Investigation of motion perceptual learning in healthy subjects, for application as a rehabilitative therapy for visual field defects following primary visual cortex damage

A thesis submitted for the degree of

Doctor of Philosophy

Michaelmas Term 2015



Stephanie Jade LARCOMBE

St John's College

The University of Oxford

Abstract

Investigation of motion perceptual learning in healthy subjects, for application as a rehabilitative therapy for visual field defects following primary visual cortex damage

Stephanie Jade LARCOMBE
St John's College, The University of Oxford

A thesis submitted for the degree of *Doctor of Philosophy*
Michaelmas Term 2015
Word count: 40,522 words.

Perceptual learning is the ability to improve performance of a perceptual task, with repeated practice. The concept of perceptual learning in the adult visual system has been established for many years, however, the neural mechanisms which mediate it have proved complex to unravel. Improved understanding could be used to guide novel rehabilitative strategies for those with damage to the brain which affects the primary visual cortex (V1) in the occipital lobe. Motion perception learning is thought to involve the brain area hMT+, which is located in the parieto-temporo-occipital cortex, distal from V1. It is possible that motion perception training may improve the vision or subjective quality of life for individuals with damage to V1.

This project initially looked at the effect of motion perception training in healthy individuals, in order to establish and quantify the potential behavioural and neural impact of behavioural training.

A five-day motion perception training paradigm applied in these experiments produced robust improvement of motion perception in healthy participants. This learning was found to be partially transferable to untrained regions of the visual field. If the training timecourse was reduced to a single day, the location specificity of learning effects was increased significantly.

Functional MRI analysis indicated that the motion perception training paradigm applied here altered activity at extrastriate visual areas and frontotemporal decision areas.

When motion perception training was combined with brain stimulation, it was shown that 20 minutes of anodal transcranial direct current stimulation (tDCS) over hMT+ had no impact on learning magnitude or timecourse.

Finally, the motion perception training paradigm was applied as a case study in a patient with damage to V1. The results were promising but inconclusive with such a minimal dataset.

Motion perception training produces robust improvements in perception in healthy individuals, which are likely mediated by visual extrastriate and decision-making areas of the brain. As such, motion perception training shows promise, with further development, as an avenue for rehabilitation of the visual system and visual perception following damage to the primary visual cortex.

Acknowledgements

Firstly, I would like to extend my sincere gratitude to my two supervisors Chris Kennard and Holly Bridge.

Chris, the input of your scientific expertise to my DPhil research has been so valuable, and I always enjoy our scientific discussions. Your confidence in my abilities has helped keep my morale high throughout my DPhil.

Holly, without your excellent supervision I'm sure my DPhil would not have been such a success! I've always found our meetings to be helpful and productive, and your input during the past three years has been significant for improving my research, presentation, and writing skills. Your unfailing support when I was writing my thesis has been invaluable. Thank you for being a fantastic supervisor!

Thank you to everyone in the Vision Groups at FMRIB and DPAG, who have provided scientific input and support throughout my DPhil. In paticular, I want to thank Gaëlle, Sara, Sarah, and Ivan. I would like to thank Andrew Parker for the use of the psychophysics room and desk in DPAG.

I would like to thank each person who participated in my experiments, as I truly appreciate the time and hassle that goes into participating in research studies.

I would never have got anywhere with my DPhil without the help of all my friends and family. Everyone who told me "You can do it!" contributed in no small way to getting me to this point.

Special mentions for:
Dad, my biggest champion, your ongoing support in anything I do never wavers and I know you are always there to help in any way you can.
Mum, I know I can call you any time and you will do a great job at distracting me from anything I'm stressed about!
My pole family (especially Laura), who have helped me through my DPhil by providing an excellent way to spend my Sunday afternoons each week.
James, for all the emotional support, proof-reading and cat pictures. I have scaled the castle and the dragon is vanquished!
Arthur, for your laid-back influence, sensible advice, and unfailing belief in my ability to make it to the end successfully.

Finally, as always and in everything, thank you Luke. You are always there for me with wise words, a cuddle, and a cup of tea.

Contents

Abstract i

Acknowledgements ii

Abbreviations vii

1 Introduction 1
- 1.1 The healthy visual system . . . 1
  - 1.1.1 Basic structure of the visual system . . . 1
  - 1.1.2 Motion processing in the brain . . . 8
  - 1.1.3 Neuroplasticity . . . 11
  - 1.1.4 Visual perceptual learning . . . 16
- 1.2 Visual processing in individuals with visual field defects . . . 18
  - 1.2.1 Introduction to visual field defects . . . 18
  - 1.2.2 Aetiology of visual field defects . . . 19
  - 1.2.3 Visual field defects and disability . . . 20
  - 1.2.4 Residual visual abilities in patients with VFDs . . . 21
  - 1.2.5 Spontaneous recovery of VFD . . . 25
  - 1.2.6 Substitution and compensatory therapies for VFDs . . . 25
  - 1.2.7 Restitutive therapies for VFDs . . . 26
- 1.3 Synopsis of thesis . . . 27

2 General Methods 30
- 2.1 Introduction . . . 30
- 2.2 General methods . . . 30
  - 2.2.1 Participants . . . 30
  - 2.2.2 Visual tasks . . . 31
  - 2.2.3 Visual stimuli . . . 35
  - 2.2.4 Data analysis . . . 37

