The ATTEND Trial

Attentional Therapy for the Treatment of Neglect Disorder

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Declaration of Authorship

I, Dr. Neena Robbie Singh, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

On the topic of Spatial Neglect (SN) post-stroke, this thesis offers a novel approach to the assessment of the condition, investigates the efficacy of a smooth pursuit eye movement therapy delivered via immersive Virtual Reality for the first time as a treatment, and finally, explores behavioural measures as a predictor for response to therapy.

In Experimental Chapter I of this thesis, I explore a unique method for the statistical analysis of gaze duration data by applying Statistical Parametric Mapping software, which allowed for a mass univariate approach to spatially extended gaze duration data. This data was collected from a 2D free visual exploration task developed for use within a Virtual Reality headset, across a visual space measuring 32^{o} either side of central fixation and 24^{o} above and below the horizontal meridian. Baseline gaze duration data from patients with SN post-stroke ($n = 17$) was compared to healthy controls ($n = 23$) to investigate for spatial biases. The patient group demonstrated a significant right-sided spatial bias, 18^{o} towards the right from the midline, and 6^{o} inferior from the horizontal meridian, $p < 0.001$.

In Experimental Chapter II, I present the results of a Phase II group randomized-controlled trial testing the efficacy of a smooth pursuit eye movement therapy delivered using immersive Virtual Reality (iVR). The Therapy Group ($n = 12$) and the Control Group ($n = 12$) received 40-minute sessions of Horizontal Therapy VR Stimulation and a Vertical Control VR Stimulation respectively, daily for 3 weeks. Outcome measures used to assess the effects of therapy included the Star Cancellation Test, the Catherine Bergego Scale and the Free Visual Exploration task developed in Experimental Chapter I. At 3 weeks, my results showed: (i) a significant group*time interaction for the Star Cancellation Test $F(1,22) = 11.52, p =$

$.003, \eta_p^2 = .344$, driven by the Therapy Group $(M = 42.00, SD = 10.72), t(11) = 10.02, p < .001$; (ii) a significant group*time interaction for the Catherine Bergego Scale, $F(1,22) = 7.97, p = .010, \eta_p^2 = .266$, driven by the Therapy Group $(M = 8.77, SD = 4.96)$, $t(11) = 5.81, p < .001, Cohen's\ d = 1.68$; (ii) significant between-session (long-term) effects on the Free Visual Exploration task, showing a leftward shift in the centre of gaze at the end of 3 weeks $P_{FWE-corrected} = 0.054$, driven by the Therapy Group, and no significant within-session (short-term) effects. At 3 month follow-up, there was a significant effect of Group $F(1,18) = 4.45, p = 0.049, \eta_p^2 = .198$, with a trend towards significance on group comparison, with the Therapy Group scoring $M = 41.78\ SD = 11.64$, and the Control Group scoring $M = 29.36\ SD = 15.36$, $t(22) = 1.881, p = 0.073, Cohen's\ d = .768$.

In Experimental Chapter III, I investigate the relationship between SN and sustained attention on the Sustained Attention to Response Task, developed for use within the Virtual Reality headset, to identify behavioural predictors of response to therapy. Data from patients $(n = 14)$ was compared with healthy controls $(n = 23)$. The Control Group had a greater accuracy of go-trials $(p < .001)$, and faster go-trials reaction times $(p = .019)$. Within the Patient Group, significant correlations were found between go-trials and changes in star cancellation scores, Pearson's $\boldsymbol{r}(12) = .586, p = .028$, 95% CI $[0.081, 0.852]$; and post-error slowing and changes in star cancellation scores, Pearson's $\boldsymbol{r}(12) = .621, p = .014$, 95% CI $[0.159, 0.860]$.

In the General Discussion, I discuss the overall conclusions drawn from the results of the Experimental Chapters, and limitations and directions for future work are summarized in the last section.

Impact Statement

Stroke represents a significant global public health challenge, being the second leading cause of death worldwide. In 2021, there were approximately 11.9 million cases of stroke globally, 7.3 million deaths attributed to stroke, and 160.5 million disability-adjusted life years lost due to stroke (1). 50-82% of patients in the acute stroke period suffer from Spatial Neglect (SN) (2), with a third of these suffering from the condition chronically (3). SN has a negative impact on independence, activities of daily living and performance in neurorehabilitation, and leads to longer inpatient stays (4). There is no gold standard assessment or treatment for SN, although several approaches using sensory stimulation, non-invasive brain stimulation and pharmacological measures have been researched, amongst others. Smooth pursuit eye movement therapy has become a promising rehabilitation method in SN (5) delivered thus far using 2D monitors or LED displays.

Through the ATTEND trial, I have tested the efficacy of smooth pursuit eye movement therapy delivered, for the first time, via immersive Virtual Reality, using engaging realistic 3D VR stimulations in a 110^{o} field of view, by conducting a Phase II randomized-controlled trial with inpatients on stroke and neuro-rehabilitation units. The results from this trial showed that the patients in the Therapy Group made significant improvements on impairment- and functional-based outcome measures of SN, following 3 weeks of daily 40-minute horizontal smooth pursuit VR Stimulation, in comparison to a vertical control VR Stimulation. These findings provide favourable evidence for ATTEND to be utilized as a potential treatment strategy for patients with SN, particularly with plans to roll it out in a manner than reduces the hardware equipment and expertise required to set it up. It provides the clinical team with a structured therapy that can be included in the standard neuro-rehabilitation programme. In addition,

the scope for the efficacy of this treatment to be explored in the chronic stages of SN could lead to the future deployment of the ATTEND app for use within home-settings using commercially available VR headsets such as the HTC Vive.

In addition, in this thesis, I have presented a novel approach to the assessment of gaze duration data collected from patients with SN freely viewing a series of 2D images within a virtual reality headset, during a free visual exploration task called the FiVE in the Vive. I have demonstrated a new application of Statistical Parametric Mapping software by applying its principles to spatially extended gaze duration data, producing sensitive statistical maps of gaze in real-word co-ordinates. This approach allows for a more accurate characterisation of the extent of their spatial bias than current methods. The impact of these results for the field includes the introduction of a method that allows for the statistical analysis of spatially distributed gaze data gathered by any method of visual capture, and can be carried out on single cases as well as on groups, preserving the richness of eye-movement based data in the co-ordinate space that it was collected. This method has many uses in the broader community, from visual assessments during tasks such as driving, to analysis of neuropsychological and neurobehavioral analysis of gaze applicable to industries such as advertising, the arts, and the cognitive neurosciences.

Lastly, I have performed an exploratory analysis investigating potential predictors of improvement in visual neglect using the Sustained Attention to Response Task. Two promising associations were identified, which set the stage for further evaluation. Identifying predictors of response would be clinically valuable, as it could help stratify likely responders from non-responders, enabling rehabilitation to be tailored more effectively and resources to be allocated more efficiently.

In summary, I think that presenting this work to the community will help demonstrate a novel assessment technique for SN, offer an immersive Virtual Reality based eye movement therapy which has been proven to be effective and applicable within an inpatient setting, and provide some interesting cognitive correlations with impairment-based outcomes that may help predict improvement.

Acknowledgements

First and foremost, I would like to thank Professor Alex Leff for his unwavering guidance and patience throughout the PhD. It is solely due to his support and encouragement to adhere to my ambitious timelines, that I have completed this part-time PhD within 3.5 years. In giving me the opportunity to undertake this clinical trial under his supervision, he has facilitated my growth as a researcher, and I will carry forward his teachings with me into the next phases of my career. I am also grateful to my secondary supervisor, Dr. Catherine Doogan, for her insights and thoughtful perspectives throughout the project, which greatly strengthened both the experimental design and the interpretation of findings.

Next, my parents, without whom I would not be half the person I am today. They have individually empowered me through the most challenging times. In their unfaltering support towards my pursuit of education and my career above all else, they have gifted me with independence, individuality, and a confidence in my choices that my female ancestors would be proud of.

My siblings, who are the constants in my life, and have been my source of escape, happiness and the occasional annoyances that are always entertaining in retrospect.

To my friends, who have arrived carrying torches in the darkness, I am lucky to have you.

And most importantly, to the incredible stroke patients and their next of kin, who chose to contribute to Science during possibly the hardest times of their lives. Your resilience is inspiring, and you have granted me insights and perspectives that will undeniably influence my clinical practice in the years to come.

Dedication

I dedicate this thesis to my grandparents.

Everything is built on the foundations they laid.

Statement of Contribution

The work presented in this thesis was funded by the National Institute for Health Research, via Professor Alex Leff's research professorship, and by the Cleveland Clinic London, via my PhD Fellowship.

The majority of the recruitment of participants for the ATTEND trial and the data collection was carried out by me, along with the data collection for the FiVE in the Vive study and the SART study. The software for the FiVE in the Vive, the VR Stimulations and the SART were developed by Pedro Leyton.

All of the data pre-processing and statistical analyses were planned conjointly with Professor Leff. The interpretations are my own, and all other contributions have been referenced.

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List of Abbreviations

ADL	Activities of Daily Living
ANOVA	Analysis of Variance
BIT	Behavioural Inattention Test
CBS	Catherine Bergego Scale
DAN	Dorsal Attentional Network
FWE	Family Wise Error
FoV	Field of View
FVE	FiVE in the Vive
HMD	Head-mounted Display
IHI	Interhemispheric Inhibition
iVR	Immersive Virtual Reality
KF-NAP	Kessler Foundation Neglect Assessment Process
LBT	Line Bisection Test
LOM	Lesion Overlap Map
LoS	Length of Stay
MCAR	Missing Completely at Random
MCID	Minimal clinically important difference
OCS	Oxford Cognitive Screen
OKS	Optokinetic Stimulation
PES	Post-Error Slowing
RT	Reaction Times
rTMS	repetitive Transcranial Magnetic Stimulation
SART	Sustained Attention to Response Task
SCED	Single case experimental design
SCT	Star Cancellation Test
SPM	Statistical Parametric Mapping
SPSS	Statistical Software Package for the Social Sciences
SPT	Smooth pursuit eye movement training
tACS	transcranial Alternating Current Stimulation
TBS	Theta burst stimulation
tDCS	transcranial Direct Current Stimulation
VAN	Ventral Attentional Network
VR	Virtual Reality
SN	Spatial Neglect
VST	Visual Scanning Therapy

1.0 Introduction

1.1 Spatial Neglect

Stroke is a leading cause of adult death and disability worldwide. In the UK, there are over 120,000 strokes per year, with two thirds of those surviving living with a significant disability (6). The overall annual cost to the NHS is £8.6 billion per year, with an additional £20.6 billion lost through impacts on productivity, disability and ongoing care (7).

50-82% of patients in the acute stroke period suffer from Spatial Neglect (SN) (2), a neurological disorder causing deficits in attention to one side of the body and space, with a third of cases persisting into the chronic phase (3). SN is a particularly disabling impairment, and its persistence is an independent strong predictor of chronic dependence (8, 9). It impacts participation in inpatient neurorehabilitation, having knock-on effects on functional gains from neurorehabilitation programmes, length of stay in hospital and overall long-term disability. It is associated in some studies with a delay of up to 8 days to discharge, and reduces likelihood of discharge home (9, 10). The James Lind Alliance have listed treatment for visual impairments after stroke as one of their top 5 priorities.

SN is characterized by a gradient of impaired attention within an egocentric reference frame, to stimuli on one side of the body or space (11). The range of space can be categorized as personal, peripersonal and extrapersonal, although a more commonly used categorization is egocentric Spatial Neglect, which alludes to patients failing to pay attention to one side with their own body midline as a reference point, versus allocentric SN, in which they fail to pay attention to one side of the object in view. Interestingly, Spatial Neglect does not quite respect the vertical meridian as one might expect in a hemianopia, rather, it possibly appears more as a gradient across a visual scene (12). It appears to have a directly proportional relationship with an increased number of distractors in a cancellation task, irrespective of the

side the distractors feature in (13). The prevalence of Spatial Neglect after an acute stroke has mostly been noted at 50% (2), however, has been observed in up to 82% of patients with a right hemispheric stroke (14), and is indeed more severe and persistent in this cohort, with moderate - severe severity in 36.2% of right hemispheric cases (15). Whilst this deficit has been noted with lesions in either hemisphere, left-sided Spatial Neglect due to a right-sided lesion is a more common phenomenon (43% as opposed to 20% following a right-sided stroke in an American study (16)), owing to the bilateral hemispheric influence of the right hemisphere on allocation of attention, instead of the unilateral impact on only right-sided attention by the left hemisphere.

Figure 1: Real-life examples of left-sided SN as demonstrated on artwork made by patients from the ATTEND trial.
The bold "L" marks the left side of the page. From top to bottom, left to right: A map drawing of the patient's residence, with all the landmarks clustered over to the right of the page; A patient's abstract self-portrait, the face featureless on the left side; A patient's drawing of the royal crown at the time of the coronation, rich with detail on the right side only; A painting of a landscape, the tree situated over to the right side of the page; an intriguing depiction of one of the VR Stimulations in the ATTEND trial (see Section 3.13.2) – the tree which appears centrally in the Stimulation forms the edge of the left side of space here, and all the apples targeted are only on the right side of the tree, gathering on the bottom right.

1.2 The Neuroanatomy of Spatial Neglect

The asymmetrical hemispheric responsibility for visuospatial function has raised important questions for the neuro-anatomical basis of Spatial Neglect. There is little overall consensus regarding the distinct anatomical correlates for this behaviourally heterogeneous condition, largely owing to variations in time of assessment from onset of stroke, different scanning modalities used amongst studies, lack of a single gold standard assessment test, and impaired performance on different assessment tests being attributable to deficits in different brain locations (17). Given its heterogeneity, and with a multitude of studies employing functional MRI, tractography, task assessment during awake neurosurgery, it appears that SN can result from damage to a range of cortical and subcortical areas, and white matter connection tracts (18). This is further supported by the manner in which it appears to likely be a cognitive function, fluctuating depending on arousal and task instructions, suggesting that it is caused by dysfunction in signalling and communication in neural mechanisms, rather than due to structural damage alone (19).

Structurally, damage to the right posterior parietal lobule, especially the temporoparietal junction, to portions of the angular and supramarginal gyri and to the posterior part of the superior temporal gyrus, has been implicated in left-sided SN (20-22). The inferior segment of the posterior parietal lobule is associated with the Spatial Neglect syndrome, whereas optic ataxia (a difficulty in correctly reaching out to visual goals) results from damage to the superior portion of the posterior parietal lobule (22). Apart from the parietal lobe, lesions affecting the inferior frontal gyrus which hosts the premotor cortex, produce deficits in cancellation tasks, marking it as a region important in visual selection tasks that involve the rejection of distractors (23). Subcortical areas including the thalamus, putamen, caudate

nucleus, pulvinar, insula and basal ganglia have also been associated by means of causing remote functional disruption (diaschisis) in the aforementioned lobes (16, 22, 24). Other distinct anatomical correlations for specific behavioural presentations have been summarized in Table 1.

These structural regions have been identified as being involved in Spatial Neglect, yet the precise mechanisms by which they cause the syndrome remain theorized. An anatomical and functional model for SN formulated from neuro-imaging data of healthy controls, comprises of two frontoparietal networks, the DAN ("dorsal attentional network" - includes the intraparietal sulcus, superior parietal lobule, precuneus and frontal eye fields) and the VAN ("ventral attentional network" - made up of the temporoparietal junction, middle and inferior frontal gyri), both of which are connected by three branches of the superior longitudinal fasciculus (25) (Figure 2). Functionally, the dorsal attention network (DAN) is primarily involved in the voluntary, goal-directed allocation of attention, whereas the ventral attention network (VAN) is engaged in detecting and reorienting to unexpected or behaviourally relevant stimuli across attentional space. Notably, the DAN is represented on both hemispheres whilst the VAN is only on the right (18).

Lesions in the VAN have a functional affect in the DAN. Functional MRI studies have demonstrated activation of both hemispheres, right more than left, during a spatial attention orientation task. DANs were intact, but functionally less activated due to the lesion in the VAN, especially at the right and left dorsal parietal regions, causing less exploration of the left hemispace (26) (Figure 3).

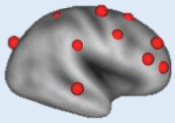
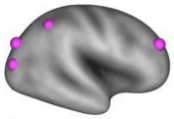
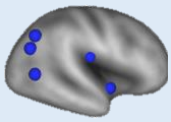
Behavioural Presentations of Spatial Neglect	Distinct anatomical correlates
Cancellation Tasks	Anterior and/or subcortical lesions – right inferior frontal gyrus, anterior dorsolateral prefrontal cortex, posterior part of the middle frontal gyrus, angular gyrus (27) 
Line Bisection Tasks	Posterior lesions - right inferior parietal lobule, angular gyrus (27) 
Allocentric SN (neglecting one side of the object in view irrespective of its position in space)	Ventral locations – Parahippocampal gyrus, temporal lobe (28, 29) 
Egocentric SN (neglecting space with own body as reference of midline)	Dorsal lesions – Premotor cortex (28, 29)
Extrapersonal SN (neglecting the contralesional hemispace)	Frontal lobe – Inferior precentral and middle inferior gyri Temporal lobe - Anterior portion and middle of superior temporal gyrus, sublenticular part of the corona radiata in the temporal lobe (30)
Personal SN (neglecting one's own contralesional hemi-body)	Parietal lobe – supramarginal and post-central, semi-oval centre of the parietal lobe Temporal lobe – Posterior portion of the superior temporal gyrus, sublenticular part of the corona radiata (30) 

Table 1: Anatomical correlates for clinical patterns of Spatial Neglect
The dotted areas are a visual representation of cortical areas associated with different deficits on clinical testing. Images obtained from (27)

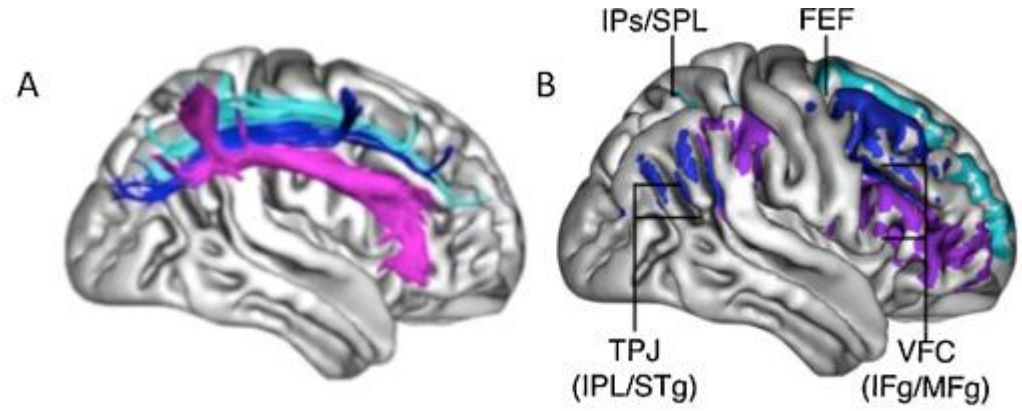


Figure 2: Summary of frontoparietal networks involved in visual attention.
(A) The superior longitudinal fasciculus is divided into 3 branches: (Light blue) Dorsal branch starts at precuneus and superior parietal lobule (SPL), projects towards superior frontal and anterior cingulate gyri); (Dark blue) Intermediate branch starts at the anterior intraparietal sulcus (IP) and the angular gyrus), and joins the posterior portions of the superior and middle frontal gyri (MFg); (Fuchsia) Ventral branch originates at temporoparietal junction (TPJ), involving the inferior parietal lobule (IPL) and superior temporal gyrus (STg) and finishes at inferior frontal gyrus (IFg) (B) Cortical projections of the 3 branches as identified by diffusion-based tractography. Obtained then adapted from (18, 31, 32)

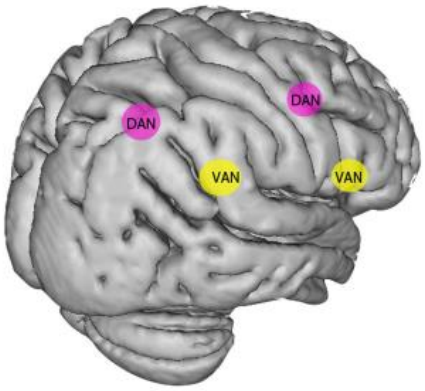


Figure 3: Visualization of the attentional networks
The Dorsal Attentional Network DAN (pink) and Ventral Attentional Network (VAN) (yellow). Cortical projections of the Superior Longitudinal Fasciculus overlap with the nodes of the DAN and VAN. The DAN, represented on both hemispheres, is responsible for controlled goal directed attention (includes the frontal eye fields anteriorly and the intraparietal sulcus posteriorly). The VAN, represented only on the right, activates for stimulus driven attention, for unexpected and automatic orientation of attention to a visual target, sustained attention and arousal (includes the inferior frontal gyrus anteriorly and the temporoparietal gyrus posteriorly). In Spatial Neglect, VAN is disrupted structurally from middle cerebral artery strokes, and the DAN is impacted functionally. Obtained then adapted from (12)

More recently, Alves et al. revisited the structural and functional neuroanatomy of the VAN and DAN by co-registering individual network maps in a unified functional space and proposed an updated model that integrates functional, structural, and neurochemical findings (33). The researchers confirmed the involvement of subcortical structures, including the pulvinar, superior colliculi, head of caudate nuclei, and several brainstem nuclei, as core components

of these networks. These subcortical regions are highly interconnected, forming structural hubs critical for functional connectivity. Notably, the pulvinar, particularly its medial region, plays a pivotal role through connections with VAN regions via frontopulvinar pathways and with DAN regions via parieto-pulvinar projections (34). The role of brainstem nuclei, such as the pedunculopontine nuclei, which house cholinergic neurons crucial for regulating attentional states and enhancing salient stimulus processing, was also emphasized (35). These brainstem nuclei project to various subcortical and cortical regions, including the pulvinar and mediodorsal thalamus, forming a functional map consistent with findings from lesion analyses and axonal tracing studies (36). Graph theory analysis supported the subcortical nuclei's hub role within the VAN and DAN, showing high centrality scores, indicating their critical function in information flow (33).

Neurochemical correlations reinforced the importance of the acetylcholine α4β2 nicotinic receptors, dopamine transporters, and serotonin transporters in the VAN and DAN (33). These neurotransmitters are essential for attentional modulation, with acetylcholine enhancing sustained attention (37), dopamine linked to improved attentiveness and selective attention (38), and serotonin influencing perceptual biases towards emotional stimuli (39).

Another hypothesis is that of an inter-hemispheric imbalance (40). Functional MRI studies have supported the theory that Spatial Neglect from right-sided lesions may occur due to hyperactivity in the left hemisphere, driving attention towards the right side (26, 41). A study using transcranial magnetic stimulation found that the right posterior parietal cortex had a unique inhibitory effect on the left homologous region (42). Therefore, a lesion on the right side leads to hyper-excitability on the left posterior parietal cortex and the frontal motor cortex, which has been observed in patients with Spatial Neglect.

Current theories therefore revolve around the neuroanatomical basis of Spatial Neglect being a complex combination of areas of focal cortical damage, contributing to neurochemically-modulated miscommunications between the dorsal and ventral attentional networks, along with impaired and/or imbalanced communication between both the hemispheres.

1.2.1 Non-lateralised Mechanisms in Spatial Neglect

Neglect syndromes frequently co-occur with non-spatially lateralised impairments, including deficits in sustained attention, working memory, and other executive processes. These can exacerbate functional disability independently of lateralised spatial bias and may interact with recovery. Husain & Rorden summarised evidence for these deficits and argued they represent important mechanisms within neglect, with non-spatially lateralised components such as vigilance, alertness, and short term memory being integral to understanding neglect and its heterogeneity (43).

Deficits in vigilance and sustained attention can lead to task disengagement, reduced therapy participation, and inconsistent performance on assessments, thereby magnifying apparent spatial bias. Similarly, working memory impairments may compromise multi step visual search or sustained scanning strategies, even when contralesional orienting is partially restored. These non-lateralised factors help explain why some patients demonstrate persistent functional impairment despite measurable improvement in spatial tasks, and they are critical for designing effective rehabilitation.

Recognising both spatially lateralised and non-lateralised components provides a more comprehensive understanding of neglect and underpins hypotheses tested later in this thesis (Experimental Chapter III).

1.3 Assessment Methods for Spatial Neglect

The assessment of SN is essential for diagnosing and managing this debilitating condition in a timely manner, in a patient cohort that may often have both cognitive and physical impairments. Various methods are employed to evaluate this condition, including pencil-and-paper tasks like cancellation tests, Line Bisection Test (LBT), and copying and drawing tasks. These tools offer valuable insights into spatial biases and attentional deficits, with cancellation tasks and the LBT being particularly effective screening options. Functional assessments such as the Catherine Bergego Scale aid in providing insights into the real-life effects of the condition. Advanced techniques, such as computer-based testing, virtual reality and eye-tracking, are newer avenues being explored to provide a more detailed and objective measure of SN (43).

The variety of assessment tests for SN and VR-based tools that have been developed in the last 9 years have been briefly described in Table 2 and Table 3 at the end of this section.

Assessment tools have been evaluated for key psychometric properties such as test-retest reliability, which measures the consistency of test results over time, and inter-rater reliability, assessing the consistency of scoring between different evaluators. Tools are also examined for construct validity, ensuring they accurately measure the underlying concept of SN, and sensitivity and specificity, which determine their ability to detect the presence or absence of SN (44). Yet, despite a plethora of research examining these features for the various tests, a gold standard approach to the assessment of SN does not yet exist (45).

1.3.1 Line Bisection Test

The Line Bisection Test involves asking individuals to locate and mark the midpoint of a horizontal line presented on an A4 paper positioned directly in front of them. The line is generally aligned with the patient's midline, and the mark is made using their unaffected or preferred hand. The test is scored by determining the degree to which the marked midpoint deviates from the actual centre of the line. A deviation towards the ipsilesional side is commonly interpreted as a sign of SN, though the extent of the deviation can vary (46, 47).

This test is considered to have construct validity and moderate reliability in retesting scenarios. Marsh et al. demonstrated its construct validity by correlating results from the Line Bisection Test with those from the Star Cancellation Test, showing a moderate negative correlation (Pearson's r = -0.40, p = .02) in a sample of 27 stroke patients undergoing rehabilitation (48). Test-retest reliability has also been reported as moderate (Pearson's r = 0.64, $p < .001$, n = 40) (49), though variability in patient responses to this test is a common issue (50).

1.3.2 Cancellation Tests

In cancellation tests, patients are required to search for and mark specific target symbols on a sheet of paper. Patients with SN often fail to identify or cancel targets located on the side of the page contralateral to the brain lesion. Various cancellation tasks exist, targeting shapes, stars, numbers, letters, lines, bells, and circles. Performance can depend on the presence of distractor symbols, the use of single or dual target stimuli, and whether the symbols are presented in structured arrays or random patterns (51). Tests incorporating distractors are generally more effective at detecting SN compared to those without distractors (52). Similarly,

tasks requiring patients to identify two distinct target types instead of one tend to have higher sensitivity (53). Cancellation tests, such as the Star and Bells Cancellation Tests, have demonstrated correlations with other clinical measures of SN (Pearson's r = 0.26–0.78), supporting their construct validity (44).

1.3.3 Copy and Drawing Tests

Copy and Drawing tests are often used as a clinical tool to assess SN following stroke. Patients are asked to copy and draw objects such as flowers, a clock face, stars, cubes, and various geometric shapes (54). Evidence of SN typically involves incomplete or distorted representations, particularly on the side opposite the brain lesion. In some cases, individuals may restrict their drawings to the side of the page corresponding to the unaffected hemisphere. The sensitivity of this test is comparatively lower at 57.5%, as opposed to the Star Cancellation and Line Bisection Tests (both demonstrating a sensitivity of 76.4%) (55, 56). In addition, the possibilities of abnormalities on these tests arising from general cognitive deficits or constructional apraxia make them a less reliable tool.

1.3.4 Behavioural Inattention Test

The Behavioural Inattention Test (BIT) is a standardized tool for assessing SN, combining six pencil-and-paper tests (line crossing, letter cancellation, star cancellation, figure copying, line bisection, and free drawing) with nine functional tasks (e.g. telephone dialling, menu reading). It uses standardized scoring based on omissions, with established cut-off scores for normal performance (57). The BIT demonstrates strong construct validity (Pearson's r = 0.92, $p < .001$), high ecological validity through correlations with real-world tasks, and excellent inter-rater and test-retest reliability (both Pearson's r = .99, $p < .001$) (58). However, it is limited to assessing peripersonal SN (59), and cannot differentiate between sensory and motor

inattention or identify personal or extrapersonal SN (60). Despite these limitations, the BIT is a valuable tool for evaluating the impact of SN on peripersonal activities.

1.3.5 Catherine Bergego Scale

The Catherine Bergego Scale (CBS) is a Likert scale for assessing SN, offering a functional approach that evaluates across personal, peripersonal, and extrapersonal spaces (61). Unlike traditional pencil-and-paper or laboratory tests, which may lack direct reflection of performance in daily life tasks, the CBS uses direct observation of real-world activities, such as self-care tasks, to capture SN's practical impact. It also surpasses general activities of daily living (ADL) measures like the Barthel Index and Functional Independence Measure by focusing on ADLs that specifically address SN-related limitations versus other disabling impairments, providing precise insights into patient abilities and guiding rehabilitation (11). Notably, the CBS is an observer-rated scale, requiring an occupational therapist to score a patient's performance during every day functional tasks, rather than being based on direct patient responses to structured test items.

Studies since its 1996 introduction have confirmed the CBS's reliability and validity, demonstrating strong correlations with other SN assessments, including the Bell Cancellation Test and the Behavioural Inattention Test subtests, as well as functional measures like the Barthel Index, Functional Independence Measure, and Postural Assessment for Stroke Scale (61). Its sensitivity to SN symptoms often exceeds that of pencil-and-paper tests, and its internal consistency ensures robust performance across items (44, 62). In addition, there has also been the development of the Kessler Foundation Neglect Assessment Process (KF-NAP) to ensure consistent and reliable administration of the CBS. This standardized process enhances the CBS's utility as a functional assessment tool for spatial inattention (63, 64).

1.3.6 Virtual Reality

The emergence of, and commercial accessibility to Virtual Reality (VR) has enabled the application of this technology to assess disorders of visual domains. Several attempts have been made to incorporate this advancement into the assessment of SN specifically.

A host of studies have explored the use of non-immersive and fully immersive virtual reality (iVR) setups for assessing SN. Non-immersive settings typically involve applications displayed on tablets (65, 66), semi-computerized line bisection tasks (67, 68), or interactions with a computer screen and auditory stimuli using a mouse or joystick (69, 70). In contrast, fully immersive settings employ head-mounted displays (HMDs), reflective markers, and motion-tracking systems like body cameras to capture eye and body movements (71-75).

The ecological validity of VR-based SN assessment is a critical advantage, offering the potential to create realistic environments for visual assessment and rehabilitation (70). Similarly, dynamic settings within VR, such as simulated driving tasks, better replicate real-life movements and scenarios, and may enhance SN detection (68). Fully immersive setups have also progressed, with some studies focusing on obstacle avoidance tasks in virtual environments, room exploration tasks with eye tracking, and scenarios such as navigating through supermarkets or street crossings (73).

Several VR-based assessments aim to digitize traditional neuropsychological tests. For example, the Neglect App recreated pencil-and-paper tasks, showing differences in omission rates between traditional and virtual versions (65). A semi-computerized line bisection test used innovative electronic-pen and digitized-paper technology but requires further validation

(67). Comparisons of VR-based, functional, and pencil-and-paper tests suggest VR methods may better detect SN but need further research due to limited sample sizes (70).

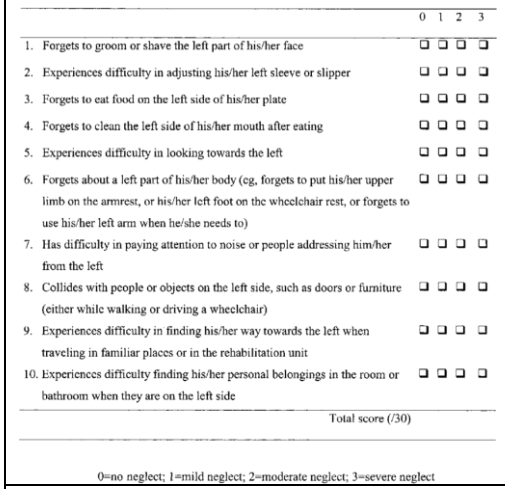
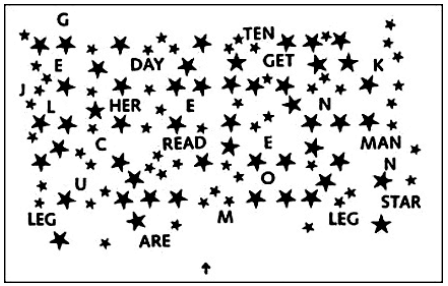
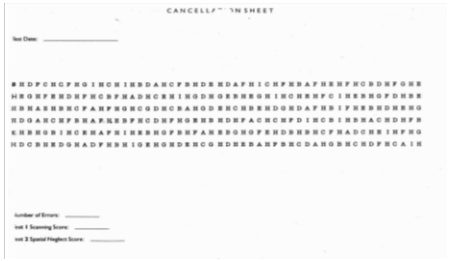
Head-mounted display (HMD) systems have shown promise for quantitative SN assessments, analysing head and eye movements. Head-mounted displays are wearable devices that enable users to experience immersive virtual environments. Such a device consists of a headset equipped with screens (or lenses) for each eye, which display stereoscopic images to create a sense of depth, as well as sensors to track the user's head movements, allowing for interaction with 3D virtual spaces. Sugihara et al. demonstrated that patients exhibited significant performance drops in HMD-based tests compared to pencil-and-paper methods, alongside distinctive rightward eye movement deviations (72). However, again, small sample sizes limit the generalizability of these findings and there are at present no attempts to establish the validity of these methods, limiting broader uptake and inclusion into the battery of tests that can be applied routinely to assess SN.

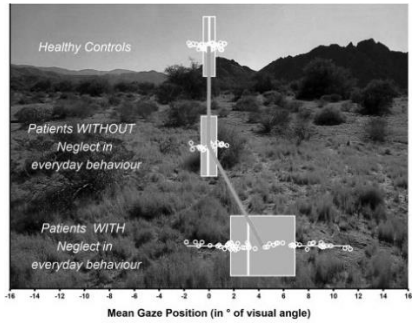
1.3.7 Free Visual Exploration

Free visual exploration is a valuable method for assessing SN, offering insights into how patients spontaneously interact with their visual environment without structured tasks or instructions. Unlike traditional tests, free visual exploration allows clinicians to observe natural gaze patterns and attentional biases, providing a more ecologically valid assessment of Spatial Neglect. Studies have shown that individuals with SN exhibit asymmetrical exploration patterns, such as reduced gaze or fixations on the contralesional side, which correlates with their functional impairments in daily life (76, 77). Eye-tracking technology is often employed to quantify these patterns, measuring gaze fixation duration, saccade amplitudes, and scan paths, which help identify the extent and nature of SN (78). By capturing

spontaneous attentional behaviour, free visual exploration provides a comprehensive assessment of SN and its functional impact.

In their 2020 study, Kaufmann et al. investigated the efficacy of eye-tracking during free visual exploration in detecting SN using a display monitor, comparing it to traditional pencil-and-paper tests (79). The study involved 78 patients with right-hemispheric strokes and 40 age-matched healthy controls. Findings indicated that free visual exploration, measured by mean gaze position on the horizontal axis, identified SN in 85% of patients, outperforming conventional tests like line bisection and cancellation tasks, which detected SN in only 21.74% to 68.75% of cases. Additionally, there was a significant correlation between mean gaze position and scores on the Catherine Bergego Scale, underscoring free visual exploration's sensitivity in mirroring SN in everyday behaviour. The study suggests that free visual exploration, facilitated by video-oculography, offers an accurate screening tool for SN, with potential for early neuropsychological diagnostics and therapy initiation.

Outcome Measure of Hemispatial Inattention	Date of Development	The Test	Cut-off score and comments
Catherine Bergego Scale (52)  0 1 2 3 1. Forgets to groom or shave the left part of his/her face ❑ ❑ ❑ ❑ 2. Experiences difficulty in adjusting his/her left sleeve or slipper ❑ ❑ ❑ ❑ 3. Forgets to eat food on the left side of his/her plate ❑ ❑ ❑ ❑ 4. Forgets to clean the left side of his/her mouth after eating ❑ ❑ ❑ ❑ 5. Experiences difficulty in looking towards the left ❑ ❑ ❑ ❑ 6. Forgets about a left part of his/her body (eg, forgets to put his/her upper limb on the armrest, or his/her left foot on the wheelchair rest, or forgets to use his/her left arm when he/she needs to) ❑ ❑ ❑ ❑ 7. Has difficulty in paying attention to noise or people addressing him/her from the left ❑ ❑ ❑ ❑ 8. Collides with people or objects on the left side, such as doors or furniture (either while walking or driving a wheelchair) ❑ ❑ ❑ ❑ 9. Experiences difficulty in finding his/her way towards the left when traveling in familiar places or in the rehabilitation unit ❑ ❑ ❑ ❑ 10. Experiences difficulty finding his/her personal belongings in the room or bathroom when they are on the left side ❑ ❑ ❑ ❑ Total score (/30) 0=no neglect; 1=mild neglect; 2=moderate neglect; 3=severe neglect	1995	Likert scale. An assessor marks the patient on a severity scale of 0 (no neglect), 1 (mild neglect), 2 (moderate neglect) and 3 (severe neglect) based on observations of 10 spatially dependent tasks of daily living. The patient can also answer the same questionnaire, using a severity scale reflecting difficulty experienced in undertaking these tasks, 0 (no difficulty), 1 (mild difficulty), 2 (moderate difficulty) and 3 (severe difficulty). The difference between the assessor's and the patient's scores generates an anosognosia score, which serves as a measure of the patient's self-aware of their hemispatial inattention.	The CBS is scored out of 30 points. There is an arbitrary severity classification (44, 62): 0 = No behavioural inattention 1-10 = Mild behavioural inattention 11-20 = Moderate behavioural inattention 21-30 = Severe behavioural inattention The minimal clinically important difference in the CBS is a reduction of 4 points (80).
Star Cancellation Test  	1987	The A4 sheet is placed in front of the patient's midline. They are advised to fix their head and trunk in the midline, whilst being instructed to cancel, with a pen stroke, only the small stars. The examiner demonstrates on two midline stars above the arrow. There are 27 small stars on either side, distributed amongst distractors of 52 big stars, 13 letters and 10 words (81).	The total score is marked out of 54 points. Cut-off for hemispatial inattention <44 stars cancelled. Laterality index/Star ratio = number of stars cancelled on the left divided by the total number of stars cancelled 0 to 0.46 = Left hemispatial inattention 0.54 to 1 = Right hemispatial inattention (82).
Letter Cancellation Test 	1974	The 8.5 x 11-inch sheet is placed in the patient's midline, and they are asked to cancel the letter "H", which appears 104 times across 6 lines of 52 letters each, 53 Hs are on the left and 51 Hs are on the right. The total time taken to complete the test is recorded (83).	The number of omitted H's (uncancelled H's) are subtracted from the perfect score or 104. The higher the score, the lesser the hemispatial inattention. Spatial preference is inferred by calculating the frequency of errors on each side from the centre of the page. Cut-off = 4 or more omissions indicate hemispatial inattention (84).

Free Visual Exploration 	2011	Video-oculography, or eye tracking, is used to collect visual fixation data across a horizontal plane. Patients are asked to freely explore 12 images and their mirror images (flipped on the vertical axis) for 7 seconds. Each image is preceded by a central fixation cross to force a common starting point of visual exploration. Head and trunk position is fixed using a chin and forehead rest. Visual fixations ranging between 100-2000 milliseconds are recorded (85, 86).	A difference of at least 2.36 standard deviations above the average mean gaze position of healthy control indicated hemispatial inattention. The higher the value, the greater the rightward shift). This generates a cut-off of >1.627° (in degrees of visual angle) (87).
Line Bisection Test 	1980	A series of 18 horizontal lines is placed on an 8.5 x11 inch page. This is placed in the patient's midline, and they are instructed to mark the centre of each line with a pencil (88). NB: There are several variations of the line bisection test, from those that have 18 lines, to those that have only 1 line (89).	The deviation of the bisection from the true centre of the line, is measured. Cut-offs: (1) Deviation of more than 6mm from the true centre of the line points towards hemispatial inattention. (2) If two or more lines are omitted (i.e. the patient does not place a mark at all) on either half of the page, this also indicates hemispatial inattention (90).
CATS Test	-	Limited information available for this test, but it contains pictures of 24 cats and patients are instructed to cancel out all 24 cats seen (91).	Unknown
Behavioural Inattention Test	1987	The BIT has 2 subtests – the Conventional and the Behavioural sub-test. The BIT Conventional subtest includes line crossing, letter cancellation, figure and shape copying, line bisection and representational drawing. The BIT Behavioural subtest includes pre-scanning, phone dialling, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation and card sorting (58).	Cut-offs: BIT Conventional = 129/146 BIT Behavioural = 67/81 Therefore BIT = 196/227 (63, 92) Index of lateralized performance: The number of tests on which the patient has demonstrated a lateralizing performance is calculated in order to determine the relative spatial location component. If there are an equal number of tests showing a lateralized and non-lateralized performance, then the total number of omissions or

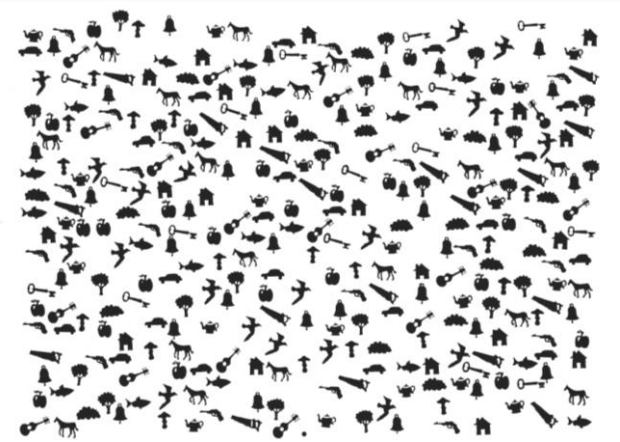
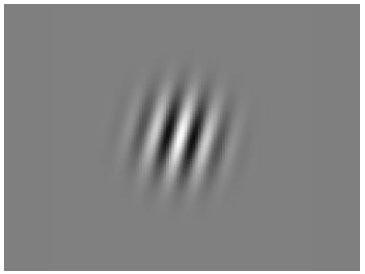
			errors made on either side in each test is calculated to determine this (93). Severity score: This is calculated on the basis of performance on the 6 tests under BIT Conventional subtests. A score of 1-6 is calculated, the higher the score the more severe the visual inattention (92).
Bell's Test 	1989	On an 8.5 x 11-inch sheet, 35 bells are equally distributed in 7 columns containing 5 bells each, amongst a total of 280 distractors such as houses, horses, guitars, birds etc. The patient is first asked to demonstrate correct object recognition on a test sheet containing an enlarged version of a bell and a distractor object. The sheet is then placed in the midline, and the patient is instructed to circle all the bells (94).	The total time taken to circle the bells is recorded, as is the total number of bells circled. Cut-off = Omitting 6 or more bells on the right or left side of the page (95).
Computerized Visual Detection Task  *A Gabor patch*	-	Patients sit in front of a computer screen. The centre of the screen is marked by a bull's eye sign. They are asked to look at the bull's eye, following which Gabor's patches (which are sinusoidal gratings used as visual stimuli) then appear on the left, right and bilateral sides of the screen at 14^{o} eccentricity. Patients then verbally state whether the Gabor patch appeared on the left, right or on both sides of the bull's eye. Changes in contrast in each trial are used to threshold the difficulty of the task (96, 97).	The number of correct hits weighted by the contrast level is measured (98).

Table 2: A list of some of the assessment tools used to assess SN
Where available, clinical cut-offs and minimally important clinical difference scores are provided

Author, year	Mode of Delivery	Type of Assessment Task
Yasuda et al., 2020	**VR space displayed in an HMD**	**To recognize a red sphere within the VR space randomly appearing in different locations, varying in distance from patient, angle from line of sight and height**
Siddique et al., 2021	**Phone app**	**In Practice mode patients move their eyes from top to bottom and left to right when touching targets. Test mode detects scanning abilities.**
Kim et al., 2021	**Stereo HMD system with Oculus Rift; No eye tracking**	**To fixate on a white cross that appears between trials, and a red cross that marks the centre of the screen. Response times and success rate are recorded.**
Spreij et al., 2020	**Screen projection and driving wheel**	**A simulated car-driving task**
Knobel et al.,2020	**HMD**	**20 stimuli to be found amid distractors**
Ogourtsova et al., 2018	**2 virtual scenes viewed in an HMD**	**Detection task and navigation task in a grocery shopping aisle**
Aravind & Lamontagne, 2018	**HMD with motion capture for the head and reflective markers on body landmarks when possible**	**Locomotor obstacle task (avoid collision with approaching obstacle whilst walking towards a target) and perceptual task in seated position (press joystick as soon as moving target detected)**
Grattan & Woodbury, 2017	**PC laptop**	**To identify targets on the left and right whilst walking down a path**
Sugihara et al. 2016	**HMD system that displays the stimuli on an LCD screen, with 2 cameras to detect eye tracking**	**Line cancellation test in the HMD**
Guilbert et al., 2016	**Laptop and headphones**	**Auditory reaction time test and lateralization task (pressing the left or right button on the mouse following the spatial position of a detected target)**
Jee et al., 2015	**e-pen, micro-pattern printed paper and computer**	**Digitalized Line Bisection Test**
Pallavicini et al., 2015	**iPad app**	**Neglect App – digitized cancellation task and card dealing task**
Aravind et al., 2015	**HMD; No eye tracking**	**Joystick-driven obstacle avoidance task and locomotor obstacle avoidance task**

Table 3: A brief description of various VR based assessment tools developed for SN since 2015

1.4 Treatment Approaches for Spatial Neglect

A range of treatments for SN have been proposed and trialled through the years, with approaches including sensory stimulation, non-invasive brain stimulation, drug therapies, and mirror and prism therapies (99). Notably, there is still no gold standard treatment for Spatial Neglect, and the most recent Cochrane review concludes, “The effectiveness of cognitive rehabilitation interventions for reducing the disabling effects of SN and increasing independence remains unproven. As a consequence, no rehabilitation approach can be supported or refuted based on current evidence from RCTs” (100).

This section has been adapted from a self-authored paper, and cited here in-keeping with UCL guidelines (99). A detailed table on the variety of studies performed on SN treatments, used from Singh and Leff (99), with a special section on Immersive and Non-Immersive VR treatments, adapted from Cavedoni et al. (43) has been included at the end of this section (Table 4).

1.4.1 Sensory Stimulation

Sensory stimulation strategies that have been trialled include, auditory spatial cueing and robot-assisted therapy and sensory feedback.

1.4.1.1 Auditory Spatial Cueing

Inattention can be expressed in any of the main sensory domains (121, 122), with the corollary being that these domains can be used as channels to stimulate lateralised attention (123, 124).

Auditory stimulation, particularly in the form of pleasant music, has been shown to activate the striatum, anterior cingulate cortex and the orbitofrontal cortex, areas that play a role in visual attention, emotion and cognition (125-127). Coupling auditory and visual stimuli so that they appear to emanate from the same position in neglected space has been shown to create an improvement in visual detection in patients with hemispatial inattention (128, 129).

Kaufmann et al. (87) conducted a proof-of-concept, controlled trial design using a novel dynamic auditory technique, with stereo sound moving from the right to the left (neglected) side. They undertook two separate experiments on two independent groups of patients in the acute phase, looking at the immediate effects of spatial auditory stimulation lasting for 10 minutes in Experiment 1, and the after effects (1 and 3 hours) in Experiment 2. The first experiment was a cross-over design with a block of auditory spatial cueing, where music appeared to travel horizontally from the right to the left, was compared with a control block where musical stimulation was identical bilaterally (no illusory horizontal movement). A cancellation test was used as the outcome measure. They found a significant improvement with auditory spatial cueing, and a large effect size, Cohen's *d* = 0.85. Experiment 2 was group randomised. Participants were randomly assigned to either the spatial auditory cueing or control condition. Free visual exploration (a sensitive impairment-based measure) was recorded at baseline and at 1 and 3 hours post exposure. While they found no significant differences in mean gaze position between both groups at the 1-hour timepoint, they did find a significant difference at the 3-hour timepoint with spatial auditory cueing leading to reduced hemispatial inattention (η^2 = 0.039) indicating a small after-effect. They posited that spatial auditory cueing has a similar bottom-up effect as smooth pursuit eye movement

training, and their results certainly encourage using spatially dynamic auditory stimulation in future multi-sensory studies, as opposed to simple music/white noise alone.

Schenke et al. (130) carried out two pilot studies in the post-acute phase. The first assessed the effects of auditory stimulation with dynamic cueing, while the second investigated whether the addition of auditory cueing to optokinetic stimulation was beneficial. Study 1 used a group randomised design, with patients receiving three weeks of daily 30-minute sessions listening to music that appeared to travel towards the affected side. The control group received neuropsychological sessions. Line bisection was the primary outcome measure. Both groups improved, but there was a significant difference favouring the auditory stimulation group with a small effect size (0.38). In the second study, eight new patients received fifteen 30-minute sessions over three weeks, where optokinetic stimulation and a spatial auditory cueing were combined. A visual scanning test was used as the outcome measure. The within-group effect size was huge (2.25), further supporting the use of dynamic auditory cueing as a complimentary combination tool for existing therapies, although the lack of a control group in the post-acute phase means that a reasonable portion of this effect was likely due to time effects alone.

Zigiotto et al. (131) undertook a prospective, randomized, single-blinded study comparing audio-visual stimulus with prism adaptation. The audio-visual treatment group received twice daily, 20-minute sessions over 10 days in the form of a training board with light emitting diodes, and loudspeakers emitting sound. Patients were asked to follow a visual target that appeared simultaneously with a sound in the same location. The prism adaptation control group did an equal number of sessions, performing a range of 12 activities using goggles that caused a 10° rightward shift of their visual field. On star cancellation, both groups improved

with time but there was a significant time*group interaction with a between group difference in favour of the multisensory group with a medium effect size. Both groups saw a reduction in CBS scores over time, with no significant time*group interaction reported.

Dynamic auditory stimulations are a very promising addition to the therapeutic arsenal. Like other sensory stimulations that re-orient attention (e.g. caloric), it seems to have a reasonable effect in the short term. It will be interesting to see if these effects can be made to persist, perhaps by pairing the stimulation with more conventional, therapist-delivered sessions. The approach is low-tech and portable so will hopefully be included in future trials.

1.4.1.2 Robot-Assisted Therapy and Sensory Feedback

Passive and active contralesional upper limb movements, even in the absence of intentional motor programming, such as with functional electrical stimulation, have been noted to create an improvement in hemispatial inattention (132, 133). The mechanism presumably involves attentional orientation in response to sensory (light touch and joint position sense) feedback from the affected limb.

Park et al. (134) conducted an assessor-blinded, randomized controlled trial to look at the effects of robot-assisted left-hand training in older adults in the chronic phase. The experimental group performed twenty 30-minute sessions, five days a week for four weeks, of training with the Amadeo Robotic device. The control group performed conventional treatments such as visual scanning training using prism and vibration on the left neck extensors and compensatory approaches. Outcome measures included the line bisection test and the CBS. On the CBS, the experimental group showed a mean raw score difference of -4.9

points, above the minimal clinically important difference (MCID). Comparison with the control group revealed a medium effect size of 0.72 favouring the use of robotic therapy.

Karner et al. (91) used an assessor-blinded, randomized controlled trial design to evaluate the effects of a robotic baby seal called PARO, capable of moving, producing sounds and reacting to speech and touch. Patients in the sub-acute phase received a total of six 30-minute sessions over two weeks, during which they had to pay attention to PARO, who would then move further into the affected hemi-space. The control group were given a book to hold. They were read aloud to for 30 minutes. The primary outcome measure was a cancellation task. The PARO group did significantly better on this test than the control group both at the immediate post therapy time point (medium effect size) and two weeks later (large effect size).

Chen et al. (135) undertook an assessor-blinded randomized controlled trial to test the effects of exoskeleton-driven robot-assisted arm training. Patients were at the sub-acute/chronic phase border. Those in the therapy arm had a 15-minute passive session (with the exoskeleton making movements in a 3D trajectory) and a 30-minute assist-as-need mode (patients played games with audiovisual feedback). Those in the control group did visual scanning therapy, passive upper limb range of movement exercises and perceptual retraining. The total dose was 45 minutes daily, five days a week for four weeks. Outcome measures included the BIT and the CBS, with the former showing a small but significant difference that favoured the robot, and the latter showing none.

Rossit et al. (136) tested the efficacy of home-based visuomotor feedback training in a single-blinded, controlled, prospective study of patients just in the sub-acute/chronic phase. The intervention group had two experimenter-led sessions followed by 10 self-administered sessions at home over two weeks, learning a task that required them to pick up a rod at its

midpoint versus the control group who were asked to pick it up at the end. They used the BIT as their outcome measure. Both the control and intervention groups showed large improvements in their mean BIT score, and although the experimental group improved more numerically, the effect was not statistically significant.

