

Understanding and rehabilitating visual deficits caused by stroke: neurochemical and neurophysiological markers of residual vision



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Abstract

Damage to the primary visual cortex, following an occipital stroke, results in a loss of conscious vision in the contralateral visual field. Despite this, there are currently no widely used treatments for such visual impairment, and when therapy is available it tends to focus on learning to compensate for the visual field loss. Many patients with visual field deficits post-stroke retain the ability to detect moving visual stimuli in their blind field. However, not all patients exhibit residual visual processing, and the reasons for this are still debated. This has led to interest in whether this residual visual processing can be improved by visual training. Recently, research has shown that training within the blind field can improve vision for both trained and untrained tasks. However, the efficacy of visual rehabilitation is highly variable among participants, and the reasons for this remain to be determined.

This thesis aims to address these questions, and specifically investigates the neural mechanisms that underlie residual vision and rehabilitation efficacy. The primary aim was to investigate whether a six-month visual rehabilitation training programme could improve vision in twenty-four stroke survivors with visual field deficits. Moreover, if successful, it aimed to understand the neural mechanisms that underlie these improvements. In addition, it aimed to understand the neural mechanisms that predict residual visual processing at the baseline visit, as these will likely be important biomarkers for recovery.

I found that lower inhibitory GABA and excitatory glutamate were strongly related to residual visual processing in the blind field at the baseline visit. Moreover, lower

functional connectivity between ipsilesional and contralesional hMT+ and contralesional extrastriate ventral visual cortex was predictive of superior residual vision at the baseline visit. These studies indicate that hMT+ is involved in residual visual processing and that greater connectivity between the ipsilesional and contralesional hemisphere may negatively impact residual vision. Stroke survivors with V1-damage also show significant improvements for both trained and untrained tasks after six-months of motion discrimination training in the blind field. Moreover, patients show increased white matter integrity of the distal dLGN-hMT+ pathway in the damaged hemisphere after six-months of visual training. These results suggest that the integrity of the dLGN-hMT+ pathway supports visual rehabilitation post-stroke.

Taken together, these results indicate the importance of hMT+ after occipital strokes for supporting residual vision and rehabilitation post-stroke. Thus, targeting hMT+ in future studies may be beneficial for enhancing residual vision and visual rehabilitation.

This thesis is approximately 45,000 words.

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Related publications

Extracts from Chapter 1 are published at PIBBs.

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Extracts from Chapter 3 are published at Stroke

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Extracts of Chapter 6 are accepted in principle as a registered report at Brain Communications

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Subsets of the data presented in Chapter 3 were also submitted as an FHS report by undergraduate student Archie Watt.

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Abbreviations

2AFC	Two-alternative forced choice
3T	3 Tesla MRI scanner
AP	Anterior-posterior
BBR	Boundary-Based Registration
BET	Brain Extraction Tool
BOLD	Blood Oxygenation Level Dependent
CMRR	Center for Magnetic Resonance Research
COVID	Coronavirus disease
Cr	Creatine
CSD	Constrained Spherical Ceconvolution Model
CSF	Cerebral Spinal Fluid
dB	Decibels
dLGN	Dorsal Lateral Geniculate Nucleus
DOI	Digital Object Identifier
DTI	Diffusion Tensor Imaging
DW	Diffusion-Weighted
DWI	Diffusion-Weighted Imaging
EPI	Echo-planar imaging
FA	Fractional anisotropy
FAST	FMRIB's Automated Segmentation Tool
FEAT	FMRIB Expert Analysis Tool
FHS	Final Honour School
FLIRT	FMRIB's Linear Image Registration Tool
fmap	Field Map
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Oxford Centre for Functional MRI of the Brain
FNIRT	FMRIB's Nonlinear Image Registration Tool
FOV	Field of View
FSL	FMRIB software library
FWHM	Full-Width-at-Half-Maximum
GABA	γ -Aminobutyric acid
GLM	General Linear Model
Glx	Glutamate, Glutamine and Glutathione
GRE	Gradient echo sequences
GRF	Gaussian random field
HCP	Human Connectome Project
HCPex	Extended Human Connectome Project multimodal parcellation atlas
hMT+	Human Middle Temporal Visual Area
HRF	Hemodynamic Response Function
HVF	Humphrey Visual Field
Hz	Hertz

IDREC	Medical Sciences Interdivisional Research Ethics Committee
iPul	Inferior Pulvinar
IQR	Interquartile Range
LCD	Liquid Crystal Display
MCFLIRT	Motion correction FMRIB's Linear Image Registration Tool
MD	Mean Diffusivity
MEG	Magnetoencephalography
MELODIC	Multivariate Exploratory Linear Optimized Decomposition into Independent Components
mm ³	Milimeters Cubed
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MT	Middle Temporal Visual Area
NAA	N-acetylaspartate
NDI	Neurite density index
NDR	Normalised direction range thresholds
NODDI	Neurite orientation and dispersion density imaging
ODI	Orientation dispersion index
PA	Posterior-anterior
PCA	principal component analysis
PD	Pattern deviation
ppm	Parts per million
pRF	Population Receptive Field
ROI	Region of Interest
S1	Primary Somatosensory Cortex
SC	Superior Colliculus
SITA	Swedish Interactive Threshold Algorithm
tCr	Total Creatine
tDCS	Transcranial Direct Current Stimulation
TE	Echo Time
TEO	Posterior Inferotemporal
TMS	Transcranial magnetic stimulation
TR	Repetition Time
UK	United Kingdom
USA	United States of America
V1	Primary Visual Cortex
VPL	Ventral Posterior Lateral Nucleus of the Thalamus
VR	Virtual Reality
VRT	Visual Restitution Therapy
W	Water
WIN	Wellcome Centre for Integrative neuroimaging

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Chapter 1: Introduction

1.1 The human visual system

1.1.1 Visual pathways

The principal visual pathway is the retino-geniculo-striate pathway (represented by the solid grey lines in Figure 1). It connects the retina to the dorsal lateral geniculate nucleus (dLGN) in the thalamus and on to the primary visual cortex (V1). Information is initially processed by light-sensitive photoreceptors in the retina in the eye. Retinal ganglion cells receive information from the photoreceptors and then transmit it along the optic nerve. At the optic chiasm, the retinal ganglion cell axons originating from each nasal retina decussate. This means that the retro-chiasmatic fibres of the optic tract represent information from the contralateral visual field from both eyes. The optic tract continues to the dLGN, and the optic radiation then carries information from dLGN to V1. V1 further processes the visual information before distributing it to the extrastriate visual areas such as V2, V3, V3A, V4, V5/MT. The retino-geniculo-striate pathway accounts for approximately 90% of the projections from the retina to the cortex, with the remaining 10% of projections involving subcortical structures (Tong, 2003).

Although the retino-geniculo-striate pathway is the major visual cortical pathway, there are additional parallel neuronal pathways from the eye to the cortex that bypass V1. The retino-tectal pathway projects from the retina to the superior colliculus, to the pulvinar and then the extrastriate cortex. The geniculo-extrastriate pathway projects from the retina to the interlaminar (koniocellular) layers of the dLGN to the extrastriate cortex (see Figure 1 for diagram of visual pathways).

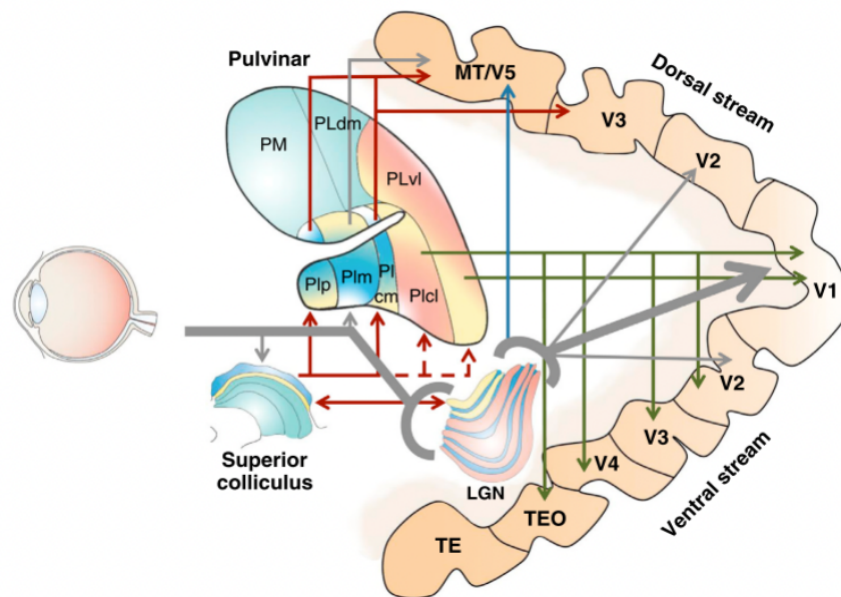


Figure 1. Schematic of the connections from the eye to the dorsal and ventral visual cortex. Grey arrows represent direct projections from the eye to V1 (retino-geniculo-striate pathway), red arrows indicate SC projections to the dorsal stream. Green arrows represent projections from the pulvinar to the ventral stream. Blue arrows represent LGN-hMT+ projections (geniculo-extrastriate pathway; Tamietto & Morrone, 2016).

1.1.2 Extrastriate visual areas

Extrastriate (or ‘visual association areas’) in the occipital cortex receive information from V1, as well as some direct subcortical input (see Figure 1 for example pathways). These regions include many areas, with the most studied being V2, V3, V4 and V5/MT, fusiform face area and lateral occipital complex. Visual information is represented in greater complexity along this visual hierarchy. For example, MT is sensitive to motion (Britten et al., 1996; Newsome et al., 1985; Newsome & Park, 1988), V4 to colour (Bartels & Zeki, 2000; Zeki, 1973), fusiform face area to faces (Kanwisher & Yovel, 2006) and lateral occipital complex to objects (Grill-Spector et al., 2001; Malach et al., 1995). The original functionality of visual areas was determined by specific loss of visual function due to damage. Damage to V4, V5, fusiform face area and lateral occipital complex results in deficits in colour perception (achromatopsia), motion processing (akinetopsia), face recognition and object recognition respectively (Smirnakis, 2016).

This hierarchy of visual information processing is thought to be divided into two processing streams known as the dorsal and ventral pathways (Goodale & Milner, 1992; Mishkin & Ungerleider, 1982; see Figure 1 for a schematic). The dorsal pathway projects from V1 to higher visual areas in the occipital and parietal cortex (including, human motion area MT and MST, collectively known as hMT+) and is involved in spatial attention, guidance of actions and recognising where objects are located (often termed the “where” pathway). The ventral pathway projects from V1 to the inferotemporal cortex (including areas V2, V3, V4 and TEO) and is involved in the recognition and identification of visual objects (often termed the “what” pathway). Recently, a third pathway was proposed which projects from the early visual cortex to the dorsal bank and fundus of the superior temporal sulcus (Pitcher & Ungerleider, 2021). This pathway is

thought to process higher socio-cognitive functions based on social cues, such as facial expression recognition.

1.2 Visual field deficits

1.2.1 Homonymous visual field deficits

Damage to different stages of the retino-geniculo-striate pathway causes varying deficits in vision. Damage to the eye or to the optic nerve results in blindness in only one eye, while due to the decussation of retinal ganglion cell axons at the optic chiasm, damage to subsequent locations in the visual pathway (for example the optic radiation, or V1) results in homonymous visual field deficits (see Figure 2 for a schematic). By studying selective gunshot wounds after the Russo-Japanese war (only recently translated in Inouye, 2000) and World War I (Holmes, 1917) it was discovered that the visual cortex is organised retinotopically, with adjacent regions of the visual field being represented by neighbouring cells in the visual cortex. Central vision is represented by the posterior visual cortex, while peripheral vision is represented by the lateral surfaces of V1. Dorsal V1 represents the upper half of each retina, and ventral V1 represents the lower half. This means that unilateral retro-geniculate damage results in specific visual field deficits in the corresponding contralateral visual field in both eyes (i.e., it is homonymous; see Figure 2 for a schematic).

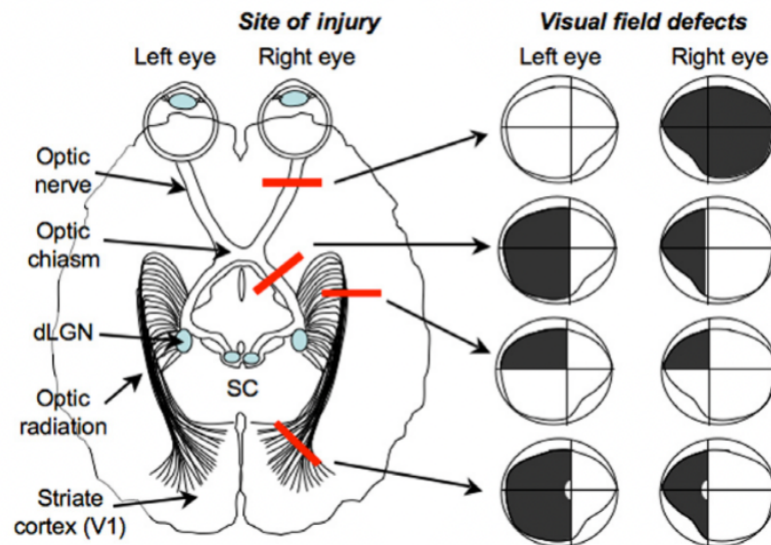


Figure 2. Diagram of the ventral view of the visual pathways in the human. Left: Damage to various visual structures indicated by red lines. Right: Schematics of corresponding visual field deficits after damage indicated by the red line (black shading; Huxlin, 2008). For example, damage to the right optic nerve results in loss of vision in the right eye, while damage to post-chiasmal visual areas results in homonymous visual field deficits.

The size of visual field loss can vary widely, depending on the extent of the damage to V1 or the thalamocortical projections to it. Patients exhibit visual field deficits that represent anything between a small scotoma, to a quadrant (known as quadrantanopia) or a full hemifield (known as hemianopia; Figure 2 for examples of visual field deficits). Total destruction of V1 is rare, and between two-thirds and three-quarters of patients will have macular sparing (represented by the occipital pole) resulting in unaffected central vision allowing participants to fixate well (Leff, 2004).

Although homonymous field deficits can be caused by traumatic brain injury, tumours (or their resections), most are caused by strokes involving the posterior or middle cerebral arteries (Leff, 2004; Zhang et al., 2006). Homonymous field deficits are

mostly caused by lesions to the occipital lobe (40%), parietal lobe (30%), temporal lobe (25%), optic tract and LGN (5%; Pambakian & Kennard, 1997). According to a recent review by the World Stroke Organisation, global incidence of stroke has risen 70% in the last 30 years, now afflicting 1 in 4 people within their lifetime (Feigin et al., 2022). This review further reported that in 2019, 63% of strokes occur in those under the age of 70 years old. This report highlights the large and fast-growing burden of stroke, especially in younger people, and indicates the importance of reducing stroke incidence and improving outcomes post-stroke. It has been estimated that 51% of stroke survivors will suffer visual field loss (Rowe, 2014), with these deficits mostly affecting men between the ages of 50 and 70 years. This is thought to be due to a link to vascular disease (Pambakian & Kennard, 1997).

Within the first 6 months post-stroke, there is thought to be some spontaneous recovery, with 50% of patients showing recovery of the visual field (Zhang et al., 2006). Most of these improvements are seen in the first 3 months (~50-60% of patients), with a marked drop off between 3-months and 6-months (~20% of patients). This is consistent with other studies that have shown that most recovery occurs in the first 10 days, with maximum recovery occurring within the first 48 hours (Gray et al., 1989; Pambakian & Kennard, 1997). However, less than 10% of patients recover their full visual field, although 50% may show partial recovery (Pambakian & Kennard, 1997). This research has led to the belief by many scientists and clinicians that after this brief, six-month period of potential spontaneous improvement, the condition is stable and permanent and is therefore referred to as the “chronic period” (Saionz et al., 2022).

1.2.2 Residual vision

Although visual deficits post-stroke are thought to be stable and permanent, some patients show preserved residual visual processing in their blind fields. In the early 20th century, Riddoch (1917) observed a dissociation between the perception of objects and motion in patients with V1 damage. Riddoch described how patients were able to consciously detect the presence of motion but no other attributes of the stimulus. This phenomenon, later coined “Riddoch syndrome”, was discounted by Holmes at the time because Riddoch did not have a plausible explanation as to why motion processing would be preserved (Zeki, 1995; Zeki & Ffytche, 1998). After a resurgence in this research in the 1970s, Weiskrantz and colleagues described a similar phenomenon known as “blindsight”. This oxymoron was used to reflect how patients are “blind” but can also “see”. Blindsight involves the ability of patients to detect, localise or discriminate stimuli within their blind fields above chance without conscious awareness (Sanders et al., 1974; Weiskrantz et al., 1974).

Although residual vision is most commonly described for large moving stimuli (Azzopardi & Cowey, 2001; Barbur et al., 1994; Morland et al., 1999), in recent years cases of residual vision have been described for wavelength (Danckert et al., 1998; Morland et al., 1999; Silvanto et al., 2008; Stoerig & Cowey, 1992), facial expressions (Celeghein et al., 2015; de Gelder et al., 1999; Tamietto et al., 2009), form (Danckert et al., 1998; Trevethan et al., 2007), shape and object recognition (van den Stock et al., 2014, 2015) and luminance (Blythe et al., 1987).

The diverse range of residual visual abilities has led to many attempts to create taxonomies. Originally, Weiskrantz differentiated patients by conscious experience into Type 1 blindsight (where the participant is unaware or unconscious of their perception)

and Type 2 blindsight (where the participant is aware of their perception; Weiskrantz, 1998). Alongside this, Danckert & Rossetti (2005) proposed three types of blindsight based on the spared visual experience: action blindsight (the ability to correctly act on stimuli through saccades or pointing), attention blindsight (the ability to attend to the blind field) and affective-blindsight (the ability to respond to emotional stimuli). Many blindsight patients exhibit multiple types of blindsight, for example famous blindsight patient G.Y shows residual spatial orienting (Kentridge et al., 1999; action blindsight), discrimination of facial expressions (de Gelder et al., 1999; affective blindsight) and colour/motion discrimination (Morland et al., 1999). Moreover, it has been argued that someone with attention blindsight (i.e., the ability to discriminate the direction of movement) would also be able to indicate the location of the movement (action blindsight; Bridge, 2020; Fox et al., 2020). In their paper, Sahraie et al. (2010) noted that the incidence of blindsight amongst those with V1 damage varies depending on the techniques and stimuli used. Blindsight was exhibited by one patient out of 20 when using spatial summation (Marzi et al., 1986), five out of 25 when using moving spots of light (Blythe et al., 1987) and eight patients out of 10 when using moving high-contrast stimuli (Sahraie et al., 2003). The fact that blindsight varies depending on the task used and is not observed in all patients with V1 damage has led to interest in understanding the neural correlates of residual vision.

1.2.3 The brain basis of residual vision

The presence of residual visual abilities suggests that visual information is still able to reach extrastriate areas through pathways that bypass the damaged area (see Stoerig & Cowey, 1997 for review). As residual visual abilities are most common for moving stimuli this led to interest in the involvement of extrastriate motion area MT (and the human homologue hMT+). In humans (Ajina, Kennard, et al., 2015; Ajina, Rees, et al., 2015; Bridge et al., 2010) and non-human primates (Rodman et al., 1989; Schmid et al., 2010) with damage to V1, there is evidence of activity (although slightly reduced) in MT when the blind field is stimulated. Moreover, there is evidence of the existence of three alternative visual pathways bypassing V1 and projecting to MT from (1) the dLGN (Sincich et al., 2004; Warner et al., 2010), (2) the superior colliculus (Berman & Wurtz, 2010), (3) the medial portion of the inferior pulvinar (Warner et al., 2010). Which of these pathways supports blindsight is a controversial topic, with human and non-human primate literature providing evidence for each pathway.

The role of the superior colliculus and pulvinar

Early research on blindsight highlighted the ability of patients to point or saccade towards targets in the blind field. As the superior colliculus is known to be involved in eye movements (see Gaymard & Pierrot-Deseilligny, 1999 for review), this provided strong support for the role of the pathway between the superior colliculus (via the pulvinar) and MT (also known as the retino-tectal pathway) in underlying the ability to localise targets within the blind field (Weiskrantz et al., 1974b; Zihl & Werth, 1984). In non-human primates there is evidence that lesions to the superior colliculus and V1 abolish MT activity (Rodman et al., 1990). Moreover, selective inactivation of either the

ventrolateral pulvinar (Kinoshita et al., 2019) or superior colliculus (Kinoshita et al., 2019; Mohler & Wurtz, 1977) impairs visually guided saccades. In humans, neuroimaging studies in hemianopia (Tran et al., 2019) and hemispherectomy (Leh et al., 2010) also indicate the role of the superior colliculus in residual vision. These studies provide evidence that the superior colliculus and pulvinar pathways to MT may underlie residual abilities to localise targets. Pathways between the superior colliculus and amygdala are also thought to underlie affective blindsight in humans (Ajina et al., 2020; Tamietto et al., 2012) and non-human primates (Rafal et al., 2015).

The role of the dLGN

After damage to V1, there is also evidence that surviving neurons between dLGN and extrastriate areas might support blindsight. In non-human primates, Schmid et al. (2010) lesioned V1 and found that inactivation of dLGN resulted in decreased activity in extrastriate regions (including MT) and abolition of blindsight behaviours. Moreover, research has shown that neurons in the dLGN of V1-lesioned marmoset monkeys respond normally to visual stimulation, with short latencies preceding neuronal activity in MT (Yu et al., 2018). This suggests that this pathway is functionally viable to support residual visual capacities. The role of the dLGN-hMT+ pathway in processing residual vision is further supported by research in humans that used diffusion-weighted imaging to show evidence of degeneration of the dLGN-V1 pathway, but no difference between the integrity of the dLGN-hMT+ in a blindsight patient when compared to controls (Bridge et al., 2010). Moreover, in a larger sample of patients, researchers have shown that the integrity of the white matter pathway (Ajina, Pestilli, et al., 2015) and functional connectivity (Ajina & Bridge, 2018) between the dLGN and hMT+ is related to blindsight.

These studies strongly support the role of the dLGN-hMT+ pathway in blindsight in non-human primates and humans.

The role of spared V1

It has also been argued that spared islands of V1 might be responsible for residual vision (Das & Huxlin, 2010; Fendrich et al., 2001; Morland et al., 2004; Wessinger et al., 1997). Neuroimaging studies have shown that in some patients, there is activity within or outside of damaged V1 (Kleiser et al., 2001; Morland et al., 2004; Radoeva et al., 2008). However, in many patients with blindsight, there is no evidence of spared V1 activity. Kleiser et al. (2001) only found V1 activity in one of three patients exhibiting residual vision.

Retinotopic mapping can be used to sequentially stimulate portions of the visual field and provide information about the topographic organisation of visual areas. Population receptive field mapping (pRF) provides voxel-based information about the cumulative response of a population of receptive fields (i.e., the area of the visual field that one fMRI voxel responds to). This method can provide the size and location of visual areas as well as the size and location of these receptive fields. Papanikolaou et al. (2014) used pRF mapping and found visual field coverage maps of spared V1 overlap with areas of blind field suggesting that blind field stimulation elicits activation in intact portions of V1. However, they also found that sighted portions of the visual field were sometimes not represented by intact portions of V1, which suggests that V1-bypassing pathways may also be mediating some vision.

Further support for this idea has come from studying hemispherectomy patients, who have had a whole cerebral hemisphere removed or disconnected. These patients do not have spared V1 but can show blindsight (see Ptito & Leh, 2007, for review) which further suggests that spared V1 alone cannot explain blindsight.

The role of the intact hemisphere

Residual vision may also be processed by the undamaged, contralesional hemisphere. The role of the intact hemisphere has been largely discussed in relation to hemispherectomy patients who are still able to exhibit blindsight, despite the removal of an entire hemisphere. Bittar et al. (1999) found that only hemispherectomy patients exhibiting blindsight showed activity in hMT+ in the intact hemisphere when viewing stimuli in their blind field. Moreover, blindsight hemispherectomy patients show projections from contralesional and ipsilesional superior colliculus to the intact hemisphere, which are not present in hemispherectomy patients without blindsight (Leh et al., 2006). In a blindsight patient, strong connections were found between the intact dLGN and damaged hMT+ and between hMT+ in the two hemispheres, which were absent in controls (Bridge et al., 2008). Additionally, the perception of static or moving phosphenes (small spots of light) can be elicited through the stimulation of V1 or hMT+ respectively using transcranial magnetic stimulation (TMS) in healthy controls. In blindsight patient GY, bilateral stimulation of hMT+ was required to produce phosphenes, suggesting that intact hMT+ may play a role in residual visual perception (Silvanto et al., 2007). These studies indicate the importance of the intact hemisphere in underlying residual vision.

Multiple mechanisms underlie blindsight

The neural mechanisms that allow patients with V1 damage to exhibit residual visual abilities remains controversial, with research indicating support for the involvement of many different brain structures. It is therefore likely that blindsight is sustained by multiple mechanisms, depending on the specific residual visual abilities tested and the patient population. Distinct neural mechanisms may support different types of residual visual abilities, with action blindsight supported by pathways between SC-pulvinar-posterior parietal cortex, attention blindsight by SC-pulvinar-extrastriate dorsal visual areas (including MT) and unconscious vision (also known as agnosopsia) by the interlaminar layers of dLGN-extrastriate ventral visual areas (Danckert & Rossetti, 2005). It is also possible for one patient to show multiple types of blindsight which will likely be supported by different neural mechanisms.

Moreover, the mechanisms in hemispherectomy patients may differ from patients with V1 damage due to the extent of damage to the visual system. Most research investigating the neural mechanisms of blindsight in humans has been carried out on case studies, such as patient G.Y. who acquired damage at the age of 8. The mechanisms that underlie residual vision in case studies may be specific to the individual and, in the case of G.Y., potentially supported by early reorganisation of function. Differences in residual vision were also evident in the work of Papanikolaou et al. (2014), who found that residual vision was mediated by spared V1 in three patients and V1-bypassing mechanisms in the remaining two patients. This suggests that different mechanisms may underlie blindsight across patients and future questions should focus on the contribution of each neural pathway to the individual's response, rather than which hypothesis is correct (Sabel et al., 2011).

Further research exploring the neural mechanisms in larger heterogeneous samples is necessary to understand the individual contribution of each pathway.

1.3 Rehabilitation of visual field deficits

1.3.1 Approaches to visual rehabilitation

Despite the high prevalence of strokes affecting the visual system, there are currently no widely accepted, standardised, or validated treatments for stroke survivors with visual loss. Visual loss from stroke is debilitating, with patients showing significantly worse quality of life compared with healthy controls. Gall et al. (2010) found that patients with visual field deficits were less impaired one-month post-stroke as compared with general stroke survivors, however, after 6-months, this was reversed with stroke survivors with visual field deficits showing lower quality of life. The discrepancy in quality of life may be related to the lack of therapy provided for visual deficits post-stroke. When offered, therapies typically focus on teaching patients to maximise their remaining vision through compensatory strategies or substitution. These methods aim to compensate for the impairment (e.g., by redirecting gaze through head and eye movements), rather than attempting to directly improve vision. In recent years, evidence has suggested that restitution techniques, that aim to improve vision within the blind field, have shown promise. In this section, compensatory, substitution, and restitution approaches to rehabilitation of visual loss post-stroke will be discussed.

Compensation therapies

Compensatory therapies, such as eye movement training, work by teaching strategies to reposition the visual world. In these training programmes, patients practise identifying objects or words in their blind fields by moving their eyes or heads to sample the blind field more effectively. Patients with visual field deficits often show a bias in gaze towards their intact hemifield, which results in less accurate and less regular saccades into the blind field. These ineffective patterns of visual search in the blind field cause a bias towards the intact hemifield. Therefore, visual search training can be used to teach patients to make more effective eye movements into the blind field (Zihl, 1995). Studies have found that visual search training can improve reading (Aimola et al., 2014; Keller & Lefin-Rank, 2010), activities of daily living (Keller & Lefin-Rank, 2010), visual search (Mödden et al., 2012; Nelles et al., 2001; Roth et al., 2009; Sahraie et al., 2020) and quality of life (Rowe et al., 2017). In addition, it can expand the visual fields (Mödden et al., 2012) and improve disability scores (Sahraie et al., 2020). Although much of this research sounds positive, a recent Cochrane review, Pollock et al. (2019) concluded that there was limited low-quality evidence that compensatory scanning training improved quality of life, or activities of daily living in randomised controlled trials.

Substitution therapies

Substitution therapies aim to substitute for the deficit by using a device or optical aid. They reposition the visual field so that objects that would normally fall in the blind field now appear in the intact sighted field. The most common substitution method uses prisms, which are applied to a spectacle lens. These lenses shift the visual world so that objects that would normally appear in the affected portion of the retina are now presented to the section of the retina which projects via intact pathways to the undamaged hemisphere. These glasses can increase the visual field by up to 20 degrees (Peli, 2000). Research suggests that prisms can improve mobility (Bowers et al., 2014; Peli, 2000), visual function (O'Neill et al., 2011; Peli, 2000) and quality of life (O'Neill et al., 2011); although, Rowe et al. (2017) found no evidence of improvement in visual function or quality of life. Moreover, after reviewing randomised control trials, Pollock et al. (2019) concluded that there was low quality evidence that prisms improve quality of life or activities of daily living, although they might improve scanning of the visual field. Many patients struggle to integrate the information resulting in problems with navigation, double vision, and visual confusion (Rowe et al., 2017). There are also higher reports of adverse events, such as headaches, for prisms compared with other therapies such as visual search (Rowe et al., 2017). These reasons may explain why very few patients continue to use prisms long-term (Giorgi et al., 2009; Rowe et al., 2013). Prescribing prism glasses to treat visual deficits from stroke should therefore be exercised with caution (Rowe et al., 2017).

Restitution therapies

In early animal models, researchers found that non-human primates with V1 lesions were able to learn to detect and saccade to a point of light in their blind field (Cowey & Weiskrantz, 1963; Mohler & Wurtz, 1977; Weiskrantz & Cowey, 1970). These improvements occurred gradually, were location specific, and did not occur spontaneously (Weiskrantz & Cowey, 1970). Pasik & Pasik (1973) found that monkeys with bilateral occipital lesions were initially unable to detect stimuli in their blind field, however 3 months after the damage, all monkeys had relearned to discriminate brightness and were able to reach for stimuli. Similarly, there is evidence in humans with V1 damage that blindsight abilities are trainable. Patient F.S. was reported to initially have shown no residual vision, but their performance improved over time (Stoerig & Cowey, 1997). Additionally, G.Y. was reported to have improved motion sensitivity and increased subjective awareness of their blind field between two testing sessions, which was attributed to extensive visual testing within the interval (Sahraie et al., 1998).

This early research led to interest in whether residual vision in the blind field can be improved through training in humans. The most well-known visual rehabilitation technique, known as “Visual Restitution Therapy” or “VRT”, was developed by Kasten and Sabel. VRT is now clinically available in Europe and the United States. This training programme involves detecting spots of light on a black screen at multiple locations in the blind and sighted fields. Early research by the group showed promising improvements in luminance detection after training (Kasten et al., 1998; Kasten & Sabel, 1995). Despite this, VRT is controversial, with many believing that improvements are due to undetected eye movements (Reinhard et al., 2005) or light scatter (Pelak et al., 2007). Moreover, VRT has been criticised for only measuring improvement on the trained task (Horton, 2005). When eye movements were tightly controlled using a scanning laser ophthalmoscope, no

significant improvements were found using VRT (Reinhard et al., 2005). Sabel argued that the negative results found in this study were due to the researchers using a scanning laser ophthalmoscope rather than more commonly used clinical perimetry such as the Tuebingen Automated Perimeter (Sabel et al., 2004). However, Schreiber et al. (2006) later reported no significant result when using the Tuebingen Automated Perimeter.

The well-known criticisms of VRT and the lack of randomised controlled trials for other visual rehabilitation techniques have caused many to doubt their efficacy (Saionz et al, 2020). Despite this initial set back in the field, in recent years, research laboratories from across the world have shown that visual training in the blind field can restore a range of visual functions. Many of these studies have aimed to address criticisms of the field by (i) using dark stimuli on a bright background to reduce light scatter and (ii) using gaze-contingent stimulus presentation with a binocular eye tracker to verify pre- and post-training task performance (for example, Huxlin et al., 2009). Improvements in vision have been found for a range of visual stimuli, including flicker sensitivity (Raninen et al., 2007), target localisation (Chokron et al., 2008a), orientation discrimination (Das et al., 2014b), letter identification (Chokron et al., 2008a; Raninen et al., 2007), direction discrimination (Cavanaugh et al., 2015, 2019; Elshout et al., 2016), direction integration (Das et al., 2014b; Huxlin et al., 2009) and contrast sensitivity (Ajina et al., 2021; Das et al., 2014b; Sahraie et al., 2006, 2010). Improvements in performance are most pronounced for trained tasks, so it could be argued that the functional gains made using these stimuli may not be useful for everyday life. It is therefore important that many of these studies have also found that improvements can transfer to untrained tasks. For example, training on coarse direction discrimination improved contrast sensitivity (Das et al., 2014b) and fine direction discrimination (Cavanaugh et al., 2015). Additionally, many studies have found that training also reduces the size of the visual field deficit, as

measured by clinical perimetry (Cavanaugh & Huxlin, 2017; Chokron et al., 2008a; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009; Sahraie et al., 2006).

While this research is promising, few of these studies have been carried out as randomised, placebo-controlled, double-anonymised trials, which led Pollock et al. (2019) to conclude that further research is needed to determine their efficacy. However, it is worth noting that it would be difficult to carry out fully placebo-controlled or double-anonymised trials for this type of research, as there is no suitable ‘placebo’ for visual training within the blind field, nor will the patient be unaware of the rehabilitation used. In addition, although there is some evidence of transfer of learning to untrained tasks, the vision recovered is not normal and has been found to be coarse and of low contrast (Das et al., 2014b), which limits its usefulness in everyday life. Recovery of visual abilities is also time-consuming and usually takes several months of daily training (Cavanaugh et al., 2015, 2019; Cavanaugh & Huxlin, 2017; Das et al., 2014b; Huxlin et al., 2009; Sahraie et al., 2010). Indeed, previous studies have found a direct relationship between amount of recovery and the number of training sessions (Cavanaugh & Huxlin, 2017; Huxlin et al., 2009). Additionally, the efficacy of visual training programmes remains highly variable among participants (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009) and the reasons for this are poorly understood. Identifying factors that underlie improvements in vision post-stroke is necessary to determine the mechanisms by which visual training works and may allow us to identify those most likely to benefit from this extensive rehabilitation.

1.3.2 The brain basis of visual rehabilitation

There are several theories about the cortical pathways that support rehabilitation of visual loss post-stroke: (1) training strengthens extra-geniculostriate pathways that may be responsible for blindsight, (2) training reactivates spared islands of intact V1, (3) training strengthens attention-related networks, (4) training induces plastic-like changes in visual cortex to represent initially blind regions.

Extra-geniculostriate pathways

As blindsight is thought to be reliant on extra-geniculostriate pathways (such as the dLGN-hMT+ pathway), it was initially theorised that visual rehabilitation may improve residual vision by strengthening these pathways (Das & Huxlin, 2010). Based on this assumption, some rehabilitation techniques have specifically targeted these blindsight pathways by using stimuli with high-temporal and low-spatial frequencies for training (Ajina et al., 2021; Chokron et al., 2008a; Perez & Chokron, 2014; Sahraie et al., 2006, 2010). Indicating the importance of the LGN, Sahraie et al. (2010) found no improvement in training in a patient whose lesion extended to the thalamus, despite them completing over 300 training sessions. Moreover, in a case study, Vaina et al. (2014) found an increase in activity in hMT+ in the damaged hemisphere after 8 months of visual training. Ajina et al. (2021) also found increased activity in hMT+ for moving stimuli at trained locations and increased pre-training hMT+ activity was predictive of rehabilitation success. These studies provide preliminary evidence for the role of extra-geniculostriate pathways in visual rehabilitation.

Spared V1

An alternative theory proposes that rehabilitation relies on spared perilesional V1. Many patients have areas of functionally impaired, but intact, V1 that may be reactivated by intensive training (Barbot et al., 2021; Huxlin et al., 2009). One resting-state connectivity study found that interhemispheric connectivity between the occipital poles was decreased in hemianopia, and this correlated with spontaneous improvements in vision (Kim et al., 2019). This indicates that connectivity between spared V1 and intact V1 may also facilitate rehabilitation. Additionally, as previously discussed, Papanikolaou et al. (2014) used pRF mapping and found visual field coverage maps of spared V1 overlap with areas of blind field suggesting that blind field stimulation elicits activation in intact portions of V1. They proposed that these regions may be optimal locations for rehabilitation. Barbot et al. (2021) also used pRF mapping to show that increased pre-training perilesional V1 activity representing perimetrically-blind portions of the visual field was predictive of post-training improvement on perimetry. Raemaekers et al. (2011) found that patients show a small shift in eccentricity of receptive fields in spared early visual areas after training, and a small increase in pRF size. Furthermore, in a recent study, Elshout et al. (2021) investigated the relationship between areas of visual field deficit that are represented by intact portions of early visual cortex, something the authors refer to as “neural reserve”. They found that neural reserve in early visual and dorsolateral and ventrolateral occipital areas was related to improvements in vision, with greatest improvements seen at these locations. However, it should be noted that specific analysis of visual areas was not possible due to the down sampling of fMRI data to match the resolution of the perimetry tests used. These studies suggest that visual restoration will be more effective in those with some spared V1. However, Raemaekers et al. (2011)

argue that although changes in receptive field properties in early visual cortex may explain local visual field enlargements, there were also large-scale improvements that could not be explained by these mechanisms. This suggests that multiple mechanisms may explain improvements even within the same patient.

Attention networks

It has also been suggested that variability in capacity for visual rehabilitation may be linked to the individuals' spatial attentional capacities (Elshout et al., 2016). Visual rehabilitation protocols generally involve fixating centrally and directing attention to an area within the blind field. It is therefore possible that better performance is modulated by this increase in attention towards the blind field. Studies have suggested that attention enhances residual vision (Poggel et al., 2006) and efficacy of rehabilitation is enhanced by attention (Poggel et al., 2004). This is further supported by fMRI studies which show that improvements in training are linked to increased activity in brain regions associated with spatial attention, such as the anterior cingulate, dorsolateral prefrontal cortex and right temporo-parietal junction (Marshall et al., 2008). Using resting-state functional connectivity, Lu et al. (2018) found that visual rehabilitation resulted in an increase in connectivity between areas involved in attention, including right temporoparietal junction to the insula and the anterior cingulate cortex. However, they found that strength of connectivity was not related to improvements in vision, suggesting that this alone cannot explain rehabilitation. Moreover, in a recent resting-state connectivity study, Halbertsma et al. (2020) found the strength of connectivity between the occipital pole and the precuneus was related to attention-modulated visual improvements. They argue that this pathway may provide a biomarker indicating a patient's potential for directing

spatial attention. These studies suggest that visual rehabilitation post-stroke may be effective in increasing attention towards the blind field.

Reorganisation

There are several small studies or case studies that suggest that visual reorganisation may promote rehabilitation. An early study by Dilks et al. (2007) found that a patient with quadrantanopia had distorted retinotopic maps, which they argued indicated cortical reorganisation of V1. Additionally, Papanikolaou et al. (2014) found evidence of a small shift in receptive field centres towards the damaged visual field and an increase in receptive field sizes in ipsilesional and contralesional V1 when compared to healthy controls. Vania et al. (2014) also found an increase in the size of retinotopically defined visual areas V1, V2v, V2d and VP in the lesioned hemisphere only. Similar results have been found in animal models, with V1-lesioned animals exhibiting increased receptive field sizes and neuronal excitability in perilesional tissue (Eysel & Schweigart, 1999; Schweigart & Eysel, 2002). Moreover, Schweigart & Eysel (2002) found that 1 hour of repetitive stimulation in the post-lesion receptive field resulted in modest increases in receptive field sizes. These studies show that pRF sizes are slightly enlarged after damage to V1 which may reflect enhanced plastic potential of V1 post-stroke. Barbot et al. (2021) also found evidence that pRF sizes in perilesional V1 were increased with visual training resulting in increased coverage of the blind field. This may explain why training-induced improvements seen in behavioural studies tend to occur along the blind field border (Barbot et al., 2021). Alternatively, the intact hemisphere may take over processing of the lesioned hemisphere. Henriksson et al. (2007) used MEG and fMRI and found that improvement on a flicker detection training programme was related to increased activity

in hMT+ and areas V1, V2, V3 and V3A in the intact hemisphere relative to baseline before the training.

Multiple neural mechanisms

As with blindsight, it is likely that multiple neural mechanisms play a role in visual rehabilitation. It is possible that even within the same patient, different spared visual abilities may depend on different neural mechanisms. There is evidence that improvement in luminance detection in perimetry relies on spared V1 (Barbot et al., 2021), however it is known that visual training can also recover a range of complex visual functions such as motion discrimination. These mechanisms are likely dependent on extrastriate motion areas such as hMT+. This is further supported by evidence that increased activity in hMT+ predicts improvements on a motion training task (Ajina et al., 2021). These studies suggest that perilesional V1 and extra-geniculostriate pathways may both be involved in visual rehabilitation. Elshout et al. (2021) found evidence that in one patient, pre-training activity in early visual areas was related to improvements, however, all other patients in the study showed more diverse patterns of activity, including areas on the dorsolateral and ventrolateral occipital surface. Additionally, evidence suggests that attention networks play a role in rehabilitation (Halbertsma et al., 2020; Marshall et al., 2008). Attributing rehabilitation to the function of a single cortical area may therefore be misjudged, and a combination of residual or reorganised processing of visual and attentional areas may be involved.