3 Investigation of the learning effects of motion perceptual training in healthy individuals 40
- 3.1 Introduction . . . 40
- 3.2 Methods . . . 42
  - 3.2.1 Participants . . . 42
  - 3.2.2 Visual tasks and stimuli . . . 42
  - 3.2.3 Assessment and training paradigms . . . 43
- 3.3 Results . . . 45
  - 3.3.1 Timing has an effect on consecutively-presented task conditions 45
  - 3.3.2 There is variability in the initial ability of participants to complete the motion direction perception task . . . 46
  - 3.3.3 Five days is sufficient for perceptual learning to occur . . . 46
- 3.4 Discussion . . . 53
  - 3.4.1 Overall effect of training . . . 53
  - 3.4.2 Transfer across colours . . . 53
  - 3.4.3 Transfer of learning between tasks . . . 54

3.4.4 Transfer between hemifields . . . 55
3.4.5 Location of learning effect . . . 56
3.4.6 Eye movements . . . 56
3.5 Conclusions . . . 57

4 Investigation of the impact of timecourse on learning effects of motion perceptual training in healthy individuals 58
4.1 Introduction . . . 58
4.1.1 Translational potential of single-day perceptual learning protocol 58
4.1.2 The role of overexposure in perceptual learning . . . 59
4.1.3 The role of sleep in perceptual learning . . . 59
4.1.4 Overtraining of motion perception . . . 60
4.1.5 Summary and experimental aims . . . 61
4.2 Methods . . . 62
4.2.1 Participants . . . 62
4.2.2 Visual tasks and stimuli . . . 62
4.2.3 Assessment and training paradigms . . . 63
4.3 Results . . . 64
4.3.1 A single day of behavioural training is sufficient for task learning to occur . . . 64
4.3.2 No transfer of learning across visual hemifields . . . 65
4.3.3 No transfer of learning across visual tasks . . . 67
4.4 Discussion . . . 70
4.4.1 Overtraining effects are not apparent using current protocol . 70
4.4.2 Waking perceptual learning is possible, but may be influenced by task difficulty and trial block size . . . 71
4.4.3 No transfer of perceptual learning to untrained visual hemifield 73
4.4.4 Improvement of untrained task due to re-test effect . . . 74
4.4.5 Eye movements . . . 75
4.4.6 Future work . . . 75
4.5 Conclusions . . . 76

5 Investigation of the changes in neural activity following motion perceptual training in healthy individuals 77
5.1 Introduction . . . 77
5.1.1 Changes in the visual cortices . . . 77
5.1.2 Changes in attentional, decision-making and other areas . . . 80
5.1.3 Consolidation of VPL . . . 81
5.1.4 Summary and experimental aims . . . 82
5.2 Methods . . . 83
5.2.1 Participants . . . 83
5.2.2 Visual tasks and stimuli . . . 83
5.2.3 Assessment and training paradigms . . . 84
5.2.4 MRI data acquisition . . . 86
5.2.5 fMRI task design . . . 86
5.2.6 fMRI data analysis . . . 90
5.3 Results . . . 93
5.3.1 There is variability in the initial ability of participants to complete the motion direction perception task . . . 93

5.3.2 Motion-training group show learning of motion direction perception task following five days of training 94
5.3.3 Motion-training group show significantly more learning in the trained visual hemifield, compared to the untrained visual hemifield 96
5.3.4 Motion training group show significantly more improvement on the motion direction perception task compared to the control group 97
5.3.5 Functional changes following motion perception training, measured using fMRI 99
5.3.6 Analysis of the visual cortex 99
5.3.7 Analysis of the non-visual cortex 110
5.4 Discussion 113
5.4.1 Behavioural effect of training was consistent with previous findings 113
5.4.2 Eye movements 114
5.4.3 Changes in BOLD signal following motion perception training 114
5.4.4 Future directions 119
5.5 Conclusions 120

6 Investigation of the impact of brain stimulation on motion perceptual training in healthy individuals 121
6.1 Introduction 121
6.1.1 Mechanism of action of tDCS 121
6.1.2 Brain stimulation of the visual system 122
6.1.3 Application of tDCS as an adjunct therapy 125
6.1.4 Summary and experimental aims 128
6.2 Methods 129
6.2.1 Participants 129
6.2.2 Visual tasks and stimuli 129
6.2.3 Assessment and training paradigms 130
6.2.4 Brain stimulation methods 130
6.3 Results 133
6.3.1 Participant withdrawal rate 133
6.3.2 Sensation reporting for anodal versus sham stimulation 133
6.3.3 Comparison of learning across training sessions for each stimulation group 134
6.3.4 Comparison of learning index for motion perception before and after training for each stimulation group 135
6.4 Discussion 137
6.4.1 Blinding and safety aspects 137
6.4.2 Effect of brain stimulation on motion perception 138
6.4.3 Future extensions of this research 140
6.5 Conclusions 141

7 Investigation of motion perceptual training in an individual with damage to primary visual cortex 143
7.1 Introduction 143
7.1.1 Visual field defects and disability 143

7.1.2 Substitutive and compensatory therapies for VFDs 144
7.1.3 Restitutive therapies for VFDs 146
7.1.4 Summary and experimental overview 152
7.2 Methods 154
7.2.1 Participant case history 154
7.2.2 Perimetry 154
7.2.3 Visual task and stimuli 155
7.2.4 Assessment and training paradigms 158
7.2.5 Data analysis 159
7.3 Results 160
7.3.1 Learning at the border of the blind field 160
7.3.2 Learning within the blind field 161
7.3.3 Changes in the seeing visual field 163
7.3.4 Changes in visual field following training 165
7.3.5 Eyetracking data 168
7.4 Discussion 171
7.4.1 Motion perception learning in the blind field following training 171
7.4.2 Changes in visual field driven by attentional improvements . . 174
7.4.3 Fast rate of learning and recovery 175
7.4.4 Future work 175
7.5 Conclusions 176