The evidence from robotic studies is promising. Those that induce passive movements (Park and Chen) seem to work well as do those requiring interaction (PARO). While a more expensive approach, the possibility of addressing both upper limb hemiparesis and lateralised inattention at the same time is enticing.

1.4.2 Non-invasive Brain Stimulation

Kinsbourne proposed the Rivalry Theory in 1977, whereby both visual hemifields receive attentional input from the right hemisphere, whilst the left hemisphere only directs attention towards the right visual field, explaining why right hemispheric lesions cause inattention more commonly and profoundly. He also suggested that the hemispheres compete with each other, with excitatory and inhibitory intercallosal reciprocation between hemispheres to allow one side to be activated when directing attention towards the contralateral visual hemifield (137-139). This opens up the possibility of using non-invasive brain stimulation as a treatment modality in inattention, 'rebalancing' disrupted patterns of resting activity (too much on the left, not enough on the right). In recent years repetitive Transcranial Magnetic Stimulation (rTMS using a theta burst stimulation TBS), transcranial Direct Current Stimulation (tDCS) and transcranial Alternating Current Stimulation (tACS) have all been trialled.

1.4.2.1 rTMS – theta burst (TBS)

Nyffeler et al. (140) studied 60 patients in the sub-acute phase with a randomized, double-blind, sham-controlled design. The 30 patients in the rTMS group were randomised into three groups: 8cTBS, 16cTBS or sham. In this context, "cTBS" refers to continuous theta-burst stimulation, which is typically considered an inhibitory protocol, in contrast to intermittent TBS, which has facilitatory effects. The other 30 patients were controls (no TMS), but oddly their data never featured into the main analyses, so it is not clear why they were also not randomised into one of the three TMS groups. The 8cTBS group received eight sessions of theta burst stimulation (an inhibitory repetitive transcranial magnetic stimulation protocol) over the left posterior parietal cortex over two days, while the 16cTBS group got double the dose over the same time period. CBS was the primary outcome measure. The authors reported a significant improvement in the CBS after both 8cTBS and 16cTDS compared to sham stimulation with a medium effect size of 0.74 and a change in the CBS of -3.75 which is just under the minimal clinically important difference (MCID) threshold. No further improvement or decrement was noted at three month follow up. These results help establish that a TBS over two days may well be beneficial, although the change in CBS is borderline in terms of clinical relevance. There was no obvious additional benefit of the higher dose 16cTBS protocol.

Vatanparasti et al. (141) used a single-blinded, randomized controlled trial design to assess the effects of combining continuous theta burst transcranial magnetic stimulation with prism adaptation. Only 14 patients in the subacute/chronic phase were randomised into either the intervention group, who received prism adaptation and cTBS over the left posterior parietal cortex 10 sessions a day for two weeks, or the control group, who had prism adaptation and

sham TMS. Star cancellation was the primary outcome measure, but there was no significant between-group effect.

1.4.2.2 tDCS

Gorsler et al. (142) executed a well-designed proof-of-principle, randomized double-blind sham-controlled study with a cross-over design to assess the differences between unilateral and bilateral tDCS protocols. Patients at the acute/sub-acute boundary received four randomized treatment sessions, during which one of the two active or sham protocols were applied whilst having neglect therapy, with a 48-hour wash-out phase between cross-over. The Centre of Cancellation index from the Bell's test was the primary outcome but there were no significant between-group effects.

Learmonth et al. (143) conducted a group-randomized open, blinded end-point feasibility trial to compare behavioural training (picking up and balancing wooden rods at the mid-point), tDCS, and a combination of both compared to a control group (picking up a wooden rod at its rightmost end). 24 participants in the chronic phase (so only six in each group) received 10 sessions of an hour each over three weeks across four hospitals in the Glasgow area. The BIT was the main outcome, but due to a low recruitment rate, statistical analyses were not carried out. They concluded that a larger scale trial would not be feasible as too many patients were excluded due to significant co-morbidity, preventing participants from undergoing the required 10 intervention sessions.

1.4.2.3 tACS

Schuhmann et al. (98) undertook a within-subject, placebo-controlled study, to look at the effects of transcranial alternating current stimulation on 16 patients in the chronic phase.

They applied sham and high definition tACS (HD-tACS) over the contralesional posterior parietal cortex in two separate sessions on two different days with at least one day between them. They used a bespoke, computerized visual detection task which assessed unilateral neglect and extinction by presenting Gabor patches just above individualised detection thresholds. They found that after HD-tACS patients were better at detecting targets (~+10%) in their affected hemifield.

In addition to these mixed results, several controlled trials have reported encouraging effects of NIBS in neglect. For example, Cha et al. (144, 145) demonstrated improvements in neglect severity and arm function following rTMS in acute and subacute stroke, while Song et al. (146) observed beneficial effects of low-frequency rTMS on visual exploration. Positive findings have also been reported for tDCS protocols: Sunwoo et al. (147) showed that dual-parietal stimulation enhanced performance on neglect tasks, Brem et al. (148) described functional gains when tDCS was combined with cognitive training; Ko et al. (149) and Bang et al. (150) found improvements in visual scanning and feedback-guided training, respectively. A recent systematic review provides a comprehensive overview of these heterogeneous results, concluding that while NIBS is unlikely to serve as a stand-alone treatment, it remains a promising adjunctive approach worthy of further investigation (151).

While rooted in the Kinsbourne Rivalry Theory, trials of brain stimulation have generally been less successful than other approaches. TMS has a stronger evidence-base than the tDCS, perhaps because the former is considered a neuro stimulator and the latter a neuro modulator, with the implication that tDCS needs to be paired with some form of sensory stimulation or task to be effective. While all studies have to deal with the hard-to-model effects of differential damage across the spatial attentional system caused by stroke, given

the focal nature of these therapies, these effects are likely amplified. Thus, lesion-based individual differences should inform future study designs.

1.4.3 Drug therapy

Drug studies in humans were first attempted in the 1980s following on from animal lesion-based studies that suggested dopaminergic depletion could cause SN. Dopamine agonists were the first to be used (Bromocriptine) and dopaminergic drugs remain the main class to be trialled in recent years, either as a pro-drug (L-Dopa), an agonist (Rotigotine) or a reuptake inhibitor (Methylphenidate). Guanfacine, a noradrenergic alpha-2A agonist, has also been utilized.

Luauté et al. (152) carried out a well-designed study investigating Methylphenidate's effects on Spatial Neglect. The drug and placebo groups both received prism training across five sessions. There was a significant time*group interaction favouring the Methylphenidate group on their primary outcome measure, the CBS. The authors did not carry out any post-hoc tests to see which time points were driving the effect, but reviewing the data suggests that a small gain was made immediately post therapy ~1.2 points on average with further gains at 30 days when compared with the placebo group. The unstandardized change in score between the groups was small (-3.7 points). This is also reflected in the small Cohen's *d* (0.33). The authors speculated that the drug effect was independent from that of the prism training.

Dalmaijer et al. (153) used a simple, one-dose, cross-over trial design to look at the effects of Guanfacine in 13 patients in the chronic phase. Their impairment-based outcome was a touchscreen cancellation task. Because drug effects have been shown to affect both sustained attention and spatial working memory, the authors measured these at multiple time points

too. They used an interesting additional statistical approach, calculating Bayes Factors, which enabled them to estimate the probability of the null hypothesis being true. They found that Guanfacine significantly improved target cancellation scores (small effect size), but that there was no lateralised effect. Their Bayesian approach allowed them to infer from their null effects that the action of Guanfacine was not via enhanced spatial working memory, response times or executive control of searching, but could not adjudicate one way or the other on whether it was affecting sustained attention.

Swayne et al. (154) studied the effects of one week of either Rotigotine or L-dopa in an open-label, within-subject, A-B-A design. Patients were on-drug during the middle week which was compared with the two off-drug weeks either side. They found a large effect at the group level which must be tempered by the non-blinded (open label) nature of the study. There was, unsurprisingly, variation within the group, and when a binarized 'overall clinical perspective' judgement was made, only 6/10 were considered to be responders. The lack of detailed neuro-psychometric outcomes meant that it was not possible to adjudicate as to the possible cognitive mechanism(s) underlying the improved target detection. The authors suggest that the best way to tackle heterogeneity issues (responders and non-responders) is via well conducted (and blinded) N-of-1 studies, rather than taking a group-randomised approach.

In common with many of the therapeutic approaches to Spatial Neglect, drug studies suffer from low numbers of patients being treated and the potential for bias affecting published results. Despite this, drug approaches seem promising. Theoretically, they are the easiest intervention to control for in terms of having a placebo. The cognitive mechanisms of drug therapy are still unclear, with rival theories positing either a direct effect on lateralised attention or an effect on non-spatial attention or even arousal. The Dalmaijer et al. study

paves the way for addressing this by having tests of key cognitive components (sustained attention, working memory and executive control of visual search) alongside the more standard impairment and function-based outcomes. Employing Bayesian statistics to help adjudicate null findings is also a good practice, and with greater numbers of patients, will likely help resolve these issues.

Dose and timing factors remain unclear, but in the post-acute phase, and if the patients are still in hospital with access to therapist-delivered neurological rehabilitation, it makes clinical sense to have therapy blocks of at least a week. However, the greatest barrier to clinical translation is between-subject heterogeneity. What factors, anatomical or behavioural, that feed into this remain unclear. I agree with Swayne et al. that designing studies so that statistical evaluation can be carried out on individuals when both on and off drug (preferably with more than one cycle of this, so ABAB) as single-case experimental designs (SCED), is probably the best way forward. These trial designs often still allow for a between-subject or group effect analysis via either a standard Analysis of Variances (ANOVA) or a multi-SCED approach.

1.4.4 Mirror and Prism Therapies

There have been many studies using these two techniques which rely on altering visual inputs in order to redirect attention to the neglected side. Space issues preclude formal assessment of individual papers, but two recent meta-analyses summarise the current evidence well, particularly Székely et al. on the use of prisms (155). Zhang et al. performed a formal meta-analysis of five studies of mirror therapy published over the last eight years. When undergoing mirror therapy, patients practice attending to their neglected side by looking at a mirror placed perpendicularly to them and just off-centre. This reflects voluntary movements that

they make with their upper limb on their unaffected side, giving the illusion that the movements are taking place on the neglected side. The premise is that while sensory feedback from their unaffected limb might drive attention away from the affected side, the fact that they are staring into affected space and experience the illusion of seeing their affected arm move, is a more powerful lateralising attentional stimulus. Studies are usually carried out on patients who are in the sub-acute phase receiving in-patient rehabilitation. Group randomisation is used with either care-as-usual or sham therapy consisting of using a non-reflective surface for the control group. Therapy sessions are typically led by a physiotherapist, last 20-60 minutes and are given at the rate of ~five sessions a week for 3-6 weeks. Zhang et al. found large effects on impairment-based outcomes (standardised mean difference of 1.62) and functional outcomes (2.09), suggesting that the approach is effective; however, they caution that the studies all suffer from potential performance bias (participants unblinded) and there were not enough studies included to rule out publication bias.

The Székely et al. meta-analysis is the most comprehensive and definitive to date, covering 16 trials from over 20 years of work. Prisms were used by Hermann von Helmholtz in the late 19th-century as a demonstration of (transient) perceptual leaning; it was not until the late 1990s that they were used to treat lateralised inattention. Prism adaptation has three phases. In the pre-exposure phase the patient points to a visual target (usually accurately). In the exposure phase, patients are fitted with prism lenses that laterally displace the visual field *away* from the neglected side (typically by 10^{o}). They now have to point at the same targets but will miss them in the direction of the displaced image. The therapeutic component occurs in this phase as they must learn to point more *toward* the neglected side in order to reach the

target accurately. In the post-exposure phase the prisms are removed and the patient will now point with an error biased *toward* the neglected side. These after-effects soon wear off, but the theory is that the procedure induces a more lasting effect of 'spatial realignment'. The parieto-cerebellar network likely mediates this effect (156).

Across the 16 studies analysed, there was wide variability in the time since stroke from the first two weeks up to several years. Length of treatment was more standardised across studies at ~14 days but the sessions were short, with the number of pointing movements during each adaptation session being no more than 100 and the total number of sessions (across all training days) averaging at only 10. The studies were judged to have a high risk of bias using the revised Cochrane criteria, although these criteria are not designed with complex interventions in mind. They found no significant publication bias. On the impairment side the standardised mean difference was 0.24 but the 95% Confidence Interval included the line of null effect. On the CBS outcome the result was similar, a standardised mean difference of 0.26 that could not exclude a null effect.

Finally, contrasting these two approaches, it seems that mirrors are more promising than prisms, although there is likely more bias in the meta-analysis of the mirror studies. If it were the case though, what might be the explanation? In terms of what happens during therapy, I have three observations: firstly, mirror therapy studies employ a considerably higher dose measured as time-on-task than prism therapies do; secondly, in mirror therapy the patient spends all their time attending visually to the affected side, while in prism therapy the exposure phase involves shifting visual attention away from the affected side and all three phases generally involve patients pointing to both the affected and unaffected sides. Lastly, mirror therapy studies have mostly been undertaken in patients in the sub-acute

rehabilitative phase, when they are interacting with therapists as well as having their reorienting therapy. Many of the prism therapy studies are done in the chronic phase where the patients may well be having little or no ongoing therapist-delivered rehabilitation.

1.4.5 Eye Movement Therapies

Eye movements have been shown to interplay with spatial attention, both at a behavioural and an anatomical level (101). The precise relationship between the two is complex, with different studies exploring which element guides the other. In 1987, Rizzolati et al. proposed the premotor theory, suggesting that spatial attention was a subthreshold, preparatory step preceding an eye movement, covertly shifting locations when the saccadic program was ready to be activated (102). Several bodies of work since have demonstrated that saccades do not require a compulsory shift in attention in order to be executed. Rather, it has been shown that they are dependent upon the allocation of attention on a region of interest (101). Indeed, stroke patients with Spatial Neglect failed to make saccades in the contralesional hemifield, and those who did required a higher number of smaller saccades to reach the target, with prolonged latencies (103). Anatomically, the superior colliculus acts as a conduit of sensory and motor signals to the cortical and subcortical areas responsible for eye movement control (104), whilst the intraparietal sulcus in the dorsal posterior parietal areas, an area around the frontal eye fields, the right temporoparietal junction and the ventral frontal cortex are involved in the various types of control of attention (31). Deficits of function in the superior colliculus can be compensated for by the frontal eye fields, and vice versa (105, 106).

This close relationship between spatial attention and eye movements, and neuro-anatomical interplay, forms the basis for eye movement based therapies for the treatment of visual inattention. Saccadic eye movements, which are fast velocity (400-800°/s) movements, serve

to move the fovea on to areas of interest (107). They are trained via Visual Scanning Therapy, a compensatory approach that aims to increase the patient's field of view by making them scan arrangements of visual stimuli on the affected side (108), thereby operating via a "bottom-up" information processing method. Saccadic eye movement control involves communication between the occipital, parietal, frontal lobes, and the basal ganglia, superior colliculus and the interconnected nuclei in the reticular formation (109). In contrast, smooth pursuit eye movements, which are of slower speeds (30-100°/s), are responsible for tracking moving targets (110). Patients are asked to follow a moving target into the affected hemispace, reorienting attention towards the affected side, making this a "top-down" process (111), given the prediction required to map the trajectory of moving stimuli.

Smooth pursuit eye movement training significantly improves SN, even in the acute phase post-stroke (112). Smooth pursuit therapy (which relies on inducing involuntary eye movements) is superior to a sham visual training therapy that requires voluntary eye movements (113-115). These therapies have only been delivered using standard, two-dimensional screens (e.g. laptops), but a recent review suggests that immersive VR may be more effective (116). In the last few years, VR approaches have been trialled, though none so far have been able to demonstrate evidence of creating lasting improvements to SN, thereby limiting their adoption as a treatment for the condition.

Several groups have investigated smooth pursuit training and screen-based, ie, *non-immersive VR tasks* as therapeutic strategies for visual neglect. These paradigms typically require patients to follow continuously moving targets across the visual field, thereby engaging oculomotor orienting, enhancing contralesional exploration, and potentially recalibrating spatial priority maps. Studies have reported improvements on standard paper-

and-pencil tasks such as cancellation and line bisection, as well as gains in visual exploration (e.g., Kerkhoff et al., (113); Pizzamiglio et al.(157), Rabuffetti et al., (158)).

With regards to immersive VR, a few studies have been conducted, but none that incorporate smooth pursuit eye movements. Elshout et al. (117) undertook a proof-of-concept, single-blinded, group randomized controlled trial, comparing congruent movement training to visual scanning training alone in patients in the chronic phase. Stimuli (filled, coloured circles) were presented on a 2D screen. The congruent movement training group had to find certain circles and touch them while the control group only made eye movements and reported how many circles of a certain type that they could see. They practiced ten 30-minute sessions for a total of 5 hours. The researchers, rather unusually, created a composite outcome score from two cancellation tests and the CBS. There was a statistically significant difference between the groups on this measure although it was in part driven by the visual scanning group's score getting worse. The effect size was medium, giving some support to the idea that reaching with both a limb and eyes is superior to reaching with eyes only.

Yasuda et al. (118) trialled a single-shot (30 minutes) immersive Virtual Reality (iVR) intervention using a within-subject, order randomized, pre-post design with no control task or blinding. 10 patients in the chronic phase took part, performing both near (a reaching task) and far space (a visual search task) training. They used the Behavioural Inattention Test (BIT) as their main outcome measure. Rather oddly, they performed no statistical tests of the interaction between space (near vs. far) and time (pre vs. post), instead reporting that the BIT increased significantly for the far training only and not near training. Even taken at face value, these results provide only weak evidence that visual scanning training may be beneficial. The VR was well tolerated by patients.

Choi et al. (119) conducted a single-blinded randomized controlled trial of 24 patients in the chronic phase. The therapy group performed 10 different tasks on the Oculus Rift iVR device at a rate of three 30min sessions a week for four weeks. The control group underwent conventional unilateral Spatial Neglect training for the same time period. After training, the mean CBS scores between the two groups did not significantly differ. The authors chose to focus on a bespoke outcome measure that did differ between the groups, the Motor Visual Perception Test – Vertical version. It comprises five impairment-based tests, but removes any horizontal bias, so the iVR did not influence lateralised attention at all.

Eye-movement based therapies remain one of the most popular approaches to treating visuospatial inattention. iVR seems a very promising technique that can treat patients with stimuli not limited to the width of a computer screen. Studies so far suggest that it is well tolerated, even in the acute phase (120). It is a bit surprising that these three iVRrecent studies all relied on inducing voluntary guided saccades as smooth pursuit methods have been shown to be more effective (113). While protocols vary in duration and stimulus characteristics, the findings from the non-immersive VR studies suggest that pursuit-based training is feasible, well-tolerated, and may generalise beyond the trained task. The ATTEND trial (Experiment Chapter II) builds directly on this evidence, employing a structured pursuit-based paradigm delivered in a VR framework to maximise intensity and ecological validity.

	Author, year	Subjects in therapy group	Drug and training interventions	Key outcome measures	Results and where available, significant differences, effect sizes, raw and standardised (Cohen's *d*)
Visual Scanning and Congruent Movement Training	Elshout et al 2019	**Single blind, group randomised** **CMT group** N = 15, Age = 59.2, TSS = 102.6 days **Visual Scanning Training** N = 15, Age = 58.7, TSS = 76.8 days	Congruent Movement Training (simultaneous eye and hand movements to same location in the affected hemifield) 10 sessions of training, 30min per session, parallel to standard rehabilitation programme. VST control group Patients instructed to make eye movements to the affected hemifield to detect a specific stimulus	Shape cancellation Line bisection task Catherine Bergego Scale	**Composite score across two cancellation tasks and CBS** *CMT group* Mean difference = -5.8 points *VST group* Mean difference = +2.5 points Cohen's *d* = 0.53 (medium)
Immersive HMD VR	Yasuda et al 2017	**Within-subject, order randomized, pre- and post- design with no control or blinding** N=10, Age=70.6, TSS= 149.3 days All patients had both "near" and "far" neglect	Oculus Rift DK2 with Leap Motion, Unity 5, far and near space training 30-minute session with each tasking running for 4 min at a time with an interval of 30 s rest between them	Line cancelation task Star cancelation task Line bisection task Letter cancelation task Timepoints: Pre and immediately post test	**Star Cancellation (median)** Near group difference = -3 stars Far group difference = +2 stars

Immersive HMD VR	Choi et al 2021	**Single-blind, randomized controlled** **Digital practice group** N=12, Age = 63, TSS= 4.33 months **Control group** N=12, Age = 61.58, TSS= 4.58 months	Oculus Rift with Leap Motion, 10 different tasks (Blocks, Element L, Warlock, Laser, Pinch Draw, RPS island, VT table tennis). 4-week practice program, 3 sessions/week, a half-hour/session Control group underwent conventional USN specific training for 30 minutes, 3 times a week for 4 weeks, for total of 12 sessions	Line Bisection Test Catherine Bergego Scale Modified Barthel Index Motor free Visual Perception Test Vertical Version Head Rotation Timepoints: Pre and Post test	**Catherine Bergego Scale:** No significant between group effect.
Immersive VR	Hugelier et al. 2020	**Feasibility Study** N=7, Age=44 – 69 years	VR game with 3 scenes, lake, garden and forest, presented at 3 different times of day (lighting effects). Cue was presented that predicted the location of a target. Patient had to press a button that corresponded to the target when it was presented, whilst receiving auditory and visual feedback	Cybersickness questionnaire Assessing correspondence between a computerized cancellation task and VR-based rehabilitation task	Paper presented view that this rehabilitation game was a promising tool for detecting SN and improving performance in orienting attention to affected side
Non-Immersive VR	Kim et al. 2015	**Within-subject, randomized design with subsampling** N=14, Age=73.1	Line bisection task done under several conditions: (i) screen - OKS: Observing a stationary horizontal red line on an LCD screen; (ii) screen+OKS: the red line is presented with background blue OKS moving leftward; (iii) HMD - OKS; (iv) HMD+OKS.	Line Bisection Task	OKS on LCD only: Overcorrected the SN and outperformed HMD OKS+HMD: more effective in decreasing rightward deviation. Leftward HMD+OKS: better correction of rightward deviation toward the midline, lesser distraction

Non-immersive VR	Faria et al. 2016	**Randomized controlled trial** **Experimental group** N=9, Age 48 - 71 years **Control group** N=9, Age 50 - 65 years	Virtual 3D city displayed on a computer screen Experimental group: Completed tasks with increasing challenges in a post office, a bank, a pharmacy, a supermarket Control Group: Performed a traditional cognitive rehabilitation	Addenbrooke Cognitive Examination Trail Making Test A&B, Picture arrangement from WAIS III Stroke Impact Scale	Experimental group: Improved on global functioning, attention, memory and visuospatial abilities, executive functions, social participation, emotion, and in the physical domain. Control group: Worsened in verbal fluency; improved in attention and processing speed
Non-Immersive VR	Fordell et al., 2016	**Within-subject clinical trial in chronic SN after stroke using pre- and post-design** N=15, Age=72.8	Visual scanning training on a computer monitor using 3D glasses and a robotic pen 5-weeks baseline followed by a 5-weeks training (3 h weekly, 15 h total)	*Star cancellation test* *Baking tray task* *Line bisection* *Extinction* *Posner task – reaction time unified index* *Catherine Bergego Scale*	Significant differences on Star Cancellation Test Mean difference -6.43 Significant differences on baking tray task Mean difference 16.1 CBS significant differences post training and at 6-months on patient self-scoring
Non-immersive VR	Glize et al., 2017	**Proof of principle study** **Patient Group:** N =7; Age=65.5 **Control Group:** N=10; Age=63.3	Virtual supermarket projected on a 60” screen in a dark room Prism Adaptation in a VR task Navigation task in virtual supermarket to find items placed on the left and right. 45-minute session. Prism Adaptation session lasting 10-20 minutes, 10 sessions over 2 weeks	6 parameters measured in the virtual supermarket including distance, duration of session, number of items purchased/omitted/side preference, number of pauses Drawing from recall	PA reduced the rightward attentional bias in a VR task, enhanced both navigation and topographic memory; improvements persist after a 1-month follow-up

Non-Immersive VR	Tobler-Ammann et al., 2017a	**Feasibility study, quasi-experimental pre-post design, uncontrolled** N =7, Age 64–78, TSS=15-180 days	9 exergames simulating real -life tasks like cooking, puzzle completion on a computer monitor Five 30- to 45-min sessions per week, over 3-weeks	Eye Tracker Neglect Test (ETNT) Zürich Maxi Mental Status Inventory (ZüMAX) Neglect Test (NET)	Primary outcome establishing safety and feasibility Secondary outcome showing improvement in cognitive and spatial exploration skills
Non-Immersive VR	Ekman et al., 2018	**Within-subject, pre- and post-design** N = 12, Age=72.7	Eye scanning task following an arrow from left to right, and then pressing a button when a target flashed on either side Two 30-min sessions with a 15-min break, including 5 min of listening to music before audio-spatial training. Patients performed 3 training sessions each week, 5 weeks total	fMRI performed 1 week before and 1 week after the VR training, and performed Posner cueing during the fMRI scan Behavioural performance measures on Posner cueing task	Increased BOLD signal on fMRI in cortical regions beyond the ventral and dorsal attentional networks
Non-Immersive VR	Wahlin et al. 2019	**Within-subject, pre- and post-design** N=13, Age=73, TSS = 43 days	5-weeks training (3 h weekly, 15 h total) with the same set-up used in the Fordell et al study	2 fMRI scans, one week before and one week after intervention; performed Posner task during scan	Increased DAN inter-hemispheric functional connectivity in patients affected by chronic SN. Increased integration of the frontal eye fields

Non-Immersive VR	Cogne et al. 2020	**Exploratory, prospective, controlled, and randomized trial** **Patient group with SN and auditory neglect post-stroke** N=22, Age=65.8 **Patient group without SN and auditory neglect post-stroke** N=14, Age=63.9 **Healthy controls** N=12, Age=67.6	3D virtual environment of a town displayed on a laptop; eye tracking done using a Tobii Pro Tx eye tracker Randomized to 1 of 3 conditions: (i) "without auditory cues" (ii) "with auditory cues" (iii) "auditory cues after prism adaptation"	Primary Outcome to test effect of auditory cues on spatial navigation Secondary task of free recall and recognition of landmarks Tertiary outcome to assess eye saccades and gaze dwell times	Summary of Results: Primary outcome – auditory cueing had a positive effect on spatial navigation in affected patients; increased benefit from Prism adaptation Secondary outcome – auditory during decreased spatial memory; compensated by adding the prism adaptation Tertiary outcome; increased dwell times following prism adaptation
Audio	Kaufmann et al. 2022	Experiment 1 (looking at short term effects of auditory stimulation with and without auditory spatial cueing) **Cross over, repeated measures, randomized and single-blinded** N=9, Age=64.78, TSS=22.67 days Experiment 2 (looking at 1- and 3-hour aftereffects of auditory stimulation with and without auditory spatial cueing) **Single-blinded, repeated-measures, cross-over design** N=12, Age=73.17, TSS=19.08 days	Experiment 1: listening to preferred music with or without auditory spatial cuing for 10 min, once a day, two days. Experiment 2: listening to preferred music with or without auditory spatial cuing for 15 min, once a day, two days.	Experiment 1: Letter Cancellation Test Experiment 2: Free view exploration All the patients in 2 experiments: Voxel based lesion symptom analysis	**Experiment 1** *With auditory spatial cueing:* Mean change = -0.264, SD = 0.237 *Without auditory spatial cueing:* Mean change = -0.106, SD = 0.107 Cohen's *d* = 0.85 (large) **Experiment 2** Mean gaze position between both groups at the 1-hour time point p=0.500 Mean gaze position with spatial cueing group at 3-hour time point p=0.045 eta square = 0.039

Audio and Multisensory (Audio+OKS)	Schenke et al 2021	Experiment 1 (dynamic auditory cueing) **Double-blinded, historical control group** N=11, age = 69.2, TSS= 35.4 days Control group N=14, age= 67, TSS=42.1 days Experiment 2 (multisensory) **Double-blinded, no control** N=8, Age = 59.8, TSS= 36.5 days	15 sessions of 30 minutes over 3 weeks Experiment 1: Dynamic auditory cuing Experiment 2: Combined therapy dynamic auditory cues and optokinetic stimulation (patients observe contralateral motion of visual patterns or targets on a screen and execute active and smooth pursuit eye movement towards the direction of the motion) Control group had general neuropsychological therapy	Experiment 1: Line Bisection Test Apple Test Timepoints Experiment 1: Baseline T1 (day 1), T2 (day 4 - just before intervention), T3 (day 25 - post 3 weeks of therapy), T4 (day 28 - intervention group only) Experiment 2: Visual Scanning of the Test Battery for Attentional Performance Timepoints Experiment 2: Baseline T1 and T2, then T3 post intervention	Experiment 1: **Line Bisection Test** Between group effect size at T1-T3 Cohen's *d* = 0.38 (small) Experiment 2: **Mean number of omissions on the left** T1 to T2 Cohen's *d* = 0.39 (small) T1 to T3 Cohen's *d* = 2.25 (huge)
Multisensory – Audio Visual versus PA	Zigiotto et al 2020	**Prospective, randomized, single-blind** **Treatment group** N=10, Age=71, TSS=3.82 months **Control group** N=10, Age=67.1, TSS= 5.33 months	Multisensory treatment: Bimodal audio-visual stimulation of visual field using Visual Field Trainer Control group: Prism Adaptation (goggles causing 10° rightward shift of the visual field) whilst doing a variety of 12 activities Both – 10 working days, 2x20 minutes sessions	Star Cancellation Bell Cancellation Letter Cancellation Line Bisection Five Element complex Drawing Sentence Reading Personal neglect Catherine Bergego Scale Timepoints: x2 baseline T1 (day -7 - one week before starting) and T2 (day 1 - on day of 1st treatment, prior to starting), T3 (day 6 - end of 1st week of training and before starting training on the 6th day, T4 (day 11 - end of second week of treatment). Subgroup had 1 month follow-up	**Star Cancellation** Between group mean difference = 46% Cohen's *d* = 0.71. (medium)

Robot-Assisted Therapy	Park et al 2021	**Assessor blinded, randomized controlled** **Experimental group** N=12, Age=69.08, TSS 9.5 months **Control group** N=12, Age=71.58, TSS 9.08 months	Both groups did conventional treatments such as visual scanning training using prism and vibration on the left neck extensors and compensatory approaches. Experimental group did 20 sessions (five days a week for four weeks) of robot-assisted hand training using the Amadeo Robotic device, each session lasting 30 minutes	Line bisection test Albert test Catherine Bergego Scale Timepoints: 1 pre and 1 post	**Catherine Bergego Scale** *Within subject results* *Experiment group difference* = -4.92 points on the CBS *Control first group difference* = -1.25 points on the CBS Between group Cohen's *d* = 0.72
Robot-Assisted Therapy	Karner et al 2019	**Assessor blinded, randomized controlled** **PARO group** N=21, age=74.21, TSS= 49 days **Control group** N=18, age=73.34, TSS= 55 days	Patients were treated for two weeks on three days per week, resulting in six sessions per patient. The duration of the individual intervention, including data collection, was 30 minutes, where the PARO robot was placed on the neglected side and patient had to grasp it. As control intervention, patients were read aloud from a book for the same time as the PARO intervention.	1^{o}: Cats Test Line Bisection Test Scores of Independence Index for Neurological and Geriatric Rehabilitation Timepoints: T0 (baseline), T1 (after the two weeks of interventions), T2 (after an additional two weeks as a follow-up)	**CATS test** Between group effect size: T0 to T1 Cohen's *d* = 0.70 (medium) T0 to T2 Cohen's *d* = 0.99 (large)

Robot-Assisted Therapy	Chen et al 2021	**Assessor-blinded, prospective, pilot randomized controlled trial** **Therapy Group** N=10, Age=46.2, TSS=97 days **Control Group** N=10, Age=48.6, TSS=86.4 days	Therapy group: 15-minute passive session (with the exoskeleton making movements in a 3D trajectory) and a 30-minute assist-as-need mode (patients played games with audiovisual feedback) Control group: Visual scanning therapy, passive upper limb range of movement exercises and perceptual retraining. Total dose was 45 minutes daily, 5 days a week for 4 weeks	Behavioural Inattention Test Catherine Bergego Scale	**Behavioural Inattention Test** Between group difference = +7.7 Cohen's *d* = 0.24 (small) **Catherine Bergego Scale** No significant between group effect.
Home-Based Visuomotor Feedback Training	Rossit et al 2017	**Single-blind, controlled prospective study** **Intervention group** N = 9, Age = 65.6, TSS= 3.1 months **Control group** N = 9, Age = 64.9, TSS= 3.2 months	Training delivered for two sessions of 30 minutes each by an experimenter and then patients self-administered it for 10 sessions over two weeks, asked to pick a rod at its midpoint versus at a corner by the control group	Behavioural Inattention Test (BIT) Line bisection Balloons Test Landmark task Room description task Subjective straight-ahead pointing task Stroke Impact Scale Timepoints: At baseline, after 2 experimenter-led sessions, after 10 self-led sessions, follow up at 4 months	**Behavioural Inattention Test score** *Intervention Group* No significant between group effect.

Non-invasive Brain Stimulation: rTMS theta burst	Nyffeler et al 2019	**Randomized, double-blind, sham-controlled** **8cTBS Group** N = 10, Age=67.8, TSS=26.8 days **16cTBS Group** N = 10, Age=74.3, TSS= 22.9 days **Sham Group** N = 10, Age=70.6, TSS= 25.8 days	3 groups: (1) Sham group (2) Continuous theta burst, 8cTBS trains (3) Continuous theta burst, 16cTBS trains	Catherine Bergego Scale Timepoints: T0 (first week after admission to the clinic for stimulation), T1 (in the last week before discharge) and T2 (at follow-up 3 months later)	**Catherine Bergego Scale** *Compared to sham stimulation, CBS score lower for both groups (no significant difference between 8c and 16c)* Average mean difference -3.75 Average Cohen's *d* = 0.74 (medium)
Non-invasive Brain Stimulation: rTMS theta burst	Vatanparasti et al 2019	**Single-blinded, randomized controlled** **PA+cTBS group** N=7, Age=67.5 **PA+sham group** N=7, Age=65.5	Intervention group: Prism adaptation and cTBS over the left posterior parietal cortex for 10 sessions a day, for 2 weeks Control group: Prism adaptation with a sham TMS	Star cancellation test Line Bisection Task Figure Copying Test Clock Drawing Task Timepoints: At baseline and at the end of the 2 weeks	**Star Cancellation Test** No significant between group effect.

Non-invasive Brain Stimulation: tDCS	Gorsler et al 2022	**Proof-of-principle, randomized double-blind sham-controlled, cross-over design** N=11, Age=71, TSS=32 days	Four factorialised treatment sessions: active vs. sham crossed with unilateral vs. bilateral tDCS over the parietal region. 48-hour wash-out phase between blocks. 4 sessions (each session separated by 2 days) of 20 minutes of tDCS or 30 seconds of sham stimulation given whilst patients did a 20-minute computerized visual exploration or saccadic eye movement training task	Centre of Cancellation index from the Bell's test Timepoints: T1 (screening), T2 (baseline) and T3 (after completion of all 4 sessions)	**Centre of Cancellation** No significant between group effect.
Non-invasive Brain Stimulation: tDCS	Learmonth et al 2021	**Prospective randomized open blinded end-point feasibility trial** **Behavioural training** N=6, Age=66.8, TSS=376 days **tDCS** N=6, Age=66, TSS=469.3 days **Combined intervention** N=6, Age=70.5, TSS=390.5 days **Control group** N=6, Age=60.5, TSS=583.3 days	4 groups: (1) Behavioural training: Picking up and balancing wooden rods at the mid-point (2) tDCS (3) Combination of both (4) Control group: Picking up a wooden rod at its rightmost end 10 intervention sessions, with stimulation or training delivered for 15 minutes (overall target period 3 weeks)	Primary Outcomes: Rate of recruitment Retention Compliance Secondary Outcomes: Line bisection test Behavioural Inattention test Timepoints: T1 (at baseline), T2 (after 3 weeks), and T3 (at 6-month follow-up)	**Behavioural Inattention Test (raw means)** *Behavioural training* T1=115, T2=130.4, T3=123 *tDCS* T1=105.17, T2=119.33, T3=136.20 *Combined intervention* T1=103.00, T2=126.20, T3=130.33 *Control group* T1=123.67, T2=130.20, T3=135.00

Non-invasive Brain Stimulation: tACS	Schuhmann et al 2022	**Proof-of-concept, within-subject, placebo-controlled** N=13, Age=57.8, TSS=87.4 days	All subjects underwent one session each of 10Hz alpha stimulation, and the sham stimulation whilst doing a computerized visual detection task lasting 10 minutes, Bell's Test and Line Bisection test 2 separate sessions (one of 10Hz alpha stimulation, and one of sham stimulation) with at least one day between sessions, stimulation lasting for a maximum of 30 minutes	Computerized visual detection task: involves assessing unilateral neglect and extinction by presenting Gabor patches just above individualised detection thresholds. Timepoints: 3 tasks done before, during and after each stimulation session	**Computerized Visual Detection Task:** Average mean difference 4.1/40 trials Average Cohen's *d* = 0.92 (large)
Drug Trials	Luauté et al. 2018	**Double-blind, group randomised**: Stratified by recruitment centre and severity of neglect **Methylphenidate group:** N = 13; age = 59; TSS = 3.7mo; severity = M9, S4. **Placebo group:** N = 8; age = 56; TSS = 5.2mo; severity = M4, S4.	Both groups received **prism training** (10^{o} rightward shift) 5 sessions of 50 pointing responses to visual targets (2-5mins). **Methylphenidate group**: 10mg BD PO for 5 days.	1^{o}: CBS 2^{o}: star cancellation, FIM (functional independence measure). Time points: 2 pre and 3 post (immediate, 7d and 30d post)	**Catherine Bergego Scale** Group*time interaction (p=0.0204) Group difference = +3.7 on CBS Cohen's *d* = 0.33 (small)
	Dalmaijer et al. 2018	**Double-blind, within-subject, order randomised, cross-over design:** N = 13; age = 63; TSS = 12.5mo; severity = M9, S4.	Subjects received a single dose of **Guanfacine** 2mg and a single placebo on day 2/ day 4 of the study.	1^{o}: Cancellation test 2^{o}: sustained attention and working memory test. Time points: days 1 (pre), 3 and 5 (post)	**Cancellation test** (no. of targets): drug vs. placebo (p=0.013) Drug difference = +5 targets (out of 64) Cohen's *d* = 0.34* (small)
	Swayne et al. 2022	**Case series, single-case, open label experimental design** (ABA): N = 10; age = 56; TSS = 8.6mo; severity = M7, S3.	N = 3 **Rotigotine** transdermal 4 mg/24 hr. N = 7 **Co-careldopa**, 100/25 mg TDS. Off-On-Off design with each block lasting a week.	1^{o}: Cancellation test % of stars cancelled to affected side.	**Cancellation test** (% of targets): drug vs. placebo (p=0.004) Drug difference = +27% targets on affected side Cohen's *d* = 2.1* (large)

Table 4: Summary table of treatments for SN
Summary of the participants, study design, intervention, outcome measures and effect sizes of SN treatments. BD = twice a day, CBS = Catherine Bergego Scale, M = moderate neglect, mo = months, N = number, PO = by mouth, S = severe neglect, TDS = three times a day, TSS = time since stroke. NB: acute = < 1month post-stroke; post-acute = >1 month but <3 months, (likely on a rehab unit); chronic = >3months (likely in the community).

Overview of this Thesis

Following on from the Introduction, this thesis is hereafter divided into three Experimental Chapters, a General Discussion and Limitations and Future Directions.

Each Experimental Chapter covers a study that I conducted as part of this PhD, with its own Focused Introduction, Methods, Results, Discussion and Limitations and Future Work sections.

Experimental Chapter I is based on the FiVE in the Vive, a free visual exploration task developed to be used within Virtual Reality. I will explain a novel statistical technique that I developed to analyse gaze duration data, and present the results of a patient versus healthy controls study performed to establish its sensitivity, with a dedicated discussion.

The ATTEND Trial is presented in Experimental Chapter II. In this chapter I will cover the details of the group-randomized controlled trial and its methods, present and discuss the findings for the Therapy and the Control Groups, at the end of 3 weeks of VR Stimulation, and at 3 month follow-up, for the various outcome measures employed.

In Experimental Chapter III, I will present the findings from an exploratory study performed on the Sustained Attention to Response Task outputs collected from a proportion of the patient cohort of the ATTEND trial, and the healthy controls from the FiVE in the Vive study, highlighting key differences between the two groups, and significant correlations found between SART outputs and changes in the impairment-based outcome measure for the patient group, as possible predictors of improvement.

In the General Discussion chapter, I will summarize key findings and discuss overarching themes that emerge from the Experimental Chapters.

Finally, I will highlight key limitations and future directions to conclude this thesis.

2.0 Experimental Chapter I

Five in the Vive: Applying Statistical Parametric Mapping to Free Visual Exploration as a Novel Method for the Assessment of Spatial Neglect

2.1 FiVE in the Vive: Developing a Novel Method

Traditionally, the techniques employed to assess Spatial Neglect (SN) have included pencil-and-paper based assessment tools and neuropsychological behavioural testing. Namely, the Star Cancellation Test, the Line Bisection Test, the Letter Cancellation Test, the Catherine Bergego Scale, and the Behavioural Inattention Test are amongst a few of the commonly used tools (covered in the Introduction), which have been utilized, often in combination with clinical examination to increase the sensitivity (159) of diagnosing SN in a timely manner.

The former lack ecological validity, as they fail to fully replicate real-world conditions and often overlook subtle deficits (58). Similarly, behavioural functional testing tools can be limited in their sensitivity to mild SN and their reliance on subjective interpretation, which may introduce variability in results (59). There also exists an element of between-test variability and detection of SN may vary depending on the test administered (160). There remains therefore, a dearth for a selected gold standard assessment test for SN.

Using eye movement tracking to better understand human cognitive processes has been in use for over a hundred years, but it is the advent of real-time video-oculography that has led to an explosion in clinical and research applications of free visual exploration over the last few decades. Today, eye tracking frequency can be recorded at 50 Hz up to 2000Hz with some trackers, leading to large datasets for even relatively short experiments.

Eye movements recorded during eye-tracking allow for the assessment of gaze behaviour, based on the following variables: saccades (rapid eye movements that relocate the eyes to a new target in the environment), fixations (the time interval spent on a certain target between

saccades) (161) and dwell times (a summation of the time spent within the co-ordinates marking a single area of interest) (162).

Modern computer software can output this data in a variety of formats, such as in the form of scan paths (usually denoted by lines connecting subsequent gaze fixations) (163), gaze plots (represented by circles marking the position of a fixation, with the radii of the circles signifying the time spent at each fixation) (164), and heat maps or attentional maps (which display the spread of visual attention, aggregating the frequency of fixations) (165, 166).

However, to date, there has been no method for producing ***spatially extended statistical maps of eye movement data***. In this study, I attempted to develop a novel system that applies Statistical Parametric Mapping software to analyse gaze duration data derived from a custom-built, free visual exploration software called the FiVE in the Vive (FVE). I have utilized this approach on 2D gaze duration or dwell time maps, but it could equally be applied to 3D data.

2.1.1 A Statistical Approach to the Assessment of Gaze Duration Data

Statistical parametric mapping (SPM) software has been used since the early 1990s, enabling neuroscientists to test spatially extended hypotheses using functional imaging data. Its introduction allowed researchers to move away from region of interest analyses, which were conducted by averaging neuroimaging data over pre-specified brain regions, and instead make valid inferences about responses anywhere in the brain.

In this study, I applied the same principles to gaze duration maps, i.e. visual fixations. SPM is mostly employed within a 3D brain volume made up of many thousands of identically shaped cubic elements (i.e. voxels). By contrast, our eye-tracking data is 2D and covers the visual field occupied by pictures displayed within a virtual reality headset; however, the statistical

approach is identical. This consists of applying linear regression at each pixel of the images being analysed, to yield a statistical map. A correction for multiple comparisons across pixels is then applied, using an approach that derives from the field of topology, called Random Field Theory. The statistical foundations and software for performing these analyses are well established and thoroughly validated, but have never been applied to gaze duration maps, until now.

2.1.2 Image Saliency

An important concept to address when using images and video-oculography to assess the presence of spatial bias, is that of visual saliency. Salient features on an image are areas of perceptual prominence that garner more attention, and therefore would be expected to have more fixations, with initiation of saccades and shifts of attention towards themselves (167). The study of gaze fixation density maps, which reflect the likelihood of pixels in an image being viewed by human observers, reveals that salient areas on an image tend to be those that are rich with structural information, and that each image will only have a limited area which has a high saliency value (168).

In our study, it was important for us to devise a method to negate the salient features in the images presented, to prevent their influence on any spatial bias. To control for intrinsic, lateralised bias in the 12 images I used to generate the 2D dwell maps, I created a laterally flipped or 'mirror' image for each one. The series of 12 pairs of images, with each pair comprising the original image and its mirror image counterpart, were presented to the participants in a pseudorandom order, to prevent a pair appearing consecutively. No images were repeated to prevent scan path repetition, and the instruction given, as detailed in the next section, promoted a bottom-up style free visual exploration of naturalistic scenes. I

devised a subtraction approach adopted within SPM to negate the salient features, which will be covered within Methods.

2.2 Aims of the Study

Does this novel approach demonstrate statistically interpretable spatial bias in patients with SN post-stroke, when compared to healthy controls?

This was a between-subject group level comparison based on gaze duration data acquired from a free visual exploration task performed at pre-intervention baseline by a proportion of patients who were recruited into the ATTEND trial (Experimental Chapter II in this thesis), and healthy controls matched for age and sex.

2.3 Methods: Participants

Two groups of participants were recruited (see **Table 5**).

Stroke Participants													
ID	Age	Gender	Time since stroke (Days)	Side of SN	Total Stars Baseline	Left	Right	Laterality Index	Total Stars post-intervention	Broken Hearts Space Asymmetry	CBS Baseline	FiVE in the Vive x-coordinate at Baseline	FiVE in the Vive x-coordinate post-intervention
CT01	53	F	17	Left	43	19	24	**0.44**	54	-	9	31	26
CT02	61	M	77	Left	**27**	1	26	**0.03**	34	**12**	**15**	26	19
CT03	51	M	128	Left	**22**	5	17	**0.22**	41	**11**	**16**	21	22
CT05	45	F	21	Left	**31**	15	16	**0.48**	54	**11**	**20**	20	16
CT07	70	F	37	Left	**33**	7	26	**0.21**	54	**9**	**14**	22	21
CT08	59	F	45	Left	45	20	25	**0.44**	50	0	**17**	15	14
CT09	69	F	45	Left	49	24	25	0.48	54	**6**	**14**	23	22
CT11	64	M	84	Left	**20**	1	19	**0.05**	46	**15**	9	24	14
CT12	72	M	32	Left	**20**	0	20	**0**	54	**26**	**12.5**	20	14
CT13	63	M	8	Left	**6**	0	6	**0**	14	**22**	**14.4**	22	22
CT14	74	M	26	Left	**37**	10	27	**0.27**	52	**7**	**26**	24	18
CT15	78	F	56	Left	**15**	0	15	**0**	41	**4**	**11.25**	27	31
CT16	82	M	43	Left	**34**	13	19	**0.40**	27	**15**	6	19	19
CT17	54	F	69	Left	**25**	4	21	**0.16**	46	**15**	9	21	17
CT18	34	F	101	Left	**7**	0	7	**0**	30	**11**	**17**	28	18
CT19	69	M	174	Left	**13**	0	13	**0**	20	**7**	**14**	19	25
CT21	67	F	30	Left	**8**	0	8	**0**	52	**19**	**27**	20	18

The patient group included 17 patients with stroke (53% female), mean age 62.46 years (SD 12.33 years). They were all inpatients, having been admitted either to an Acute Stroke Unit or a Neuro-Rehabilitation Unit in one of 4 centres, including the National Hospital for Neurology and Neurosurgery, the Charing Cross Hospital, the St. Pancras' Rehabilitation Unit, and Luzerne Hospital, Switzerland. These patients had been identified by the multi-disciplinary teams as suffering from SN, as part of the recruitment process for a phase II randomized controlled trial called the ATTEND trial, which is covered in Section 3.0. The inclusion criteria were: (i) 18 years or older; (ii) any type of acute stroke; (iii) evidence of clinically significant SN; (iv) able to tolerate use of VR hardware and software; (v) willing and able to provide written informed consent.

The second group included 23 age-matched healthy controls (65% female), mean age 68.96 years (SD 9.56 years). They were recruited through advertising via the Institute of Neurology mailing lists and adverts distributed to attendees at the World Stroke Day Forum held in October 2022. The inclusion criteria were: (i) no previous history of stroke; (ii) no ophthalmological issues.

Both groups were matched for age, $p = 0.8$ and for gender, $p = 0.433$. All the stroke patients included were noted to suffer from left-sided SN.

2.4 Screening

The presence and severity of SN was formally assessed using the following screening tools:

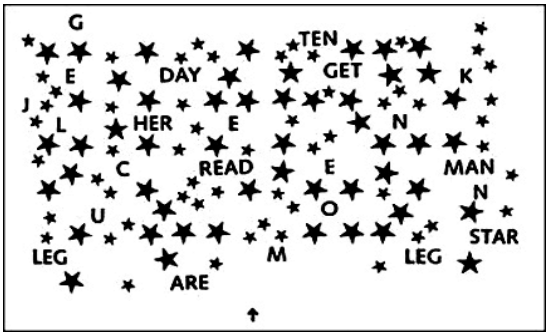
(1) clinical examination

(2) two impairment-based cancellation tests: (a) the Star Cancellation Test; (b) the Broken Hearts Test (the latter taken from the Oxford Cognitive Screen)

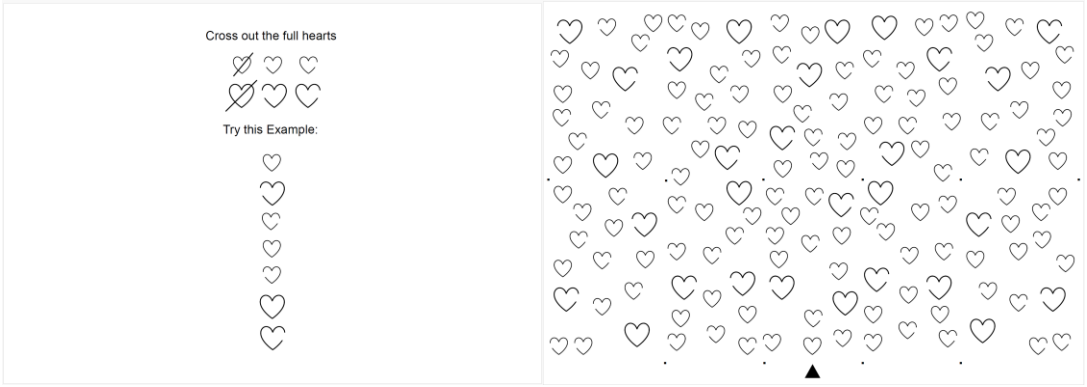
(3) a functional-based test - the Catherine Bergego Scale (scored by the patient's Occupational therapist).

The screening tests have been extensively covered in Section 3.0, and briefly summarized here in Figure 4.

(a)



(b)



(c)

	0	1	2	3
1. Forgets to groom or shave the left part of his/her face	❑	❑	❑	❑
2. Experiences difficulty in adjusting his/her left sleeve or slipper	❑	❑	❑	❑
3. Forgets to eat food on the left side of his/her plate	❑	❑	❑	❑
4. Forgets to clean the left side of his/her mouth after eating	❑	❑	❑	❑
5. Experiences difficulty in looking towards the left	❑	❑	❑	❑
6. Forgets about a left part of his/her body (eg, forgets to put his/her upper limb on the armrest, or his/her left foot on the wheelchair rest, or forgets to use his/her left arm when he/she needs to)	❑	❑	❑	❑
7. Has difficulty in paying attention to noise or people addressing him/her from the left	❑	❑	❑	❑
8. Collides with people or objects on the left side, such as doors or furniture (either while walking or driving a wheelchair)	❑	❑	❑	❑
9. Experiences difficulty in finding his/her way towards the left when traveling in familiar places or in the rehabilitation unit	❑	❑	❑	❑
10. Experiences difficulty finding his/her personal belongings in the room or bathroom when they are on the left side	❑	❑	❑	❑
Total score (/30)				

0=no neglect; 1=mild neglect; 2=moderate neglect; 3=severe neglect

Figure 4: SN assessment tests part of the screening battery
(a) Star Cancellation Test: The A4 test sheet is placed in the midline and the subject is asked not to move. It contains 54 small stars, larger stars, letters, and short words distributed across the page, and 2 example stars in the centre. Following a demonstration by cancelling the 2 example starts, subjects are instructed cancel out only the small stars.
(b) Broken Hearts Test: The A4 test sheet is kept in the midline. The top section on the example sheet (featured on the left) is used to demonstrate the aim of the task to the subject, and the practice section is used to ensure comprehension before doing the test, the instruction being to cross out only the complete hearts, whilst pointing to the line to guide attention. In the main test, the A4 sheet contains 10 blocks of "complete" hearts, hearts with gaps on the left and hearts with gaps on the right. The instruction is to cancel out only the complete hearts. The test sheet (featured on the right) features 10 blocks, each with a mixture of complete and left/right gap hearts. The examiner ensures the page is centred, holding it in the centre if needed, and not at the edges so as avoid giving cues about the page's width. The test time is noted.
(c) The Catherine Bergego Scale - Likert scale. An assessor marks the patient on a severity scale of 0 (no neglect), 1 (mild neglect), 2 (moderate neglect) and 3 (severe neglect) based on observations of 10 spatially dependent tasks of daily living.

