080/09602011.2020.1779754

Excluded

Bailey, M. J., & Crome, P. (2008). Effects of prism adaptation upon sitting balance, “pushing” behaviour and hemineglect in older stroke patients. In Age and ageing (Vol. 37, Issue 1 Suppl 1, pp. i51–i51).

Barrett, A., Diaz-Segarra, N., Patel, K., Gillen, R., Kaplan, E., & Gonzalez-Snyder, M. (2019). A care pathway for post-stroke spatial neglect: Initial analysis of a practice-based rehabilitation research network. Neurology, 92(15 Supplement 1).

Barrett, A. M. (2009). Prism Adaptation Therapy for Spatial Neglect. In Prism Adaptation Therapy for Spatial Neglect: theoretical and Practical Outcomes.

Hauer, B., & Quirbach, A. (2007). On the economy and effectiveness of prism adaptation as therapy for unilateral neglect. Unilateraler Neglect: Prismenadaptation Als Okonomische Und Effektive Therapie?, 18(3), 171–181. https://doi.org/http://dx.doi.org/10.1024/1016-264X.18.3.171

Hreha, K., Gillen, G., Noce, N., & Nilsen, D. (2018). The feasibility and effectiveness of using prism adaptation to treat motor and spatial dysfunction in stroke survivors with multiple incidents of stroke. Topics in Stroke Rehabilitation, 25(4), 305–311. https://doi.org/https://dx.doi.org/10.1080/10749357.2018.1437937

Jacquin-Courtois, S., Rode, G., Pavani, F., O’Shea, J., Giard, M. H., Boisson, D., & Rossetti, Y. (2010). Effect of prism adaptation on left dichotic listening deficit in neglect patients: Glasses to hear better? Brain, 133(3), 895–908. https://doi.org/10.1093/brain/awp327

Ladavas, E., Bonifazi, S., Catena, L., & Serino, A. (2011). Neglect rehabilitation by prism adaptation: different procedures have different impacts. Neuropsychologia, 49(5), 1136–1145. https://doi.org/https://dx.doi.org/10.1016/j.neuropsychologia.2011.01.044

Ladavas, E., Giulietti, S., Avenanti, A., Bertini, C., Lorenzini, E., Quinquinio, C., & Serino A. (2015). a-tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment in neglect. Restorative Neurology and Neuroscience, 33(5), 647–662. https://doi.org/http://dx.doi.org/10.3233/RNN-140464

Luaute, J., Villeneuve, L., Hovantruc, P., Sarraf, T., Quelard, F., Jacquin-Courtois, S., Roux, A., Decullier, E., Chapuis, F., Ciancia, S., Sancho, P. ., Rode, G., & Boisson, D. (2014). Rehabilitation of hemispatial neglect. Utility to combine prism-adaptation and methylphenidate. RITAPRISM study. Annals of Physical and Rehabilitation Medicine, 57(SUPPL. 1), e140. https://doi.org/http://dx.doi.org/10.1016/j.rehab.2014.03.1580

Mizuno, K., Tsuji, T., Takebayashi, T., Fujiwara, T., Hase, K., & Liu, M. G. (2011). Prism Adaptation Therapy Enhances Rehabilitation of Stroke Patients With Unilateral Spatial Neglect: A Randomized, Controlled Trial. Neurorehabilitation and Neural Repair, 25(8), 711–720. https://doi.org/DOI: 10.1177/1545968311407516

Ronga, I., Franza, M., Sarasso, P., & Neppi-Modona, M. (2017). Oculomotor prismatic training is effective in ameliorating spatial neglect: A pilot study. Experimental Brain Research, 235(6), 1771–1780. https://doi.org/http://dx.doi.org/10.1007/s00221-017-4923-6

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., & Perenin, M. T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature, 395(6698), 166–169. https://doi.org/10.1038/25988

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Serino, A., Barbiani, M., Rinaldesi, M. L., & Ladavas, E. (2009). Effectiveness of prism adaptation in neglect rehabilitation: A controlled trial study. Stroke, 40(4), 1392–1398. https://doi.org/10.1161/STROKEAHA.108.530485

Vangkilde, S., & Habekost, T. (2010). Finding Wally: Prism adaptation improves visual search in chronic neglect. Neuropsychologia, 48(7), 1994–2004. https://doi.org/http://dx.doi.org/10.1016/j.neuropsychologia.2010.03.020

Vatanparasti S Yoonessi A, Oveisgharan S, K. A. (2019). The Effect of Continuous Theta-Burst Transcranial Magnetic Stimulation Combined with Prism Adaptation on the Neglect Recovery in Stroke Patients. In Journal of stroke and cerebrovascular diseases (Vol. 28, Issue 11, p. 104296). W.B. Saunders.