8 General Discussion **178**
8.1 Thesis overview 178
8.2 Summary of key findings 180
8.3 Future work 181
8.3.1 Expanded investigation of the healthy visual system 181
8.3.2 Expanded investigation of the visual system when V1 is damaged182
8.4 Final Conclusions 185

9 Bibliography **186**

Abbreviations

ANOVA Analysis of variance

BOLD Blood oxygenation level dependent signal

COPE Contrast of parameter estimates

DC Direct current

df Degrees of freedom

DLPFC Dorsolateral prefrontal cortex

DTI Diffusion tensor imaging

EV Explanatory variable

F Observed F-value

FEAT fMRI expert analysis tool

fMRI Functional MRI

FMRIB Functional magnetic resonance imaging of the brain centre

FWHM Full-width half maximum

FSL FMRIB's software library

GABA Gamma-aminobutyric acid

GLM General linear model

hMT+ Human motion processing complex

LGN Lateral geniculate nucleus of the thalamus

MNI Montreal Neurological Institute

MPRAGE Magnetisation-prepared rapid acquisition gradient-echo sequence

MRI Magnetic resonance imaging

MST Middle superior temporal area

MT/V5 Middle temporal area/Visual area 5

NPC Non-parametric combination analysis

p Significance level (p-value)

REM Rapid eye movement sleep

ROI Region of interest

RF Receptive field

SEM Standard error of the mean

SWS Slow-wave sleep

t Test statistic

tDCS Transcranial direct current stimulation

TDT Texture discrimination task

TE Echo time

TR Repetition time

V1 Primary visual cortex

VFD Visual field defect

VRT Vision restitution training

VARCOPE Variance of COPE

1 Introduction

1.1 The healthy visual system

1.1.1 Basic structure of the visual system

Vision is the process which allows organisms to see the world. Vision begins at the eyes, which have cells with light-sensitive properties. However, the vast majority of visual information processing occurs in the brain. Once light is detected by the eyes, the sensory signal is passed to the brain. The first place in the brain that visual information arrives is the thalamus (Bishop, 1953). The thalamus is a relay area: sensory information of all types arrives at this location first, and is then passed to the appropriate area of the cortex for further more specialised processing. In the case of visual information, the thalamus transfers signals to the primary visual cortex (V1), which is located in the occipital lobe (Panizza, 1855).

The eye is the visual sensory organ. At the back of the eye are several layers of cells, which are collectively termed the retina (Wässle & Boycott, 1991). Within the retina are light-sensitive cells called photoreceptors. The photoreceptive cells have proteins which change their shape when they interact with photons (Wald, 1968). Light activation of such proteins initiates a cell signalling cascade, which leads to hyperpolarisation of the photoreceptor cell. Activation of photoreceptors by light leads to increased activity of bipolar cells, which in turn stimulate retinal ganglion cells. Lateral processing of visual signals in the retina also occurs between the photoreceptors and ganglion cell layers by the horizontal and amacrine cell populations. The axons of retinal ganglion cells exit the eye and form the optic nerve, providing a pathway of entry for visual information into the brain.

The optic nerves from each eye come together in the brain at a location called the optic chiasm (Laties & Sprague, 1966), termed as such because it forms a cross-shaped structure. At the optic chiasm, visual information is reorganised such

that post-chiasmic optic tracts represent each visual hemifield, rather than each eye (Figure 1). For the left optic nerve, which has transmitted information from the left eye, information from the nasal part of the retina representing the left visual hemifield crosses at the chiasm. This information is then sent contralaterally to the right brain hemisphere. Information from the temporal part of the retina of the left eye, representing the right visual hemifield, does not cross over and is sent ipsilaterally to the left brain hemisphere. The opposite occurs for the right eye, and so all information about the left visual hemifield (viewed by the nasal part of the left eye and temporal part of the right eye) is sent to the right brain hemisphere, and information about the right visual hemifield (viewed by the temporal part of the left eye and nasal part of the right eye) is sent to the left brain hemisphere.