Cut-offs were used to screen-in patients suffering with at least a moderate degree of Visual Inattention. Moderate severity on these measures is marked by the following cut-offs: cancelling less than 42 stars out of a total of 54 stars on the Star Cancellation Test and a laterality index between 0-0.46 (indicating left-sided SN); for the Broken Hearts Test, a space asymmetry score higher than 4; or, a score of at least 11 out of 30 points on the Catherine Bergego Scale (higher scores denote more severe inattention).

In the patient cohort, the mean Star Cancellation score was 25.4 stars (SD 12.99) and the mean laterality index was 0.18 (SD 0.19); on the Broken Hearts Test (which was completed by 16 out of the 17 patients), the mean Space Asymmetry score was 11.88 (SD 6.51); and the average CBS score was 14 (SD 4.69). One of the patients reached the diagnostic threshold on one of the four tests, two did so on two of the tests, three did so on three of the tests, and the remaining 11 on all four. The control subjects were at ceiling on the two cancellation tests.

All the participants were provided with an information sheet describing the use of a Virtual Reality headset with eye tracking to capture information about gaze, and written consent was gained. Data from the patient population was collected on the inpatient wards, while the healthy control group were invited locally to the University.

2.5 Ethics

Ethics approval was awarded by the UCL Research Ethics Committee for the Project ID 22941/001.

Stroke Participants													
ID	Age	Gender	Time since stroke (Days)	Side of SN	Total Stars Baseline	Left	Right	Laterality Index	Total Stars post-intervention	Broken Hearts Space Asymmetry	CBS Baseline	FiVE in the Vive x-coordinate at Baseline	FiVE in the Vive x-coordinate post-intervention
CT01	53	F	17	Left	43	19	24	**0.44**	54	-	9	31	26
CT02	61	M	77	Left	**27**	1	26	**0.03**	34	**12**	**15**	26	19
CT03	51	M	128	Left	**22**	5	17	**0.22**	41	**11**	**16**	21	22
CT05	45	F	21	Left	**31**	15	16	**0.48**	54	**11**	**20**	20	16
CT07	70	F	37	Left	**33**	7	26	**0.21**	54	**9**	**14**	22	21
CT08	59	F	45	Left	45	20	25	**0.44**	50	0	**17**	15	14
CT09	69	F	45	Left	49	24	25	0.48	54	**6**	**14**	23	22
CT11	64	M	84	Left	**20**	1	19	**0.05**	46	**15**	9	24	14
CT12	72	M	32	Left	**20**	0	20	**0**	54	**26**	**12.5**	20	14
CT13	63	M	8	Left	**6**	0	6	**0**	14	**22**	**14.4**	22	22
CT14	74	M	26	Left	**37**	10	27	**0.27**	52	**7**	**26**	24	18
CT15	78	F	56	Left	**15**	0	15	**0**	41	**4**	**11.25**	27	31
CT16	82	M	43	Left	**34**	13	19	**0.40**	27	**15**	6	19	19
CT17	54	F	69	Left	**25**	4	21	**0.16**	46	**15**	9	21	17
CT18	34	F	101	Left	**7**	0	7	**0**	30	**11**	**17**	28	18
CT19	69	M	174	Left	**13**	0	13	**0**	20	**7**	**14**	19	25
CT21	67	F	30	Left	**8**	0	8	**0**	52	**19**	**27**	20	18

Table 5: Stroke Participant Demographics
Star Cancellation values, laterality indices, Broken Hearts Space Asymmetry scores and Catherine Bergego Scale scores for patients. Bold values are those in the diagnostic range for lateralised inattention. The table presents, for each participant, Star Cancellation total scores at baseline and after the intervention [described in Experimental Chapter II] (higher values indicate improvement in Spatial Neglect), alongside the baseline and post-intervention FiVE in the Vive gaze displacement measure (x-coordinate of centre of gaze during free visual exploration; higher values indicate greater rightward bias, 32 beng the final co-ordinate on the right, and 16 being the midline). These data were used in validation analyses to examine the association between conventional paper-and-pencil measures and the FiVE in the Vive, as well as to explore change in both measures following intervention.

2.6 Lesion Overlap Map

I was able to obtain MRI brain scans for 16 out of the 17 patients. Using SPM (169) I created a lesion overlap map to display the extent and commonalities of their lesion topography (Figure 5). The greatest intensity (red) is in the Right Middle Cerebral Artery territory, which includes the right parietal lobe and its frontal connections, areas most commonly implicated in people with left-sided SN (2).

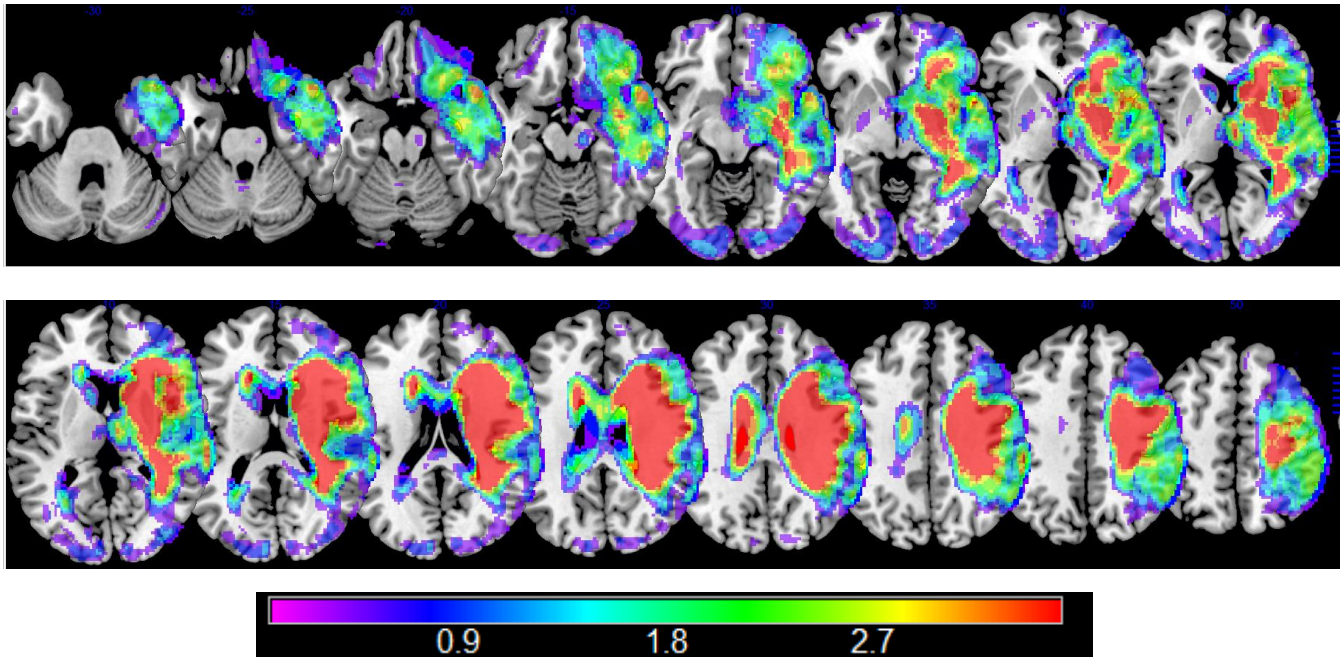


Figure 5: Lesion Overlap Map
The patients' lesions have been displayed on a canonical MRI T1 weighted image in standard MNI space. A thresholding cut-off of 2 was applied. Axial slices in ascending steps of 2,3 or 5mm are oriented in neurological convention (right side of the brain on the right of the images). The colour intensity scale demonstrates increasing number of overlapping voxels.

2.7 Materials

An HTC Vive Pro Eye headset, equipped with eye-tracking capabilities and room-scale tracking through positional tracking base stations, was utilized to record gaze fixation data. The SteamVR platform, developed by Valve, served as the supporting software system for the HTC Vive Pro Eye headset. Calibration of the headset was performed using the SteamVR dashboard, aligning it to the participant's midline and adjusting for their height, whether they were positioned in an inpatient bed or seated in a chair. The system operated on an MSI GT73VR GRF Titan Pro laptop featuring an Intel Core i7-6700HD processor running at 2.60 GHz, 16GB of dual-channel DDR4 RAM, an NVIDIA GeForce GTX1080 graphics card, and a 64-bit version of Windows 10 Home.

2.8 Virtual Reality: Stimulus Presentation

The free visual exploration task was developed by Kaufmann et al (170) as a sensitive diagnostic assessment tool for SN for use in a hospital setting. In their study, subjects were asked to view a series of naturalistic scenes displayed on a 2D monitor while their eye movements were measured using a remote, infrared-based, video-eye-tracking system (79). In our study, I imported the 2D landscape formatted images into custom written software so that they could be displayed in the HTC Vive Headset (Figure 6). There were two main advantages to doing this: firstly, the images were made to subtend a greater visual angle in the Vive (64^{o} by 48^{o}, as opposed to 28^{o} by 21^{o} in the original version (170)); secondly, eye movements were measured using the built-in Vive eye tracker which corrects for any head movements. I named this the "FiVE in the Vive" (FVE) task, as free visual exploration was being conducted within the Vive headset.

The 24 images (comprising of 12 pairs of original images and their mirror images) were presented to each participant in a pseudorandom order (no two images of a pair could appear consecutively) for seven seconds each (Figure 2). The interstimulus interval was two seconds and consisted of a white cross on a black background displayed at the centre of the field of view. The images remained centrally fixated within the headset, irrespective of head movements. Participants were given a verbal instruction to view the images without providing any verbal descriptions or feedback. The total test time was approximately 4 minutes.

Figure 6: Naturalistic Image Pairs
Six out of the 12 pairs of original images and their reflected mirror images displayed within the Vive headset.

2.9 Eye Movement Data

The HTC Vive Pro Eye Headset utilizes Tobii technology to power its eye-tracking capabilities. Within the headset, illuminators shine near-infrared light on to the user's eyes, creating reflections which are captured in high-resolution by built-in cameras. This information is fed into image processing algorithms that extract data relating to a variety of outputs such as gaze origin, gaze direction, pupil position, pupil size and eye openness. The headset has a 110°

trackable field of view, with binocular gaze data sampling frequency of 120Hz, and an accuracy of 0.5°–1.1° (within a 20° field of vision). During blinking, the eyelids close thereby obstructing any pupillary or corneal reflections of near-infrared light, and therefore do not register as data points.

In the case of our study, using custom-written software, gaze duration data for each image viewed in the FiVE in the Vive was outputted into a Microsoft Excel Comma Separated Values (.csv) file (Figure 7). Each Excel .csv file can be thought of acting as a 2D grid over each image, comprised of 24 x 32 square cells, each one representing 2^{o} of visual angle wide. Each cell that the participant's gaze fixated in for more than 100 milliseconds generated a value corresponding to the total gaze duration for that cell to the nearest 100ms. For example, if the gaze fixation time on a particular cell was 220ms, this would generate a value of "2" in that cell. Dwell time was cumulative so could be generated by one or more fixations. The data was outputted in an Excel spreadsheet with integer values for each cell, one sheet for each image viewed.

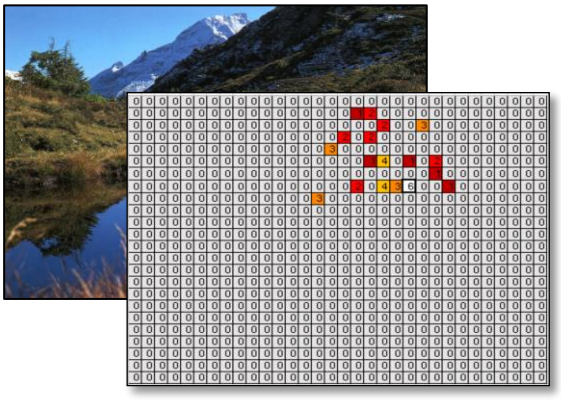


Figure 7: The Excel .csv file super-imposed upon the original image.
The integers demonstrate where a gaze fixation was made, for example, "1" denotes the cell that the participant's gaze fixated at for 100 milliseconds. I have manually coloured-in the integers cells to represent the colour thresholds applied when the .csv file coverts to a NIfTI file, as will be seen in Figure 8.

2.10 SPM Pipeline and Analysis

All analysis was performed using software programme Statistical Parametric Mapping (SPM12) in Matlab 2021b.

2.10.1 Pre-Processing

Each Excel spreadsheet (one for each image viewed), was then converted into a NIfTI (.nii) file (Figure 8), to allow for further analysis within SPM.

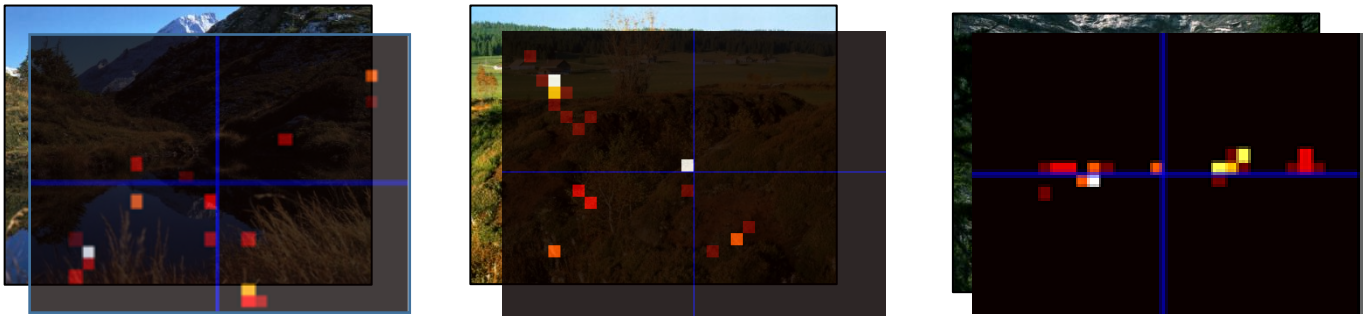


Figure 8: The .nii NIfTI file super-imposed on the original image
The .csv file seen in Figure 7 get converted into a .nii file for utilization within SPM. The first image on the left with the semi-transparent raw heatmap demonstrates the super-imposition of converted .nii files representing the 24 x 32 cells grid over the image underlying it, with each coloured point representing gaze fixation over that cell for >100milliseconds. These raw heatmaps were generated for each image, as can be seen in the next two images. The colour gradient from white to yellow to orange to red reflects duration of dwell time, starting with a minimum of 100ms (red) to the maximum dwell time (white). The blue crosshair is at the centre of the heatmap.

Each .nii file was smoothed using a Gaussian smoothing kernel with 8mm full-width half maximum in the pre-processing step in order to increase the signal to noise ratio (Figure 9 i,ii).

For each participant, the 24 .nii files were then separated into 2 groups of twelve, titled the 'Original Image' group which included the .nii files of 12 different images, and the 'Mirror Image' group, which included the respective .nii files for the corresponding Mirror images for each Original image.

2.10.2 Negating any horizontally expressed salient features

Visual saliency had to be specifically considered in this work as I used images and video-oculography to assess the presence of spatial bias. Salient features, or "saliency points" were regions on the image that were prone to garnering more attention due to their perceptual prominence (167). As part of exploring spatial bias, a specific step in the methods was incorporated to negate any horizontally expressed salient features.

Firstly, all the smoothed 'Mirror Image' dwell time maps were flipped horizontally (along the y axis), using the Image Calculator feature within SPM, with the expression *flip(i1,1)*. This enabled us to then proceed to the next step, during which I subtracted the Flipped Mirror Image from its corresponding Original Image, once again using the Image Calculator feature, with the expression *(i1-i2)* (Figure 9 A-H).

These steps provided a 2D average dwell time map for any given image with horizontally expressed salience features factored out.

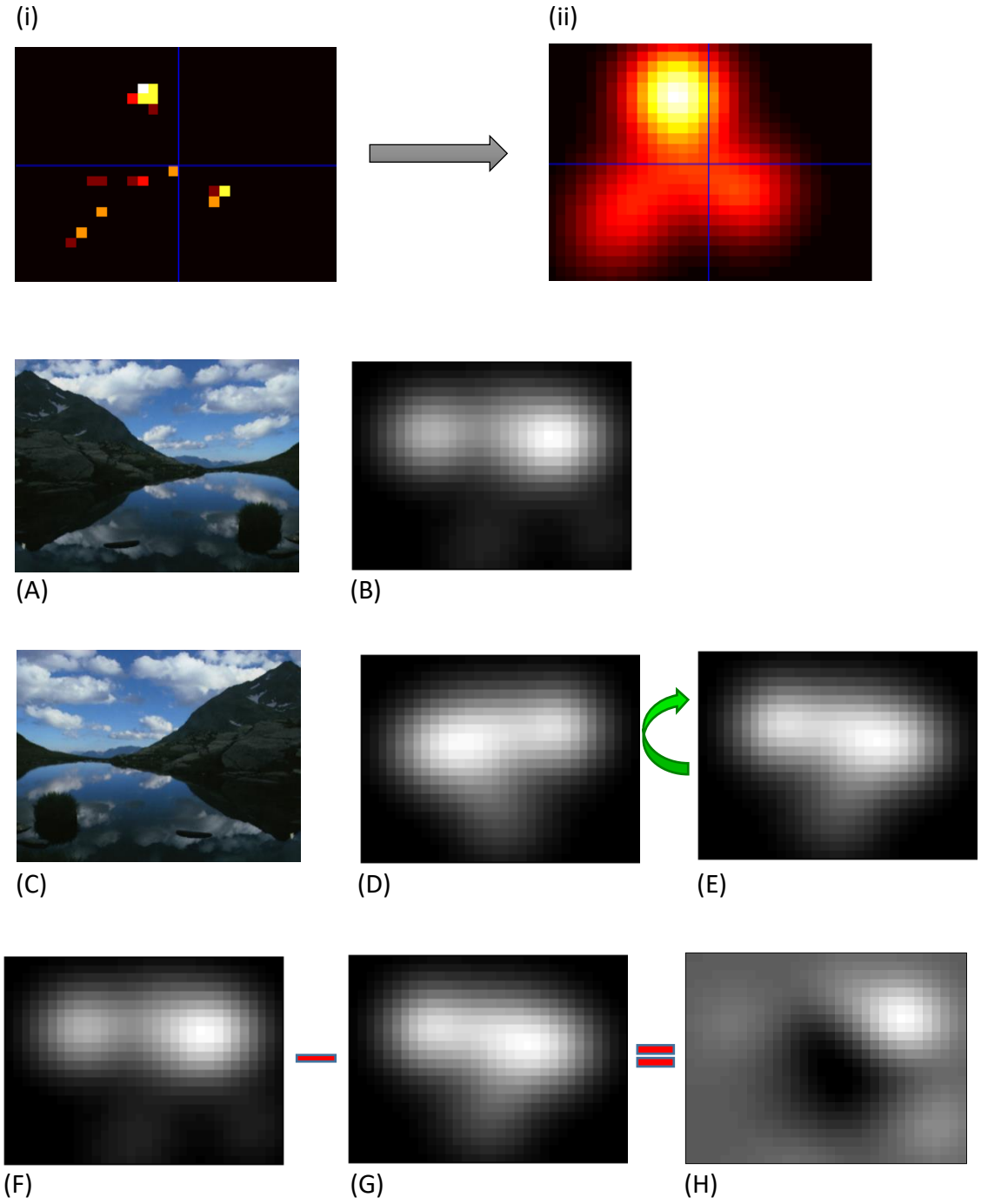


Figure 9(i,ii, A –H): From Smoothing to Subtraction
(i) to (ii) shows the .nii file smoothed using an 8mm scale in the pre-processing stage (A) An example of an Original Image and (B) the resultant smoothed heatmap (greyscale) of dwell times from a single subject viewing the image for 7 seconds. (C) The Mirror Image of the original (D) with corresponding smoothed dwell time heatmap. (E) The Flipped version of the Mirror Image smoothed heatmap. (F-H) Subtracting the Flipped Mirror Image heatmap [G] from the Original Image heatmap [F] (with the Saliency points aligned and therefore cancelling each other out) to produce the "Original Minus Flipped Mirror Image" [H] for each pair.

A subject viewing both scenes by fixating on exactly the same features would produce a null subtraction image. A subject who viewed both images with a lateralised spatial attentional

bias would have areas with high positive values (to the side where gaze was preferentially directed, i.e. in our study towards the right side) with high negative values towards the neglected side.

2.10.3 1st Level Analysis: Within-Subject

For each subject, a statistical map was generated by performing a linear regression at each pixel of the image using the standard tools in SPM. For the pixel with index i, the General Linear Model (GLM) was specified:

$$y_i = X\beta_i + e_i$$

Where y_i is a vector of values from the 12 subtracted images for the i-th pixel and X is the *design matrix*, the columns of which are hypothesised effects (a.k.a covariates, regressors or explanatory variables). For this example, the design matrix consisted only of a column of ones, in order to calculate the average of the images. Residuals e_i were estimated using the standard Restricted Maximum Likelihood (REML) scheme implemented in the SPM software. The output of this stage of the analysis was an image of regression parameters for each subject.

2.10.4 2nd Level Analysis: Between-subjects (Patients with SN versus Healthy Controls)

The 23 regression parameter images from the 1st level analysis for the control subjects, were compared against the 17 parameter images for the patients. This was implemented by specifying a design matrix consisting of a dummy variable for each group (Figure 10A). In terms of modelling variance, the groups were treated as independent with unequal variance, meaning that any potential heteroscedasticity was modelled by estimating separate

covariance components for each group. An F-contrast of [1, -1] was used to test for a difference in lateralised gaze dwell times across the two groups (top part of Figure 10A). The p-value threshold was set to 0.05 with a Family Wise Error (FWE) rate calculated using random field theory (171).

2.10.5 Analyses of Validity of FiVE in the Vive

To explore the validity of this novel measure, I examined correlations with established assessments of Spatial Neglect. Specifically, I tested associations with the Star Cancellation Test, which was used to confirm neglect at recruitment, and with the Catherine Bergego Scale, which has previously been employed as a reference in validation work (e.g. Kaufmann et al. (79)). In addition to this, I tested whether the gaze measure discriminated neglect laterality, and whether changes in gaze location correlated with changes in Star Cancellation performance following an intervention using a one-tailed t-test. The one-tailed test was justified given the directional hypothesis that both measures would improve together.

2.11 Results

The group results of the comparison between control subjects and patients are displayed in Figure 9B, thresholded at p <0.05 FWE corrected. This SPM is in image space measuring 64^{o} by 48^{o} of visual angle. Two areas of significant differences were identified, a cluster of 256 voxels to the right side of space where the patients had higher dwell times than the controls, and a cluster of 271 voxels to the left, where they had lower dwell times (Figure 10B and Table 6).

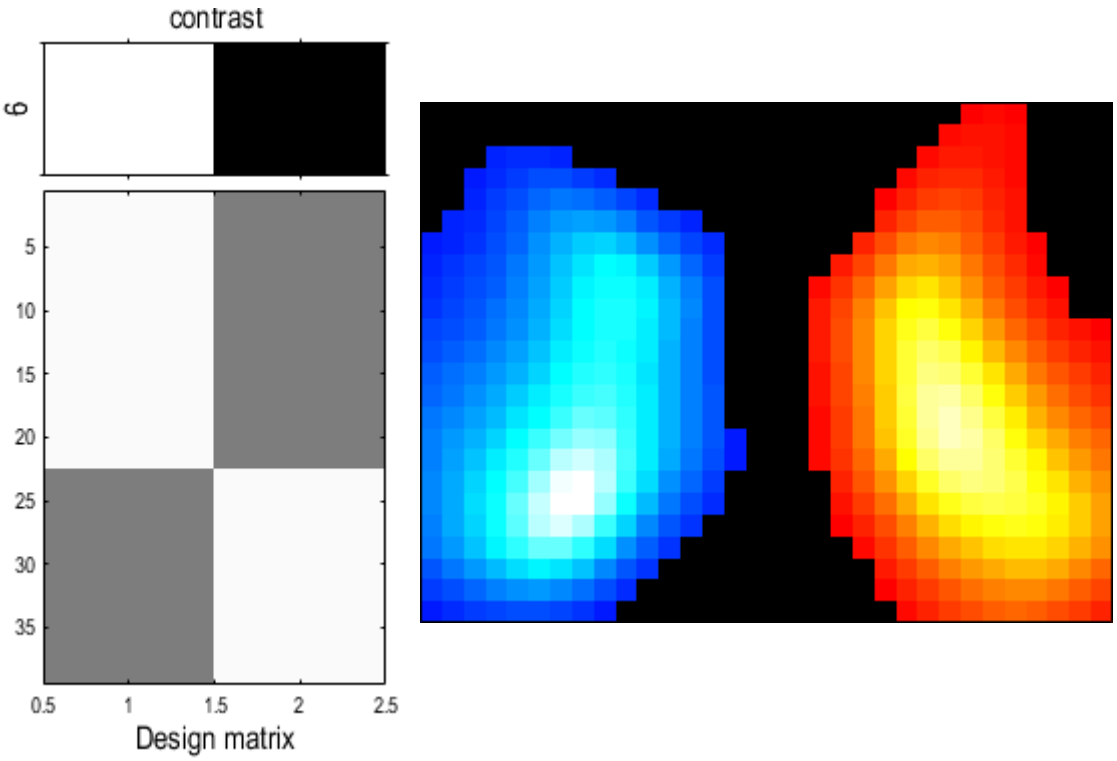


Figure 10A&B: The Design Matrix for the 2nd Level Analysis and the original SPM result
The Design Matrix on the left (A) displays the schematic of the f contrast of 1 -1 applied to the 2 groups, with controls' images entered into the left column and patients on the right. The SPM on the right (B) shows the two areas where patients' gaze dwelt significantly more (warm colours) and less (cool colours) than the control subjects.

Cluster Level				**Peak level**				**Co-ordinates**
P_{FWE} Corrected	K_E	$p_{Uncorrected}$		P_{FWE} Corrected	F	Z_E	$p_{Uncorrected}$	
p<0.001	271	p<0.001		p<0.001	66.28	6.01	p<0.001	7 6 1
p<0.001	256	p<0.001		p<0.001	59.82	5.81	p<0.001	25 9 1

Table 6: Statistical results for the cluster level and peak-voxel level
Cluster level (in purple) and peak voxel (in green) significance levels from the SPM in Fig 6. P_{FWE} is the p value corrected using Family Wise Error correction for multiple comparisons. KE is the size of the cluster in contiguous voxels. The co-ordinates are in the image space and give the location of the two peaks of difference in the SPM. The bottom left voxel of the SPM has the co-ordinate of 0 0 1 (x, y, z). The SPM is 2D so has a thickness (z) of 1 throughout.

The peak voxel for the Patient Group is highlighted in Figure 11 with the data from the two groups at this point extracted and plotted as a bar graph (Graph 1).

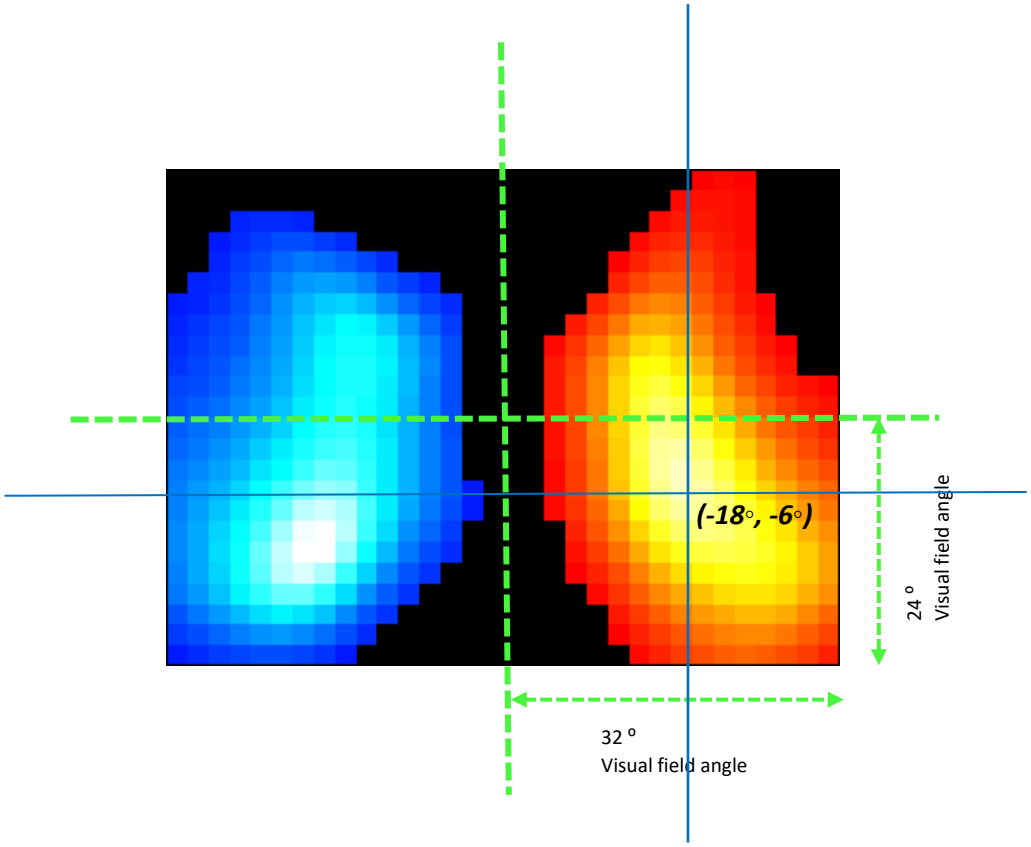
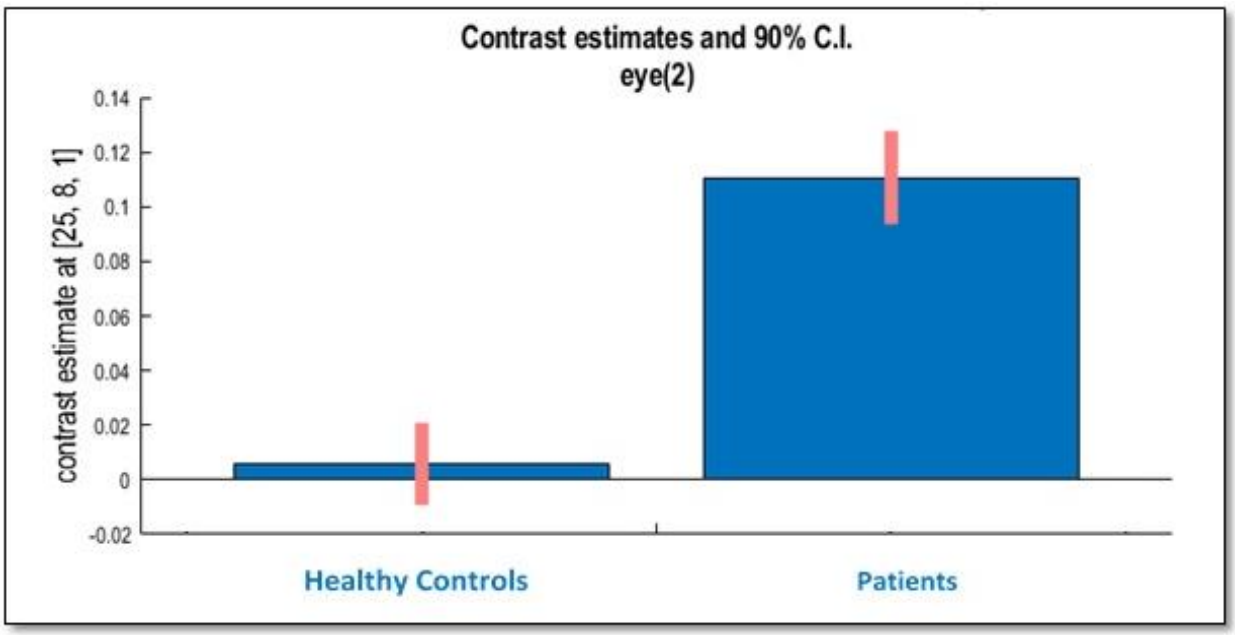


Figure 11: The peak voxel for the patient group
The SPM image from Figure 10 is reproduced but with the centre of the image marked with green cross hairs. The peak average centre of gaze for the patient group (blue crosshairs) deviated from the midline by 18° over to the right of centre, and 6° below the horizontal meridian. Data from the peak voxel is plotted on the right (NB: Y-axis is in arbitrary units)



Graph 1: Data from the peak voxel is plotted and extracted for the 2 groups

Correlations between baseline Star Cancellation Test scores and the FiVE in the Vive x-coordinates were not significant. Correlations between the FiVE in the Vive and the Catherine Bergego Scale were also not significant. Examination of the raw gaze coordinate data showed that 16 out of 17 participants demonstrated a rightward shift in centre of gaze consistent with left-sided neglect. The single exception was a participant who also failed to meet neglect criteria on the Broken Hearts Test. In addition, exploratory analyses of longitudinal change demonstrated a trend towards correlation between improvement in Star Cancellation Test scores and reduction in rightward gaze displacement following intervention (Spearman's $\rho = 0.39$, $p = 0.077$, one-tailed).

2.12 Discussion

The introduction of video-oculography has opened up new possibilities for analysing gaze location and duration, while also presenting challenges in maintaining the spatial richness of the data within its original co-ordinate framework during statistical analysis. I have proposed, for the first time, a method for performing statistical analyses on spatially distributed gaze duration data using statistical parametric mapping.

I selected patients with Spatial Neglect for this study due to their characteristic lateralized spatial gaze bias; however, this method is applicable to any fixation-based or dwell time eye movement data. While I demonstrated its use on group data, the approach can also be applied to individual subjects, provided they are exposed to sufficient stimuli. Unlike traditional techniques that produce visual heatmaps or attentional maps, my method enables formal hypothesis testing on spatially distributed gaze duration data using a conventional frequentist statistical approach.

Video-oculography has proven to be more sensitive in detecting visual inattention than conventional paper-based tests (172). Further to this, eye tracking within virtual reality headsets carries the advantage of an increased field of view over more traditional 2D displays. In the case of my study, whilst the HTC Vive Headset allows up to 110^{o} field of view, the 2D images that I uploaded allowed me to measure 64 x 48^{o} visual angle, enabling the detection of spatial bias more accurately. Kaufmann et al., who also utilized a free visual exploration task by displaying their images on a large monitor (79), were only able to test a maximum of 28^{o} of visual angle along the horizontal plane. My technique doubles this along both visual planes, allowing the sampling of four times the visual area. This likely makes the test more reliable in terms of detecting the extent of any spatial bias. The average displacement in this study was 18^{o} to the right of centre. The standard pencil-and-paper test of SN, the Star Cancellation Test on an A4 sheet of paper, when viewed at 50 cm distance, only subtends a maximum angle of 15^{o} to either side.

By using flipped versions of each naturalistic scene, I was able to correct the gaze data for any inherent lateralized spatial biases inherent in the images. I did not do this for the vertical components, and this probably explains why I identified a significant vertical displacement of 6^{o} below the horizontal meridian. This is in the opposite direction from what one might expect. A vertical SN component (albeit of smaller magnitude compared to that seen in the horizontal plane) has been described previously in people with SN, with a bias appearing in the upper quadrants (173, 174). The naturalistic images used in my free visual exploration task generally contained more areas of interest and higher salience in the lower quadrants as many were outdoor scenes comprising more featureless sky at the top.

With regards to the validation analyses, correlations between the FiVE in the Vive gaze displacement measure and baseline Star Cancellation Test were not significant. This is may be explained by the fact that the two tasks induce very different visual behaviours: Star Cancellation requires participants to engage in an abstract, strategy-driven search until they believe all targets have been found, whereas free visual exploration is closer to natural scene viewing with the sole requirement to 'look at the picture'. Moreover, all participants were recruited on the basis of meeting diagnostic criteria for neglect on the Star Cancellation Test at baseline, which biases this comparison and may have introduced ceiling effects.

When considered against other measures, the findings are more encouraging. Sixteen of the 17 patients also met diagnostic criteria for Spatial Neglect on the free visual exploration task, with the single exception being a participant who also fell below cut-off on the Broken Hearts Test (CT08). In this respect, both the Broken Hearts Test and the FiVE in the Vive showed identical sensitivity, suggesting that even with a small sample size the novel measure performs comparably to established clinical tools in identifying neglect. A comparison with the Catherine Bergego Scale was not significant, which may reflect the fact that these tools capture different aspects of neglect: the CBS is an observer-rated measure of functional performance, whereas the gaze displacement task quantifies attentional bias during laboratory-based free exploration.

Finally, although the measures did not align on neglect severity at baseline, longitudinal analyses suggested convergence over time. A trend-level correlation was observed between improvements in Star Cancellation Test scores and reductions in rightward gaze displacement following intervention (Spearman's $\rho = 0.39$, $p = 0.077$, one-tailed). This indicates that the two measures tended to move together during recovery, raising the possibility that both are

sensitive to treatment-related change. This supports the view that gaze-based measures may provide a complementary perspective on neglect, capturing dynamic shifts in attentional bias during free exploration that are not always evident in structured, paper-and-pencil tasks.In conclusion, the results generated in this study serve as an archetypal example of a statistical outcome from this novel method that allows for the statistical analysis of spatially distributed gaze data, regardless of the visual capture method utilized. This approach to eye-movement behaviours in response to visual stimuli offers numerous applications across a variety of disciplines, such as task-based visual assessments like driving, neuropsychological and neuro-behavioural gaze assessments relevant to industries like advertising, the arts and cognitive neuroscience. The method successfully applies Statistical Parametric Mapping software on to a challenging data set, at a time that is particularly relevant given the rise of advanced video-oculography and eye-tracking data now available from online testing platforms.

2.13 Limitations and Future Work

Limitations of this study include the use of a patient cohort that only suffered from left-sided SN. While is it intuitive to assume that the FVE task would also pick-out a right-sided spatial deficit were it to be present in subjects with right-sided SN, it would be useful to capture gaze data from that patient cohort in order to develop the SPM pipeline for the data analysis of a mixed cohort of left- and right-sided SN.

In addition, this technique would also be especially useful to capture altitudinal visual attentional deficits. At present, the images of the landscapes utilized do contain vertically present salient features which have not been negated, as the images were only flipped along the y-axis in order to subtract the salient features contributing to horizontal spatial bias. This

would be a useful alteration to apply to the software to enable it to tease out altitudinal defects in a way that they can be reliably explored.

The scope of the visual angles can also be expanded given that the current images amass a horizontal visual angle of 64^{o}, and the available visual angle within the HTC Vive Headset is 110^{o} horizontally.

A key requirement of any new technique, particularly in the field of eye-tracking and SN assessment, would be the need for robust reproducibility and validation. Future considerations include replicating this new method with larger sample sizes, across diverse settings and populations to establish the reliability of the method. Validation processes, including assessments of sensitivity, comparisons with traditional pencil-and-paper based tasks, and investigating test-retest reliability would be useful to build this tool as a reliable contender for the assessment of SN, particularly in scenarios where motor or cognitive functions might limit engagement with traditional tests.

Given the technological aspects of the data collection, issues with reproducibility could arise from variations in hardware, software, and experimental protocols, marking the importance of standardized protocols for calibration, data collection, and analysis.

A further potential concern is that gaze deviation could reflect oculomotor disorders such as optic ataxia or ocular apraxia, rather than attentional neglect per se. We did not formally screen for these syndromes, which is a limitation. In the current study, inspection of raw gaze data confirmed that participants were able to saccade to both hemifields, indicating preserved basic oculomotor function. Therefore, while we acknowledge the limitation of not

screening formally, it is unlikely that ocular apraxia is driving the rightward gaze deviation observed.

Lastly, future work would involve the use of this FVE task as an assessment tool that serves as an outcome measure for SN in a clinical intervention trial that involves the treatment of SN, which is exactly the role that the FiVE in the Vive will feature in, in the next experimental chapter.

3.0 Experimental Chapter II

The ATTEND Trial

Attentional Therapy for the Treatment of Neglect Disorder

3.1 The ATTEND Trial

Treatment approaches for Spatial Neglect, ranging from sensory stimulation (visual, audio and somatic), non-invasive brain stimulation and drugs, have been trialled with varying effects, and none of these are yet recognized as a gold standard treatment (99).

Under the umbrella of visual stimulation, smooth pursuit eye movement training (SPT), which relies on inducing involuntary eye movements, has been shown to ameliorate Spatial Neglect (112), in comparison to a sham visual training therapy requiring voluntary eye movements (113-115). Whilst this has been mainly demonstrated using two-dimensional screens such as laptops, there have been suggestions that delivering this therapy using immersive Virtual Reality might be more effective (116).

ATTEND stands for Attentional Therapy for the TrEatment of Neglect Disorder. The ATTEND trial was a small-scale, Phase II group randomized controlled clinical trial which aimed to test the clinical efficacy of a smooth pursuit eye movement therapy delivered using immersive Virtual Reality for the treatment of Spatial Neglect caused by a stroke. Two randomized groups, each comprising of 12 inpatients, received daily sessions of VR Stimulation over a course of 15 days. One group received a Horizontal "Therapy" VR Stimulation and the other a Vertical "Control" VR Stimulation. The primary objective was to assess if horizontal smooth pursuit stimulation using VR improved SN, as compared to a control stimulation.

3.2 Aims of the Trial

3.2.1 Primary Aims

Does horizontal smooth pursuit stimulation using VR improve the symptoms and signs of patients with SN compared with a control stimulation?

This was a between-subject group level comparison but based on test-retest data from individual patients, so I compared change scores across the two experimental groups for the following measures of SN:

1. Impairment Based Measure – Star Cancellation Test (a pencil-and-paper based test of Spatial Neglect)
2. Functional Measure – Catherine Bergego Scale (10 point measure of SN severity on functional activities, marked by the treating Occupational Therapist who was kept blinded to the randomisation)
3. Impairment Based Measure – Free visual exploration task called FiVE in the Vive Task (a task that asked subjects to silently view standardised images as eye dwell time data was gathered to plot gaze location)

1 and 2 have been grouped under "Behavioural Outcome Measures" and 3 is referred to as "FiVE in the Vive Outcome Measure" in this thesis.

3.2.2 Secondary Aims

Does horizontal smooth pursuit stimulation using VR improve the length of stay of patients with SN compared with a control stimulation?

3.3 Methods: Trial Design

The ATTEND trial was a Phase II group randomized controlled clinical trial involving stroke inpatients based across 4 sites – National Hospital for Neurology and Neurosurgery, St.

Pancras' Rehabilitation Unit, Charing Cross Hospital, and St. George's Hospital. The trial design consisted of 4 time points, T1 to T3 based over the course of 15 days, and a single follow-up time point at 3 months, T4 (Figure 12, Table 7).

Information about the trial along with in-person demo sessions conducted by me, were disseminated among the Hyper-Acute Stroke Units, Acute Stroke Units, and the Neurorehabilitation Units in the listed recruitment sites. Appropriate inpatient participants meeting the inclusion and exclusion criterion were identified by members of the clinical or therapy teams, and referred to me.

At T1, the participant underwent a screening assessment with the Star Cancellation Test and the Oxford Cognitive Screen (OCS). The OCS also included the Broken Hearts Test and a clinical examination of visual fields. If appropriate, the participant was provided with a Patient Information Sheet and given a 24-hour time period prior to consenting. The participant was specifically reassured that the ATTEND sessions would not interfere with pre-timetabled activities, would not limit any standard rehabilitation care being provided on the units, and information was relayed to the next of kin upon participant request.

At T2, the participant was randomized (using minimization) to one of two groups, either the Therapy Group receiving a horizontal VR Stimulation, or the Control Group, receiving a vertical VR Stimulation. Both groups received the same exposure to VR Stimulation, quantified at 4 x 10 minute blocks amounting to a total of 40 minutes per day for 15 days, with each daily session preceded and followed by the FiVE in the Vive free visual exploration task in order to collect eye dwell time data for the analysis of gaze location. The patient and their Occupational Therapist were blinded to the randomization, as the latter was responsible for completing the Catherine Bergego Scale at T2 and T3. Baseline testing at T2 prior to starting

the first VR Stimulation session comprised of baseline measures for the Primary Outcome (Start Cancellation Test) and the two Secondary Outcomes (Catherine Bergego Scale and FiVE in the Vive):

a) Star Cancellation Test (please note that if T2 took place within a day or two of T1, this was not repeated)

b) Catherine Bergego Scale

c) FiVE in the Vive, performed 3 times on Day 1 prior to any VR Stimulation in order to collect robust data marking the patient's baseline gaze location, and once after the VR Stimulation. Performed once before and after the VR Stimulation each day on Days 2-15.

A baseline Sustained Attention to Response Task (SART) was also performed within the VR Headset, and this will be covered in Experimental Chapter III in Section 4.0 of this thesis.

From Day 2-15 of the VR Stimulation, only the FiVE in the Vive outcome measure was performed on a daily basis, once before and once after the VR Stimulation. A side effects checklist was maintained daily to check for eye strain, headache, nausea, and fatigue in order to flag immediate concerns with VR use. As no issues were raised with VR use by patients, this checklist will not be explored further in my thesis.

T3 marked the end of 15 days of VR Stimulation. T3 testing comprised of repeating the outcomes measures:

a) Star Cancellation Test

b) Catherine Bergego Scale

c) FiVE in the Vive (as was done on every single day before and after VR Stimulation)

A qualitative exit interview was also performed assessing patient experience to contribute to future qualitative research projects. All interviews were audio recorded. They will not be discussed in this thesis.

The date of discharge was also noted or tracked if the participant remained an inpatient much beyond T3.

3 months from the end of the trial, at outpatient follow-up timepoint T4, the patient was either invited to the Laboratory at the Institute of Cognitive Neuroscience, University College London (UCL), or a home/nursing home visit was made to perform the follow-up, which included a Star Cancellation Test and a single FiVE in the Vive free visual exploration task.

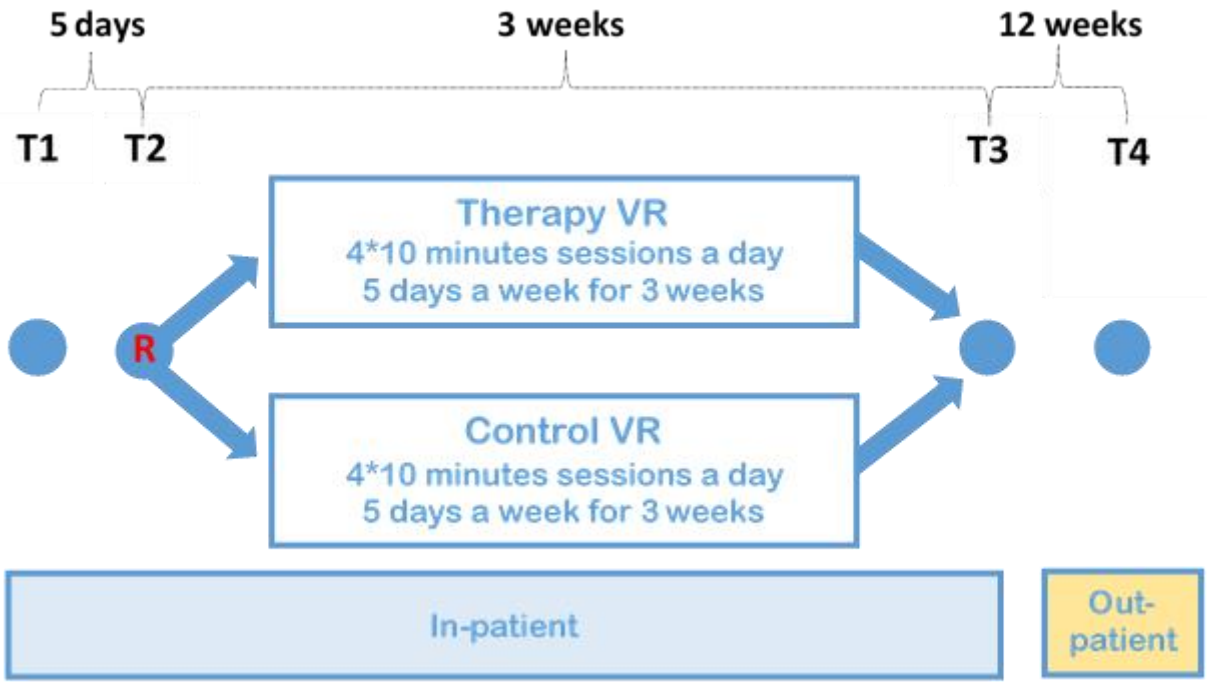


Figure 12: The ATTEND Trial Design
T1 Screening with Star Cancellation Test and Oxford Cognitive Screen. T2 R = randomization point and start of VR Stimulation, 4 x 10-minute blocks daily, preceded and followed by FiVE in the Vive daily. T3 end of 15 days of VR Stimulation. T4 3-month outpatient follow-up visit.

Timepoint	Actions Performed
T1 **SCREENING**	Oxford Cognitive Screen -includes a hemianopia screen -includes Broken Hearts Test Star Cancellation Test
T2 **RANDOMISATION** **CONSENT** **START VR STIMULATION**	Catherine Bergego Scale (completed by blinded Occupational Therapist) Star Cancellation Test* FiVE in the Vive -Day 1: x3 Pre and x1 Post-VR Stimulation Sustained Attention to Response Task
Daily Testing	FiVE in the Vive -x1 Pre and x1 Post-VR Stimulation Side effects checklist post VR Stimulation
T3 **END OF 15 DAYS OF VR STIMULATION**	Catherine Bergego Scale (completed by blinded Occupational Therapist) Star Cancellation Test FiVE in the Vive -x1 Pre and x1 Post-VR Stimulation Qualitative exit interview Discharge date
T4 **OUT-PATIENT**	Star Cancellation Test FiVE in the Vive

Table 7: Actions at each Timepoint
****Please note that if T2 took place within a day or two of T1, the Star Cancellation Test was not repeated.***

3.4 Participants

34 inpatients from the Acute Stroke Units or the Neuro-Rehabilitation Units of the participating patient recruitment sites were recruited for the study. The participants in both groups were matched for age and gender (Table 10). 6 patients' data was excluded from the analyses due to a confounding factor of participation in a separate smooth pursuit therapy programme for the treatment of SN. 4 patients dropped-out of the trial between T1 and T3 – one demonstrated inconsistent signs of SN on baseline testing; two participants were withdrawn due to prolonged medical illness; one participant was unable to continue with their participation due to disruptive disinhibited behaviour post-stroke. Therefore, in this

thesis, the data analysed and presented are for 24 patients. Notably, out of these, data at T4 (follow up at 3 months) was missing for 4 patients – two were lost to follow-up; one unfortunately passed away; and the last patient's follow-up date was scheduled at a date beyond the completion of this thesis. Therefore, at T4, data was analysed and presented for 20 patients. Length-of-stay data was also missing for 3 patients as one passed away, and the last 2 patients in the trial remained in hospital at the time of authoring this thesis. The CONSORT diagram has been presented in Figure 13. Key demographic and baseline data has been tabulated in Table 8.

3.5 Inclusion and Exclusion Criterion

The inclusion criteria were: (i) 18 years or older; (ii) any type of acute stroke; (iii) evidence of clinically significant SN; (iv) able to tolerate use of VR hardware and software; (v) willing and able to provide written informed consent.

The exclusion criteria were: (i) no major co-existing neurological or psychiatric diagnosis; (ii) no difficulty adequately understanding verbal or written explanations as a result of communication impairment follow the stroke.

Written informed consent was obtained from each patient prior to starting the trial.

3.6 Screening

The presence and severity of SN was formally assessed with clinical examination and two impairment-based cancellation tests – the Star Cancellation Test and the Broken Hearts Test (the latter taken from the Oxford Cognitive Screen) (Table 8,Table **9**). In order to screen in,

patients had to show moderate severity of SN and unilaterality on at least one of the impairment-based measures.

The cut-offs were: (i) cancelling less than 42 stars out of a total of 54 stars on the Star Cancellation Test (which indicates moderate severity); (ii) a laterality index between 0-0.46 on the Star Cancellation Test (which indicates left sided SN) (55, 175); (iii) a Space Asymmetry score of 4 and above on the broken hearts test (minimum cut-off for the mild-moderate category) (176); (iv) a positive Space Asymmetry score (which indicates left sided SN) (177).