Moreover, the neural mechanisms underlying recovery almost certainly differ among patients depending on the type or location of damage (see Discussion for further consideration). Research investigating the neural basis of rehabilitation is

heterogeneous, with variations in training types, neuroimaging techniques used, and brain areas studied. Additionally, many of these studies have focused on case studies (Henriksson et al., 2007) or relatively low sample sizes (e.g., 6 in Ajina et al., 2021 and 11 in Barbot et al., 2021). The limited number of studies investigating the neural basis of visual rehabilitation and this heterogeneity in research leads to ambiguity about the neural underpinnings of rehabilitation. It is of paramount importance to understand how training programmes are working (or not in some cases) to identify which patients will be most likely to benefit from extensive training. This knowledge will allow us to develop even more effective rehabilitation programmes by targeting the systems involved.

1.4 Synopsis of this thesis

1.4.1 Aims of thesis

The primary aim of this thesis is to investigate whether visual rehabilitation training can be used to improve visual loss post-stroke, and if so, to understand the neural mechanisms that underlie improvements. There are currently no widely used treatments for visual loss from stroke, and those that are available are time-consuming and their efficacy variable. Research is needed to determine why visual recovery is variable among participants. This thesis has two components: 1) to understand the neural mechanisms that underlie residual vision before training, and 2) to identify whether residual vision can be improved with training and, if so, what the underlying neural mechanisms are.

Chapter 3: GABA and glutamate in hMT+ link to individual differences in residual visual function after occipital stroke at baseline.

The functioning of hMT+ has been suggested to underlie residual vision (or “blindsight”) within the blind field following V1 damage. This chapter investigated whether residual blind-field perception at baseline could be explained by the concentration of neurotransmitters GABA and glutamate or activity in the visual motion-processing, hMT+. Proton magnetic resonance spectroscopy (MRS) was used to measure concentrations of GABA and glutamate, while functional MRI (fMRI) measured changes in BOLD signal change in hMT+. GABA and glutamate concentrations in hMT+ strongly predicted residual vision with lower neurotransmitter levels reflecting superior residual vision. There was no relationship with BOLD signal change in hMT+.

Chapter 4: Residual vision after V1 damage is related to functional connectivity between hMT+ and ventral visual areas at baseline.

In the Chapter 3, no relationship was found between task-related BOLD signal change in hMT+ and residual vision at baseline. Previous studies suggest that a functional connection between dLGN and hMT+ supports blindsight. In this chapter, the relationship between resting-state functional connectivity and residual vision in the blind field at baseline was explored. Functional connectivity between ipsilesional hMT+ and contralesional hMT+ and the rest of the brain was quantified. Superior residual vision was related to lower functional connectivity between both ipsilesional and contralesional hMT+ and contralesional ventral visual cortex.

Chapter 5: Visual rehabilitation in the blind field improves trained and untrained behaviour

Although many patients with V1 damage show residual vision within the blind field, there are currently no widely used treatments for vision loss post-stroke. Recent evidence suggests that visual training in the blind field can improve vision. In this chapter, I investigated behavioural changes after six months of visual training. After six months of visual training in the blind field, participants significantly improved at both the trained and two untrained tasks. These results suggest that visual rehabilitation is successful at improving vision post-stroke. However, the amount of improvement was variable between participants, and the reasons for this remain unclear.

Chapter 6: Increased white matter integrity of the dLGN-hMT+ pathway after visual rehabilitation.

As discussed in Chapter 5, visual rehabilitation training is highly variable among participants, and it is likely that variation in neural mechanisms might underlie this. Previous studies have shown a relationship between residual vision and the integrity of the white matter pathway between the dLGN and motion area hMT+. Moreover, research in healthy controls and motor stroke survivors indicate that training strengthens white matter connections. In this chapter, I aimed to understand whether visual rehabilitation strengthens connections between the dLGN and hMT+ and whether these changes are related to improvements. There was evidence of a significant increase in white matter integrity due to increased neurite density and reduced neurite dispersion after six months of visual training in the distal (non-overlapping) portion of the dLGN-hMT+ pathway. This suggests that the dLGN-hMT+ underlies improvements in vision after visual training in the blind field.

Chapter 2: General Methods and Procedures

2.1 Introduction

The methods and procedures used in this thesis are described in this chapter. First the demographics of the participants involved are provided. Then the procedures for data collection on each testing day, and the visual rehabilitation protocol are outlined. The behavioural methods used to assess visual field deficits and residual vision are discussed. Finally, the MRI methods used to investigate the structure, function and neurochemistry that underlies residual vision and rehabilitation are described.

2.2 Participant demographics

Twenty-four healthy stroke survivors with damage to V1 resulting in visual field deficits were recruited to take part in a nine-month visual rehabilitation study (median=49 years, range=24-74 years, 6=Female). All participants were at least six months post-stroke (chronic phase) at the baseline visit with the median being 29.5 months post-stroke (range=6-297 months; see Table 1 for participant demographics).

Participants had no history of diagnosed cognitive or psychiatric disorders (including executive deficits), previous eye disease or impairment other than visual loss after stroke (including all forms of visuospatial neglect). All participants provided informed consent and experiments were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The study was approved by the University of Oxford IDREC Committee (R60132/RE001).

Twenty participants (out of 24) completed the six months of visual rehabilitation and returned for a research visit after six months. Four dropped out of the study either due to time constraints (R001; R008; R009) or due to inability to complete the training at home (R012).

Twelve of these participants (R002, R003, R004, R005, R006, R007, R010, R011, R013, R014, R015 and R019) also returned for a follow-up visit after a further three-months without training (nine-month visit). In this thesis, the baseline data will be discussed in Chapters 3 and 4, and the 6-month change data for those who completed the six months of visual rehabilitation will be discussed in Chapters 5 and 6. The 9-month visit data will not be discussed in this thesis.

Table 1. All participant demographics

Participant	Stroke Type	Sex	Age	Months Since Lesion	Deficit Side
R001	unknown	m	54	68	left
R002	unknown	f	28	39	right
R003	ischemic	m	33	58	both
R004	haemorrhagic	f	51	31	left
R005	haemorrhagic	m	61	21	left
R006	ischemic	m	24	13	left
R007	haemorrhagic	m	47	7	left
R008	unknown	m	45	32	left
R009	unknown	m	35	25	left
R010	ischemic	m	63	47	right
R011	unknown	m	64	7	left
R012	unknown	m	74	58	left
R013	haemorrhagic	m	71	26	right
R014	ischemic	f	34	30	right
R015	ischemic	f	37	29	right
R016	haemorrhagic	m	60	40	right
R017	ischemic	m	66	6	right
R018	ischemic	m	35	26	right
R019	ischemic	f	41	31	left
R020	unknown	f	46	297	left
R021	unknown	m	58	11	left
R022	ischemic	m	47	14	right
R023	unknown	m	68	49	right
R024	ischemic	m	60	13	left

2.3 Data collection

The research study involved completing six months of visual training at two locations within the perimetry-defined blind field. Participants were required to attend three research visits at baseline, after six months of training (post-training) and then again after three months of no training (follow up; Figure 3 for outline).

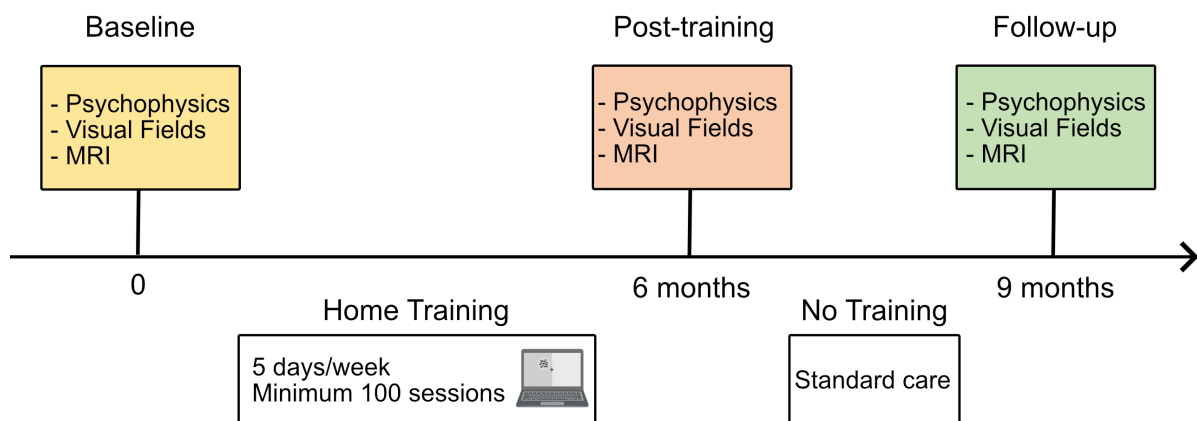


Figure 3. Outline of the visual rehabilitation research study. Participants attended three research visits at baseline, after six months of visual training at home (post-training) and after a further three-months without training (nine-month visit). They completed six months of training in between the baseline and post-training visit (minimum 100 sessions) and standard care was provided between the 6-month visit and 9-month visit.

Each research visit involved collecting extensive behavioural data (including psychophysics and virtual reality task), an MRI scan (structure, function, and neurochemistry) and visual field tests (see Figure 4 for outline of each research visit). For each research visit, participants were asked to refrain from drinking caffeine on the day of the scan and avoid alcohol in the preceding 48 hours to minimise effects on the

neurochemistry scans. During the pre-training visit, additional time was spent finding the optimal training locations for each participant and setting up their training programmes (see “Training locations” section below for details on procedure). In the two follow-up visits, the duration of the visit was shorter because only trained locations were tested, and training programmes were not set up.

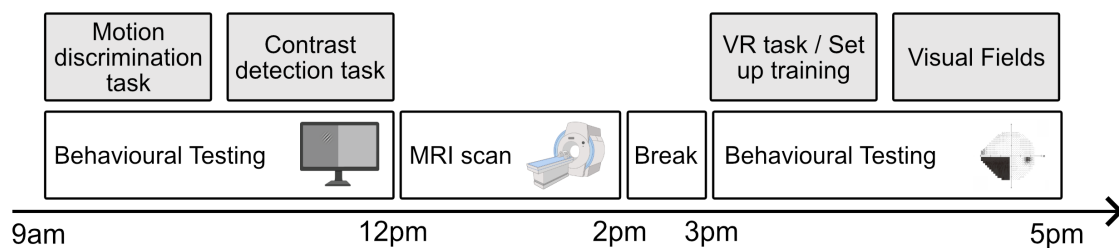


Figure 4. Outline of each research visit. Participants completed behavioural testing in the morning, an MRI scan 12-2pm followed by further behavioural tests (including visual fields) in the afternoon.

2.4 Behavioural methods

2.4.1 Assessment of visual field deficit

Background

The extent of visual field loss from damage to V1 is measured using visual field tests. Visual field tests, known as perimetry, use different types of stimuli of varying intensities to systematically measure visual field function at selective locations within the visual field (Hepworth & Rowe, 2018). Stimuli can either be kinetic (moving) or static (stationary but on/off). In kinetic perimetry, a stimulus is moved from a non-seeing location of the visual field into a seeing area and the location at which the stimulus is first seen is recorded. Static perimetry on the other hand involves presenting a non-moving stimulus at defined points in the visual field.

The most common visual field test used for stroke survivors is the Humphrey Visual Field tests (HVF; Hepworth & Rowe, 2018). During this test, participants fixate centrally while static spots of light of varying luminance appear across retinotopically determined test points. Head position is controlled using a forehead and chin rest and eye position is monitored to ensure fixation is maintained throughout the test. Participants perform the test monocularly and are instructed to indicate, using a button press, when they see a light appear anywhere in the field of view. Throughout the test false positives (being “trigger happy” and responding when the stimulus was not present), false negatives (failing to detect a light that should have been detected, for example after detecting a light of the same or lower threshold previously) and fixation losses (moving the eyes from the fixation point) are monitored. These provide a measure of the reliability of the test and the accuracy of fixation.

The field of view of the HVF test can be varied. Even though the normal monocular visual field extends roughly 60 degrees superiorly, 70 degrees inferiorly, 60 degrees nasally, and 100 degrees temporally (Ramulu, 2012), tests typically use a radius of the central 10, 24 or 30 degrees of visual angle. These tests are known as the 10-2, 24-2 and 30-2 respectively. The Humphrey Visual Field Analyzer uses the Swedish Interactive Threshold Algorithm (SITA). This algorithm estimates threshold values for each location based on responses to stimuli at that location and nearby locations (Bengtsson et al., 1997, 1998). This algorithm reduces the time needed to acquire visual field tests and has three test options: SITA standard (~7 minutes per eye), SITA FAST (~4 minutes per eye) and SITA FASTER (~2 minutes per eye).

These visual field tests can be used to determine the size and location of the visual field deficit in stroke survivors. Visual loss caused by damage to V1 results in loss of visual function in the contralateral visual field and the size and location of the visual loss depends on the location of the damage to V1. Total destruction of V1 in one hemisphere results in hemianopia (loss of half the visual field). A smaller lesion, impacting the upper or lower bank of V1 could result in quadrantanopia (loss of a quarter of the visual field). Stroke survivors can also have damage anywhere between these two, or even less than one quarter. We generally refer to this as a scotoma, which is an area of depressed visual sensitivity surrounded by normal vision. Examples of hemianopia, quadrantanopia and a scotoma are presented in Figure 5 with the corresponding damage to V1.

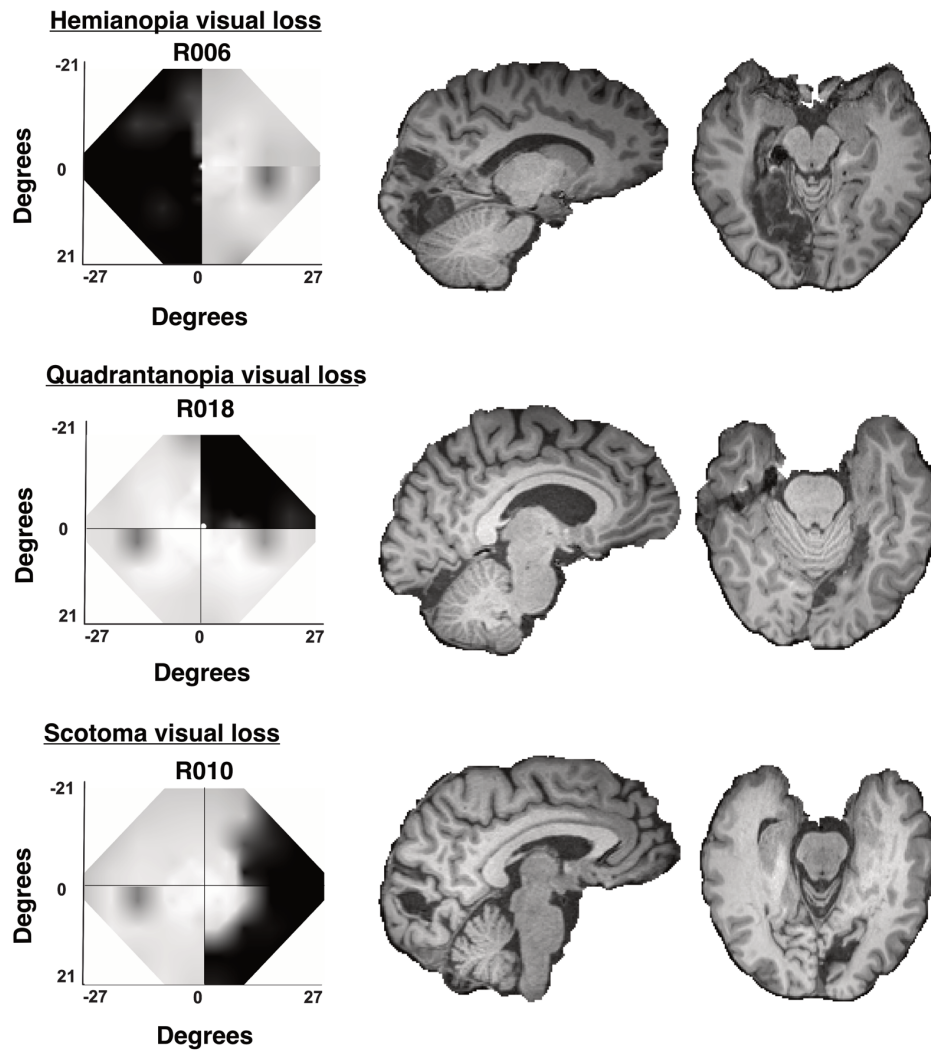


Figure 5. Example of visual loss and corresponding damage to the primary visual cortex. Humphrey perimetry defined visual loss (left) and corresponding damage to V1 (right) are shown for a participant with hemianopia (upper), quadrantanopia (middle) and a scotoma (lower). For the participant with hemianopia (R006), there is almost total destruction of V1 in the right hemisphere, which results in loss of vision on the entire left-hand side of visual space. For the participant with quadrantanopia (R018), there is only partial destruction of V1 in the left hemisphere. The upper bank of the calcarine sulcus (representing the lower visual field) is preserved, resulting in blindness in the upper visual field only. For participant R010, there is only partial destruction of V1 in the left hemisphere resulting in a scotoma of visual loss in the right visual field.

Humphrey visual field acquisition

In the current thesis, visual field deficits were quantified using two sets of HVF tests (24-2 and 10-2). These were performed monocularly with each eye using a Humphrey Field Analyser (SITA fast and SITA standard programmes respectively) to estimate the visual fields of each participant pre- and post-training. Visual acuity was corrected to 20/20 and eye-tracking was monitored to ensure central fixation during this task. Data from participants who showed fixation losses, false positives, and negative errors outside of the normal range ($\geq 20\%$) in either eye at any time point were removed from further analyses. If this occurred, participants were required to repeat the test to try and reach a normal range. The same two trained researchers performed each assessment, and these tests were used to map the spatial extent of each participant's visual field deficit.

Humphrey visual field data pre-processing

HVF data were analysed as described previously (Cavanaugh et al., 2019; Cavanaugh & Huxlin, 2017; Saionz et al., 2020). The 24-2 and 10-2 Humphrey software provides the following information: 1) the deviation from the mean for each HVF testing location compared to an age-corrected normal population (pattern deviation), 2) the overall sensitivity difference between the tested and expected hill of vision compared to an age-corrected, normal population (perimetric mean deviation), and 3) the 10-2 HVF also gives a test-retest variance (short term fluctuations). Examples of 24-2 and 10-2 tests for the left and right eyes in the same participant are shown in Figure 6.

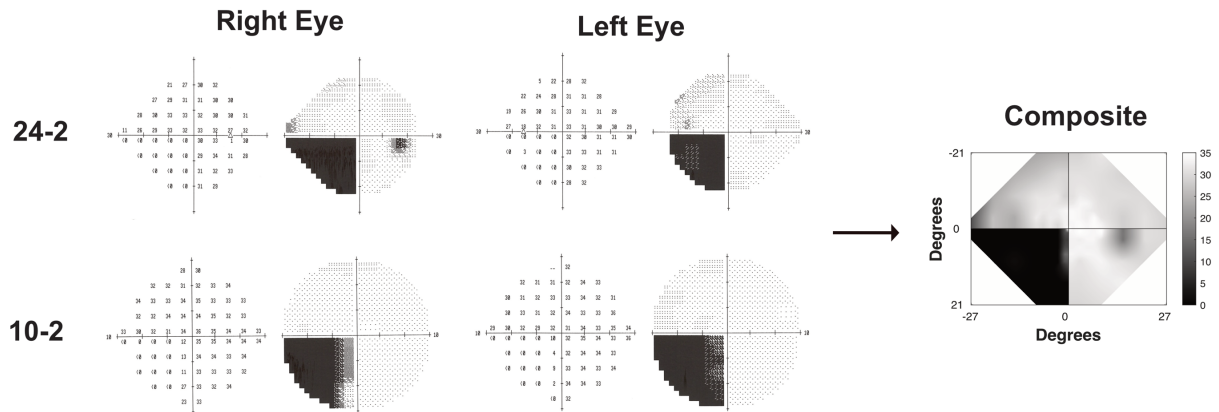


Figure 6. Example Humphrey Visual Field tests for one participant. Individual 24-2 and 10-2 Humphrey Visual Field tests for the right and left eye (left) for participant R004 at baseline. The HVF for both eyes were averaged together to make a binocular HVF for the 24-2 and 10-2. The tests were then combined at overlapping regions to make composite visual fields for each participant (right).

Given the homonymous nature of hemianopic visual field deficits in this patient population, composite binocular HVF were calculated by averaging monocular luminance detection thresholds (dB) for both eyes. Binocular 24-2 and 10-2 HVFs were then combined at overlapping regions (see Figure 6 for example composite HVF). The area of visual field impairment was defined as those areas with an impaired binocular average sensitivity of below 15dB.

2.4.2 Visual rehabilitation training

Training Task

A psychophysical motion discrimination task was used for the visual rehabilitation programme. The motion discrimination task was designed in MATLAB (MathWorks) using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Participant's eyes were positioned 42cm away from the computer screen with a chin-forehead rest. Participants were asked to make coarse, left-right discriminations of global motion directions of random dot stimuli. Random dot stimuli consisted of black dots on a grey background (dot speed $10^\circ/\text{s}$, dot lifetime 250ms, stimulus duration 500ms; aperture 5° diameter; see Figure 7 for schematic of the training task). Dots moved globally in a range of directions, and these were distributed uniformly in either leftward or rightward directions. Participants were then asked to respond whether the global direction of motion was leftwards or rightwards.

Training difficulty was modulated using a 3:1 staircase procedure for direction range of the dots so that as participants performed better at the task, the directions the dots moved in increased. After three correct responses, the range of dot directions was increased from 0 to 360° in 40° steps and after one incorrect response it was decreased by 40° (Huxlin et al., 2009; Das et al., 2014, Cavanaugh et al, 2015). Auditory feedback signalled correct and incorrect responses on each trial. Performance for each session was calculated as a function of direction range level. A Weibull function was then fitted to the data with a criterion threshold of 72% correct.

The session threshold was normalised to the maximum range of dot directions (360°) to generate a normalised direction range (NDR) using the following equation:

$$\text{NDR threshold (\%)} = (360^\circ - \text{Weibull-fitted direction range threshold}) / 360^\circ \times 100$$

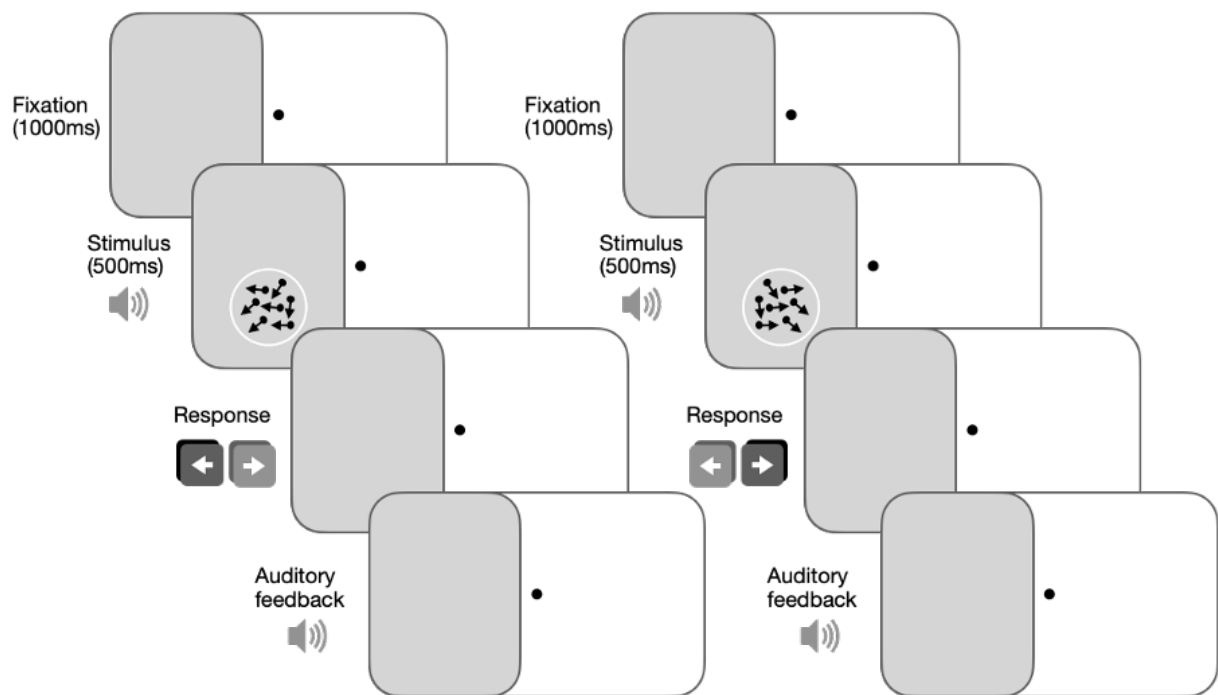


Figure 7. Training paradigm. Throughout training participants fixated centrally, and motion stimuli were presented at the given training location inside the blind field. Presentation of the stimulus was accompanied by an auditory tone. Participants were asked to discriminate the global direction of movement (leftward or rightward) of the dots in the stimulus after each presentation. The participant was then provided with auditory feedback signalling whether their response was correct on each trial. This was repeated for 300 trials at each blind-field location.

Training locations

Two training locations within the perimetry-defined blind field were selected in all participants. Training-based improvements are location specific (Huxlin et al., 2009) and are related to the number of training locations and sessions (Cavanaugh & Huxlin, 2017). Therefore to optimise the efficacy of visual rehabilitation, participants were trained at two locations at the same time. At the pre-training visit, 100 trials of the motion discrimination task were performed at different locations within the blind field to find the optimal training locations. Initial vertical locations were selected so that training locations would span the full visual field, but did not overlap (i.e., a participant with hemianopia would have one location in the superior field and one in the inferior; whilst a participant with quadrantanopia would have two non-overlapping locations within their quadrant). Once initial vertical locations were determined, final training locations were then selected by measuring NDR thresholds sequentially, starting with the edge of the stimulus at the vertical meridian, and moving 1° laterally until performance drops to chance (50% correct) and NDR thresholds were unmeasurable (designated as 100%).

For all training locations, the full diameter of the stimulus was inside the Humphrey-defined blind field border. During at-home training, as performance at each location reached 72% correct and NDR thresholds stabilised over 5-10 consecutive sessions (less than 30% coefficient of variation), this training location was moved to a new location 1° further into the blind field, along the x-axis (Cartesian coordinate space), and daily training began anew.

Home-based training

Participants were trained on 300 trials of the motion discrimination visual training programme at two locations within their blind field (Huxlin et al., 2009; Das et al., 2014; Cavanaugh et al, 2019). Each training location took approximately 15 minutes (~30 minutes in total for two daily training sessions). A subset of participants (R017, R023 and R024) only trained at one location due to time constraints and difficulties with motivation.

Participants used lab-issued chin-forehead rests and software customised to their own computer and monitor specifications (dimensions, resolution, refresh rate). Individualised programmes for each training location were compiled in MATLAB using the Compiler app (MathWorks) and sent to each participant. At the pre-training visit, the research team assisted with setup of the programme and ensured participants were aware of how to use it appropriately. Each participant was given instructions detailing how to set the training up at home to ensure consistency, for example positioning the computer 42cm away from the eye. Participants were encouraged to train when they were most awake, and the exact time was recorded in the daily logs produced by the training programme. Before training began, the programme presented a square and participants were asked to measure the size to ensure the screen dimensions they had provided to the research team were accurate.

After each at-home training session was completed, the software automatically generated a log file detailing trial by trial performance. These log files were then emailed to the laboratory weekly by participants, allowing researchers to compute thresholds, and follow their progress. An example of one participant's home-training is provided in Figure 8.

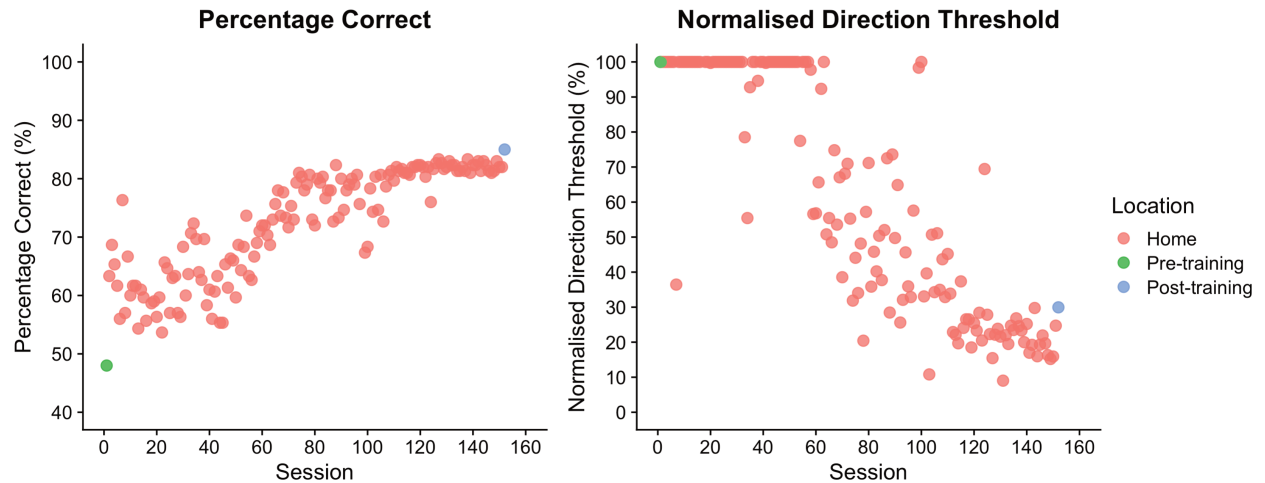


Figure 8. Example improvements in training in one participant. *Left: An example participant's (R018) training showing steady improvements in percentage correct on the motion discrimination training at home (red) between the pre-training (green) and post-training visits (blue). In this example, the participant performs at 48% correct at baseline. They then steadily improve over each daily session until they plateau at ~80% correct. They then return after 6 months of training and verify their at-home training by performing 85% correct at the post-training visit. Right: An example participant's (R018) training showing corresponding improvements in normalised direction range (NDR) thresholds at home (red) between the pre-training (green) and post-training visits (blue). When the percentage correct improves above 72% correct (left), the normalised direction range thresholds can then be fit (see details of how fit is calculated above). In this example, at baseline the percentage correct is 57% and so the NDR thresholds are unfittable (denoted here as '100'), as the percentage correct steadily improves above 72%, it is possible to fit NDR thresholds and these slowly drop reflecting an improved ability to discriminate motion.*

Participants were asked to fixate centrally throughout home training and were reminded that fixation would be essential to ensure the visual target was presented at the intended training location in their blind field. If they moved their eyes, the location of the target in the brain would change, which would affect the training. A failure to fixate correctly during at-home training produced anomalies in the training data that were easily detectable by researchers. If participants were looking at the stimulus rather than fixating, sudden improvements in their percentage correct and NDR thresholds were expected.

2.4.3 Assessment of visual function

Motion discrimination task

Motion discrimination ability was also measured at the pre-training and post-training visits at the two trained locations within the perimetry-defined blind field and a matched sighted field location to determine whether participants improved at the trained task. An Eyelink 1000 Plus eye tracker (SR Research Limited, Ontario, Canada) was used at both research centre visits to verify fixation and ensure fixation-contingent stimulus presentation. Only after at-home training results and threshold improvements were verified in-lab with controlled fixation, were participants classified as having experienced visual improvement at their training locations.

Contrast detection task

A moving contrast detection task (Ajina et al., 2021; Ajina, Rees, et al., 2015) was used to measure residual vision (or 'blindsight') at the two training locations and matched sighted field location at the baseline research visit. Changes between the pre- and post-training research visits were also used to determine whether training on a motion discrimination task generalised to an untrained task.

For this task, stimuli were generated using MATLAB (Mathworks) and Psychtoolbox (Brainard et al., 1997) and were presented on a uniform grey background. They were presented at the two training locations and the matched sighted field location. This task has been described in detail elsewhere (Ajina et al., 2015, 2021); briefly, it involved indicating the interval in which a drifting, achromatic, Gabor stimulus (diameter=5°; sigma=0.8°; stimulus duration=500ms; spatial frequency=1c/°, temporal frequency=10Hz; viewing distance=42cm; uniform grey background with a luminance of 16.5cd/m²) of varying contrasts (1%, 5%, 10%, 50% and 100%) appeared (See Figure 9 for task details). After each trial, the participant also responded whether they were aware of the stimulus (yes or no). Since most stroke survivors only show above chance contrast detection ability in their blind field for high contrast stimuli (Ajina et al., 2015, 2021), the present experiments only report percent correct performance and awareness for high contrast stimuli (i.e., averaged across trials that involved 50% and 100% contrast stimuli). Participants were instructed to fixate on the central cross. Eye position was monitored throughout using an Eyelink 1000 eye tracker (SR Research Limited, Ontario, Canada).

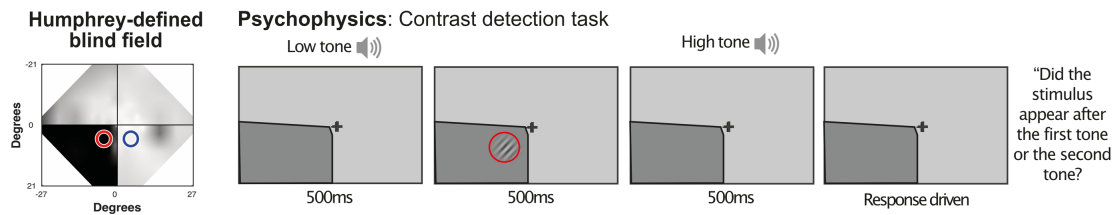


Figure 9. Schematic of contrast detection task. Humphrey Visual Field defined blind field (left) with schematic of moving contrast detection (right) task locations and presented. Humphrey Visual Fields: Grey-scale Humphrey-derived sensitivity (24-2 SITA FAST and 10-2 SITA Standard programmes) averaged across the two eyes for an example participant with quadrantanopia (left). Blind (red circle) and sighted (blue circle) field locations for the achromatic moving contrast stimulus in the behavioural task are indicated. Psychophysical task: The drifting achromatic diagonally oriented Gabor patch was presented in the Humphrey-defined blind field, while participants were asked to determine whether it appeared after the first tone or the second tone (2AFC). The experiment was repeated in the equivalent location of the sighted field (right).

2.5 MRI methods

All MRI data were acquired on a 3T Siemens Prisma (Siemens Healthcare AG, Erlangen, Germany) using a 64-channel head/neck coil at the Wellcome Centre for Integrative Neuroimaging (WIN). The scan session lasted 90 minutes and included the collection of a T1-weighted MRI scan, a motion localiser (fMRI), MRS spectroscopy in two voxels (hMT+ and sensorimotor cortex, SMC), fMRI for two tasks (Gabor and Speed), a field map, resting-state fMRI, and diffusion-weighted imaging (see Figure 10 for schematic of scan sequences). At the baseline and 6-month timepoints, MRI data acquisition was identical.

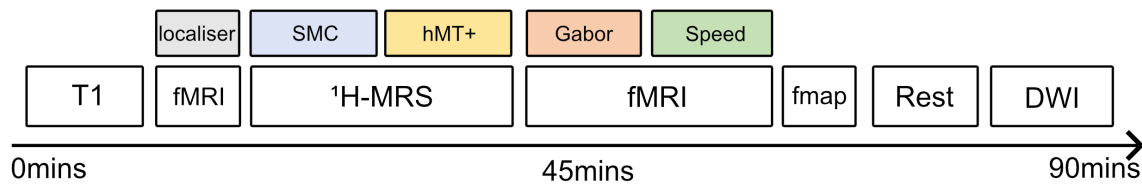


Figure 10. Schematic outlining the scanning procedure for each research visit. Scans acquired included T1-weighted images, single voxel MRS (in two voxels: hMT+ and SMC), fMRI (two tasks: Gabor and Speed), field map (fmap), resting state (rest) and diffusion-weighted imaging (DWI)

2.5.1 Structural

A high-resolution whole-head T1-weighted isotropic MPRAGE anatomical image (1x1x1 mm³, TR=1900 ms, TE=3.97 ms, field of view = 192 mm x 192 mm, flip angle = 8°) was collected for each participant at each timepoint. T1-weighted images were pre-processed using BET (Smith, 2002) to remove all non-brain tissue and were used primarily for registration and lesion identification (see below).

Regions of interest

Masks for all regions-of-interest (ROI) were created for each participant. Ipsilesional hMT+ masks were created using the intersection of the unthresholded motion localiser activity (see “Functional” section below for task details), unthresholded Jülich histological atlas hMT+ mask and MRS voxel volume. Contralesional hMT+ masks were created by taking the intersection of the motion localiser activity and Jülich histological atlas hMT+ mask. These masks were then thresholded to produce a mask between 1500

and 2000 mm³ guided by the volume of hMT+ in the human literature (Ajina et al., 2021; Kolster et al., 2010). Masks for additional visual ROIs (bilateral V1; ipsilesional dLGN; ipsilesional pulvinar) and control sensorimotor ROIs (ipsilesional ventral posterior lateral nucleus of the thalamus, VPL; primary somatosensory cortex, S1) were derived from the extended Human Connectome Project multimodal parcellation atlas (HCPex; (Huang et al., 2022)). Superior colliculus masks were drawn based on anatomy in standard space.

Lesion masks were manually delineated for each participant by 2-4 trained researchers. Researchers were instructed to define the lesion as the full area of damaged tissue (including areas that were damaged, abnormal, or absent). Lesion masks were then thresholded to include only voxels identified by at least two researchers. The lesion was then subtracted from ipsilesional V1 masks (or bilateral V1 mask for participant R003) using the FSL tool *fslmaths* and only intact portions of V1 were used for further analyses.

2.5.2 Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) can be used to measure the integrity of white matter tracts within the brain by measuring the diffusion of water molecules in different directions. In areas with few barriers (e.g., in cerebrospinal fluid), diffusion of water molecules occurs at the same rate in all directions, which is known as isotropic diffusion. In white matter tracts, however, water molecules can diffuse more freely along the length of the tract rather than perpendicular due to the physical barriers of myelin and cell membranes. This is known as anisotropic diffusion. The directionality of the diffusion of water molecules allows us to infer the tract orientation as well as the fibre microstructure. The anisotropy of the water molecules and the principal direction of movement are influenced by many factors such as fibre density, fibre diameter and myelination.

Using the diffusion tensor model (DTI), diffusion at each voxel can be described using a tensor or ellipsoid which allows us to estimate the average diffusion across all directions (known as mean diffusivity, or MD) and the directional dependence of the diffusion of water (known as fractional anisotropy, or FA). FA tells us about the level of anisotropy in each voxel in the brain and is generally used as a measure of tract integrity. The range of values are from 0 (complete isotropic diffusion) to 1 (diffusion along only one axis). FA is lowest in areas with high isotropic diffusion, for example in the ventricles, low in cortical grey matter (~ 0.2) and highest within white matter, although the values range from ~ 0.45 in subcortical white matter to ~ 0.8 in highly ordered white matter tracts such as the corpus collosum (Beaulieu, 2014). It is also modulated by local tissue microstructure, for example FA is higher with high axon packing and low axon diameter (Takahashi et al., 2002; Zatorre et al., 2012) and is lower in areas of damaged myelin

(Beaulieu & Allen, 1994; Gulani, 2001). It is also affected by crossing fibres. Reduction in FA can be caused by reduced neurite density or increased dispersion of neurite orientation (Zhang et al., 2012). This means that DTI measures of white matter cannot be attributed to specific changes in tissue microstructure.

In recent years, biophysical models of diffusion data have been developed that rely on assumptions about the underlying tissue (Kamiya et al., 2020). These models aim to provide a more specific characterisation of tissue microstructure. The neurite orientation dispersion and density imaging (NODDI; Zhang et al., 2012) characterises microstructural properties of the tissue, such as the density and orientation of neuronal fibres. This model distinguishes three microstructural environments (intra-cellular, extra-cellular and cerebrospinal fluid) that are modelled in a biologically informed manner. Axons and dendrites (intra-cellular) are modelled as zero radius cylinders, or “sticks”, reflecting space that is restricted by membrane neurites. The volume fraction of this compartment corresponds to neurite density, and the degree of deviation of the fibres’ direction reflect the orientation dispersion. The extracellular compartment represents space around neurites and encompasses everything except neurites and free water, including microglia, astrocytes, oligodendrocytes, neuronal cell bodies. Diffusion in this compartment is hindered by neurites, but it is not restricted and is therefore modelled using Gaussian anisotropic diffusion. The final cerebrospinal fluid compartment representing free water is modelled using isotropic Gaussian diffusion. The NODDI model then uses three scalar parameters to characterise microstructure: neurite density index (NDI), orientation dispersion index (ODI; 1 represents completely isotropic and 0 perfectly aligned straight fibres) and free water fraction (Kamiya et al., 2020). This

method enables estimates of neurite density and orientation dispersion to be calculated, disentangling two factors that are known to contribute to changes in FA.