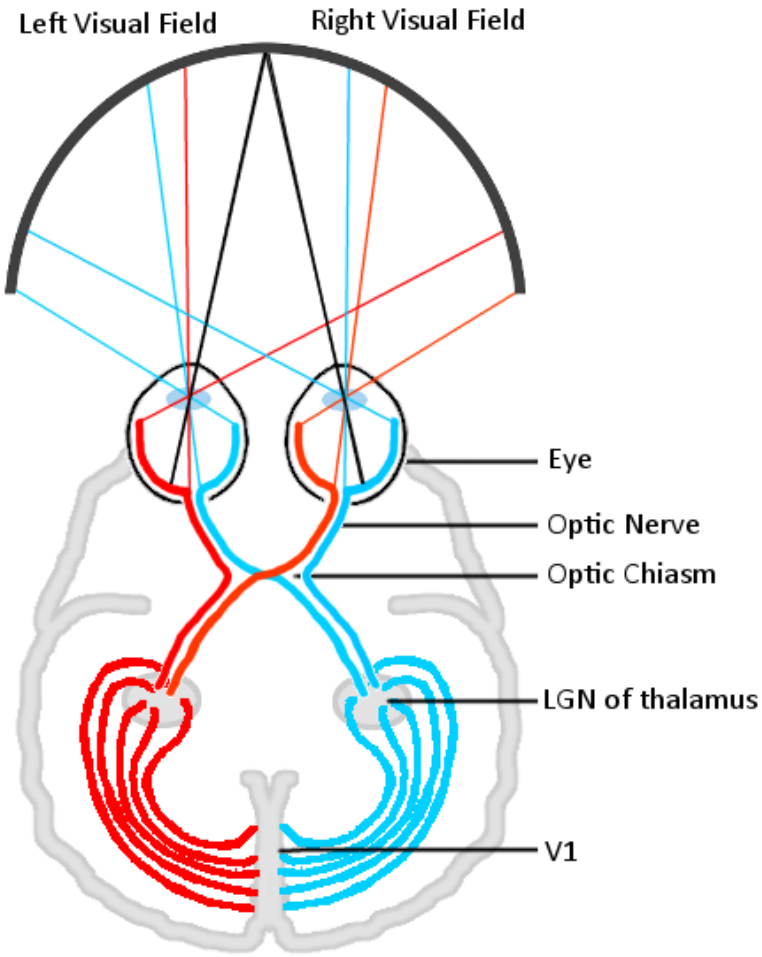


Figure 1: The main route of visual information flow in the human brain. Visual processing begins at the eye. From the eye, information travels along to the optic nerve to the optic chiasm, where it is separated by visual hemifield at the optic chiasm. Visual information about the left visual hemifield (blue) is sent to the right lateral geniculate nucleus (LGN) of the thalamus, and the inverse also occurs (red). The thalamus then sends information to the primary visual cortex (V1).

From the optic chiasm, visual information is sent to the lateral geniculate nucleus (LGN) of the thalamus (Figure 2). The LGN is the region of the thalamus involved in the processing of visual over other sensory signals, and is organised into six anatomical layers in primates. Contralateral information (left eye to right thalamus, and right eye to left thalamus) is sent to layers 1, 4, and 6. Ipsilateral information (right eye to right thalamus, and left eye to left thalamus) is sent to layers 2, 3, and 5.

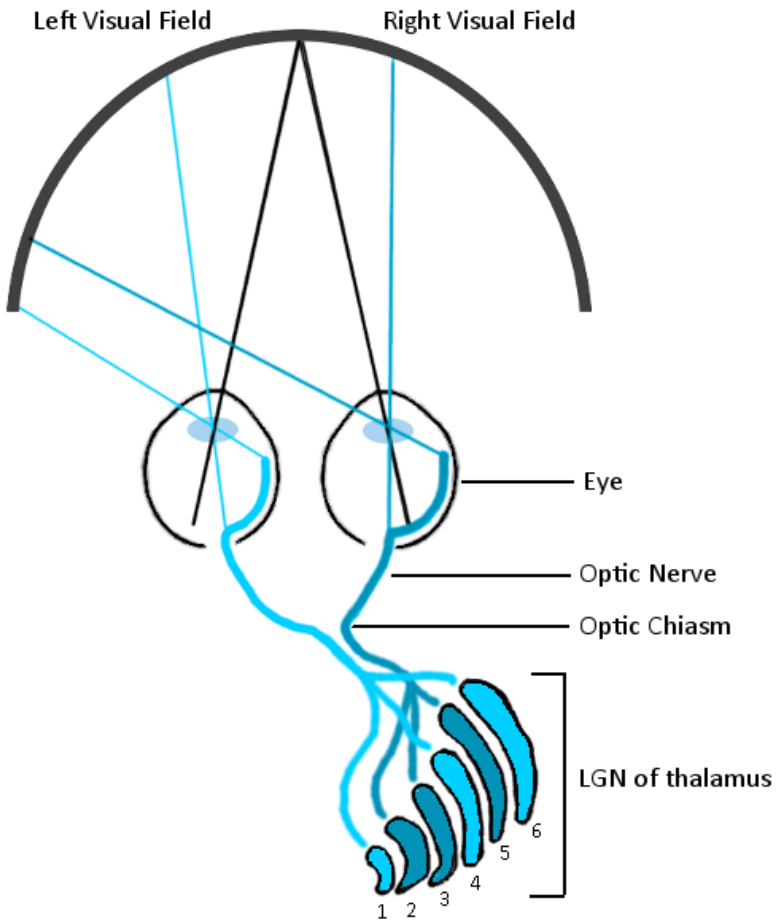


Figure 2: Organisation of the lateral geniculate nucleus (LGN) of the thalamus. Objects in the left visual hemifield are sent to the right LGN of the thalamus (blue), and the inverse also occurs (not shown on this diagram). Information from the ipsilateral eye is sent to layers 2, 3, and 5 (dark blue) and contralateral information is sent to layers 1, 4, and 6 (light blue). The thalamus then projects to the primary visual cortex (V1).

Visual information is sent onwards from the thalamus to V1, also called the striate cortex, located along the medial region of the calcarine sulcus in the occipital lobe (Panizza, 1855). V1 conducts visual analyses at the most basic level. From V1, information is sent to other early visual processing areas, termed visual areas 2, 3, and 4 (V2-4).

A receptive field (RF) refers to an area of visual space to which a cell will respond when visual stimuli are presented at that location. Presenting a visual stimulus outside of the RF of a cell will have no effect on its activity in the absence of a stimulus falling within the RF. In the visual areas of the brain, cells are ordered in such a way that neurones with adjacent RFs are found near to each other in the brain. So, a stimulus which causes neighbouring cells in the retina to activate, also causes neighbouring cells in the cortex to fire. This organisation is called retinotopy: the mapping of visual space onto the visual cortex.