In my patient cohort, the $Mean\ Star\ Cancellation\ score = 20.13\ (SD = 10.16)$, $Mean\ Laterality\ Index = 0.11\ (SD = 0.16)$, and the $Mean\ Space\ Asymmetry\ score = 13.83\ (SD = 8.19)$. 22 of the patients reached the screening thresholds on all 4 conditions (star cancellation severity, star cancellation laterality index, a positive Space Asymmetry score, a Space Asymmetry score of at least 4 and above) and 2 did so on three of the conditions.

3.7 Sample Size

The sample-size calculation was based on data from Kerkhoff et al., who studied 24 patients with SN caused by stroke in the post-acute phase (113). Data was entered into an online sample size calculator called ClinCalc (https://clincalc.com/stats/SampleSize.aspx). Values for the change in Functional Neglect Index were taken from (Figure 3) of Kerkhoff 2014. Specifically, these values included the therapy group value change = 5.18 (SD = 1.2), control group value change = 3 (SD = 1.6), Alpha error = 5% and Power (1-Beta error) = 90%. I went for the higher power (90% instead of 80%) as small-scale trials have been criticized for being underpowered.

This generated a sample size of 9 for each group, with an expectation of a 30% drop-out rate, making the total target 24 patients in total. For this study, eventually 12 patients were recruited for each group giving a total sample size of 24.

3.8 Minimization

Following consenting, and confirmation of eligibility, the minimization procedure was carried out centrally by the Principal Investigator. Patients were assigned a unique identifier with the letters "CT" followed by a number, starting with 01 for first participant, 02 for the second, and so on.

After the participant agreed to consent into the trial, they were allocated via minimization (178) to ensure that the groups remained balanced on two key binary baseline variables: age (>63 vs. 63 or younger) and SN severity (as judged by the severity classification on the Star Cancellation Test – a score of <22/54 stars cancelled indicating "severe" SN, and a score of 22-41/54 indicating "moderate" SN). When the groups were balanced, true randomization was used through an approved website (http://www.randomization.com/), which occurred on three occasions when the group allocation for the incoming patient was in equipoise. This determined which type of the VR Stimulation the participant was allocated to: Therapy (receiving a horizontal VR Stimulation) or Control (receiving a vertical VR Stimulation).

3.9 Unblinding

The patient and the treating Occupational Therapist (completing the T2 and T3 CBS form) were kept blinded through the trial. The patient was not informed about whether the VR Stimulation they were assigned to was "Therapy" or "Control". As far as possible, the patient sessions were conducted in a private environment where the stimulation visible to me as the

operator on the MSI laptop screen was not visible to other staff. Both VR Stimulation tasks required a relatively similar movement with the handheld remote, also preventing leaking of the stimulation-type. If requested, the Occupational Therapist was unblinded after the completion of the T3 CBS form, and the patient after the 3 month follow-up at T4.

3.10 Ethics

Ethical approval for this study was granted by the UCL REC (IRAS Project ID: 276250).

ID	Gender	Age	Centre	ASU/ NRU	Group Allocation (Therapy vs Control)	Time since stroke (days)	Type of Stroke	Side of SN	Total number of VR Stimulation Days	Length of stay (days)	T4 Follow-up	T2 Baseline Stars			Baseline Laterality Index	T3 Stars			T4 Stars			Baseline CBS	T3 CBS
													L	R			L	R		L	R		
CT01	F	53	NHNN	ASU	Therapy	17	Ischaemic	Left	13	79	Yes	43	19	24	**0.44**	54	27	27	53	26	27	9	5
CT02	M	61	NHNN	ASU	Control	77	Ischaemic	Left	15	277	Yes	**27**	1	26	**0.04**	34	16	18	36	12	24	15	12
CT04	M	69	NHNN	ASU	Control	40	Haemorrhagic	Left	15	266	Yes	**9**	1	8	**0.11**	4	0	4	8	0	8	22	22
CT05	F	45	NHNN	ASU	Control	21	Ischaemic	Left	11	125	No	**31**	15	16	0.48	54	27	27	-	-	-	20	9
CT11	M	64	CXH	NRU	Control	84	Haemorrhagic	Left	15	114	Yes	**20**	1	19	**0.05**	46	21	25	48	21	27	9	5
CT12	M	73	NHNN	ASU	Therapy	32	Haemorrhagic	Left	15	74	Yes	**20**	0	20	**0**	54	27	27	53	26	27	12.5	2
CT13	M	63	NHNN/SPRU	ASU	Control	8	Ischaemic	Left	11	28	Yes	**6**	0	6	**0**	14	0	14	50	25	25	14.4	11
CT15	F	79	CXH	NRU	Control	56	Haemorrhagic	Left	15	120	Yes	**15**	0	15	**0**	41	19	22	48	22	26	11.25	21.25
CT16	M	82	CXH	NRU	Control	43	Ischaemic	Left	15	100	Yes	**34**	13	21	**0.38**	27	2	25	20	4	16	6	2
CT17	F	55	NHNN	ASU	Therapy	69	Ischaemic	Left	12	176	No	**25**	4	21	**0.16**	46	21	25	-	-	-	9	4
CT18	F	34	CXH/NHNN	NRU	Therapy	101	Haemorrhagic	Left	15	289	Yes	**7**	0	7	**0**	30	5	25	38	14	24	17	6
CT19	M	70	NHNN	NRU	Control	174	Ischaemic	Left	15	255	Yes	**13**	0	13	**0**	20	0	20	16	0	16	14.4	11.1
CT22	F	76	CXH	NRU	Therapy	47	Haemorrhagic	Left	15	189	Yes	**19**	0	19	**0**	51	26	25	54	27	27	22	8
CT23	M	56	NHNN	NRU	Therapy	148	Ischaemic	Left	15	204	Yes	**10**	0	10	**0**	22	0	22	18	0	18	20	17
CT24	M	48	NHNN	NRU	Therapy	173	Haemorrhagic	Left	15	218	Yes	**22**	1	21	**0.05**	43	17	26	43	17	26	13.3	8.88
CT25	M	39	NHNN	NRU	Control	252	Haemorrhagic	Left	15	313	Yes	**27**	8	19	**0.30**	37	12	25	21	6	15	6	5
CT26	M	63	CXH	NRU	Therapy	26	Ischaemic	Left	15	239	Yes	**20**	0	20	**0**	42	19	23	49	25	24	23	10
CT27	F	23	CXH	NRU	Control	58	Ischaemic	Left	13	77	Yes	**36**	15	21	**0.42**	49	22	27	49	23	26	7	4
CT28	M	54	NHNN	NRU	Therapy	166	Haemorrhagic	Left	15	299	Yes	**9**	0	9	**0**	31	6	25	45	18	27	21	16.6
CT29	M	55	CXH	NRU	Control	29	Ischaemic	Left	14	59	Yes	**30**	4	26	**0.13**	41	18	23	35	9	26	16	7
CT30	M	41	NHNN	ASU	Control	54	Ischaemic	Left	15	192	Yes	**10**	0	10	**0**	10	0	10	43	24	19	12	7.77
CT32	M	68	NHNN	NRU	Therapy	135	Ischaemic	Left	15	RIP	No	**12**	0	12	**0**	32	5	27	-	-	-	18.75	13.75
CT33	M	63	NHNN	NRU	Therapy	48	Ischaemic	Left	15	-	Yes	**26**	2	24	**0.08**	49	22	27	50	24	26	25	10
CT34	F	52	CXH	NRU	Therapy	70	Ischaemic	Left	14	-	No	**12**	1	11	**0.08**	50	23	27	-	-	-	23	4

Table 8: Participant Demographics and T2, T3 and T4 data

Abbreviations: Male (M); Female (F); National Hospital for Neurology and Neurosurgery (NHNN); Charing Cross Hospital (CXH); St. Pancras Rehabilitation Unit (SPRU); Acute Stroke Unit (ASU); Neuro Rehab Unit (NRU) – this column indicates the clinical setting at the time of recruitment. Patients in NRU are admitted with a predetermined minimum length of stay, which constrains any analysis of Length of stay as an outcome measure. Data in bold are values reaching Screening thresholds. Missing data is denoted by "-".

	Oxford Cognitive Screen													
	Language			Memory				Numerical Cognition		Praxis	Attention			
ID	Picture Naming	Semantics	Sentence Reading	Orientation	Verbal Memory Recall	Verbal Memory Recognition	Episodic Memory Recognition	Number Writing	Calculations	Meaningless Gestures	Visual Field Test	Object Asymmetry	Space Asymmetry	Executive Task
CT01	*OCS not done*													
CT02	4	3	0	4	0	0	3	2	4	11	4	12	**12**	Invalid
CT04	0	2	1	1	2	3	3	2	4	12	2	3	**7**	Invalid
CT05	3	3	13	3	0	4	4	3	4	12	4	12	**11**	5
CT11	4	3	15	4	2	3	4	2	4	12	2	6	**15**	-1
CT12	4	3	15	4	3	3	4	2	4	12	3	2	**26**	4
CT13	4	3	15	4	2	4	2	1	3	12	4	-1	**22**	2
CT15	4	3	15	4	1	3	3	3	3	12	2	-1	**4**	3
CT16	4	3	15	4	3	4	4	3	4	12	4	0	**15**	8
CT17	4	3	15	4	4	4	4	2	2	12	4	0	**15**	4
CT18	2	3	1	4	4	4	2	1	2	12	4	2	**11**	1
CT19	4	3	15	4	4	4	3	3	4	12	4	0	**7**	2
CT22	4	3	15	4	4	4	4	1	4	11	4	2	**12**	10
CT23	4	3	12	4	4	4	4	3	3	12	4	0	**5**	1
CT24	4	3	15	4	4	4	4	3	4	12	4	4	**10**	0
CT25	3	3	15	4	3	3	3	2	4	12	2	3	**13**	2
CT26	4	3	15	4	4	4	3	3	4	9	4	11	**23**	3
CT27	4	3	15	4	1	3	4	3	2	12	4	2	1	2
CT28	4	3	15	4	3	3	3	3	3	12	4	1	**20**	4
CT29	4	3	15	4	4	4	4	3	4	12	4	25	**38**	3
CT30	4	3	15	4	4	4	4	0	4	12	4	12	**20**	2
CT32	2	3	14	3	1	1	4	2	4	12	4	3	**12**	2
CT33	4	3	14	4	3	4	4	1	3	12	4	-2	**10**	0
CT34	4	3	15	4	3	4	4	2	3	12	4	4	**9**	1

Table 9: Participant Oxford Cognitive Screen scores
Abbreviations: Oxford Cognitive Screen (OCS). Data in bold are values reaching Screening thresholds.

Variable	Mean±SD / No. (%) Groups		*p*
	Therapy $(n = 12)$	**Control** $(n = 12)$	
Age (years)	**58.1±11.5**	**57.7±17.4**	**.95**
Gender			**.37**
Female	5 (41.7)	3 (25.0)	
Male	7 (58.3)	9 (75.0)	
Time since stroke (days)	**86.00±54.18**	**74.67±70.11**	**.67**
Type of stroke			**.39**
Ischaemic	**7 (58.3)**	**8 (66.7)**	
Haemorrhagic	**5 (41.7)**	**4 (33.3)**	
Total number of VR stimulation days	**14.50 ± 0.92**	**14.08 ± 1.44**	**.45**
Mean Baseline Stars (total)	**18.75±9.55**	**21.50±10.14**	**.52**
Mean Baseline CBS	**17.80±5.59**	**12.75±5.22**	**.03**

Table 10: Descriptive Statistics for key demographic and baseline data

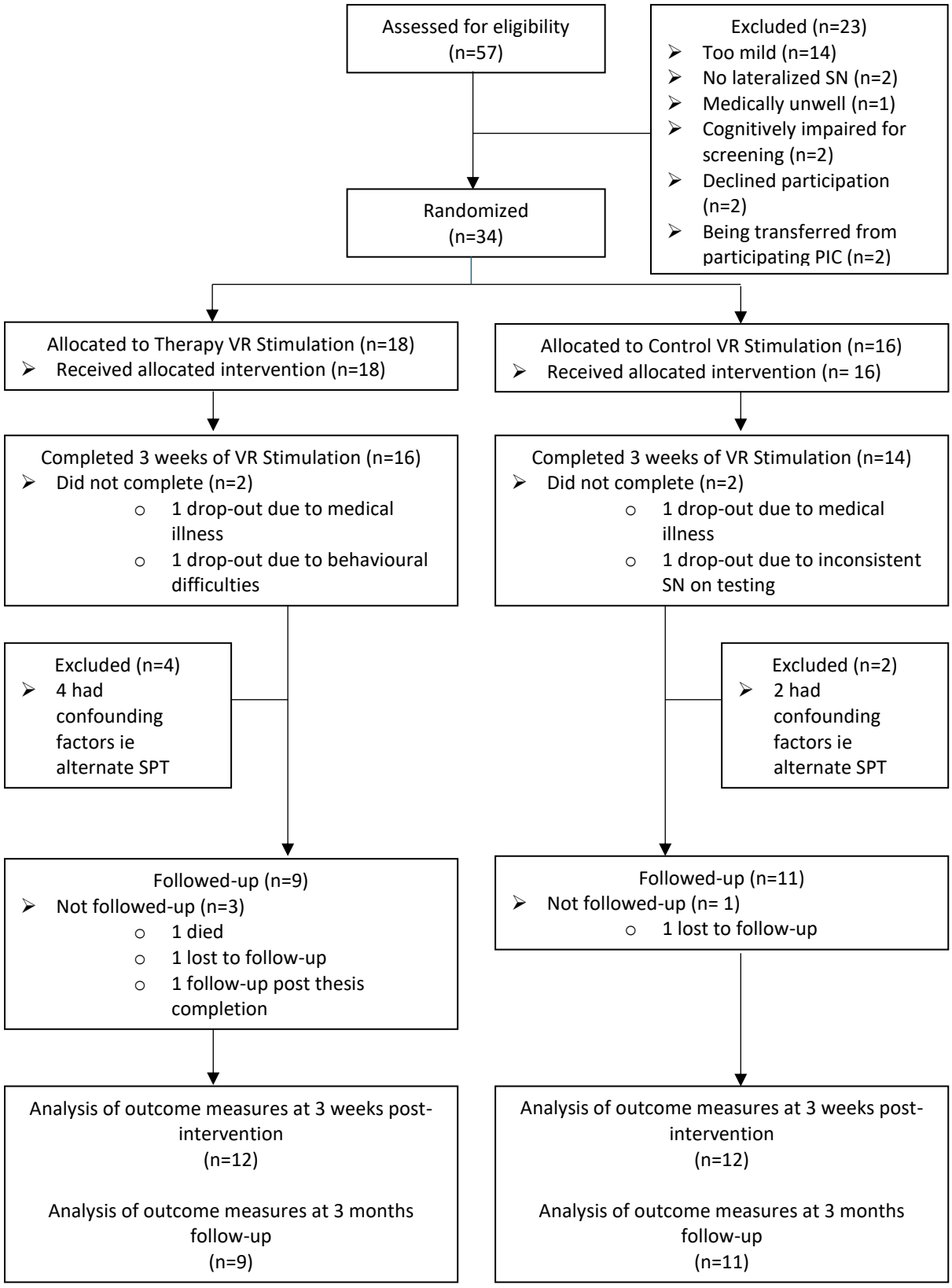


Figure 13: CONSORT Diagram for the ATTEND trial

3.11 Lesion Overlap Map

Using SPM (169), a lesion overlap map (LOM) was created for 23 patients whose post-stroke scans were retrieved, 20 of which were MRI Head scans and 3 of which were CTs (Figure 14). The LOM displays the distributions of the patients' lesions across the brain. All patients suffered a right hemispheric stroke affecting the right middle cerebral artery territory. The majority of patients had extensive and widespread damage, involving the temporal, parietal and frontal lobes. Colour shades represent the number of patients with overlapping lesions. A Mann-Whitney U test was conducted to compare brain lesion volumes between the Therapy Group and the Control Group. Although the median lesion volume in the Therapy Group (164.92, interquartile range 138.63) was higher than in the Control Group (101.85, interquartile range 150.80), there was no statistically significant difference in lesion volumes between the two groups, $U = 48.00, Z = -1.11, p = .268$.

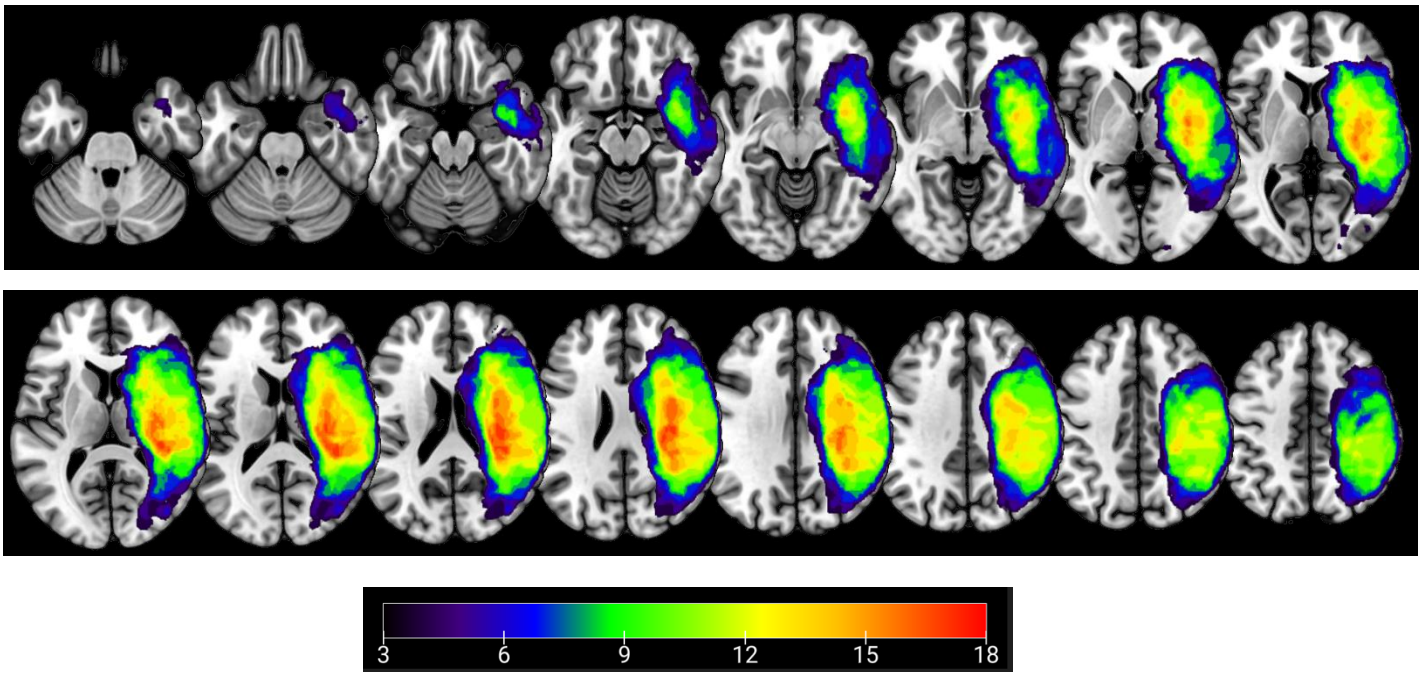


Figure 14: Lesion Overlap Map
Lesions for 23 of the patients in the ATTEND trial have been displayed on a canonical MRI T1 weighted image in standard MNI space. A threshold of 3 was applied. Axial slices in ascending steps of 5mm are oriented in neurological convention (right side of the brain on the right of the images). The colour intensity scale demonstrates the increasing number of patients having overlapping voxels.

3.12 Materials

An HTC Vive Pro Eye Headset, which has eye-tracking and room-scale tracking via the use of positional tracking base stations, was used to capture gaze fixation data during FiVE in the Vive and deliver the VR Stimulations. The HTC Vive Pro Eye Headset integrates Tobii technology for advanced eye-tracking functionality, which has previously been covered in Section 2.7. It has an estimated horizontal field of view of 110^{o}. Steam VR, developed by Valve, is a virtual reality hardware and software platform which supports the HTC Vive Pro Eye Headset. The headset was calibrated via the Steam VR dashboard, to the midline of the participant and to their respective height whilst in the inpatient bed or a chair. The software was operated on an MSI GT73VR GRF Titan Pro laptop, equipped with an Intel Core i7-6700HD @ 2.60HZ processor, 16GB dual-channel DDR4 RAM, NVIDIA GeForce GTX1080 graphics card, running on a 64-bit version of Windows 10 Home. Both the headset and laptop were CE marked.

3.13 Gamification of the Therapy and Control Stimulation

Gamification refers to the application of game-design elements in non-game contexts. It has emerged as a powerful tool in neurorehabilitation, offering innovative ways to enhance patient engagement, motivation, and functional recovery. By incorporating features such as rewards, feedback and changes in difficulty level, gamification turns rehabilitation exercises into engaging activities that encourage motivation, adherence, and shield against the effects of boredom and fatigue that can be associated with repetitive exercises (179, 180).

Both the Therapy and Control VR Stimulations created for the ATTEND Trial were gamified.

The MSI laptop, HTC Vive Headset and the Base Stations were set up around the patient's bed, or bedside chair on the ward, or in the therapies kitchen at Charing Cross Hospital if it was available for a private session (Figure 15).

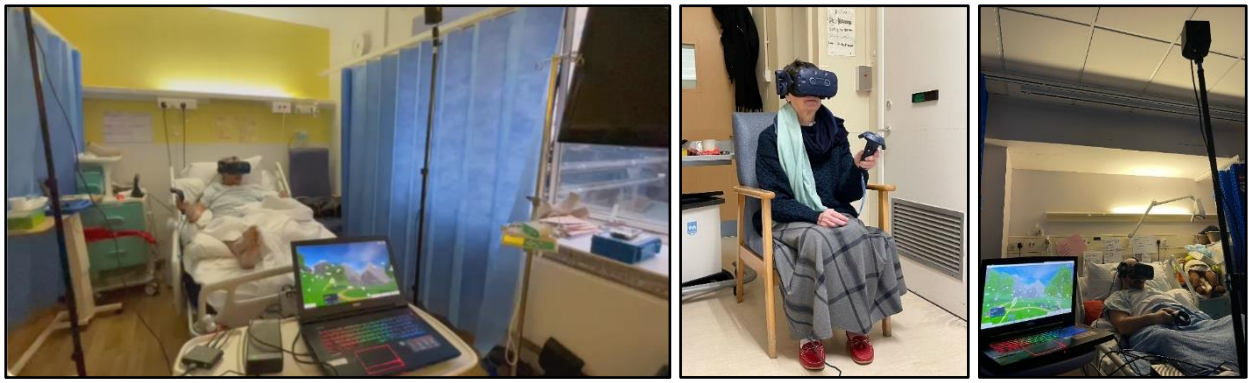


Figure 15: The ATTEND VR set-up on the ward.
Components visible here are the 2 base stations on the tripods, the HTC Vive Headset as worn by the patients, the handheld HTC remote, the MSI Titan Pro laptop and hardware connections

The VR Stimulations were delivered via the HTC Vive Pro Eye with built-in eye tracking. The headset was calibrated to the midline of the patient to prevent worsening SN. For patients with a hemicraniectomy, care was taken to ensure safety by securing the wheelchair seatbelt if necessary, and the protective helmet was removed. I applied the headset encouraging open feedback with regards to comfort and fit. Verbal cues were employed throughout the process to inform the patient if I was approaching them, etc, mindful that they were unaware of their real-life environment whilst in the in the Virtual world. The patient was familiarized with the handheld HTC remote which was turned on, paired with the headset, and handed to them prior to the initiation of the VR Stimulation. Haptic feedback on the remote was turned on, providing a gentle vibration on successful catches/target shooting. The headset speakers were adjusted to lay in line with their ears, so that they could hear the Doppler sound effect linked to active eye tracking within the Therapy VR Stimulation, and a sound effect linked to shooting a target in the Control VR Stimulation.

For both VR Stimulations, as mentioned previously, the patients completed 4 x 10-minute blocks of the VR Stimulation, therefore totalling 40 minutes a day. If they wished to take a break between blocks, the headset was removed, and a drink was offered for a brief rest before continuing. If the patient required the use of the toilet and had to be hoisted out of bed, etc., then the entire calibration was checked before re-starting again.

3.13.1 Horizontal Therapy VR Stimulation

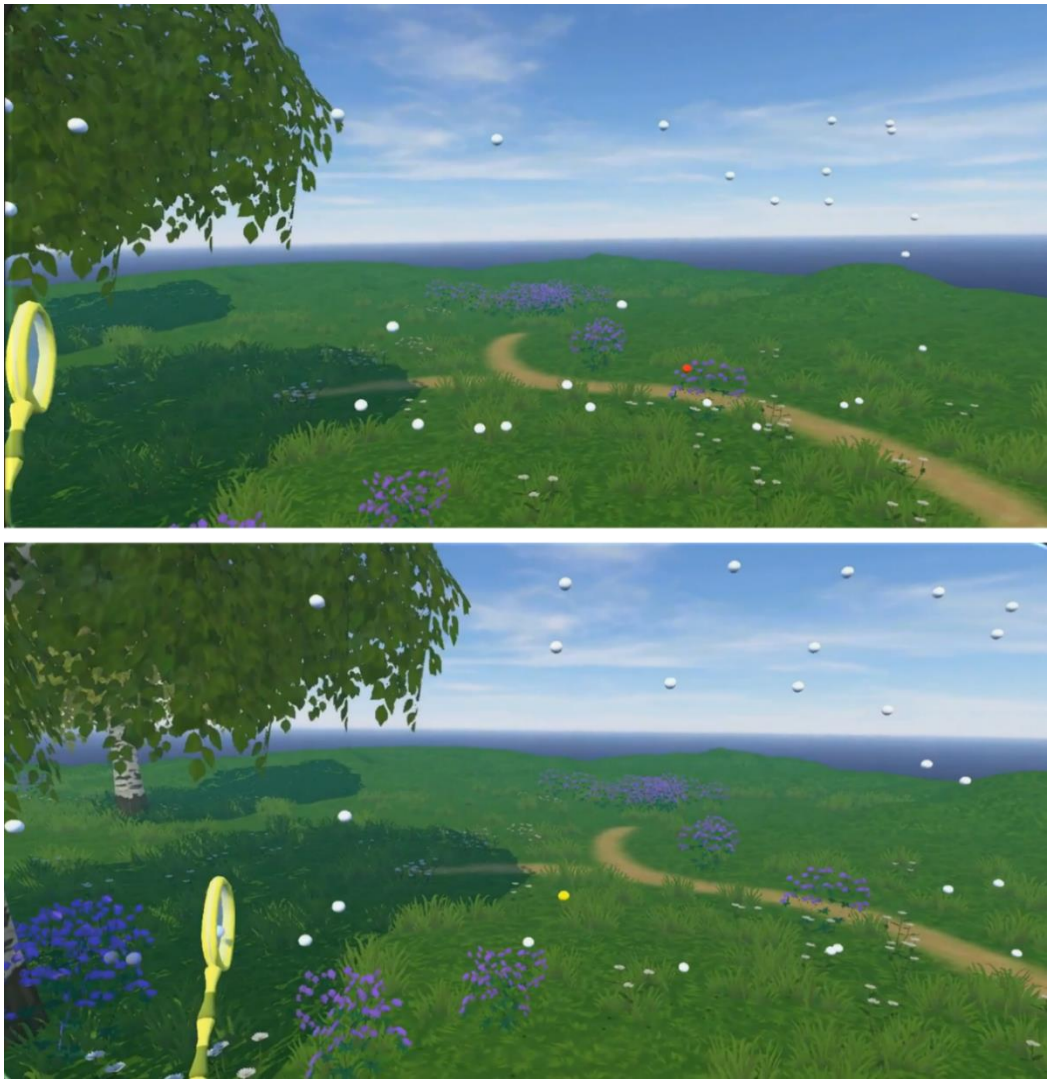


Figure 16: Horizontal Therapy VR Stimulation
Top: A red ball appears amongst the white. Bottom: The red ball changes to yellow as soon as eye tracking begins. The aim of the "game" is to track the yellow ball across the horizontal plane (in this case, from right to left for a patient with left-sided Spatial Neglect), until they catch it in the net

In the Therapy VR Stimulation, the aim of the therapy was to induce horizontal smooth pursuit eye movements. The patient saw several white balls move horizontally from the unaffected side to the affected side, for example, from the right to the left for someone with left-sided SN. On the left, the patient saw a racket. The position of this racket was at a fixed point horizontally, and it only moved vertically. One of the balls was red in colour, and the aim of the game was for the patient to track the red ball all the way to the left along its horizontal trajectory, and catch it in the racket. This was done repetitively during the session (Figure 16, top).

The red ball turned yellow in colour once eye-tracking was initiated, and would remain yellow along the trajectory only if continually tracked successfully (Figure 16, bottom). The change in colour from red to yellow provided feedback of successful tracking to both the patient and me. The patient moved the remote up or down to control the racket in order to catch the ball. A successful catch made the yellow ball blow up in a puff of smoke, as a visual reward for the catch. It was also associated with haptic feedback on the remote. A Doppler sound effect was also activated with successful tracking. As the patient caught more targets, the environment became “richer” with the appearance of flowers, shrubs etc., serving as a visual feedback reward.

Settings were adjustable in the game for direction of travel, size of balls, size of racket, horizontal position of racket, vertical position of balls, vertical range of balls, frequency of targets, speed of balls, and depth-related distance of balls in space. Please note, standard settings were used for all patients in order to reduce variance of experience and area of eye scanning.

3.13.2 Vertical Control VR Stimulation

Figure 17: Vertical Control VR Stimulation.
The patient has to use the stick to shoot the apple targets on the tree. The size of the "apples" can be altered from large to small by 10 degrees of size.

In the Control VR Stimulation, the aim of the game was to induce mainly vertical eye movements and prevent any horizontal smooth pursuit. The patient saw a central tree with red apples stacked vertically with limited deviation horizontally. The tree appeared in the midline of the patient as opposed to on the right (for someone with left-sided SN) in order to prevent worsening of SN. In this game, the patient controlled the stick with the handheld remote, and pressed a trigger on the underside of the remote to release a tiny white ball in order to shoot down the vertically placed apples (Figure 17). There was haptic feedback, sound effects, and a score that appeared next to the bark of the tree for reward-based feedback. Once the apple was shot down it rolled vertically downwards towards the patient.

In this game, the only adjustable settings were the size of the apples, for an additional challenge to prevent monotony and boredom in case a patient became proficient at shooting targets of a certain size. The Control VR vertical stimulation acted as a control for the Therapy VR horizontal stimulation effects, for the purposes of performing an activity in VR for a set period of time, for preferred/contralateral handheld remote use, and for the effects of time.

3.14 Baseline Behavioural Assessments

At T1 and T2, baseline behavioural tests were conducted to assess various domains (Table 11). Of these, the Star Cancellation Test and the Catherine Bergego Scale will be covered under "Behavioural Outcome Measures".

Baseline Behavioural Assessment	Domains	Severity cut-offs	Laterality Pointers
Oxford Cognitive Screen (OCS)	Language Praxis Number processing Memory Spatial and Controlled Attention	Space Asymmetry Severe >12 Severe - Moderate: 9–12 Moderate-mild: 4–8 Mild: <4 (minimum required score of 3)	Positive Space Asymmetry score = Left sided SN Negative Space Asymmetry score = Right sided SN
Star Cancellation Test	Spatial Neglect	Severe: total number of stars cancelled <22 Moderate: 23 to 42 stars cancelled Mild: 43 to 50 stars cancelled	Laterality index 0-0.46 = Left sided SN Laterality index 0.54-1 = Right sided SN
Catherine Bergego Scale (CBS)	Spatial Neglect	Severe: score of 21-30 Moderate: 11-20 Mild: 1-10	N/a
Sustained Attention to Response Task (SART)	Sustained Attention	N/a	N/a

Table 11: Baseline Behavioural Assessments

3.14.1 Oxford Cognitive Screen

The Oxford Cognitive Screen is a validated, stroke specific cognitive screening assessment that was developed to screen for and assess cognitive difficulties post- stroke. This freely-available paper based tool measures the key cognitive domains often impacted following stroke – language, attention including unilateral SN, executive functioning, memory, praxis and number processing (176). A specific advantage is its utility for the assessment of neurocognitive deficits in dysphasic patients because test items are presented both orally and visually, and other answers can be selected from a multiple-choice list.

In the ATTEND trial, the OCS was performed at T1 in order to aid deductions about a participant's ability to engage and participate with the VR Stimulation. In particular, the Broken Hearts Test was used as a SN screening tool for the patients. This part of the assessment involved placing an A4 sheet in landscape orientation in the midline of the patient as guided by a triangle marked on the centre of the page. The page contained ten blocks (arranged in two rows of five) with each block containing five complete hearts, five with a left-sided gap and five with a right-sided gap. The patient was then asked to cross through only the complete hearts they could see. A practice page was used to ensure comprehension of the task before performing the main test, which had a time limit of three minutes.

In terms of scoring, I computed a "Space Asymmetry" score, which measures egocentric SN, and "Object Asymmetry" score, which measures allocentric SN. As I was focused on assessing egocentric SN in the ATTEND trial, I concentrated on Space Asymmetry score as part of the screening assessment, which was calculated by subtracting the number of hearts cancelled in the four left-most blocks from the number of hearts cancelled in the right-most four blocks (see Table for scores). A positive value indicated left-sided SN whereas a negative value

indicated right-sided SN. For information, the Object Asymmetry score was calculated by subtracting the number of hearts with a right-sided gap from the total number of hearts with a left-sided gap. A positive value showed left allocentric SN whereas a negative score showed right allocentric SN. Severity cut-offs for Space Asymmetry were guided by Demeyere et al. (176) who looked at severity indication based on quartiles in a sample of 176 patients who completed the Broken Hearts Test, out of which 87 showed an impairment (Table 11 for cut offs).

The OCS was completed for 23 out of 24 patients. For the purposes of this thesis, Space Asymmetry scores only were analysed. Of the 23 patients, 10 were severe, 8 were moderate to severe, 4 were mild to moderate and 1 did not meet the minimum cut-off. The $Mean\ Space\ Asymmetry\ score = 13.83\ (SD = 8.19)$.

3.14.2 SART

The Sustained Attention to Response Task (SART) is a widely used cognitive assessment tool designed to measure sustained attention and response inhibition (181). Developed by Robertson et al. (182) SART is a computer-based go/no-go task in which participants respond to frequently presented stimuli while withholding responses to infrequent target stimuli. The task typically requires participants to press a key for every non-target digit (numbers 1–9) and to withhold a response for a designated no-go target (the digit 3). This frequent-response setup creates a habitual motor response, making the inhibition of responses to no-go targets a test of sustained attention and executive control. Errors of commission (failure to correctly withhold a response to a no-go target) indicate lapses in sustained attention, errors of omission (failure to respond to non-targets) may reflect problems with attention processing and post-error slowing reflects error awareness.

In the ATTEND trial, the SART was conducted with participants at T2 in order to assess their sustained attention. The task was programmed to appear within the VR headset, in 2D format, with numerical stimuli presented at a fixed central point in order to keep attentional focus fixed and reduce the need for visual scanning. Whenever the participant saw a go trial (digits 1,2, 4-9; n=200), they were required to press a trigger on the HTC Vive handheld remote, and were required to withhold a response (i.e. do nothing) whenever the digit 3 appeared on the screen. A practice session was performed prior to the main task to ensure comprehension.

The SART will be covered separately in-depth in its dedicated chapter in this thesis, in Section 4.0.

3.15 Behavioural Outcome Measures

3.15.1 Star Cancellation Test (Primary Outcome Measure - Impairment Based Measure)

The Star Cancellation Test (SCT), developed by Wilson et al. in 1987 (58), is a subcomponent of the Behavioural Inattention Test, and is a widely used pencil-and-paper based clinical tool for assessing SN (Figure 18). The test requires the participant to cancel a total of 54 small stars (27 in each hemi-space) amongst distractors including 52 large stars, 13 letters and 10 words. The A4 sheet is placed in the midline of the patient, as indicated by the midline arrow on the page, and the patient is requested not to shift position. An example of cancellation is demonstrated by the examiner by cancelling 2 example small stars in the centre of the page.

The SCT is highly sensitive to detecting SN severity, distinguishing between mild and severe cases, and has been validated against other measures of SN (44). An examination of its test-

retest reliability, looking at 85 patients with SN and 83 without, demonstrated it to be excellent (Intraclass correlation coefficient of 0.89) (55).

The total score achievable is cancelling 54 out of 54 stars (indicating no SN). The lower the score, the greater the severity of SN. The severity scale cut-offs used in this study are also taken from Bailey et al., severity is classed as severe if the total number of stars cancelled are less than 22, moderate if between 23 to 42, and mild if 43 to 50 are cancelled (out of 54 stars) (55). A laterality index (derived by dividing the number of stars cancelled on the left by the total number of stars cancelled) is used to check for laterality of SN – a laterality index of 0-0.46 indicates left-sided SN, whilst 0.54-1 indicates right-sided SN (82).

In the ATTEND trial, the Star Cancellation Test was performed at T1/T2 for screening and as a baseline measure, at the end of 15 days of participation at T3, and at follow-up T4, as a primary impairment-based outcome measure. The star cancellation severity was one of the minimization factors used during allocation by minimization. The mean baseline star cancellation scores for the Therapy and the Control Groups were matched, $p = .52$.

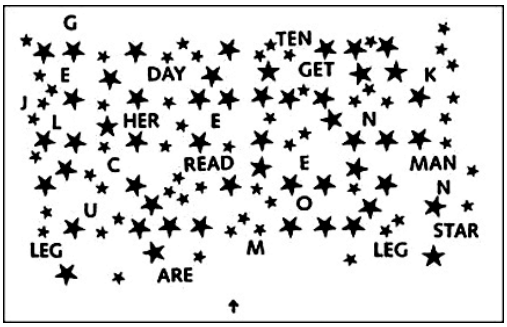


Figure 18: The Star Cancellation Test.
The sheet is placed in the midline of the patient, and 2 stars in the middle (above the arrow) are cancelled as a demonstration. The patient is then asked to cancel only the small stars, without altering the position of the sheet.

3.15.2 Catherine Bergego Scale (Functional Based Measure)

The Catherine Bergego Scale (CBS) is a validated observational tool designed to assess the severity and functional impact of SN, across 10 activities of daily living, such as grooming, eating, navigating, and interacting with objects in space (183) (Figure 19). Each of the 10 items are given a rating of 0/1/2/3, indicating "never"/"sometimes"/"most of the time"/"all the time", respectively. It is usually completed by a healthcare professional or a carer, based on direct observation and interaction with the patient. The CBS can also be used as a self-assessment tool by the patient to try and capture their insight and awareness of their SN, generating an "anosognosia score" (62). The CBS has been shown to be sensitive in detecting both personal and peripersonal SN and effective in tracking changes over time, such as during recovery or in response to intervention (184). Azouvi et al. found adequate to excellent internal consistency when testing the CBS in 83 stroke patients (15).

The final score ranges from 0 (no SN) to 30 (severe SN). Arbitrary severity cut-offs are considered to be 1-10 for mild behavioural SN, 10-20 for moderate behavioural SN and 21-30 for severe behavioural SN (44, 62). Higher scores indicate higher severity, and therefore a reduction in score indicates improvement. For items on the CBS that are not possible to assess, for example, questions 8 and 9 – "Collides with people or objects on the left side, such as doors or furniture, either while walking or driving a wheelchair" and "Experiences difficulty in finding his/her way towards the left when travelling in familiar places or in the rehabilitation unit" respectively – these are left blank. The total score is calculated by:

$$Score = \frac{Sum\ of\ points}{Total\ number\ of\ questions\ answered} \times 10$$

If all 10 questions are answered then the sum of points is the final score (185). Notably, a reduction of at least 4 points has been regarded as a minimal clinically important difference (MCID) (80).

In the ATTEND trial, the CBS was a primary functional outcome measure, and was completed at T2 and T3 by the patient's treating Occupational Therapist blinded to the randomisation, based on their day-to-day assessment and observation of the patient. In cases where the patient was transferred to a different unit during the trial, the T2 and T3 CBS was completed by two different treating Occupational Therapists, both of whom would remain blinded. The patient also completed a self-assessment at T2 and T3, but anosognosia scores were not analysed for this thesis.

0=no neglect; 1=mild neglect; 2=moderate neglect; 3=severe neglect	0	1	2	3
1. Forgets to groom or shave the left part of his/her face	❑	❑	❑	❑
2. Experiences difficulty in adjusting his/her left sleeve or slipper	❑	❑	❑	❑
3. Forgets to eat food on the left side of his/her plate	❑	❑	❑	❑
4. Forgets to clean the left side of his/her mouth after eating	❑	❑	❑	❑
5. Experiences difficulty in looking towards the left	❑	❑	❑	❑
6. Forgets about a left part of his/her body (eg, forgets to put his/her upper limb on the armrest, or his/her left foot on the wheelchair rest, or forgets to use his/her left arm when he/she needs to)	❑	❑	❑	❑
7. Has difficulty in paying attention to noise or people addressing him/her from the left	❑	❑	❑	❑
8. Collides with people or objects on the left side, such as doors or furniture (either while walking or driving a wheelchair)	❑	❑	❑	❑
9. Experiences difficulty in finding his/her way towards the left when traveling in familiar places or in the rehabilitation unit	❑	❑	❑	❑
10. Experiences difficulty finding his/her personal belongings in the room or bathroom when they are on the left side	❑	❑	❑	❑
Total score (/30)				

Figure 19: The Catherine Bergego Scale
These are the 10 questions for activities of daily living that comprise the CBS.

3.16 Behavioural Data Analysis

All data analysis was completed using Statistical Software Package for the Social Sciences 29 (SPSS).

The primary research question was whether horizontal smooth pursuit eye movements delivered using VR brought about an improvement in SN as compared to vertical eye movements in the Control VR Stimulation. The behavioural outcome measures used to investigate this question were the impairment-based Star Cancellation Test and the functional-based Catherine Bergego Scale. Change scores for each of these from Baseline (before VR Stimulation, timepoint T2) to 3 weeks (end of 15 days of VR Stimulation, timepoint T3) were analysed. Additionally, for the Star Cancellation Test, change scores from 3 weeks (end of 15 days of VR Stimulation, timepoint T3) and 3 months (3 month follow-up, timepoint T4) were analysed.

3.16.1 Data Preparation

Scores at Baseline (pre-VR Stimulation, T2) and 3 weeks (end of 15 days of VR Stimulation, T3) were arranged by group. Raw data was used for analysis within SPSS, and 95% Confidence Intervals for within-subject designs were calculated using the Loftus and Masson 1994 procedure (186) (for display in graphs in the Results Section 3.21).

3.16.2 Handling of Missing Data

Whilst the datasets for the Baseline and 3 weeks was complete for both behavioural outcome measures, data was missing for 4 subjects (16.7% of the total sample) at the 3 month time point Star Cancellation Test. 2 were lost to follow-up, 1 died in hospital prior to the follow-up date and 1 is scheduled to have their follow-up after the completion of this thesis.

A missing value analysis was performed in SPSS, and the missing data were determined to be Missing Completely at Random (MCAR), based on Little MCAR's test, $\chi^2(2) = 2.856, p = .240$. There was also no significant difference in the mean Baseline and 3 weeks scores without the missing subjects, $p = .98$ and $p = .12$ respectively.

Therefore, a listwise deletion was done. The final sample size for the 3 month analysis for the Star Cancellation Test was $n = 20$.

3.16.3 Response to Therapy versus Control VR Stimulation

Descriptive statistics were calculated for the Baseline and 3 weeks scores for each group.

A repeated measures analysis of variance (ANOVA) was used to investigate the change in behavioural measures scores from Baseline to 3 weeks for both the groups, and look for a Group*Time interaction. As the main hypotheses were based on Group*Time interactions, any significant effects were further investigated with a series of planned, post-hoc tests.

3.16.4 Post-Hoc Tests for Group*Time Interaction

Following the emergence of a significant Group*Time interaction, post-hoc tests were completed:

1) A paired samples t-test was performed on the data for each group in order to examine the differences between Baseline and 3 weeks scores.

2) An independent samples t-test was performed for a between group comparison, to compare group scores between Baseline and 3 weeks.

3) Effect sizes were calculated to quantify the size of the significant differences. The commonly used arbitrary values for Cohen's d to interpret effect sizes, as guided by Cohen (187, 188), are small effect size $d = 0.2$, medium effect size $d = 0.5$ and large effect size $d = 0.8$; and for the η_p^2, effect size is considered small when it is 0.01, medium when it is 0.06, and large when it is 0.14 (189).

3.16.5 Maintenance Effects

The maintenance effects of the VR Stimulation were explored using the Star Cancellation Test scores at 3 weeks (end of 15 days of stimulation, timepoint T3) and 3 months (3 month follow-up, timepoint T4), by performing a repeated measures ANOVA. As there was a main effect of group, a post-hoc analysis was conducted using an independent samples t-test.

3.17 FiVE in the Vive Task

Definitions of terms used in this section:

FiVE in the Vive (FVE) Task: A single free visual exploration task consisting of viewing 6 pairs of images and their mirrored versions

VR Stimulation session: A 40-minute session of VR Stimulation (Therapy or Control) comprised of 4 x 10-minute blocks

"Pre-Stimulation": The FVE Task that was performed before the VR Stimulation session on any given day

"Post-Stimulation": The FVE Task that was performed after the VR Stimulation session on any given day

Gaze fixation: Period during which the eyes remain focused on a certain target between saccades (190)

Gaze duration / dwell times *(used interchangeably):* A summation of the time spent focused on a specific area or object, including consecutive fixations within that region, reflecting sustained visual attention (191)

The background for the FiVE in the Vive Task or FVE Task, has been covered in its dedicated chapter in Section 2.0, which also established its role as a sensitive diagnostic assessment tool to demonstrate spatial bias in patients with SN. In the ATTEND trial, the FVE was used as an impairment based secondary outcome measure. Its role was to capture gaze duration data daily at the start and end of the VR Stimulation, to answer the question as to whether the centre of gaze location changed following the horizontal Therapy VR Stimulation as compared to the vertical Control VR Stimulation.

The hardware materials, set-up and calibration process were the same as described in Section 2.7, and as for the delivery of the VR Stimulations described earlier in Section 3.12. Gaze duration data was captured using the built-in Tobii technology within the HTC Vive Eye Pro headset, for precise eye tracking, employing near-infrared light and high-resolution cameras that capture gaze direction, pupil size, and eye openness. As data capture requires reflections from the pupils, the act of blinking induces eyelid closure which blocks infrared reflections, preventing data capture in that moment.

To briefly recap, with the aid of a software company named SoftV, 24 naturalistic 2D images (12 pairs of original and their mirror images) from Kaufmann et al. (170) were imported into the HTC Vive Pro Eye headset. This (i) allowed the patient to perform the FVE task at the start

and end of every session using the same hardware; (ii) the 110^{o} trackable field view within the headset meant that the images could cover a wider visual angle of 64^{o} by 48^{o}, as opposed to 28^{o} by 21^{o} on a traditional screen; (iii) and the head-stabilising functions of the headset ensured that the image remained fixed at the centre of the viewing field irrespective of any head movements.

3.17.1 Procedure

In the FVE Task, out of the 12 pairs, 6 pairs of images and their mirror images were drawn and presented to the patient one by one, in pseudorandom order, programmed in a way the two images from a pair did not appear consecutively. Each image was displayed within the headset for 7 seconds, followed by a 2 second gap marked by a centrally fixed white cross. The instruction to the patient was to view the images silently as specific instructions can influence the way images are viewed and tracked (192, 193). The total task time was 108 seconds.

To briefly recap from Experimental Chapter I, when the patient viewed the image within the headset, the Tobii eye-tracking technology logged wherever the patient fixed their gaze for more than 100 milliseconds. Using custom-made software, these dwell times were outputted as an integer into an Excel Comma Separated Values (.csv) file, for example, “1” would equal 100 milliseconds of gaze dwell time. The Excel spreadsheet of 24 x 32 cells can be thought of as a “grid” over the image, each cell representing 2^{o} of visual angle. As dwell times are cumulative, the value in a single cell could be the result of multiple gaze fixations. Each image outputted a single .csv file which was the raw data for the FVE analysis.

Each patient performed the FVE Task at the start and end of the daily 40-minute VR Stimulation session (Table 12). On Day 1, the patient performed the FVE Task 3 times Pre-Stimulation (this was done in order to collect a larger amount of baseline Pre-Stimulation visual data representing their baseline gaze location) and 1 FVE Task Post-Stimulation. On the remaining days, the patient performed a total of 2 FVE Tasks, 1 Pre-Stimulation and 1 Post-Stimulation.

	Day 1			Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
Pre-Stimulation FVE Task	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1
Post- Stimulation FVE Task			x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1	x1

Table 12: A timetable of the FVE Tasks

3.18 FiVE in the Vive Task Analysis

All analysis was performed using software programme Statistical Parametric Mapping (SPM12) in Matlab 2021b. Refer to Figure 29 for a summary of the SPM analysis.

3.18.1 Data Handling and Pre-Processing

If the patient did not actually view an image at all (eyes closed/technical fault), then no dwell times were captured for that particular image, so no integers were logged on that .csv file. In this case, the empty .csv file, (consisting only of zeros) was discarded in order to maintain the integrity of the statistical model and avoid errors or biases in pre-processing and analysis. Similarly, if less than 8 images were viewed in an FVE Task, that day's dataset was excluded. Because each set of images was given an equal weighting in the next steps of statistical modelling, removing incomplete data sets prevented distorting variance estimation, reducing

statistical power, or undermining the comparison across conditions, which would affect the reliability and validity of the results.

The .csv file was converted into a NIFTI (.nii) file to allow for analysis within SPM. Each file was smoothed using a Gaussian kernel with 8mm full-width half maximum in the pre-processing step in order to increase the signal to noise ratio (Figure 20).

This generated a set of 12 smoothed images for every single FVE Task. Presuming a complete dataset, this meant a total of 384 smoothed images per patient.

Each “x1” FVE Task presents 12 images therefore {Day1} (4 FVE Tasks x 12 images each) + {Days 2-14} (2 FVE tasks x 12 images each x 14 days) = 32 FVE tasks x 12 images each = 384 images per data set.

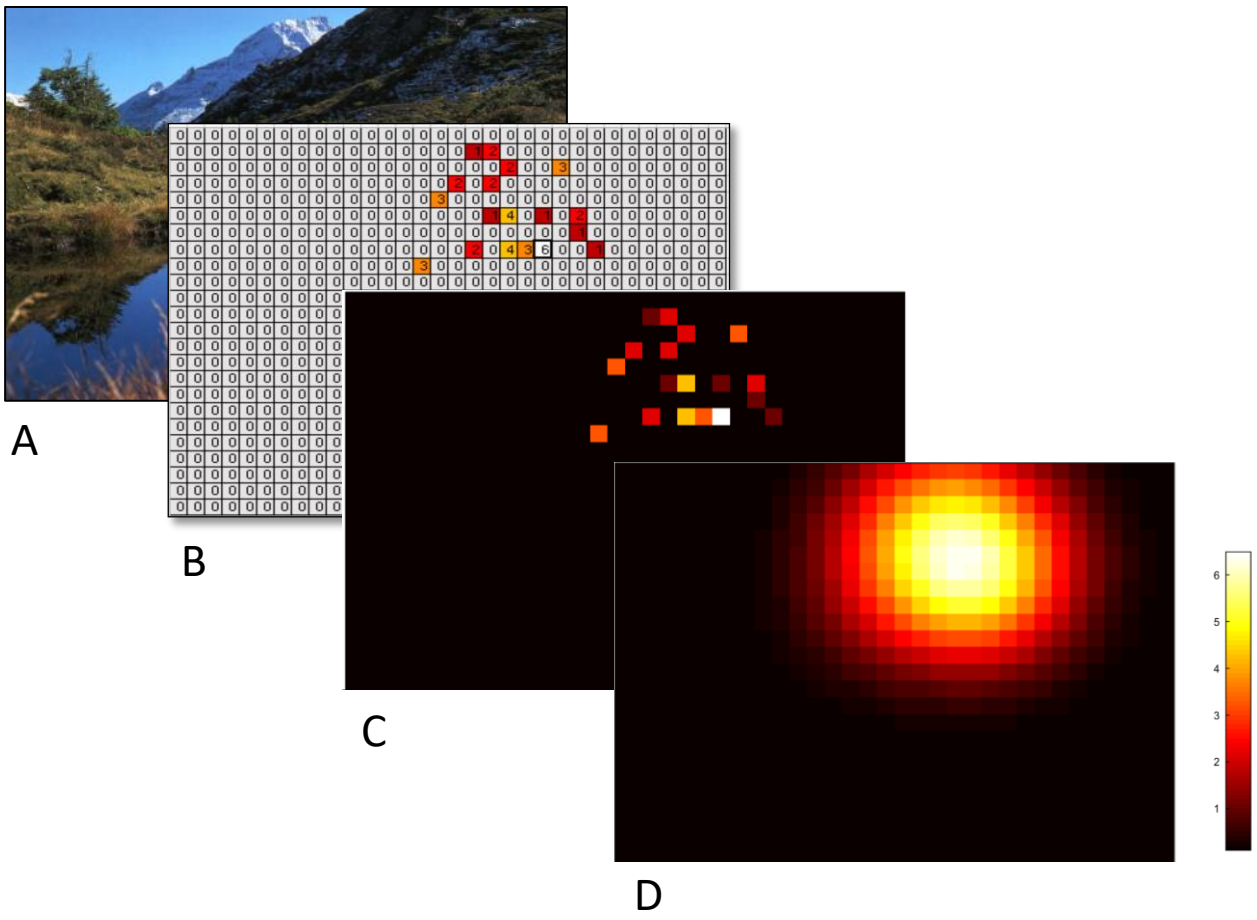


Figure 20: The journey of a free visual exploration image from original to a pre-processed smoothed .nii file. (A) An example of an original image viewed by a patient in the HTC Vive headset during the FVE Task. (B) The output Excel .csv file with integers logged for every point of gaze fixation. In this image, I have manually colour-coded the integers to highlight them. (C) The converted .nii file showing the corresponding gaze fixation points. Colour legend shows black to white transitions from areas of no fixations (0=black) to maximum fixations (in this case 6=white). (D) The .nii file after undergoing smoothing using a Gaussian kernel with 8mm full-width half maximum

3.18.2 1st Level Analysis

The next step of the process was the within-subject 1st Level Analysis for each participant. A Design Matrix using a one-way ANOVA was created, in order to check the average gaze patterns over time and model the variance between the images. The images in the design matrix were arranged sequentially, starting with Day 1 Pre-Stimulation images followed by Day 1 Post-Stimulation images, then Day 2 Pre-Stimulation images followed by Day 2 Post-Stimulation images, continuing in this pattern for all 15 days. The Independence was set as "No" and the variance as "Equal" for this within-subject design, as at this stage I was looking

at a repeated measure across time. The resultant design matrix was used as the foundation for applying the set of contrasts for the 2nd Level Analysis (Figure 21).