Diffusion-weighted data were acquired for each subject at pre-training and post-training sessions using the UK Biobank sequence (Miller et al., 2016). A spin-echo echo-planar imaging sequence (EPI; TR = 3600ms, TE=92ms, voxel size =2x2x2mm) was acquired in the anterior-posterior encoding direction with 50 b=1000 s/mm² and 50 b=2000 s/mm² diffusion-weighted volumes acquired with 100 distinct diffusion-encoding directions and 3x multiband acquisition. Five volumes without diffusion weighting (b0 volumes; b-value = 0s/mm²) and three additional b0 volumes (b-value = 0s/mm²) with posterior-anterior encoding were also acquired to correct for image distortion.

2.5.3 Functional

Functional MRI allows us to measure brain activity during a specific task (task-related fMRI) or while at rest (resting-state fMRI). fMRI measures changes in blood oxygenation to give the blood oxygenation-level dependent (BOLD) response. BOLD-fMRI is based on the core assumption that changes in cerebral blood flow, cerebral blood volume and cerebral metabolic rate of oxygen consumption are related to neural activity.

Task-related fMRI

Task-related BOLD-fMRI is modelled using a canonical haemodynamic response function (HRF). This model involves an initial dip as oxygen in the area is depleted due to increased

activity followed by increased demand for oxygen due to the increased metabolic needs and increased blood flow to the area. These changes in blood flow are assumed to reflect changes in neural activity and are the basis for the BOLD contrast in fMRI. Research has shown that the BOLD signal is a reliable, although indirect, measure of neural activity (Logothetis et al., 2001).

Three fMRI experiments were used during this protocol: a motion localiser task, a moving Gabor task and a moving dot speed task. In all three experiments, stimuli were generated using MATLAB (2015b or 2018b) and Psychtoolbox (version 3.0.11) and presented on a screen at the back of the MRI scanner bore (viewing distance=127.5 cm). A multiband gradient echo sequence (Feinberg et al., 2010; Xu et al., 2013) was used to acquire fMRI data for the motion localiser (2.4 mm isotropic resolution, TR =1000 ms, TE=39.0 ms, flip angle=52°, multi-band factor=6) and fMRI tasks (2mm isotropic resolution, TR =1050 ms, TE=37.0 ms, flip angle =60°, multi-band factor=6).

The functional motion localiser task was used to identify visual motion area hMT+ during the scan to guide the MRS voxel placement in each participant. White dots were presented within two rectangles either side of fixation (width 10°, number of dots = 400, dot size =0.12°, dot speed=15°/s) on a uniform grey background, with a central red fixation cross. The block design (15s) presented 4 alternations of stationary and coherently moving blocks (15°/s per block, total run duration=120s). The direction of movement (45, 90, 135, 180, 225, 270°) varied randomly every ~2.5 seconds.

The moving contrast Gabor fMRI task has been described previously (Ajina et al., 2021; Ajina, Rees, et al., 2015), and involved passively viewing a drifting achromatic Gabor patch (same stimulus parameters as psychophysical task) presented at the same location in the blind field and the equivalent location in the sighted field in a block design.

In each 20s block, a single contrast (1%, 5%, 10%, 50%, 100%) or rest block was presented. During the contrast block, each stimulus was presented 8 times (2-s duration, interstimulus interval of 500ms). Each participant completed three runs with the total scan time being 11.09 minutes. Participants were required to maintain fixation on a static cross and press a button when the colour of the cross changed from black to red. Colour changes were random and lasted for 300ms (see Figure 11 for task details). In four cases, the visual field loss was in the far periphery. The fixation cross was then positioned eccentrically to enable the Gabor stimulus to be presented in the blind region, within the scanner's field of view. The speed fMRI task has also been described previously (Ajina et al, 2018), but was not included in this thesis.

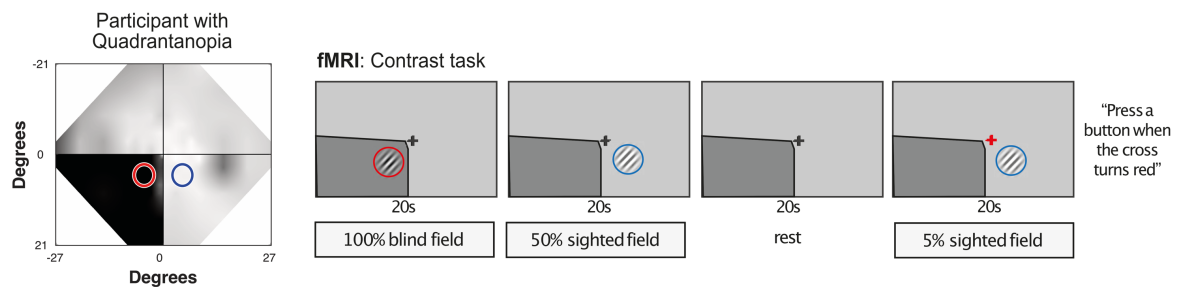


Figure 11. Schematics of the fMRI contrast Gabor task. Participants were required to fixate centrally and respond with a button press when the fixation cross turned from black to red. Throughout the experiment, moving achromatic contrast Gabor stimuli of varying contrasts were presented at the same intact and blind-field locations as during behavioural psychophysics task. A block design was used that alternated contrast levels and stimulus presentation with rest periods. Stimulus contrast alternated between 1, 5, 10, 50 and 100% contrast in two locations (blind and matched sighted field). Three runs of each contrast and location were completed for each participant.

Resting state fMRI

Resting-state fMRI is a technique to investigate functional activity that is not reliant on stimulus-evoked BOLD signals and consequently is not modelled using the canonical haemodynamic response function. Resting-state fMRI is used to investigate functional networks while the brain is at rest. It relies on the analysis of spontaneous BOLD signal changes across brain areas showing similar fluctuations in BOLD signal (Biswal et al., 1995), suggesting that the two areas are functionally connected.

Resting-state fMRI data were collected in each participant at the pre-training and post-training visits. Data were acquired on a 3T Siemens Prisma (Siemens Healthcare, Erlangen, Germany) using a 64-channel head/neck coil. 490 echo planar volumes were acquired (64x2.4mm slices, TE=39.00ms, TR=735ms, FOV=210×210mm, multi-band acceleration factor=8). During resting-state scanning, participants viewed a black screen with a red cross. This was displayed on an LCD BOLDscreen (Cambridge Research Systems) at the end of the scanner bore. The screen measured 518x324mm (resolution=1920x1200). The participant viewed the screen through a mirror mounted on the head coil. Optical correction was provided if needed. Participants were instructed to look at the cross and keep their eyes open for the duration of the scan. An eye-tracker was used to monitor the participants eyes throughout the scan to ensure they were awake.

2.5.4 Neurochemistry

Proton magnetic resonance spectroscopy (^1H -MRS, often referred to as MRS) allows the non-invasive quantification of *in vivo* metabolite concentrations in the brain. Unlike other neuroimaging methods, which rely on the magnetic signal from protons within water molecules, MRS uses the signal produced by protons bound to other brain metabolites to inform us about metabolic processes and brain chemistry. Protons within different chemical environments exhibit different resonant frequencies (referred to as chemical shift) which can be used to distinguish between different metabolites. To identify a molecule, the shift in the resonant frequency (measured in parts per million, or ppm) of a peak relative to a reference molecule (such as water) is measured.

The strength of the MR signal (which is proportional to the number of protons resonating at that frequency of chemical shift) can then be plotted as a function of its resonant frequency (see Figure 12 for example). This produces an MRS spectrum with a series of peaks each of which corresponds to a nucleus of interest bound in different molecules. In this spectrum, protons within different chemical environments appear at different positions, while those within the same environment appear at the same location. As molecules often contain multiple protons in different chemical environments, the spectral peaks are separated into distinct signals on the spectrum (Ip & Bridge, 2022). The area under the curve is then used to quantify the concentration of the molecule of interest relative to the reference. Most metabolites of interest resonant between 4.7 and 0 ppm (Ip & Bridge, 2022).

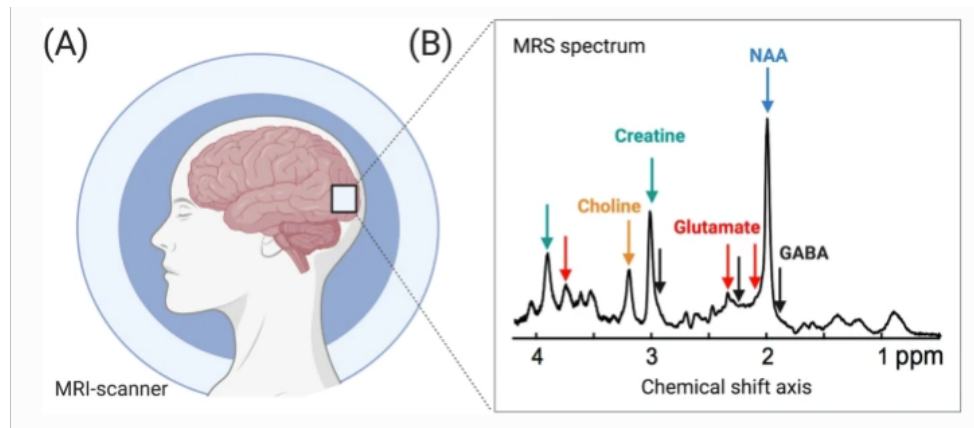


Figure 12. An example MRS (unedited) spectrum from a region of interest in the *visual cortex*. The y-axis represents the strength of the MR signal, while the x-axis reflects the resonant frequency of the molecules (ppm; Ip & Bridge, 2022).

As the peaks and frequencies of many neurochemicals are known, this allows them to be identified using a Fourier transform. The neurochemicals of interest have concentrations approximately 1000x smaller than water and therefore water suppression is generally used in MRS sequences. Despite the suppression of water, the peaks of the neurochemicals are still small and therefore large voxels ($\sim 8\text{cm}^3$), and long acquisition times (~ 8 minutes) are used to ensure adequate signal-to-noise ratio.

The compounds that are detectable using MRS include N-Acetylaspartate (NAA), Creatine (Cr) and phosphocreatine, Cholines, Glutamate, Glutamine, myo-Inositol, and γ -Amino-butyric acid (GABA). The main metabolites of interest in this thesis that are quantifiable using MRS are the major inhibitory and excitatory neurochemicals, GABA, and glutamate respectively. To measure GABA, spectral editing using techniques such as MEGA-PRESS are needed because the GABA peaks are spectrally overlapping with more abundant neurochemicals, such as creatine. This technique uses an editing pulse applied at 1.9ppm to change the signal of the GABA peak. It then subtracts the edit 'ON' from the

edit 'OFF' spectrum to remove all other spectral peaks and only retains the peaks affected by the editing pulses (Mullins et al., 2014). GABA measured in this way is still contaminated by macromolecules (Harris et al., 2015) and homocarnosine (Rothman et al., 1997) so it is generally referred to as GABA+ (3.0ppm). In addition, at lower field strengths (e.g., 3T) there is almost a complete overlap between the peaks for glutamate and glutamine, therefore a composite measure known as Glx (glutamate, glutamine, and glutathione at 3.75ppm) is used.

Single voxel MRS involves using three orthogonal slice-selective pulses to measure signals from a volume-of-interest (see Figure 12 for an example voxel placed in the occipital lobe) where the three slices intersect. Crusher field gradient pulses are then applied to remove the signals from all other regions. Single-voxel MRS is limited to a single acquisition in each region at one time. In this thesis, MRS data were acquired in two separate scans from 25x25x20 mm³ voxels in the damaged (ipsilesional) hemisphere. In the case with bilateral damage (R003), the voxels were placed in the hemisphere with the worse visual function (left hemisphere). The main voxel of interest was placed using the T1-weighted structural image in extrastriate visual motion area hMT+. It was positioned parallel to the lateral cortical surface (Schallmo et al., 2019) and then adjusted based on the activity from the functional motion localiser. The control sensorimotor (SMC) voxel was centred on the "hand knob" in the ipsilesional central sulcus and positioned parallel to the dorsolateral cortical surface (Yousry et al., 1997). Data acquisition from each voxel required around 20 minutes of scanning including setup.

GABA+ and Glx were measured from spectra acquired using a locally developed MEGA-PRESS sequence, derived from the CMRR spectroscopy package MEGA-PRESS

sequence (<https://www.cmrr.umn.edu/spectro>; Marjańska et al., 2013; Tremblay et al., 2014) with the following parameters: 320 transients (160 per editing condition); 2048 data points; 4000 Hz spectral width; TR=1500 ms; TE=68 ms; VAPOR and dual-band editing pulse water suppression; 22.3 ms editing pulse with a 53 Hz bandwidth, centred at 1.9 ppm (“on” condition) and at 7.5 ppm (“off” condition) in alternating transients; 16-step phase cycling. For each voxel, a single transient was also collected with water suppression disabled (TR=2500 ms). GRE shimming was used to ensure that vendor-reported full-width-at-half-maximum (FWHM) were below 20Hz, and that water-unsuppressed MRS-measured FWHM were <12Hz.

Chapter 3: GABA and glutamate in hMT+ link to individual differences in residual visual function pre-training after occipital stroke at baseline

3.1 Abstract

Damage to V1 following an occipital stroke causes loss of conscious vision in the contralateral hemifield. Yet, some patients retain the ability to detect moving visual stimuli within their blind field. The present study asked whether such individual differences in blind-field perception following loss of V1 could be explained by the concentration of neurotransmitters GABA and glutamate, or activity of the visual motion-processing area, hMT+.

Nineteen patients with chronic occipital stroke took part in this study. Proton magnetic resonance spectroscopy (MRS) was used to measure the concentration of neurotransmitters GABA and glutamate in hMT+ and a control sensorimotor voxel. Task-based fMRI was used to measure functional activity in hMT+. A 2-interval forced choice detection task using high-contrast, moving Gabor patches was used to measure of residual vision in the blind field. The relationships between residual vision in the blind field, and *in vivo* neurotransmitter concentrations, as well as visually evoked fMRI activity in hMT+ was then assessed.

MRS-derived GABA and glutamate concentrations in hMT+ (but not sensorimotor cortex) strongly predicted blind-field residual visual detection abilities. Performance was

inversely related to levels of both inhibitory and excitatory neurotransmitters in hMT+ but, surprisingly, did not correlate with visually evoked BOLD signal change in hMT+.

Levels of GABA and glutamate in hMT+ appear to provide superior information about motion detection capabilities inside perimetrically-defined blind fields compared to BOLD signal changes – in essence, serving as biomarkers for the quality of residual visual processing in the blind-field. Whether they also reflect a potential for successful rehabilitation of visual function remains to be determined.

3.2 Introduction

Damage to V1 due to a stroke, results in blindness in the contralateral visual hemifield. Nonetheless, it is well established that many patients with V1 damage show significant residual vision (also known as ‘blindsight’) within their blind fields, particularly for high luminance, moving stimuli (Cowey, 2010a). Although V1 is damaged, motion stimuli continue to specifically activate hMT+ (Ajina et al., 2015; Baseler et al., 1999; Ffytche et al., 1996; Morland et al., 2004; Papanikolaou et al., 2019; Zeki & Ffytche, 1998), an extrastriate cortical region specialised for processing visual motion (Britten et al., 1996; Newsome et al., 1985; Newsome & Park, 1988). This suggests that alternative visual pathways, that bypass V1 and provide direct input to key extrastriate visual areas such as hMT+, may remain intact. These V1-bypassing pathways are thought to underlie residual vision in the blind-field (Tamietto & Morrone, 2016). Understanding how hMT+ mediates residual processing would be beneficial for selecting future rehabilitation targets.

Over recent years it has become possible to non-invasively measure the neurochemistry of specific brain regions *in vivo* in addition to structure and function. Proton magnetic resonance spectroscopy (MRS) can be used to quantify neurochemicals in the brain, including inhibitory neurotransmitter γ -aminobutyric acid (GABA) and excitatory neurotransmitter, glutamate. GABA is involved in inhibiting the activity of nerve cells, while glutamate is known to be involved in neuronal signalling. MRS-derived measures of GABA often include macromolecular contamination, and therefore are referred to as GABA+, while measures of glutamate include glutamate, glutamine and glutathione and is therefore often referred to as Glx.

In stroke survivors with damage to the motor system, a reduction in the inhibitory neurotransmitter GABA+ has been related to increased plasticity and rehabilitation efficacy (Blicher, Near, Næss-Schmidt, Stagg, Johansen-Berg, Nielsen, Østergaard, & Ho, 2015; Ferreiro de Andrade & Conforto, 2018; Mooney et al., 2019). While little is known about the neurochemistry of the visual system following stroke, in the healthy visual system, decreased occipital GABA+ is related to improved performance on learning and plasticity tasks (Lunghi et al., 2015; Frangou, Correia and Kourtzi, 2018) and to increased occipital BOLD activity (Frangou, Correia and Kourtzi, 2018). Additionally, higher levels of Glx are related to higher neural activity in hMT+ and superior performance on a motion discrimination task (Schallmo et al., 2019). In stroke survivors with V1-damage, the presence of BOLD activity in hMT+ has been related to blindsight performance (Ajina, Rees, et al., 2015), and increased baseline BOLD signal change in both V1 (Barbot et al., 2021) and hMT+ (Ajina et al., 2021) appears to be predictive of visual rehabilitation success. Together these studies suggest that the activity and chemistry of hMT+ may be predictive of residual vision in stroke survivors with V1 damage. In the current study, MRS measures of inhibitory GABA+ and excitatory Glx, and task-related BOLD signal

change in ipsilesional hMT+ were related to measures of residual vision in the blind field. Moreover, GABA+ and Glx in ipsilesional control sensorimotor voxel, SMC, were also compared to residual vision.

Hypotheses

Hypothesis 1: Lower GABA+ in hMT+ (but not SMC) would be related to superior residual motion processing in the blind-field at baseline.

Hypothesis 2: Higher Glx in hMT+ (but not SMC) would be related to superior residual motion processing in the blind-field at baseline.

Hypothesis 3: Increased BOLD signal change in hMT+ would be related to superior residual motion processing in the blind-field at baseline.

3.3 Methods

3.3.1 Participants

Nineteen healthy stroke survivors with damage to V1 resulting in visual field deficits were included in this analysis (median=46 years, range=24-74 years, 6=Female). All participants had sustained damage in adulthood, at least six months prior to the study (median=30; range=6-297 months). To reduce effects on the MRS scans, participants were asked to refrain from drinking caffeine on the day and alcohol in the preceding 48 hours before the scan.

3.3.2 Psychophysical testing

A two-alternative forced choice psychophysical task was used to measure residual vision in the perimetrically-defined blind and sighted fields. This task has been described in detail in Chapter 2. In summary, this task involves indicating the time interval in which a drifting, achromatic, Gabor stimulus of varying contrasts (1%, 5%, 10%, 50% and 100%) appeared. As discussed in Chapter 2, percent correct performance for high contrast stimuli (i.e., averaged across trials that involved 50% and 100% contrast stimuli) was used because stroke survivors typically only show above chance performance for high contrast (Ajina et al., 2021; Ajina, Pestilli, et al., 2015). Participants were instructed to fixate on the central cross. Eye position was monitored throughout using an Eyelink 1000 eye tracker (SR Research Limited, Ontario, Canada).

3.3.3 Imaging acquisition

fMRI acquisition

A multiband gradient echo sequence was used to acquire fMRI data for the motion localiser and contrast fMRI task (see Chapter 2 for scan parameters). A high-resolution whole-head T1-weighted isotropic MPRAGE anatomical image was also collected for each participant.

Two fMRI tasks were used: (1) localise hMT+ for MRS placement (functional localiser task), and (2) determine BOLD signal change in hMT+ (contrast fMRI task). Stimuli were generated using MATLAB (2015b or 2018b) and Psychtoolbox (version 3.0.11) and presented on a screen at the back of the MRI scanner bore (viewing distance=127.5 cm).

The contrast fMRI task has been described previously (Ajina et al., 2021; Ajina, Rees, et al., 2015), and is described in detail in Chapter 2. In summary, participants viewed a drifting achromatic Gabor patch that varied in contrast in a block design. In each block, a single contrast (1%, 5%, 10%, 50%, or 100%) was presented at the same blind and sighted field locations as the psychophysical contrast detection task. Participants fixated on a central cross throughout the task and responded when the colour of the cross changed from black to red. Total acquisition time = 11:09 minutes.

A functional motion localiser task was used to identify area hMT+ during the scan to guide the MRS voxel placement. During this task, participants viewed alternating moving and stationary dots in a block design while fixating on a central red cross (see Chapter 2 for further details).

MRS acquisition

Single-voxel MRS data were acquired in two separate scans from 25x25x20 mm³ voxels in the damaged (ipsilesional) hemisphere. In the case with bilateral damage, the voxel was located in the hemisphere with the worse visual function (left hemisphere; see Chapter 2 for details of voxel positioning). Total acquisition time per voxel = 9:33 minutes. Data acquisition for both voxels required around 20 minutes of scanning including setup (e.g., voxel placement). As a result, it was not possible to also acquire data from the contralesional hemisphere or from any additional brain areas, given patient tolerance and timing constraints.

GABA+ and Glx were measured from spectra acquired using a locally developed MEGA-PRESS sequence, derived from the CMRR spectroscopy package (see Chapter 2 for

MEGA-PRESS sequence details). Figure 13 shows the average voxel position and spectra across participants.

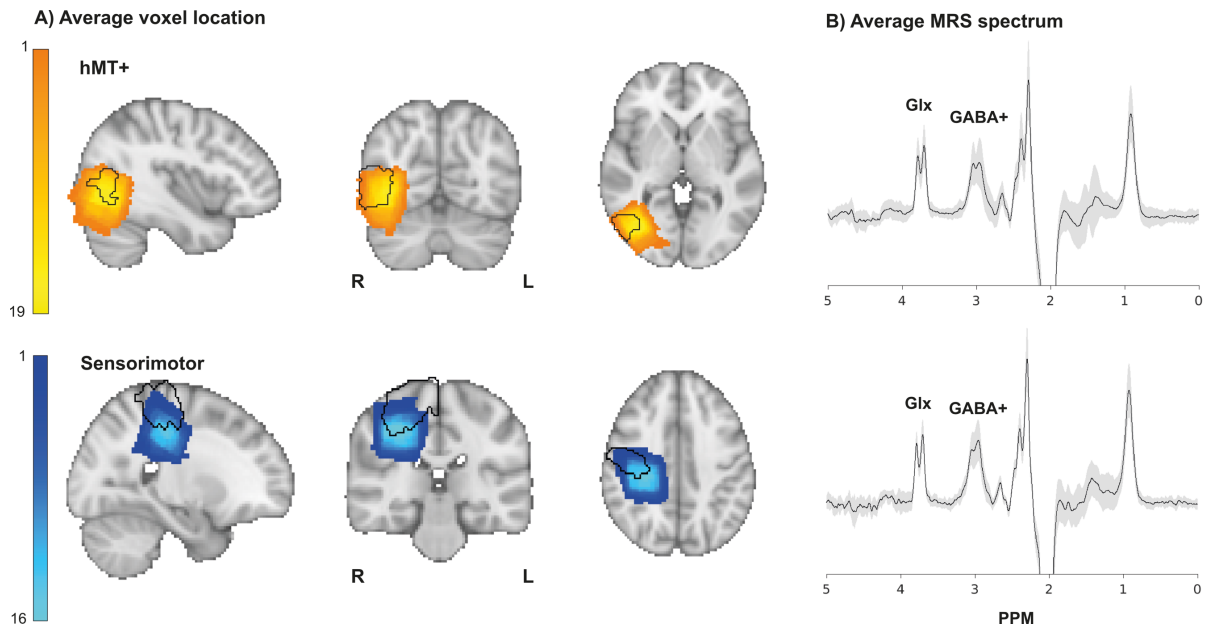


Figure 13. Average voxel placement and spectra for hMT+ and sensorimotor (SMC) voxels in the ipsilesional hemisphere. (A) Average placement for the visual motion area (hMT+; $n=19$) and sensorimotor cortex (SMC; $n=16$) MRS voxels. The MRS voxels of participants who had left hemisphere strokes were flipped so that all voxels are shown in the same hemisphere across participants (right). Yellow (hMT+, top) and blue (SMC, bottom) heat maps represent the group average voxel placement displayed on the MNI-152 standard brain. Black outlines represent Jülich histological atlas masks for hMT+/V5 and SMC. **(B)** Average spectra for the hMT+ (top; $n=19$) and SMC voxels (bottom; $n=16$). Black lines represent the average spectrum across all participants, with grey representing the standard deviation of the spectra.

In 12 participants, the lesion-affected zone (defined as damaged tissue and fluid-filled space resulting from the stroke) overlapped with the hMT+ voxel, occupying on average $5.68\% \pm 9.86\%$ (mean $\pm$ SD) of the voxel volume. In seven of these participants, the overlap was greater than 2.5%, with the largest overlap being 36.8% (see Figure 14 for average lesion location). During MRS acquisition participants watched a nature documentary to reduce boredom and sleepiness. Participants were instructed to keep their eyes open throughout, and this was monitored using the eye tracker.

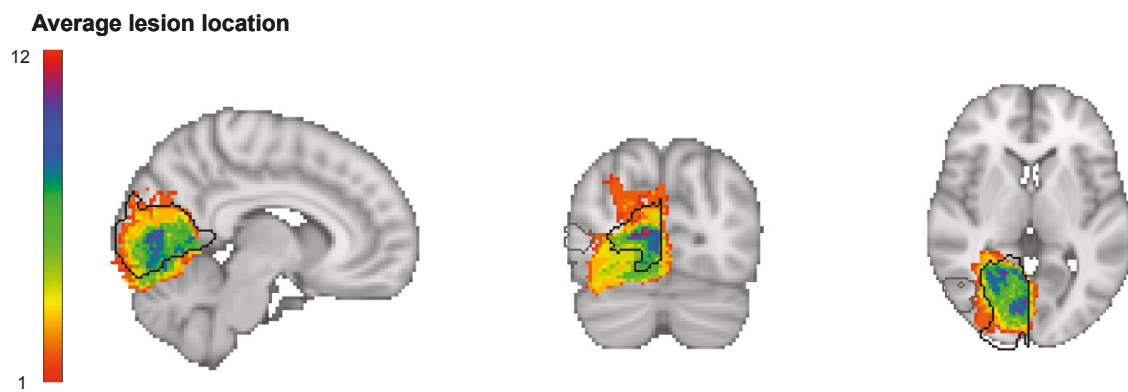


Figure 14. Average lesion location. Average lesion location ($N=19$; rainbow heatmap) standardised across patients to have the lesion in the right hemisphere displayed on the MNI-152 standard brain. Heatmap indicates that the main overlap of lesions across participants was centred on the anatomical location of V1, the calcarine sulcus. Jülich regions of interest of hMT+ (grey) and V1 (black) are indicated.

MRS data were excluded from further analyses if (1) Gannet failed to fit the data, (2) the neurochemical concentrations exceeded 3 S.D. from the mean, (3) the voxel was incorrectly positioned. Based on these criteria, all data were included in the hMT+ MRS analysis ($N=19$). Data from three participants were excluded ($N=16$) from the SMC MRS analysis due to processing failure in Gannet (R018), GABA+ or Glx data exceeding 3 S.D. from the mean (R010; R014) and incorrect voxel positioning in the contralesional hemisphere (R001).

3.3.4 Imaging analysis

fMRI analysis

Pre-processing and statistical analysis of the contrast fMRI task were carried out using FSL (version 6.0, FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>). The following steps were used: 1) brain extraction with BET (Smith, 2002), 2) motion correction with MCFLIRT (Jenkinson et al., 2002), 3) distortion correction using a field map 4) spatial smoothing using 5mm Gaussian kernel and 5) high pass temporal filtering (cut off 90%). Functional images were registered to structural images using FLIRT (Jenkinson & Smith, 2001; BBR method). To allow for easier comparison, structural and functional images from all left hemisphere strokes were flipped (*fslswapdim* tool in FSL) to simulate right hemisphere strokes (Ajina et al., 2021). Using FEAT (Woolrich et al., 2001) the visual contrasts (1%, 5%, 10%, 50% and 100%) were included as explanatory variables. However, as in the behavioural data, the contrast of interest was set to high contrast (50% and 100%) compared with rest for sighted and blind field presentation within the GLM model.

To ensure blind-field data were reliable, only participants with BOLD activity in the intact hemisphere for sighted-field stimulation were included. Data in one participant

was excluded from fMRI analysis on this basis (R017). In addition, data from two participants were not included due to an inability to present stimuli in their blind field, given the eccentricity of the vision loss (R001; R008). Thus 16 participants were included in the fMRI analyses.

Ipsilesional hMT+ masks were created for each participant using the intersection of the motion localiser activity, Jülich histological atlas hMT+ mask and MRS voxel volume (see Chapter 2 for details). The FSL *Featquery* tool was used to calculate BOLD percentage signal change within the composite hMT+ mask.

MRS analysis

MRS data from both voxels were analysed using Gannet 3.1, an open-source toolbox for analysis of edited MRS data (<http://www.gabamrs.com/>). Pre-processing included frequency and phase correction in the time domain, 3Hz exponential line broadening and zero-filled by a factor of 16. A five-parameter Gaussian model was used to fit the GABA peak between 2.19 and 3.55ppm. GABA and Glx peaks were quantified relative to total creatine (tCr). Creatine was calculated from the total creatine (tCr) integral of a two-Lorentzian model of creatine and choline metabolites in the OFF spectrum. Metabolite concentrations are given as a ratio to total creatine (referred to as GABA+:tCr and Glx:tCr).

Total creatine was used as a reference metabolite rather than water for several reasons, with the principal one being the overlap of the lesion-affected zone within the MRS voxel in some participants. To investigate the effects of the fluid in the lesion-affected zone, the correlation between the percentage overlap with the voxel and GABA+

and Glx referenced to both tCr and water (W) were measured. No relationship between GABA+:tCr ($r=-0.32$; $p=0.185$) or Glx:tCr ($r=-0.23$; $p=0.344$) and percentage overlap was found. However, when the two metabolites were referenced to water, the amount of overlap was significantly correlated with the ratios in both cases (GABA+:W – $r=-0.63$; $p=0.004$; Glx:W – $r=-0.57$; $p=0.010$). Therefore, water was not used as a reference signal in this analysis.

Voxels were reconstructed using FSL-MRS (Clarke et al., 2021) and proportions of grey matter, white matter and cerebral spinal fluid were calculated to determine the proportion of grey matter within each voxel.

MRS data quality

The output of Gannet was visually inspected for evidence of lipid contamination or poor water suppression. Fit error (under 15%; Cao et al., 2018; Song et al., 2020; Wenneberg et al., 2020) and full-width at half-maximum (FWHM; Chan et al., 2019; Harris et al., 2015; Kurcyus et al., 2018; Pitchaimuthu et al., 2017) were calculated and all values in both voxels were comparable to previous reported values (see Table 2).

Table 2. Data quality checks

<i>Voxel</i>	<i>Mean GABA fit error (sd)</i>	<i>Mean Glx fit error (sd)</i>	<i>Mean GABA FWHM (sd)</i>	<i>Mean Glx FWHM (sd)</i>
<i>hMT+</i>	6.98 (1.75)	6.06 (1.74)	22.37 (2.85)	15.15 (3.89)
<i>SMC</i>	7.35 (1.77)	6.92 (1.18)	22.65 (2.36)	13.28 (2.00)
<i>t-tests</i>	$t=0.62, p=0.539$	$t=1.72, p=0.094$	$t=0.32, p=0.748$	$t=-1.83, p=0.078$

3.4 Statistical analysis

Multiple linear regression and correlation analyses were carried out in R studio (version 4.1.2) to investigate the relationships between residual vision, fMRI in hMT+, and neurochemicals in hMT+ and SMC. Partial correlation analyses were carried out using the *ppcor* package. Multiple linear regression analyses, accounting for age, time since lesion and grey matter volume, and Bonferroni-Holm adjusted p-values were calculated using the *stats* package. Outliers of more than 3 standard deviations from the mean were removed from all analyses. Data were checked to ensure they met the assumptions of regression and correlation analyses.

3.5 Results

3.5.1 Descriptive statistics

Residual blind-field visual performance was measured in each participant using a two-alternative, forced-choice, psychophysical, contrast detection task, presented within their perimetry-defined blind field. The ability to detect a high-contrast (50% and 100%), moving, achromatic Gabor patch varied across participants (mean $\pm$ SD accuracy=77 $\pm$ 19.6% correct; range=30-100% correct). Twelve participants performed above chance (50% correct), determined using a statistical threshold of $p < 0.05$ and a cumulative binomial distribution (Ajina, Pestilli, et al., 2015). Percentage correct on this contrast detection task was used as the measure of residual vision for all subsequent analyses.

Single-voxel MRS was used to measure GABA+ and Glx (relative to total creatine; tCr) in two voxels: one in hMT+ and a control voxel in sensorimotor cortex (SMC). Figure 13A shows the average location of the two voxels across all participants. In each case the voxel was placed in the ipsilesional hemisphere but is illustrated in the right hemisphere in the image. The mean MRS spectra for each of the voxels across participants are shown in Figure 13B, with standard deviation indicated by the grey region. GABA+:tCr concentration ratios averaged 0.10 ± 0.02 in hMT+ and 0.14 ± 0.04 in SMC. Glx:tCr was 0.07 ± 0.02 in hMT+ and 0.08 ± 0.02 in SMC. These measures were then compared to percentage correct on the moving contrast detection task.

Neurochemistry

There was a significant negative relationship between GABA+ measured within the hMT+ voxel and behavioural contrast detection performance (Figure 15A: *adjusted $R^2=0.41$, $F(4,14)=4.08$; Holm-Bonferroni corrected $p=0.011$, $\beta=-0.61$). A comparable, negative relationship was also present between Glx and behavioural performance (Figure 15B: *adjusted $R^2=0.53$, $F(4,14)=6.13$; Holm-Bonferroni corrected $p<0.001$, $\beta=-0.68$). There was no significant relationship between contrast detection performance and either GABA+ (Figure 15D: *adjusted R^2 value=0.12; $F(4,11)=1.51$; $p=0.896$; $\beta=0.04$) or Glx concentrations (Figure 15E: *adjusted R^2 value=0.12; $F(4,11)=0.35$; $p=0.897$; $\beta=-0.04$) in the SMC voxel.****

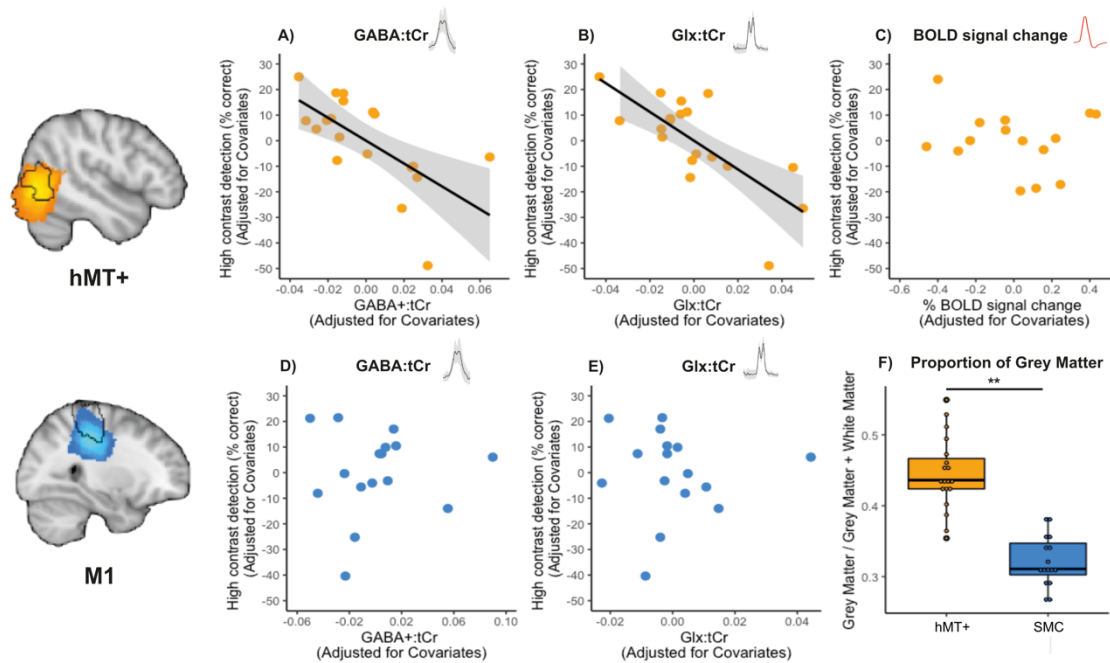


Figure 15. Plots showing the relationship between contrast detection in the blind field, neurochemicals, and BOLD signal change. (A-E) Partial regression plots showing the relationship between contrast detection in the blind field and **(A)** GABA+:tCr in ipsilesional hMT+, **(B)** Glx:tCr in ipsilesional hMT+, **(C)** percentage BOLD signal change in ipsilesional hMT+, **(D)** GABA+:tCr in ipsilesional sensorimotor voxel (SMC), **(E)** Glx:tCr in ipsilesional SMC. Lower concentration of GABA+:tCr and Glx:tCr was related to better performance on contrast detection within the blind field. There was no relationship between fMRI BOLD signal change in hMT+ and contrast detection within the blind field. There was also no significant relationship between residual vision in the blind field and concentrations of GABA+ or Glx in SMC. Significant regression lines are plotted in black, with standard errors in grey. **(F)** Box plot indicating proportion of grey matter in each voxel. The hMT+ voxel contained significantly more grey matter than the SMC voxel.

A significant, positive correlation between GABA+ and Glx concentrations in hMT+ (correlation coefficient=0.78, $p<0.001$, Spearman correlation), but not in the SMC voxel

(*correlation coefficient=0.20, $p=0.471$, Spearman correlation*) was found. There was a significant difference in the proportion of grey matter between the two voxels (*t-test; $t(31.87)=-8.38; p<.001$*). Patient age, months since lesion and proportion of grey matter volume within the voxel were therefore controlled in all analyses.

Control analyses

To ensure that controlling for covariates was not driving the results in these analyses, I also computed simple linear regressions between behaviour and GABA+ and Glx. These analyses indicate a significant relationship between behaviour and GABA+ (*adjusted $R^2=0.26$; $F(1,17)=7.45$; $p=0.01$*) and Glx (*adjusted $R^2=0.36$; $F(1,17)=11.17$; $p=0.004$*) in hMT+, even when not controlling for potential covariates.

As GABA+ and Glx were both negatively related to behaviour, it is possible that the relationship might be due to shared variance, rather than changing metabolite pools (Prisciandaro et al., 2023). One potential confounding variable is spectral quality. Line width is often used as a measure of signal quality as larger linewidths are generally associated with lower quality spectral acquisition (Harris et al., 2014). To ensure that relationships between behaviour and GABA+ and Glx were not driven by spectral quality, I explored the relationship between behaviour and tNAA linewidth, water linewidth, creatine linewidth and fit error. There was no significant correlation between behaviour and tNAA linewidth ($R=-0.34$, $p=0.153$), water linewidth ($R=-0.29$, $p=0.216$), creatine linewidth ($R=-0.22$; $p=0.355$), GABA+ fit error ($R=0.39$; $p=0.093$) or Glx fit error ($R=0.19$; $p=0.441$). Additionally, to further determine whether the associations between each metabolite and behaviour were driven by common variance, I modelled the relationship

between GABA and behaviour using a linear regression and then looked at the correlation between the residuals from this model and Glx. No significant correlation was found between the two ($R=-0.29$; $p=0.225$). To conclude, these control analyses confirmed the relationship between GABA+ and Glx and behaviour is not driven by these confounds.

fMRI activity

Percentage BOLD signal change in hMT+, measured while participants viewed a moving, achromatic, Gabor patch of high contrast in their perimetry-defined blind fields, was compared to rest periods. There was no significant relationship between visually induced BOLD signal changes during fMRI and 2-interval visual detection performance measured psychophysically in the blind-field (*Figure 15C: adjusted $R^2=0.41$; $F(3,11)=4.24$; Holm-Bonferroni corrected $p=0.577$, $\beta=-0.13$).*

3.6 Discussion

The present study shows – for the first time – that MRS-derived measures of neurochemistry in hMT+ are directly related to individual differences in the ability to detect drifting, high-contrast, Gabor patches inside perimetrically-defined blind fields in chronic stroke patients with V1 damage. Specifically, participants with lower levels of both GABA+ and Glx in hMT+ were better at performing this contrast detection task in their blind field than those with higher levels of both neurotransmitter classes. In contrast, there was no relationship between BOLD signal change in hMT+ when exposed to the same stimulus, and blind-field ability to detect it during psychophysical testing.

3.6.1 Lower levels of GABA+ and Glx link to greater residual vision in the blind field after occipital stroke

In chronic motor stroke survivors, GABA+ and Glx both decrease in M1 relative to controls, and greater decreases in GABA+ correlate with improvement due to rehabilitation (Blicher, Near, Næss-Schmidt, Stagg, Johansen-Berg, Nielsen, Østergaard, Ho, et al., 2015). Here, I posited that, as in the motor system (Grigoras & Stagg, 2021), decreased inhibitory activity in the residual visual system long after occipital stroke – especially in intact extrastriate visual areas - could play a significant role in supporting neuroplastic mechanisms. In the healthy visual system, Frangou et al. (2019) found that reduced GABA in the occipital lobe was related to the ability to detect targets in clutter, although they also found GABA to be increased when discriminating fine feature differences. The psychophysical task used to measure residual perceptual abilities in the blind-field required detection of a moving Gabor patch rather than fine feature discrimination. Given that the V1-damaged visual system appears to suffer from

increased levels of internal processing noise (Cavanaugh et al., 2015), a plausible hypothesis emerging from the present results is that GABAergic disinhibition in the motion-processing visual cortical area hMT+ may work to enhance target detection by increasing signal-to-noise. The current findings are also consistent with Lunghi et al. (2015) who showed that decreased GABA following short-term monocular deprivation correlated with greater plasticity of binocular vision in the healthy system.