Retinotopy was initially proposed in humans following studies of patients with traumatic brain damage (Holmes, 1918). Such studies demonstrated that damage to the visual cortex was associated with blindness in a portion of the visual field. The exact location of damage determined the pattern of associated loss of visual field. This indicated that a map of visual space, consistent across different patients, was present in the visual cortex. Studies in the non-human primate provided direct evidence of retinotopy in V1. These studies employed invasive electrophysiological techniques, which permit direct recording of the activity of cells in the striate cortex during presentation of visual stimuli. It was shown that if a visual stimulus is moved progressively across the visual field, it will cause a systematic activation of corresponding cells in V1 (Hubel & Wiesel, 1968; Hubel & Wiesel, 1974; Van Essen et al., 1984). These neurophysiological data therefore confirmed the retinotopy of V1.

The retinotopic map in the cortex is distorted by cortical magnification. The central area of the retina, called the fovea, is more densely-packed with photoreceptors

compared to other parts of the retina. Because of its increased sensitivity, the foveaa is represented by a disproportionately large cortical area, compared to peripheral regions of the retina. As such, cells in V1 which represent the fovea have smaller receptive fields than cells representing more eccentric regions of visual space.

Retinotopy remains present at visual areas of the brain outside of V1, however its stringency decreases. In accordance with this, cell RF size also gets larger. The most stringent retinotopy and smallest RFs are found in V1, with stringency decreasing and RF size increasing progressively from V2, to V3, V4, and V5 (Essen & Zeki, 1978; Felleman & Van Essen, 1987; Gattass et al., 1981).

Since invasive electrophysiological studies in humans are not possible, functional MRI scanning techniques have been applied to verify if the retinotopy and RF properties of the visual system of humans are comparable to the visual system of non-human primates. Such studies have indeed shown that the properties of the human visual system mirror those of other primates (Amano et al., 2009; Dumoulin & Wandell, 2008; Smith et al., 2001; Wandell & Winawer, 2011).

Following processing in early visual areas, visual information can be sent along one of two main branches for further processing; the dorsal stream leading to the parietal lobe and the ventral stream leading to the temporal lobe (Mishkin & Ungerleider, 1982). The dorsal stream is commonly referred to as the 'where' pathway, or 'pathway for action', as it is responsible for the localisation of objects and for visually-guided behaviours. Similarly, the ventral stream is referred to as the 'what' pathway or 'pathway for perception', as it processes perceptual object identification (Goodale & Milner, 1992).

So far, this introduction has discussed the retino-geniculo-striate visual pathway (primary visual pathway). Firstly, it should be highlighted that the brain is not a simple feedforward system. At each level of processing mentioned, there is two-way communication via reciprocal connectivity. It should also be noted that there are many alternative pathways which deliver visual information to the brain (Diamond

& Hall, 1969). To demonstrate the complexity of the visual system, a diagram which illustrates many of the areas and connections involved in visual processing is included for reference (Figure 3; Felleman & Van Essen, 1991.). Other key visual pathways include direct retinal projections to the suprachiasmatic nucleus (SCN), called the retino-hypothalamic tract, involved the establishment and maintenance of circadian rhythms (Gooley et al., 2001) and the retino-pulvinar tract which projects via the superior colliculus, and is involved in eye movements (Mishkin, 1972).

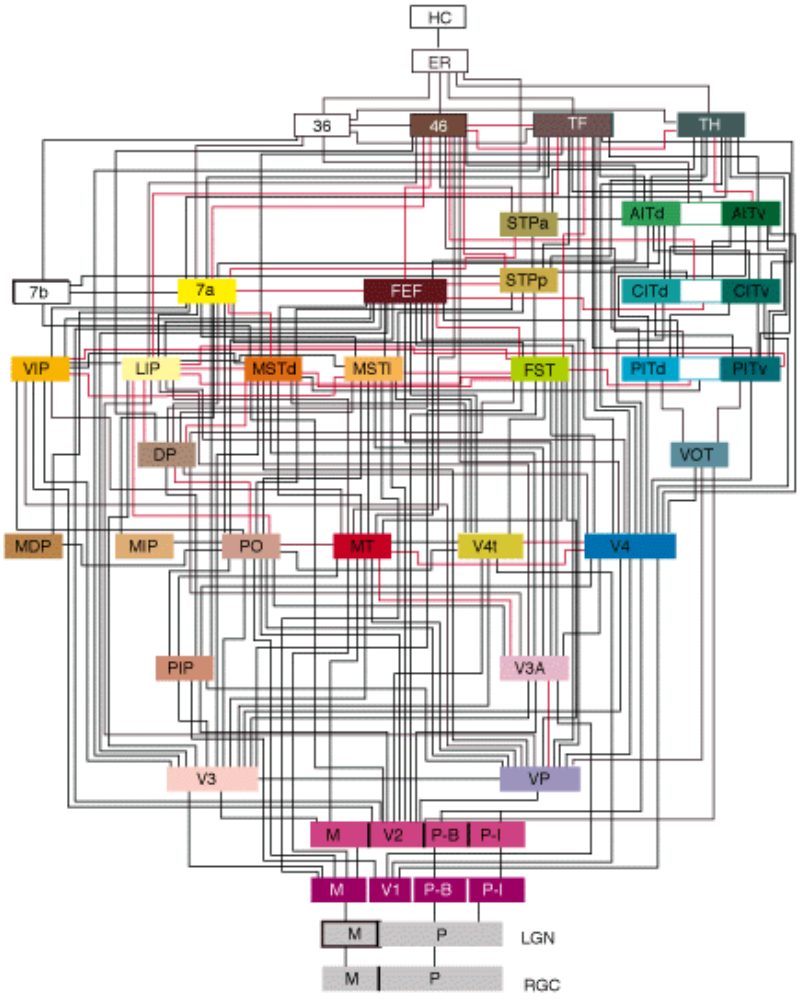


Figure 3: Circuit diagram of connectivity in the primate visual cortex. The diagram shows areas in the brain related to visual processing. It includes regions in the visual cortex, subcortical regions, and some non-visual areas. 187 linkages are shown, most of which are reciprocal. Image reproduced from Felleman & Van Essen, 1991.