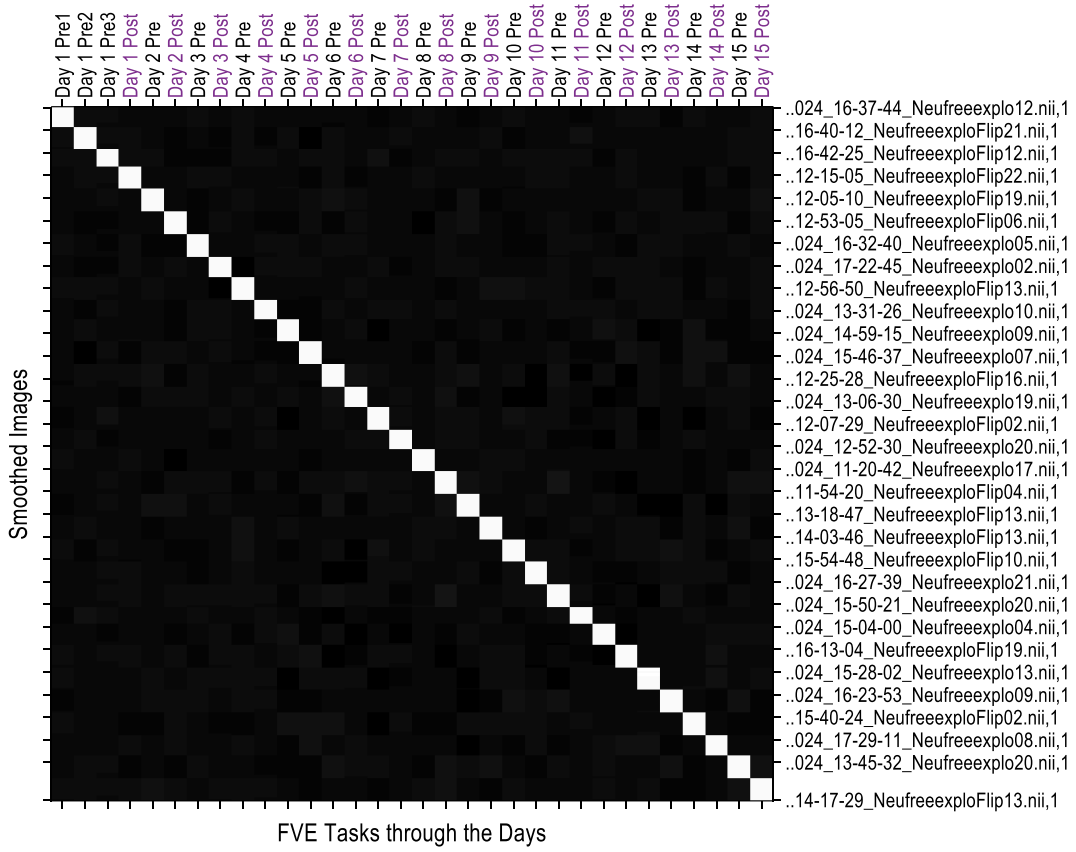


Figure 21: The within–subject SPM Design Matrix at the first level.
The images from Pre-Stimulation and Post-Stimulation per day, arranged across the 15 days. The x-axis shows the Day count and the Pre and Post arrangement, with each white box representing the images. The y-axis lists the saved titles of the smoothed images (12 images each for 32 Pre and Post FVE Tasks in total).

This within-subject design matrix was created for each of the 24 participants.

Next, two separate t-contrasts were applied to this design matrix for each participant, one to investigate long-term effects, and one to investigate short-term effects.

3.18.2.1 Long-Term Effects

To investigate whether there were any long-term spatial shifts present over the course of the 15 days of VR Stimulation, I looked at the Pre-Stimulation images only for each day. The

expectation being that, as time passes, the centre of gaze should shift more to the affected side; the null hypothesis being that there is no consistent shift in centre of gaze across time.

For each day, a t-contrast was defined for the Pre-Stimulation images for that specific day (e.g., [1] for Day 1 Pre and [0] for all other days) (Figure 22). NB: for the part of the analysis looking at long-term effects, for all patients, only the first set of Pre-Stimulation images on Day 1 (instead of all 3 sets) were entered into the design matrix, as not all patients did x3 Pre-Stimulation FVE Tasks on Day 1.

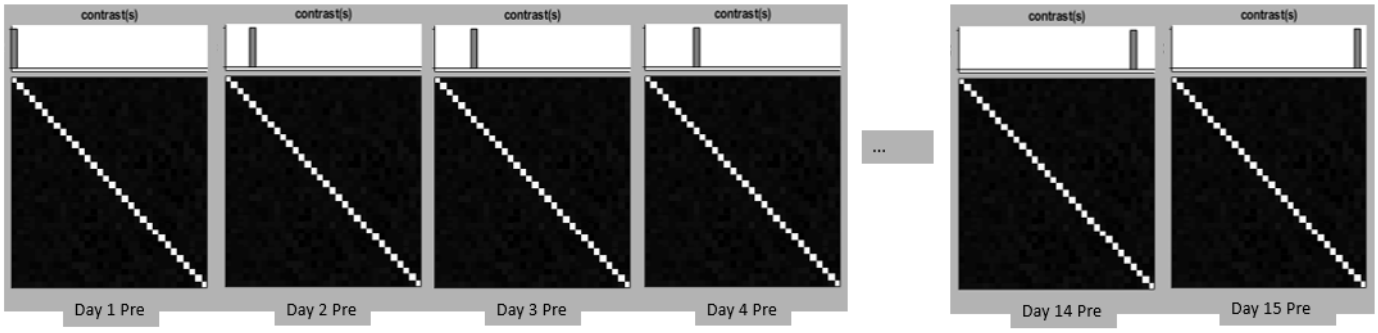


Figure 22: t-contrast for Pre-Stimulation images per day
The grey bars in the top demonstrate where the t-contrast [1] has been applied, in this case, for every day's Pre-Stimulation images only.

A single contrast (con.nii or "con") image was generated for each day. The con image was a voxel-wise statistical map of the average gaze location prior to VR Stimulation for that specific day (Figure 23).

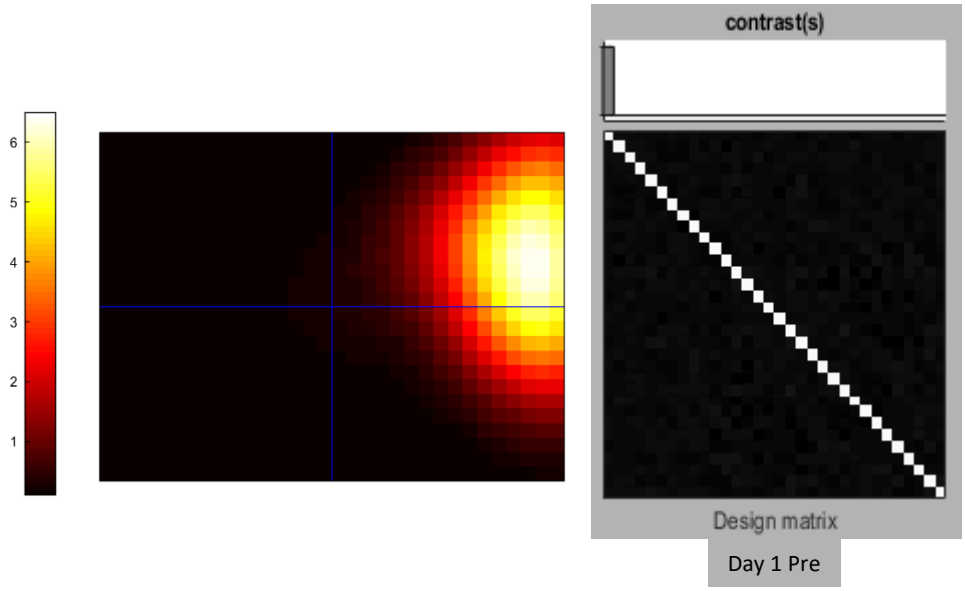


Figure 23: An example of a con image for a single subject from the Pre-Stimulation t-contrast for a single day
This contrast image was generated by applying the afore-mentioned t-contrast to the Day 1 Pre-Stimulation 12 images, marked by the standalone bar for Day 1 Pre-Stimulation images in the design matrix. The area of brightest intensity (also denoted by the colour legend) marks the average centre of gaze location for that subject (with left sided inattention) on that day, prior to the reception of any stimulation. The blue crosshairs denote the centre of the field, 64^{o} across and 48^{o} vertically.

As this t-contrast was applied to the Pre-Stimulation images of each day, the output of this step was a total of 15 con images, each one representing the average centre of gaze from the Pre-Stimulation images per day.

3.18.2.2 Short-Term Effects

To investigate the effect of the 40 minutes of VR Stimulation on gaze location, each day.

A t-contrast [-1 1] was defined for the Pre-Stimulation and Post-Stimulation images on a single day, with [0] for all other images on all the other days (Figure 24). NB: *for the analysis of the short-term effects, for the patients who had done x3 Pre-Stimulation FVE Tasks on Day 1, the contrast applied for Day 1 was [-1 -1 -1 3].* This allowed me to look for differences in gaze location induced by the VR Stimulation; the null hypothesis being that there is no change in centre of gaze immediately after VR Stimulation.

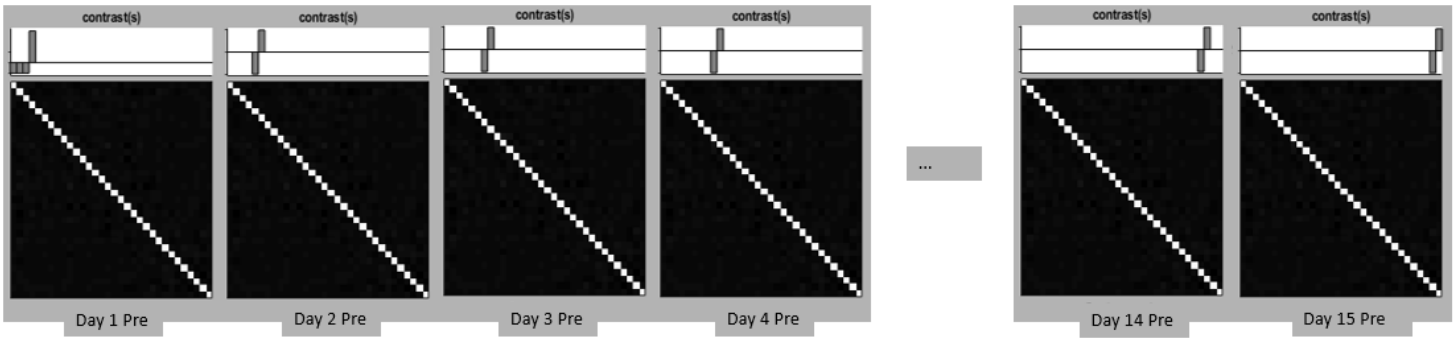


Figure 24: t-contrast for Pre- and Post- Stimulation images per day
The grey bars in the top demonstrate where the t-contrast [-1 1] has been applied, in this case, for every day's Pre and Post images. Please note that for the analysis of the short-term effects, for the patients who had done x3 Pre-Stimulation FVE Tasks on Day 1, the contrast applied for day was [-1 -1 -1 3], hence the visualization here for Day 1 Pre (first box) of three bars at the bottom for the x3 Pre and one bar at the top for the x1 Post.

For each t-contrast applied to each Day's Pre-Stimulation and Post-Stimulation images, a single con.nii image was generated for each day. This con image was a statistical map of the voxel-wise differences in gaze location before and after the 40 minutes of VR Stimulation. 15 con images were generated for the 15 days per subject.

3.18.3 2nd Level Analysis

3.18.3.1 Long-Term Effects Rationale

At the second level of analysis, I aimed to assess whether there was a spatial shift in the average centre of gaze location over the course of the 15 days. In order to do this, I introduced a parametric modulator into the design matrix, which would allow me to examine whether there were areas in the field of view where gaze dwell times moved systematically as a result of gaze location shifting in space. The modulator was a list of linear (numbers 1-15 entered in day order and centred). The following assumptions were made:

1. For the long-term effects that there would be a consistent, detectable spatial shift of centre of gaze from day to day.

2. By entering low values for day 1 and higher values for subsequent days, this contrast should identify voxels where there is no or low centre of gaze at the start of the trial but where gaze shifts as the trial progresses.
3. I hypothesised that this should identify voxels in neglected space. The null hypothesis being that there is no appreciable, consistent spatial shift in centre of gaze over the 15 days of VR Stimulation.

3.18.3.2 Short-Term Effects Rationale

At the second level of analysis, I aimed to assess whether there was a spatial shift in the average centre of gaze location induced by the 40 minutes of VR Stimulation.

The following assumptions were made:

1. As the VR Stimulation was not altered during the course of the trial, any within-session effects should be expressed in the same spatial reference frame.
2. That this effect would be best captured by interrogating the average gaze position across all 15 days of VR Stimulation.
3. The null hypothesis being that there is no appreciable, consistent spatial shift in the centre of gaze induced by the VR Stimulation session.

The rationales have been summarized in Figure 25.

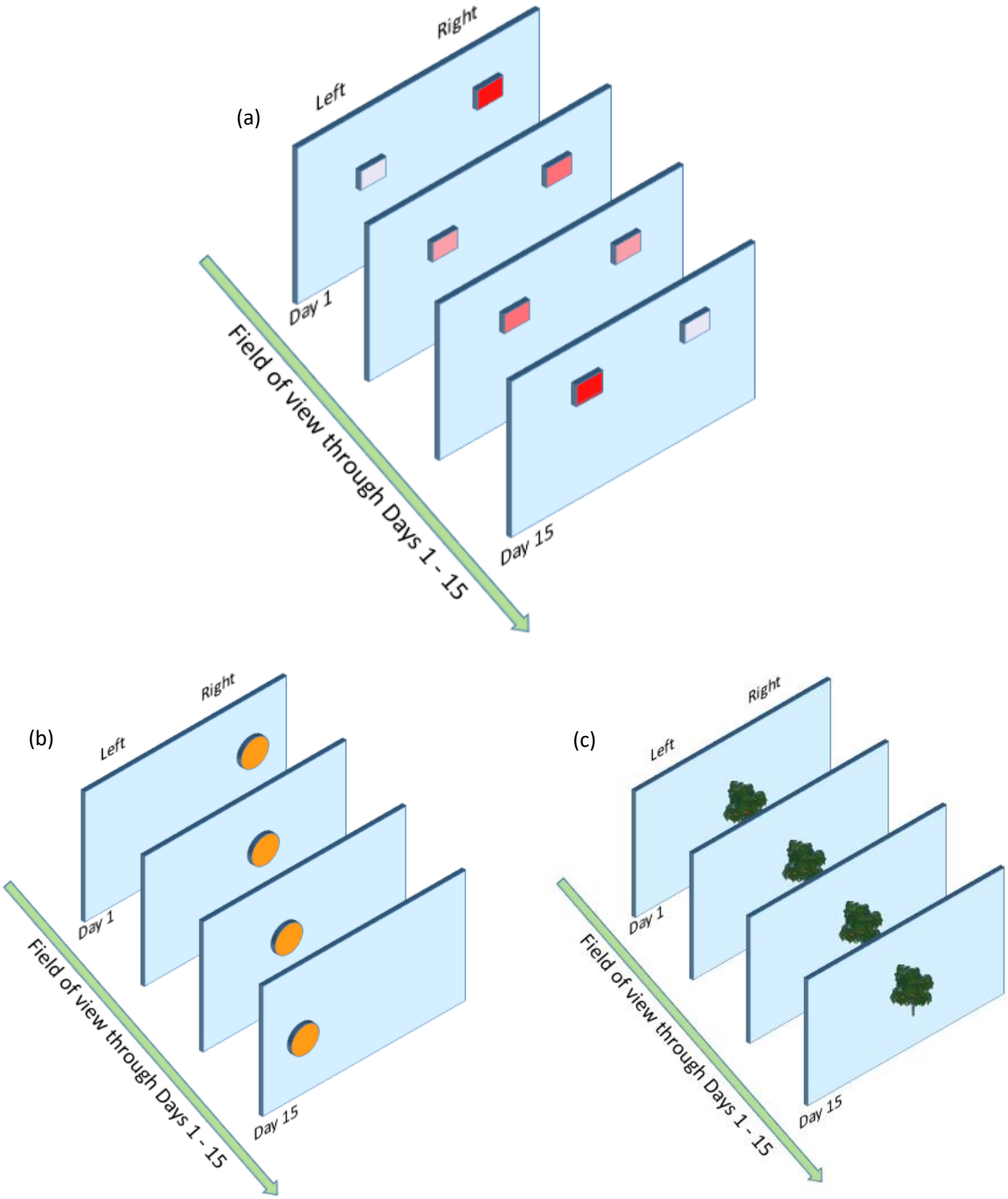


Figure 25: Rationale behind the Parametric Modulator explained
This schematic of the field of view explains the rationale behind introducing the parametric modulator, and the modelling being done to pick up spatial shifts. The 4 field of view screens are an example of days through the 15-day period. The small red boxes represent a single exemplary voxel in the field of view, through the days, one on the right side of space, and one on the left. The more intense the red colour, the "higher" the dwell times within that voxel. Consider that for a subject with left sided visual inattention, the right sided voxel would start off with higher values i.e. higher dwell times, but if their gaze location moves spatially overtime, the right sided voxel would record progressively lower values, and the opposite trend would occur for an equivalent voxel on the left. The parametric modulator should identify those voxels in the field of view where these values start low and go progressively higher.
(b) Long-term effects – the yellow dot denotes the daily Pre gaze location. The hypothesis here is that there will be a consistent, spatial shift over the course of the trial, which the parametric modulator in (a) will identify.
(c) Short term effects – the Control VR Stimulation i.e. the central tree from the vertical Control VR Stimulation is used as an example to demonstrate the consistent area over which any shift in centre of gaze might occur over a 40-minute stimulation session. The hypothesis here is that any stimulation-induced shift in centre of gaze will occur over the same voxels across days.

The 15 con images from each of the above contrasts were entered into a second level analysis, using a one sample t-test (Figure 26).

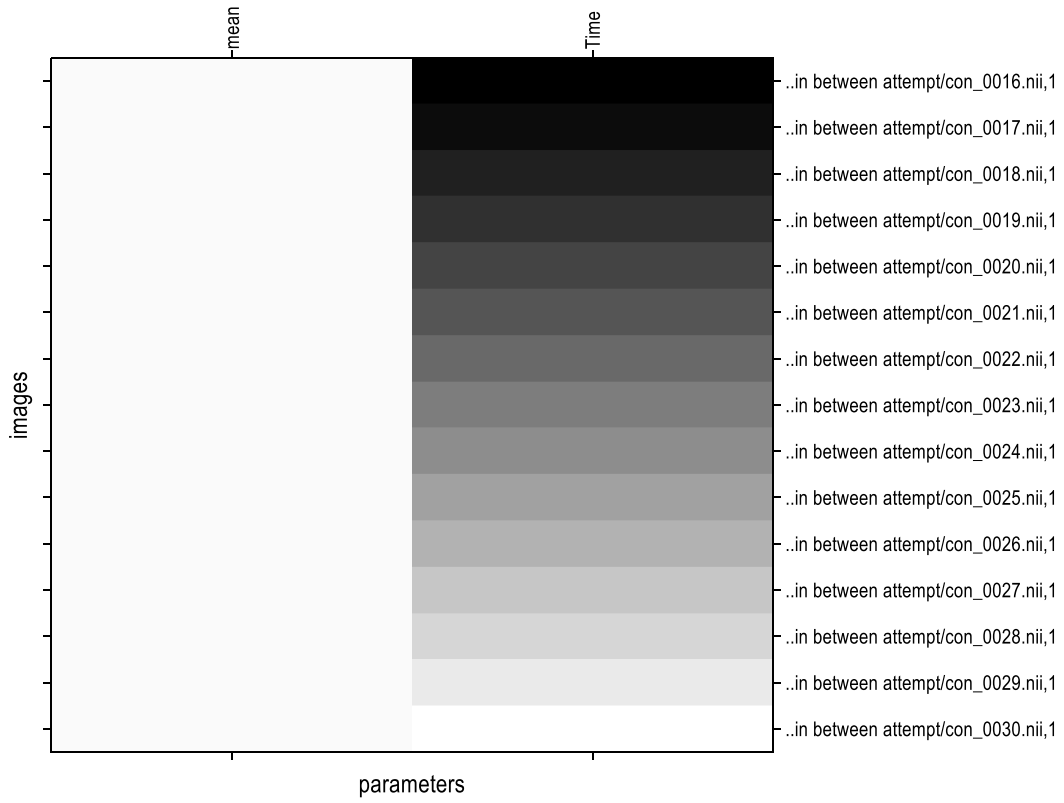


Figure 26: Second-level Design Matrix structure for both short and long-term analyses.
This is a single-subject analysis. The 15 con images are entered in order into two different design matrices (one for long-term effects using the contrasts generated in Figure X above [Pre-Stimulation images only], and one for the short-term effects using the contrasts generated in Figure X above [Pre-Stimulation – Post-Stimulation images]. Column 1 models the average gaze duration (white column on the left), while column 2 models the linear effects of time (the graduated column on the right)

Long-term effects: contrast

A t-contrast of [0 1] was applied to the design matrix investigating long-term effects, in order to assess whether there was a spatial shift in gaze location over the course of the 15 days. This interrogates the second column (parametric modulator) while controlling for any average effects (first column).

Short-term effects: contrast

A t-contrast of [1 0] was applied to the design matrix for the short-term effects. This interrogated the average effect (first column) while controlling for any parametric effects (second column).

The outputs from each of the two different design matrices were a single con image for each participant, representing long-term effects for the first analysis and short-term effects for the second. These were then entered into two separate third-level design matrices to test for any long or short-term effects of VR Stimulation at the group level.

3.18.4 3rd Level Analysis: Group Comparison

Group comparisons were conducted at the third level. The design matrix was the same for both long-term and short-term analyses (Figure 27). The design matrix was an independent samples t-test, with equal variance, assuming homoscedasticity. Con images for the control group $(n = 12)$ were entered into the first column while those for the therapy group $(n = 12)$ were entered into the second column.

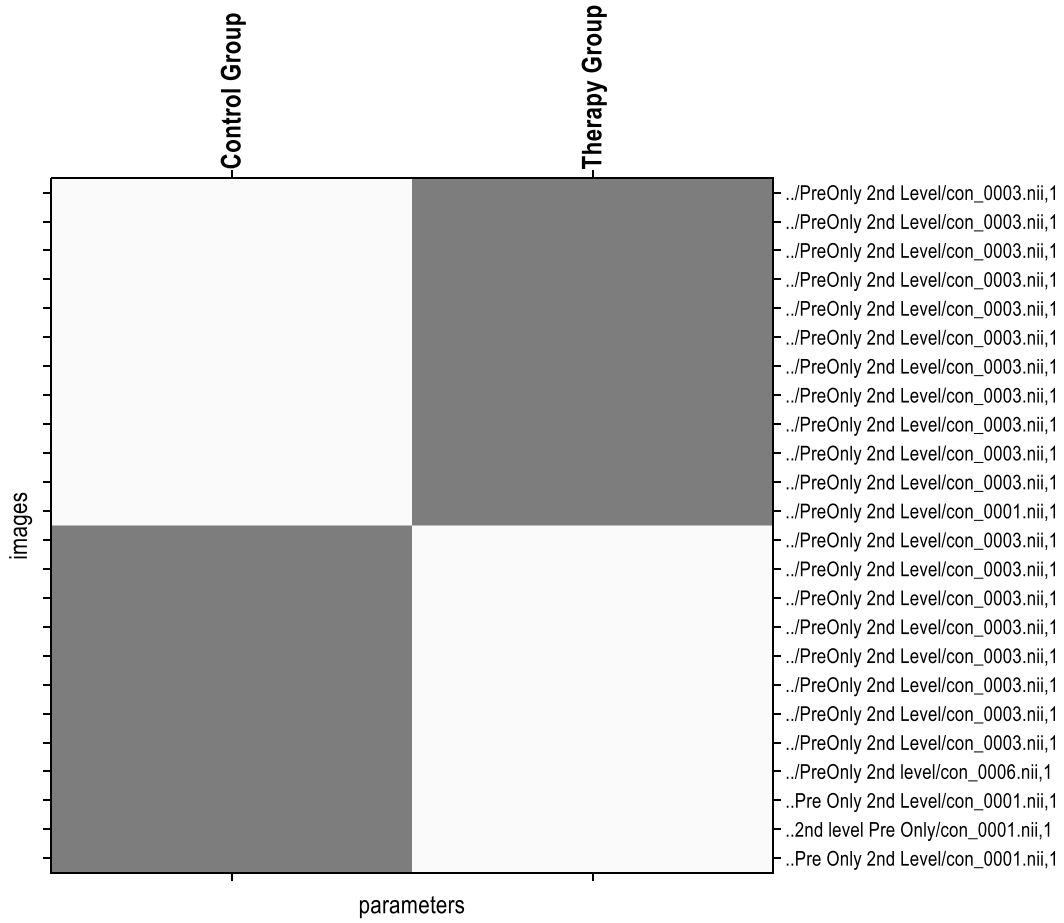


Figure 27: Design Matrix for the 3rd Level Group Comparison
The independent samples t-test design matrix has 2 columns, on the left the con images from the 2nd level analysis are entered for the Control Group, and on the right are those from the Therapy Group.

For each of the two analyses, the one-tailed t-contrast was defined as [-1 1] in order to test the hypothesis that there is a difference in the centre of gaze location over the course of 15 days of VR Stimulation between the two groups, and that this difference will be in the neglected side of space (Figure 28).

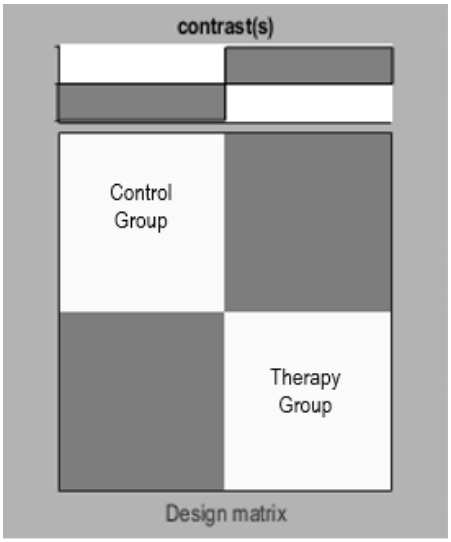


Figure 28: The t-contrast at the 3rd Level
The t-contrast of [-1 1] assigns a -1 to the Control Group, and a [1] to the Therapy Group, interrogating the field of view for areas where the Therapy Group had greater centre of gaze values compared with the Control Group.

I thresholded the results at a peak voxel level of p = 0.05 (corrected using FWE (family-wise error) as is standard in SPM analyses of brain imaging data. I applied a small volume correction using a binary image of the left-hand side of space as the t-contrast would identify relative shifts in average gaze duration (Therapy Group > Control Group) and we expected these to be in the left-hand side of space. For display purposes only (in the figures), the SPM threshold was set at 0.001 uncorrected peak threshold, as is customary in SPM analyses of brain imaging data.

Finally, the cluster was displayed in world space orientation to aid visualization of the cluster in the context of the field of view, and a plot was created, from the peak voxel data, to show the size and direction of the effect for each group within that cluster, along with a 90% Confidence Intervals.

3.18.5 Post-Hoc Analysis

I planned to carry out two post hoc analyses if there were any significant effects at the group level for long or short-term differences in centre of gaze analyses. I planned to look at each group in turn to see if changes in centre of gaze were being driven by one or both of the groups.

3.18.6 Maintenance Effects

In order to check for maintenance effects, the single smoothed image per patient from the 3 month follow-up timepoint at T4 was utilized for a group comparison using a two sample t-test.

In addition, to investigate for a spatial shift in the centre of gaze location from the end of VR Stimulation T3 to 3 months at T4, the following steps were implemented:

1) At the 2nd Level analysis for a single subject, a t-contrast [1] was allocated to the Pre-VR Stimulation image from the last day of VR Stimulation, and [-1] to the follow-up T4 image, and [0] for everything else.

2) The contrast image generated from this was then used to set up a group comparison at the 3rd Level, in order to investigate for a spatial shift from the end of VR Stimulation to follow-up at 3 months between the groups.

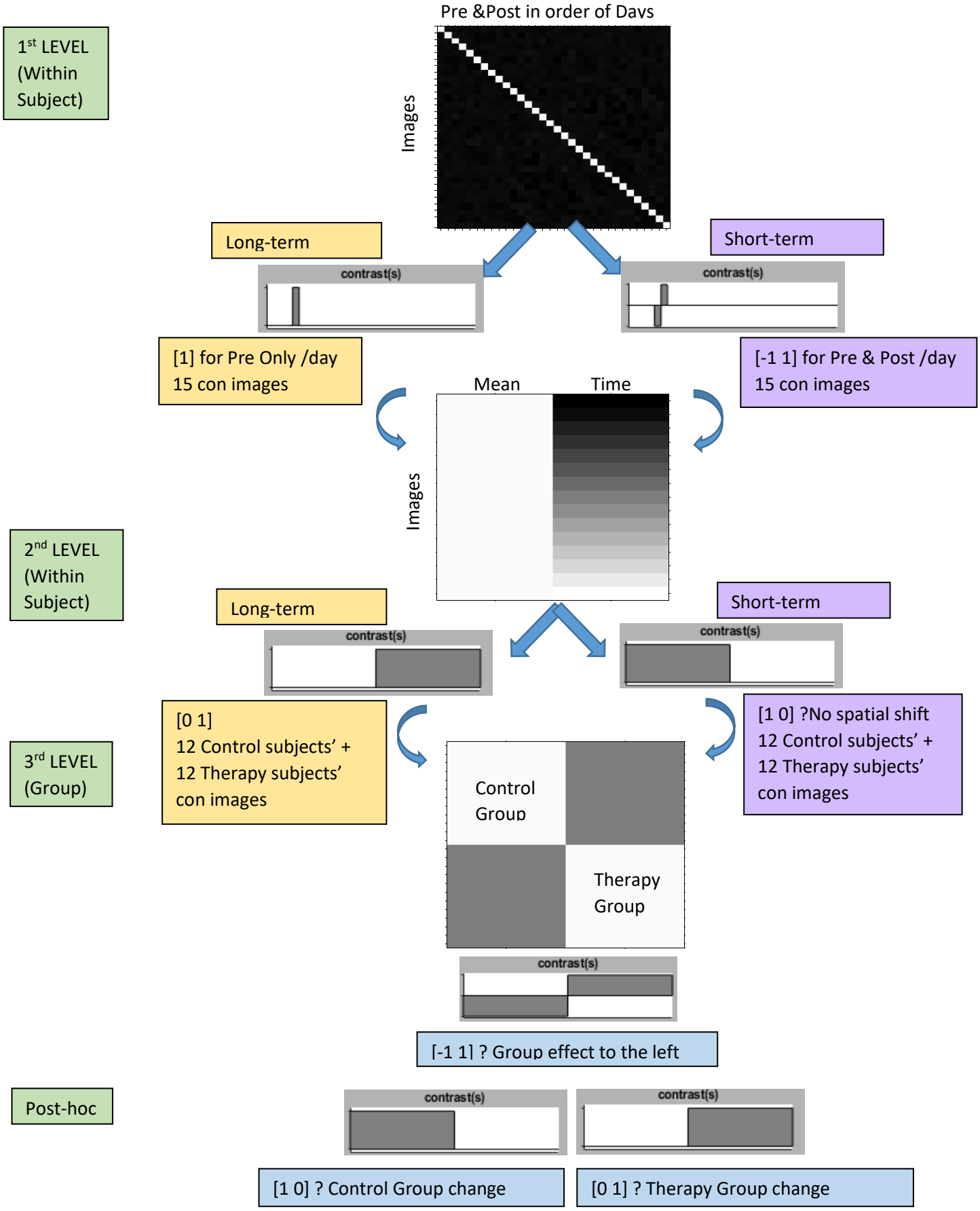


Figure 29: A summary diagram of the three levels of FiVE analysis carried out in SPM12

3.19 Length of Stay Analysis (Secondary Outcome Measure)

All data analysis was conducted using Statistical Software Package for the Social Sciences 29 (SPSS).

The aim of the analysis was to investigate if there was a difference in length of stay between the Therapy Group and the Control Group.

The discharge date from hospital was recorded for the patients. Data was missing for 3 participants in the Therapy Group, as one passed away, and two were still inpatients at the time of writing this thesis. Therefore, the total number of patients for this analysis was $n = 21$, 9 in the Therapy Group, and 12 in the Control Group. Data was entered into an independent samples t-test to investigate for differences between the length of stay for the two groups.

3.20 Semi-Structured Qualitative Interviews

Semi-structured interviews were conducted following the end of the 15 days of the VR Stimulation at T3, with the patient, to gain feedback about the ATTEND trial and patient views on outcomes. The interview consisted of an introduction, followed by an opening question about the experience of the ATTEND trial, and 9 questions about context and drivers for participation, previous research experience, thoughts about research, changes noted during the trial, impacts on mood, feedback on improvement or suggestions for alternate methods, and whether they would recommend participation in the trial. The interview concluded with gratitude for participating in the research and asking for any additional thoughts. All interviews were audio-recorded for the purposes of future qualitative research. The interviews will not be further discussed in this thesis.

3.21 Results: Behavioural Outcome Measures

3.21.1 Aims

Investigating the change in behavioural SN outcomes in response to Horizontal Therapy VR Stimulation in comparison to Vertical Control VR Stimulation

Aim 1: To investigate whether there was an improvement on the impairment-based Star Cancellation Test and the functional-based Catherine Bergego Scale from Baseline to 3 weeks in response to the Horizontal Therapy VR Stimulation

Aim 2: To investigate whether there was a maintenance effect of the Horizontal Therapy VR Stimulation from 3 weeks to 3 months on the Star Cancellation Test

3.21.2 Hypotheses

Hypotheses 1: Participants in the Horizontal Therapy VR Group will show a significant improvement on the behavioural outcome measures of SN as compared to the Vertical Control VR Group, from the start (T2) to the end (T3) of the VR Stimulation.

Hypothesis 2: The improvements made by the Horizontal Therapy VR Group at the end of the VR Stimulation session (T3) will persist as assessed on the Star Cancellation Test at follow-up at 3 months (T4).

3.21.3 Participants

Data from 24 participants are included in the analysis for response to VR Therapy from T2 to T3, and data for 20 participants are included in the analysis for maintenance effects from T3

to T4. The notable demographic and baseline data are presented in Section 3.4 of Methods for the ATTEND trial.

3.21.4 Methods

The statistical methods have been extensively covered in the previous chapter, but a repeated measures ANOVA was used to compare changes between T2 and T3, and T3 and T4 with post-hoc tests as required. All the reported p-value results are from two-tailed tests.

3.21.5 Response to Horizontal Therapy VR Stimulation

3.21.5.1 Star Cancellation Test

At Baseline, the Therapy Group ($n = 12$), had a mean adjusted score of $M = 18.75$, $SD = 9.97$, while the Control Group $(n = 12)$ had a mean adjusted score of $M = 21.50, SD = 10.60$.

At 3 weeks, the Therapy Group increased to a mean adjusted score of $M = 42.00, SD = 10.72$ showing an improvement, compared to the Control Group which had a smaller increase and improvement, to a mean adjusted score of $M = 31.42, SD = 16.28$.

The repeated measures ANOVA was conducted in order to assess the effects of time and group.

Group*Time Interaction

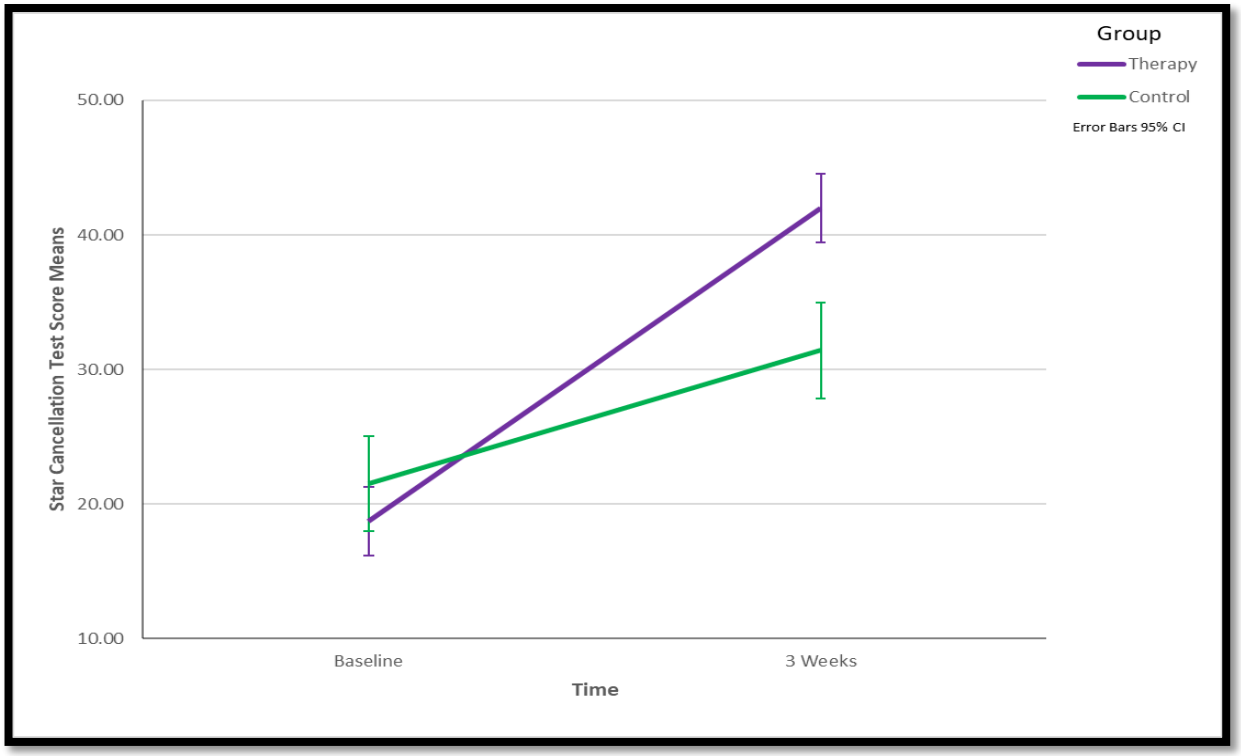
A significant Group*Time interaction was found, $F(1,22) = 11.52, p = .003, \eta_p^2 = .344$, showing that change in scores over time was different for the Therapy and the Control group (Graph 2).

Main Effect of Time

A significant main effect of time was found, $F(1,22) = 71.28, p < .001, \eta_p^2 = .764$, indicating that the scores significantly increased from Baseline to 3 weeks post-VR Stimulation showing an overall improvement.

Main Effect of Group

There was no significant group effect, $F(1,22) = .737, p = .400, \eta_p^2 = .032$.



Graph 2: Star Cancellation Test Group*Time Interaction
A graph illustrating the Group*Time interaction, highlighting the differential change in star cancellation scores over time for the Therapy and Control Groups. The Therapy Group's scores increased steeply from Baseline to post-VR Stimulation, pointing towards the impact of the Horizontal Therapy VR Stimulation. In comparison, the Control Group's scores improved, but less so, over the same period. The non-parallel lines in the plot emphasize the significant interaction effect.

3.21.5.1.1 Post-Hoc Results for Star Cancellation Test

Post hoc analyses were performed to further investigate the Group*Time interaction and to examine changes within the groups.

A paired samples t-test was conducted in order to assess changes in the scores from Baseline to 3 weeks for each group.

The Therapy and Control Groups had no significant differences in Baseline scores, $p = .52$.

The subjects in the Therapy Group showed a significant increase in scores from Baseline ($M = 18.75, SD = 9.97$) to 3 weeks ($M = 42.00, SD = 10.72$), $t(11) = 10.02, p < .001$. The effect size was large ($Cohen's\ d = 2.89$) indicating a sizeable improvement in the horizontal VR Therapy group.

The subjects in the Control Group also showed a significant increase in their scores from Baseline ($M = 21.50, SD = 10.56$) to 3 weeks ($M = 31.42, SD = 16.28$), $t(11) = 3.12, p = .010$, however, the effect size here was lesser ($Cohen's\ d = 0.90$), around a third of the Therapy Group, thereby suggesting a smaller improvement in comparison to the latter.

3.21.5.2 Catherine Bergego Scale

At Baseline, the Therapy Group ($n = 12$), had a mean adjusted score of $M = 17.80$, $SD = 5.59$, while the Control Group ($n = 12$) had a mean adjusted score of $M = 12.75, SD = 5.22$.

At 3 weeks, the Therapy Group's mean score had a reduction by 9.03 points, improving to a mean adjusted score of $M = 8.77, SD = 4.96$, whilst the Control Group's mean score had a reduction by 2.98 points, with a mean adjusted score at 3 weeks of $M = 9.77, SD = 6.33$.

The repeated measures ANOVA aimed to investigate the effects of time (Baseline versus 3 weeks) and group (Therapy versus Control) in order to establish whether the change in the scores at 3 weeks differed by group.

Group*Time Interaction

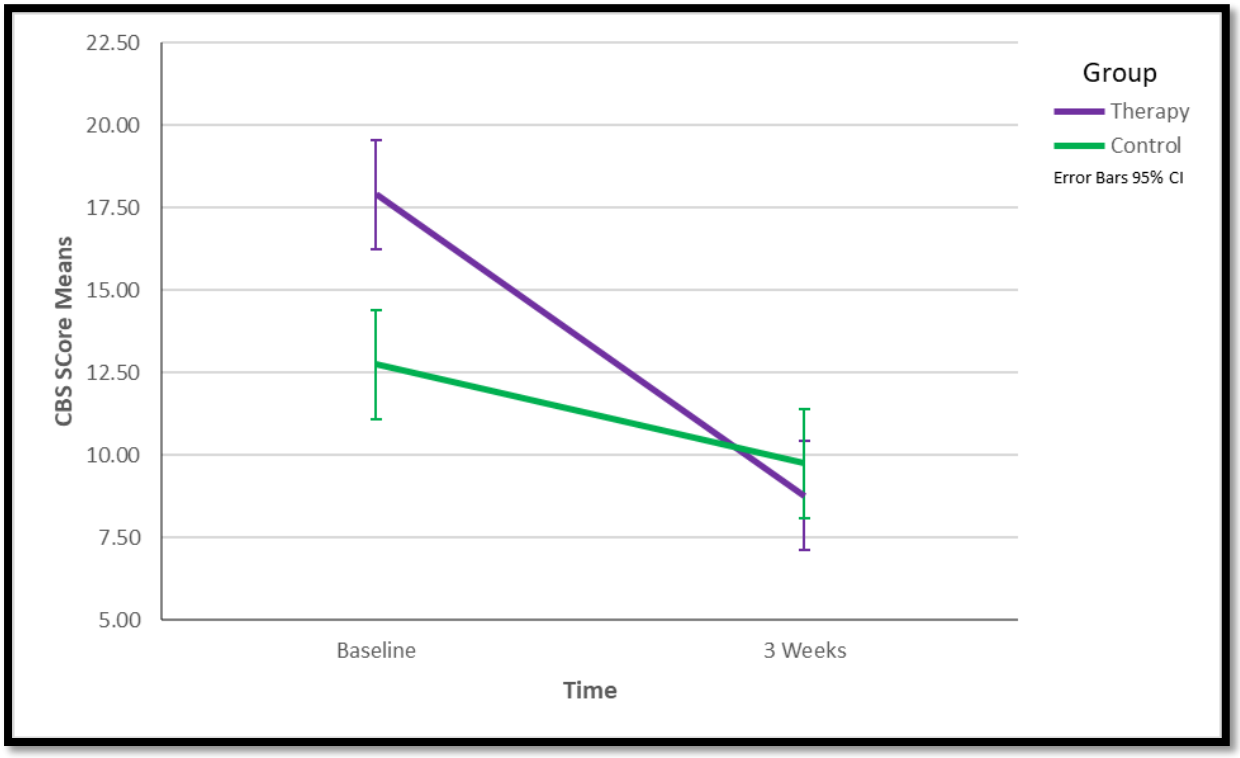
With respect to the main hypothesis, there was a significant interaction between time and group, $F(1,22) = 7.97, p = .010, \eta_p^2 = .266$ showing that the Therapy Group improved significantly more than the Control Group (Graph 3).

Main Effect of Time

There was a significant main effect of time, $F(1,22) = 31.53, p < .001, \eta_p^2 = .589$, indicating that the scores significantly improved from Baseline to 3 weeks post-VR Stimulation for all subjects.

Main Effect of Group

There was no significant group effect, $F(1,22) = 1.02, p = .323, \eta_p^2 = .044$.



Graph 3:Catherine Bergego Scale Group*Time Interaction
This graph demonstrates the Time*Group interaction effect and the steeper decline in scores (reflecting a greater improvement) in the Therapy Group as compared to the more modest decline in the Control Group, driving the interaction effect. The error bars represent 95% confidence intervals. The non-parallel lines further confirm the differential impact of time on the two groups.

3.21.5.2.1 Post-Hoc Results for CBS

In order to understand the Group*Time interaction further, further post-hoc analyses were done with a paired samples t-test and an independent samples t-test in order to determine which group was driving the significant difference, as covered in detail in Section 3.16.4 in Methods.

At Baseline, there were between group differences, as the Control group had significantly lower scores ($M = 12.75, SD = 5.22$) as compared to the Therapy group ($M = 17.80, SD = 5.59$), $t(22) = 2.28, p = .032, Cohen's\ d = 0.93$, reflecting that the Therapy group was more severe at Baseline.

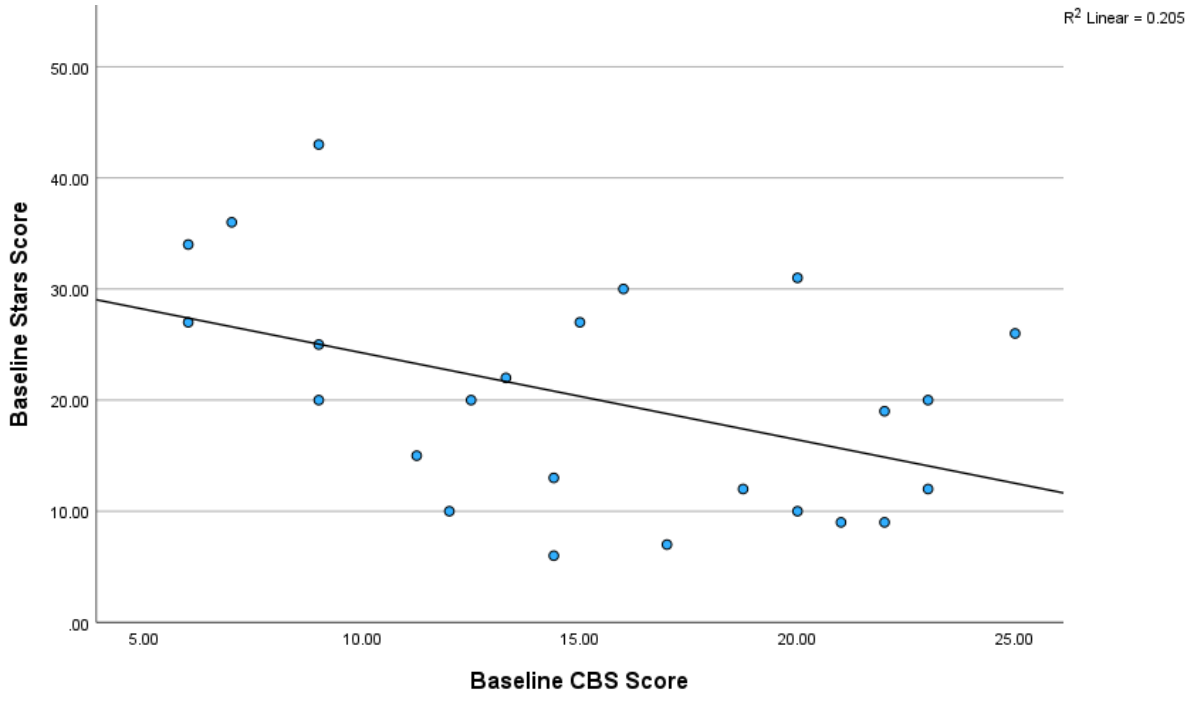
The Therapy group showed a significant improvement in scores from Baseline ($M = 17.80, SD = 5.59$) to 3 weeks ($M = 8.77, SD = 4.96$), $t(11) = 5.81, p < .001, Cohen's\ d = 1.68$. The effect size was large indicating a substantial improvement.

The Control group showed a smaller improvement from Baseline ($M = 12.75, SD = 5.22$) to 3 weeks ($M = 9.77, SD = 6.33$), $t(11) = 2.03, p = 0.067$, which was not statistically significant but showing a trend towards improvement; $Cohen's\ d = 0.59$.

3.21.5.3 Differences in Baseline Severity

Given the group differences in baseline severity for the two behavioural outcome measures, I also conducted a Pearson correlation analysis on baseline scores of the 24 patients on the Star Cancellation Test and the Catherine Bergego Scale. There was a moderate, statistically significant negative correlation between the Star Cancellation baseline scores and the CBS baselines scores, $Pearson's\ r(22) = -0.45, p = .026, 95\%\ CI = [-.72, -.06]$. A scatter plot with a fitted regression line was generated, and the R^2 value was 0.205, indicating that

approximately 20.5% of the variance in the Star Cancellation baseline scores could be explained by the CBS baseline scores (Graph 4).



Graph 4: A scatter plot with the baseline Star Cancellation scores on the y-axis and the baseline CBS scores on the x-axis. The negative slope depicts the negative correlation, with an R^2 linear coefficient of 0.205.

3.21.6 Maintenance Effects

At the 3 month follow-up time point (T4), the patients repeated the Star Cancellation Test.

Following listwise deletion for missing data, the final sample size was $n = 20$, with Therapy Group $n = 9$ and Control Group $n = 11$.

A repeated measures ANOVA was used to investigate differences between T3 and T4, and an independent samples t-test was used to assess for maintenance effects.

The means for T2, T3 and T4 are shown for both the groups in Table 13.

	Baseline Star Cancellation score		3 weeks Star Cancellation score		3 Months Star Cancellation score	
Group	Mean	SD	Mean	SD	Mean	SD
Therapy n=9	18.75	9.97	41.78	11.64	44.78	11.36
Control n=11	21.50	10.60	29.36	15.36	34.00	15.24

Table 13: Mean adjusted Star cancellation scores at Baseline, 3 weeks, and 3 Months for n=20

The repeated measures ANOVA rendered a significant effect of Group, $F(1,18) = 4.45, p = 0.049, \eta_p^2 = .198.$

An independent samples t-test showed a trend towards significance for the mean scores at 3 weeks, with the Therapy Group $(M = 41.78\, SD = 11.64)$ and the Control Group $(M = 29.36\, SD = 15.36)$, $t(22) = 1.881, p = .073, Cohen's\ d = .768,$ but there was no statistical difference between the two groups at the 3 month timepoint T4, $t(18) = 1.76, p = .096, Cohen's\ d = .789.$

3.22 Results: Five in the Vive SPM Analysis

3.22.1 Aims

Investigating the change in centre of gaze location in response to Horizontal Therapy VR Stimulation in comparison to Vertical Control VR Stimulation

Aim 1: Long-term effects - To investigate if there was a consistent spatial shift in the centre of gaze over the 15 days of VR Stimulation, from T2 to T3.