Of note, it was surprising to find that reduced Glx levels in hMT+ were related to superior motion detection in the blind field, despite initially hypothesising the opposite effect. Research from the animal literature indicates that excitatory and inhibitory activity must remain in balance in the brain, with individual neurons receiving roughly equal levels of excitation and inhibition (Froemke, 2015). This mechanism is necessary to prevent the system from becoming overactive (high excitation; low inhibition) or overly suppressed (low excitation; high inhibition). Previous MRS studies in humans indicate that the balance between excitation and inhibition depends on the anatomical region being measured. For example, studies in humans have found a positive relationship between GABA+ and Glx in the medial parietal cortex (Steel et al., 2020) but not the early visual cortex (Rideaux, 2021). However, a subsequent study by the same authors using a large data set found a positive relationship between GABA+ and Glx in the early visual cortex but not in the prefrontal cortex (Rideaux et al., 2022). Moreover, evidence from the same anatomical location as the current study, extrastriate hMT+ (Song et al., 2021), indicates a positive relationship between GABA+ and Glx. Our results provide further evidence for the balance of GABA+ and Glx in the dorsal extrastriate region hMT+ of patients with occipital lobe stroke. It was originally hypothesised that increased plasticity after stroke, and superior residual vision, would be associated with lower GABA+. If this were the case, an equivalent reduction in Glx would be required to

maintain the inhibitory-excitatory balance. Although it is not possible to determine whether the differences observed are driven by GABA+ or Glx, I theorise that the higher levels of Glx and GABA+ in those who have the least residual vision may reflect reduced plastic potential of hMT+, driven by higher GABA+. However, future studies are needed to explore how these neurochemicals relate to training-induced recovery.

3.6.2 No relationship between BOLD response and residual vision

While prior studies investigating residual vision or blindsight reported activity in hMT+ when moving stimuli were passively presented in the blind-field (Ajina, Rees, et al., 2015; Baseler et al., 1999; Ffytche et al., 1996; Papanikolaou et al., 2019; Zeki & Ffytche, 1998), they did not relate the extent of activity to performance of a detection task with respect to these stimuli, as done here. Nonetheless, they provided evidence that the pathway between the dLGN and hMT+ likely carried relevant visual information (Ajina, Pestilli, et al., 2015; Ajina & Bridge, 2018; Schmid et al., 2010). This motivated our hypothesis that V1-independent residual vision for moving Gabor patches might be linked to increased BOLD signal in hMT+. However, no such relationship was found in the present study.

BOLD signal changes are thought to indirectly reflect changes in neural activity through neurovascular coupling; however, the relationship between neural activity and the haemodynamic response depends on a combination of cerebral blood flow, blood oxygenation levels and blood volume, some of which may be abnormal in stroke survivors. In strokes affecting the motor system, the BOLD signal is delayed and of lower amplitude in the affected and unaffected sensorimotor cortex (Pineiro et al., 2002). Furthermore, multimodal imaging studies in motor stroke survivors have shown the presence of neuronal responses measured with magnetoencephalography (Rossini et al., 2004) and transcranial magnetic stimulation (Binkofski & Seitz, 2004) even in the

absence of a BOLD response. The lack of relationship between motion detection and BOLD signal evoked by passive exposure of a motion stimulus while performing an attentional task at fixation in the current study may therefore not reflect a lack of neuronal activity in hMT+ in stroke survivors with V1 damage.

Alternatively, it is possible that this lack of relationship between BOLD signal change and behaviour is related to a lack of signal to noise in the fMRI signal. The Gabor task involved passively viewing moving achromatic Gabor patches with varying contrasts. Although participants completed three runs of each contrast, only the high contrast (50% and 100%) were included in this analysis. It is possible that due to the relatively short duration of stimulus presentation (60s total per contrast), and the noisy nature of fMRI data acquisition, sufficient signal to noise was not achieved. To increase signal to noise, future studies could use only high contrast stimuli and collect a larger number of runs.

While there was no relationship between performance and BOLD activity in this and previous studies, recent work found that increased baseline BOLD activity in hMT+ (Ajina et al., 2021) and perilesional V1 (Barbot et al., 2021), and BOLD resting-state connectivity between the anterior precuneus and the occipital pole network (Halbertsma et al., 2020) correlate with the extent of improvement following rehabilitation. This suggests that the relationship between the BOLD signal and residual vision is likely to be complex.

3.6.3 Limitations

The extensive time required to setup and acquire MRS data from each voxel (~20mins) meant that it was not possible to collect MRS data from more than two voxels. While it may have been beneficial to also collect data from contralesional hMT+, there is a known interhemispheric interaction between hMT+ after damage to V1 (Silvanto et al., 2007) meaning it would not be a 'pure' control structure.

A second limitation is that, because the data were collected during the baseline session of a rehabilitation study, there is no control group with normal visual function. Thus, while relationships between neurochemical concentrations and residual visual detection in the blind-field can be investigated, it remains to be determined whether there is a change in concentration as a result of the occipital stroke itself. This is compounded by the lack of any normative data for neurochemical concentrations in hMT+ and the variability in concentrations across different brain regions, individuals, or time.

Although MRS is a valuable technique that allows us to quantify measurements of neurochemicals *in vivo*, there are several limitations of the technique that must be considered when interpreting the relationship between neurochemicals and behaviour. Firstly, MRS measures total concentration of each neurochemical within a defined area of cortex (~8cm³) averaged across the duration of the scan (~8 minutes). At these spatial and temporal scales, it is not possible to obtain a direct measure of synaptic activity, nor to determine where within the voxel the neurochemical concentration may vary. Moreover, using GABA-editing MEGA-PRESS sequences in a 3T scanner it is not possible to separate the resonances of glutamate and glutamine (resulting in the combined measure of Glx) and the GABA signal is contaminated by macromolecules (Harris et al.,

2015) and homocarnosine (Rothman et al., 1997). This means that MRS derived quantifications of GABA and glutamate may be driven by these alternative signals. It is possible that acquiring spectra at higher fields to separate glutamate and glutamine, or using macromolecular suppression to reduce contamination of GABA, could produce different results.

Additionally, MRS-derived measures of GABA and glutamate are usually quantified as a ratio relative to another neurochemical (e.g., creatine) or endogenous reference such as water. The specific reference used varies across studies, with creatine, NAA or an unsuppressed water signal commonly used. In the current study I referenced GABA and glutamate to creatine, a commonly used method in MRS studies (Blicher, Near, Næss-Schmidt, Stagg, Johansen-Berg, Nielsen, Østergaard, Ho, et al., 2015; Chen et al., 2020; Glodzik-Sobanska et al., 2006). Creatine is an organic compound found in high concentration in the brain, believed to have a role in energy storage, high-energy phosphate shuttle, osmoregulation, and neurotransmission (Rackayova et al., 2017). While creatine is not a reliable reference for MRS in acute stroke (Maniega et al., 2008), it has been used for most MRS studies in chronic stroke patients (Blicher, Near, Næss-Schmidt, Stagg, Johansen-Berg, Nielsen, Østergaard, Ho, et al., 2015; Chen et al., 2020; Cirillo et al., 2020; Głodzik-Sobańska et al., 2004; Glodzik-Sobanska et al., 2006). The advantages of referencing to creatine are that it largely removes the need to control for CSF (Near et al., 2021) and tissue composition, while also controlling for variation due to instrumentation as the reference metabolite experienced the same acquisition environment. Importantly, in the current study, the GABA+ and Glx signals referenced to water were significantly correlated with the extent of overlap between the stroke-induced fluid-filled zone and the MRS voxel. This was not the case when they were referenced to creatine, suggesting that water did not provide a suitable reference. This

analysis does not, however, guard against the possibility of creatine also changing differently to GABA/Glx in lesioned tissue.

3.6.4 Conclusions

In conclusion, the current study is the first to explore neurochemistry in the visual system of chronic stroke survivors with visual loss. It shows that lower levels of GABA+ and Glx in the motion-selective extrastriate region hMT+ are linked to better residual visual detection performance in the blind field. Despite the lack of normative data, the presence of this significant relationship suggests that the neurochemistry of hMT+ is altered to different degrees in different patients with V1 damage. Importantly, neurochemistry in hMT+ may provide useful information about neural functioning that are not captured by BOLD signal change. It may thus serve as a biomarker for enhanced visual processing abilities inside the blind-field, which in turn, may reflect an increased capacity for neurorehabilitation.

Chapter 4: Residual vision after V1 damage is related to functional connectivity between hMT+ and ventral visual areas

4.1 Abstract

In the previous chapter, I showed that that reduced GABA and glutamate were linked to superior residual vision in the blind field of stroke survivors with V1 damage. However, there was no significant relationship between residual vision and BOLD signal change in ipsilesional motion area hMT+. Here, I aimed to understand whether resting-state functional connectivity between ipsilesional hMT+ and the rest of the brain is predictive of residual vision in the blind field.

Functional connectivity was assessed by correlating the time-series of the BOLD signal among brain regions. Two analyses were used to investigate this: (1) a whole-brain approach to determine brain areas that were functionally connected to the region of interest (ipsilesional hMT+; contralesional hMT+) and were related to residual vision, GABA in ipsilesional hMT, or glutamate in ipsilesional hMT+, (2) a region-of-interest based analysis, in which I assessed the functional connectivity between ipsilesional hMT+ and specific regions-of-interest (ipsilesional dLGN, ipsilesional superior colliculus; ipsilesional inferior pulvinar, contralesional hMT+, bilateral V1) and related the strength of these connections to residual visual ability.

In the whole-brain analysis, better residual vision was related to lower functional connectivity between both ipsilesional and contralesional hMT+ and contralesional

extrastriate ventral visual cortex. Moreover, prior to stringent statistical correction for multiple comparisons, higher functional connectivity between ipsilesional hMT+ and ipsilesional early visual areas was also predictive of residual vision. Surprisingly, residual vision was not related to connectivity between any visual regions-of-interest implicated in previous blindsight research. Taken together, these findings suggest that connectivity between the damaged and undamaged hemisphere may negatively impact residual vision, while connectivity within the damaged hemisphere may facilitate it. Future studies should investigate whether downregulation of activity in the undamaged hemisphere (for example, using brain stimulation) might aid in rehabilitation of visual loss after V1 damage.

4.2 Introduction

Previous brain imaging studies in stroke survivors with visual loss show activity in hMT+ during blind field stimulation (Ajina, Rees, et al., 2015; Baseler et al., 1999; Ffytche et al., 1996; Morland et al., 2004; S. Zeki & Ffytche, 1998), implicating the functioning of hMT+ in residual vision. The importance of hMT+ in residual visual processing was further supported by evidence in the previous chapter of a strong relationship between inhibitory GABA and excitatory glutamate in ipsilesional hMT+ and residual vision. It is therefore surprising that no relationship between task-related BOLD signal change in hMT+ and residual vision was found in Chapter 3.

The precise neural pathways that support residual vision remain to be determined, and it is likely that this vision relies on more than one neural mechanism. Research in humans (Ajina, Pestilli, et al., 2015; Ajina & Bridge, 2018; Bridge et al., 2010)

and animals (Schmid et al., 2010; Yu et al., 2018) suggests the V1-bypassing extrageniculostriate pathway between dLGN and hMT+ in the damaged hemisphere support residual blindsight capabilities. Moreover, blindsight patient G.Y. shows strong inter-hemispheric connections between hMT+ bilaterally (Bridge et al., 2008; Silvanto et al., 2007). Alongside this, other V1-bypassing pathways (superior colliculus-hMT+ and pulvinar-hMT+) and spared perilesional V1 cortex (Morland et al., 2004; Papanikolaou et al., 2014) have also been implicated in residual vision.

In this study, I investigated whether task-free resting-state functional connectivity may underlie residual vision in the blind field after V1-stroke. Resting-state fMRI is a technique to explore functional activity that is not reliant on evoked BOLD signals or modelled using the canonical haemodynamic response function. Resting state fMRI is used to investigate functional networks while the brain is 'at rest'. It relies on the analysis of spontaneous BOLD signal changes with functionally similar cortical areas showing similar fluctuations (Biswal et al., 1995), suggesting that the two cortical areas are functionally connected. Previous studies have found a relationship between blindsight and functional connectivity between dLGN and hMT+ (Ajina & Bridge, 2018) and hMT+ bilaterally (Bridge et al., 2008; Silvanto et al., 2007). Moreover, studies in the motor system have found that inhibitory GABA modulates resting-state functional connectivity (Sampaio-Baptista et al., 2015; Stagg et al., 2014). Based on these previous studies, I hypothesised that functional connectivity between ipsilesional dLGN and ipsilesional hMT+ would be related to residual vision, and this connectivity may be modulated by neurochemistry in hMT+.

Hypotheses

Hypothesis 1: Increased resting-state functional connectivity between ipsilesional dLGN and ipsilesional hMT+ will be related to residual vision.

Hypothesis 2: Increased resting-state functional connectivity between ipsilesional dLGN and ipsilesional hMT+ will be related to MRS measures of GABA+ and Glx in ipsilesional hMT+.

4.3 Methods

4.3.1 Participants

Twenty-one healthy stroke survivors with damage to V1 resulting in visual field deficits were included in this study (median=47 years, range=24-74 years, 6=Female). An additional three participants (out of 24 participants total) were excluded: two as no MRI scan was performed (R016; R021) and one because resting state fMRI data were not acquired (R022). All participants were at least 6-months post-stroke (chronic phase) with the median being 30 months post-stroke (range=6-297 months). All participants were enrolled in a rehabilitation study and only the baseline data, acquired before training, was analysed here.

4.3.2 Psychophysical testing

A two-alternative forced choice (2AFC) psychophysical moving contrast detection task (see Chapter 2 for task details), presented fully within the perimetry-defined blind field, was used to measure each participant's residual vision.

4.3.3 Imaging acquisition

MRS acquisition

The single-voxel MRS data described in the Chapter 3 were also used here (see Chapter 2 and Chapter 3 methods section for more details). In summary, MRS measurements of GABA+ and Glx relative to total creatine (tCr) were acquired in ipsilesional voxels (25x25x20 mm³) placed over hMT+ and SMC. Total acquisition time per voxel = 9:33 minutes. Data from all participants were included for the hMT+ voxel, while data from three participants were removed for the SMC voxel due to processing failure in Gannet (R018), GABA+ or Glx data exceeding 3SD from the mean (R010) and incorrect voxel positioning in the contralesional hemisphere (R001). To reduce boredom and tiredness, participants watched a nature documentary during MRS acquisition. Participants were instructed to keep their eyes open and watch the movie. Participants eyes were monitored using an Eyelink 1000 eye tracker (SR Research Ltd) throughout the scan to ensure they were awake.

Resting-state acquisition

Resting-state fMRI data were acquired using the sequences outlined in Chapter 2. Total time of acquisition = 6.10 mins. During resting-state scanning, participants viewed a black screen with a red cross. This was displayed on an LCD BOLDscreen (Cambridge Research Systems) at the end of the scanner bore. The screen measured 518x324mm (resolution=1920x1200). The participant viewed the screen through a mirror mounted on the head coil. Optical correction was provided if needed. Participants were instructed to look at the cross and keep their eyes open for the duration of the scan. An eye tracker was used to monitor the participants' eyes throughout the scan to ensure they were awake.

4.4. Analysis

4.4.1 Behavioural analysis

As has been previously described in Chapter 3, performance on a moving contrast detection task was used as a measure of residual vision. Percent correct for 50% and 100% contrast were averaged together to provide an individual score of residual vision for each participant.

4.4.2 MRS analysis

As described in Chapter 3, MRS data were analysed using Gannet 3.1 (<http://www.gabamrs.com/>; see Chapter 3 for pre-processing details). Metabolite concentrations are given as a ratio to total creatine (referred to as GABA+:tCr and Glx:tCr).

4.4.3 Functional connectivity analyses

Pre-processing

The resting state data was pre-processed using FSL (Jenkinson et al., 2012; Smith et al., 2004). Independent components analysis was implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components; Beckmann & Smith, 2004). The following pre-processing steps were included: motion correction using MCFLIRT, brain extraction using BET, no spatial smoothing, high-pass filtering (100s). fMRI scans were corrected for magnetic field inhomogeneities using a b0 fieldmap.

Functional images were registered to structural images using FLIRT (BBR method; Jenkinson et al., 2002; Jenkinson & Smith, 2001) and from structural space to a standard MNI (2mm) brain using FNIRT nonlinear registration with a warp resolution of 10mm and resampling resolution of 4mm (Andersson et al., 2007a, 2007b). All MRI data from left hemisphere strokes (N=9) were flipped across the midline so that all analyses were aligned in the right hemisphere across participants.

Regions-of-interest

Masks for all regions-of-interest (ROI) were created for each participant (see ROIs in standard space in Figure 16). Individualised ipsilesional and contralesional hMT+ masks were created for each participant using the spatial conjunction of motion localiser activity, the MRS voxel (only for ipsilesional hMT+) and the Jülich histological atlas, as described in Chapter 2. Masks for visual ROIs (ipsi- and contralesional V1; ipsilesional dLGN; ipsilesional pulvinar) and control sensorimotor ROIs (ipsilesional ventral posterior lateral nucleus of the thalamus (VPL); primary somatosensory cortex, S1) were derived from the extended Human Connectome Project multimodal parcellation atlas (HCPex; Huang et al., 2022).

Lesion masks were manually delineated for each participant (details in Chapter 2). The lesion was then subtracted from ipsilesional V1 masks (or bilateral V1 mask for participant R003) using the FSL tool *fslmaths* and only intact portions of V1 were retained for further functional analyses.

Superior colliculus masks were drawn based on anatomy in standard space. All ROI masks were then transformed into functional space using FLIRT. The functional time-

series within each ROI mask were then extracted from each individual's pre-processed resting state data using the FSL tool *fslmeants*.

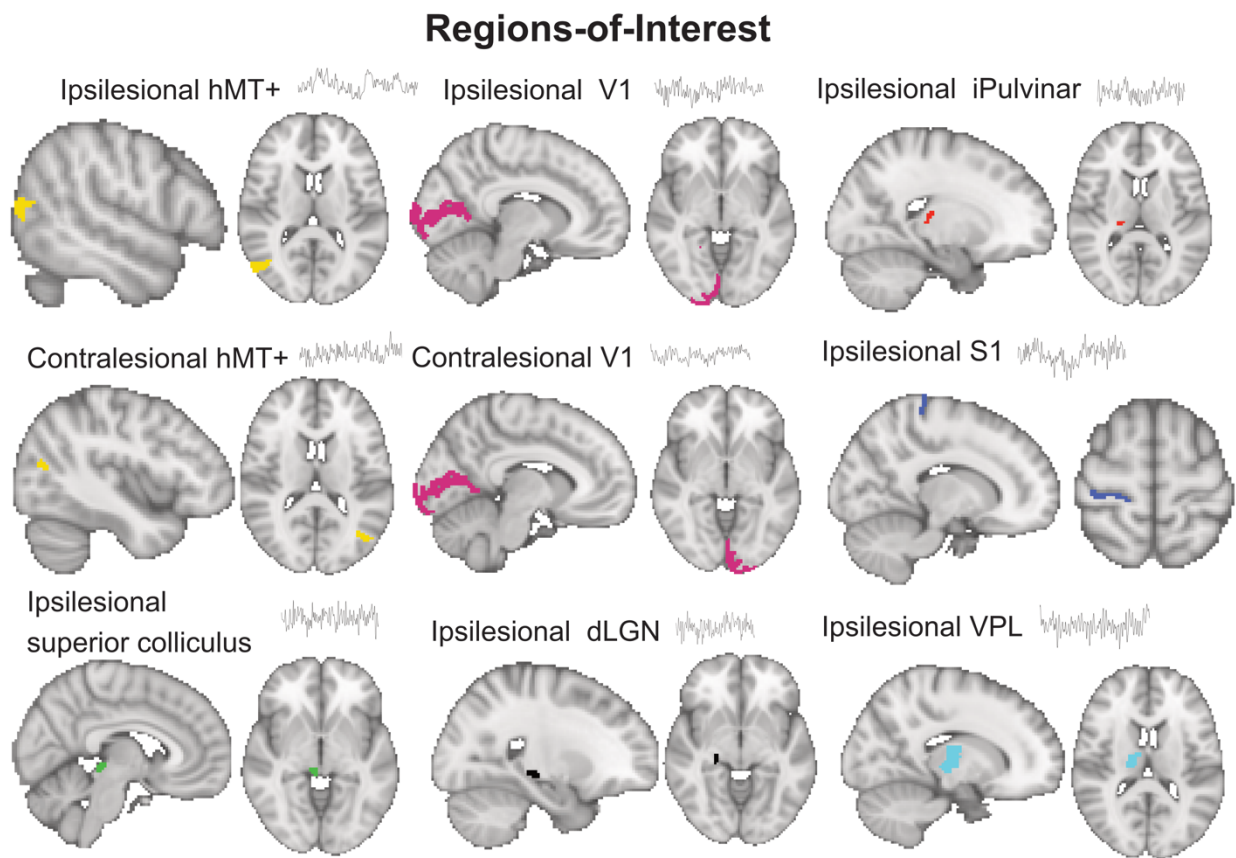


Figure 16. *The regions-of-interest used for the connectivity analyses overlaid on the MNI standard brain. Visual ROIs (yellow=Bilateral hMT+; green=superior colliculus; pink=Bilateral V1; black=dLGN; red=inferior pulvinar) and control sensorimotor ROIs are presented (dark blue=S1; light blue=VPL). Example resting state time-series within each ROI from a single participant (R001) are also shown.*

Whole-brain analysis

A whole-brain analysis was used to measure voxels in the brain where the timeseries of BOLD signal was significantly correlated with the timeseries from two regions-of-interest (ipsilesional hMT+ and contralesional hMT+). The timeseries from each participant's ROI was used as a regressor in individual-level FEAT analyses to define all areas of the brain showing correlated patterns of activity. The resulting individual-level maps indicating correlated activity with the region-of-interest were then entered into three group-level FEAT analyses with quantifications of demeaned residual vision, GABA+ and Glx as regressors of interest. These analyses also controlled for age, time-since-lesion, and amount of grey matter within the MRS voxel as covariates of no interest.

Region-of-interest analysis

In a separate analysis, correlation coefficients between pairs of selected ROIs were calculated. Correlation coefficients were then transformed using Fisher's R to Z transformation. These correlation coefficients were then compared with measures of residual vision for each participant.

4.5 Statistical analysis

All statistics for the whole-brain analysis were carried out in FSL using FEAT (Woolrich et al., 2001, 2004). Statistical tests for the seed-based analysis were carried out in R studio (R version 4.1.2). Correlation analyses were carried out using the *stats* package, whilst conversions of R correlations to Z scores was carried out using the *FisherZ* tool in the R package *DescTools*.

4.6 Results

4.6.1 Descriptive statistics

Participants showed a range of preserved visual abilities on the 2AFC contrast detection task in the blind field, with average performance of 78.57% correct (sd=19.31% correct; range=35-100% correct). As described in Chapter 3, percentage correct on this contrast detection task was used as the measure of residual vision and was then compared to functional connectivity. Quantifications of GABA+ and Glx also varied across participants in hMT+ (GABA+: mean= 0.1, sd=0.03; Glx: mean=0.07, sd=0.02) and SMC (GABA+: mean= 0.14, sd=0.04; Glx: mean=0.08, sd=0.02).

4.6.2 Resting state whole brain analysis

An exploratory approach was used to investigate the areas in the brain where temporal fluctuations in BOLD signal most closely matched the time-series of activity in specific regions-of-interest (ipsilesional hMT+, contralesional hMT+; see Figure 17 for mean activity across ROIs). These connectivity maps were then further analysed to determine whether these connections could be explained by differences in residual vision, GABA+ or Glx.

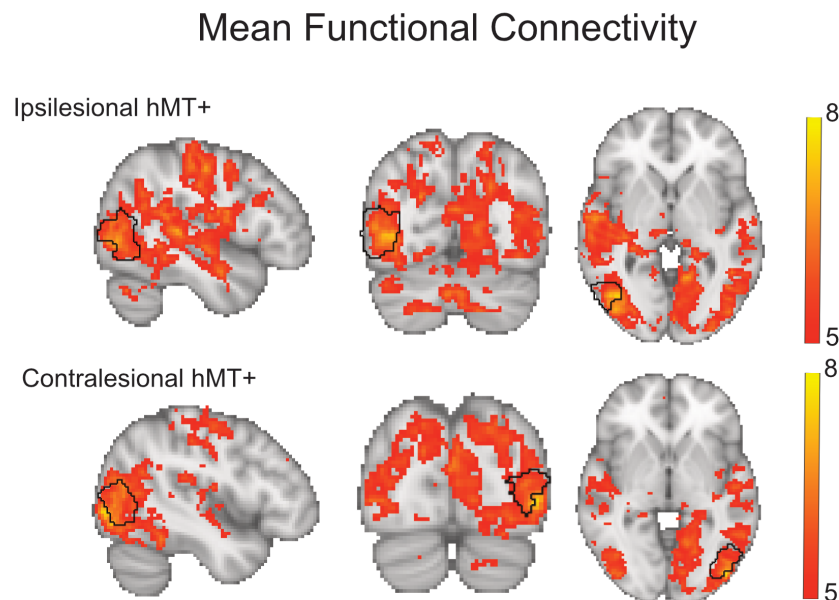


Figure 17. Mean functional connectivity of ipsilesional hMT+ and contralesional hMT+ with the rest of the brain. Mean connectivity between ipsilesional hMT+ (upper) and contralesional hMT+ (lower) with the rest of the brain overlaid on a standard MNI brain (2mm). Seed regions-of-interest are indicated with black outlines. Bilateral hMT+ masks were extracted from the Jülich histological atlas. Colour bar shows $z > 5$ (red colour bar). Connectivity maps indicate regions in the brain that are strongly correlated with the region-of-interest.

Residual Vision

Superior residual vision was predicted by lower functional connectivity between ipsilesional hMT+ and extrastriate ventral visual cortex in the intact hemisphere (*Figure 18; $p=0.033$; corresponding to ventral V2, V3 and V4*). Furthermore, superior residual vision was also predicted by lower connectivity between contralesional hMT+ and the same regions in the intact hemisphere (*Figure 18; $p=0.003$*).

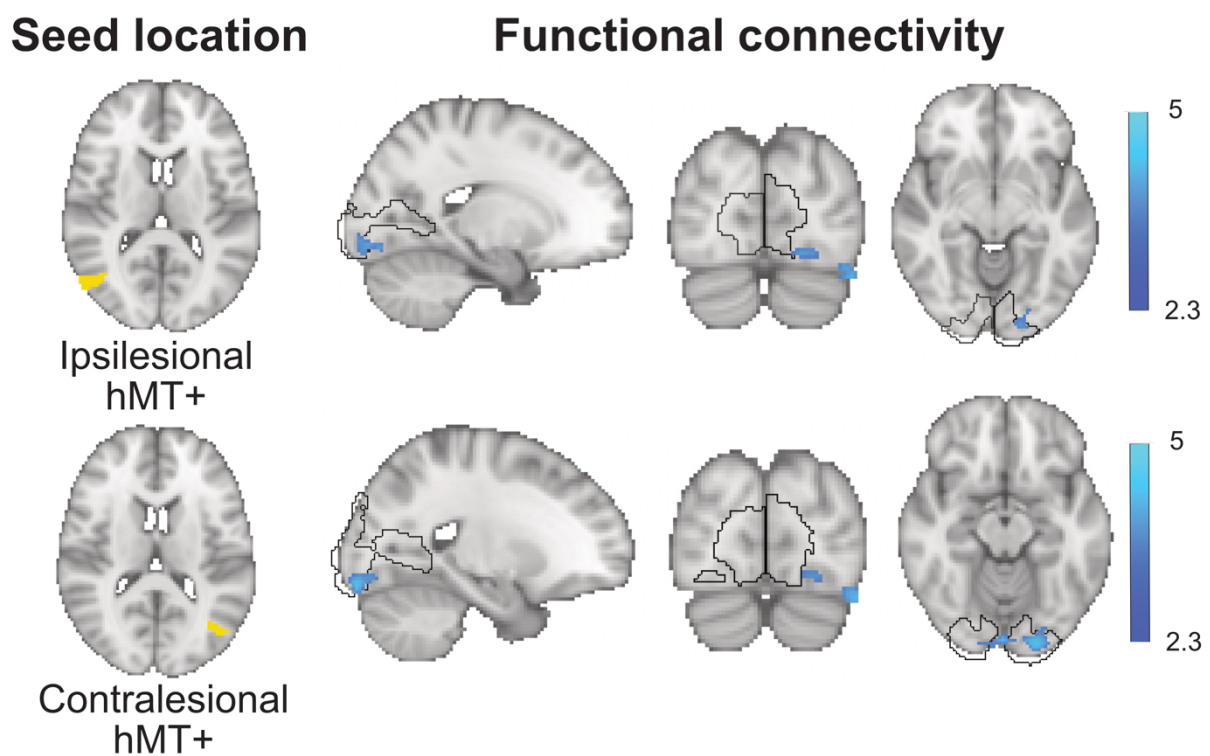


Figure 18. Negative correlation between whole-brain resting state connectivity and residual vision. Whole-brain connectivity between ipsilesional hMT+ (top) and contralesional hMT+ (bottom) shows areas where functional connectivity negatively correlated with residual visual processing in the blind field viewed on a standard MNI brain (2mm). Black outlines indicate V1 from the Jülich histological atlas. Connectivity maps were corrected for multiple comparisons using cluster-based correction with the z threshold set at 2.3 (blue colour bar) and a cluster significance threshold of $p=0.05$.

There was also a relationship between increased functional connectivity between both ipsilesional and contralesional hMT+, and ipsilesional visual areas, including V1 and dorsal V2 (see Figure 19) and superior residual vision. This suggests that ipsilesional intact early visual areas may support residual visual processing in the blind field. However, the extent of the brain regions showing this relationship was not sufficient to pass the correction using GRF theory so should be interpreted with caution.

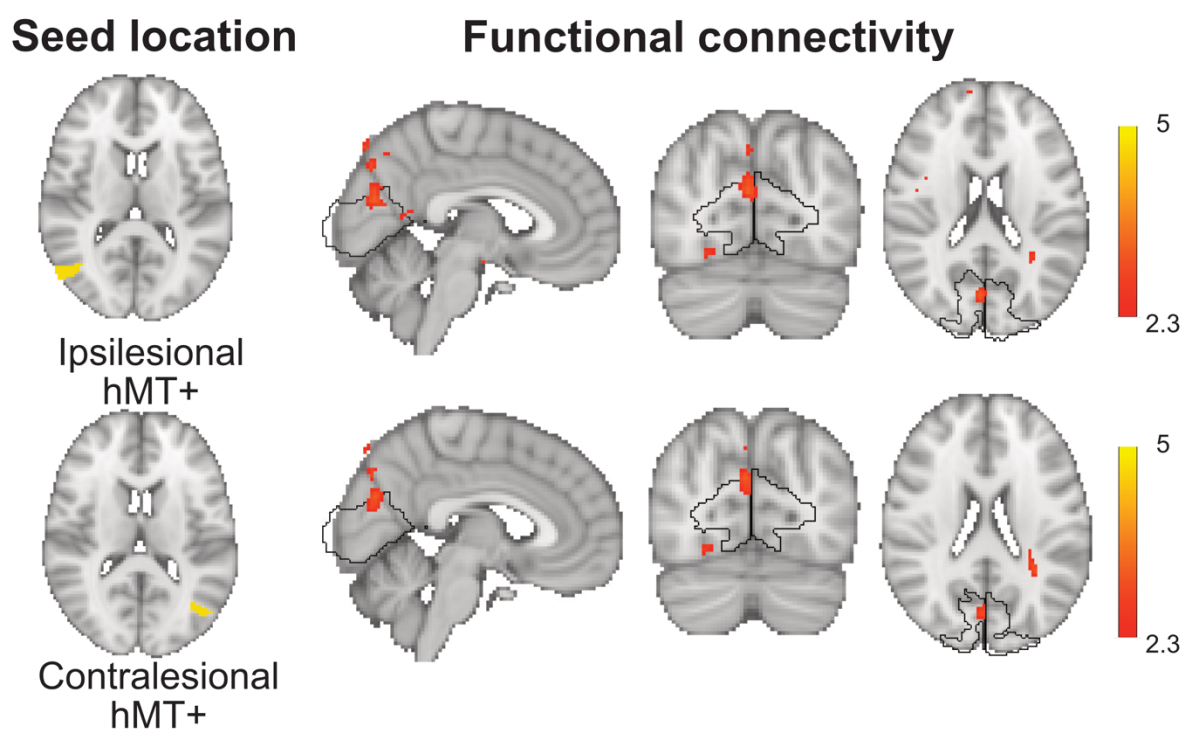


Figure 19. Positive correlation between whole-brain resting state connectivity and residual vision. Whole-brain resting state connectivity of the ipsilesional hMT+ (upper) and contralesional hMT+ (lower) shows areas where functional connectivity positively correlates with residual visual processing in the blind field viewed on a standard MNI brain (2mm). Black outlines indicate V1 from the Jülich histological atlas. Connectivity maps are thresholded at $z=2.3$ (red colour bar) but were not corrected for spatial extent.

Neurochemistry

In the previous chapter, there was no relationship between neurochemistry in ipsilesional hMT+ and BOLD signal change in hMT+. Here, I also investigated whether GABA+ and Glx in ipsilesional hMT+ was related to functional connectivity between ipsilesional hMT+ and the rest of the brain. As can be seen from Figure 20, increased GABA+ and Glx in ipsilesional hMT+ was related to increased connectivity between ipsilesional hMT+ and portions of contralesional hMT+, along with other portions of the temporal lobe, inferior parietal cortex and thalamus. Moreover, increased GABA+ and Glx in ipsilesional hMT+ was also related to reduced connectivity between ipsilesional hMT+ and ipsilesional visual areas, including V1 (and cerebellum). However, these results are not cluster corrected.

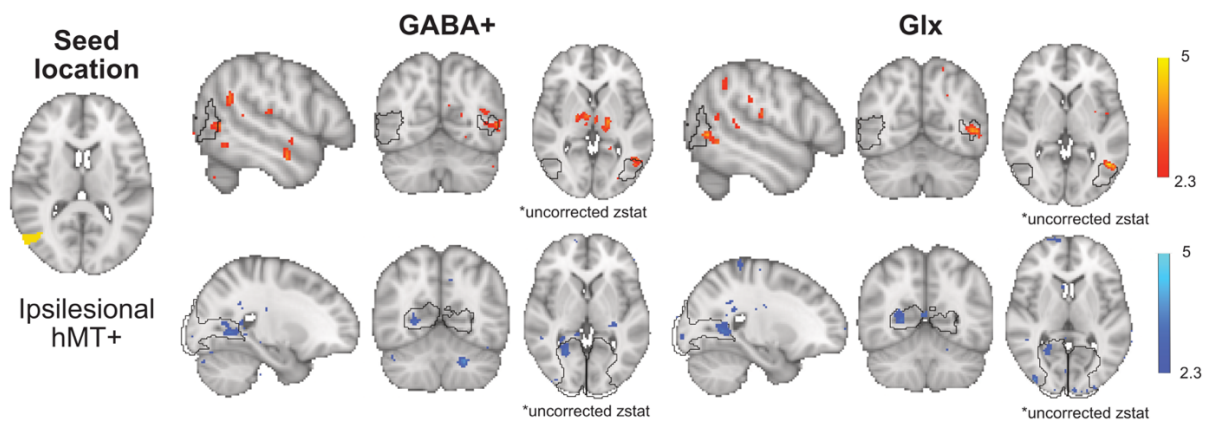


Figure 20. Relationship between whole-brain resting state connectivity of the ipsilesional hMT+ and neurochemicals. Shows areas where functional connectivity positively (red) and negatively (blue) correlates with GABA+ and Glx in the ipsilesional hMT+ viewed on a standard MNI brain. Black outlines indicate hMT+ bilaterally (upper image) and V1 (lower image) from the Jülich histological atlas. Connectivity maps are thresholded at $z=2.3$ (red and blue colour bar) but were not corrected for spatial extent.

4.6.3 Resting state region-of-interest analysis

Functional connectivity between each region-of-interest was calculated by conducting a Pearson's correlation between the timeseries. It was then converted to a Fisher Z correlation coefficient. These coefficients were then compared with measures of residual vision.

The functional connectivity between ipsilesional hMT+ and each visual ROI varied (see Figure 21): ipsilesional dLGN (median $z = 0.19$; IQR $z = 0.21$), ipsilesional SC (median $z = 0.08$; IQR $z = 0.11$), ipsilesional inferior pulvinar (median $z = 0.17$; IQR $z = 0.29$), ipsilesional V1 (median $z = 0.57$; IQR $z = 0.52$), contralesional hMT+ (median $z = 0.87$; IQR $z = 0.37$), contralesional V1 (median $z = 0.65$; IQR $z = 0.33$). The functional connectivity between ipsilesional S1 and ipsilesional VPL (median $z = 0.42$; IQR $z = 0.21$) and contralesional S1 (median $z = 1.05$; IQR $z = 0.48$) also varied (see Figure 21).

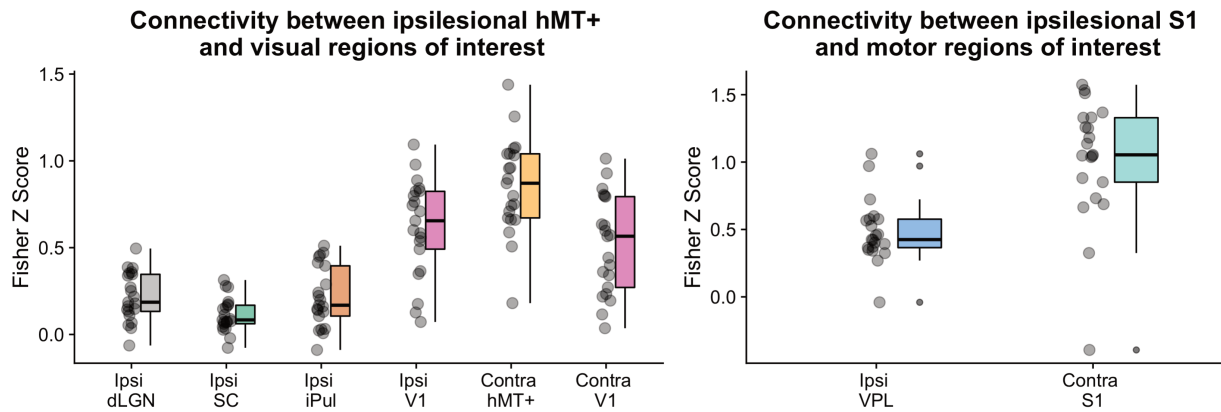


Figure 21. Connectivity between regions of interest. Left: Ipsilesional hMT+ and visual ROIs. Scatter and box plots showing correlations between ipsilesional hMT+ and ipsilesional dLGN (grey), ipsilesional superior colliculus (SC; green), ipsilesional inferior pulvinar (iPul; orange), ipsilesional V1 (pink), contralesional hMT+ (orange) and contralesional V1 (pink) for all participants. Right: Connectivity between ipsilesional S1 and sensorimotor ROIs. Scatter and box plots showing correlations between ipsilesional S1 and ipsilesional VPL and contralesional S1. Box plots indicating the median (black line) with the upper and lower hinge reflecting the 25% and 75% quantile respectively. The whiskers represent the smallest (lower whisker) and largest (upper whisker) values that are no further than $1.5 \times \text{IQR}$ from the hinge. Grey scatter points represent the data from each individual participant.

Ipsilesional regions-of-interest

Pearson's correlation analyses were run to determine whether residual vision was related to functional connectivity between ipsilesional hMT+ and ipsilesional dLGN ($R=-0.09$, $p=0.73$), ipsilesional superior colliculus ($R=0.31$, $p=0.17$), ipsilesional inferior pulvinar ($R=-0.18$, $p=0.43$) and ipsilesional V1 ($R=-0.15$, $p=0.51$). As can be seen in Figure

22, there were no significant relationships between residual vision and the functional connectivity of ipsilesional hMT+ and any of the regions-of-interest.