1.1.2 Motion processing in the brain

The detection, processing, and perception of moving objects is a function that involves multiple regions of the human brain (Blake et al., 2003). 'First-order' motion, which is where a moving object is defined by luminance signals, is the most basic type of visual motion. First-order motion perception occurs when a luminance change is detected at a particular location in the visual field, and is correlated with a subsequent luminance change in a neighbouring region of the visual field (Cavanagh & Mather, 1989; Reichardt, 1961). 'Second-order' motion processing is defined by non-luminance functions such as contrast, texture or flicker detection (Chubb & Sperling, 1988; Derrington & Badcock, 1985; Lelkens & Koenderink, 1984).

The most basic processing of visual motion occurs in V1. V1 contains some neurones which show at least partial motion direction selectively, demonstrated initially in the macaque monkey (Hubel & Wiesel, 1968). Motion direction selectivity is where cells activate in response to motion in a particular direction, but show less activation in response to motion of other directions. In the macaque monkey, the portion of V1 showing such motion direction selectivity is significant (Schiller et al., 1976), with the majority of such cells localised to the upper portions of cortical layer 4 (Hawken et al., 1988). Motion direction selectivity has also been demonstrated in monkey superior colliculus (Davidson & Bender, 1991). In humans, motion direction selectivity has been demonstrated in V1 (Huk et al., 2001) and in the superior colliculus (Schneider & Kastner, 2005). The cells found in V1 have very small receptive fields, and for this reason cannot unambiguously determine larger-scale direction of motion (global motion). Therefore, further processing of motion must occur in extrastriate visual areas.

Evidence from the macaque monkey indicated that there is a progressive increase in the portion of cells with motion direction selectivity from area V1 to V3 (Felleman & Van Essen, 1987; Gegenfurtner et al., 1997; Hubel, 1988). In humans, extrastriate area V3A has been shown to be of particular importance for motion perception processing.

This dorsal extrastriate area shows strong direction selectivity, and responds more strongly to coherent motion compared to random noise motion (Braddick et al., 2001).

MT+ in the non-human primate

The principal areas of the macaque monkey brain involved in motion processing are the middle temporal area (MT), also sometimes referred to as V5, and the middle superior temporal visual area (MST). Area MST has very strong connectivity with V5/MT, and collectively, V5/MT and MST are known as the motion complex (MT+). Nearly all cells in MT+ show motion direction selectivity (Dubner & Zeki, 1971; Zeki 1974) and this directionality is represented topographically (Albright et al., 1984).

Studies in the macaque monkey established the role of MT+ in motion perception. Using single-unit recordings, neurones in MT+ have been shown to respond to motion patterns, unlike cells in early visual regions, indicating a role for MT+ in the perceptual processing of visual motion (Rodman & Albright, 1989). This finding has been supported by studies of animals with lesioned MT+. Lesions induced by transient excitotoxicity elevated the thresholds required for motion detection, indicating impaired motion perception (Marcar & Cowey 1992; Newsome & Paré 1988). The role of MT in motion perception in macaque monkeys was perhaps most unequivocally established by Britten et al. (1992), where direct recording of neurones in area MT were acquired alongside psychophysical measures of motion perception. The psychometric function for performance of a motion task was established, and could be fully accounted for by the relationship between the firing frequency of neurones in MT and the strength of the motion signal in the task. Furthermore, the activity in MT cells has been shown to be statistically linked to motion perception behaviours (Britten et al., 1996). Modification of the firing rate of neurones in MT using microstimulation has been shown to modify perception of motion (Salzman et al., 1990, Salzman et al., 1992).

Human MT+

Early indications of a human homologue of MT+ were established by investigations of patients with brain lesions. Zihl et al. (1983) described a patient with bilateral damage to the lateral temporo-occipital cortex, which resulted in a specific deficit of visual motion perception. This patient was able to carry out simple detection of moving stimuli, however, was unable to judge temporal frequency or velocity of such stimuli, indicating a disruption of motion processing at the global level (Hess et al., 1989). Furthermore, this patient was able to perceive coherent motion, but only in the complete absence of noisy, incoherent dot motion (Newsome & Paré, 1988). The inability of the patient to extract a global motion percept amongst noise motion further implicates the lesioned area of the lateral temporo-occipital cortex as an important mediator of global motion processing (Baker et al., 1991).

In the healthy human visual system, an MT+ homologue was first established using positron emission tomography (PET) imaging (Zeki et al., 1991). PET measures regional cerebral blood flow (rCBF). To determine the locations in the brain where motion perception may occur, subjects viewed moving or stationary visual patterns. The rCBF was contrasted for the two visual stimuli. An area located at the temporo-parieto-occipital junction was found to be more active when participants viewed moving visual stimuli than when static visual stimuli were viewed. Since this region is in a similar anatomical location to non-human primate area MT+, and is involved in motion perception, the region of the temporo-parieto-occipital junction has been termed the human motion complex (hMT+). Additional evidence has further established the role of hMT+ in the extrastriate visual processing of motion (Culham et al., 2001; Howard et al., 1996).

The hMT+ region is located at the temporo-parieto-occipital junction, and can be functionally separated into equivalents of areas V5/MT and MST (Huk et al., 2002). Human V5/MT is retinotopically organised, with RF sizes of 10-18°, which increase in size with retinal eccentricity (Amano et al., 2009). Area MST has even larger

receptive fields, which can extend even into the ipsilateral visual field (Huk et al., 2002).