Aim 2: Short-term effects - To investigate if there was a consistent spatial shift in the centre of gaze immediately induced by the VR Stimulation session.

Aim 3: Maintenance effects - To investigate if was a difference in the centre of gaze between the Therapy and the Control groups at the 3 month timepoint, T4.

3.22.2 Hypotheses

Hypotheses 1: Participants in the Horizontal Therapy VR Group will show a significant change in their centre of gaze location as compared to the Vertical Control VR Group, from the start (T2) to the end (T3) of the VR Stimulation.

Hypotheses 2: Participants in the Horizontal Therapy VR Group will show a significant change in their centre of gaze as compared to the Vertical Control VR Group within a 40-minute VR Stimulation session.

Hypotheses 3: There will be a difference in the centre of gaze between the Horizontal Therapy VR Group and the Vertical Control VR Group at follow-up at 3 months (T4).

3.22.3 Participants

Data from 24 participants are included in the analysis for response to VR Therapy from T2 to T3, and data for 20 participants are included in the analysis for maintenance effects from T3 to T4.

3.22.4 Methods

(1) For every single subject, at the first level analysis, two contrast images were generated, one for the Pre-VR Stimulation images from every day (looking at the long-term effects), and another from the Pre-Post VR Stimulation images per day (looking at the short-term effects).

(2) These 2 contrast images were used in the 2nd Level analysis, each one set up along with a Parametric modulator. This generated a contrast image each for every subject.

(3) They were carried forward into the 3rd level group comparison, comparing the Therapy group to the Control group for long term and short-term effects.

(4) For maintenance effects, contrast images for each patient from follow-up at T4 were compared between Groups, along with a subtraction image from the last day of VR Stimulation and the follow-up FiVE in the Vive for each patient, that was carried into a 3rd level group comparison.

3.22.5 Response to VR Stimulations

3.22.5.1 Long-Term Effects

The statistical results for the 3rd Level Group comparison between the Therapy and the Control Groups for long-term effects from the start of VR Stimulation at T2 to the end of VR Stimulation at T3 over 15 days are displayed in Figure 30. A small volume correction mask using a binary image of the left-hand side of space was applied to restrict the search to the left side of space, where changes were expected. The results were thresholded at $p < 0.05$ FWE corrected.

Statistics: ***search volume: image mask: .\Mask left side of space.nii***

cluster-level				peak-level					mm mm
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.177	0.424	78	0.424	0.054	0.120	3.04	2.75	0.003	5 23 1

Figure 30: Statistical Result for the 3rd Level Group Comparison Long-Term Effects Peak-Level Voxel

One cluster was identified with a size of 78 voxels to the left side of space, where the dwell times were different between the Horizontal Therapy VR Group and the Vertical Control VR Group, over the course of the 15 days, marking an area showing consistent spatial shift in the centre of gaze. There was a cluster with a peak-voxel, the $P_{FWE-corrected} = 0.054$, showing a trend towards significance.

The SPM figure represents an image space measuring 64^{o} by 48^{o} of visual angle (Figure 31). It shows the location of this cluster, which is in the left upper quadrant of space, and the peak voxel is marked by the blue crosshairs.

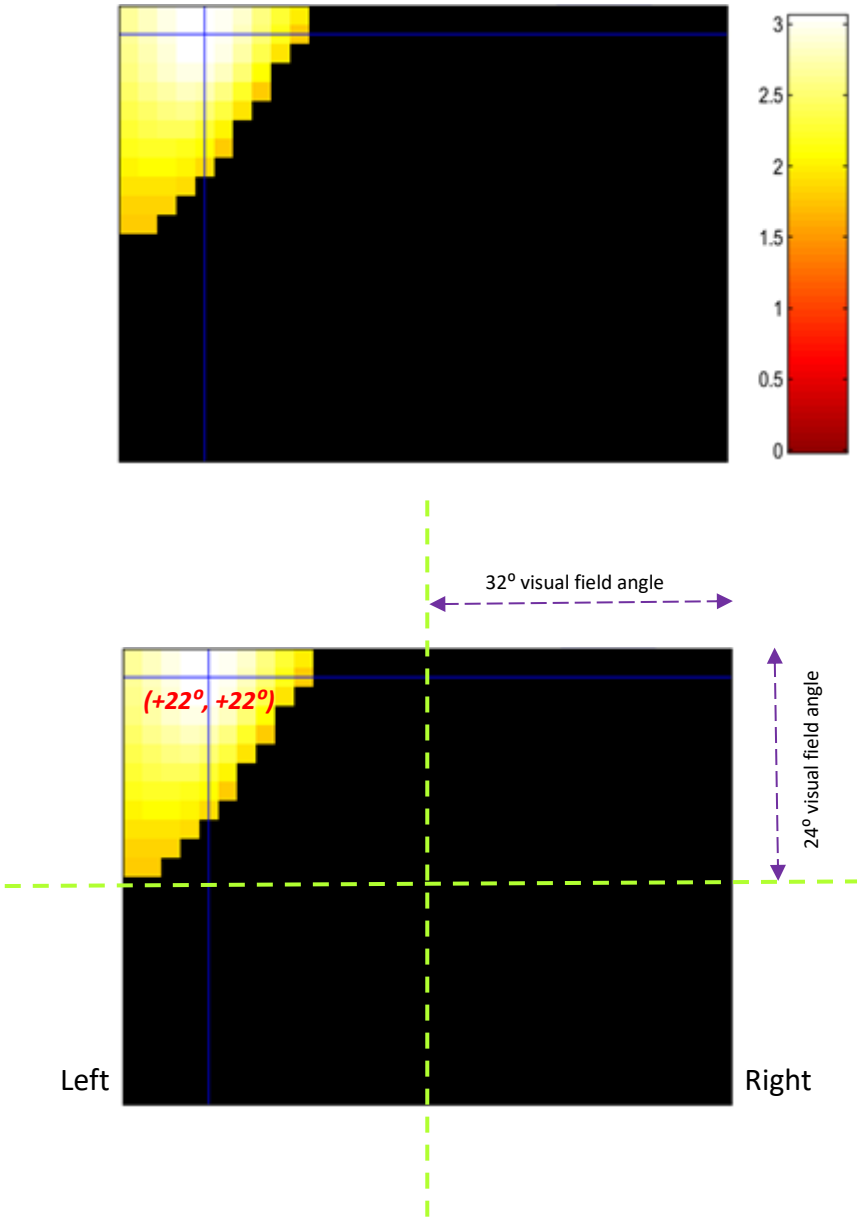
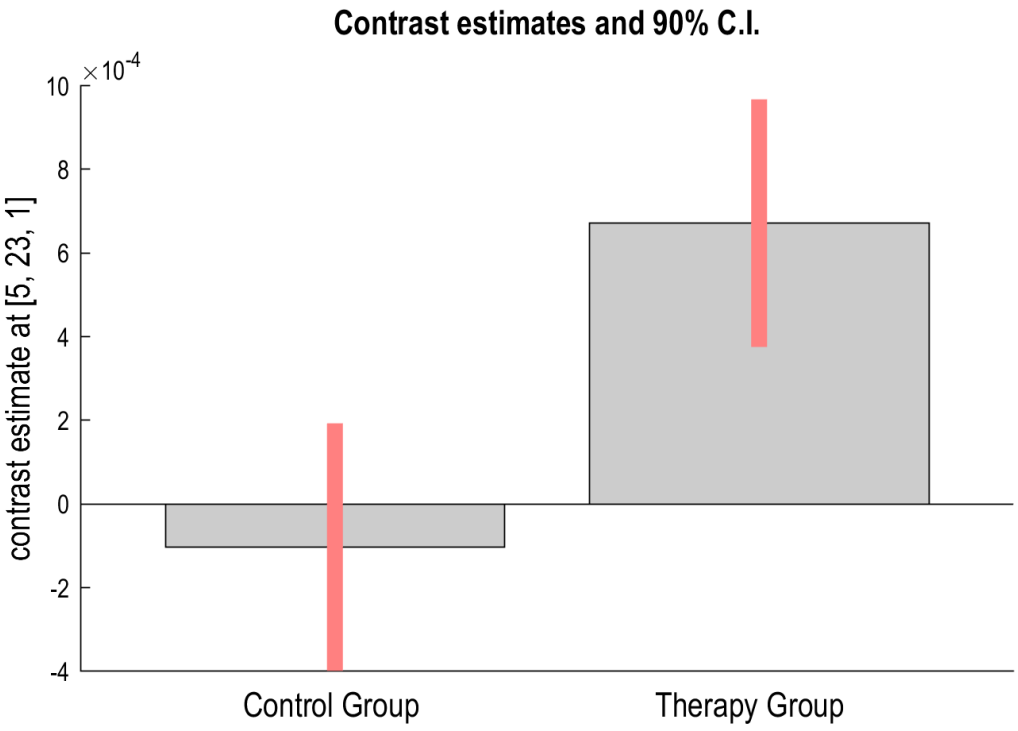


Figure 31: SPM figure of the Group Comparison long-term effects result
(Top) The original result SPM figure shows the peak voxel marked by the blue crosshairs where there was a difference in dwell times between the two groups. The colour legend denotes the brightest colour intensity (white) corresponding to the highest dwell times in those voxels.
(Bottom) On the annotated figure, the cross hairs mark the co-ordinates where the peak voxel for the centre of gaze was located, 22° horizontally to the left from the midline, and 22° upwards from the horizontal meridian.

To further explore this result, the data for both groups was extracted and plotted at the peak voxel. The Therapy Group showed a significant positive contrast estimate, with confidence intervals not overlapping zero, while the Control Group showed no significant activity. These

findings suggest that the dwell times of the Therapy Group were responsible for the trend toward significance at this voxel (Graph 5).



Graph 5: Both groups plotted at the peak-level voxel for long-term effects
Graph showing both the groups' data plotted for the peak level voxel, with the dwell times of the Therapy Group being the significant driver at that voxel.

For a post-hoc analysis, the average centre of gaze for each group was examined separately. The p value was thresholded at $p < 0.05$ FWE corrected and a small volume correction with the left-sided binary mask was applied.

For the horizontal Therapy Group, a significant cluster of 239 voxels was identified at the co-ordinates of (5 20 1), with the peak voxel lying 22° towards the left from the midline, and 16° upwards from the horizontal meridian. At the peak-voxel level, the $Z = 3.55, P_{FWE-corrected} = 0.006$, demonstrating a robust significance after correcting for

multiple comparisons within the left sided area of interest. The bar graph plotted from the data of the horizontal Therapy Group at this voxel showed a positive contrast estimate and the confidence interval did not overlap with 0, reliably demonstrating the increased dwell times and the leftward spatial shift in this group (Figure 32, Graph 6).

For observational comparison the contrast image showing the baseline average centre of gaze from Day 1 Pre-VR Stimulation was also demonstrated, where the peak voxel had a $Z = 4.51, P_{FWE-corrected} = 0.001$, at co-ordinates (24 11 1) which corresponded to a starting average centre of gaze that was located 16^o rightward from the midline, and 2^o downwards from the horizontal meridian (Figure 32).

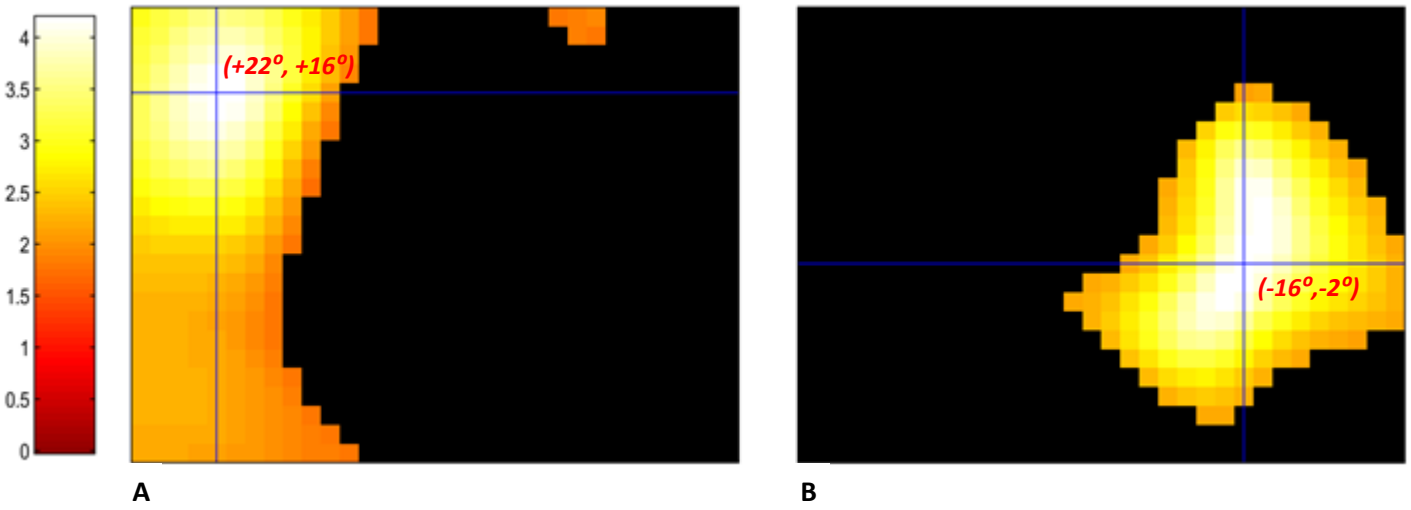
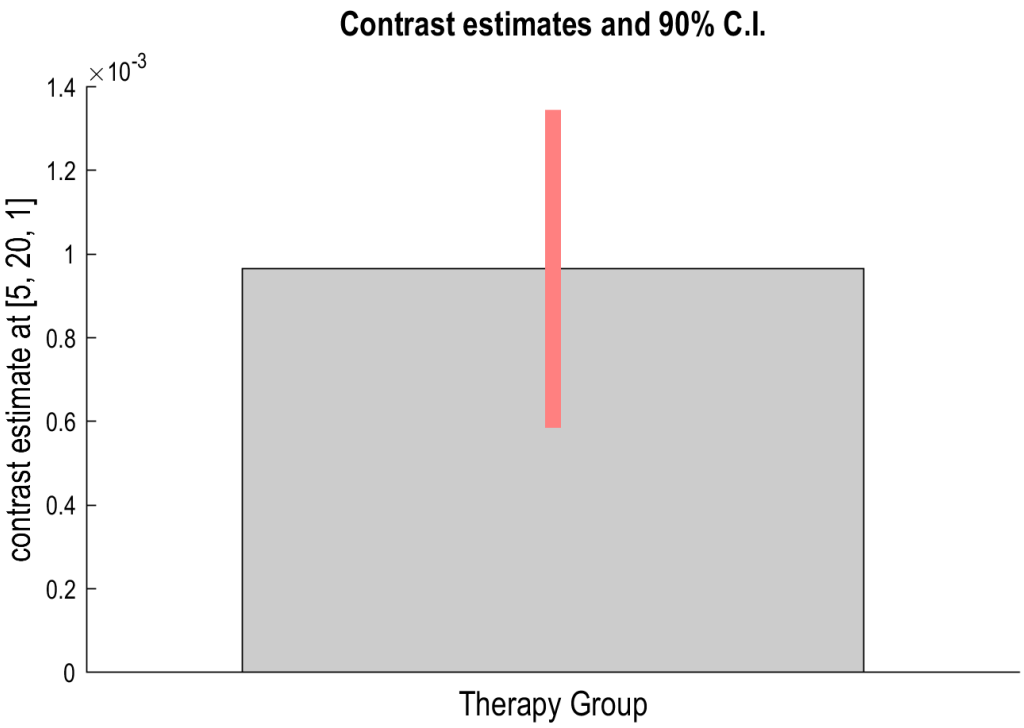


Figure 32: Post-Hoc Analysis Long-Term Effects – Therapy Group
(A) The SPM figure showing the peak voxel marked by the blue crosshairs for the Therapy Group showing a spatial shift in centre of gaze of 22^o towards the left from the midline, and 16^o upwards from the horizontal meridian following the 15 days of VR Stimulation, as compared to (B) their baseline average centre of gaze from Day 1 before starting VR Stimulation, located at 16^o towards the right from the midline, and 2^o downwards from the horizontal meridian



Graph 6: Therapy Group plotted at its individual peak-level voxel
A bar graph showing the positive dwell times for the Therapy Group at the peak-voxel cluster for the spatially shifted average centre of gaze following 15 days of VR Stimulation

Upon investigating the average centre of gaze for the vertical Control VR Group, a cluster of 104 voxels was observed at co-ordinates (15 15 1) with the peak voxel having a $Z = 2.66, P_{FWE-corrected} = 0.066$, indicating a trend towards significance after correcting for multiple comparisons. The centre of gaze for the Control group shifted only by 2^o to the left from the midline and 6^o upwards. The contrast estimates from the peak voxel were extracted and plotted and displayed in Graph 7. The contrast image showing the baseline average centre of gaze from Day 1 Pre-VR Stimulation was also demonstrated for the Control Group, where the peak voxel had a $Z = 4.28, P_{FWE-corrected} = 0.001$, at co-ordinates (25 13 1) which corresponded to a starting average centre of gaze that was located 18^o rightward from the midline, and 2^o upwards from the horizontal meridian (Figure 33, Graph 7).

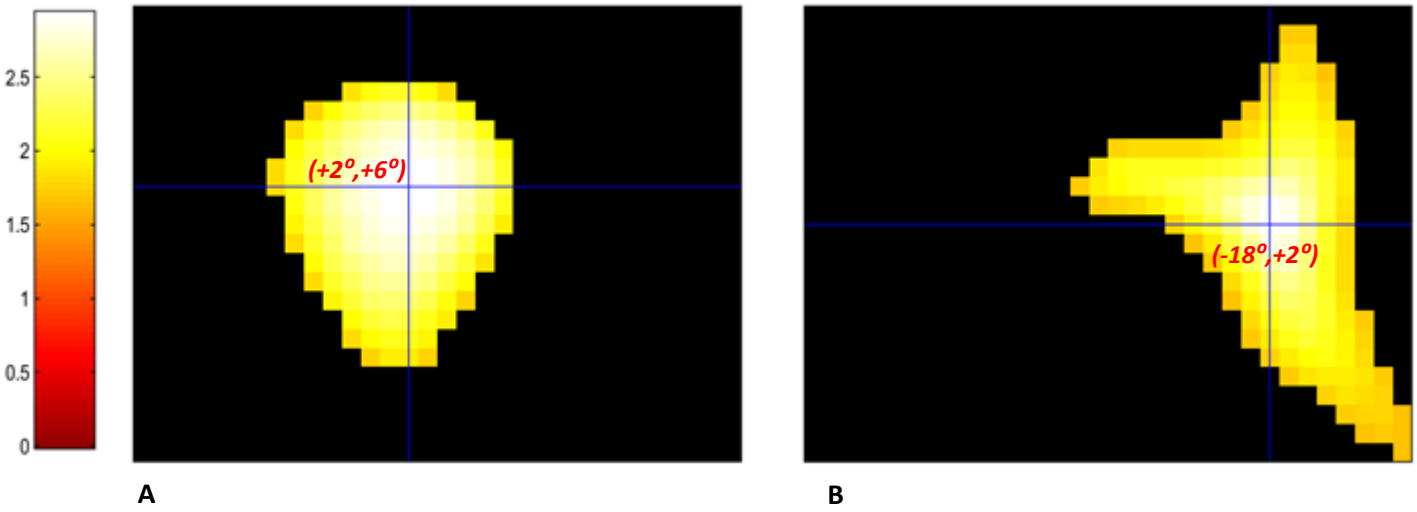
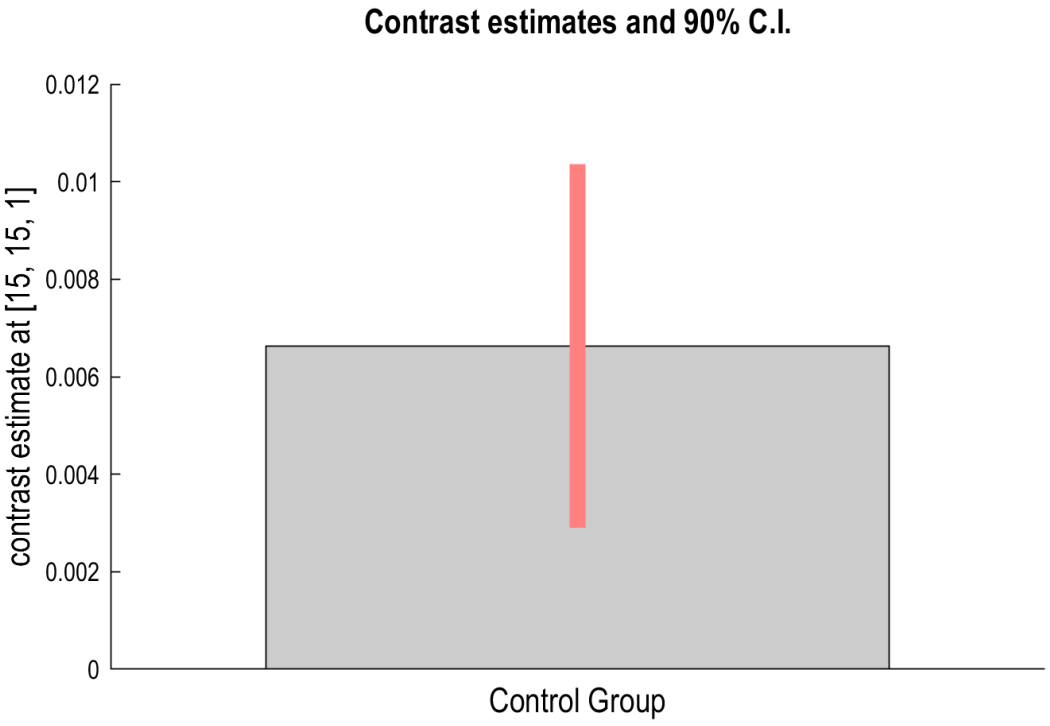


Figure 33: Post-Hoc Analysis Long-Term Effects – Control Group
(A) The SPM figure displaying the centre of gaze for the Control Group following the 15 days of VR Stimulation. The shift in gaze was 6° upwards, and only by 2° to the left from the midline. (B) In comparison, the baseline average centre of gaze before starting VR Stimulation was located 18° rightward from the midline, and 2°upwards.



Graph 7: Control Group plotted at its individual peak-level voxel
A bar graph showing the positive dwell times for the Control Group at the peak-voxel cluster for the centre of gaze following the 15 days of VR Stimulation

3.22.5.2 Short Term Effects

The statistical results at the 3rd Level Group comparison, for the short term effects, when looking for a consistent spatial shift before and after a VR Stimulation session are displayed in Figure 34.

Statistics: *search volume: image mask: .\Mask left side of space.nii*

set-level		cluster-level				peak-level					mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.020	3	0.357	0.889	17	0.778	0.084	0.621	2.92	2.65	0.004	1	7	1

Figure 34: Statistical Result for the 3rd Level Group Comparison Short-Term Effects Peak-Level Voxel

Only a single cluster made of 17 voxels survived small volume correction at co-ordinates (1 7 1). The peak-level voxel had a $Z = 2.92, P_{FWE-corrected} = 0.084$, suggesting a trend towards significance after correction for multiple comparisons. This centre of gaze spatial shift was marked by a 30° leftward and 10° downward shift following a VR session. The data for both groups were extracted and plotted at this peak voxel, and demonstrated a positive contrast estimate for the Therapy Group only, with confidence intervals that did not overlap 0, indicating that the surviving voxel represented the spatial shifts in dwell times for the Therapy Group, as opposed to the Control Group that had negative contrast estimates and a confidence interval below 0 (Figure 35, Graph 8).

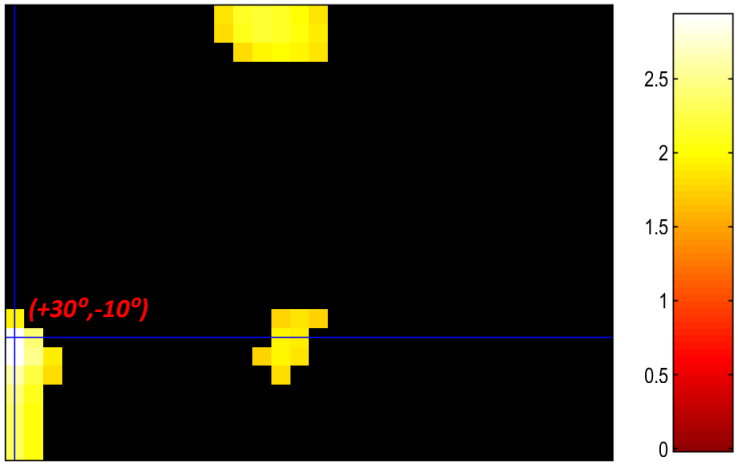
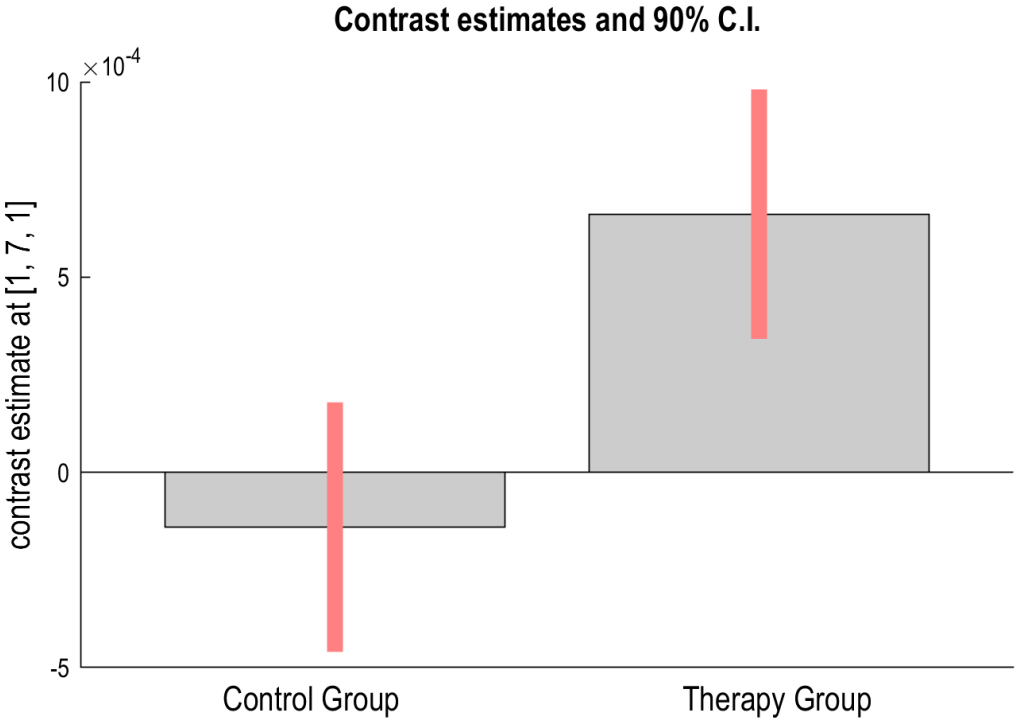


Figure 35: SPM figure of the Group Comparison short-term effects result
The only cluster with the peak-level voxel that shows a trend towards significance is in the left lower quadrant, showing a spatial shift of 30° to the left from the midline and 10° downwards following a VR Stimulation session.



Graph 8: Both groups plotted at the peak-level voxel for short-term effects
The bar chart demonstrates that the Therapy Group's dwell times were responsible for the spatial shift in gaze location seen on the SPM image.

In order to further explore the drivers for the borderline changes observed for the short-term effects, each group was examined individually. The Control Group did not have any surviving clusters, confirming that the left-sided peak voxel was contributed to by the spatial shift in centre of gaze location in the Therapy Group, immediately after a VR Stimulation session. The Therapy group had one surviving cluster of 35 voxels at the co-ordinates (1 6 1), 30^{o} to the left from the midline and 12^{o} downwards from the horizontal meridian, almost directly overlying the peak-voxel that emerged from the Group comparison analysis. For the peak-voxel level in this cluster, the $Z = 3.27, P_{FWE-corrected} = 0.017$ meaning that it was a significant voxel surviving correction for multiple comparisons. The data at that peak-voxel was extracted and plotted and confirmed positive dwell times for the Therapy Group driving the spatial shift noted at that location (Figure 36, Graph 9).

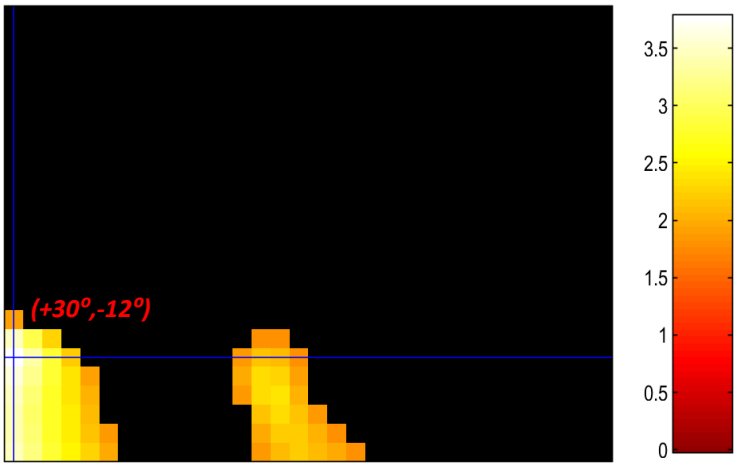
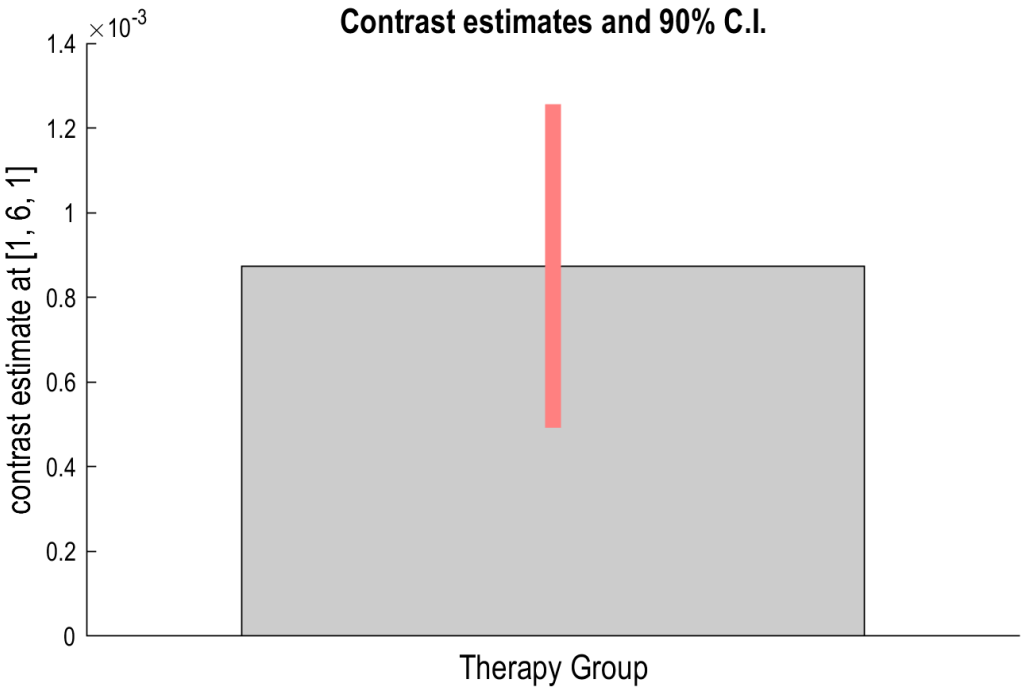


Figure 36: Post-Hoc Analysis Short-Term Effects – Therapy Group
The centre of gaze location for the Therapy Group when investigating short-term effects, showing a spatial shift of 30^{o} to the left from the midline and 12^{o} downwards from the horizontal meridian after a VR Stimulation session



Graph 9: Therapy Group plotted at its individual peak-level voxel
Positive contrast estimates for the Therapy Group at the peak-level voxel showing positive dwell times driving the spatial shift in that location after a VR Stimulation session.

3.22.6 Maintenance Effects

The analysis for the maintenance effects did not show a statistically significant difference in the gaze location of both groups at the 3 month timepoint T4, nor was there a statistically significant spatial shift in the centre of gaze from the last day of VR Stimulation at T3 to T4 for either of the groups.

3.23 Results: Length of Stay

Length of stay (LoS) data was tabulated for both groups in Table 8. For the Therapy Group ($n = 9$), the mean was 196.3 days ($SD = 79.6$) and the median was 204 days. The mean and median LoS for the Control Group ($n = 12$) were 160.5 days ($SD = 96.02$) and 112.5 days, respectively. There were no statistically significant differences in LoS between the 2 groups, $p = .14$.

3.24 Discussion: Behavioural Outcome Measures

The behavioural outcome measures included performance on the impairment-based Star Cancellation Test and the functional-based Catherine Bergego Scale, which were analysed with the use of a repeated measures ANOVA from Baseline (T2) to end of VR Stimulation at 3 weeks (T3). The analysis aimed to evaluate the efficacy of the horizontal Therapy VR Stimulation which induced smooth pursuit eye movements delivered through a virtual reality headset in comparison to a sham vertical Control VR Stimulation.

3.24.1 Response to VR Stimulation

The results from the behavioural outcome measures provided strong support for the efficacy of the horizontal Therapy VR Stimulation in improving SN as compared to the sham vertical Control VR Stimulation.

The horizontal Therapy VR Stimulation induced significantly greater improvements on the Star Cancellation Test and the CBS as compared to the vertical Control VR Stimulation. On the Star Cancellation Test, there was a significant Group*Time interaction, with the statistical significance of the Therapy Group's changes in scores from Baseline to 3 weeks being markedly greater than the Control Group, and the magnitude of effect size in the former far exceeding the latter. The comparison of the Baseline scores between the two groups revealed no difference, supporting the minimization process that included Star Cancellation severity as a factor, giving both groups a comparable starting point. These findings from the impairment-based Star Cancellation Test were paralleled in significantly greater improvements on the functional measure, i.e., the CBS. There was a significant Group*Time interaction, with only the Therapy Group making a statistically significant improvement with a very large effect size

at the end of 3 weeks of horizontal VR Stimulation, reducing their score by 9.03 points, surpassing the requirement of a score reduction by at least 4 points to reflect to a minimal clinically important difference (MCID). In contrast, the Control Group showed a more modest reduction in scores, trending towards statistical significance, with the mean reduction not meeting the MCID threshold. Notably, on the CBS, the Therapy Group started off with significantly higher scores indicating greater severity at Baseline as compared to the Control Group.

Whilst both groups improved on the Star Cancellation Test, the difference in strength of statistical significance and effect size suggests that the horizontal Therapy VR Stimulation played a crucial role in improving SN, more so than just the natural effects of time on recovery, or familiarity with the Star Cancellation Test. The fact that initial severity on the Star Cancellation Test was matched removed any advantages for enhanced natural recovery due to milder severity at the outset, underscoring the therapeutic efficacy of the horizontal VR Stimulation as the driving factor for the improvement. Additionally, the Therapy group were not earlier in their recovery than the Control group: the mean time post-stroke at recruitment was 74 days for Controls and 86 days for the Therapy group, a difference that was not statistically significant. This reduces the likelihood that natural recovery trends can explain the observed group differences.

On the functional front, unlike the Star Cancellation Test, the groups were not matched for initial severity on the CBS. The ATTEND trial cohort was a mixture of acute and sub-acute patients. Sub-acute patients receiving neurorehabilitation may have learned to compensate for SN symptoms in visual search tasks, making assessments of function more accurate at detecting SN for these patients (194). In addition, the CBS has been noted to be more sensitive

than any of the pencil-and-paper tests considered alone, and dissociations have been observed between the two types of evaluation (194). In fact, in keeping with the negative correlation that I found between the mean baseline scores for the Star Cancellation Test and the CBS for my patient cohort, other studies that compared the CBS with pencil-and-paper tasks, found correlations with the Line Bisection Test (195), the Bells Cancellation Test, the copying and drawing test and the sentence reading test (196), but not, as far as I have found, the Star Cancellation Test. These could be possible reasons for the disparity in initial severity between the Star Cancellation Test and the CBS.

The practical impact of the Therapy Group being more severely functionally impaired at baseline could possibly have been the presence of more room for improvement and therefore more scope for reduction on the CBS. In comparison, in the Control Group, patients who scored on the milder side of severity on the CBS would have been prone to contributing towards floor effects, with inadequate room for making an improvement that would reach the MCID threshold. In spite of this, for the Therapy Group to have commenced from a point of greater severity, and conclude at a point of milder severity, only highlights the beneficial effect of the horizontal Therapy VR Stimulation on functional gains.

In receiving the horizontal Therapy VR Stimulation, which required repeatedly tracking a moving target from the lesser affected side to the more affected side, the Therapy Group was essentially responding to large-field visual motion (optokinetic stimulation) within the 110^{o} field of view in immersive Virtual Reality, inducing left-sided horizontal smooth pursuit eye movements (all patients in the trial suffered from left-sided SN). In comparison, the Control VR Stimulation required focusing attention on a fixed tree in the center of the field of view, shooting down vertically arranged targets within a narrow horizontal frame, with a

successfully shot target rolling vertically downwards towards the patient within 3D Virtual Reality. The eye movements induced here were therefore firstly predominantly along the vertical axis, and comprised of a combination of vertical saccades to shift focus between targets, and possibly some vertical smooth pursuit *if* the patient tracked the shot-target rolling towards them, which was not a formal instruction of the task. Importantly, as one of the main actions of the Control VR Stimulation, there was no scope for horizontal smooth pursuit eye movements.

Left-sided smooth pursuit eye movement training in response to optokinetic stimulation (OKS) has shown significant promise in improving the symptoms of SN (109, 197). Several mechanisms by which OKS induces a therapeutic effect have been hypothesized. On the basis of functional imaging studies that have shown widespread activation of networks including the occipitotemporal, parietal, insular and occipital cortex, basal ganglia, cerebellum, and the brain stem in response to OKS (198, 199), Kerkhoff et al. proposed that the therapeutic effects of OKS may be due to its role in altering an attentional priority map. This is a neural representation computed by the cortico-subcortical networks in these regions, integrating multi-sensory input to determine the relative importance of stimuli at different spatial locations (200-202). Through this action, OKS recalibrates spatial orientation, shifting attention towards the affected hemispace (203). Balslev et al. have suggested that interventions that alter extraocular muscle proprioception could also displace the locus of attention (204, 205). More recently, Chan et al. found that OKS in healthy participants caused an adaptation in the eye proprioception and a lateral bias in spatial attention in the direction of a moving stimulus. They hypothesized that when a task requires orientation of attention, a retinotopic memory trace of salient visual locations is combined with an estimate of eye

position when a target needs to be localized in space. OKS causes a shift in perceived gaze which causes a shift in where attention is allocated. The improvements noted in the Therapy Group that received only horizontal smooth pursuit eye movements in the ATTEND trial, provide further evidence for this as a promising treatment strategy.

3.24.2 Comparison with Other Studies

The difference between other Smooth Pursuit Eye Movement Therapy (SPT) trials and the ATTEND trial, is the use of immersive Virtual Reality for the first time to deliver SPT for the treatment of SN. Previous studies have analysed the efficacy of SPT delivered via conventional 2D Displays, and demonstrated, like with the ATTEND trial, that SPT is a promising treatment modality for SN.

Kerkhoff et al. conducted a randomized controlled trial comparing SPT with Visual Scanning Therapy (VST) in patients with chronic stroke exhibiting both visual and auditory inattention (115). The SPT group demonstrated significant improvements in standardized measures such as digit cancellation, line bisection, and paragraph reading. These effects were statistically significant ($p < 0.05$) and associated with moderate to large effect sizes (Cohen's d). The improvements persisted at a 2-week follow-up, highlighting the sustained benefits of SPT. The sample size was of 50 patients, with a dose of 50 minutes of therapy for a total of 5 days, 7 to 9 days apart delivered via a PC monitor, with a singular follow-up at 2 weeks. In comparison, ATTEND targeted patients in the acute and sub-acute phases post-stroke (albeit a smaller sample size), employed a more intensive dose and frequency of therapy, and incorporated a functional outcome measure to demonstrate real-world functional changes. The persisting gains in the ATTEND Therapy Group as found at 3-month follow-up could suggest that the

more intensive dose and frequency, inducing SPT in a broader field of view, and using it as an early treatment may have contributed to longer sustained effects over time.

In another study, Kerkhoff et al. performed a bedside SPT versus VST randomized controlled trial with a sample size of 24 patients, using a laptop screen, delivering 20 treatment sessions lasting 30 minutes each over 4 weeks, with assessments including functional measures, and a 2 week follow-up (113). Some of these features were similar to the ATTEND trial, and similar to my findings, the 12 patients in Kerkhoff's SPT group showed significantly greater functional improvements at the end of therapy and persisting effects at 2-week follow-up. Notably, significant Group*Time interactions were found on two out of three functional outcome measures, namely on the Functional Neglect Index ($F(2, 44) = 5.84$, $P = .006$), and on the Unawareness and Behavioural Neglect Index ($F(2, 44) = 6.39$, $P = .004$), with significant differences between baseline and post-treatment measurements. On the Barthel Index, the SPT group did not show a significant difference from baseline to post-treatment, rather from baseline and post-treatment to follow-up. The main functional improvements noted in these patients were in activities such as finding and grasping objects in the neglected near space, finding more pictures in near space, and improving the perception of the subjective midline. The Functional Neglect Index incorporates 4 tasks, including a tray test (the object of which is to find targets and grasp them), pointing at drawings (another search task), horizontal stick bisection and gaze deviation. The Unawareness and Behavioural Neglect Index judges SN related performance on 6 items that assess unawareness, and 4 items that assess the presence of SN in ADLs. The ATTEND trial, in comparison, utilized the CBS, which offers a more rounded 10 item assessment of function related to tasks that rely on spatial attention. The CBS has been found to be superior to other functional assessments in capturing the real-life

effects of SN, and of the existing 28 standardized assessments (which include the tests employed by Kerkhoff et al.), the CBS is the only one that may assess performance in all spatial sectors (61, 63, 206, 207). My patient cohort demonstrated significant improvements in the Therapy Group from baseline to the end of VR Stimulation on the CBS, complementing the therapeutic effects of the horizontal Therapy VR Stimulation, reflecting improvements that spanned a wider degree of functional activities than demonstrated in the compared study. Therefore, whilst both the Kerkhoff study and the ATTEND trial findings help add to the evidence base of the value of SPT as a notable contender amongst the treatments that have been trialled for SN, it is worth considering that inducing SPT in a more intensive manner, over a larger field of view using Virtual Reality may have superior therapeutic effects than more traditional techniques.

Two other SPT studies are worth noting - Kerkhoff et al. examined the use of repetitive optokinetic stimulation combined with smooth pursuit eye movements in patients with left-sided SN (200), and Keller et al. conducted a pilot study combining SPT with prism adaptation and arm movements (111). The former demonstrated significant improvements in both auditory and visual inattention measures, persisting 2 months beyond the treatment period. The latter showed the value of combined SPT and prism adaptation on cancellation tasks, although the incorporated arm movements seemed to exacerbate SN symptoms. This previous work sheds light on interesting future directions for ATTEND, in the form of adding beneficial adjuncts to the treatment programme to create an intensive, integrated treatment strategy for SN.

3.24.3 The Feasibility of ATTEND as a Treatment for Inpatients

An important aspect of the ATTEND trial was to assess whether it would be possible to deliver a SN treatment in the acute/sub-acute period post-stroke on the Acute Stroke Units and Neuro-Rehabilitation wards. With regards to bedside treatment of SN in the acute phase, some SN treatments such as visuomotor feedback training with physical rods have been shown to be effective and feasible (208, 209), prism adaptation has had mixed results (80, 210), and on the technological front, Kerkhoff et al. presented their laptop-based SPT as a bedside treatment for SN, carried out on a ward with acute stroke inpatients (211).

Certainly, through the completion of the ATTEND trial, it has been demonstrated that in a research setting, with a designated researcher conducting the trial, it is in fact possible to deliver high-quality, high-intensity treatment in the acute/sub-acute inpatient setting. At this stage, the results too are promising, with a clear advantage leveraged by the horizontal Therapy VR Stimulation, making it a very useful addition to the artillery of neurorehabilitation tools for SN treatment.

However, the possibility of implementing ATTEND in the real-world is one that needs careful consideration in various contexts. Inpatient immersive VR is currently being used in a handful of pilot studies in inpatient psychiatric units (212-214) as a relaxation tool, although this patient cohort differs from stroke patients in the burden of motor-related disability, allowing them to visit a room that has the VR equipment set-up, rather than the set-up being taken "to them". Given the large volume of experience I gained in delivering the VR Stimulations to inpatients across different units, I will cover my opinions and ideas on the practical and logistical implications of using a VR-based therapy in the context of inpatients with stroke.

3.24.3.1 Hardware Set-up

The multiple unique features in the ATTEND trial, such as the use of immersive VR, in-built headset eye tracking and gamification of the SPT, all rely on correct and reliable hardware equipment and set-up.

The realistic logistics of conducting the ATTEND sessions was complex. I transported the kit which included the VR Headset, the two base stations, the MSI gaming laptop, two tripod stands for the base stations, a link box, connector cables, laptop charger and a retractable 4-way extension cord, which was set up at the start of every session, and packed up at the end, on a daily basis, for each patient session.

My education involved learning how to set up the hardware; build self-awareness of environmental factors that could interfere with the base stations (such as the reflective plastic divider screens that gained popularity during COVID, windows, metallic surfaces) and take these into consideration during set-up to provide the patient with a seamless experience; monitor the position of the headset on the patient's face, as this would sometimes "slip" down over the course of 40 minutes, impairing the patient's view of the VR world and interfere with accuracy of eye-tracking (a phenomenon observed more commonly in the patients with hemicraniectomy due to skull asymmetry); learn troubleshooting techniques for both hardware and software issues; understand the "dimensions" of the game area and ensure that the angle, height and distance of the base stations from the headset were appropriate; make adaptations such as lowering the bedside frame to allow a greater range of movement for the patient's contralateral limb operating the remote; and monitor the area during the session to prevent accidental moving of the tripods which would impact calibration and cause glitching within the game.

Concluding steps included ensuring the patient was comfortable and their real environment had been restored, pack-up of the components and safe storage. For an experienced person, set-up including calibration would take between 10-15 minutes, however, this would not include the time it may take to get the patient into their bed or chair as per their preference, depending on their mobility status and staff help available; prior- or within-session toilet use which would be longer for hoist transfers; and possible needs for re-calibration.

To rid of the repeated set-up and pack-up, the most ideal solution would be to have a designated area of the ward, such as the gym, or a treatment room, for example, customized for VR-use. This would mean that the base stations are wall/ceiling-mounted, with a fixed marked point for standard calibration, depending on whether the space could accommodate a bed, or a chair, or both. The room would have a desktop or a laptop in place to run ATTEND as it is currently modelled.

Alternatively, the more convenient set-up would involve the use of a "standalone VR headset". These have a built-in processor that powers the VR experience, and do not require base stations. Whilst some provide eye-tracking within the headset, others do not. Such a system would greatly simplify hardware set-up demands and training, with a simplified version of the ATTEND game accessible as an app from within the headset. It may be that the eye-tracking component (i.e. the target ball changing colour from red to yellow when being tracked successfully) in the game is sacrificed in the interest of converting it into a smaller within-headset app, as now that we have established the clinical superiority of the horizontal VR Stimulation, so long as the patient adheres to the instruction of catching the ball, it could be assumed that they are complying to the tracking. Such a headset could be moved around the ward from patient to patient easily, and operated from the bedside itself.

3.24.3.2 Operator Training and Timetabling

In the ideal setting, a standardized protocol would be built with instructions and learning materials on the various elements of the process as relayed in my account above. Members of staff would require training for the application of the headset onto the patient, operating the VR system, with knowledge of troubleshooting common issues. Given that at present, ward-based strategies and treatments for SN fall under the remit of the Occupational Therapists' role, integration of ATTEND sessions into the standard neurorehabilitation care programme would have to be a collaborative effort with them. Strictly speaking, other members of the team such as a peer supporter, psychology assistant, social worker, healthcare assistant, or rehab assistant, could be trained to operate the VR system as well. Importantly, a member of staff would need to supervise the session throughout its entirety, owing to patient-fatigue, break requirements, disability preventing self-removal of the headset, and to attend to any physical or medical concerns.

If implemented as a daily therapy session, the ATTEND session would need to be formally scheduled in addition to existing activities. Through my close interaction with the patient and their treating team, I usually scheduled ATTEND towards the end of the working day at 4pm, so as to not create interferences with scheduled activities. Care would need to be taken for patient preference with regards to the timing of the session, as in my experience, most patients preferred a late afternoon slot, after a post-lunch nap. The repetitive nature of the activity, and the generally calming nature of the virtual environment, could easily push one into a restful state or sleep, particularly if fatigued. Therefore, most successful completion of sessions was generally achieved at a time when patients were alert, well-rested, and motivated to participate.

3.24.3.3 Patient Interest

Patients were drawn to the concept of the ATTEND trial given its novelty, the possibility of improvement in SN and attraction of experiencing a virtual environment. Patients reported positive anticipation for their daily sessions (provided they were not medically unwell, fatigued from poor night-time rest or excessive daytime activities) due to elements of "escapism enjoyment", both through the act of 'escaping' the ward into the virtual environment and the dopamine releases that are involved in the act of playing a game and 'winning' (215, 216). My explanation that the games were an "exercise session only for the eyes", with the actions within the game resembling sporting activities, for example, tennis for the horizontal VR Stimulation, and target practice for the vertical VR Stimulation, may have allowed the patients with stroke to perceive them as a sort of 'exergame', which is game that mimics and involves some form of exercise, introducing another layer of positive incentive (217). From a motivational perspective, I think, even more so now, with the added incentive of conclusive results from a randomized clinical trial, patients would be very eager to engage with this treatment on the ward, particularly if there is the possibility to build it into their timetable as a structured, monitored activity. Positive impacts on mood and indeed response of SN to treatment may have constructive effects on participation in other aspects of neurorehabilitation.

3.24.3.4 Location

Through the ATTEND trial, most of the patients were recruited following transfer to a Neurorehabilitation Unit, with a small number of patients initiating their participation whilst on the Acute Stroke Unit. In general, in my experience, the Acute Stroke Unit is subject to a

faster turn-around of patients, daily as opposed to weekly timetabling, greater susceptibility to staff shortages given the variability in demand in an acute stroke setting, and more frequent rotations of therapy team members. I personally feel that the Neurorehabilitation Unit would be a more appropriate setting for ATTEND to be offered as a treatment for SN, due to the longer-stay of patients, more time to build rapport with staff and familiarize themselves with the ward, weekly structured timetabling, and a greater permanency of key staff. Given the fact that the VR Stimulation would need to be delivered for 15 days, it would also be beneficial to ensure that patients are not subject to repatriation to a non-participating unit causing an interruption in the number of recommended sessions.

3.24.3.5 Cost Benefit

A compelling argument for the implementation of ATTEND would have been differences in the length of stay between the Therapy and the Control Groups. For reasons that will be discussed ahead, this was not the case in the patient cohort for the ATTEND trial. As per cost analyses, a Level I bed in a Neurorehabilitation Unit on average costs £530 per day (218), whereas the baseline operational cost of a bed on a Hyper-Acute or Acute Stroke Unit in London was estimated to be £600 per day in a 2014 report (219), and may well be higher in today's economic climate. It has been reported that the impact of SN includes longer hospital stays, delaying discharge by up to 8 days (9, 10). In comparison, VR Headsets, depending on features and capabilities, start at a price of £300 if we were to look at the most basic model that would be suitable to host ATTEND. In a circumstance where discharge solely depended on physical and cognitive recovery, and differences in length of stay were found to be a positive secondary outcome as a result of this trial, the cost benefit ratio would make for a clear-cut argument to recommend ATTEND to appropriate units.

However, I do not think that the absence of this is a deterrent to adopting ATTEND in the clinical setting, as patients would still benefit from the enhanced recovery from SN in way of improved functionality, reduced symptoms of SN, possibly greater independence and better engagement and participation in broader rehabilitation programmes, all of which are convincing non-financial advantages.

3.24.4 The Improvement in the Control Group

The purpose of the vertical Control VR Stimulation was to control for factors such as VR exposure, gamification, maintaining attention on a task for a set period of time, and motor interaction with visual stimuli. The key distinction between the conditions was the type of eye movements induced: horizontal smooth pursuit in the horizontal Therapy VR Stimulation, and vertical saccades and vertical smooth pursuit in the vertical Control VR Stimulation. To briefly re-iterate, the vertical Control VR Stimulation comprised of a tree in the centre of the field of view, the task being to knock-off vertically arranged targets on the tree, whereas the horizontal Therapy VR Stimulation required tracking a ball towards the more affected side.

When observing the scores on both behavioural outcome measures for the Control Group, from Baseline to 3 weeks, they did make improvements on the Star Cancellation Test, attaining statistical significance with a moderate effect size, and showing a trend towards statistical significance on the Catherine Bergego Scale.