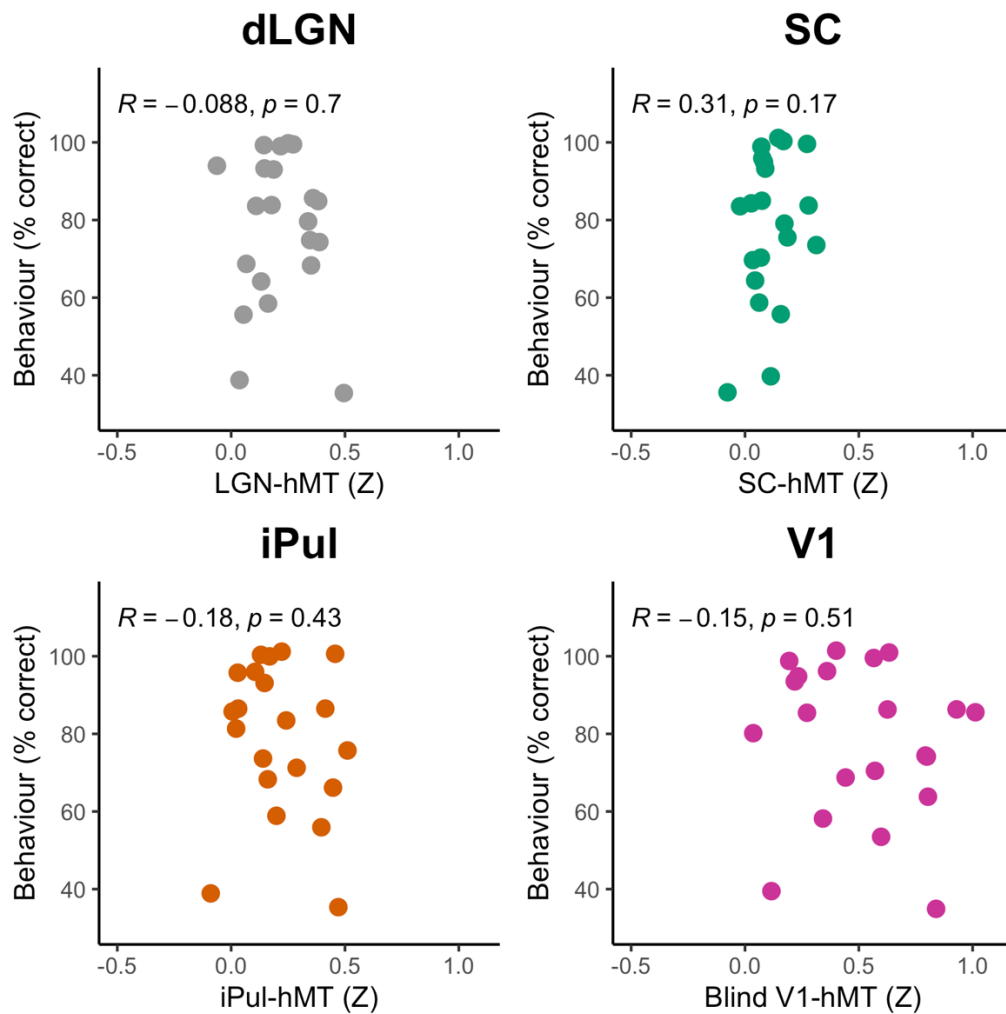


Figure 22. Region of interest analysis plots indicating the relationship between residual vision and connectivity between ipsilesional hMT+ and ipsilesional ROIs. Plots indicate the relationship between residual vision (behaviour % correct) and functional connectivity between ipsilesional hMT+ and dLGN (grey), superior colliculus (green), inferior pulvinar (orange) and ipsilesional V1 (pink). Residual vision (behaviour % correct) is indicated on the x axes, and connectivity between ROIs (correlation coefficients converted to Fisher Z scores) are shown on the y axes.

Contralesional regions-of-interest

Moreover, as previous studies have implicated the role of the intact hemisphere in residual vision after V1-damage, I also looked at the relationship between ipsi- and contralesional hMT+ and between ipsilesional hMT+ and contralesional V1. There was no correlation between residual vision and functional connectivity of ipsilesional hMT+ with either contralesional hMT+ ($R=-0.004$, $p=0.98$) or contralesional V1 ($R=-0.01$, $p=0.95$; Figure 23).

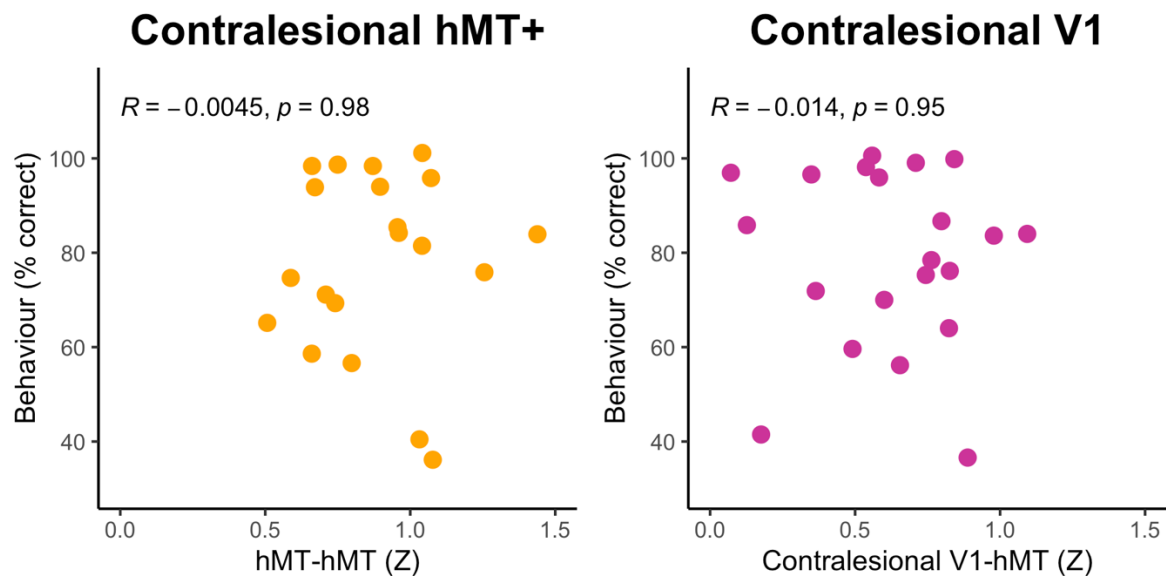


Figure 23. Region of interest analysis plots indicating the relationship between residual vision and connectivity between ipsilesional hMT+ and contralesional ROIs. Plots indicate the relationship between residual vision (behaviour % correct) and functional connectivity between ipsilesional hMT+, and contralesional hMT+ (yellow) and contralesional V1 (pink). Residual vision is indicated on the x axes, and connectivity between ROIs (correlation coefficients converted to Fisher Z scores) are shown on the y axes.

Control regions-of-interest

Further correlation analyses were also calculated to determine whether residual vision was related to functional connectivity among control regions. As expected, I found no relationship between residual vision and connectivity of ipsilesional S1 with either ipsilesional VPL ($R=-0.39$ $p=0.11$) or contralesional S1 ($R=-0.44$, $p=0.07$; Figure 24).

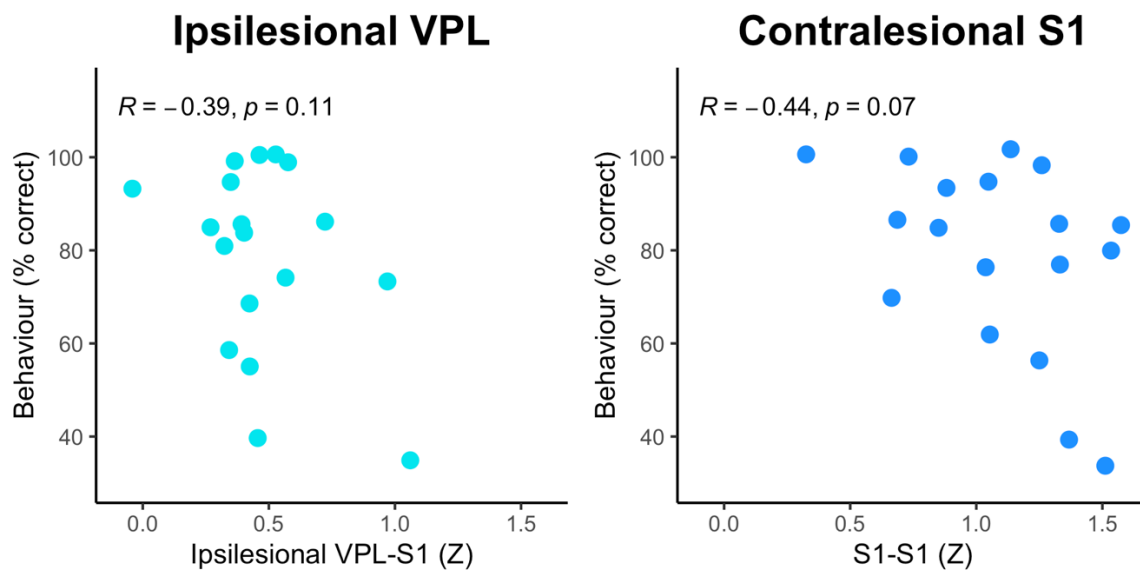


Figure 24. Region of interest analysis plots indicating the relationship between residual vision and connectivity between ipsilesional S1 and sensorimotor ROIs. Plots indicate the relationship between residual vision (behaviour % correct) and connectivity between ipsilesional S1 and VPL (light blue) and contralesional S1 (dark blue). Residual vision is indicated on the x axes, and connectivity between ROIs (correlation coefficients converted to Fisher Z scores) are shown on the y axes.

4.7 Discussion

Here, I aimed to understand whether resting-state functional connectivity was related to residual visual ability in the blind field, or MRS measures of neurochemicals (GABA+ and Glx) in ipsilesional hMT+. I investigated resting-state connectivity using two methods: (1) an exploratory whole-brain analysis with seeds in ipsilesional hMT+ and contralesional hMT+ and (2) using a regions-of-interest analysis for ipsilesional hMT+ with ipsilesional dLGN, ipsilesional superior colliculus, ipsilesional inferior pulvinar, ipsilesional V1, contralesional hMT+ and contralesional V1. In the whole-brain analysis, superior residual vision was predicted by lower functional connectivity between both ipsilesional and contralesional hMT+ and contralesional extrastriate ventral visual cortex. Additionally, prior to correction for multiple comparisons, higher functional connectivity between ipsilesional hMT+ and ipsilesional early visual areas was also related to superior residual vision. In the regions-of-interest analysis, functional connectivity between ipsilesional hMT+ and any of the regions-of-interest was not predictive of residual vision.

4.7.1 Residual vision is related to lower functional connectivity between ipsilesional hMT+ and contralesional ventral visual areas

Previous studies in stroke survivors with V1 damage report that the undamaged hemisphere shows hyperactivity to visual stimulation compared to healthy controls (Das & Huxlin, 2010). Moreover, two rehabilitation studies found that visual training within the blind field reduces activity in the contralesional visual cortex (Das & Huxlin, 2010; Larcombe et al., 2018). These studies suggest that higher activity within the

contralesional visual cortex may negatively impact visual processing in the blind field. Accordingly, in the current study, superior residual vision was found to be related to lower functional connectivity between both ipsilesional and contralesional hMT+ and contralesional ventral visual areas. This further suggests that the connectivity between the ipsilesional and contralesional hemisphere in stroke survivors with V1 damage may negatively impact residual vision.

4.7.2 Residual vision is related to higher functional connectivity between ipsilesional hMT+ and ipsilesional dorsal visual areas

Research has previously indicated that activity in spared perilesional visual areas may underlie residual vision in the blind field (Fendrich et al., 2001; Morland et al., 2004; Wessinger et al., 1997). Furthermore, it has been argued that the receptive fields of these regions may overlap with perimetry-defined blind field thus supporting residual visual abilities (Papanikolaou et al., 2014). In the current study, higher functional connectivity of both ipsilesional hMT+ and contralesional hMT+ with ipsilesional early visual areas was also related to superior residual vision. This further suggests that connectivity between ipsilesional hMT+ and spared perilesional visual areas may facilitate residual vision. However, these analyses did not pass statistical thresholding for spatial extent so should be interpreted with caution.

4.7.3 Neurochemistry in ipsilesional hMT+ is related to connectivity between hMT+ and contralesional visual areas

Previous studies have reported a relationship between GABA and glutamate and resting-state fMRI, which is consistent with the role of GABAergic inhibition and glutamatergic excitation in neural processing (Kapogiannis et al., 2013; Sampaio-Baptista et al., 2015; Stagg et al., 2014). In the current study, increased inhibitory GABA and excitatory glutamate was found to be related to higher connectivity between ipsilesional hMT+ and portions of the contralesional hMT+. Moreover, increased GABA and glutamate in ipsilesional hMT+ was related to decreased connectivity between ipsilesional hMT+ and ipsilesional early visual areas. As reduced GABA has previously been linked to plasticity (Blicher et al., 2015; Lunghi et al., 2015), this suggests that reduced plasticity in ipsilesional hMT+ is linked to higher functional connectivity to the contralesional hemisphere and lower functional connectivity to the ipsilesional hemisphere. This further supports the previous findings that indicate an important role of ipsilesional visual areas in supporting residual vision, and the negative impact of the contralesional hemisphere. However, these analyses also did not pass statistical thresholding for spatial extent, so should be interpreted with caution.

4.7.4 No relationship between residual vision and functional connectivity between visual regions-of-interest

Previous studies have suggested that multiple brain regions might be involved in residual vision after V1-damage, including dLGN (Ajina, Pestilli, et al., 2015; Ajina & Bridge, 2018; Schmid et al., 2010), superior colliculus (Mohler & Wurtz, 1977; Rodman et al., 1990), inferior pulvinar (Kinoshita et al., 2019), spared perilesional V1 (Kleiser et al., 2001; Morland et al., 2004; Radoeva et al., 2008) and areas in the intact hemisphere (Bittar et al., 1999; Bridge et al., 2008). In the current analysis, I aimed to determine whether the connectivity between ipsilesional hMT+ and any of these structures might explain residual vision. In contrast to previous research, I found no significant relationship between residual vision and functional connectivity between ipsilesional hMT+ and any of the target regions-of-interest investigated.

4.7.5 Limitations and future directions

One limitation of this analysis is the use of BOLD signal changes in stroke survivors. In the previous chapter, neurochemistry in hMT+ (GABA and glutamate) was significantly related to residual vision. However, I found no relationship between BOLD signal change in hMT+ and residual vision, despite previous studies finding evidence of activity in hMT+ in blindsight patients (Ajina, Rees, et al., 2015; Ajina & Bridge, 2018). Task-related fMRI relies on a canonical haemodynamic response function, which assumes that the neurovascular response is normal. Although resting-state fMRI does not rely on evoked BOLD signal, or the canonical haemodynamic response function, it is still reliant on the relationship between BOLD signal change and cerebral blood flow and cerebral metabolic

rate of oxygen. Therefore, as stroke survivors have abnormal neurovascular coupling, differences in functional networks may not reflect neuronal activity, but instead reflect differences in neurovascular coupling (Veldsman et al., 2015). Investigating BOLD signal change in stroke survivors should always be interpreted with this understanding in mind.

Another limitation of the current analysis is the use of a single task to determine residual vision. As discussed in the introduction, many patients with damage to V1 show residual visual abilities for a range of tasks, including moving stimuli, colour, and form (see Danckert & Rossetti, 2005 for review). Moreover, the neural basis of residual vision is controversial, with studies finding support for multiple neural pathways (Rodman et al., 1989; Schmid et al., 2010). The discrepancy in the current literature is likely due to variability in tasks used, with different visual pathways underlying specific blindsight abilities (Tamietto & Morrone, 2016). In the current study a moving contrast detection task (Ajina, Pestilli, et al., 2015; Ajina, Rees, et al., 2015) was used to determine residual vision and consequently this study focussed on connectivity with hMT+. It is possible that if another task was used to determine residual vision alternative pathways would have been implicated.

An additional limitation of the current research is the use of regions-of-interest for all analyses. As discussed previously, the exact neural mechanisms that underlie residual vision remain to be determined and vary depending on the task or the patient population used. Although regions-of-interest were selected based on the current literature, no significant relationships were found in the current study. The exploratory whole-brain approach indicated that wider visual areas, such as ventral and dorsal early visual areas might be involved in residual vision after V1 stroke. Therefore, future studies should explore whether resting-state networks, including visual and attentional

networks are related to residual vision or neurochemistry. Alternatively, a graph theory-based approach could be used to model the brain as a complex network of graphical nodes and edges to visualise the connectivity pattern of the whole brain. These methods may be informative about how wider brain areas are involved in residual vision.

The current study found a relationship between decreased connectivity between ipsilesional hMT+ and contralesional ventral visual areas, which might indicate that connectivity between the damaged and the undamaged hemisphere negatively impacts vision. This suggests that downregulation of activity within the undamaged hemisphere may facilitate improvement of residual vision. Two rehabilitation studies in patients with V1-damage found that visual training within the blind field reduces the activity in the contralesional visual cortex (Das & Huxlin, 2010; Larcombe et al., 2018). Therefore, future studies could focus on aiming to reduce hyperactivity within the undamaged hemisphere. Moreover, it is possible that baseline functional connectivity relates to capacity for neurorehabilitation post-stroke. A previous study found that connectivity between the occipital poles was decreased after damage to V1 when compared to controls, and this connectivity correlated with spontaneous improvements (Kim et al., 2019). Moreover, Halbertsma et al. (2020) found that functional connectivity between the anterior precuneus and the occipital pole network was related to improvement on a visual rehabilitation task. As the participants in this study were enrolled in a rehabilitation program, future analyses will investigate whether baseline resting-state connectivity between ipsilesional hMT+ and the rest of the brain can predict improvement in vision post-stroke.

4.8 Conclusion

In conclusion, a whole-brain analysis revealed that superior residual vision is related to lower functional connectivity between ipsilesional hMT+ and contralesional hMT+ and between ipsilesional hMT+ and extrastriate ventral visual cortex in the contralesional hemisphere. Additionally, residual vision was also related to higher functional connectivity between ipsilesional hMT+ and ipsilesional early visual areas, although this did not survive correction for multiple comparisons. Using a region-of-interest analysis, no relationship was found between ipsilesional hMT+ and any regions-of-interest previously associated with residual vision. These results suggest that neural activity in the contralesional hemisphere, and connectivity between the ipsilesional and contralesional hemispheres may negatively impact residual vision. If this hypothesis were correct, downregulation of activity in the contralesional visual cortex may improve residual vision and could provide a target for rehabilitation strategies.

Chapter 5: Visual rehabilitation in the blind field improves trained and untrained behaviour

5.1 Abstract

Damage to the primary visual cortex (V1), following a stroke, results in loss of conscious vision in the contralateral hemifield. There are currently no widely used treatments for such visual impairment. When therapy is available it tends to focus on learning to compensate for the visual field deficit through eye and head movements. Recently, training to detect stimuli in the blind field has been shown to be effective in improving vision. This study aimed to replicate the findings from previous studies showing that training in the blind field improves performance on visual tasks, and to investigate whether such improvements generalise to untrained tasks.

Twenty stroke survivors with damage to V1 resulting in contralateral visual field deficits completed six months of visual motion discrimination training at two blind field locations. Each participant trained at least 5 days a week for the six-month period averaging 155 training days. Training significantly improved performance on the trained motion discrimination task in the blind field. Furthermore, there was significant improvement on the untrained contrast detection task and significant reductions in the size of the visual field deficit. I conclude therefore that training to detect visual motion in the blind hemifield can successfully improve performance on tasks of visual behaviour as previously demonstrated. It is worth noting, however, that there was considerable variability among participants. It is important to understand the cause of these different

responses to treatment. In the remainder of the thesis, I will discuss whether measures of brain structure can predict outcomes of training.

5.2 Introduction

The sudden loss of vision caused by a stroke to V1 significantly impacts quality of life, as often stroke survivors have difficulties navigating crowded environments, are not allowed to drive, and consequently have reduced independence (Pollock et al., 2019). Rehabilitation opportunities post-stroke are currently limited, with the majority focused on training compensatory eye movements rather than restitution of the visual field (Rowe et al., 2013). There is also evidence that without visual training, visual fields show decreased sensitivity which might reflect retrograde degeneration of neurons in the dLGN and retina (Cavanaugh & Huxlin, 2017). Therefore, developing rehabilitation techniques for visual loss from stroke is of fundamental importance.

Most studies on rehabilitation of visual loss post-stroke focus on chronic stroke survivors. A recent study found, however, that starting rehabilitation in the sub-acute phase (less than six months post-stroke) can have greater impact, as rehabilitation is quicker and improvements generalise deeper into the blind field and to untrained tasks (Saionz et al., 2020). This suggests that rehabilitation should be provided to stroke survivors directly after their stroke for greater benefit. For this to be viable, it is important that effective and simple rehabilitation methods are developed for healthcare professionals to implement. Before this is possible, it is important to know: (1) the most effective type of stimuli for training, (2) whether the rehabilitation is simple enough to administer without extensive training, (3) whether the rehabilitation is effective in new

contexts (especially outside of the laboratory), (4) how long participants need to train and (5) whether training-induced improvements generalise to untrained tasks.

In recent years, several laboratories across the world have attempted to improve sensitivity in the blind field using techniques that repeatedly stimulate a specific portion of the blind field. These rehabilitation programmes require patients to detect or discriminate visual stimuli within their blind field. Such programmes have been successful in reducing the size of the visual deficit (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009; Sahraie et al., 2006) and improving contrast sensitivity (Das et al., 2014a; Sahraie et al., 2006), direction discrimination, and orientation discrimination (Cavanaugh et al., 2015, 2019; Das et al., 2014a). These studies indicate that the adult visual system can relearn simple and complex visual discriminations in the blind field (Melnick et al., 2016).

Previous studies have investigated the most effective type of rehabilitation, with improvements shown for flickering (Raninen et al., 2007; Sahraie et al., 2006, 2010), static (Chokron et al., 2008b; Das et al., 2014a) and moving stimuli (Cavanaugh & Huxlin, 2017; Das et al., 2014a; Huxlin et al., 2009). Moreover, there is also some evidence that training generalises to untrained stimuli such as contrast sensitivity (Das et al., 2014a), fine direction discrimination (Cavanaugh et al., 2015), or luminance detection as measured by the Humphrey Visual Fields (Cavanaugh & Huxlin, 2017). However, whether these techniques are simple to administer and effective in new contexts remains to be determined.

The Huxlin laboratory, based at the University of Rochester, New York, USA have carried out extensive work in visual rehabilitation. Here, I investigated whether a motion discrimination training programme used previously by the Huxlin laboratory (Cavanaugh

et al., 2019; Das et al., 2014a; Huxlin et al., 2009) could be easily implemented in a different laboratory and country (the Vision Laboratory, University of Oxford, UK). I also set a specific timeframe of six months, approximately 120 training sessions, to understand whether improvements can be demonstrated within a timeframe achievable in a clinical setting. Finally, I aimed to understand whether I could replicate the generalisability of the rehabilitation to untrained tasks, such as contrast detection and perimetry using Humphrey Visual Fields.

Hypotheses

Hypothesis 1: There will be a significant improvement in average motion discrimination ability (trained task) in the blind field after six months of training.

Hypothesis 2: There will be a significant improvement in moving contrast detection ability (untrained task) in the blind field after six months of training.

Hypothesis 3: There will be a significant reduction in visual field deficit size (as measured by the Humphrey Visual Field) in the blind field after six months of training.

Hypothesis 4: There will be significantly more areas of improvement than areas of worsening in the blind field after six months of training.

5.3 Methods

5.3.1 Participants

Twenty (out of 24) stroke survivors completed the six months of visual rehabilitation. Four participants did not complete training (see Chapter 2 for details). The median age for this cohort was 49 years (range=24-71; female=6). All participants were at least six months post-stroke (chronic phase) with the median being 27.5 months post-stroke (range=6-297 months). All participants completed at least 100 sessions of visual rehabilitation over the six months (median=155; range=102-271 sessions). See Figure 25 for visual fields for each participant.

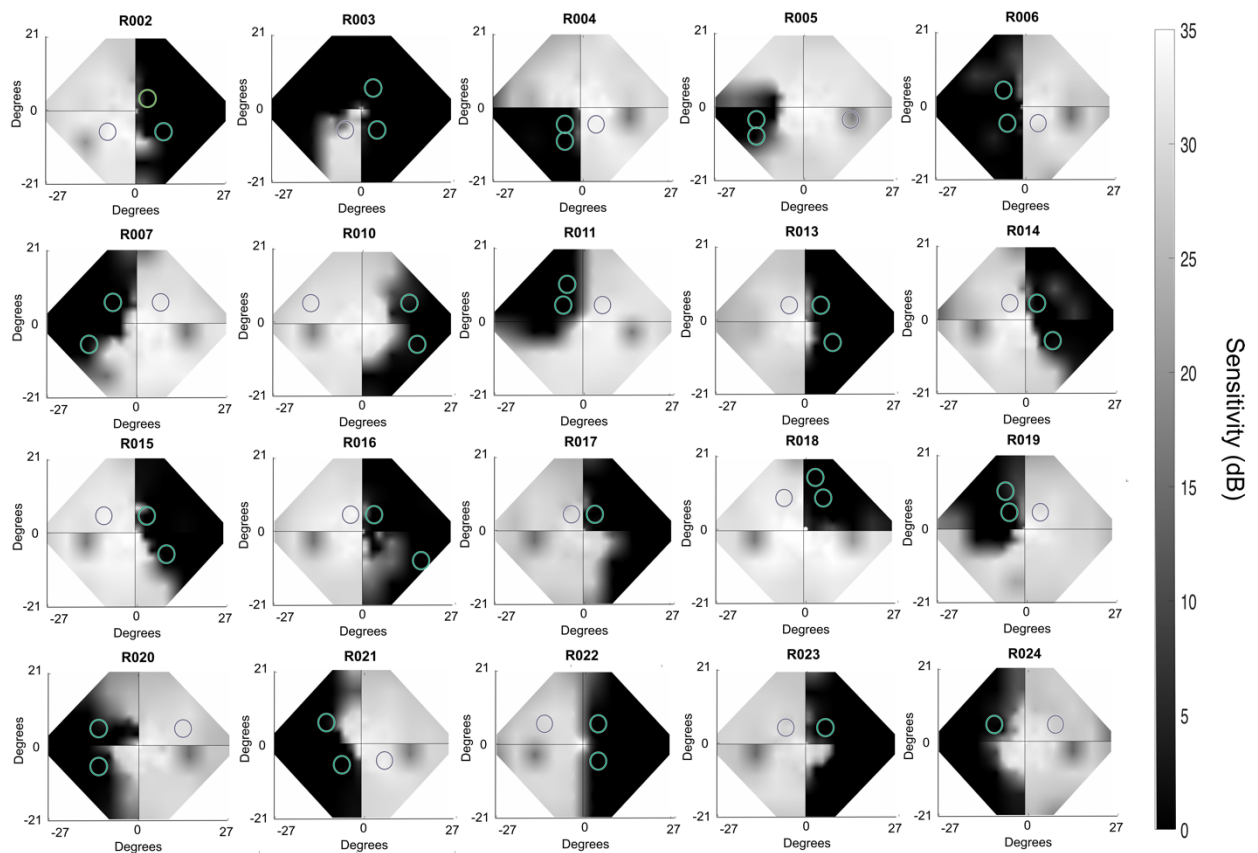


Figure 25. Binocular composite Humphrey Visual Fields for all participants. The two blind field training locations are indicated in green and a matched sighted field location in grey. Three participants (R017, R023 and R024) only trained at one location in the blind field due to time constraints. See Chapter 2 for details of how binocular composite fields were generated.

5.3.2 Study design

Study design was outlined in Chapter 2. In summary, each participant visited the research centre for assessments on two occasions: pre-training (baseline) and post-training (~six months) and completed at-home training between these two timepoints. At-home training involved two sessions of visual training (~40 minutes total per day), at least five days per week, for six months at two separate locations within the blind field. The two blind field locations were chosen during the pre-training visit based on the following criteria: 1) they spanned the full visual field (for example one in the superior and inferior quadrant for a hemianope), 2) were non-overlapping and 3) percentage correct was at chance on the motion discrimination task (with unmeasurable normalised direction range thresholds; see Chapter 2 for full details). Seventeen participants completed training at two locations in the blind field; due to time constraints, the remaining three participants only completed training at one location (R017, R023 and R024).

5.3.3 Psychophysics

Visual training (Motion discrimination) task

Participants were trained on a psychophysical motion discrimination task at two locations within their blind field for six months. As improvements are known to be location specific (Huxlin et al., 2009) and are related to number of training locations (Cavanaugh & Huxlin, 2017), two locations were used to enhance improvements in the blind field (see Chapter 2 for details.). The same psychophysical task was used at the pre- and post-training visits to verify whether participants had improved on the trained task

with fixation controlled. At the pre- and post-training visits, percentage correct and normalised direction range (NDR) thresholds were calculated at each location. These were then averaged together to give overall change in percentage correct and NDR thresholds across the blind field locations. If a participant trained at one location (R017; R023; R024), the score at their trained location was used.

Contrast detection (Untrained task)

A moving contrast detection task was used to measure whether improvement on the motion discrimination task generalises to another task (see Chapter 2 for task details). During this task, participants were asked to indicate the interval in which a drifting, achromatic, Gabor stimulus appeared (first or second) and whether they were aware of the stimulus (yes or no).

Since most stroke survivors only show above chance contrast detection ability in their blind field for high contrast stimuli (Ajina et al., 2021; Ajina, Pestilli, et al., 2015), here I report percent correct performance and awareness for high contrast stimuli only (i.e., averaged across trials that involved 50% and 100% contrast stimuli). At the pre- and post-training visits, percentage correct and percentage of aware trials were calculated at each location. These were then averaged together to give overall change in percentage correct and percentage of aware trials across the blind field locations. If a participant trained at one location (R017; R023; R024), the score at their trained location was used.

5.3.5 Humphrey Visual Fields (Clinical task)

Humphrey visual field pre-processing

Humphrey Visual Field (HVF) data were acquired as described in Chapter 2. Data from participants who showed fixation losses, false positives, and negative errors outside of the normal range ($\geq 20\%$) in either eye at any time point were removed from further analyses. HVF data from participant R002 and R014 were removed due to fixation losses outside of the normal range.

HVF data were analysed as described previously (Cavanaugh et al., 2019; Cavanaugh & Huxlin, 2017; see Chapter 2 for full details). Composite binocular HVF were calculated across both eyes and both tests (24-2 and 10-2) for each participant at each timepoint (pre- and post-training). Difference maps were generated by subtracting the pre-training composite maps from the post-training composite maps. This method quantifies the change in area of the HVF-defined visual deficit (defined by pattern deviation $< -5\text{dB}$; deficit size; Figure 26B) and the area of HVF where the sensitivity improved or worsened by more than 6dB relative to pre-training (area of improvement and area of worsening respectively; Figure 26A). The area of visual field impairment was defined as those areas with an impaired binocular average sensitivity of below 15dB.

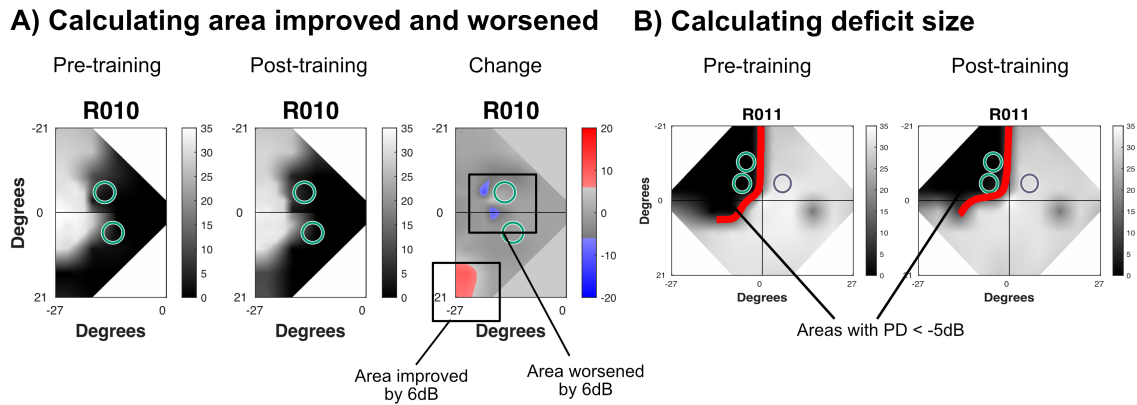


Figure 26. Diagram indicating how perimetry changes were calculated. A) Example Humphrey Visual Field locations which correspond to areas of improvement (red) and areas of worsening (blue) of more than 6dB. B) Example Humphrey Visual Field showing the change in the deficit border (outlined with a red line) between the pre-training and post-training visit. Deficit size was calculated as all areas with a pattern deviation (PD) of <-5dB. Blind field training locations are indicated in green, and sighted field location in grey.

5.4 Statistical analysis

All statistical tests were carried out in R studio (R version 4.1.2). Wilcoxon tests were carried out using the *rstatix* package. Spearman correlations were carried out using the *stats* package. Change scores were calculated for the motion discrimination task, moving contrast detection task and deficit size by subtracting the pre-training score from the post-training score. One-sample Wilcoxon tests were then used to investigate whether changes in behaviour were significantly different from zero (no change). Binomial tests using a Monte Carlo simulation were calculated using custom code generated in MATLAB. Finally, a paired Wilcoxon test was used to investigate whether there was a significant difference between the size of the area improved compared to the area worsened on the Humphrey perimetry. Spearman correlations were used to determine whether improvements in the trained task were related to improvements on the other tasks. Bonferroni-Holm adjusted p-values were calculated using the *stats* package.

5.5 Results

5.5.1 Improvements in behaviour

Motion discrimination (Training task)

Motion discrimination performance in the sighted and blind fields was measured pre-training and post-training in all participants. Due to the staircase procedure and the difficulty of the task, the maximum percentage correct for the motion discrimination task was ~85%. Average blind field scores pre- and post-training are shown in Table 3. Change scores for improvements in percentage correct for sighted and averaged blind field locations were calculated and one-sample Wilcoxon tests were used to determine whether average improvements were significantly greater than zero (Figure 27).

Table 3. Average blind field motion discrimination pre- and post-training results

Participant	Pre-training (% correct)	Post-training (% correct)	Pre-training (% correct NDR)	Post-training (% correct NDR)
R002	55	65	100	71
R003	53	50	100	100
R004	57	64	100	95
R005	53	49	100	100
R006	53	53	100	100
R007	57	84	100	33
R010	64	69	100	74
R011	48	67	100	55
R013	52	68	100	95
R014	49	65	100	73
R015	54	69	100	56
R016	57	78	100	51
R017	49	83	100	17
R018	52	72	100	64
R019	57	69	100	66
R020	61	64	100	73
R021	57	78	100	48
R022	59	77	100	57
R023	56	50	100	100
R024	48	71	100	89
Median	54.25	68	100	72

There was limited change in the sighted field (median=0%; IQR=4%) and this was not significantly different from zero ($W=81$; Holm-Bonferroni corrected $p=0.849$; effect size $r = 0.05$, magnitude=small). Additionally, although there was a moderate amount of variability in NDR change in the sighted field (median=-4.22%; IQR=22.95%), this was not significantly different from zero ($W=72$; Holm-Bonferroni corrected $p=0.462$; effect size $r = 0.28$, magnitude=small). These results indicate that although there is some variability in sensitivity to motion direction in the sighted field between the two visits, as measured by NDR thresholds, this change was not significant after training.

As can be seen in Figure 27, in the blind field, there was a large amount of improvement in percentage correct (median=15.5%; IQR=16.38%) and this was highly statistically different from zero ($W=180$; *Holm-Bonferroni corrected* $p=0.002$; *effect size* $r = 0.76$, *magnitude=large*). Moreover, there was also a large reduction in motion discrimination thresholds (median=-28%; IQR=38.97%) and this was also significantly different from zero ($W=136$; *Holm-Bonferroni corrected* $p=0.002$; *effect size* $r = 0.84$, *magnitude=large*). These results indicate that after six months of visual rehabilitation in the blind field, percentage correct and motion discrimination thresholds were improved on the trained task in the blind field but not in the sighted field.

Motion discrimination change

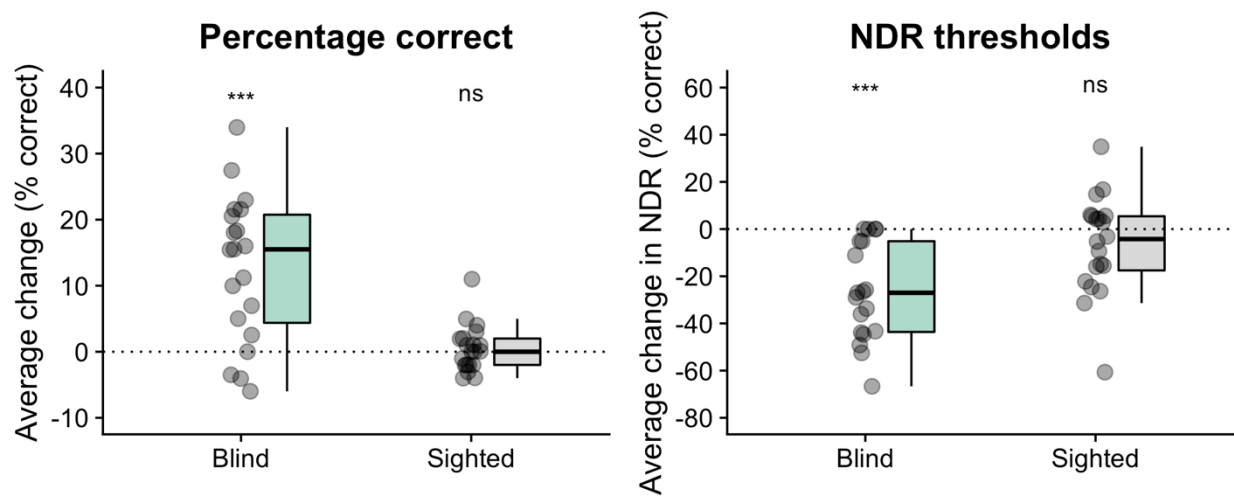


Figure 27. Scatter and box plots indicating the change in percentage correct and normalised direction range thresholds on the trained motion discrimination task between pre- and post-training visits. Change in percentage correct is presented on the left and change in NDR thresholds on the right. Change is shown for the averaged blind field (green) and sighted field (grey) locations. One-sample Wilcoxon tests were used to determine whether the change was significantly different from zero. Significance is indicated with *, and non-significance with 'ns'. Grey scatter points represent the data from each individual participant. Box plots indicate the median (black line) with the upper and lower hinge reflecting the 25% and 75% quantile respectively. The whiskers represent the smallest (lower whisker) and largest (upper whisker) values that are no further than $1.5 \times \text{IQR}$ from the hinge. The average change in percentage correct (left plot) and normalised direction range thresholds (right plot) were significantly different from zero in the blind field, but not in the sighted field.

Contrast detection (Untrained task)

The change in percentage correct and percentage of aware trials was calculated for each participant in the sighted and blind field for the contrast detection (untrained) task (see Figure 28). Average blind field scores pre- and post-training are shown in Table 4.

Table 4. Average blind field contrast detection pre- and post-training results

Participant	Pre-training (% correct)	Post-training (% correct)	Pre-training (% awareness)	Post-training (% awareness)
R002	80	85	8	28
R003	85	95	18	45
R004	100	80	63	60
R005	50	43	0	0
R006	40	73	0	18
R007	73	85	20	60
R010	75	60	20	30
R011	65	63	5	3
R013	45	60	8	13
R014	90	95	55	55
R015	85	98	30	20
R016	70	88	20	28
R017	75	95	10	60
R018	85	85	30	35
R019	68	68	10	8
R020	88	100	15	35
R021	58	93	13	75
R022	58	98	13	60
R023	85	95	40	60
R024	100	95	85	90
Median	75	86.3	16.25	35

As expected, there was limited change in percentage correct in the sighted field (median=0%; IQR=5%) and this was not significantly different from zero ($W=36.5$; *Holm-Bonferroni corrected* $p=0.756$; *effect size* $r = 0.17$, *magnitude=small*). Moreover, there was also limited change in the percentage of aware trials in the sighted field (median=0%;

IQR=15%) and this was not significantly different from zero (*no change*; $W=71$; Holm-Bonferroni corrected $p=0.756$; effect size $r = 0.08$, magnitude=small).

Two participants (R004; R024) performed at ceiling (100% correct) at both blind field locations at the pre-training visit which meant that there was no possibility of improvement due to training. As there was no expectation that participants would perform worse at a task after training, these participants were removed from this analysis. As can be seen Figure 28, for the averaged blind field location, there was a large amount of change in percentage correct (median=10; IQR=13.12) and this was statistically different from zero ($W=118$; Holm-Bonferroni corrected $p=0.029$; effect size $r = 0.62$, magnitude=large). When the two participants at ceiling were included in this analysis, the change was more moderate (median=7.5%; IQR=13.75%), but the effect was still significant ($W=134.5$; $p=0.034$; effect size $r = 0.48$, magnitude=moderate).

Additionally, there was a significant increase in percentage of aware trials after training (median=8.75%; IQR=21.25%) and this was significantly different from zero ($W=154.5$; Holm-Bonferroni corrected $p=0.012$; effect size $r = 0.66$, magnitude=large). These results suggest that training on a motion discrimination task in the blind field for six months can improve contrast detection ability and awareness in the blind field.