There are multiple routes by which visual information may reach hMT+. In the macaque cortex, motion direction sensitive cells in area V1 send direct projections to V5/MT (Movshon & Newsome, 1996). Neurones in V1 also connect to V5/MT via indirect projections which pass through V2 or V3 (Gegenfurtner et al., 1997). More recent research in humans has established that visual information motion can activate V5/MT in the absence of V1 (Ajina et al., 2015), indicating there are pathways to MT+ which bypass V1. There are two such potential pathways: direct connectivity from the LGN to V5/MT, and projections which connect the thalamus to V5/MT via the superior colliculus. These pathways are further discussed later in this chapter.

1.1.3 Neuroplasticity

Neuroplasticity refers to the changes which can occur in the structure and function of the brain with experience. To fulfil its role as the controller of behaviour, the brain must be able to adapt to environmental pressures and physiological changes. This drive results in neuroplasticity: changes at the molecular and cellular level of the brain which can eventually impact at the behavioural level.

Critical periods

A critical period is defined as an epoch of neural development, where the brain is particularly plastic and sensitive to learning a distinct function. If the function is not acquired during this period, it is more difficult, or perhaps even impossible, to learn later in life. The landmark study of critical periods in vision was carried out in the cat visual system. It was shown that cats deprived of vision in one eye for the first three months of life were behaviourally blind in the deprived eye, and

that cells in V1 did not respond to stimulation of the deprived eye (Wiesel & Hubel, 1963). These impairments did not occur if adult cats were monocularly deprived for an entire year, indicating that the timing of deprivation during development is key to determining the response of the brain. These findings were later confirmed to be consistent in humans (Lewis & Maurer, 2009).

Although critical periods are important for informing the understanding of neuroplasticity in the visual system, the existence of critical periods should not be taken as evidence that structural and functional changes are impossible outside of the neural development period. In fact, many types of neuroplasticity occur in the adult visual system.

Neurogenesis, synaptogenesis, and dendritic arborisation

The idea that the growth of new neurones (neurogenesis) was impossible in the adult brain had been established dogma since the 1800s (Cajal, 1991). Although there were early indications of neurogenesis in the adult mammalian brain (Altman, 1962), by the 1980s the idea had still not been generally accepted by the scientific community (Rakic, 1985). However, novel cell labelling techniques (Miller & Nowakowski, 1988) eventually led to evidence that neurogenesis did indeed occur in the adult human hippocampus (Eriksson et al., 1998) and neocortex (Gould, 2007).

As well as neurogenesis, neuroplastic changes can take the form of increased neural connectivity. Experience-dependent synaptogenesis and dendritic arborisation have been demonstrated in grey matter (Draganski et al., 2004; Turner & Greenough, 1985; Volkmar & Greenough, 1972). The next section discusses in further detail the mechanism driving such changes.

Long-term potentiation

Long-term potentiation (LTP) describes the persistent strengthening of synaptic connectivity of neurones in the brain. Long-term depression (LTD) is the term used to refer to synaptic weakening. LTP and LTD were originally demonstrated in the hippocampus in the 1970s (Bliss & Lømo, 1973), but have since been demonstrated to occur also throughout the adult brain, including the cortex (Bear & Kirkwood, 1993; Fox, 2002). For a review of the signalling components involved in LTP, see Lüscher & Malenka, 2012. A summary of the signalling cascade is briefly described below.

LTP occurs between two neurones (Figure 4). When the pre-synaptic neurone is stimulated, the excitatory neurotransmitter glutamate is released at its synapse. Glutamate can bind to two different types of receptor on the post-synaptic cell: AMPA receptors and NMDA receptors (McLennan, 1983). When glutamate binds to an AMPA receptor, there is an influx of sodium ions into the post-synaptic cell (Harvey & McIlwain, 1968). This influx of positively-charged ions causes the cell to depolarise. This depolarisation causes magnesium ions to unbind from NMDA receptors (Nowak et al., 1984). Activated NMDA receptors which have been unblocked will permit the influx of calcium ions into the cell. This key action leads to many downstream cell signalling effects, which can lead to longer-term post-synaptic cell excitability (Dunwiddie & Lynch, 1979). The influx of calcium ions causes the activation of calcium-calmodulin (CaM) protein, which is an upstream regulator of the enzymes adenylate cyclase and CaM-dependent protein kinase II (CaMK II). Adenylate cyclase catalyses the conversion of ATP to cAMP (Rall & Sutherland, 1962). The secondary messenger cAMP has multiple downstream effects, such as activation of protein kinase A (PKA) which can increase the excitability of AMPA receptors (Wang et al., 1991), and CREB which is an important modulator of synaptic gene transcription (Montminy & Bilezikjian, 1987). CaMK II is a regulator of MAP kinases, which in turn regulate the transcription of proteins involved in building dendrites (Sano &

Kitajima, 1992). Therefore, by acting at AMPA and NMDA receptors, sustained activation of a pre-synaptic cell can induce significant changes in the post-synaptic cell leading to upregulation of synaptogenic and dendrogenic gene transcription.