Considering the natural progression of SN following stroke, recovery has been shown to follow a heterogeneous trajectory, with substantial spontaneous improvement typically occurring within the first three months post-stroke, as noted in a meta-analysis by Durfee et al. (220). During this critical period, more than 70% of patients demonstrate measurable

recovery, driven largely by neuroplasticity and the resolution of acute neural inflammation. Despite this encouraging early progress, up to 33% of patients continue to exhibit persistent deficits six months or more post-stroke, establishing chronicity in some cases. There can be a subtle residual SN which can persist for years, affecting approximately 10–15% of patients even in the chronic phase, although this often remains undetected in routine clinical assessments (221).

In the ATTEND trial, the median time since stroke for the Therapy Group was 54 days and interquartile range was 43 to 138 days. In the Control Group, the median was 55 days, and interquartile range was 37 to 79 days. This is to draw attention to the point that the VR Stimulations were delivered to inpatients who were still very much within the acute to sub-acute windows post-stroke, therefore during a time when natural spontaneous recovery was likely to be an active feature, and thus a large contributory factor for the improvement seen in the Control Group. The use of the vertical Control VR Stimulation to function as a control for the natural effects of time highlighted the limitations of relying solely on natural progression for the improvement of SN, in comparison to the additional gains made by the Therapy Group. Both groups of patients continued to receive the standard neuro-rehabilitation programmes at their site of inpatient stay, which may have also contributed to some of the changes observed in the Control Group.

In addition, a noted pre-discussed condition of the ATTEND trial was its aim to not worsen SN in the Control Group. Reflecting real life observations during the trial, when the headset was applied to a patient with SN, and they entered an unfamiliar (virtual) environment, without the trained orienting measures and repetitive reminders that they may have learned to apply within the ward or bed space as part of standard care, it was observed that their head and

neck would drift towards the right side of space, seeming to exacerbate their SN (in patients with left-sided SN). Whilst there is limited direct evidence linking unfamiliar environments to an exacerbation of symptoms of SN, certain studies have suggested that increased attentional demands and complex visual scenes can intensify SN symptoms. For instance, Rapcsak et al. observed that patients with right-hemispheric lesions exhibited more pronounced SN when required to discriminate target stimuli from distractors, indicating that tasks with higher attentional demands can exacerbate SN symptoms (222, 223). It could be possible that the increased attentional load experienced when entering a new environment such as that of the Virtual world accounted for this observation.

This is why extra care was taken to build a condition into the protocol for the ATTEND trial that ensured that for all patients, the virtual environment would be calibrated to the normal midline, rather than to their perceived midline post-SN. This was also the rationale behind placing the tree in the vertical Control VR Stimulation in the normal centre of the field of view, in order to prevent worsening of SN. As a result of this, particularly in the initial phases of undergoing the VR Stimulation, the patient required frequent verbal reminders to orientate them to the midline; in severe cases, occasionally needing a gentle re-direction of the head to the midline to “learn” the position of the tree. Therefore, even the Control Group was receiving at least some degree of forced-attention to the centre, away from the right-side. Whether this contributed as a therapeutic effect towards improving SN is difficult to say (as I did not have, for example, a third group who performed a visual task restricted to the unaffected side of space, for the ethically driven reasoning explained above) but remains a possibility for consideration.

3.24.5 Impact of SN Severity on Recovery and Insights Gained from the ATTEND Trial

Rengachary et al. emphasized that the initial severity of SN significantly influenced recovery potential, with milder cases showing almost complete resolution by six months, and severe cases exhibiting lingering impairments (224). Similarly, Cassidy et al. examined the natural recovery of SN in a group of right hemisphere stroke patients. They found that while many patients showed significant improvements within the first three months post-stroke, the degree of recovery was influenced by the initial severity of SN. Patients with more severe SN at onset tended to have a slower and less complete recovery, underscoring the prognostic value of early diagnosis and assessment, and in practical terms, emphasizing the importance of early therapeutic interventions (225).

This formed the basis for including severity on the Star Cancellation Test as a factor for minimization in the ATTEND trial. The Star Cancellation Test has been shown to have excellent test-retest reliability and good validity in assessing the severity of SN (226, 227). In the ATTEND trial, both groups were matched for severity on this test, and were therefore comparably vulnerable to slower and lower rates of recovery. The fact that there was a Group*Time interaction driven by the Therapy Group suggests that the horizontal VR Therapy played a constructive role in terms of treating SN despite the initial severity. In the same vein, higher scores on the Catherine Bergego Scale, reflecting increasing severity, have been closely linked to greater impairments in daily activities, extended rehabilitation periods, and diminished functional recovery (62, 228). The fact that the Therapy Group was in fact more severely impaired at Baseline than the Control Group on the CBS suggests that the horizontal Therapy VR Stimulation had quite a marked therapeutic effect helping the Therapy Group catch up with the Control Group (who started off less severe) by the end of the 3 weeks. This

further establishes the role of ATTEND as an effective early therapy for patients with severe SN.

3.24.6 Maintenance Effects

The scores for 20 patients on the Star Cancellation Test from the end of 3 weeks of VR Stimulation, T3, to follow-up at 3 months, T4, were also analysed and presented in the Results section in order to explore the maintenance of the therapeutic effects.

The analysis revealed a significant main effect of group, indicating a sustained difference in performance between the Therapy and the Control Group at the 3 month follow-up. There was no significant main effect of time or a Group*Time interaction from T3 to T4 suggesting that, across both groups, test scores remained relatively stable during the 3 month period. The lack of a significant reduction in scores indicates that the Therapy Group retained their gains over time, with no evidence of regression in their degree of residual SN, even after 3 months without additional support. The sustained benefit of the horizontal Therapy VR Stimulation points towards its potential for long-term efficacy. Ultimately even at the 3 month time point, the natural recovery with time did not prove to be strong enough to equalize the groups, making a further case for the therapeutic VR Stimulation.

I think that these maintenance effects results are promising, given their statistical significance, rather than conclusive. At this stage, a more cautious interpretation is probably the sound way to proceed. Focusing on the limitations, the sample size at T4 was reduced to $n = 20$, consisting of 9 patients in the Therapy Group, and 11 patients in the Control Group. This is quite a small sample size, and although it was ensured that the group means were unaffected by the missing data, this small sample may have limited the ability to detect

smaller effects. Performing a post-hoc power analysis using the ClinCalc as mentioned in Methods (https://clincalc.com/stats/SampleSize.aspx), the power of the T3 to T4 analysis was rated at 44.1%, which makes the follow-up study an underpowered one, increasing the likelihood of a Type I error. It must also be noted that the standard deviations in the Control Group scores were very large, and this might have contributed to increased error variance, making it more challenging to detect accurate differences between groups.

Future considerations would include increasing the sample size in order to improve the robustness of the results and allow for greater statistical power. Assessing participants at longer intervals would also help provide additional insights into the durability of the horizontal Therapy VR Stimulation's therapeutic effects. It would also be useful to assess its role in the more chronic phases of SN to understand its potential as a treatment at that stage, or even as a "booster" treatment to enhance or sustain effects.

3.25 Discussion: FiVE in the Vive SPM Analysis

The FiVE in the Vive impairment measure involved capturing gaze duration data from free visual exploration tasks performed Pre- and Post-VR Stimulation sessions daily. 1st Level Analysis involved setting up a one way ANOVA for the Pre- and Post-Stimulation images day by day, with two contrasts applied, one looking at only the Pre-Stimulation images per day to examine long-term effects, and the other looking at Pre-Post Stimulation images on each day, in order to examine short-term effects. Each of these contrast images were then taken into a 2nd Level Analysis, where they were set up against a parametric modulator to model the effects of time, in order to ascertain if there were consistent spatial shifts in the centre of gaze over the course of 3 weeks of VR Stimulation reflecting long-term effects, and immediately within a session across the days, reflecting short-term effects. Finally, a 3rd Level Group Comparison

analysis was conducted between the Therapy and Control Groups for both effects, and post-hoc tests were performed to investigate driving factors for the results. Maintenance effects were investigated by looking for changes in gaze location from the last day of VR Stimulation to the follow-up day, and by looking at gaze location on the follow-up day only.

3.25.1 Response to VR Stimulation

When assessing for differences in consistent spatial shift from the start of VR Stimulation at T2 to the end 3 weeks later at T3, between the Therapy Group and the Control Group, it emerged that there was a shift in gaze location to the left upper quadrant, driven by the Therapy Group, with a p-value corrected for multiple comparisons, lying just on the edge of statistical significance. Looking at the groups individually, after 3 weeks of horizontal Therapy VR Stimulation, the Therapy Group's average centre of gaze location shifted spatially by 38^{o} towards to the left, and 18^{o} upwards from their baseline average centre of gaze, achieving strong statistical significance. In comparison, the Control Group's average centre of gaze location after 3 weeks of vertical VR Stimulation shifted by 20^{o} towards the centre, and 4^{o} upwards, with the p value showing a trend towards significance.

The FiVE in the Vive gives a visual representation of the spatial shifts in the centre of gaze made over the course of 3 weeks of VR Stimulation, providing an additional layer of context to the performance of both groups on the behavioural outcome measures. The presence of a spatial shift towards the left quadrant in the Therapy Group further consolidates the therapeutic effects driven by leftward smooth pursuit eye movement therapy. The change in centre of gaze location arose from performing repetitive eye-tracking from right to left within a standardized reference frame, which was not expanded as the days progressed. In practical terms, this means that the starting point of the red ball and the position of the racket

remained the same throughout the 15 days within the 110^{o} field of view in the HTC Vive. It is interesting to note that this range of eye tracking was adequate to achieve a shift of 38^{o} along the horizontal plane.

When assessing short-term effects, over whether the Groups had any differences in the spatial shifts occurring within the VR Stimulation session per day, there was a peak-voxel that emerged as showing a difference, although the statistical significance of this did not reach threshold but trended towards it. The Therapy Group was driving this change, and the Control Group did not in fact have any spatial shifts during the VR Stimulation sessions. During the vertical Control VR Stimulation sessions, the patients in the Control Group were required to focus their attention on shooting vertically positioned targets on a tree in the centre of the field of view, theoretically restricting their eye movements within a small area of focus. The short-term effects were modelled using a parametric modulator, the aim of which was to capture voxels where gaze dwell times changed from the start to the end of a 40 minute VR Stimulation session. During the session, if the Control Group's gaze was mostly contained within a fixed area of exploration (in this case the central tree), gaze dwell times would be restricted in the voxels in that area; similarly, other voxels outside of this area, where gaze was *not* being drawn towards, would not show positive values across space and time. Together these two effects would result in the lack of spatial shifts noted from the start to the end of a session.

3.25.2 The "Bigger" Picture

The Therapy Group practiced 40 minutes of horizontal smooth pursuit eye movement therapy for an average of 14.5 days. All the patients had left-sided SN, and they followed a target repetitively from the right to the left for the duration of the VR Stimulation session. This

exercise seems to have shifted their focus to the left upper quadrant over time, causing not just a horizontal shift, but also an altitudinal shift upwards.

The shift appears to be quite markedly towards the left of the recordable field of view limits of the FiVE in the Vive assessment measure, sitting at 22^{o} to the left and 16^{o} upwards from the midpoint. Whilst on initial review, this may seem as though the Therapy Group almost "over-corrected", this shift needs to be contextualized in terms of real-world field of views of the human eye.

The recordable visual angle range of the FiVE in the Vive assessment, when measured from the midline, is 32^{o} on either side horizontally and 24^{o} vertically from the midpoint, totalling is 64^{o} horizontally and 48^{o} vertically, which is far superior to the 2D screen-based test that it was inspired from, which had a total visual angle of 28^{o} by 21^{o} in the original version (170). However, considering the human eye has a monocular visual angle of up to 98^{o} horizontally and 70^{o} vertically in a single direction from the resting line of sight, this places the location of the centre of gaze post-response to the VR Therapy Stimulation in more comprehensible context and less "over-corrected".

Therefore, the gaze location data that I am analysing and plotting are locked within the confines of the field of view of the FiVE in the Vive, which does not reflect the real-world range of gaze, rather, what it does show in a way, is the "maximal point" of attention across the horizontal plane that patients have at baseline (denoted by the centre of gaze location at baseline, presuming that when exploring the image, -16^{o} in the right lower quadrant was the maximum point towards the midline that the Therapy Group could fixate at), and the location of the centre of gaze at the end of the trial denotes a spatial shift to the left extreme end of

the available field of view, meaning that they gained the ability to scan all the way across on the FiVE in the Vive images, and therefore perhaps even beyond in the real world (Figure 37).

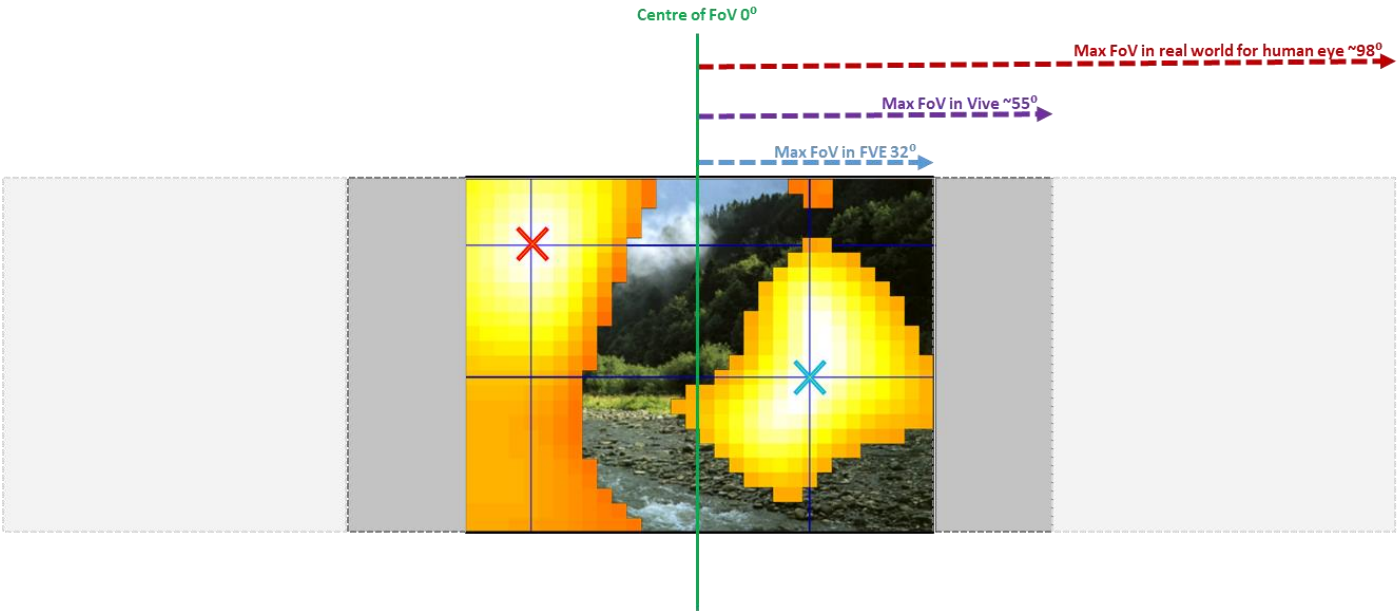


Figure 37: Contextualizing the FiVE in the Vive Results in real world terms
Abbreviations: Field of view (FoV), FiVE in the Vive Task (FVE), Vive Headset (Vive). In this schematic diagram, the green line marks the centre of the field of view. Only the horizontal FoV has been illustrated and discussed in this Figure. The coloured picture is an example of the image seen during the FVE task. This accounts for a field of view angle of 32° from the midline in either direction. The dark grey box represents the maximum field of view within the Vive Headset, amounting to approximately 55°. The light grey box represents the field of view in one direction for the human eye, approximately 98°. The areas of gaze location for the Therapy Group has been super-imposed on to the view in the FVE Task (on the right is the centre of gaze location marked by the blue cross at Baseline, and on the left is the centre of gaze location marked by the red cross at 3 weeks) in order to give us an idea of gaze location in the context of the bigger picture of the real world field of view

With regards to the altitudinal shift, a systematic review conducted by Moretta et al. reported that vertical SN occurred more frequently in the lower quadrants (due to occipitoparietal injury) (229, 230) than in the upper quadrants, commonly co-occurred with horizontal SN, and was most often associated with vascular (particularly ischaemic) lesions (231, 232). They did note that deficits in upper vertical space do also occur (due to occipitotemporal injury) (233).

In the ATTEND trial, the centre of gaze location was situated quite close to the horizontal meridian at baseline for both patient groups and they did not appear to have an altitudinal

bias (2^o in the lower quadrant for the Therapy Group and 2^o in the upper quadrant for the Control Group). Following the 3 weeks of VR Stimulation, the Therapy Group shifted upwards by 18^o, and the Control group by 4^o. This finding is interesting. Unfortunately, with the exception of a single case study using VR to treat vertical SN in a solitary patient with mild functional SN, which was undetectable on pencil-and-paper tests, with no controls or repeated measures analysed (234), there does not appear to be much evidence of the evolution of vertical SN in response to treatments for horizontal SN. It is possible that as patients improved towards the left, their attention was also drawn towards the vertically positioned salient features in the images which were not controlled for (the mirror images presented in pairs were flipped along the y-axis to negate for horizontal salient features, but not along the x-axis). Therefore, it is possible that the naturalistic images (landscapes, mountain tops, waterfalls, rainbows, sky, etc.) featured salient features in the vertical plane and attention was drawn more there hence the upward shift noted for the Therapy Group.

3.25.3 Changes in the Control Group

The long-term spatial shift for the Control Group, from the start of VR Stimulation to the end at 3 weeks, though not statistically significant, also warrants discussion. Their centre of gaze shifted from -18^o (right-ward),$+2^o$ (downward) to $+2^o$ (left-ward), $+6^o$ (upwards), localized quite centrally in the field of view. This spatial shift could reflect the natural improvement of SN with the passage of time.

A further consideration is the nature of the control task. This confined eye movements to the vertical plane and did not require lateral smooth pursuit. It could also point towardsIt is possible that there may have been the possibility of some therapeutic benefit from the calibration to normal midline and central position of the tree in the Control VR Stimulation. In

addition, whilst not instructed to do so, it is possible that some smooth pursuit may have occurred in case participants tracked the apples as they fell from the tree and rolled downwards towards them. Therefore, it is possible that some degree of smooth pursuit was present. When designing the trial, we considered the potential placement of the control stimuli and deliberately chose to locate them at the midline, as positioning them laterally might have risked exacerbating neglect in one direction. This design decision means that the control task may itself have carried a small therapeutic component by encouraging attention towards the midline, particularly in more severely affected patients. Accordingly, the observed differences between therapy and control groups may represent a conservative estimate of the true treatment effect.

When examining the short-term effects of the VR Stimulation, there did not appear to be any spatial shifts in the Control Group, which would be reasonable to expect given that the eye movements were restricted within a very narrow horizontal margin, with no smooth pursuit eye movements, and mainly vertical eye movements whilst shooting the apples off the tree. In contrast, it is an expected result to see the short-term effects only emerging for the Therapy Group, as a result of the intensive smooth pursuit movements exercised during the horizontal VR Therapy Stimulation. It is notable that the short-term difference in centre of gaze between the two groups did not actually gain statistical significance. Possible reasons for this could include day-to-day variations in sessions, dependent on engagement, mood, motivation to participate for the entirety of the sessions, fatigue, etc.

3.25.4 A Comment on Interhemispheric Inhibition

The use of the non-paretic limb to control the handheld remote draws into call the need to discuss the role of interhemispheric inhibition (IHI) in recovery in stroke patients. In healthy

individuals, IHI maintains a balance between hemispheres, but post-stroke, damage to one hemisphere reduces its inhibitory influence on the intact hemisphere, which subsequently exerts excessive inhibition on the side with the lesion (41). This imbalance exacerbates SN by suppressing the damaged hemisphere's ability to process contralesional space while amplifying the intact hemisphere's representation of ipsilesional space. Rebalancing IHI using interventions such as high and low-frequency rTMS has been shown to improve spatial attention by restoring activity in the damaged hemisphere (235). The use of the non-paretic limb could be argued as activating the intact hemisphere, however, in the ATTEND trial, all the patients in both groups utilized their non-paretic limb to operate the remote, using upwards and downwards motions, so there was no mismatch in the impact on IHI between the groups, if any. In addition, the fact that the Therapy Group improved despite this, points towards the fact that this phenomenon did not impact SN recovery in this instance.

3.25.5 Maintenance Effects

No differences emerged between the groups when looking at maintenance effects. Firstly, with only 9 participants in the Therapy Group and 11 in the Control Group, the follow-up analysis was likely underpowered to detect subtle or small effects in change of gaze location. The small sample size may have reduced the likelihood of identifying statistically significant differences, and the analysis therefore may not have had the power to detect significant differences. This, in combination with the fact that at 3 months, the method involved only gathering one set of FiVE in the Vive images as a one-off measurement of gaze location, meant that I did not have a large amount of data to utilize at timepoint T4, as opposed to the daily FiVE in the Vive Tasks from T2 to T3 providing a richer dataset. The single follow-up FiVE in the Vive Task may have reduced the ability to detect consistent spatial shifts in gaze location,

increasing susceptibility to noise. The reduced dataset at follow-up also may have impacted the degrees of freedom, reducing the sensitivity of the analysis to detect group differences.

3.26 Discussion: Length of Stay

Functional outcomes closely mirror the degree of recovery from SN. For example, improvements in attention to the neglected side have been shown to enhance independence in activities of daily living by up to 50%, as measured by the Barthel Index (236). As these functional improvements play a direct role in the ability to participate and engage with neurorehabilitation, SN has been associated with increased length of hospital stay. In one study, stroke patients with SN had an average length of stay of 32.4 days, whereas those without were discharged within an average of 25.2 days (237). In the ATTEND trial, the steep increases in the scores of the Therapy Group seem to suggest that the patients might have had an accelerated beneficial advantage from their neuro-rehabilitation programmes, due to an increased ability to participate and attend to the side of space previously affected by the SN. The fact that this therapy was administered within the first 3-6 months of time since stroke meant that it featured as an early intervention for acute and sub-acute strokes.

However, in the case of our study, this early improvement in the Therapy Group was not associated with any significant differences in the length of stay between the two groups. This is unsurprising, as the study was not powered to detect changes in LOS, and in the Level 1 neurorehabilitation settings, which is where the majority of patients were recruited from (see Table 8), the minimum length of stay is predetermined at admission.This means that, regardless of functional progress, patients are expected to remain for a fixed duration, which directly constrains any calculation of length of stay and reduces its value as an outcome measure in this context.

Several studies have looked into the multitude of factors, apart from lateralized deficits in physical domains, which play a role in time to discharge from neurorehabilitation units, such as functional status, cognitive impairments, medical co-morbidities, and social support set-ups.

Pellicciari et al. demonstrated that higher modified Barthel Index scores at admission (indicating better baseline functional status) strongly predicted better functional outcomes at discharge (236). Everink et al. highlighted that better cognitive functioning increased the likelihood of home discharge, particularly in older patients (238). Ottiger et al. observed that stroke patients living alone required higher levels of independence in daily activities to qualify for home discharge compared to those living with family, which had knock-on effects on length of stay due to the waiting times for appropriate long-term discharge destinations such as nursing homes or residential homes (239). Saab et al. found that advanced age and medical complexities, such as bowel incontinence, were associated with discharges to nursing homes, etc (240).

Given the fact that length of stay particularly within neurorehabilitation is governed by such a multitude of factors, both practical and holistic, it is unsurprising perhaps, that improvements in another physical domain may not directly translate to a decreased length of stay. Future studies might therefore focus on more sensitive and proximal markers of benefit, such as participation levels in physiotherapy and occupational therapy, which may better reflect a patient's functional readiness for discharge, independent of the logistical and non-physical factors that impact stay in hospital.

3.27 Limitations and Future Directions

The ATTEND trial has its limitations. The sample size for each group was $n = 12$, which is relatively small for detecting significant effects in the event of a further reduction in data, such as I experienced when assessing maintenance effects. Therefore, using a larger sample size would be a consideration for future work as if the existing trends could be replicated in a larger sample, and show more accurate reflections of statistically significant differences between the Therapy and Control Groups, then the case for the horizontal VR Therapy Stimulation would strengthen as a SN treatment. There was notable variability in the scores for the groups, in particular, the Control Group that had a large standard deviation at the end of 3 weeks of VR Stimulation on the Catherine Bergego Scale score. Larger variability in the Control Group could be attributed to heterogeneity within the sample. There are a few factors to consider within our cohort with regards to heterogeneity:

1) Stroke syndromes are heterogeneous in their presentations, having knock-on effects on physical and cognitive abilities, motivation, mood, and therefore, participation in neurorehabilitation (241).

2) The syndrome of SN itself is heterogeneous in terms of symptoms and subtypes, which could have a consequential effect on recovery (242).

3) It is known that there is a relationship between lower SN severity and potential for spontaneous recovery. In our cohort, even though patients were matched for severity at baseline on the star cancellation test, they were in fact statistically significantly different on the Catherine Bergego Scale (the Control Group being less severe). This might have impacted

the natural recovery element in the patients within the Control Group, causing increased variability in scores towards the end.

4) The combination of variance in the degree of natural recovery in the Control Group, and a possible therapeutic effect from calibration to normal midline and focused attention on the central tree in the Control VR Stimulation, may have also caused some to improve considerably more than others.

Therefore, future directions would include considering matching patients on both impairment-based assessments and functional assessments if possible, incorporating larger sample sizes to tackle some of the heterogeneity factors mentioned, and considering the use of a control which does not fix an object in the centre, rather, could possibly be a bush across the visual field, where apples appear (using eye tracking software) only where the patient looks, and they can then target them and shoot them down.

I did not assess for changes in inattention in other modalities, such as auditory and haptic inattention. Kerkhoff et al. found significant improvements on this front, including significant changes in patients' self-awareness of their inattention (211), following smooth pursuit eye movement therapy. These would be useful expansions in future work, to test the hypothesis for the modality-independent increase in cortico-subcortical networks that has been observed in response to horizontal smooth pursuit (200, 202).

Another limitation is that no patients with left hemisphere stroke and right-sided neglect were recruited into this study. This likely reflects both the recruitment pathway and clinical practice. We did not systematically screen all stroke admissions; instead, patients were referred by clinical teams. It is possible that milder cases of right-sided neglect were under-

diagnosed and therefore not referred, given that right neglect is often more subtle and less clinically obvious than left neglect. Consequently, the trial sample predominantly represents patients with left-sided neglect following right hemisphere stroke. While this limits the generalisability of the findings, it is consistent with the literature that left neglect is more frequent, more severe, and more persistent.

Video-oculography during free visual exploration offers a promising alternative: Kaufmann et al. (243) demonstrated that FVE detected subtle right-sided neglect in left-hemispheric stroke patients with aphasia, a group particularly prone to missing via paper-pencil tests, due to language deficits. This supports the sensitivity of gaze-based methods and suggests that such a measure in clinical practice may be useful in detecting subtle neglect that is clinically overlooked.

This is the first application of the FiVE in the Vive technique in a clinical trial. Given the small sample size in the ATTEND trial, it would be useful to increase the number of images being viewed in the FVE task to further enrich the gaze duration data evaluate the impacts of a greater amount of data on the statistical differences that are teased out by SPM. The issue with vertically salient features introducing an altitudinal bias was explored in the Section 3.25. This is a useful opportunity to explore altitudinal SN as well, and future work could also include subtracting any vertically positioned salient features on the images by including vertically reflected mirror images allowing for altitudinal shifts to be studied more accurately. Extending further on the issue of saliency, the types of images could also be replaced by tessellating patterns with a fixed shape but different colours, which may help reduce the issues with bias arising from salient features. I could also attempt to broaden the field of view that can be covered with the FiVE in the Vive assessment, given that the HTC Headset allows for a

maximum of 110^{o} field of view. It would be useful to look at the structural imaging of the patients and assess for associations with response to VR Stimulations.

Last but not the least, now that it has been shown that the horizontal Therapy VR Stimulation treats SN, technically, a roll-out of the ATTEND neuro-therapeutic app does not require eye-tracking hardware and software – so long as a participant is catching the target on the affected side, and is able to follow the instruction to track the target, it could be assumed that smooth pursuit eye tracking is taking place. This would make the ATTEND app much more accessible on cheaper hardware, and less complex to set-up for the treating Occupational Therapy teams in a hospital setting. In addition, it could also open up channels to assess its efficacy in the chronic phases of SN, as if downloadable as an app on a VR Headset, it could even be implemented at home (with formal training and familial support for example, to help set-up the headset). The roll-out games could be made more varied to prevent fatigue and boredom. In addition, in the ATTEND trial, I standardized the game-play for all the Therapy patients so as to not introduce variability in the size of the smooth pursuit area, etc, but in the future, gaming-programming features such as 'Dynamic Difficulty Adjustment', or 'Adaptive Difficulty', where a game adjusts its challenge level based on a player's performance, could be incorporated into the gameplay to increase the scanning field, or make the targets move faster, etc (244). Finally, the concept of booster-therapy, to enhance improvement from SN, at a fixed interval, would also be an interesting area to explore, to assess if improvement can be encouraged further, or if it eventually plateaus, adding invaluable information and understanding towards the complex field of therapy-based recovery from SN.

4.0 Experimental Chapter III

The Relationship between the Sustained Attention to Response Task and Spatial Neglect

4.1 Sustained Attention

Sustained attention is defined by Robertson et al. as “the ability to self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing qualities, would otherwise lead to habituation” (182). This ability is a key element in being able to perform tasks that require continuous monitoring and engagement, ranging from ordinary daily activities such as reading, to more complex ones such as driving (182, 245). In real-life settings, sustained attentional lapses have been shown to be linked to real-world consequences in relation to the constant vigilance attention required in high-stakes professions such as monitoring flight operations or handling medical emergencies (246, 247).

Stroke disrupts this capability through damage to neural networks associated with attention, including the prefrontal cortex, parietal regions, and subcortical structures such as the thalamus and basal ganglia. The right hemisphere is particularly implicated, given its dominant role in attentional processing (31). In addition to the range of motor and cognitive deficits that hinder recovery and independence post-stroke, impairments in sustained attention cause frequent lapses and affect the ability to filter distractions, sustain goal-directed behaviour, increasing the risk of accidents and secondary complications (248).

4.2 Sustained Attention and Spatial Neglect

Spatial Neglect, occurring most often as a consequence of stroke affecting the right hemisphere, is not solely a defect in spatial attention, as it has been increasingly linked to broader impairments in non-spatial attention, resulting from damage to interconnected cortical or subcortical structures, predominantly in the right hemisphere (21, 249, 250). Whilst the hallmark feature of SN is a failure to respond to stimuli on the contra-lesional side of

space, often accompanied by an apparent unawareness of the affected side (251), several studies have recorded patients also demonstrating difficulties with non-spatially lateralized attention, such as with working memory, successive signal recognition and sustained attention (252, 253). These deficits often affect the patient's ability to maintain focus and process sequentially presented information, irrespective of its spatial location. Intriguingly, these non-spatial impairments are frequently stronger predictors of chronic SN in the post-acute recovery phase, more so than the issues with spatial inattention itself (254, 255).

The relationship between sustained attention and SN can be observed in tasks requiring vigilance, where patients with SN often exhibit increased variability in reaction times and a higher frequency of attentional lapses (254, 256). In terms of neuro-imaging correlates, reduced activity in the right parietal and frontal regions during sustained attention tasks correlates with the severity of SN (19, 257). Malhotra et al. demonstrated the temporal dynamics between sustained attention and SN, showing that SN was often exacerbated by task duration, with attentional performance deteriorating over time, indicating a sustained attention component (258).

4.2.1 Tonic and Phasic Attention

Spatial processing deficits in SN appear to be impacted by alterations in tonic attention and phasic attention. Tonic attention, which plays a key role in sustained attention, provides the cognitive foundation for higher-order functions like working memory and executive control, with fluctuations over minutes to hours (259, 260). Impairments in tonic attention have been shown to exacerbate SN symptoms, demonstrating its role in acting as a regulatory framework that stabilizes cognitive functions necessary for spatial awareness (261). Phasic attention, in contrast, fluctuates over fractions of a second, typically triggered by alerting

stimuli such as a loud noise, and is crucial for processes such as orienting and selective attention (262). Therefore, in SN patients, problems with tonic attention affect the baseline attentional states required for spatial attention, and problems with phasic attention contribute to an inability to reorient focus to previously neglected stimuli, further compounding the spatial bias (257, 260).

4.2.2 Shared Neural Mechanisms

Corbetta et al. proposed explanations for the links between spatial and non-spatial attention on the basis of neural networks. They posited that the presence of SN reflects impairments in non-spatial processes like arousal, reorienting, and the detection of novel stimuli, which are disrupted by damage to the right hemisphere, particularly ventral regions such as the superior temporal cortex, temporoparietal junction, inferior parietal lobule and insula. The interaction between these non-spatial mechanisms and spatial attention systems, points towards a link between damage to ventral regions and abnormal physiology in the dorsal attentional network. The damage to the right hemisphere ventral frontoparietal cortex hypo-activates the ipsilesional dorsal network, unbalances the activity of the dorsal attentional network, leading to imbalances in inter-hemispheric activity, favouring the left hemisphere. This imbalance shifts spatial attention and eye movements towards the right visual field, causing SN on the left (19).

4.3 The Sustained Attention to Response Task

The Sustained Attention to Response Task (SART) is a cognitive assessment tool extensively utilized in psychological and neurocognitive research. Initially developed by Robertson et al., the SART offers a nuanced examination of sustained attention and response inhibition, both

of which are critical for understanding cognitive performance in complex and demanding environments. Over the years, it has evolved into a cornerstone methodology for exploring the dynamics of attentional lapses, error-prone behaviour, and the neural mechanisms underpinning these phenomena (181, 182).

The SART is informed by several foundational theories of attention. Posner and Petersen's attention systems suggested three “core networks” that contribute to successful task performance - alerting, orienting, and executive control (245). The SART predominantly engages the alerting and executive control systems, as participants are required to maintain readiness while selectively inhibiting “prepotent” responses (263). Additionally, the “default mode network theory” has been proposed to interpret attentional lapses observed during the SART, positing that mind-wandering reflects a shift from task-focused to internally-directed processing (264).

The SART is a “go/no-go” task that typically involves a rapid sequential presentation of stimuli called “trials”, commonly $n = 225$, often single-digit numbers (1–9), on a screen. Participants are instructed to press a response key for every number (1,2,4-9; called “go trials”, $n = 200$) except a designated target (commonly the digit "3"; called a “no-go trial”, $n = 25$) requiring them to inhibit their habitual response to frequent stimuli. The low frequency of targets creates a cognitive scenario that requires constant vigilance, favours automatic response tendencies, thus amplifying the cognitive demands of inhibitory control (181).

It has been extensively used in a variety of disciplines to examine the influence of variables such as age, gender, and education on sustained attention (265, 266). It has also served as a tool for studying traumatic brain injury (267-269) and to evaluate attention challenges in individuals with ADHD (270). Different adaptations of the SART have been utilized to

investigate conditions such as schizophrenia (271), sleep disorders (272), and depression (273). It has also been used to explore the relationship between sustained attention and SN (274).

Key performance outputs derived from the SART include: (i) Reaction Time Variability: indicative of attentional fluctuations, increased variability is a sensitive marker of stroke-related cognitive impairment, and has been linked to cognitive fatigue and mind-wandering (275); (ii) Errors of Commission: reflect failures to withhold a response to a no-go trial, reflect a profound state of task disengagement; (iii) Errors of Omission: failure to respond to a go-trial target, represent lapses in sustained attention. (iv) Post Error Slowing: individuals slow down their response times following an error, thought to reflect increased cognitive control and error monitoring (276).

Robertson and his colleagues proposed that errors of commission (failure to withhold a response to a no-go trial) provide a sensitive measure of the ability to sustain attention (182). They have argued that reversing the relative probability of go- and no-go trials would lead to a scenario where participants' responses to the go-trials would simply become mindless and automatized. Therefore, they employed a continuous performance task that required frequent key presses for go-trials and occasional withholding of responses for no-go trials. They suggested that this design requires a high degree of sustained attention while minimizing the influence of other cognitive functions, such as memory, planning, or intellectual effort. Robertson and his team tested their hypothesis through extensive experiments, examining how SART performance related to everyday attentional lapses and cognitive failures in healthy individuals, as well as the link between attention failures, SART outcomes, and brain injury severity in those with traumatic brain injuries.

However, what happens in the situation where there are a high number of missed go-trials? This could occur if the patients are overwhelmed by the task or the speed of the trials, or influenced by fatigue, which is also what I observed within a proportion of my patient cohort who struggled to perform the SART. The resultant effect would be a proportionately higher rate of no-go trials that are apparently correct. This was a problem that I encountered in my patient cohort, and I adjusted the errors of commission for the overall go-trial hit rate (covered in Section 4.10). O'Halloran, Robertson et al. encountered a similar issue when they used the SART in an elderly cohort to explore the relationship between sustained attention and risk of falls (277). A proportion of participants had difficulties performing the SART for the whole length of the task, to the extent that they had to reduce the number of trials from the original design. This was attributed to fatigue, or difficulty understanding the task instructions, particularly amongst older participants with lower cognitive scores. As a result, this led to a high rate of missed trials (errors of omission), and an inflated rate of "correct" no-go trials (errors of commission). For this reason, Robertson et al switched to the go-trial error rate as the main measure of sustained attention in the study as it turned out to be the most discriminative between the groups of fallers and non-fallers, and correlated significantly with falls, suggesting lapses of attention as a contributor for this. Following advice from Tom Manly (who has played a key role in the development and application of the SART) and Professor Leff, I also opted to use go trials therefore errors of omission as an indicator of sustained awareness in my study.

Lastly, the third key output of the SART relevant to this study, is post-error slowing. This is a phenomenon characterized by a systematic slowing of response times following an error (276), and is considered a key measure of error awareness (as there is no feedback from the

SART when an error is made). Error awareness, or the subjective recognition of errors, is central to adaptive behaviour and the regulation of performance (278, 279). Functional accounts propose that post-error slowing reflects a cognitive adaptation mechanism aimed at improving performance through a more cautious response strategy after error detection (280, 281). Studies have reported an association between error awareness and post-error slowing, showing increased reaction times following errors that participants were aware of (282-284). However, this relationship is not universally observed, but this inconsistency may be due variations in task demands, particularly response-stimulus intervals (285, 286). This was not a feature that impacted my study however, as the intervals were fixed within the version of the SART task that was used in this study.

4.4 The Role of SART in the ATTEND Trial

Given the intricate interplays between spatial and non-spatial attention, the SART was included as a baseline test in the ATTEND trial in order to have a measure of, and gain an understanding of the status of non-spatial attention in a patient cohort that was participating in a clinical trial testing a treatment option for SN. Notably, the ATTEND trial was already underway by the time the SART was introduced into it, so data for only a limited number of patients was available (this is detailed in Section 4.6). I was able to compare these patients' performance on the SART with that of healthy controls, data that was obtained from the latter group when they participated as healthy controls for the FiVE in the Vive study.

In the ATTEND trial, both groups improved over the course of the intervention. With the exception of the Star Cancellation Test, on which the change from Baseline to 3 weeks was statistically significant for both groups (albeit of a considerably larger effect size in the Therapy Group), on the CBS and the FiVE in the Vive, only the change in the Therapy group

was statistically significant. In this chapter, due to only a small number of patients who completed the SART, I decided to treat these patients as a single group, and conducted a solely exploratory analysis, to look for correlations between behavioural outputs from the SART and impairment-based change scores on the Star Cancellation Test from the ATTEND trial, in order to try to understand why some patients improved more than others, regardless of which type of VR Stimulation they received.

From the variety of inferences that can be made from the SART behavioural outputs, the two specific measures that I chose to assess in these patients with right hemispheric strokes and SN were (i) Sustained Attention and (ii) Error Awareness.

4.4.1 Rationale for Studying Sustained Attention

There were multiple reasons for choosing to explore Sustained Attention in this cohort, because of the manner in which this cognitive measure is impaired in patients with right hemisphere lesions and SN, the ways in which it enhances deficits related to SN, and the role it plays in recovery, both as a treatable feature in rehabilitation, and as a predictor of outcome.

The right hemisphere plays a dominant role in attention, particularly in sustained and non-spatial aspects (287). Stroke-induced right hemispheric lesions disrupt critical networks, including the frontoparietal attention network and the locus coeruleus-noradrenergic system. Spaccavento et al. found that 44.4% of stroke patients demonstrated deficits in both intensive (tonic and phasic alertness) and selective attention, with right hemisphere lesion patients showing the greatest impairments, especially in tonic and phasic alertness (287). Additionally, right hemispheric lesions disrupt the activity of noradrenaline (which plays a key role as the

neurotransmitter primarily involved in communicating between various parts of the attention network), leading to reduced vigilance and task engagement (288). Patients with right hemispheric lesions and SN also show an inability to maintain cognitive engagement over time, a phenomenon referred to as "vigilance decrement." This decline severely limits their ability to perform tasks that require prolonged focus, such as rehabilitation exercises (287, 288). Stone et al. demonstrated that when performing sustained attention tasks such as Go/No-Go tasks, patients with right hemispheric lesions and SN performed significantly worse than those without SN (14). Similarly, Robertson et al. [30] showed that patients with right hemispheric lesions and SN were significantly less accurate in tone counting than patients without SN. This interplay between SN and sustained attention deficits creates a compounded barrier to recovery (289).

4.4.1.1 The Role of Sustained Attention in Recovery and Rehabilitation

Sustained attention is a foundation stone for rehabilitation. It drives the ability to participate in therapeutic tasks, follow instructions, and engage in repetitive learning activities. Patients with sustained attention deficits often struggle to maintain focus during critical rehabilitation exercises, such as motor retraining, cognitive exercises, or daily living skill practice. This results in slower recovery and poorer outcomes (287, 290).

Beyond structured rehabilitation, sustained attention is crucial for relearning and performing activities of daily living. Tasks such as cooking, dressing, or using public transport require prolonged focus to sequence actions correctly and adapt to environmental cues. Patients with sustained attention deficits are at increased risk of errors, omissions, and safety hazards, further reducing their independence (291).

Robertson and Murre highlight that sustained attention deficits can disrupt Hebbian plasticity, the principle of "cells that fire together, wire together," which is foundational for learning and recovery (292). Rehabilitation tasks designed to leverage plasticity – such as repetitive practice of motor or cognitive tasks – become less effective when sustained attention lapses. They emphasized the importance of interventions targeting sustained attention, such as cueing systems and vigilance-based therapies. These interventions aim to re-engage disrupted attention networks, leveraging neuroplasticity to enhance recovery (292).

As detailed in Section 4.3, in my study, I used errors of omission (from go trials) as the SART output to determine sustained attention effects.

4.4.2 Rationale for Studying Error Awareness

Error awareness, the ability to detect and respond to one's own mistakes, is an essential component of cognitive control and performance monitoring. It relies on a distributed neural network involving the anterior cingulate cortex, dorsolateral prefrontal cortex, and the right inferior parietal lobule. These regions are integral to performance monitoring, which involves comparing intended actions to executed actions to identify errors (293, 294).

After stroke, these regions often sustain damage or disconnection, leading to deficits in error awareness. For example, the anterior cingulate cortex generates the error-related negativity, a neural signal that occurs rapidly after errors, while the posterior regions contribute to error positivity, reflecting conscious error detection (295, 296). Disruption in these processes hinders the ability to recognize mistakes, which is particularly pronounced in patients with right hemisphere lesions and SN due to impaired attentional control over the contralesional

space (296). Noradrenaline plays a critical role in modulating error awareness through its effects on arousal and attention. The locus coeruleus-noradrenergic system, which has dense projections to the anterior cingulate cortex and dorsolateral prefrontal cortex, is activated during error detection tasks (288). Pharmacological studies show that enhancing noradrenaline activity with drugs like Atomoxetine improves error detection signals in these regions, highlighting its potential as a therapeutic target for patients with impaired error awareness (297).

4.4.2.1 The Role of Error Awareness in Recovery and Rehabilitation

Impaired error awareness has significant implications for stroke recovery. Patients with reduced awareness of their errors fail to engage in compensatory strategies or adjust their behaviour during therapeutic activities, limiting their ability to relearn impaired skills. For instance, patients undergoing motor rehabilitation may not notice when their movements deviate from the intended trajectory, resulting in repeated errors and slower progress (287). In another example, cognitive tasks requiring error monitoring or multi-step problem-solving rely on error awareness to ensure consistent processing of incorrect action and adaptive responses. When attention wavers, errors increase, the learning process is disrupted, limiting the gains made from rehabilitation activities (287).

Moreover, SN exacerbates these deficits. Patients with right hemisphere lesions and Spatial Neglect often fail to detect errors in contralesional space, leading to further disengagement from rehabilitation tasks. This combination of impairments contributes to worse functional outcomes, including decreased independence in activities of daily living (288, 296).

In my study, I have used post-error slowing as the SART output for error awareness, because of their very frequent association in several studies (282, 283, 293, 298).

4.5 Aims of the Study

Are there any correlations between the behavioural outputs from the SART test and the impairment-measure based change scores from the Star Cancellation Test in the ATTEND trial that may explain the variance between patients' degrees of improvement?

This was a simple correlations analysis performed on change scores obtained by subtracting the star cancellation scores at T2 (Baseline) from T3(end of 3 weeks of VR Stimulation), and measures of sustained attention and error awareness acquired from the SART test.

A linear regressions analysis was also performed with Star Cancellation change scores as the dependent variable and the SART measure (go-trials and or post-error slowing) as the explanatory variable. The following covariates were included based on clinical relevance: initial severity (baseline star cancellation score), time since stroke, and group.

4.6 Methods: Participants

Two groups of participants were recruited (Table 14).

The patient group included 14 patients with stroke (27% female), mean age 64.25 years (SD 9.96 years), from the cohort of inpatients who participated in the ATTEND trial. These patients had been identified by the multi-disciplinary teams as suffering from SN, as part of the recruitment process for the ATTEND trial, as covered in Chapter 3.0.

The SART test was prepared for use within Virtual Reality and introduced into the ATTEND trial after the clinical trial was already underway, which meant that it was administered as a baseline test only from patient ID CT09 (the 9th patient in the trial) onwards. There were 3 drop-outs from that point onwards and 3 patients were unable to attempt the SART as they were unable to see the numbers correctly due to the severity of their SN. In addition, in keeping with the guidance from the Science of Behaviour Change website on SART analysis (https://measures.scienceofbehaviorchange.org/measuredetails/8e2bedf2-86b0-4377-89be-d0b6ae000481) with regards to elimination of subjects who missed a certain proportion of trials, I selected an arbitrary cut-off of excluding patients with less than 100 out of 225 trials. Data from a further 5 patients was therefore excluded. As such, SART data from 14 patients has been analysed and presented in this study.

The second group included 23 age-matched healthy controls (65% female), mean age 68.96 years (SD 9.56 years). They were recruited through advertising via the Institute of Neurology mailing lists and adverts distributed to attendees at the World Stroke Day Forum held in October 2022. The inclusion criteria were: (i) no previous history of stroke; (ii) no ophthalmological issues.

Both groups were matched for age, $p = .44$ but not for gender, $p = .02$.

4.7 Ethics

The Ethics approval for this study was the same as for the ATTEND trial, granted by the UCL REC (IRAS Project ID: 276250).

4.8 Materials

The HTC Vive Pro Eye headset used for the ATTEND trial, featuring integrated eye-tracking and room-scale positional tracking via base stations, was used to run the SART test in 2D format. A detailed description of the support software and hardware is in Section 3.11.

4.9 SART within the Virtual Reality

In our study, I imported the SART task using custom-built software for utility within the HTC Vive headset (Figure 38). It was performed at Baseline (T2) during the ATTEND trial, as a one-off test prior to receiving any VR Stimulation.

In the SART procedure, 225 single digits (25 of each of the nine digits) were presented visually over a 4.3 minute period. There were therefore 200 go-trials, digits 1,2,4-9, and 25 no-go trials, digit 3. Each digit was presented for 250 milliseconds, followed by a 900 millisecond mask. The mask following each digit consisted of a ring with a diagonal cross in the middle. Both digits and mask were presented centrally in white against a grey background. This remained centrally fixed within the HTC Vive headset, irrespective of head and neck movements.

The target digit was distributed throughout the 225 trials in a pre-fixed quasi-random fashion, with no “3”s in a row, and at least one “non-3” trial in between. The period from digit onset to digit onset was 1150 msec. The digits were presented in one of 5 randomly allocated font sizes to enhance the demands for processing the numerical value, rather than simply setting a search template for some peripheral feature of the no-response target.

Subjects were instructed that the task required them to “press the trigger on the HTC Vive hand-held remote whenever a digit that was not 3 appeared on the screen, and withhold a response when 3 appeared”. This instruction was repeated until the subject was able to repeat it back and show retention and recall of the task instruction. Subjects were familiarized with the HTC Vive remote prior to wearing the HTC Vive headset. Subjects were asked to give equal importance to accuracy and speed in doing the task. Healthy controls used their preferred hand whilst patients used the non-paralytic limb. No feedback was provided during the task.

Each session was preceded by a practice period consisting of 18 presentations of digits, two of which were targets. Trial-by-trial feedback was provided for the practice period only.

Figure 38: A demonstration of the SART task as it appears in the Vive
Digits between 1-9 appear in a quasi-random manner, fixed centrally. Each digit is separated by a mask consisting of circle with a cross in the centre. Subjects are instructed to press the trigger (denoted here by the green and yellow action lines) whenever they see a number that is not 3, and withhold a response when they see 3.

4.10 Data Outputs

The SART produced an output into an Excel spreadsheet, of the digits that appeared, the subject's response (correct response to a go-trial, no response to a go-trial, correct inhibition at a no-go trial, failure of inhibition at a no-go trial) and response reaction time.

The following outputs were computed from this data. The outputs used in my analysis, and related outputs used to compute these are in italics. Additional data columns that are present in Table 14 have also been defined.

Total number of trials:	*This was the sum of the number of correct response go-trials and the number of no-go trials*
Total number of go-trials:	Measuring accuracy of correct go-trials
Percentage of go-trials:	*This was the number of correct response go-trials divided by 200, multiplied by 100*
Go-trial reaction time (RT) mean:	*The average of the correct go-trial reaction times*
Go-trial reaction time standard deviation:	The standard deviation of the correct go-trial reaction times
Number of no-go trial errors:	*Errors of commission, i.e. the number of failure of inhibitions on a no-go trial*
Adjusted no-go trial errors:	*Normalized measure of errors of commission, adjusted for the patient's go-trials accuracy*
Number of no-go correct trials:	*Number of no-go trials with an accurate inhibition response*
Percentage of correct no-go trials:	No-go trial accuracy percentage
Post-error slowing (PES) mean:	*Average of the reaction times immediately after an error of commission*
Away from error:	This was the mean of the reaction times that were 3 values away from any pre-error and post-error reaction times
Mean of 3 Pre-Error Speeding:	Pre-error speeding was the 3 reaction times preceding an error of commission. This was the mean of all the pre-error of commission reaction times

Mean of 3 Post-Error Slowing:	Post-error slowing was the 3 reaction times following an error of commission. This was the mean of the all the post-error of commission reaction times
Post-error slowing percentage (PES %):	*This is the post-errors of commission slowing relative to the mean reaction time that excluded error-related cognitive adjustments (pre-error speeding or post-error slowing), expressed as a percentage. A percentage greater than 100 indicates that post-error reaction times were slower than baseline reaction times, reflecting post-error slowing. A percentage below 100 indicates little to no slowing, suggesting minimal error-related adjustments.*
Speeding percentage:	This is the pre-errors of commission speeding relative to the mean reaction time that excluded error-related cognitive adjustments (pre-error speeding or post-error slowing), expressed as a percentage. A percentage less than 100 indicates that pre-error reaction times were faster than baseline reaction times, reflecting pre-error speeding. A percentage above 100 indicates little to no speeding before errors, suggesting more stable responses leading up to the errors.
Stimulation:	The type of VR Stimulation received by the patient in the ATTEND trial
Stars T2:	Star cancellation score at Baseline
Stars T3:	Star cancellation score at end of 3 weeks of VR Stimulation
CBS T2:	CBS score at Baseline
CBS T3:	CBS at end of 3 weeks of VR Stimulation
Delta Stars:	The change score in the star cancellation test, calculated by subtracting the score at T2 from T3
Delta CBS:	The change score in the CBS, calculated by subtracting the score at T2 from T3

4.11 Data Analysis

All data analysis was completed using Statistical Software Package for the Social Sciences 29 (SPSS).

To explore the differences in the various SART outputs between the patients and the healthy controls, an independent samples t-test was performed.

To explore the possible explanations for variances in patients' degree of improvement, the following rationale was applied:

1) I utilized the change scores from the impairment-based outcome measure, i.e., the change in star cancellation scores from T2 to T3 (called "Delta Stars") as the dependent variable.

2) I first investigated if there were correlations between baseline severity on the behavioural outcome measures from ATTEND (baseline star cancellation scores and baseline CBS scores) and Delta Stars, to check if initial severity explained variances in the degree of improvement.

3) Following this, I investigated the presence of correlations between key SART outputs and the Delta Stars to look for explanations for the variances in patients' degree of improvement.