Contrast detection change

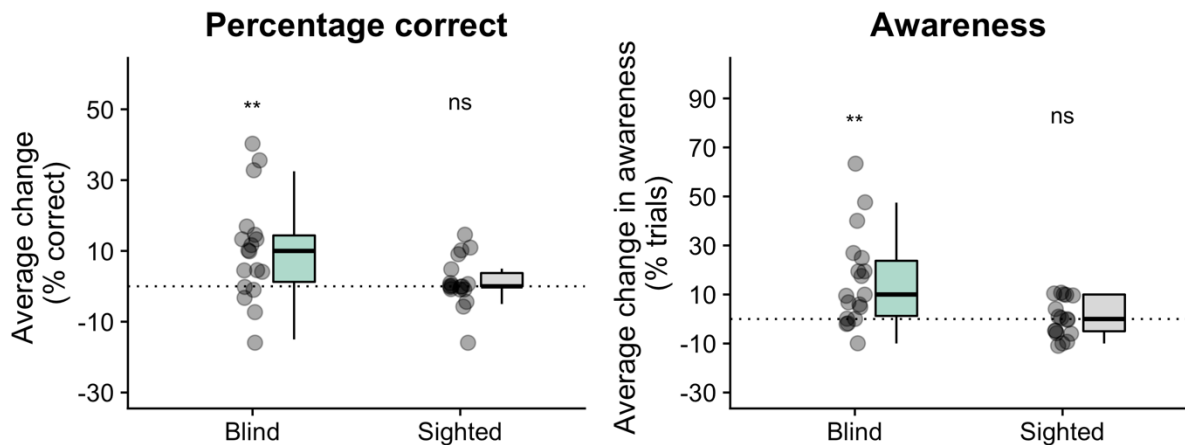


Figure 28. Scatter and box plots indicating the change in percentage correct and percentage of aware trials on the untrained moving contrast detection task between pre- and post-training visits. Change is shown for the averaged blind field (green) and sighted field (grey) locations. See previous figure for graph details. The average change in percentage correct (left) and percentage of aware trials (right) were both significantly different from zero in the blind field, but not in the sighted field. R004 and R024 performed at ceiling at this task at the pre-training visit and were therefore removed from this analysis.

5.5.2 Variability in improvements

It is clear from the previous analyses that there was significant variability in improvements among participants for both the trained and untrained tasks. Next, I wanted to investigate whether there was also variability between the two blind field locations. As the blind field locations were chosen arbitrarily and were therefore not necessarily comparable, for this analysis, the locations were split into the location that showed the greatest change in percentage correct on the motion discrimination task (referred to as the “most improved” location) and the location that showed the least change in percentage correct on the motion discrimination task (referred to as the “least improved” location).

To determine whether there was a significant difference between the pre-training and post-training results for each participant, a binomial test was conducted using a Monte Carlo simulation (1000 samples). This was carried out for each training location (“the most improved” and “least improved”) for the motion discrimination and contrast detection tasks.

An additional binomial test was conducted to determine whether these scores were significantly above chance (50% correct) for each task depending on the number of trials (100 trials for motion discrimination task; 20 trials for the contrast detection task). Based on this test, scores were considered to be significantly above chance if they were above 63% for the motion discrimination task and 80% for the contrast detection task.

Motion discrimination (trained) task

Based on these tests, for the motion discrimination task, both locations significantly improved between the pre- and post-training visit for five participants (R007, R011, R016, R021 and R022), one location improved for 11 participants (R002, R004, R010, R013, R014, R015, R017, R018, R019, R020 and R024), and neither location improved for four participants (R003, R005, R006 and R023). Although it should be noted that R017, R023 and R024 only trained at one location. Moreover, the post-training scores were significantly above chance for both locations for five participants (R007, R013, R016, R021 and R022), for one location for 11 participants (R002, R004, R010, R011, R014, R015, R017, R018, R019, R020, R024) and for neither location for 4 participants (R003, R005, R006 and R023). These results indicate all but four participants showed some improvement between the pre- and post-training visits on the trained task, with scores being significantly above those expected by chance. .

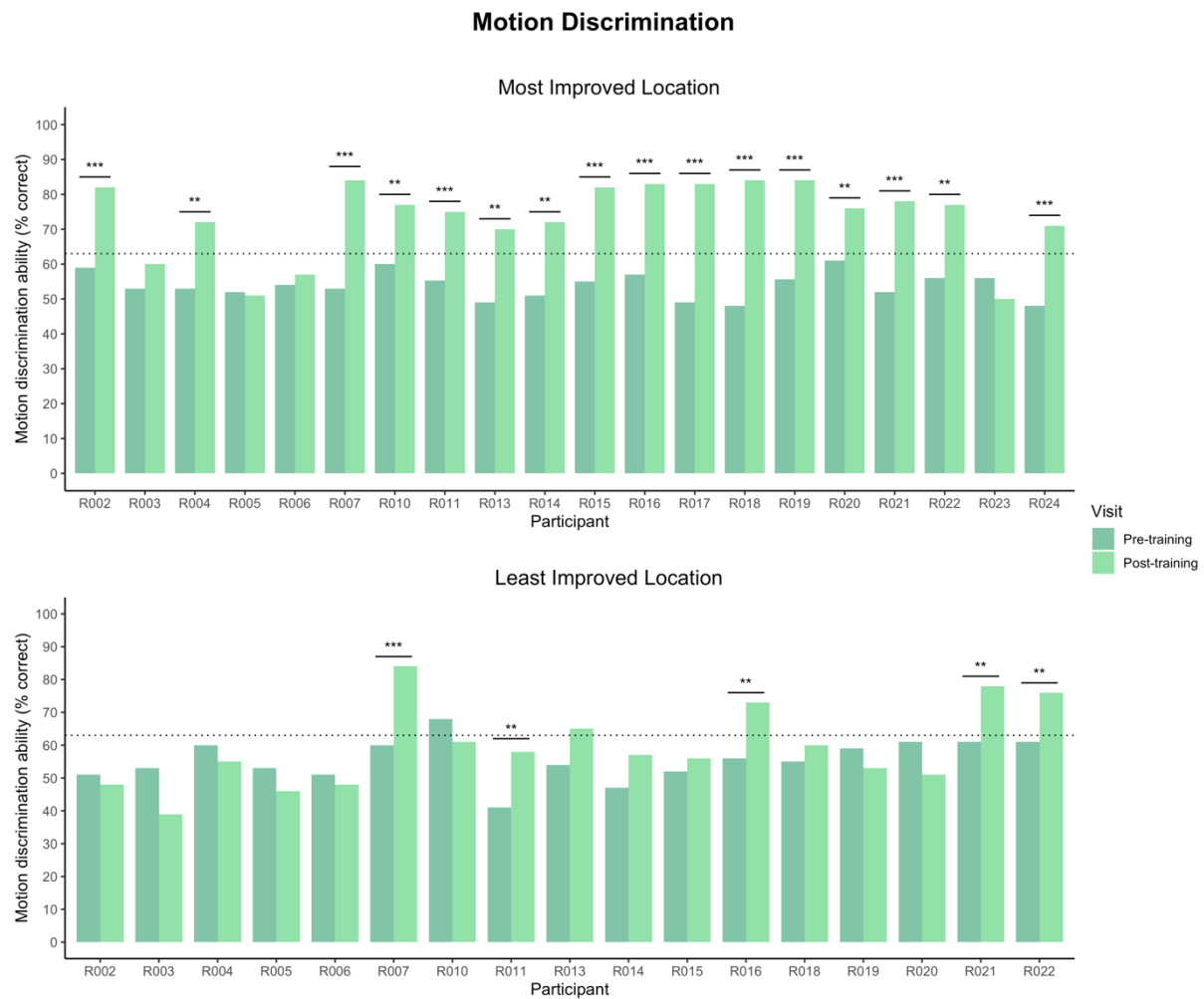


Figure 29. Bar charts indicating the change in percentage correct between the pre-training and post-training visit for each participant at each training location for the motion discrimination task. Locations were split into “most improved” and “least improved” depending on which location they showed greatest change on the trained motion discrimination task. Percentage correct at the most improved (upper) and least improved (lower) blind field locations for the motion discrimination task are presented for the pre-training (light green) and post-training (dark green) visits. Dotted black lines indicate scores considered significantly above chance as determined by a binomial test. Significance levels indicate changes between the pre- and post-training visits as determined by a binomial test (***= $p < 0.001$; **= $p < 0.01$; *= $p < 0.05$)

Contrast detection (untrained) task

The same analyses were performed for change in percentage correct on the contrast detection task. Based on these tests, two participants improved at both locations (R006, R022), three improved at one location (R015, R016, R020) and neither location improved for 15 participants (R002, R003, R004, R005, R007, R010, R011, R013, R014, R017, R018, R019, R021, R023, R024). However, it is possible that participants did not significantly improve because they were already able to perform the task. As can be seen from Figure 30, at the post-training visit, 9 participants performed significantly above chance at both locations (R002, R003, R004, R014, R015, R016, R020, R021, R022), seven at one location (R006, R007, R010, R017, R018, R023 and R024) and four participants at neither location (R005, R011, R013, R019). These results suggest that although a large number of participants did not improve at the contrast detection task, they were still performing significantly above chance.

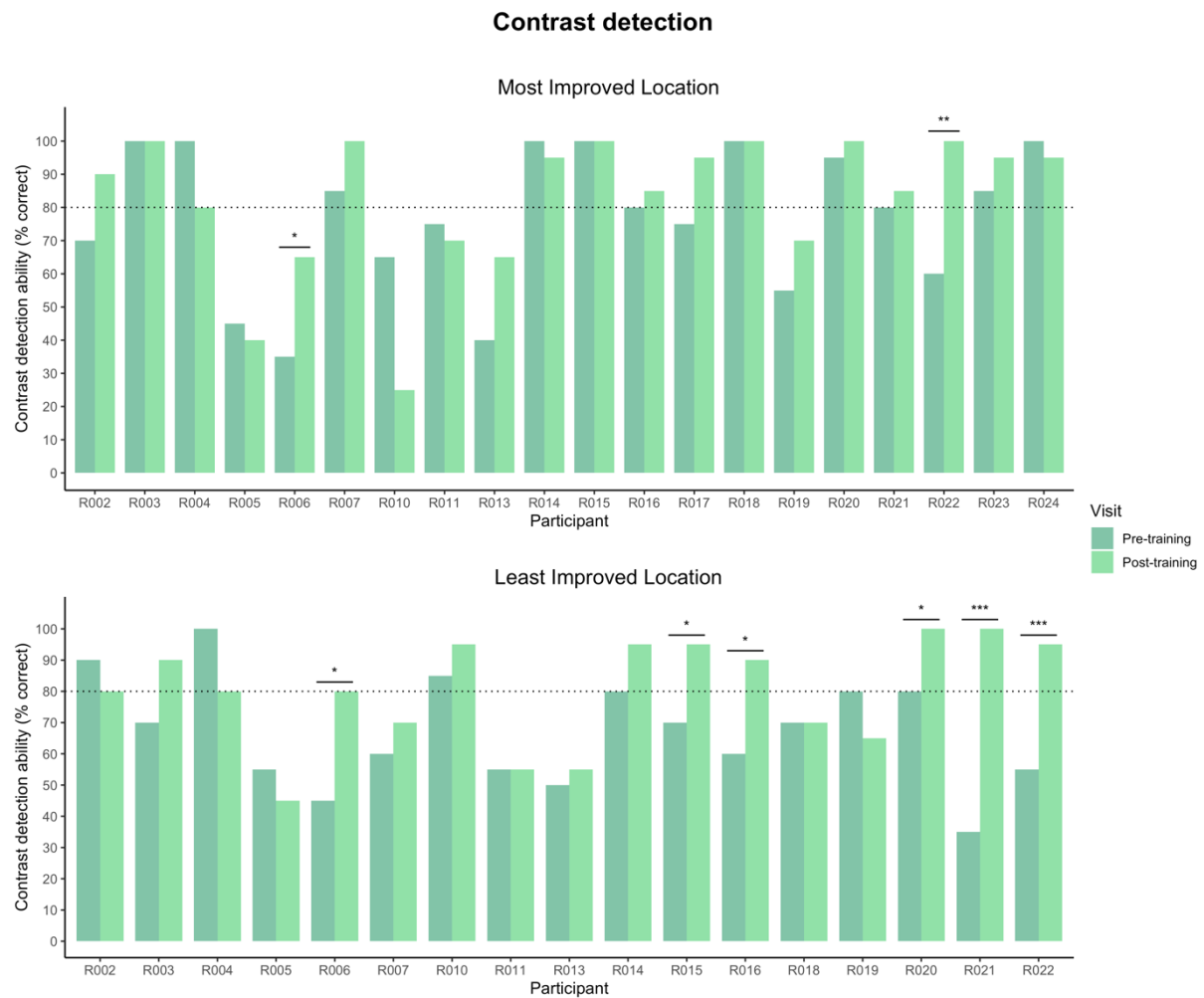


Figure 30. Bar charts indicating the change in percentage correct between the pre-training and post-training visit for each participant at each training location for the **contrast detection task**. Locations were split into “most improved” and “least improved” depending on which location they showed greatest change on the contrast detection task. See previous figure for graph details.

Alternative covariates

Although the amount of training at the “most improved” (range=19-154) and “least improved” (range=10-149) locations in the blind field varied slightly, there was no significant difference between the two (*paired t-test*; $t(1,16)=-0.12$; $p=0.908$). This suggests that amount of training at each location cannot explain why some locations improved and others did not. However, as can be seen in Figure 31, there was a significant positive correlation between number of training sessions completed overall and average improvements seen on the trained task, with those who completed more training improving more ($R=0.49$; $p=0.033$). Participant R017, who completed significantly more training than all other participants (271 sessions), was considered an outlier and therefore removed from this analysis. There was also a significant negative correlation between average improvement on the training in the blind field and months since lesion, with participants with more recent strokes showing greater improvements ($R=-0.63$; $p=0.004$). Participant R020 was removed from this analysis, as their lesion occurred 297 months before the pre-training visit, compared to between 6 and 58 months in all other participants, and was therefore considered an outlier. There was no relationship between average improvement on the training in the blind field and age ($R=0.19$; $p=0.42$). Moreover, there was no relationship between time since lesion and number of training sessions ($R=0.19$; $p=0.48$). These results suggest that months since lesion and number of training sessions are both related to the efficacy of rehabilitation. Moreover, it seems that this relationship is not driven by those with more recent strokes completing more training.

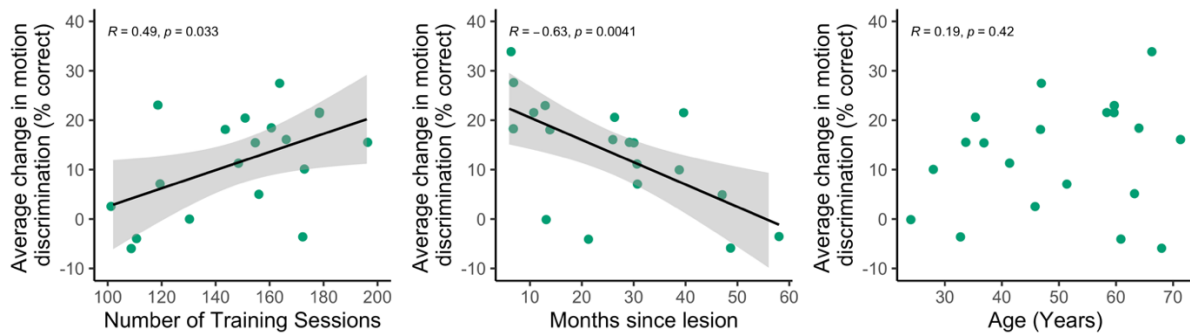


Figure 31. Scatter plots showing the relationship between average blind field change in motion discrimination percentage correct and number of training sessions, months since lesion and age. There was a significant correlation between average blind field change in motion discrimination percentage correct and number of training sessions (left) and months since lesion (middle), but not age (right). Significant regression lines are plotted in black, with standard errors in grey.

5.5.3 Improvements on Humphrey Visual Fields (Clinical task)

Areas of improvement and worsening

All but one of the 20 participants showed improvement in their visual fields on the Humphrey perimetry task after six months of training. Areas of improvement were quantified as those showing increased sensitivity greater than 6dB of change (see Chapter 2 for details). As can be seen from Figure 32 (red portions of the visual field), only one participant (R004) had no areas of improvement after training. The extent of the area improved varied across participants (median=19.44deg², IQR=36.69deg²). In addition, many of the participants showed some areas of worsening (defined as areas showing decreased sensitivity greater than 6dB of change) on the visual field test between the pre- and post-training visits (see blue portions of the visual field in Figure

32). Participants R003, R011, R013, R015, R018 and R022 did not show any areas of worsening. The amount of area worsened varied between individuals (median=4.62deg², IQR=11.01deg²).

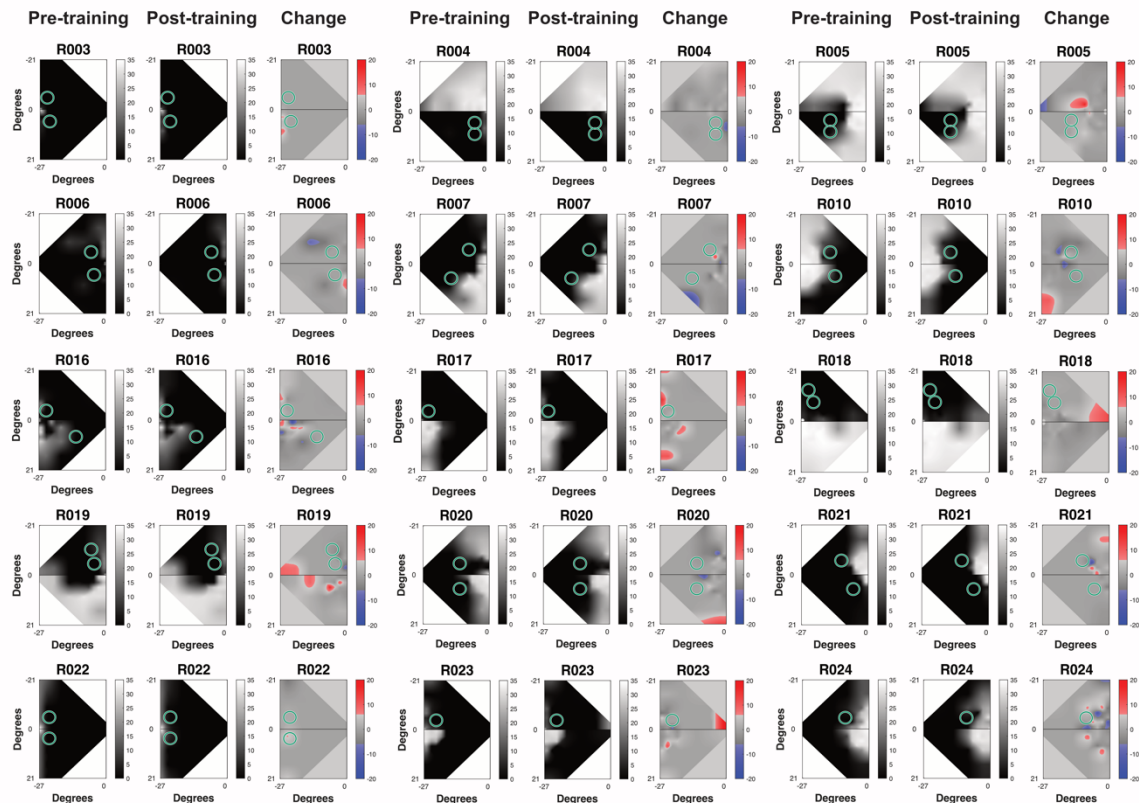


Figure 32. Change in binocular composite Humphrey Visual Fields for all participants. Showing the pre-training visual field (left), post-training visual field (middle) and the change between the two (right). Areas highlighted in red are “areas of improvement” by more than 6dB, while areas highlighted in blue are “areas of worsening” by more than 6dB. The two training locations are indicated in green. Participants R017, R023 and R024 only trained at one location. Participants R002 and R014 were removed from analyses due to errors outside the normal range on one of the visual field tests.

The extent of the area improved was significantly greater than the extent of the area worsened (*paired Wilcoxon test*; $W=176$; $p=0.008$, *effect size* $r=0.59$; *magnitude=large*; see Figure 33). Together these results indicate that six months of visual rehabilitation can lead to significant improvement on the HVF clinical test. Moreover, there appears to be limited worsening over the 6-months.

Change in deficit size

The size of the deficit at each timepoint was calculated (areas with a pattern deviation of less than 15dB; see Chapter 2 for details). On average, the size of the participants' visual field deficit decreased (median change = -11.94mm^2 , $\text{IQR}=24.02\text{mm}^2$) between the pre- and post-training visits and the average change was significantly different from zero (*one-sample Wilcoxon test*, $W=36$; $p=0.008$; *effect size*=0.58; Figure 33). Although for most participants, the deficit size decreased, there was an increase in deficit size for five participants (R004, R006, R007, R016 and R020) between the pre- and post-training visits (Figure 33 for change in deficit size across participants). This suggests that visual training may be effective in reducing the deficit size, however, this there is variability in its efficacy.

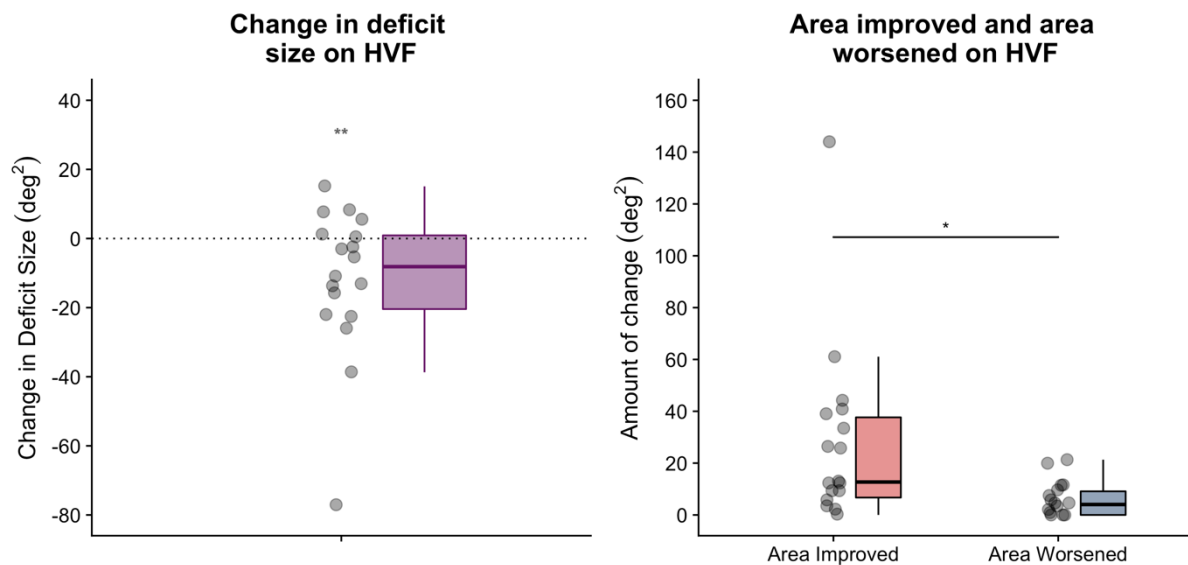


Figure 33. Scatter and box plots showing changes in deficit size and area of improvement and worsening after six months of training. See previous figures for graph details. The change in deficit size was significantly different from zero (no change; left) indicating that deficit size reduced after six months of visual training. Moreover, there was a significantly greater extent of area of improved (red) than worsened (blue; right).

As can be seen in Figure 32, participant R011 showed a greater area of improvement due to training (144.00deg^2) compared to other participants (median= 19.44deg^2 , IQR= 36.69deg^2). Moreover, their deficit size changed the most (-76.99deg^2) compared to the average change (median change = -11.94mm^2 , IQR= 24.02mm^2). There was no evidence that these changes were due to measurement error, and this participant did not show abnormal fixation losses, false positives, or negative errors outside of the normal range ($\geq 20\%$) in either eye at any time point. However, this participant responded well to the training, showing significant improvements at both locations. They completed 160 sessions of training, which was just above the average (median=155), and they began training after 7 months post-stroke. As

a significant relationship was found between improvements on the trained task and both number of training sessions and time since stroke, these factors might have played a role in seeing significantly greater improvements in HVF when compared to the other participants. When R011 was removed from all analyses, there was still a significant difference between the extent of the area improved and area worsened (*paired Wilcoxon test*; $W=156$; $p=0.015$) and change in deficit size (*one-sample Wilcoxon test*, $W=36$; $p=0.016$)

5.5.4 Relationship between the different tasks

Spearman correlation analyses were used to investigate whether average improvement on the training task in the blind field was related to changes on the contrast detection task or HVF (deficit size, area of improvement). There was no significant correlation between average change in percentage correct on the motion discrimination task and average change in contrast detection (*Figure 34A*; $R=0.28$, $p=0.23$), change in deficit size (*Figure 34B*; $R=-0.13$ $p=0.59$) or area of improvement (*Figure 34C*; $R=0.14$; $p=0.54$). These results suggest that improvements on the trained task are not directly related to changes on the two untrained tasks (contrast detection and HVF). Moreover, there was no relationship between change in percentage correct on the motion discrimination task and residual vision (or “blindsight” ability; see Chapter 3 and 4 for details on calculation) at baseline (*Figure 34A*; $R=-0.21$; $p=0.40$). This suggests that having residual vision at baseline is not related to improvements on the trained task.

Motion Discrimination (% correct)

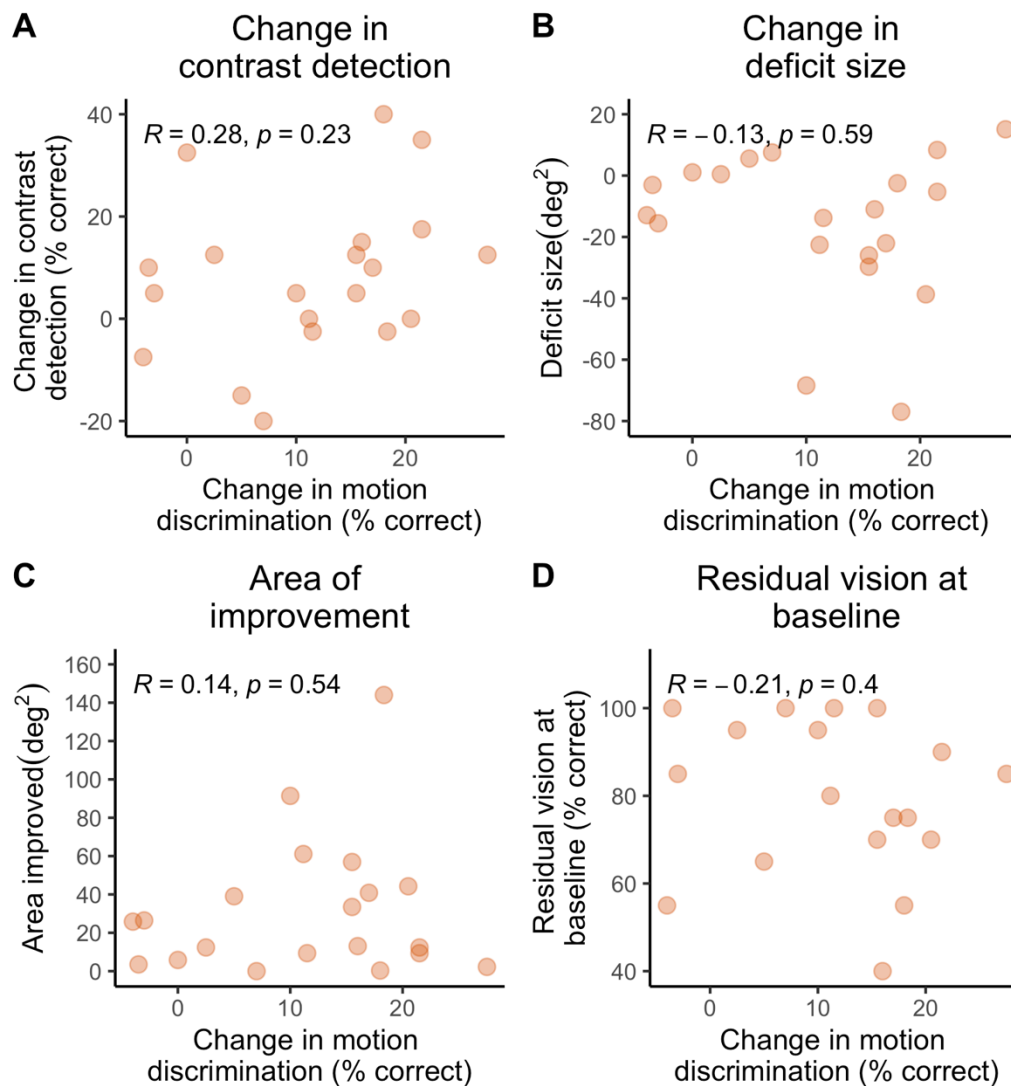


Figure 34. Scatter plots showing the relationship between change in percentage correct on the motion discrimination task and other behavioural measures. (A) Change in percentage correct on the contrast detection task (B) change in deficit size, (C) area of improvement and (D) residual vision at the pre-training visit. Spearman correlation coefficients and p values are shown in the top left. There was no significant relationship between change in percentage correct on the motion discrimination task and any of the other behavioural measures.

Additionally, Spearman correlation analyses were used to investigate whether improvement in averaged normalised direction range thresholds in the blind field were related to changes on the two untrained tasks. No significant correlation between change in normalised direction range thresholds and change in contrast detection (*Figure 35A*; $R=-0.31$, $p=0.18$), change in deficit size (*Figure 35B*; $R=0.11$, $p=0.65$) or area of improvement (*Figure 35C*; $R=-0.23$; $p=0.33$) was found. Moreover, there was no relationship between change in percentage correct on the motion discrimination task and residual vision (or “blindsight” ability) at the pre-training visit (*Figure 35D*; $R=0.17$; $p=0.49$).

Motion Discrimination (NDR % correct)

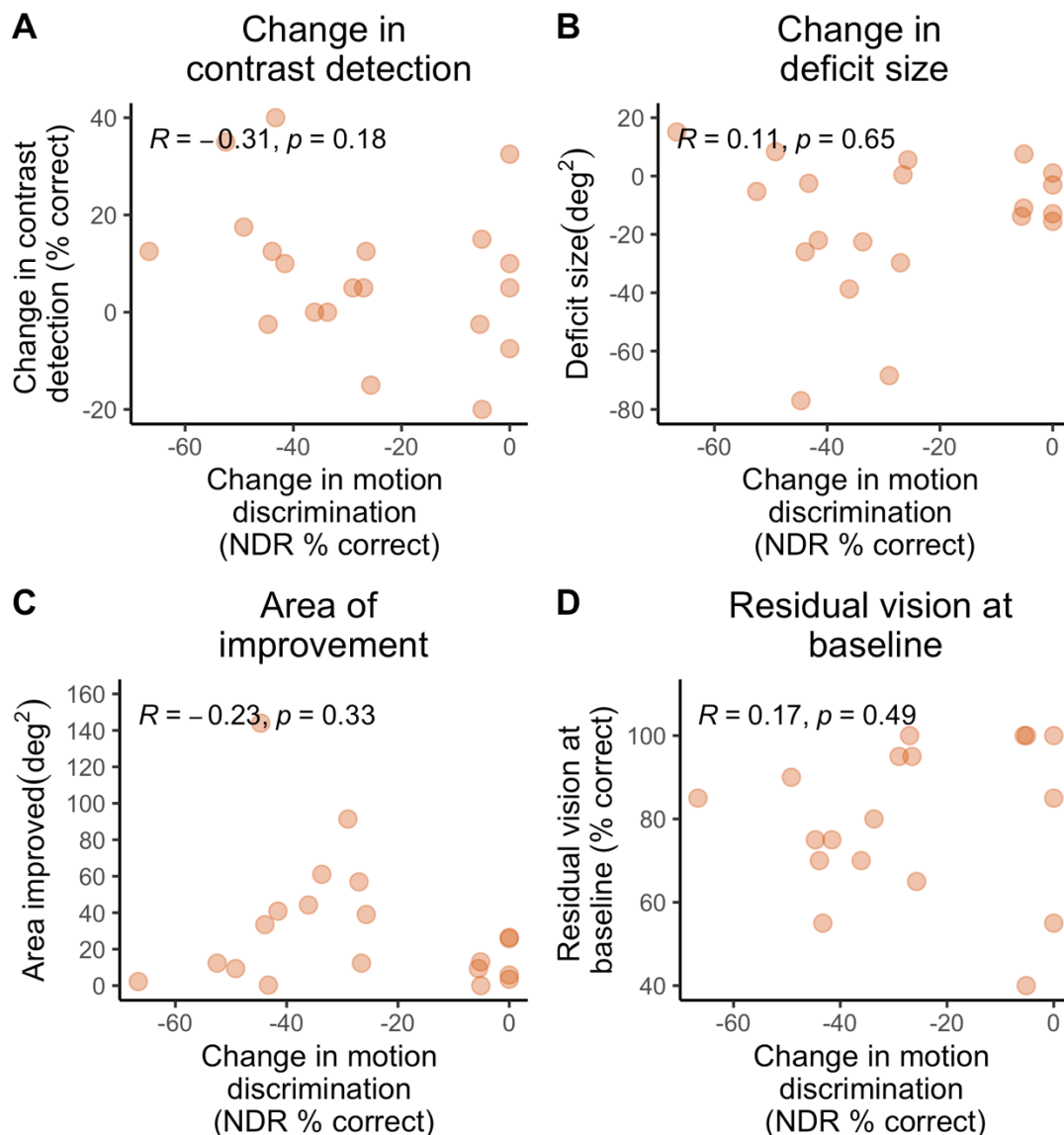


Figure 35. Scatter plots showing the relationship between change in normalised direction range thresholds on the motion discrimination task and other behavioural measures. (A) Change in percentage correct on the contrast detection task (B) change in deficit size, (C) area of improvement and (D) residual vision at baseline. Spearman correlation coefficient and p values are shown in the top left. There was no significant relationship between change in normalised direction range thresholds on the motion discrimination task and any of the other behavioural measures.

5.6 Discussion

Here, I aimed to replicate previous studies using the same visual training technique to improve visual function. Outcomes in terms of visual function was measured using three tasks: 1) motion discrimination ability (the trained task), 2) contrast detection (an untrained task) and 3) luminance detection on the Humphrey Visual Fields (an untrained clinical task). There was significant evidence of improvement in vision across trained and untrained tasks after six months of visual training in the blind field.

5.6.1 Visual training improves the trained task

As predicted, after six months of visual training within the blind field, participants showed significant improvements on the trained task. Change in percentage correct and normalised direction range thresholds averaged across the two blind field locations were significantly different from zero indicating improvements in vision on the trained task. This result replicates findings from previous literature showing that visual training in the blind field can improve performance on the trained task (Cavanaugh & Huxlin, 2017; Huxlin et al., 2009). However, previous studies found that average percentage correct improved to 81% correct after training (Cavanaugh & Huxlin, 2017). In the current study, percentage correct averaged across both blind field locations at the post-training visit was lower than previously reported (median=68%). Moreover, even when the percentage correct at the post-training visit for the “most improved” location was taken, this was only slightly higher (median=76.5%). This suggests that the current study had more modest effects than previously reported.

5.6.2 Visual training improves an untrained contrast detection task

Furthermore, participants showed a significant improvement on the moving contrast detection (untrained) task after six months of visual training. Thus, training on a motion discrimination task may generalise to another task, which is consistent with previous studies that have found improvements on contrast sensitivity (Das et al., 2014a), fine direction discrimination (Cavanaugh et al., 2015). Surprisingly, there was no significant correlation between improvements on the training and improvements on the contrast detection task. This suggests that although contrast detection performance does improve, it is not directly related to the trained task. Additionally, there was a significant increase in awareness of the stimuli in the blind field. Residual vision in the blind field (or “blindsight”) is famously unconscious, which has led to debate about how useful this vision is to participants with V1 damage (Cowey, 2010b). However, evidence here suggests that training in the blind field also increases awareness of stimuli and therefore the regained vision might be functionally useful to patients in daily life.

5.6.3 Visual training improves untrained clinical luminance detection task

Additionally, I found that almost all participants showed a significant reduction in deficit size (as measured by the HVF) and more areas of improvement than worsening after six months of visual rehabilitation. HVF tests involve detecting spots of light that vary in luminance across the visual field. This suggests that training on a motion discrimination task also generalises to luminance detection. Previous studies have also found that visual training can reduce the size of the visual deficit (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009; Sahraie et al., 2006). In their study, Cavanaugh & Huxlin (2017) reported improvements in luminance detection sensitivity

>6db was 108.1 deg^2 ($sd=22.8 \text{ deg}^2$). In the current study, I found less improvement in luminance detection sensitivity (mean= 31.59 deg^2 , $sd=35 \text{ deg}^2$). This further indicates that more modest effects of the rehabilitation training were found in the current study relative to previous ones (see limitations section below for discussion).

Surprisingly, there was no relationship between improvement on the training in the blind field and reductions in deficit size, or areas of improvement. These changes to the visual field were not related to improvement on the trained task. For example, all participants (except R004), including those who did not improve on the trained task (R005, R006, R023) showed improvements on the Humphrey Visual Fields. This suggests that attending to the blind field alone may help to improve vision.

5.6.4 Efficacy of visual rehabilitation is variable

Although the visual training was successful in improving vision on the trained and untrained tasks, one of the key findings in this study was that the improvement among participants and across blind field locations was variable. Using binomial test it was determined that five participants improved at both locations, 11 improved at only one location and four participants did not show any improvements on the trained task. For these four participants, task performance remained at chance at both locations within the blind field suggesting that visual rehabilitation was ineffective. Moreover, there were several participants who did not show any improvement at one location in the blind field, despite training at that location for six months. This suggests that visual training in the blind field can improve visual function on a trained task, however improvements are variable and the reasons for this are not clear. Previous studies have also found that

rehabilitation is highly variable across participants (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009). Moreover, similar to previous studies, I also found that number of training sessions, but not age, were related to improvements (Cavanaugh & Huxlin, 2017). Unlike previous studies (Cavanaugh & Huxlin, 2017), I also found a significant relationship between improvements and months since lesion, suggesting that those who begin training earlier show greater improvements. This suggests that the amount of training completed by each participant and how early post-stroke they start training might be able to explain some of the variation. However, there was no significant difference in number of training sessions completed at each blind field location and therefore this cannot explain why there is variability in improvements across the blind field. It remains to be determined why some participants do not improve, and why there is variability between blind field locations. It is likely that neuroimaging data will be able to explain this, and this will be discussed in the following chapter.

5.6.5 Limitations and future directions

There were several limitations to this study which could be explored in future research. Firstly, in the current study, the improvements in vision were more modest than previous reports (Cavanaugh & Huxlin, 2017). Previous rehabilitation studies have trained participants for on average 10-12 months (Barbot et al., 2021; Fahrenthold et al., 2021) and up to 46 months in some cases (Barbot et al., 2021). In the current study, participants were only trained five days a week for six months (on average 155 sessions) which is half the amount of training completed in these previous studies. Moreover, the number of training sessions was related to amount of improvement in the current study and Cavanaugh & Huxlin (2017). This suggests that increased duration of training would enhance improvements made in the current study. However, training for more than six months is unlikely to be viable in a clinical setting, as supervision is needed to ensure training is being carried out effectively. In motor stroke survivors, many studies have shown that combining training with brain stimulation (such as transcranial direct current stimulation; tDCS) can enhance improvements in motor function (Fregni et al., 2005; Hummel & Cohen, 2005; Stagg et al., 2012). This suggests that future studies could investigate using other methods such as medication or brain stimulation alongside visual rehabilitation may enhance improvements (see General Discussion for further discussion).

In addition, in the current research only two blind field locations were selected for training over six months. Training locations were chosen semi-arbitrarily to ensure that they were fully within the blind field, non-overlapping and generally transcending the full visual field (e.g., a hemianope would have one location in the upper field, and one in the lower). This meant that training locations were different between participants (see

Figure 32 for all training locations). In the current study, visual improvement was highly variable among participants and between trained locations. The limited improvement seen at some locations and by some participants could have been due to ineffective selection of training locations, rather than an inability to improve. The current study was limited by time constraints as all data collection needed to be finished within one day. Therefore, it was not possible to test all locations within the blind field to find the optimum location for training. A future study might prioritise mapping the entire blind field to determine the most effective training location for each participant. Moreover, neuroimaging data might be effective in localising potentially effective targets for rehabilitation. A recent population receptive field study in patients with damage to V1 showed that spared V1 activity representing perimetrically-blind locations of the visual field was predictive of training-induced recovery (Barbot et al., 2021). Therefore, population receptive field mapping could be used prior to selecting visual field locations to determine the most effective targets.

A further limitation of this research is that only three tests of visual function were used to investigate changes in vision: the trained motion discrimination task, and two untrained tasks (the moving contrast detection and luminance detection from the Humphrey Visual Fields). This means that improvements, and any generalisations to new tasks, can only be tested on these three tasks. It is possible that training on a motion discrimination task may also improve other parameters of vision that are untested here. Throughout training, participants reported noticing changes in their visual fields, for example one participant reported now being able to detect the arm of their partner move within their blind field, when their partner changed gear in the car. Another participant reported that they were now able to pick up motion and shapes within their blind field.

These complex changes to vision and effects on daily living are difficult to quantify using psychophysical tests, and therefore may not be represented by the limited tasks presented here. One way to determine whether visual training impacts activities of daily living would be to use a questionnaire to measure quality of life. There are currently no questionnaires which are specifically designed for stroke survivors with visual loss (Hepworth et al., 2015). However, recently Hepworth et al. (2019) developed a 15-item questionnaire aimed at capturing changes in visual quality of life of stroke survivors with visual deficits. Once validated, this tool may be able to capture changes in daily living due to training in future studies.