Appendix J: Systematic Review: GRADE Ratings of Evidence Quality (Cognitive Outcomes)

GRADE Quality of Evidence: Cognitive Outcomes

Author(s):
Question: PAT compared to Control for improving cognitive measures of spatial neglect
Setting: Patient participants with spatial neglect followed up as soon as possible after the intervention period.
Bibliography: Checketts M, Fisher G, Vail A, Bowen A. Efficacy of prism adaptation training for spatial neglect following adult brain injury: a systematic review. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAT	Control	Relative (95% CI)	Absolute (95% CI)		
Cognitive PAT vs. Control												
9	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	129	128	-	SMD **0.02 higher** (0.4 lower to 0.43 higher)	⊕◯◯◯ VERY LOW	
Cognitive PAT vs. Control - < 10 degree prisms												
2	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	29	27	-	SMD **0.05 higher** (0.48 lower to 0.58 higher)	⊕◯◯◯ VERY LOW	
Cognitive PAT vs. Control - 10 degree prisms												
6	randomised trials	serious [e]	not serious	not serious	very serious [f]	none	90	91	-	SMD **0.05 higher** (0.96 lower to 1.06 higher)	⊕◯◯◯ VERY LOW	
Cognitive PAT vs. Control - > 10 degree prisms												
1	randomised trials	serious [g]	not serious	not serious	very serious [h]	none	10	10	-	SMD **0.1 lower** (0.98 lower to 0.77 higher)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. The studies included in these analyses were rated as having high or unclear risk of bias in three or more of the following: random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
b. The studies yielding useful data for meta-analysis of cognitive outcomes recruited a grand total of 96 patient participants - 49 receiving PAT, and 47 controls.
c. One of the studies included in this analysis was rated as having high or unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures. The other study was rated as having high or unclear risk of bias in blinding of participants and personnel and blinding of outcome measures.
d. Both of the small studies pooled in this category yielded data from a total of 56 patient participants (29 intervention, 27 control).
e. The studies included in this analysis were rated as having high or unclear risk of bias in three or more of the following: random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
f. Only one of the six studies pooled in this category yielded useful data for meta-analysis, with 10 patients in the intervention arm and 6 patients in the control arm. The total number of patient participants across these studies was 181 (90 intervention, 91 control), which would still be insufficient.
g. The study included in this analysis was rated as having high or unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
h. Only one study was included in this category, with only 20 patients in total split evenly across the intervention and control arms.

Appendix K: Systematic Review: GRADE Ratings of Evidence Quality (Open-Loop Pointing)

GRADE Quality of Evidence: Open-Loop Pointing

Author(s):
Question: PAT compared to Control for improving pointing accuracy in patients with spatial neglect
Setting: Patient participants with spatial neglect followed up as soon as possible after the intervention period.
Bibliography: Checketts M, Fisher G, Vail A, Bowen A. Efficacy of prism adaptation training for spatial neglect following adult brain injury: a systematic review. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAT	Control	Relative (95% CI)	Absolute (95% CI)		
VOLP Post-Intervention PAT vs. Control												
9	randomised trials	serious [a]	not serious	not serious	very serious	none	129	128	-	SMD **0.34 higher** (0.59 lower to 1.28 higher)	⊕◯◯◯ VERY LOW	
VOLP Post-Intervention PAT vs. Control - < 10 degree prisms												
2	randomised trials	serious [b]	not serious	very serious [c]	serious [c]	none	29	27	-	see comment	⊕◯◯◯ VERY LOW	
VOLP Post-Intervention PAT vs. Control - 10 degree prisms												
6	randomised trials	serious [d]	not serious	very serious [e]	very serious [e]	none	90	91	-	SMD **0.34 higher** (0.59 lower to 1.28 higher)	⊕◯◯◯ VERY LOW	
VOLP Post-Intervention PAT vs. Control - > 10 degree prisms												
1	randomised trials	serious [f]	not serious	very serious [g]	very serious [g]	none	10	10	-	SMD **0** (0 to 0)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. The studies included in these analyses were rated as having high or unclear risk of bias in three or more of the following: random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
b. One of the studies included in this analysis was rated as having high or unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures. The other study was rated as having high or unclear risk
c. One of these studies did not formally measure post-adaptation pointing bias; the other study did not report descriptive statistics for meta-analysis.
d. The studies included in this analysis were rated as having high or unclear risk of bias in three or more of the following: random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
e. Only one of the studies in this category formally measured post-adaptation pointing bias, but only in the intervention arm. Other studies either did not formally measure or did not report pointing bias.
f. The study included in this analysis was rated as having high or unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome measures.
g. The study included in this category either did not measure or did not report post-adaptation pointing bias.