To perform this analysis, simple Pearson correlations were employed. The Therapy Group and the Control Group were collapsed into a single patient group to provide greater numbers for this analysis.

To perform the linear regressions analysis, I modelled the Star Cancellation Change scores as the outcome in separate regressions for each SART construct: (i) go-trials and (ii) post-error slowing (PES). For each construct I first fitted the full model including baseline Stars (indicating initial severity), time since stroke, and group. For completeness, I also checked

models entering covariates one at a time; the pattern of results did not materially change. Model fit is reported with R^2/Adjusted R^2, and standardised β with p-values for predictors of interest.

Subject	Total # trials	#Go Trials	%Go trials	Go RT Mean	No Go Error	Adjusted No Go	No Go Correct	No Go % Avoided	PES Mean	PES Normalized	Away from error	Mean 3Pre Error	Mean 3Post Error	PES New %	Speeding %	Stimulation	Stars T2	Stars T3	CBS T2	CBS T3	DeltaStars	DeltaCBS
Stroke Participants																						
CT11	164	139	69.5	0.70	5.00	7.20	20.00	80.00	0.90	128.11	0.69	0.63	0.92	131.76	90.53	Vertical	20.00	46.00	9.00	5.00	26.00	4.00
CT13	149	124	62	0.72	16.00	25.80	9.00	36.00	0.83	115.87	0.71	0.75	0.72	101.87	106.51	Vertical	6.00	14.00	14.40	11.00	8.00	3.40
CT15	217	192	96	0.54	12.00	12.50	13.00	52.00	0.52	96.05	0.53	0.54	0.57	107.39	102.18	Vertical	15.00	41.00	11.25	21.25	26.00	-10.00
CT16	112	87	43.5	0.61	12.00	27.60	13.00	52.00	0.62	101.62	0.61	0.65	0.57	94.52	107.43	Vertical	34.00	27.00	6.00	2.00	-7.00	4.00
CT19	109	84	42	0.66	7.00	16.70	18.00	72.00	-	-	0.67	0.58	0.61	91.45	85.91	Vertical	13.00	20.00	14.10	11.10	7.00	3.00
CT22	219	194	97	0.57	5.00	5.20	20.00	80.00	0.73	128.90	0.57	0.52	0.65	114.21	90.91	Horizontal	19.00	51.00	22.00	8.00	32.00	14.00
CT23	137	112	56	0.61	7.00	12.50	18.00	72.00	0.53	87.03	0.65	0.41	0.59	91.27	64.11	Horizontal	10.00	22.00	20.00	17.00	12.00	3.00
CT24	163	138	69	0.44	4.00	5.80	21.00	84.00	0.44	101.28	0.44	0.42	0.43	97.71	94.17	Horizontal	22.00	43.00	13.30	8.80	21.00	4.50
CT26	137	112	56	0.61	7.00	12.50	18.00	72.00	0.53	87.03	0.65	0.41	0.59	91.27	64.11	Horizontal	20.00	42.00	23.00	10.00	22.00	13.00
CT28	178	153	76.5	0.72	15.00	19.60	10.00	40.00	0.69	95.38	0.71	0.75	0.77	108.38	106.77	Horizontal	9.00	31.00	21.00	16.60	22.00	4.40
CT29	177	152	76	0.67	3.00	3.90	22.00	88.00	0.59	89.35	0.67	0.62	0.64	95.36	93.22	Vertical	30.00	41.00	16.00	7.00	11.00	9.00
CT32	125	100	50	0.65	13.00	26.00	12.00	48.00	0.58	88.86	0.65	0.68	0.63	96.92	104.82	Horizontal	12.00	32.00	18.75	13.75	20.00	5.00
CT33	213	188	94	0.66	6.00	6.40	19.00	76.00	0.58	87.46	0.66	0.67	0.68	103.99	102.25	Horizontal	26.00	49.00	25.00	10.00	23.00	15.00
CT34	152	127	63.5	0.72	9.00	14.20	16.00	64.00	0.05	7.52	0.71	0.78	0.76	107.91	109.68	Horizontal	12.00	50.00	23.00	4.00	38.00	19.00
Healthy Controls																						
HS01	225	200	100	0.42	3.00	3	22.00	88.00	0.46	108.21	0.42	0.37	0.43	101.44	86.76							
HS02	225	200	100	0.37	19.00	19	6.00	24.00	0.37	98.80	0.37	0.35	0.39	106.02	93.73							
HS03	217	192	96	0.42	11.00	11.5	14.00	56.00	0.53	127.26	0.42	0.29	0.57	137.58	68.78							
HS04	201	176	88	0.38	16.00	18.2	9.00	36.00	0.47	124.52	0.36	0.38	0.42	115.37	105.53							
HS05	225	200	100	0.37	13.00	13	12.00	48.00	0.43	115.67	0.35	0.36	0.42	118.72	101.75							
HS06	219	194	97	0.36	23.00	23.7	2.00	8.00	0.39	107.89	0.32	0.31	0.46	143.16	95.79							
HS07	225	200	100	0.43	12.00	12	13.00	52.00	0.29	66.57	0.47	0.33	0.35	74.22	70.11							
HS08	225	200	100	0.40	7.00	7	18.00	72.00	0.48	119.24	0.41	0.35	0.42	102.80	87.05							
HS09	214	189	94.5	0.38	15.00	15.9	10.00	40.00	0.28	73.16	0.38	0.33	0.43	112.45	88.41							
HS10	225	200	100	0.45	5.00	5	20.00	80.00	0.50	111.18	0.45	0.41	0.44	98.96	91.02							
HS11	217	192	96	0.33	7.00	7.3	18.00	72.00	0.41	122.72	0.34	0.31	0.35	102.52	91.16							
HS12	225	200	100	0.36	10.00	10	15.00	60.00	0.31	85.25	0.37	0.38	0.30	81.73	103.73							
HS13	225	200	100	0.37	8.00	8	17.00	68.00	0.40	108.13	0.37	0.34	0.40	108.53	93.21							
HS14	225	200	100	0.42	5.00	5	20.00	80.00	0.54	128.28	0.42	0.41	0.44	106.36	97.99							

HS15	224	199	99.5	0.40	3.00	3	22.00	88.00	0.42	103.52	0.40	0.41	0.43	106.06	100.67
HS16	221	196	98	0.38	8.00	8.2	17.00	68.00	0.47	123.61	0.37	0.38	0.47	127.87	102.12
HS17	222	197	98.5	0.51	5.00	5.1	20.00	80.00	0.35	69.18	0.51	0.55	0.40	78.73	106.82
HS18	221	196	98	0.38	16.00	16.3	9.00	36.00	0.41	109.55	0.39	0.35	0.38	99.35	90.47
HS19	224	199	99.5	0.39	7.00	7	18.00	72.00	0.68	174.94	0.38	0.34	0.54	143.42	89.48
HS20	223	198	99	0.40	5.00	5.1	20.00	80.00	0.50	125.49	0.40	0.37	0.46	114.61	92.62
HS21	224	199	99.5	0.32	12.00	12.1	13.00	52.00	0.29	91.80	0.32	0.32	0.34	105.37	99.01
HS22	223	198	99	0.53	6.00	6.1	19.00	76.00	0.51	95.78	0.54	0.42	0.50	91.89	76.72
HS23	217	192	96	0.36	19.00	19.8	6.00	24.00	0.49	134.83	0.35	0.30	0.44	127.12	86.99

Table 14: SART outputs for the Stroke patients and the healthy controls
Abbreviations: RT – Reaction Times; SD – Standard Deviation; PES – Post Error Slowing

4.12 Results

4.12.1 SART Group Results

An independent samples t-test was conducted to compare the performance of the patient group and healthy controls across various variables from the SART. The group results for the notable SART outcomes that will be discussed in this chapter are tabulated in Table 15.

Variable	**Mean (No./%) ± SD Groups**		***p***
	Stroke Patients $(n = 14)$	**Healthy Controls** $(n = 23)$	
#Go Trials (#)	135.86 ± 36.73	196.39 ± 5.55	***<.001***
%Go trials (%)	67.93 ± 18.37	98.20 ± 2.77	***<.001***
Go RT Mean (sec)	0.63 ± 0.08	0.40 ± .049	***<.001***
No Go Error (#)	8.64 ± 4.21	10.22 ± 5.62	*.186*
PES % (%)	102.43 ± 11.19	108.89 ± 18.54	*.124*

Table 15: Descriptive statistical results for the SART outputs for Patients and Controls
The definitions of each term are listed in Methods. The unit of measure is indicated within brackets - #: Number; %: percentage value; sec: seconds. Significant p-values are highlighted in bold. Abbreviations: RT – Reaction Times; PES – Post-error slowing

There was a significant difference in the number of correct go-trials between the patient group (M = 135.86, SD = 36.73) and healthy controls (M = 196.39, SD = 5.55), **t**(35) = -7.83, **p**< .001, 95% CI [-76.23, -44.83], with the healthy controls showing greater accuracy. The effect size, measured by Cohen's *d*, was -2.65, indicating a very large effect. The percentage of go-trials followed suit. Go-trials reaction times were significantly slower in the patient group (M = 0.63, SD = 0.08) compared to the healthy controls (M = 0.40, SD = 0.049), **t**(35) = 11.29, **p** < .001, 95% CI [0.19, 0.28]. Cohen's *d* was 2.98, indicating a very large effect.

Notably, the two groups did not differ on No Go Errors **t**(35) = -.903, **p** = .186, 95% CI [-5.11, 1.96], or on the PES % t(35) = -1.18, p = .124, 95% CI [-17.60, 4.70].

4.12.2 Correlations to explore variance in improvement

Correlations were performed in order to look for explanations for the variances in patients' degree of improvement.

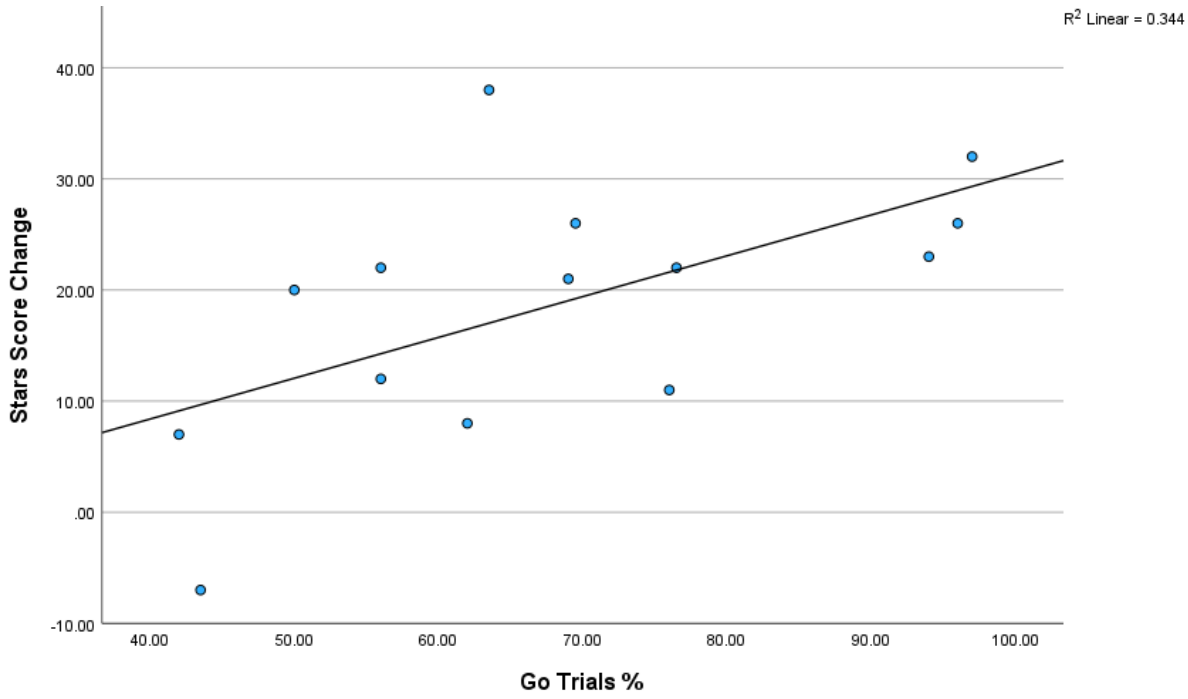
4.12.2.1 Relationships between baseline severity and change scores

To start with, I evaluated relationships between the Baseline scores on the Star Cancellation Test and CBS, and the Delta Stars (which reflected the change in scores on the Star Cancellation Test from T2 to T3).

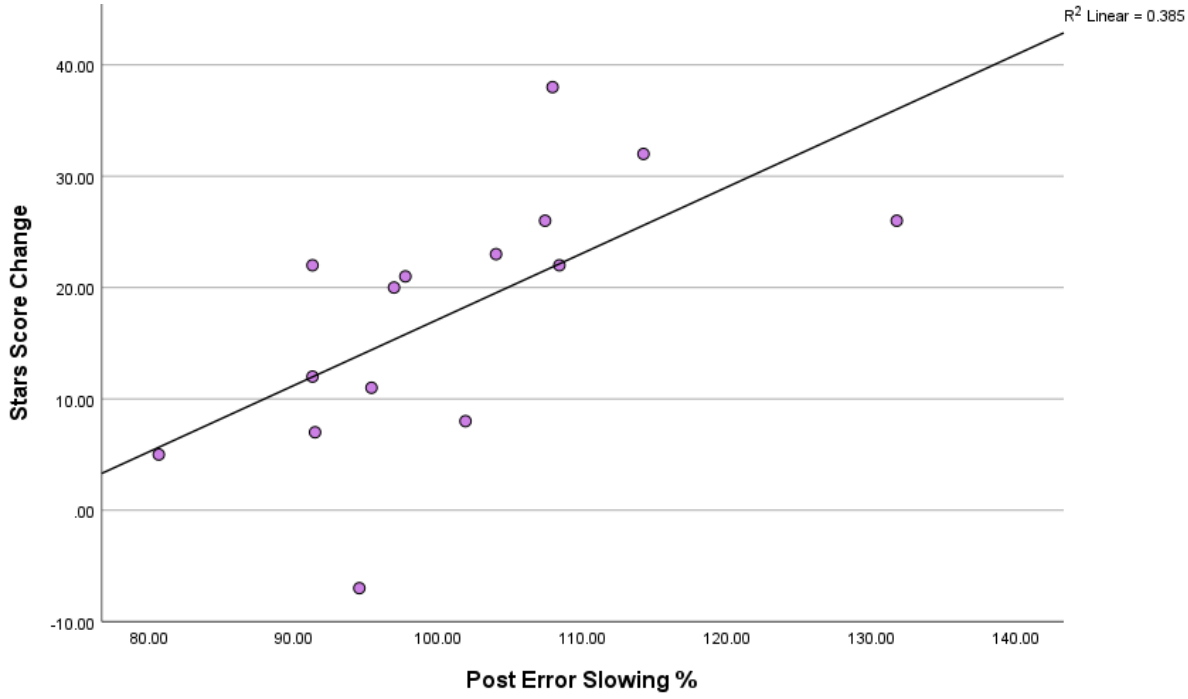
There was no significant correlation between Baseline star cancellation score and the Delta Stars, Pearson's **r**(22) = -.12, **p** = .59, 95% CI [-.496, .302], nor between Baseline CBS score and Delta Stars, Pearson's **r**(22) = .33, **p** = .11, 95% CI [-.082, .649].

4.12.2.2 Relationships between SART outputs and change scores

A statistically significant positive correlation was found between Go Trials % and Delta Stars, Pearson's **r**(12) = .586, **p** = .028, 95% CI [0.081, 0.852], and also between PES % and Delta Stars, Pearson's **r**(12) = .621, **p** = .014, 95% CI [0.159, 0.860] (Graph 10, Graph 11).



Graph 10: A scatter plot with Change scores on the Star Cancellation Test on the x-axis and Go Trials % on the y-axis. The line of best fit shows the linear relationship between the two variables.



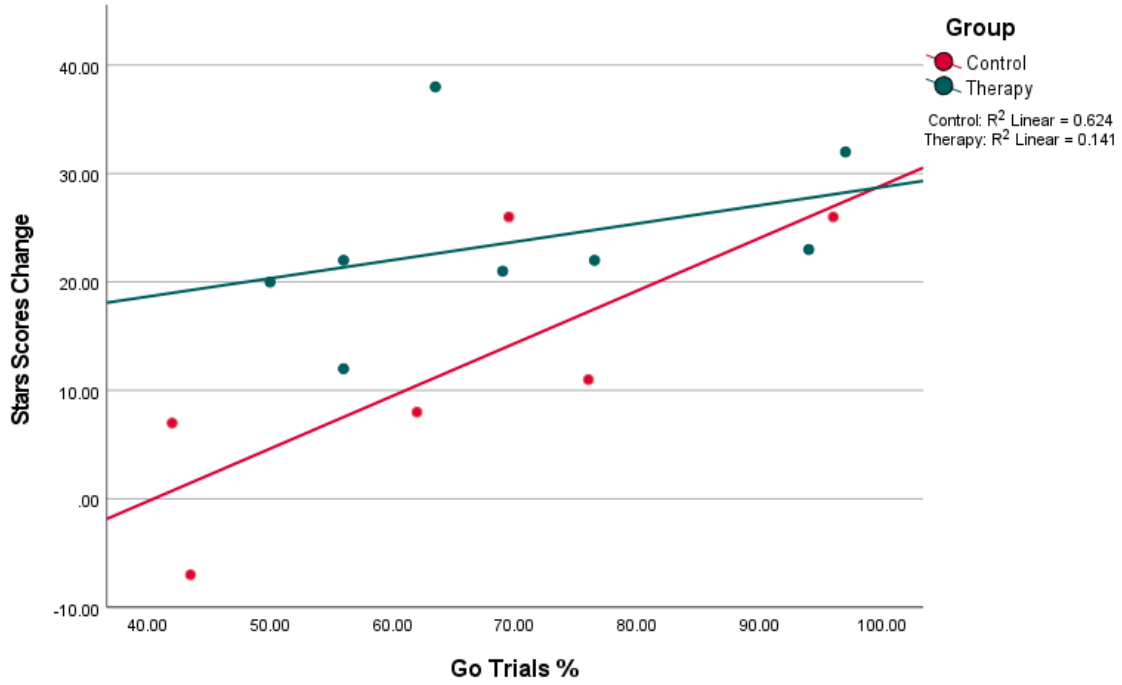
Graph 11: A scatter plot with Change scores on the Star Cancellation Test on the x-axis and Post-Error Slowing % on the y-axis.
The line of best fit shows the linear relationship between the two variables.

4.12.3 Regression of change in Star Cancellation on SART measures

4.12.3.1 Go Trials

In the full model including initial severity, time since stroke, and group, go-trials significantly predicted Star Cancellation Change scores (β = .53, p = .042). The model explained 61% of the variance (R^2 = .61; adjusted R^2 = .44) and the omnibus test was trend-level (F(4,9) = 3.57, p = .052), reflecting limited power. Baseline severity and time since stroke were not significant; group showed a borderline effect (β = .41, p = .104).

For transparency, when covariates were entered one at a time, the association between go-trials and Star Cancellation Change scores remained significant in each model (β range .52–.64, all p < .05), with variance explained R^2 = .38–.55. In the model with group only, both go-trial accuracy (β = .52, p = .029) and group (β = .45, p = .050) contributed.

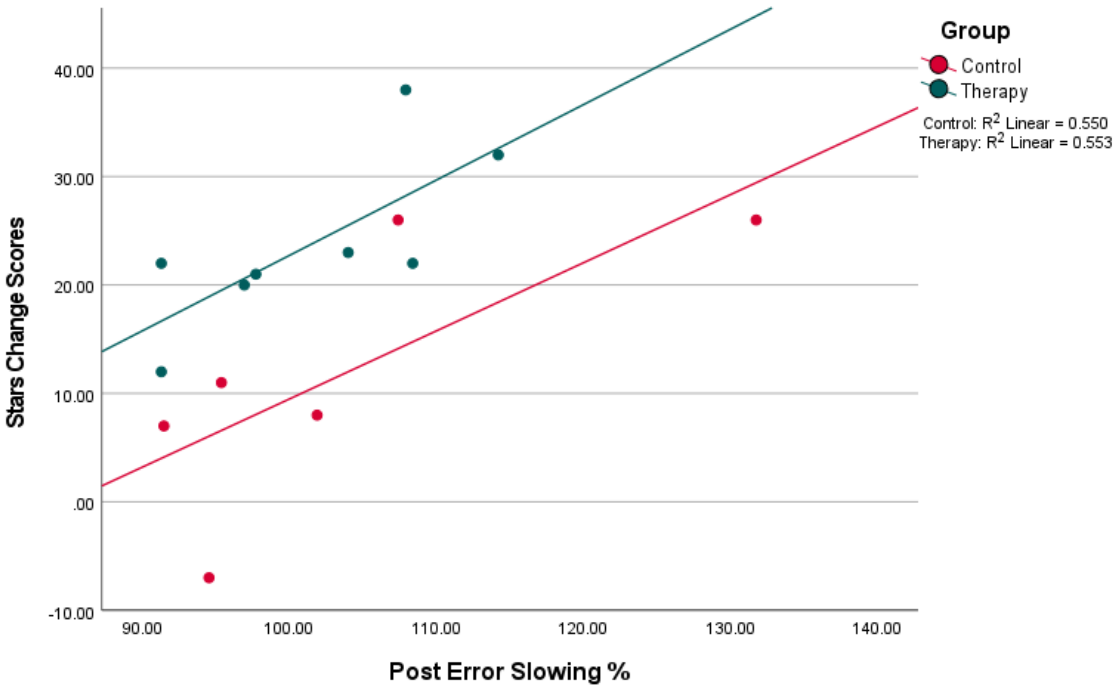


Graph 12: Change in Star Cancellation scores plotted against go-trial accuracy. Points coloured by group (therapy vs control). Lines show fitted linear regression with 95% CI.

4.12.3.2 Post-Error Slowing

In the full model including initial severity, time since stroke, and group, PES was a robust predictor of Star Cancellation Change scores (β = .60, p = .010). Group was also significant (β = .61, p = .011). The model explained 71% of the variance (R^2 = .71; adjusted R^2 = .59; F(4,9) = 5.60, p = .015).

Consistent patterns held when covariates were entered one at a time: PES remained significant in models with baseline (β = .55, p = .040) or time since stroke (β = .58, p = .040). The model including group alone showed strong effects of both PES (β = .63, p = .004) and group (β = .60, p = .005), R^2 = .68.



Graph 13: Change in Star Cancellation scores plotted against post-error slowing (PES). Points coloured by group; fitted regression with 95% CI.

4.13 Discussion

The interplay between spatial and non-spatial attention has been widely explored, from understanding the neuro-anatomical basis of dorsal and ventral attentional networks and their connectivity impacting interactions between spatial and non-spatial mechanisms (299, 300), to exploring the relationship between spatial allocation of attention and temporal dynamics of phasic and tonic alertness (301), to noting that non-spatial factors impacting sustained attention like fatigue, arousal (302), multi-tasking (303) and cognitive loading can influence spatial attention (304).

In the ATTEND trial, I used the SART to assess differences in sustained attention and error awareness between a patient cohort suffering from SN, and healthy controls. I also explored whether some of the explanations for the variance between patients' degrees of improvement may lie within cognitive measures gained from the SART. The SART test was introduced later into the ATTEND trial, due to issues with preparation for use within the VR HTC headset, and the importance of getting the trial underway as a matter of priority.

4.13.1 Summary of Group Results

I compared the results of key SART outcomes of 14 patients to 23 control subjects. The controls scored significantly better than the patients on the accuracy of go-trials, indicating fewer errors of omission and better sustained attention. The patients missed more go-trials, which is a common finding in patients post-stroke due to lapses in sustained attention exacerbated by damage to the right parietal cortex and frontal areas (182, 305).

The reaction time was significantly different in favour of the controls; stroke patients have shown greater reaction time variability (182), which suggests unstable attentional control and

vigilance lapses, leading to an inconsistency in task performance. Looking at the errors of commission in this SART task, there were 25 potential no-go errors to be made during the task. The controls on average made 10 errors, the patients made 8, and there were no significant differences between them. A possible explanation for this is that cognitively vulnerable groups are more likely to perform the SART slower, which could be either due to frequent failures to engage with the task, or conversely, a purposefully cautious approach, a consequence of which is a high error rate with increased errors of omission, and paradoxically, fewer errors of commission (277, 306).

Finally, I looked at post-error slowing, a phenomenon where self-awareness of an error (in the absence of feedback as is the case in the SART) causes an increase in subsequent reaction times due to reflective adaptive cognitive control processes aimed at reducing further errors (280). In our study, a PES percentage of greater than 100 indicated increased post-error slowing. There were no statistical differences between the patients and the controls, indicating relatively similar levels of error awareness.

4.13.2 Correlations to explain variance in improvement

4.13.2.1 Initial Severity

The overarching question of why some patients improve more in response to treatments better than others continues to be explored, with neuro-anatomical location of lesion and lesion volume playing a large role in acting as biomarkers of severity and outcome (307). From the SART outcomes gained from this sub-study conducted as part of the ATTEND trial, I wished to examine sustained attention through the lens of identifying associations that may help predict response to therapy in patients with SN. I treated the entire patient cohort as a whole

as they all made improvements over time, although the Therapy Group improved markedly more so.

I first assessed the relationship between the baseline score on the Star Cancellation Test and the CBS as an explanatory variable, and the change score as the dependent variable. This is a widely used approach in cognitive and clinical research to explore whether initial levels of performance may influence the capacity to improve and respond to treatment, thereby predict the magnitude of improvement or decline following intervention (308). These associations must be interpreted with caution though, because a significant correlation between baseline and change scores may result from "mathematical coupling", as change scores are partially dependent on baseline values by definition, and therefore be susceptible to floor or ceiling effects. This can inflate correlations and lead to spurious associations between initial status and change (309). In addition, making inferences from regression to the mean is risky in a patient cohort where some improvement is expected over time given the natural history of SN. In the case of my study however, initial severity did not explain the variances in degree of improvement in patients, and therefore cannot be used as a predictive marker.

4.13.2.2 Sustained Attention and Go-Trials

Focusing on the positive correlations, firstly, Go-Trials, used as a way to measure sustained attention, were significantly fewer in stroke patients compared to healthy controls, indicating impaired attentional engagement post-stroke. This finding is in keeping with previous research suggesting that deficits in sustained attention are prevalent among stroke survivors and are associated with poorer functional outcomes and balance impairments, with motor recovery post-stroke at 2 year follow-up significantly correlating with sustained attention

(290, 291). As Hyndman et al. noted in their study, sustained and divided attention scores correlated with balance, ADL ability and fall-status, and the balance and function of subjects with normal attention was better than those with abnormal scores (291).

The positive association between Go-Trial performance and improvements in the Star Cancellation Test suggests that sustained attention may contribute to recovery. This raises the possibility that better sustained attention could enhance patients' ability to engage in rehabilitation tasks and support visuospatial performance, although this requires confirmation in larger studies. Robertson et al. observed that sustained attention scores two months post-stroke could predict functional and motor recovery at 2 two years in people with right hemisphere lesions, supporting the role sustained attention plays in determining improvement (290).

In the case of the ATTEND trial, both the horizontal and vertical VR Stimulation tasks required sustained as well as a space-directed attention (tracking and catching a target and shooting a target at distance, respectively). Taking the example of the horizontal VR Stimulation, higher degrees of sustained attention would equip patients with the alertness required to observe a new red ball once the previous one was caught, be able to hold their attention on the ball as they tracked its trajectory, and also be able to multi-task towards the end of the ball's trajectory-span as they moved the racket to catch it. It could be quite easy to slip into a "mindless" state whilst pursuing the ball from the right to the left, but better sustained attention would encourage tracking across the entire span of the field of view until the ball was successfully caught. The task is a repetitive one, with 4 blocks of 10 minutes, and preserved sustained attention would help keep focus throughout, thereby maximizing the gains made from continuous smooth pursuit movement if every single target is tracked and

caught. In the vertical VR Stimulation, the patient had to maintain focus on a target and the perceived trajectory to shoot it successfully as they planned their approach. In this case as well, patients would perform better if they had higher sustained attention scores.

4.13.2.3 Error Awareness and Post-Error Slowing

Post-error slowing (PES) %, defined as the slowing of reaction times following an error, and a marker of error awareness, was not significantly different between stroke patients and controls, suggesting that error awareness might be less severely affected in stroke survivors compared to sustained attention. These findings are supported by evidence that performance monitoring and error detection may be relatively preserved in stroke survivors (296). In their study, Niessen et al. did not observe any behavioural impairments related to performance monitoring and error processing in their cohort of stroke patients, despite significant cognitive deficits. This preservation of error awareness could have the potential to act as a compensatory mechanism during rehabilitation (296).

In the context of improvement, in my study, the intact post-error slowing PES % and its positive association with change scores may reflect adaptive cognitive control processes that could support rehabilitation outcomes, though this interpretation should be viewed as preliminary. According to Fievez et al., who looked at the processes involved in post-error slowing in 43 healthy subjects, they found that post-error slowing can reflect either adaptive or maladaptive processes (310). Adaptive PES facilitates performance improvement through "cautious decision-making" (311, 312), while maladaptive PES may actually impair performance in circumstances where slowing does not lead to increased accuracy (313, 314). The association between PES % and improvement on the Star Cancellation Test change score suggests that patients with greater error awareness might be better able to make cognitive

adjustments, potentially supporting performance on tasks requiring attention and visuospatial processing.

It could be considered whether this “adaptive process” may play a role in facilitating cognitive or behavioural adjustments, leading to better self-monitoring during the VR Stimulations, resulting in patients recognizing missed targets and adjusting their strategies during the task, leading to increased gains from the therapy. For example, in the horizontal VR Stimulation task, when the ball was successfully caught, it disappeared in a puff of smoke. When there was a failure to capture the ball, this feedback did not occur. Preserved error awareness would enable a patient to be wary of this, thereby increasing the chances of catching targets successfully, which in practical terms translates to eye-tracking up to the end of the field of view. In the vertical VR Stimulation task, having a higher degree of error awareness was paramount to making adjustments in trajectory-planning in order to shoot the target successfully. Additionally, it may also be that individuals with higher error awareness at baseline may have stronger cognitive or attentional resources, allowing them to receive a greater benefit from the VR Stimulations. However, it should be borne in mind that as indicated by the linear regression, despite the strength and direction of this relationship between PES % and a change in scores, 61.5% of the variance in change in scores remains unexplained, implying other factors at play.

The SART study was therefore a useful exploratory addition to the ATTEND trial, not only in the context of demonstrating that smooth pursuit therapy delivered via Virtual Reality is beneficial for neglect, but also in tentatively identifying cognitive factors beyond initial severity, such as sustained attention and post-error awareness, that may contribute to explaining variability in patients’ degrees of improvement.

4.13.3 Linear Regressions Analysis to account for Covariates

The simple correlations analysis suggested that both measures were associated with improvement on the Star Cancellation test. The regression analyses extended these findings: go-trial accuracy remained a significant predictor of change in Star Cancellation even after adjusting for baseline severity, time since stroke, and group allocation. Post-error slowing emerged as an even stronger predictor, explaining a substantial proportion of variance in recovery, and remained significant after covariate adjustment. Group allocation also contributed independently in some models.

These findings support the view that recovery from neglect may be shaped not only by lateralised spatial mechanisms but also by broader aspects of sustained attention and error monitoring. Specifically, patients with better sustained attention and greater post-error slowing tended to show greater gains in visual exploration, consistent with models in which domain-general attention systems scaffold spatial recovery.

However, these analyses must be interpreted cautiously. The sample size was small, follow-up data incomplete, and the regression models may have been underpowered. The omnibus model fit for go-trial accuracy, for example, narrowly missed significance despite a significant predictor coefficient. As such, the results should be viewed as exploratory and hypothesis-generating rather than definitive.

Future studies with larger cohorts and more comprehensive neuropsychological profiling will be required to test these relationships more robustly and to clarify the mechanistic contribution of non-spatial attentional processes to neglect recovery.

4.14 Limitations and Future Work

The sample size for the patient group was certainly small, and this must be taken into consideration as these findings need to be further explored and reproduced with larger sample sizes before they can be generalized. In addition, the scatter plots demonstrate data points which are dispersed at distance from the trend line, indicating variability which would warrant further exploration.

Future research directions can draw inspiration from the study by Dalmaijer et al., who employed a rigorous randomized, double-blind, placebo-controlled crossover design to evaluate the effects of the alpha-2 agonist Guanfacine on SN following stroke (153). Their innovative approach included the investigation of cognitive variables that influenced treatment response, using Bayesian statistical methods. These methods, which utilize existing knowledge to determine the probability of a null hypothesis (315), allowed the researchers to make meaningful conclusions about negative findings (such as providing robust evidence that Guanfacine did not improve spatial working memory). Such insights are valuable for redirecting research focus away from weak associations and towards more relevant predictive correlations.

Overall, the findings from this Chapter should be regarded as exploratory and hypothesis-generating. They highlight potentially important links between non-spatial attentional processes and neglect recovery, but require replication in larger, adequately powered studies before firm conclusions can be drawn.

5.0 General Discussion

5.1 Key Insights from the Thesis

Through the experiments conducted for this thesis, I have examined the current landscape of the assessment and treatment of visual spatial inattention and attempted to offer novel directions that may give researchers and clinicians new avenues to explore for this challenging clinical syndrome that remains devoid of gold standard approaches to date.

The three broad aims of this thesis were:

1. Experimental Chapter I: to develop a robust statistical method for the analysis of gaze duration data in order to quantify the degree and severity of SN.

2. Experimental Chapter II: to test the clinical efficacy of smooth pursuit eye movement therapy delivered using virtual reality across a wide field of view, for the first time.

3. Experimental Chapter III: to explore the relationship between sustained attention and visual spatial inattention to identify possible behavioural predictors for response to therapy.

In Experimental Chapter I, I built on the strides that Kaufmann et al. made using free visual exploration as an assessment tool for SN (79). I imported the images of naturalistic landscapes into the HTC Vive virtual reality headset to create the FiVE in the Vive task, expanding them in a manner that would capture gaze duration data from a broader field of view than has been previously available through pencil-and-paper based tasks or desktop monitors. I then developed a statistical method applying statistical parametric mapping software to gaze duration data, taking into special regard the need to eliminate horizontal salient features when using imagery to assess spatial bias. Marrying the two concepts together, enabled the creation, for the first time, of statistical heat maps that captured the most statistically

significant clusters and peak voxels denoting the centre of gaze location, surviving correction for multiple comparisons. In order to establish the validity of the spatial bias captured through this work in the post-stroke SN patient cohort, I compared them to healthy controls.

In doing so, I was able to demonstrate the presence of a significant right-sided spatial bias in the patient cohort, with their pre-intervention baseline average centre of gaze situated 18° over to the right from the central line of sight and 6° into the lower quadrant, below the horizontal meridian. By applying an f-contrast in SPM, I was able to capture, within the spatial reference frame of 64° horizontally and 48° vertically, not just where the patients were ”looking” more, but also where they were looking lesser, as compared to healthy controls. As is to be expected, the latter was found to be in the left hemi-space. Whilst this is an intuitive expectation in left-sided SN, this ability to precisely capture deficits in gaze has considerable implications in the world of neurorehabilitation. Gaining such insights, which have already been shown to be more sensitive than pencil-and-paper based tests of SN (79, 86), could form the basis for individually-tailored approaches towards patients, be utilised to monitor progression temporally, and grant a borrowed understanding into what the world looks like for a patient with SN, a visual that is difficult to imagine off of traditional assessment techniques.

The vertical component of spatial bias that emerged following analysis of the patient group, located in the lower quadrant, is different to the more commonly found upper quadrant biases that have been observed in patients with SN (231). The use of naturalistic landscape images to capture gaze duration data automatically introduced issues with image salience, defined as areas of an image that are more inclined to draw attention than elsewhere (167). Whilst I negated these features along the horizontal plane, I did not on the vertical. This is a

likely explanation for the patients to have been drawn to vertically occurring salient features on the images in the lower quadrants. Therefore, this study could not reliably contribute to inferences about altitudinal SN, although the scope to do so clearly exists.

Addressing the concept of gaze duration data analysis poses an interesting challenge to assessing specially extended data, whilst preserving its richness, rather than simply decimating large amounts of eye movement data to compute a single average X-coordinate. By using SPM, I have applied its mass univariate approach to make spatial topological inferences about gaze, utilizing as much collected data as possible, and subjecting it to rigorous statistical testing by correcting for multiple comparisons. This method could evolve the manner in which data gained from video-oculography is analysed and presented – not just in the SN space, but also in the broader community, for applications such as visual assessments during tasks such as driving, to the neuropsychological and neuro-behavioural analysis of gaze applicable to industries such as advertising, the arts and the cognitive neurosciences.

In Experimental Chapter II, I put the aforementioned assessment technique to the test, by using it as a primary impairment-based outcome measure, along with two behavioural outcome measures in the form of the Star Cancellation Test and the Catherine Bergego Scale, in the ATTEND trial. Smooth pursuit eye movement therapy has been shown to be effective, and in fact superior to visual scanning therapy that relies on saccades (113, 114). As far as I am aware, computerised-based versions of smooth pursuit eye training has been undertaken thus far only on 2D monitors and laptops. This makes the ATTEND trial the first of its kind in attempting to deliver repetitive horizontal smooth pursuit eye movements using immersive Virtual Reality.

The drivers behind using Virtual Reality were its immersive capabilities, allowing a realistic 3D experience of the custom-designed VR Stimulations with realistic depth components; its ability to mimic real-world environments adding to its ecological validity; a broader field of view (110° on the HTC Vive); absolute control over real-world visual distractions in the peripheral environment interfering with eye movement therapy sessions; and creating an engaging, enjoyable activity for the patients, with the additional gamification benefits against boredom and fatigue that often accompany repetitive exercises (316).

Following on from this, the 2 groups of patients who participated in the Therapy Group and the Control Group, screened in using multiple measures of severity and lateralization, minimized to match on severity and age, and measured on both cancellation and functional assessors of SN (all of which add value to the generalizability of results), proceeded to show statistical differences in their degrees of improvement. The Therapy Group made strong statistically significant gains on both behavioural outcomes, far exceeding the improvements in the Control group, the latter likely attributable to time effects and perhaps some therapeutic benefit from purposeful midline calibration and central attentional focus during the Control VR Stimulation.

The horizontal Therapy VR Stimulation has therefore been proven to be superior in creating an accelerated recovery from SN in the acute to sub-acute phase post-stroke, causing shifts in centre of gaze towards the affected side of space over the course of 3 weeks of daily stimulation. The gains made by the Therapy Group persisted at 3 month follow-up as noted on the Star Cancellation Test, securing these effects as long-lasting and making this work a promising finding for the treatment strategies presently available for SN. On the FiVE in the Vive, however, no significant differences emerged in the centre of gaze location between the

two groups at 3-month follow-up, although the effect was trending towards significance. The quantity of data available at this later time point was markedly smaller, which may have introduced additional noise and made it harder to detect differences. The small overall sample size of the trial would also have contributed, given the low power for this exploratory outcome. I also emphasise that the trial was powered for the Star Cancellation test, not FiVE in the Vive, and was therefore not optimised to detect between-group effects on this novel measure. It is also important to note that both groups improved on FiVE in the Vive, with the Control Group showing relatively greater gains than on the Star Cancellation test. One possible explanation is that FiVE in the Vive involves naturalistic picture viewing, which may be more engaging and reflective of everyday visual exploration than the abstract star array, thereby capturing a degree of spontaneous recovery across both groups. In addition, the Star Cancellation test requires a motor response (marking stars with a pen) whereas FiVEin the Vive is a purely observational task, and these differing task demands may also contribute to the discrepancy in sensitivity between the measures. Nevertheless, the recovery seen in the Control Group on FiVE did not translate into equivalent improvement on the Star Cancellation task, which continued to differentiate the Therapy Group. This pattern supports the specific benefits of the horizontal VR Therapy stimulation, while highlighting that the novel FiVE measure may be sensitive but requires validation in larger samples. The therapeutic effects noted present ATTEND as a considerable contender in the treatment of SN, and in my opinion, with organized forward planning in collaboration with Neurorehabilitation Teams, could be offered to patients as part of existing neurorehabilitation programmes.

Certainly, the overall consistency of the results across the 3 outcome measures (Star Cancellation, CBS and FiVE in the Vive) from T2 to T3, and between the Star Cancellation Test

and the FiVE in the Vive from T3 to T4 are complimentary to the newly-developed FiVE in the Vive and point towards its potential for future-use as well.

The mechanisms underlying the therapeutic effect observed in the ATTEND trial remain uncertain and, as we did not collect functional imaging data, any inferences here are necessarily speculative. Future studies with a similar design incorporating fMRI or connectivity analyses would be required to adjudicate between potential mechanisms. One possibility is that therapy enhanced recruitment of left-hemisphere attentional networks to compensate for right-hemisphere damage, or alternatively that residual right-hemisphere regions were recruited to support recovery. Another way to frame this is in terms of bottom-up versus top-down contributions. While repetitive smooth pursuit with proprioceptive feedback could plausibly act via bottom-up reinforcement, this explanation seems less likely in the present case, given that both groups undertook visually engaging activity. Instead, the more parsimonious interpretation is that improvements reflect top-down attentional control processes, consistent with the view that attention is predominantly considered a top-down phenomenon (317). The task required participants to monitor, sustain, and direct their attention actively, which may have strengthened supervisory attentional systems. Thus, although speculative, the findings are most consistent with a top-down mechanism of recovery.

Although the rapid gains made by the Therapy Group were not accompanied by a measurable reduction in inpatient length of stay, this should not be over-interpreted. In Level 1 neurorehabilitation units, where most participants were recruited from, the minimum duration of admission is predetermined at the point of entry, making length of stay a metric that is not directly indicative of functional improvements. Moreover, the trial was not

powered to detect LOS differences, so the absence of an effect does not imply that therapy lacks potential economic benefit.Therefore, mongst the facets of care that are directly within the treating team's control, having the option to offer a treatment that works is not only empowering but also motivating and up-lifting for a patient cohort that is particularly prone to the psychological burdens that accompany lesser motor abilities, increased dependence, immediate impacts to pre-morbid lifestyle and environmental monotony.

Finally, in Experimental Chapter III, as the last offering from this PhD, I compared the performance of SN patients from the ATTEND trial and healthy controls on the Sustained Attention to Response Task, and investigated cognitive measures that could predict patients' degree of improvement. My primary interest lay in exploring relationships between cognitive measures and therapeutic outcomes, as opposed to baseline scores and outcomes, given the risks of mathematical coupling and over-interpretation associated with regression to the mean in a cohort that may improve over time (309). Indeed, the analysis of SART performance revealed a strong positive correlation between sustained attention (go trials) and error awareness (post-error slowing) and changes in the Star Cancellation score among SN patients, accounting for nearly 34% and 39% of the variances in improvement, respectively.

Sustained attention deficits, as evidenced in stroke patients, have been linked to poorer functional outcomes, increased fall risk, and diminished rehabilitation engagement (291). Post-error slowing, a phenomenon where individuals slow their reaction times following errors to prevent subsequent mistakes, reflects adaptive cognitive control mechanisms (280). The fact that sustained attention and error awareness can explain a third of the variances observed on change scores in this study hints that both measures play a role in improvement on an impairment-based measure. Interventions targeting sustained attention, such as

attention training, may further enhance patients' ability to engage, whereas strategies to improve error awareness could optimize adaptive processes and self-monitoring during rehabilitation (2). In addition, noting performance on these measures at baseline could potentially help distinguish therapy responders from non-responders.

Whilst generalizations should be approached very cautiously, given the small sample size of 14 patients in my study which was solely exploratory in nature, these findings highlight the potential utility of SART performance analysis in evaluating SN treatment responses. If validated in larger cohorts, these positively correlating cognitive measures could potentially act as cognitive predictors of recovery and provide a framework for identifying appropriate cohorts for therapeutic interventions in SN.

6.0 Limitations and Future Direction

6.1 Past and Future Reflections

The experiments performed in this thesis would benefit from undergoing higher-powered studies with larger sample sizes in order to improve the applicability of results.

On the FiVE in the Vive task, the presence of salience features on the vertical plane impeded drawing inferences from the altitudinal spatial biases noted. It would be useful to negate these in future work and utilize the assessment tool to add insights to vertical SN, and assess its true response to treatment. In addition, only patients with left-sided SN were referred. Whilst right-sided SN is less common (318), it would be interesting to explore the patterns of gaze duration data on the FiVE in the Vive from this cohort.

Another limitation of the FiVE in the Vive task was that I did not examine its sensitivity within the VR Headset. Although this has been established when performed on a monitor (79), it would be worth confirming this against a comprehensive screening battery such as the Behavioural Inattention Test. Future work could also evaluate whether the FiVE in the Vive task can make predictions about functional deficits from SN.

In the ATTEND trial, the dose and frequency of the treatment was fixed. A question for future work could be based around the optimal dose intensity and frequency schedule that would be required to improve outcomes. If the VR Stimulations were to be rolled-out into inpatient units, further studies could be undertaken to analyse dose-outcome relationships. This could be assessed using an adaptive trial design in order to ascertain effective doses on the basis of markers of response to therapy such as initial severity or a cognitive outcome such as post-error slowing.

All patients in the ATTEND trial were calibrated to midline and the control stimulation in the ATTEND trial involved focusing attention on to a central tree. This may have caused some therapeutic effect in the Control Group, therefore perhaps future work may incorporate a third group that is left to explore open space without orientation aids.

Patients in the Therapy Group heard a Doppler sound effect as they performed eye-tracking. The effects of this on performance were not separately explored in the trial or in this thesis. Spatial cueing from one side to the other has been shown to have beneficial effects on SN (87), and it would be useful to incorporate this into the VR Stimulation, synchronized with the direction of eye-tracking.

Patients underwent semi-structured interviews with a mixture of open and closed questions which were not analysed as part of this thesis. It would be useful to assess these in order to gain insights into user experience and apply game-related feedback to the VR Stimulations. A common verbally expressed emotion from patients was that of delight in anticipation of the VR session, as a distraction from the inpatient ward setting and possible game-related dopamine release (319). It would be useful to utilize an inpatient mood questionnaire such as the hospital anxiety and depression scale to objectively measure changes in mood in response to VR Stimulations. On the topic of patient feedback, I did also collect self-scored CBS assessments from patients as part of Experimental Chapter II. These were not analysed for this thesis, but exploring prosopagnosia scores and changes within them over time and in response to VR Stimulations would add interesting information about patient insight into their SN.

Pharmacological treatments for SN have been trialled including dopaminergic, cholinergic, and noradrenergic treatments (320). A cross-over trial design with a drug treatment could be

designed as a future clinical trial in order to assess the combined efficacy of the Horizontal Therapy VR Stimulation and a drug.

Lastly, with regards to the immediate future direction of ATTEND, the fact that eye-tracking within the VR headset is not required now that the efficacy of treatment has been established, that the stimulation has potential to run as an app within the headset without the elaborate set-up that was required for the trial, and that costs of VR headsets are rapidly declining, altogether make this an exciting real-life treatment that could be built into the standardized inpatient neuro-rehabilitation treatment programmes within the NHS.

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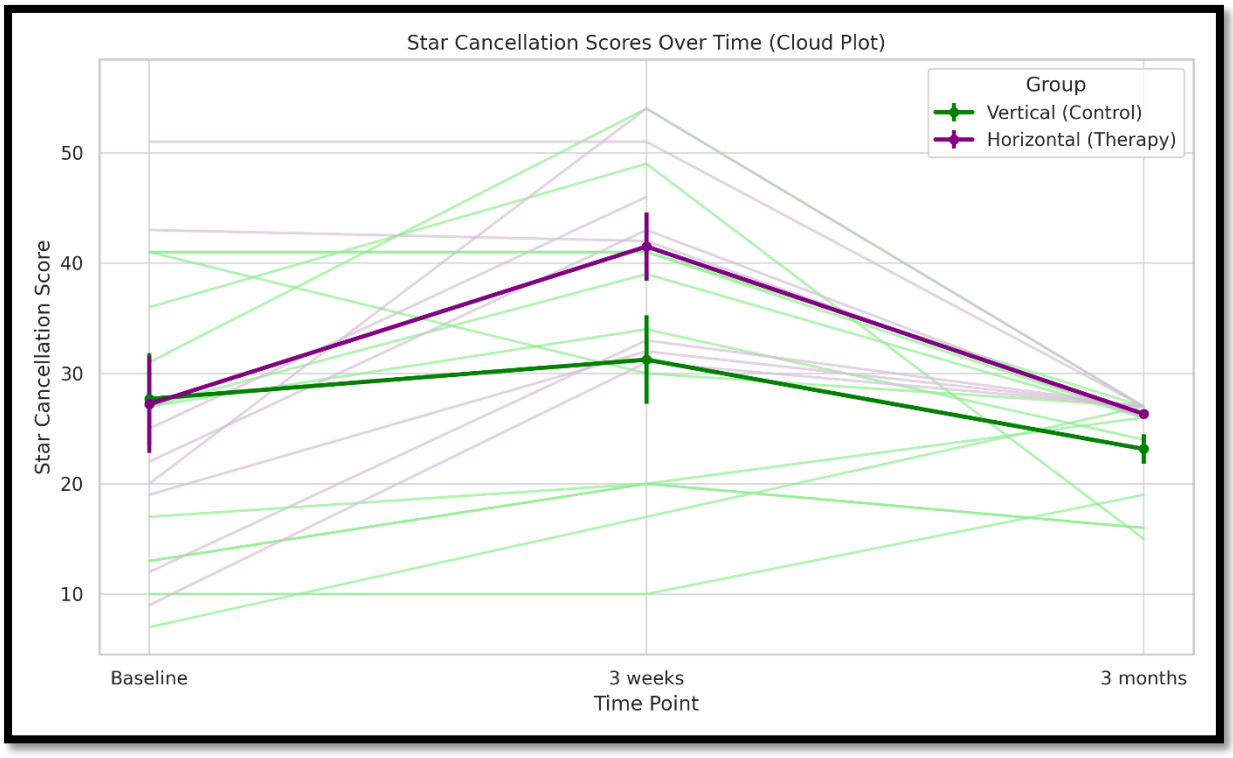
Appendix

A table summarizing all the patients who were recruited as part of this work, highlighting the Experimental Chapters that they were included in.

Patient ID	Age at consent (years)	Gender	Date of Stroke	Centre	FiVE in the Vive *	ATTEND **	SART ***
CT01	53.04	F	24/01/2021	NHNN			
CT02	61.15	M	30/11/2020	NHNN			
CT03	51.1	M	09/11/2020	Luzerne			
CT04	69.48	M	10/02/2021	NHNN			
CT05	45.53	F	02/03/2021	NHNN			
CT06			*Drop-out*				
CT07	70.54	F	24/03/2021	Luzerne			
CT08	59.68	F	25/04/2021	Luzerne			
CT09	69.51	F	25/06/2021	Luzerne			
CT10			*Drop-ouy*				
CT11	64.26	M	30/06/2021	Charing Cross			
CT12	72.59	M	08/10/2021	NHNN			
CT13	62.88	M	16/11/2021	NHNN/SPRU			
CT14	74.79	M	14/01/2022	Luzerne			
CT15	78.59	F	20/12/2021	Charing Cross			
CT16	82.07	M	17/04/2022	Charing Cross			
CT17	54.75	F	20/04/2022	NHNN			
CT18	34.13	F	30/04/2022	Charing Cross/NHNN			
CT19	69.64	M	01/03/2022	NHNN			
CT20			*Drop-out*				
CT21	67.16	F	04/09/2022	Luzerne			
CT22	76.18	F	30/11/2022	Charing Cross			
CT23	56.27	M	06/12/2022	NHNN			
CT24	48.53	M	15/11/2022	NHNN			
CT25	39.49	M	29/10/2022	NHNN			
CT26	63.71	M	05/06/2023	Charing Cross			
CT27	23.39	F	13/05/2023	Charing Cross			
CT28	54.09	M	22/04/2023	NHNN			
CT29	54.7	M	09/10/2023	Charing Cross			
CT30	41.16	M	22/12/2023	NHNN			
CT31			*Drop-out*				
CT32	68.06	M	05/03/2024	NHNN			
CT33	63.11	M	06/06/2024	NHNN			
CT34	52.22	F	24/07/2024	Charing Cross			

Blacked out rows indicate patients who dropped-out. *FiVE in the Vive: Experimental Chapter I; **ATTEND: Experimental Chapter II; ***SART: Experimental Chapter III. Abbreviations: NHNN – National Hospital for Neurology and Neurosurgery; SPRU – St. Pancras Rehabilitation Unit; F – Female; M – Male.

(2) The cloud plot below illustrates individual patient trajectories on the Star Cancellation task, with group means and standard errors superimposed, demonstrating greater improvement over time in the therapy group compared to the control group.



Individual patient trajectories are shown as light lines (green = Vertical control group; purple = Horizontal therapy group). Bold lines indicate group means with standard error of the mean bars. Time points represent baseline (T2), 3 weeks (T3), and 3 months (T4). The plot demonstrates considerable variability at the individual level but a clearer group-level improvement in the therapy group compared to the control group.