Another limitation of this study is that it remains unclear why some locations improved, and others did not. Previous studies have shown that increased baseline BOLD signal change in hMT+ (Ajina et al., 2021), activity in perilesional V1 (Barbot et al., 2021) are related to extent of visual improvement post-training. These studies suggest that baseline activity in the visual cortex might explain variations. Moreover, Barbot et al. (2021) found that population receptive fields were enlarged following training resulting in increased blind field coverage, which may explain why some locations are more likely to improve than others. Alternatively, rehabilitation might be supported by changes in attention towards the blind field, with one study finding increased BOLD resting-state connectivity between the anterior precuneus and occipital pole network after training (Halbertsma et al., 2020). These studies suggest that neuroimaging data may better inform why some participants and some locations are more likely to improve. In the next chapter I will explore whether white matter integrity of visual pathways underlies this improvement in vision.

5.7 Conclusions

This chapter demonstrates that visual training in the blind field can improve visual function (as measured by the trained motion discrimination task and an untrained contrast detection and clinical perimetry test). However, there was considerable variability among participants, with some participants showing improvement at both locations, and other participants showing no improvement on the trained task in either location. Furthermore, improvements on the untrained contrast detection or clinical perimetry test were not dependent on improvement on the trained task. The reasons for this extensive variability are unknown, but changes in the integrity of white matter pathways may underlie these improvements and will be explored in the following chapter.

Chapter 6: Increased white matter integrity of the dLGN-hMT+ pathway after visual rehabilitation.

6.1 Abstract

Recent evidence suggests that visual training in the blind field can partially reverse visual loss from stroke at trained locations. However, as shown in the previous chapter, the efficacy of visual training to improve vision is highly variable across participants, and the reasons for this are poorly understood. It is likely that variance in residual functional or structural neural circuitry following the insult may underlie the variation among patients. Previous research indicates that an intact structural and functional connection between the dorsal lateral geniculate nucleus (dLGN) and the human extrastriate visual motion-processing area (hMT+) supports residual vision. This suggests that changes in this white matter pathway will underlie improvements in motion discrimination training.

Eighteen stroke survivors with unilateral, homonymous field defects from retro-geniculate brain lesions completed six months of motion discrimination training at home. Visual training involved performing two daily sessions of a motion discrimination task, at two non-overlapping locations in the blind field, at least five days per week. Motion discrimination ability, Humphrey perimetry, as well as structural and diffusion-weighted MRI were collected pre- and post-training. Diffusion-weighted data were analysed using the open-access platform brainlife.io. Diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) models were fit to the data to provide measures of white matter microstructure including fractional anisotropy (FA;

DTI model), mean diffusivity (MD), neurite density index (NDI; NODDI model) and orientation dispersion index (ODI; NODDI model).

Changes in diffusion-weighted microstructural markers were analysed in two visual tracts: (1) between the ipsilesional dLGN and hMT+, and (2) between the ipsilesional dLGN and V1. The [non-visual] tract between the ventral posterior lateral nucleus of the thalamus (VPL) and the primary somatosensory cortex (S1) was also analysed as a control. Tractographic changes were compared between the pre- and post-training visits and to improvements in motion discrimination and Humphrey perimetry-derived metrics.

There was no significant increase in mean FA between the pre- and post-training visits across the dLGN-V1 or dLGN-hMT+ tracts nor in the VPL-S1 control tract as expected. Change in FA in these pathways was unrelated to either motion discrimination performance or Humphrey perimetry-derived metrics. However, when the distal portion of the dLGN-hMT+ (which does not overlap with dLGN-V1) was compared between pre- and post-training there was a significant increase in FA. Moreover, there was a corresponding increase in NDI and decrease in ODI. This suggests that neurite density increases, and dispersion of axons reduces with training which might reflect increases in myelination. Moreover, it provides evidence that changes in the dLGN-hMT+ fibre tract underlies visual rehabilitation post-stroke.

This study has the potential to lead to greater understanding of the white matter microstructure of pathways underlying the behavioural outcomes resulting from visual training in retro-geniculate strokes. Understanding the neural mechanisms that support visual rehabilitation is fundamental to the development of more targeted, and thus effective treatments for this underserved patient population.

6.2 Introduction

As discussed in the previous chapter, visual training within the blind field can be used to improve vision loss post-stroke. These techniques involve repeatedly stimulating a portion of the blind field and require patients to discriminate visual stimuli within their blind field (Melnick, Tadin and Huxlin, 2016). These programmes have successfully reduced the size of the visual deficit (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009; Sahraie et al., 2006) and improved contrast sensitivity (Das et al., 2014b; Sahraie et al., 2006), direction discrimination and orientation discrimination (Cavanaugh et al., 2015, 2019; Das et al., 2014b).

Despite their success, the efficacy of visual training programmes remains highly variable across participants (Cavanaugh & Huxlin, 2017; Elshout et al., 2016; Halbertsma et al., 2020; Huxlin et al., 2009) and the reasons for this are poorly understood. Furthermore, the precise neural mechanisms underlying improvements in vision are yet to be determined. Variability in the extent and location of stroke damage may help to explain the inconsistency in visual improvement due to the specific fibre tracts that are affected and their potential for plastic change to improve visual function. Here, I used neuroimaging to measure changes in brain structure in relation to training and recovery of vision in stroke survivors with visual loss. The aim of the study was to inform our understanding of the neural mechanisms underlying training-induced visual recovery after occipital stroke.

Functional training changes the microstructure of white matter pathways and can be quantified using diffusion-weighted imaging. Diffusion tensor imaging (DTI) is often used as an estimate of tissue microstructure and is sensitive to the degree of anisotropic

water diffusion. For example, training in the motor system produces increases in fractional anisotropy (FA; a measure of myelination and organisation of fibre tracts), which is directly related to improvements in motor skill after training (Scholz et al., 2009). In stroke survivors, training increases FA in motor tracts and relates to motor improvement (Fan et al., 2015). FA is also predictive of motor outcomes in skill training in healthy controls and stroke survivors (Jang, 2010; Sampaio-Baptista, Sanders and Johansen-Berg, 2018). It was predicted, therefore, that improvements in vision due to training in stroke survivors with visual loss would produce measurable changes in FA in white matter pathways connecting areas activated by training.

While vision loss post-stroke leads to the loss of normal, conscious vision, some patients retain the ability to detect or discriminate visual information in their blind field. This is known as 'blindsight' and has been shown to improve with training (Stoerig & Cowey, 1997). Studies suggest that intact pathways between the ipsilesional dLGN and extrastriate motion area hMT+ are necessary for residual vision (Ajina, Pestilli, et al., 2015; Ajina & Bridge, 2018; Bridge et al., 2010; Schmid et al., 2010). Based on these studies, it was predicted that increases in FA in the dLGN-hMT+ pathway will underlie training-related improvements in motion discrimination thresholds in visual loss post-stroke (hypothesis 1).

Blindsight is most reliably elicited by large (>4 degrees), moving stimuli (5-20Hz; (Das, Tadin and Huxlin, 2014). However, evidence suggests that vision beyond blindsight ability, such as luminance contrast detection, can also be improved by visual training in visual loss post-stroke (Cavanaugh and Huxlin, 2017). Receptive fields in V1 are driven by small spots of light that vary in luminance (Barlow et al., 1957; Hubel & Wiesel, 1959), such as those used in Humphrey perimetry. Thus, training induced improvements beyond

blindsight abilities may result from bringing functionally impaired, spared V1 back 'online' (Barbot et al., 2021; Papanikolaou et al., 2014). I therefore additionally hypothesised that increases in FA in the dLGN-V1 pathway would underlie training-related improvements in luminance contrast detection (Humphrey Visual Fields; hypothesis 2).

Hypotheses

Hypothesis 1: Increase in FA in the ipsilesional dLGN-hMT+ pathway would be related to improvement in motion discrimination thresholds.

Hypothesis 2: Increases in FA in the ipsilesional dLGN-V1 pathway would be related to improvements in luminance detection (Humphrey Visual Fields).

6.3 Methods

6.3.1 Participants

Eighteen (out of 24 participants total) healthy stroke survivors with damage to V1 resulting in visual field deficits took part in this study (median=47 years, range=24-71 years, 6=Female). All participants were at least six-months post stroke (median=27.5; range=6-297 months). Six participants were excluded from this study: four participants did not complete the six-month training programme (R001; R008; R009; R012), and MRI data were not collected in two additional participants (R016; R021). All participants completed at least 100 sessions of training, with the median being 152.5 sessions (range = 102-271 sessions).

6.3.2 Study design

As discussed in Chapter 2, each participant completed six months of visual rehabilitation in the blind field (two locations, five days per week). Each participant visited the research centre for assessments on two occasions: pre- and post-training. Psychophysical motion discrimination ability, Humphrey perimetry and MRI data were collected at each assessment.

6.3.3 Psychophysics

Visual training

Participants trained on a psychophysical motion discrimination task at two locations within their blind field for six months. Two locations were used to maximise the amount of rehabilitation each participant would complete. The locations were chosen semi-arbitrarily so they would span the entire visual field (e.g., one in each quadrant for a hemianope; see Chapter 2 for details). Three participants (R017; R023; R024) only trained at one location due to time constraints.

Visual improvements

The motion discrimination trained task was also used to determine whether percentage correct improved between the pre- and post-training visit with fixation controlled. Additionally, Humphrey visual fields were collected and analysed to calculate areas of improvement. See Chapter 5 for full details of behavioural analysis. These metrics were then compared to brain imaging data to determine whether changes in brain connectivity could explain variability in improvements.

6.3.4 Imaging acquisition

Diffusion acquisition

Diffusion-weighted data were acquired for each participant at the pre- and post-training sessions using the UK Biobank sequence (Miller et al., 2016; see Chapter 2 for scan parameters).

6.4 Analysis

6.4.1 Behavioural analysis

At the pre- and post-training visits, percentage correct on the motion discrimination task was calculated at each trained blind field location. These were then averaged together to give overall change in percentage correct in the blind field. Area of improvement on the Humphrey Visual Fields between the pre- and post-training visits was also calculated (see Chapter 2 for details). These changes in behaviour due to training were then compared to diffusion-weighted metrics in this analysis.

6.4.2 MRI analysis

All data acquired for this project were managed and analysed using the open science platform brainlife.io. Initially, data were securely stored in a private project on brainlife.io and processed using state-of-the-art reproducible Apps (Pestilli, 2018; Avesani *et al.*, 2019; see Figure 36 for diagram of processing pipeline).

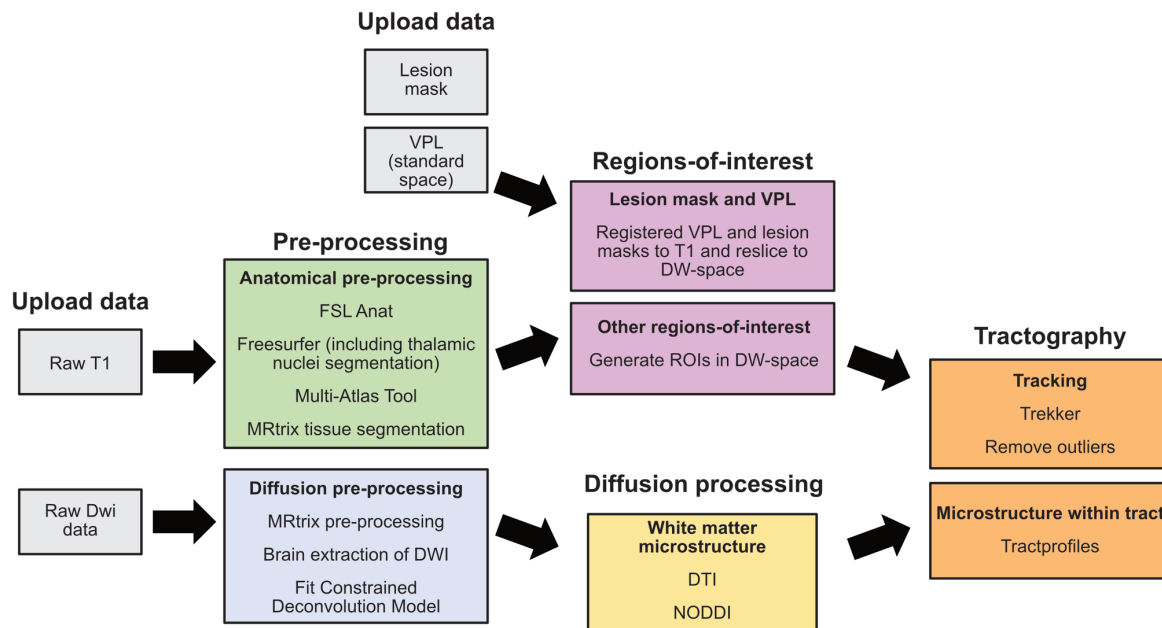


Figure 36. Processing pipeline in Brainlife.io. Raw anatomy, DWI data, lesion masks and VPL masks in standard space (grey) were uploaded for each participant and timepoint. Anatomical data were pre-processed using apps listed (green). Once pre-processing had completed, regions-of-interest were defined (pink). Lesion and VPL masks were registered to anatomical data and then resliced into diffusion-weighted (DW) space. Additional regions-of-interest from the Glasser atlas were generated using Freesurfer parcellations and resliced into DW-space. Diffusion data were pre-processed using apps listed (blue). Once data were pre-processed, DTI and NODDI models were fit to the data to quantify white matter microstructure. Tractography was then run between dLGN-V1, dLGN-hMT+ and VPL-S1 using the Trekker app. Tract outliers were removed using the remove outliers app. Finally, Tractprofiles was used to calculate white matter microstructure along the tract.

All data products were generated by tracking their provenance (i.e., keeping a record of the combination of the generated data product and processing application used to generate the data; Avesani et al., 2019). All apps used are listed in Table 5 with weblinks and digital object identifiers.

Table 5. Description, weblinks and DOI for the open cloud app services used to process these data.

	Application	Github Repository	Open Service DOI
Anatomical pre-processing	FSLAnat	https://github.com/brainlife/app-fsl-anat	10.25663/brainlife.app.273
	Freesurfer	https://github.com/brainlife/app-freesurfer	10.25663/bl.app.0
	Multi-atlas tool	https://github.com/faskowit/app-multiAtlasTT	10.25663/brainlife.app.470
	Tissue-type segmentation	https://github.com/brainlife/app-mrtrix3-5tt	10.25663/brainlife.app.239
Diffusion pre-processing	mrtrix3 preprocess	https://github.com/brain-life/app-mrtrix3-preproc	10.25663/bl.app.68
	Brain extraction of DWI	https://github.com/brainlife/app-FSLBET	10.25663/brainlife.app.163
Regions of interest	<u>Apply warp from subject-to-standard space to ROIs (T1w)</u>	https://github.com/brainlife/app-register-rois-mni	10.25663/brainlife.app.715
	Reslice ROIs to DWI space	https://github.com/bacaron/app-reslice-rois-dwi	10.25663/brainlife.app.671
	Generate all ROIs from Glasser parcellation	https://github.com/brainlife/app-roiGenerator	10.25663/brainlife.app.592
	Generate visual ROIs from Glasser parcellation	https://github.com/brainlife/app-roiGenerator	10.25663/brainlife.app.411
	Combine ROI	https://github.com/svincibo/app-combineROI	10.25663/brainlife.app.313
	FSLmaths	https://github.com/hanna-willis/app-roi-fslmaths	10.25663/brainlife.app.680
Diffusion processing	FSLDTIFIT	https://github.com/brainlife/app-fslDTIFIT	10.25663/brainlife.app.292
	NODDI	https://github.com/brainlife/app-noddi-amico	10.25663/brainlife.app.365
Tractography	Trekker ROI Tracking (DWI)	https://github.com/brainlife/app-trekker-roi-tracking	10.25663/brainlife.app.355
	Remove Tract Outliers	https://github.com/brainlife/app-removeTractOutliers	10.25663/brainlife.app.195
	Tract Analysis Profiles	https://github.com/brainlife/app-tractanalysisprofiles	10.25663/brainlife.app.361

Anatomical pre-processing

Raw anatomical (T1) images were pre-processed using the FSL tool *FSLanat* (brainlife/app-fsl-anat). These images were cropped and reoriented to a standard MNI152 template using a linear transform. Pre-processed images were then processed in Freesurfer (brainlife/app-freesurfer) to generate cortical and white matter surfaces. The Human Connectome Project multimodal parcellation (hcp-mmp) was then mapped to the Freesurfer surfaces using the multi-Atlas Tool (brainlife/app-multiAtlasTT). Pre-processed images were then segmented into tissue-types (gray matter, white matter, CSF) using the MRTrix 5ttgen function (brainlife/app-mrtrix3-5tt).

Regions-of-interest

Masks for dLGN, V1, hMT+ and S1 were created for each participant in brainlife using the Freesurfer parcellations and resliced into diffusion space (brainlife/app-roiGenerator). VPL was derived from the FSL Oxford Thalamic Connectivity Probability Atlas and was uploaded to brainlife. Lesions masks were manually delineated for each participant and uploaded to brainlife. Lesion and VPL masks were then registered to acpc-aligned anatomical images (brainlife/app-register-rois-mni) and resliced into diffusion space (brainlife/app-reslice-rois-dwi). V1 in the damaged hemisphere was then masked by the lesion to ensure that only brain tissue was included in the definition (brainlife/app-roi-fslmaths).

Diffusion pre-processing

Raw diffusion images were pre-processed using MRTrix3 (brainlife/app-mrtrix3-preproc). Pre-processing steps included 1) reorientation to standard MNI152 template (*Fslutils* tool, FSL; Jenkinson et al., 2012), 2) gradient orientation check (*dwigradcheck* command in MRTrix3; Jeurissen et al., 2014), 3) PCA denoising (*dwidenoise* command in MRTrix3; Veraart et al., 2016), 4) Gibbs deringing (*mrdegibbs* command in MRTrix3; Kellner et al., 2016), 5) susceptibility-weighted distortion correction of the reverse phase encoding directions (AP and PA) using FSL's *topup* function (Smith et al., 2004; Woolrich et al., 2009), 6) Eddy-current and motion-correction using the *Eddy* tool in FSL (Andersson & Sotiropoulos, 2016), 7) debias using ANT's *n4* functionality (Tustison et al., 2014), 8) registration of DWI to the anatomical image (*epi_reg* in FSL; Jenkinson et al., 2002; Jenkinson & Smith, 2001) and reslicing to 1mm isotropic voxels. The FSL Brain Extraction tool in Brainlife (brainlife/app-FSLBET; Smith, 2002) was used to create brain masks of the pre-processed, acpc-aligned diffusion images.

Following pre-processing, the diffusion tensor imaging (DTI) models (brainlife/app-fslDTIFIT; Pierpaoli et al., 1996) and neurite orientation dispersion and density imaging (NODDI) models (brainlife/app-noddi-amico; (Daducci et al., 2015; Zhang et al., 2012) were fit to the pre-processed data. The constrained spherical deconvolution model (CSD; Tournier et al., 2007) was also fit to the pre-processed data to guide tractography using functions from MRTrix3 (brainlife/app-mrtrix3-act).

Tractography

Tractography between dLGN-hMT+, dLGN-V1 and VPL-S1 was conducted using Trekker (brainlife/app-trekker-roi-tracking; Aydogan & Shi, 2020). For the VPL-S1 and dLGN-V1 pathways, minimum and maximum length of streamlines were set at 10 and 200 respectively and a single lmax was used (set at 8). Due to sparse fascicles when tracking the dLGN-hMT+ pathway, the parameters were adjusted, setting the minimum and maximum length of streamlines at 50 and 150 respectively and ensemble tracking (Takemura et al., 2016) across 4 spherical harmonic orders (i.e., lmax) was used. Hemisphere exclusions were used for all tracts to ensure that they remained within the same hemisphere. The optimum radius of curvature, step size and fibre orientation distribution were determined by the Trekker algorithm. 1000 streamlines were tracked for each pathway. Streamlines were only included if they touched both regions-of-interest and travelled within white matter in the same hemisphere. Examples of the three tracts of interest in one participant are shown in Figure 37.

Outlier fascicles were then removed from analyses so that the tract estimate was conservative (brainlife/app-removeTractOutliers). Outlier fascicles were defined as those located more than 2.6 standard deviations away from the core of the tract or 2.8 standard deviations longer than the mean tract length, using a Gaussian distribution to represent fascicle length and distance. If this calculation was not possible due to the sparse fascicles (<10), it was assumed that tracking was not possible between two areas of interest. Data were removed for 3 participants (R004, R006, R010) for the dLGN-V1 tract and 2 participants (R004 and R006) for the dLGN-hMT+ tract due to difficulties with tracking between regions-of-interest for at least one timepoint. No data were removed from the VPL-S1 tract.

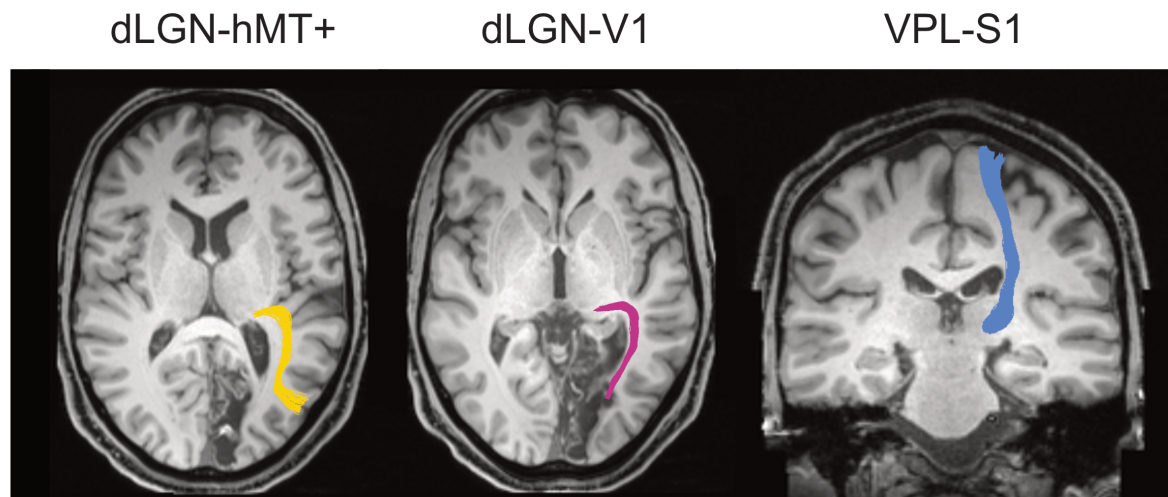


Figure 37. Example of the three ipsilesional tracts of interest. Data are presented for participant R022 shown on the high resolution structural T1. Yellow: dLGN-hMT+; Pink: dLGN-V1; Blue: Control tract VPL-S1.

White matter microstructure

Diffusion metrics within tracts were then processed using the Track Analysis Profiles app in brainlife (brainlife/app-tractanalysisprofiles; Yeatman et al., 2012). DTI and NODDI models were used to estimate the microstructural properties of the white matter tracts at each time point. These microstructural parameters were combined with the spatial information of each tract trajectory to give an average of each parameter weighted by distance from the mean of the tract at each trajectory. Each tract was resampled to 100 nodes, distributed equally along the length of the tract (Yeatman et al., 2012). The initial and last 15 nodes (1-15 and 85-100) were removed to limit grey matter contamination and partial volume effects. These clipped profiles were then used to calculate measures of mean microstructural parameters in and along each tract of interest.

6.5 Statistical analysis

All statistical analyses were carried out in R studio (R version 4.1.2). Non-parametric paired Wilcoxon tests were used to investigate whether diffusion-weighted metrics changed between the pre- and post-training visit. Wilcoxon tests were carried out using the *rstatix* package. Change scores were calculated for the motion discrimination task and diffusion metrics (FA, MD, NDI and ODI) by subtracting the pre-training score from the post-training score. Linear regression analyses were then used to determine the relationship between improvements in training and tract measures using the *stats* package. Linear mixed effects models were used to determine differences along the distal dLGN-hMT+ tract between timepoints using the *lme4* package. Bonferroni-Holm adjusted p-values were calculated using the *stats* package.

6.6 Results

6.6.1 Variability in training efficacy

Ability on the trained motion discrimination task and untrained Humphrey perimetry task was measured for each participant at the pre- and post-training visits. As discussed in Chapter 5, there was a significant improvement in performance on the trained task between the pre- (median=53.25%; IQR=5%) and post-training visits (median=67%; IQR=7%) and this change was significantly different from zero ($W=180$; Holm-Bonferroni corrected $p=0.002$; effect size $r = 0.76$, magnitude=large; see Chapter 5 results for further details). These results suggest after six months of visual training, participants improved at the trained task. However, as discussed in the previous chapter, improvements on the trained task were variable among participants (range=48.5%-84% correct). In addition,

the extent of the area improved on the untrained Humphrey perimetry varied across participants (median=19.44deg², IQR=36.69deg²).

6.6.2 Change in white matter microstructure after training

dLGN-hMT+ tract

Paired Wilcoxon tests were used to determine whether the median differed between the pre- and post-training visits for all diffusion metrics (FA, MD, NDI and ODI) in the dLGN-hMT+ tract. Results of these tests are presented in Table 6. There was no significant change in FA, MD, NDI or ODI between the pre- and post-training visits ($p \leq 0.05$).

Table 6. Diffusion measures for the dLGN-hMT+ tract.

Diffusion measure	Pre-training Median	Post-training Median	Pre-training IQR	Post-training IQR	W	P-value	Effect size
FA	0.353	0.355	0.030	0.032	42	0.330	0.26 (small)
MD	0.954	0.955	0.059	0.079	49	0.056	0.16 (small)
NDI	0.512	0.511	0.052	0.091	53	0.720	0.10 (small)
ODI	0.158	0.150	0.021	0.022	74	0.454	0.21 (small)

dLGN-V1 tract

Additionally, paired Wilcoxon tests were also used to investigate whether there was a change between the pre- and post-training visits for the diffusion metrics (FA, MD, NDI and ODI) in the dLGN-V1 tract (see Table 7 for summary statistics). There was also no significant change in FA, MD, NDI or ODI between the pre- and post-training visits ($p \leq 0.05$).

Table 7. Diffusion measures for the dLGN-V1 tract.

Diffusion measure	Pre-training Median	Post-training Median	Pre-training IQR	Post-training IQR	W	P-value	Effect size
FA	0.365	0.366	0.04	0.05	41	0.303	0.28 (small)
MD	1.022	1.02	0.104	0.078	59	0.978	0.01 (small)
NDI	0.462	0.472	0.05	0.043	49	0.561	0.16 (small)
ODI	0.118	0.124	0.028	0.028	62	0.934	0.03 (small)

VPL-S1 tract

Finally, paired Wilcoxon tests were used to compare the median diffusion metrics (FA, MD, NDI and ODI) between the pre- and post-training visits in the control sensorimotor tract (VPL-S1; see Table 8 for summary statistics). Unsurprisingly, there was also no significant change in FA, MD, NDI or ODI between the pre- and post-training visits ($p \leq 0.05$).

Table 8. Diffusion measures for the VPL-S1 tract.

Diffusion measure	Pre-training Median	Post-training Median	Pre-training IQR	Post-training IQR	W	P-value	Effect size
FA	0.353	0.358	0.04	0.019	76	0.702	0.1 (small)
MD	0.874	0.874	0.035	0.043	74	0.64	0.12 (small)
NDI	0.606	0.604	0.043	0.041	61	0.304	0.25 (small)
ODI	0.182	0.183	0.035	0.027	78	0.766	0.08 (small)

6.6.3 Relationship between behavioural improvements and changes in white matter microstructure

Improvements on training

In the previous section, no changes in any DTI (FA; MD) or NODDI (NDI; ODI) measures of white matter integrity were found between the pre- and post-training visits between any of the tracts of interest (dLGN-hMT+, dLGN-V1 or VPL-S1). However, as can be seen in Figure 38, there was significant variability in FA and MD among participants at the pre- and post-training visits. Participants also varied in the amount of improvement made following visual rehabilitation for both the trained and untrained tasks. This variability among participants might reduce sensitivity to changes based on group averages. Furthermore, variability in the rehabilitation outcomes might be explained by variability in changes in white matter microstructure. In the next analysis, I investigated the relationship between tract measures and improvements on the trained task.

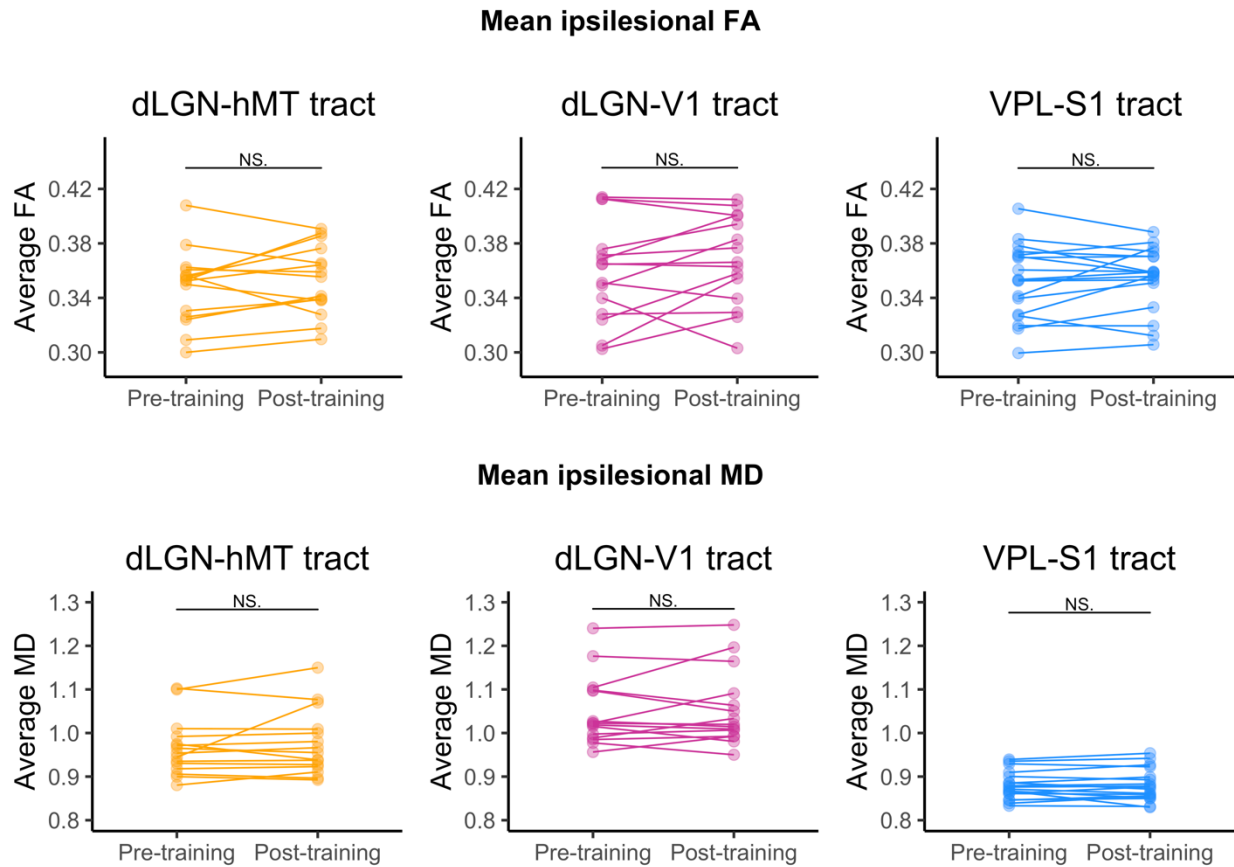


Figure 38. Mean change in FA and MD in tracts of interest. Change in FA (upper) and MD (lower) is shown in ipsilesional LGN-hMT+ (yellow), LGN-V1 (pink) and VPL-S1 (blue) between pre- and post-training. Joined scatter points represent datapoints for each participant at each timepoint.

Surprisingly, as can be seen from Figure 39, there was no relationship between change in FA in the dLGN-hMT+ tract and improvement on the trained task ($R^2=0.09$, $F(1,14)=2.4$, $p=0.144$). Nor was there a significant relationship between mean FA in the dLGN-V1 tract and improvements ($R^2=-0.08$, $F(1,13)=0.01$, $p=0.906$). As expected, there was no significant relationship between mean FA change in VPL-S1 and improvements on the task ($R^2=-0.05$, $F(1,16)=0.18$, $p=0.679$). Moreover, when baseline levels of FA were controlled using multiple linear regression, there was still no relationship between

changes in FA and improvement on the trained task in the dLGN-hMT+ tract ($R^2=0.15$, $F(2,13)=1.14$, $p=0.173$), dLGN-V1 tract ($R^2=-0.17$, $F(2,12)=0.007$, $p=0.907$) or control VPL-S1 tract ($R^2=-0.12$, $F(2,15)=0.08$, $p=0.731$).

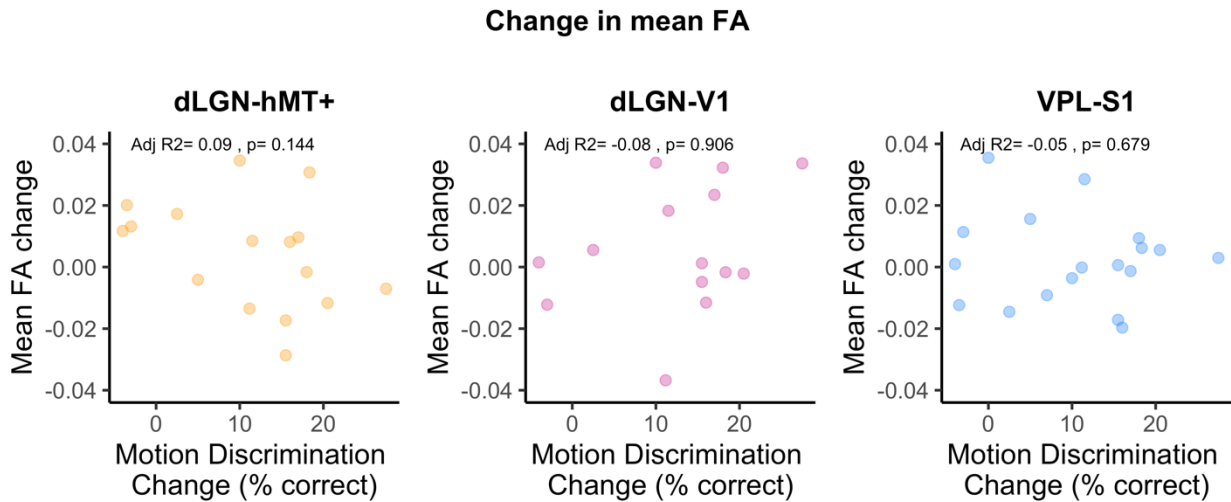


Figure 39. Scatter plots showing the relationship between mean FA change tracts of interest and improvements in percentage correct on the trained task. Plots show the relationship between FA in dLGN-hMT (yellow), dLGN-V1 (pink), VPL-S1 (blue) and change in percentage correct on the trained motion discrimination task between the pre- and post-training timepoints. Adjusted R^2 and p values from linear regressions are indicated. There was no significant relationship between improvement on the trained task and mean FA change across any of the tracts.

As can be seen from Figure 40, there was also no relationship between improvements on the trained task and MD in dLGN-hMT+ tract ($R^2=-0.02$, $F(1,14)=0.76$, $p=0.398$), the dLGN-V1 tract ($R^2=0.09$, $F(1,13)=2.37$, $p=0.147$) or control tract VPL-S1 ($R^2=-0.02$, $F(1,16)=0.62$, $p=0.442$).

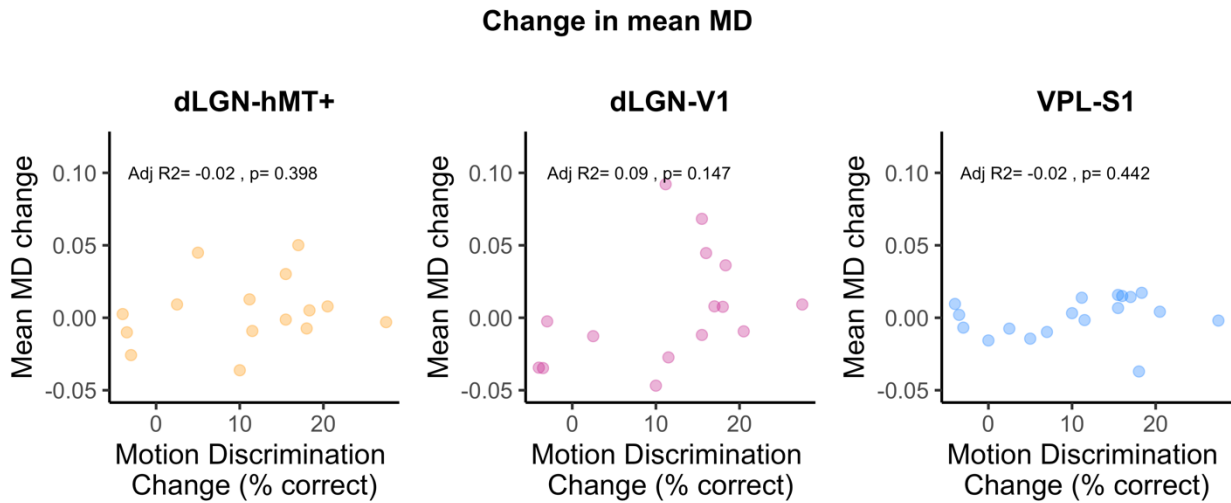


Figure 40. Scatter plots showing the relationship between mean MD change tracts of interest and improvements on the trained task. Plots show the relationship between mean MD change in dLGN-hMT (yellow), dLGN-V1 (pink), VPL-S1 (blue) and improvement in percentage correct on the motion discrimination task. Adjusted R^2 and p values from linear regressions are indicated. There was no significant relationship between improvement on the trained task and mean MD change across any of the tracts.

Improvements in the visual field

It was hypothesised that improvements on the Humphrey visual field tests would be related to strengthening of the dLGN-V1 pathway. However, no relationship between change in FA (Adjusted $R^2=0.13$, $F(1,11)=2.72$, $p=0.128$) or MD (Adjusted $R^2=0.1$, $F(1,11)=2.3$, $p=0.157$) in the dLGN-V1 tract and area of improvement was found (see Figure 41). Moreover, there was no relationship between change in FA (Adjusted $R^2=-0.01$, $F(1,12)=0.87$, $p=0.369$) or MD (Adjusted $R^2=-0.08$, $F(1,12)=0$, $p=0.984$) in the dLGN-hMT tract and area of improvement. Unsurprisingly, there was also no relationship between change in FA in the control VPL-S1 tract (Adjusted $R^2=-0.07$, $F(1,14)=0.01$, $p=0.917$). There was a significant relationship between change in MD and area of improvement, however

this did not survive correction for multiple comparisons (*Adjusted $R^2=0.22$, $F(1,14)=5.35$, Holm-Bonferroni corrected $p=0.216$*).

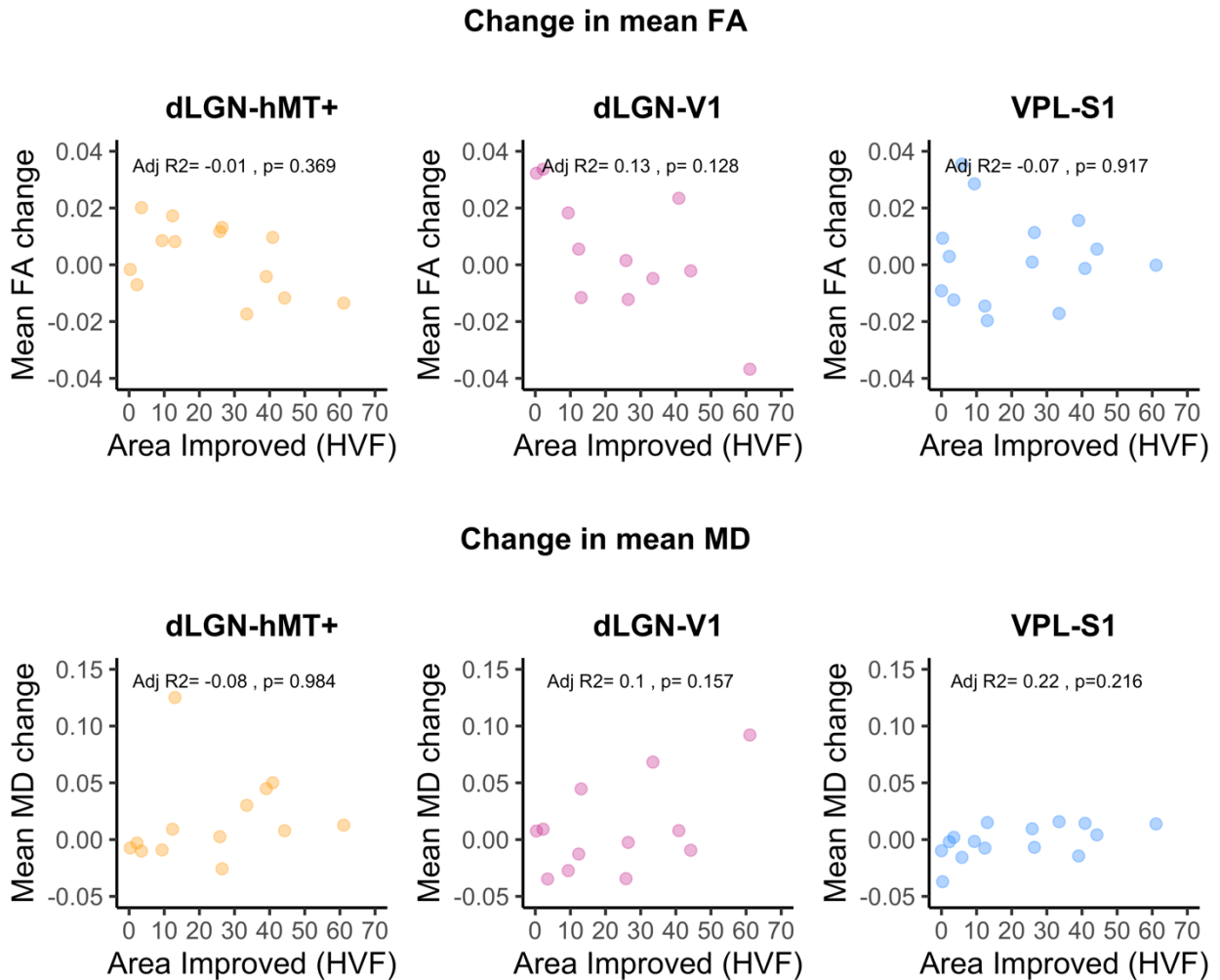


Figure 41. Scatter plots showing the relationship between mean FA and MD change tracts of interest and improvements on the untrained task. Plots show the relationship between mean FA (upper) and mean MD (lower) change in dLGN-hMT (yellow), dLGN-V1 (pink), VPL-S1 (blue) and area of improvement on the Humphrey Visual Fields. Adjusted R^2 and Holm-Bonferroni adjusted p values from linear regressions are indicated. There was no significant relationship between improvement on the Humphrey perimetry and mean FA or MD change across any of the tracts.

6.6.4 White matter microstructure along the tract

One limitation of diffusion-weighted imaging analyses is that diffusion properties are usually averaged over the length of the tract (for example, mean FA). However, it is known that diffusion properties vary along the length of the tract (Yeatman et al., 2012). Averaging along the length of the tract in the previous analyses may have obscured significant changes in white matter properties due to training. In humans, there is significant overlap between the dLGN-V1 and dLGN-hMT+ tracts (see Figure 42A, for example participant). There is also known to be significant transsynaptic retrograde degeneration of the optic radiation that projects from dLGN to V1 after strokes to the occipital lobe (Bridge et al., 2011; Millington et al., 2014). This degeneration of the dLGN-V1 tract post-stroke might therefore mask training-induced changes in the dLGN-hMT+ tract. The distal, non-overlapping, portion of the dLGN-hMT+ (between 60-85% of the total tract length) has been previously linked to residual vision after V1 stroke (Ajina, Pestilli, et al., 2015).

Based on this previous study, I compared the same distal portion (nodes 60-85) of the dLGN-hMT+ pathway after it branches away from the geniculate-radiation bundle between pre- and post-training. For this analysis, diffusion measurements were quantified at 100 nodes along the tract, before being clipped to contain only nodes 60-85 to investigate whether distinct portions of the tract profiles changed with training. As can be seen in Figure 42B, FA varies along the dLGN-hMT+ tract between the pre- and post-training visits.

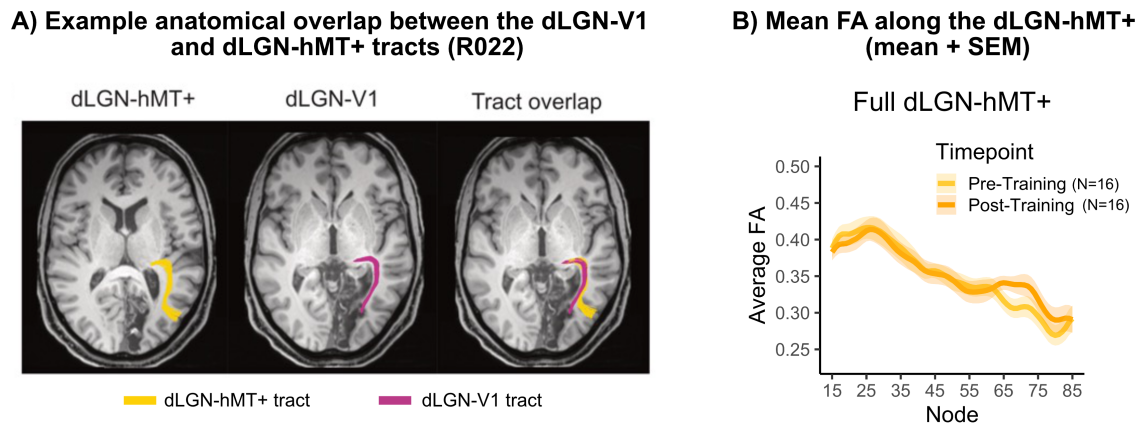


Figure 42. The distal dLGN-hMT+ tract. (A) Example overlapping visual tracts. Ipsilesional dLGN-hMT+ (left) and dLGN-V1 (middle) in one representative participant (R022) demonstrating the significant overlap (right). (B) Average FA tract profile for the full dLGN-hMT+ tract for the Pre-Training and Post-Training timepoints. Lines represent the mean FA across participants at each node, while shaded error bars reflect the standard error of the mean.

Changes in FA, MD, NDI and ODI in the distal dLGN-hMT+

As can be seen in Figure 43, there was a significant increase in FA across the distal portion of the tract between the pre- and post-training visits ($\beta = -0.02$, 95% CI $[-0.03, -0.01]$, $t(772) = -6.51$, Holm-Bonferroni corrected $p < .001$; Std. $\beta = -0.32$, 95% CI $[-0.42, -0.23]$). Moreover, there was a slight reduction in mean diffusivity between the pre- and post-training visits but this was not statistically significant ($\beta = 8.06e-03$, 95% CI $[-4.47e-04, 0.02]$, $t(772) = 1.86$, Holm-Bonferroni corrected $p = 0.063$; Std. $\beta = 0.07$, 95% CI $[-3.86e-03, 0.14]$). There was also a significant increase in neurite density index (NDI) ($\beta = -8.47e-03$, 95% CI $[-0.01, -3.34e-03]$, $t(772) = -3.24$, Holm-Bonferroni corrected $p = 0.002$; Std. $\beta = -0.11$, 95% CI $[-0.18, -0.04]$) and significant decrease in orientation dispersion index

between the pre- and post-training visit ($\beta = 0.02$, 95% CI [0.01, 0.02], $t(772) = 5.16$, Holm-Bonferroni corrected $p < .001$; Std. $\beta = 0.24$, 95% CI [0.15, 0.34]).

Diffusion Metrics along the distal dLGN-hMT+ tract (mean + SEM)

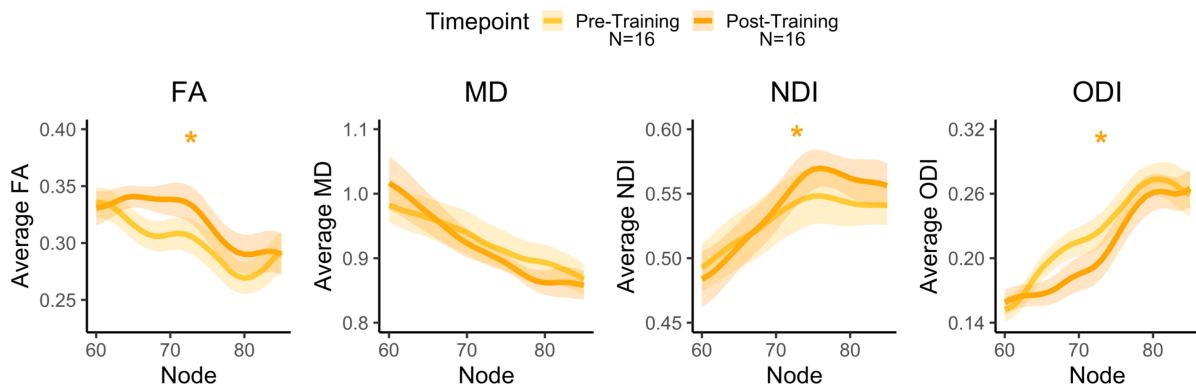


Figure 43. Diffusion metrics along the distal portion of the dLGN-hMT+. Plots shows change in FA, MD, NDI, and ODI for distal dLGN-hMT+ tract (nodes 60-85) at pre- (yellow) and after six months of visual training (orange). There is a significant increase in FA and NDI, and decrease in ODI between the pre- and post-training visit. No significant change in MD was found.

Relationship to behaviour

There was no relationship between improvements in percentage correct in the blind field on the trained task and changes in FA ($\text{adjusted } R^2 = -0.07$, $F(1,14) = 0.03$; $p = 0.863$), MD ($\text{adjusted } R^2 = 0.03$, $F(1,14) = 1.47$; $p = 0.246$), NDI ($\text{adjusted } R^2 = 0.001$, $F(1,14) = 1.02$; $p = 0.330$) or ODI ($\text{adjusted } R^2 = -0.06$, $F(1,14) = 0.13$; $p = 0.728$) in the distal dLGN-hMT+ tract. Nor was there any relationship between area of improvement on the perimetry and changes in FA ($\text{adjusted } R^2 = -0.07$, $F(1,14) = 0.03$; $p = 0.856$), MD ($\text{adjusted } R^2 = -0.07$, $F(1,14) =$

0.03; $p=0.861$), NDI (*adjusted* $R^2=-0.07$, $F(1,14)=0.07$; $p=0.789$) or ODI (*adjusted* $R^2=-0.06$, $F(1,14)=0.16$; $p=0.696$) in the distal dLGN-hMT+ tract.

6.7 Discussion

This chapter investigated whether diffusion-weighted imaging measures of white matter microstructure were related to visual rehabilitation post-stroke. Here, I explored whether measures of white matter microstructure changed with training, and whether these changes were related to improvements on the trained motion discrimination task, or improvements on the clinical Humphrey visual fields. No significant change in white matter integrity was found between the pre- and post-training visits in any of the full tracts of interest. However, a significant increase in FA and NDI, and reduction in ODI was found after training in the distal, non-overlapping portion of the dLGN-hMT+ tract.

6.7.1 Visual rehabilitation is associated with changes in white matter microstructure of the distal dLGN-hMT+ pathway

Previous studies in the motor system have found that training increases FA in healthy participants (Scholz et al., 2009) and stroke survivors (Fan et al., 2015). Moreover, in stroke survivors with visual loss, residual vision has been linked to the integrity of the white matter pathway between the distal portion of the dLGN-hMT+ pathway (Ajina, Pestilli, et al., 2015). An initial analysis found no significant difference between DTI (FA or MD) or NODDI (NDI and ODI) measures between the two timepoints for either the dLGN-V1 or dLGN-hMT+ pathways. However, as discussed in Ajina et al. (2015), there is significant overlap between the dLGN-V1 and dLGN-hMT+ pathways which might have obscured changes in the dLGN-hMT+ pathway due to training. A further analysis,

investigating the distal, non-overlapping portion of the dLGN-hMT+ found a significant increase in FA and NDI and decrease in MD and ODI after training.

Increased FA and reduced MD after training suggests an increase in anisotropic, hindered water diffusion in the distal dLGN-hMT+ tract which . These changes might reflect increased white matter integrity or improved organisation of this pathway after training driven by increased myelination or the reduction of crossing fibres (Beaulieu, 2014). Moreover, a corresponding increase in NDI and decrease in ODI indicate that these changes are due to an increased density of neurites and greater fibre orientation coherence in this pathway after training (Zhang et al., 2012). Increased NDI and reduced ODI have previously been related to increased axonal regrowth and myelination (Jelescu et al., 2015; Kamiya et al., 2020) and therefore these mechanisms might be supporting rehabilitation from visual training. These results suggest the dLGN-hMT+ pathway underlies visual rehabilitation post-stroke. This finding fits with the current literature in humans (Ajina, Pestilli, et al., 2015) and non-human primates (Schmid et al., 2010) that implicates the dLGN-hMT+ pathway in residual vision after damage to V1. Moreover, measures of both FA and MD were similar to Ajina et al. (2015), which suggests these are representative values.

6.7.2 No evidence of ongoing degeneration over six months

In the current study, I also found no evidence of a decrease in FA or increase in MD in either the dLGN-V1 or dLGN-hMT+ tracts after training. There is significant evidence that the dLGN-V1 pathway, also known as the optic tract, shows signs of retrograde degeneration after damage to V1. Retinal ganglion cells project from the retina to the dLGN along the optic nerve, and on to the occipital cortex via the optic tract. Following occipital lesions, the transsynaptic target of these retinal ganglion cells is damaged leading to transsynaptic retrograde degeneration of retinal ganglion cells and neurons in the dLGN. In non-human primates (Covey et al., 2011; Hendrickson et al., 2015) and humans with V1 lesions (Bridge et al., 2011; Millington et al., 2014) there is evidence of a reduction in optic tract size and integrity. Additionally, in non-human primates, Covey et al. (2011) found that retrograde degeneration was most pronounced for the optic tract for the first 3-years post-stroke and was followed by continued decline in ganglion cells. Most participants (13/18 participants) in the current study were less than 3 years post-stroke, suggesting that they would still be experiencing retrograde degeneration of the optic tract. In their study, Millington et al. (2014) found that diffusion-weighted measures of FA were correlated with anatomical indicators of degeneration, suggesting this technique is sensitive to these changes. Therefore, it might be expected that FA would decrease and MD to increase over a six-month period in stroke survivors due to retrograde degeneration. Since this was not evident, it may be that visual training acted to counteract retrograde degeneration post-stroke. However, future studies with a control group who did not complete training would be needed to determine if this is the case.

6.7.3 Limitations and future directions

Variability between timepoints

The current longitudinal study required scanning at two timepoints with extensive behavioural training in between. For most participants, the scanning sessions were roughly six months apart (median=155, range=102-271 sessions), however some participants (for example R017) trained for almost a year (271 sessions). There are several sources of variability in diffusion-weighted imaging, including noise, movement, participant alignment, partial volume effects and changes in MRI scanner characteristics. It is therefore possible that variability of these sources at the different timepoints impacted the current results. We would not expect whole-brain white matter to change with training, therefore, to investigate whether changes in diffusion-weighted imaging metrics were due to variability between scanning sessions, future analyses could normalise to whole brain, or regional white matter. Alternatively, as discussed in Chapter 2, data were also collected from a subset of participants after a further three months without training (9-month visit). We would also not expect white matter to change between timepoints without training and therefore this could additionally provide confidence that changes found here are due to training. Despite these concerns, previous studies have shown high reproducibility for diffusion-weighted measures of FA and MD (Bonekamp et al., 2007; Grech-Sollars et al., 2015; Vollmar et al., 2010). However, these studies compared participants scanned within short scan intervals (usually days) and therefore might have underestimated the sources of variability when compared to a longitudinal study like the present one. Studies using longer time frames have also explored the test-retest reliability of DTI after one year (Danielian et al., 2010; Takao et al., 2012) and NODDI models after 4 weeks (Lehmann et al., 2021) and found good

evidence of reproducibility of diffusion-weighted metrics. It is likely that the current study would show similar levels of reproducibility, however, further analyses are needed to determine the influence of variability between sessions.

No relationship between diffusion changes and rehabilitation efficacy

Surprisingly there was no direct relationship between diffusion-weighted measures of white matter integrity and averaged improvements on the training or perimetry tasks. However, participants trained at two locations in the blind field and there was substantial variability in the improvements made across these locations. Some participants improved at both locations (N=5), while others improved at only one location in the blind field (N=11). There were also a small number of participants who did not show any improvement (N=4). In the current study, an average measure of improvement across both locations was used. However, it is possible that dividing the group into those who improved or did not improve might be more sensitive to differences. Due to the limited sample size in the current study, there was not have sufficient power to do this here. A future study could aim to recruit a larger sample size and determine whether there are any group level differences in white matter microstructure in the distal dLGN-hMT+ pathway and efficacy of visual training. Nonetheless, the current results suggest that training in the blind field alone is effective at strengthening distal dLGN-hMT+ irrespective of the strength of improvements.

Future directions

These results suggest that visual training can increase microstructural integrity of the dLGN-hMT+ pathway. Moreover, as most participants showed some level of improvement, this indicates that this pathway may support these improvements. Based on these results, visual rehabilitation appears to be effective at strengthening alternative visual pathways known to be associated with residual vision post-stroke (Ajina, Pestilli, et al., 2015). Therefore, future research could focus on targeting this pathway to try and enhance rehabilitation success. Non-invasive brain stimulation has been used to enhance motor learning in healthy controls (Nitsche et al., 2003; Reis et al., 2009) and stroke survivors (see Flöel, 2014 for review; Hummel & Cohen, 2005; Stagg et al., 2012). Moreover, in the visual system, non-invasive brain stimulation can enhance vision in healthy controls (Kraft et al., 2010; Olma et al., 2011; Salamanca-Giron et al., 2021) and has been proposed to improve vision loss from a range of disorders (see Antal et al., 2011 for review). One study showed that brain stimulation enhanced visual rehabilitation after stroke (Plow et al., 2012), although this study had a small sample size (N=8), and brain stimulation was applied over the occipital pole to target both affected and unaffected hemispheres. In their recent study, Salamanca-Giron (2021) placed electrodes over V1 and hMT+ to facilitate motion discrimination performance. This suggests, alongside the current results, that the optimum location for visual recovery of motion discrimination ability would be hMT+. Therefore, future studies should apply brain stimulation over ipsilesional hMT+ to facilitate rehabilitation success.

6.8 Conclusion

To conclude, using state-of-the-art diffusion-weighted tractography on open-access platform brainlife.io, I have shown that FA and NDI increased, while ODI decreased in the distal, non-overlapping dLGN-hMT+ pathway after six months of visual training in the blind field. This suggests that neurite density increases in this pathway and dispersion of axons decreases, further indicating that, as hypothesised, the dLGN-hMT+ pathway underlies visual rehabilitation. Although no direct relationship was found between rehabilitation success and white matter microstructure, most participants showed some level of improvement and therefore future studies should explore whether integrity in this tract can explain variability in improvement.

Chapter 7: General Discussion

7.1 Thesis overview

This thesis contributes to our current understanding of visual loss from stroke, and the potential for visual rehabilitation. In this thesis I aimed to (1) further understand the neural mechanisms that underlie residual vision, or “blindsight”, in stroke survivors with damage to V1, and (2) to investigate whether this residual vision could be improved using a visual training paradigm, and if so, the neural mechanisms that underlie this change. Thus, Chapters 3 and 4 consider the baseline data whereas Chapters 5 and 6 measure changes resulting from a 6-month visual training programme that participants undertook.

7.1.1 Chapter 3

In the first experimental chapter, I used MR-spectroscopy to measure neurochemicals GABA+ and glutamate (Glx) and fMRI to measure percentage BOLD signal change in hMT+ at baseline. I then compared these quantifications to measures of residual vision (as measured by a 2AFC moving Gabor detection task). I found that GABA+ and Glx were inversely related to residual vision in hMT+ but not in control sensorimotor voxel (SMC). Moreover, BOLD signal change in hMT+ was not related to residual vision.

7.1.2 Chapter 4

In this chapter, I set out to investigate whether resting-state functional connectivity was predictive of residual vision. Functional connectivity was assessed by correlating the time-series of BOLD signal change between brain regions. Lower functional connectivity between ipsilesional and contralesional hMT+ and contralesional extrastriate ventral visual cortex was predictive of superior residual vision. Moreover, prior to stringent statistical correction for multiple comparisons, higher functional connectivity between ipsilesional hMT+ and ipsilesional early visual areas was also related to residual vision.

7.1.3 Chapter 5

In this chapter, the efficacy of a visual rehabilitation programme designed to improve vision after V1 stroke was discussed. In this program participants completed visual training within the blind field, at least five days a week, for six months. Improvements on the trained motion discrimination task and an untrained contrast detection task were quantified. Moreover, changes in deficit size were determined using clinical perimetry. After six months of visual training in the blind field, participants significantly improved at both the trained and two untrained tasks highlighting the efficacy of visual rehabilitation to improve vision post-stroke. Despite this, the amount of improvement observed varied among participants and across the blind field.

7.1.4 Chapter 6

In the final experimental chapter of this thesis, I aimed to investigate whether improvements in vision due to visual rehabilitation were related to changes in the white matter pathway between the dLGN and hMT+. Diffusion-weighted MRI were collected before and after six months of visual rehabilitation training. Diffusion-weighted data were analysed using open-access platform brainlife.io. Tractography was used to measure white matter tracts between visual areas of interest (dLGN-hMT+ and dLGN-V1) and control sensorimotor areas (VPL-S1). Measurements of tract integrity, including fractional anisotropy, neurite density index and orientation dispersion index were measured within each tract. There was evidence of a significant increase in white matter integrity due to increased neurite density and reduced neurite dispersion after six months of visual training in the distal (non-overlapping) portion of the dLGN-hMT+ pathway. This suggests that the dLGN-hMT+ tract may underlie improvements in vision after visual training in the blind field.

7.1.5 Summary of key findings

1. Lower GABA and glutamate in ipsilesional hMT+ are related to superior residual vision in the blind field at baseline.
2. Lower connectivity between the damaged and undamaged hemispheres is related to superior residual vision in the blind field at baseline.
3. Visual rehabilitation training can be used to improve residual vision for trained and untrained tasks after V1 strokes.
4. White matter integrity of the distal (non-overlapping) dLGN-hMT+ pathway increased with rehabilitation, which might underlie improvements in residual vision.

7.2 General limitations

7.2.1 Sample limitations

No control groups

One of the major limitations of the current study is the lack of specific control groups. In Chapters 3 and 4, all participants had damage to V1. The lack of control group without damage therefore means that we cannot determine whether neural measures and their relationship to residual vision are isolated to stroke survivors, or whether healthy participants have similar mechanisms. Furthermore, in the final two chapters, there was no control group of stroke survivors who did not complete training. This means that we cannot determine whether changes in behaviour or neural measures would also occur over a six-month period, irrespective of intervention. The lack of control groups was

largely due to the impact of the COVID-19 pandemic, as the research facility closed for nine months in 2020 and data collection was not permitted. Further lockdowns and restrictions meant that data collection was significantly delayed throughout the project. Consequently, to finish the study in time, we prioritised having a larger sample size rather than collecting additional data from either healthy controls or a non-training control group.

In a future study, I plan to collect MRI data in healthy control participants to investigate whether the relationship between neural measures and residual vision found in Chapters 3 and 4 are common mechanisms or are specific to occipital stroke survivors. Moreover, to determine whether the neural changes found in Chapter 6 were related to completing visual training, I plan to analyse existing data in the same participants prior to training. For a subset of eight of the participants who took part in training, structural and diffusion-weighted imaging data were acquired between 2018 and 2019 using the same parameters. In this analysis I will determine whether there are any changes in diffusion-weighted measurements between this initial research visit and the baseline visit from the current study. This will allow us to investigate whether the changes found in the current study are due to rehabilitation.

Heterogeneity

A major challenge in all stroke-related research is the heterogeneity among stroke survivors. Damage caused by stroke is highly variable, even when it is confined to a single area, such as the occipital cortex, and is dependent on factors such as age and type of stroke (Saionz et al., 2022). A large proportion of the research investigating residual vision after damage to V1 has focussed on individual case studies (Barbur et al., 1994; Bridge et al., 2010; Morland et al., 1999; Weiskrantz et al., 1995). When larger sample sizes are used, patients with a variety of aetiologies, including stroke, trauma, or tumour resections are often included (Ajina, Pestilli, et al., 2015; Ajina, Rees, et al., 2015). In the current study, as in several more recent publications (Cavanaugh & Huxlin, 2017; Fahrenthold et al., 2021; Halbertsma et al., 2020), I aimed to minimise the variability by limiting our inclusion criteria to damage due to stroke in adulthood. Nonetheless, variability in lesion size, visual field deficit location, and the extent of damage to extrastriate visual areas was not controlled. These factors might explain the variability in residual vision or rehabilitation efficacy.

In the current study, 24 stroke survivors with damage to V1 acquired in adulthood were recruited, 18 of whom completed six months of visual rehabilitation with neuroimaging data also collected. Previous rehabilitation studies that have also collected neuroimaging data have recruited similar or smaller samples sizes (for example N=6 in Ajina et al., 2021; N=11 in Barbot et al., 2021; N=11 in Fahrenthold et al., 2021; N=20 in Halbertsma et al., 2020). Therefore, in comparison to previous studies, the current sample size is relatively large. However, to achieve the sample size for the study, it was not possible to control for the type of stroke, deficit size or amount of damage to extrastriate areas.

Moreover, evidence suggests that different participants may have different neural mechanisms underlying residual vision (Papanikolaou et al., 2014) which might also explain why the results of neuroimaging rehabilitation research are mixed, with evidence supporting the role of spared V1 (Barbot et al., 2021), V1-bypassing geniculate-striate pathways (Ajina et al., 2021) and attention networks (Halbertsma et al., 2020). Variation in neural mechanisms underlying residual vision or rehabilitation among participants may not be characterised well in these limited sample sizes. Future studies with an increased sample size, or homogeneous samples will be needed to investigate this further.

7.2.2 Measuring vision

Another limitation of the current research is the methods used to measure residual vision or improvements in vision. In this project, vision at the pre-training and post-training visits was measured using perimetry and psychophysical tasks (i.e., performance on a motion discrimination or contrast detection task) at two locations in the blind field. These locations were determined by mapping the visual field, starting at the blind field border, and then selecting the first location where the stimulus was fully within the perimetry-defined blind field, and performance was at chance (Barbot et al., 2021; Cavanaugh et al., 2015, 2019; Cavanaugh & Huxlin, 2017; Fahrenthold et al., 2021). An additional psychophysical contrast detection task was also performed at these training locations and performance on this task was used as a measure of residual vision in the blind field. This meant that only a small proportion of the blind field was tested, and only a limited number of tests were used to investigate residual vision or improvements.

Residual vision or blindsight

One debate in this research field is how best to determine whether an individual has residual vision or “blindsight”. Previously, patients have been characterised as exhibiting residual vision if they perform above chance on a specific task within their blind field, for example the ability to detect a moving stimulus with varying contrasts (Ajina, Pestilli, et al., 2015; Ajina & Bridge, 2018), or detect or localise bright flashes of light (Blythe et al., 1987). The benefits of categorising participants as exhibiting residual vision (i.e., blindsight positive), or not (i.e., blindsight negative) allows comparisons between groups which may increase sensitivity to differences, however, it does not account for variability in performance among participants. For example, slight differences in lesion size or location might be able to explain why one patient performs at 100% on a given task, while another performs at 75%. Understanding these differences is important, especially when developing rehabilitation techniques, as differences in neural structures before training are known to affect the success of visual rehabilitation (Ajina et al., 2021; Barbot et al., 2021).

In this thesis, instead of characterising participants as blindsight positive or negative, a continuous measure of residual vision was used instead. Residual vision at specific locations in the blind field was compared either to neural measures (Chapters 3 and 4) or across time (Chapters 5 and 6). The aim was to investigate whether individual differences in brain function or neurochemistry could predict variability in residual vision which might later be informative for rehabilitation. However, this method is likely to be underpowered with smaller sample sizes, especially given the heterogeneity among stroke survivors. Therefore, future studies should explore how residual vision is related to neural measures in an increased sample size.

Variability in the blind field

Additionally, in the current study, the amount of residual vision varied across locations tested in the blind field, for example some patients showed superior residual vision or improvements due to rehabilitation at one location within the blind field compared with the other. This suggests that residual visual behaviour varies across the blind field and therefore taking psychophysical performance at one location may not fully characterise a participant's residual visual ability. This means that it may be difficult to determine whether an individual exhibits residual vision or blindsight without testing the entire blind field.

In the current study, I was limited by time constraints and was therefore unable to test the entire blind field during each visit. Instead, I defined residual visual processing based on one or two locations in the blind field. V1 is known to be retinotopically organised (Holmes, 1917) and therefore it is possible that variations in damage to specific locations in V1 may explain this phenomenon. Functionally impaired yet intact regions of V1 may represent locations exhibiting residual vision, while damaged regions may represent areas that do not show residual vision. Researchers have found that population receptive fields in perilesional V1 still respond to areas of the blind field (Papanikolaou et al., 2014) and this is predictive of improvements in vision after training (Barbot et al., 2021). However, previous research has also implicated V1-bypassing pathways to hMT+ in supporting residual vision (Ajina, Kennard, et al., 2015; Ajina, Pestilli, et al., 2015; Schmid et al., 2010). Although MT/hMT+ is also retinotopically organised (Allman & Kaas, 1971), the population receptive fields are larger in hMT+ (between 5 and 11 degrees; Amano et al., 2009) than in V1 (between 0.5 and 2.4 degrees; Alvarez et al., 2015; Dumoulin & Wandell, 2008). This means that neurons within hMT+

respond to greater portions of the visual field compared with V1 but, if these neurons are supporting residual vision and rehabilitation, it is less clear why residual vision in nearby locations in the visual field would differ. Future studies investigating population receptive fields in V1 and hMT+ will be important to answer these questions.

Variability in residual vision

While the current study focussed on motion discrimination and contrast detection, previous studies have found evidence of residual vision for wavelength (Danckert et al., 1998; Morland et al., 1999; Silvanto et al., 2008; Stoerig & Cowey, 1992), facial expressions (Celeghin et al., 2015; de Gelder et al., 1999; Tamietto et al., 2009), form (Danckert et al., 1998; Trevethan et al., 2007), shape and object recognition (van den Stock et al., 2014, 2015) and luminance (Blythe et al., 1987). In the current study, only tasks involving movement (motion discrimination and moving contrast detection), or luminance detection (Humphrey perimetry) were used and therefore may not have fully captured each participants residual vision, or their subjective improvements in vision due to training. Moreover, these limited psychophysical tasks also do not tell us whether this residual vision, or improvement in residual vision, is functionally useful to the participant. Future studies could aim to use a more diverse range of tasks, including questionnaires that measure activities of daily living, to fully characterise each participant's level of residual vision, and how performance changes with visual training.

7.2.3 Future directions and open questions

Understanding neural measures of improvement

In addition to the neuroimaging data discussed in this thesis, there were additional scans that were collected as part of this protocol. At the pre- and post-training research visits, extensive neuroimaging data were collected, consisting of resting state and task-related fMRI, MRS, structural and diffusion-weighted imaging. In the current study, a subset of these data were analysed, specifically the baseline MRS and task-related fMRI (Chapter 3) and resting state (Chapter 4), and the diffusion-weighted imaging data after six months of training (Chapter 6). Future planned analyses will investigate the additional neuroimaging measures to understand whether there are changes in task-related functional activity, resting-state functional connectivity, brain structure or neurochemistry after six months of visual training. These data will provide further insight into neural changes in the brain as a result of visual rehabilitation. This will allow us to understand the mechanisms that underlie improvements and will be informative for developing more effective rehabilitation techniques in the future.

Furthermore, these neuroimaging data will allow us to investigate biomarkers of recovery. In strokes that affect the motor system, a reduction in the inhibitory neurotransmitter GABA⁺ has been related to increased plasticity and rehabilitation efficacy (Blicher, Near, Næss-Schmidt, Stagg, Johansen-Berg, Nielsen, Østergaard, & Ho, 2015; Ferreiro de Andrade & Conforto, 2018; Mooney et al., 2019). Moreover, in stroke survivors, training increases diffusion-weighted imaging measures of FA in motor tracts and relates to motor improvement (Fan et al., 2015). FA is also predictive of motor outcomes in skill training in healthy controls and stroke survivors (Jang, 2010; Sampaio-Baptista, Sanders and Johansen-Berg, 2018). In the visual system, increased baseline

activity in perilesional V1 (Barbot et al., 2021) and hMT+ (Ajina et al., 2021) have been found to relate to improvements in vision due to training. Additionally, in a recent paper, Fahrenthold et al. (2021) also found that the amount of retrograde degeneration of the optic tract was predictive of efficacy of restoration training. These studies suggest that the integrity and functioning of the visual system at baseline might be informative about those likely to benefit from rehabilitation and this will be explored in future studies.

As the final stage of this research study, 12 participants returned after a three-month period of ‘no training’. The same behavioural and neuroimaging datasets were collected at this visit. Although researchers have found that rehabilitation can improve vision (Ajina et al., 2021; Barbot et al., 2021; Cavanaugh et al., 2019; Cavanaugh & Huxlin, 2017; Fahrenthold et al., 2021; Huxlin et al., 2009), there is currently little understanding of whether these changes persist after a period without training. Therefore, these analyses will allow us to understand whether improvements in vision persist after three months without training, and if so, what are the neural measures that underlie this persistence.

Enhancing plasticity

Visual rehabilitation takes months of daily practice to attain through training alone. In the current project, participants completed six months of visual training. However, in previous studies participants trained on average for 10-12 months (Barbot et al., 2021; Fahrenthold et al., 2021; Vaina et al., 2014) and up to 46 months in some cases (Barbot et al., 2021). Moreover, Vaina et al. (2014) found most improvements in vision were seen between 8 months and 11 months of visual training. A relationship

between the number of training sessions and the degree of improvement, was also found in the current and previous studies, with those completing more training showing greater improvements in vision (Cavanaugh & Huxlin, 2017; Huxlin et al., 2009). Extensive training is therefore needed to obtain significant improvements, and this limits the practical clinical applications of these techniques. Currently, this type of visual training involves extensive support from a research team to monitor progress, customise training locations as needed, and ensure participants train correctly. Supervising patients to complete months of visual rehabilitation is therefore unfeasible for clinical practice. Future research is needed to enhance effects of visual training to allow it to be incorporated into clinics, or to develop standalone, easy-to-use home-based training.

In the adult visual system, damage to the brain is thought to shift the balance of excitation and inhibition in surviving visual circuits towards excessive inhibition (Spolidoro et al., 2009). This may limit plasticity and recovery by raising the threshold for activation of necessary circuits and explain why recovery is slow, often variable, and spatially restricted. This suggests that to promote recovery, it will be beneficial to decrease intra-cortical inhibition or enhance excitability. Studies employing pharmacological and behavioural strategies indicate that the visual system has greater levels of plasticity than previously suspected. Evidence suggests that in animal models, environmental enrichment (i.e., providing wide cages with a variety of toys that are changed regularly; Sale et al., 2007, 2009) and pharmacological interventions (for example selective serotonin reuptake inhibitors such as fluoxetine; Steinzeig et al., 2019; Vetencourt et al., 2008) can reactivate critical period-like plasticity. Recovery in both these studies was associated with reduced GABAergic inhibition. In humans, the effects of fluoxetine have been less promising, with studies finding no enhancement of

perceptual learning in healthy participants (Lagas et al, 2016), or acuity in amblyopia (Huttunen et al., 2018). A preliminary study in 17 sub-acute stroke survivors with V1 damage found a trend towards fluoxetine facilitating post-stroke recovery, although the results were non-significant (Schneider et al., 2022). However, in this study, patients were in the subacute period and did not complete visual training alongside treatment. Therefore, large-scale multi-site trials with sub-acute and chronic stroke survivors will be needed determine whether fluoxetine alongside visual rehabilitation might facilitate effects seen in the current study.

Non-invasive brain stimulation can also alter inhibition and excitation in cortical areas. Transcranial direct current stimulation is thought to influence the excitability and firing rate of neurons by depolarising or hyperpolarising the neuronal membrane permeability, while transcranial noise stimulation modulates ongoing cortical oscillations resulting in increased cortical excitability. Transcranial noise stimulation is less focal than transcranial direct current stimulation and therefore can modulate the entire network (Fertonani et al., 2011). Studies have found that anodal transcranial direct current stimulation results in decreased GABAergic inhibition in the visual (Barron et al., 2016) and motor cortex (Bachtar et al., 2015; Kim et al., 2014). In the healthy visual system, non-invasive brain stimulation has been shown to enhance perceptual learning (Contemori et al., 2019; Falcone et al., 2012; Fertonani et al., 2011; He et al., 2022; Wu et al., 2020, 2022). Moreover, studies in patients with acquired motor and developmental language disorders have indicated enhanced benefits of combining behavioural therapies and non-invasive brain stimulation and these improvements persisted after six weeks (Chesters et al., 2018) and three months (Allman et al., 2016). Studies in stroke survivors have also indicated increased fMRI activity and grey matter after anodal tDCS paired with

motor training (Allman et al., 2016). In patients with V1 damage, studies have shown that non-invasive brain stimulation coupled with visual training can improve vision in shorter timeframes. Plow et al. (2011) combined visual training with three months of transcranial direct current stimulation to the occipital cortex and found significant improvements in perimetry, activities of daily living and fMRI activity in perilesional and higher-level visual areas. Additionally, Herpich et al. (2019) paired visual training with bilateral transcranial noise stimulation over early visual areas for 10 days and found a significant improvement in vision. Surprisingly, Herpich et al. (2019) did not find any effect of transcranial direct current stimulation, highlighting variability between studies. When compared to the extensive behavioural training needed to improve vision, these results are promising. Further research is needed to determine whether non-invasive brain stimulation can facilitate improvements in vision post-stroke, and if so, what the optimum techniques and locations are for recovery.

Visual plasticity could also be optimised by starting training in the subacute phase following stroke. There is thought to be spontaneous recovery from stroke early on (Cramer et al, 2007), but after six months the deficit is thought to be permanent (Gray et al., 1989; Zhang et al., 2006). Most of the research investigating rehabilitation of vision has focussed on chronic stroke survivors (Ajina et al., 2021; Barbot et al., 2021; Cavanaugh et al., 2019; Cavanaugh & Huxlin, 2017; Fahrenthold et al., 2021; Halbertsma et al., 2020). However, the first few weeks or months post-stroke are critical for neural plasticity (Bernhardt et al., 2017). In strokes affecting the motor system, there is evidence that earlier intervention is beneficial (Horn et al., 2005; Maulden et al., 2005). In the visual system, there is a lack of research into the efficacy of visual rehabilitation in the subacute period. However, a recent paper found that administering visual training in the subacute

period was quicker (~6x faster), generalised deeper into the blind field and covered a wider range of untrained tasks than was achieved in the chronic period (Saionz et al., 2020). Moreover, there is evidence that transsynaptic retrograde degeneration occurs after strokes to V1 (Atapour et al., 2021; Bianchi Marzoli et al., 2023; Bridge & Plant, 2011; Millington et al., 2014; Van Buren, 1963) and this occurs within the first two months after a stroke and continues up to 2 years post-stroke (Rajanala et al., 2019). Hagan et al. (2020) also found that fewer MT neurons were direction selective after 6-12 months post-lesion, when compared to measures obtained shortly after lesions. By building a network model of MT, authors were able to attribute this to a local imbalance in inhibition and excitation. These neural changes post-stroke suggest that starting interventions earlier might capitalise on these preserved visual processes (Saionz et al., 2022).

Improved training

Alongside facilitation of plasticity mechanisms, the rehabilitation methods could also be improved to enhance efficacy. It is possible that some participants responded better to visual rehabilitation due to variation in training practice, rather than neurological differences. Participants were provided with extensive instructions on how to set up their training at home and completed all training with a head-and-chin rest. The research team also provided technical and logistical support throughout training to try to ensure that all participants completed training as expected. Despite this, slight variations in how each participant set up the training might have resulted in differences in training efficacy. Training-induced improvements in this patient group are spatially specific, and due to time constraints, only a limited number of locations in the blind field were tested pre- and post-training. This means that a small shift in viewing distance when setting up the

training could have resulted in different locations in the visual field being trained than expected. Moreover, many participants would move their training set up over the six-month period, which might also have resulted in slightly different locations being trained. Additionally, eye tracking was not monitored throughout training. Participants were reminded to maintain fixation to ensure the trained location was consistent throughout training, however measurements of eye position were not recorded. It therefore cannot be ruled out, that those participants that did not improve might have set their training up incorrectly or failed to fixate throughout training. The recent commercialisation of affordable, accessible, and standalone virtual reality headsets has allowed therapies to incorporate gamification principles into perceptual learning paradigms. There are many benefits of developing rehabilitation in virtual reality headsets, including the ability to control viewing distance and luminance of the screen. Additionally, these devices have a wider visual field than laptop computers, and therefore those with far peripheral visual deficits would also be able to be included in studies. Many of these devices (such as the Vive Pro) also have in built eye trackers, which would allow for fixation to be monitored during training. Importantly, VR paradigms could be used to provide more realistic and engaging rehabilitation tasks that might better reflect daily life. For example, training could involve detecting moving objects within a colourful and realistic 3D world. Incorporating competition between participants might also increase motivation to complete training, and to train more often, resulting in greater improvements. Recently, studies in glaucoma (Li et al., 2020), visual loss from stroke (Dehn et al., 2020) and amblyopia (Godinez et al., 2021) have used virtual reality paradigms to show improvements in perceptual learning. Future studies could incorporate the visual training with virtual reality to ensure all participants train effectively and to improve engagement in training.

7.3 Final conclusions

In this thesis, I investigated the neural mechanisms that underlie residual vision and rehabilitation of residual vision after occipital strokes. I carried out a longitudinal rehabilitation study in which stroke survivors completed six months of visual training within their blind field and collected extensive neuroimaging data, including task-related fMRI, resting-state fMRI, MR spectroscopy, and diffusion-weighted imaging at the pre- and post-training visits. Using the baseline data, I found that reduced GABA and glutamate (but not BOLD signal change) in hMT+ were related to residual vision in the blind field. Additionally, reduced resting-state functional connectivity between ipsilesional hMT+ and intact contralesional early ventral visual areas was also related to superior residual vision at baseline. Using the longitudinal data, I found that six months of visual training within the blind field can significantly improve vision on trained and untrained tasks, and this training is related to increased white matter integrity of the distal dLGN-hMT+ pathway in the damaged hemisphere. These results will be important for future rehabilitation studies as the neural mechanisms that underlie residual vision and visual rehabilitation will provide optimal targets for developing treatments for visual loss from stroke.

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