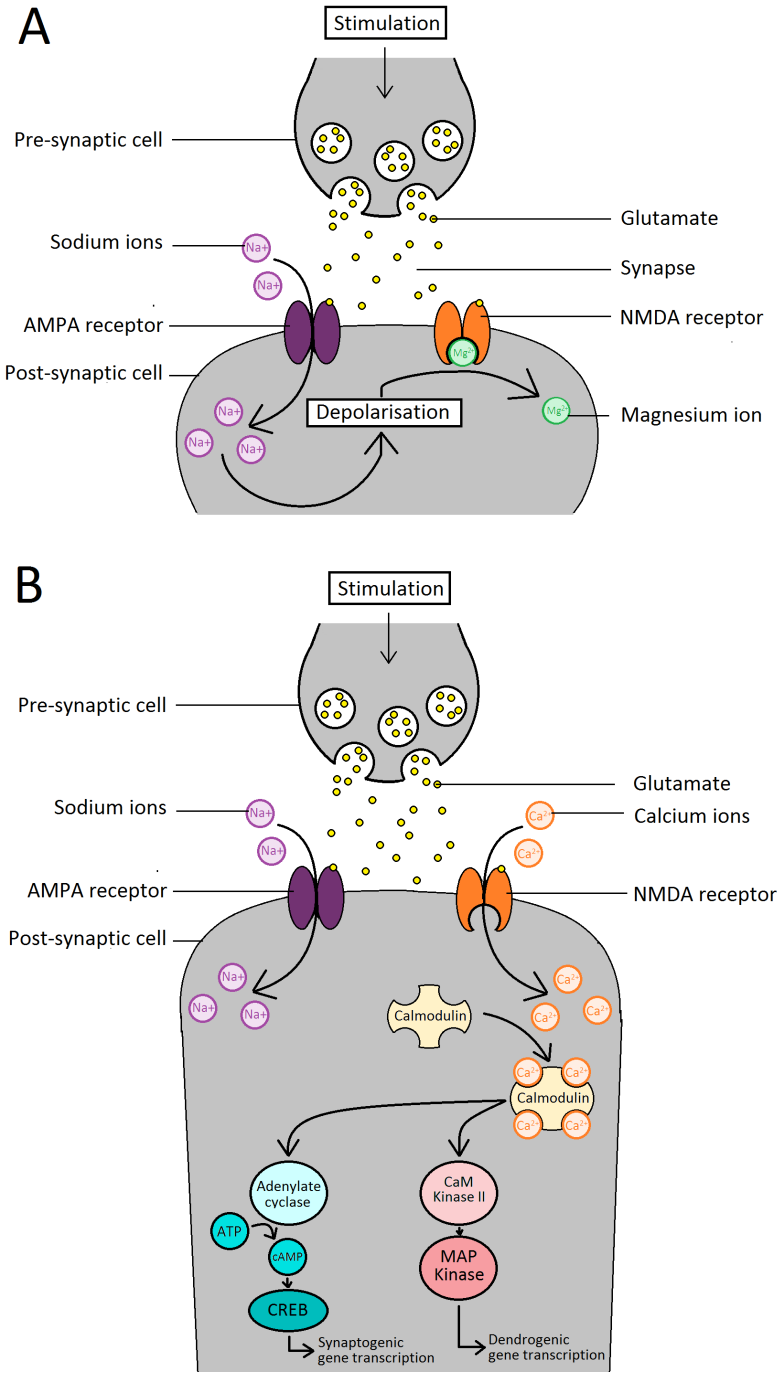


Figure 4: Cell signalling during long-term potentiation. **(A)** Stimulation of the pre-synaptic cell causes release of glutamate at the synapse. Glutamate binds to the NMDA receptors, but no ions can pass through the ion channels because they are blocked with magnesium ions. Glutamate binds to the AMPA receptors, causing an influx of sodium ions into the post-synaptic cell. The subsequent depolarisation of the cell relieves the magnesium block of the NMDA receptors. **(B)** Unblocked NMDA receptors stimulated with glutamate allow an influx of calcium ions into the post-synaptic cell. Calcium binds to Calmodulin, and the complex activates two enzymes. Adenylate cyclase upregulates the production of cAMP, which leads to activation of CREB. CREB can initiate gene transcription of proteins involves in the production of new synapses. Calcium-calmodulin (CaM) kinase II activates MAP kinases, which lead to the upregulation of gene transcription of proteins involved in creating new dendrites.

1.1.4 Visual perceptual learning

It is well understood that neuroplastic changes can occur at the molecular and cellular level. However, how these changes in neuronal connectivity may act to influence high-level processes such as visual perception is more complex. Visual perceptual learning (VPL) is the ability to improve at a visual task following repeated practice (Fahle & Poggio, 2002; Gibson, 1953). In recent years there have been many advances in the understanding of the mechanisms behind such learning (Lu et al., 2011; Sasaki et al., 2010).

Specificity of visual perceptual learning

Early literature found that the effects of VPL were highly specific to the trained retinal location (Karni & Sagi, 1991; Shiu & Pashler, 1992). If the location of the training stimulus is shifted by only a few visual degrees, there is no transfer of learning effects to the new area of the visual field. VPL can also be highly specific to trained stimulus features such as orientation (Crist et al., 1997; Fiorentini et al., 1980; Poggio et al., 1992; Schoups et al., 2001) and motion direction (Ball & Sekuler, 1987; Vaina et al., 1998; Watanabe et al., 2002). Since early visual areas are highly retinotopic (Rosa, 2002) and are often more finely tuned for orientation (Vanduffel et al., 2002), early literature concluded that the learning was likely mediated by the primary visual cortex and other early visual areas (Karni & Sagi, 1991). Further evidence that VPL is mediated by V1 comes from fMRI studies which showed that activity changes in V1 can be associated with perceptual learning (Furmanski et al., 2004; Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008).

However, more recent data suggest that learning can be transferable, both spatially and across tasks. Learning transfer to a different region of the visual field has been demonstrated specifically when those areas have been trained on a different visual task (Mastropasqua et al., 2015; Xiao et al., 2008). Furthermore, simultaneous or

subsequent passive exposure to untrained stimulus attributes (such as an untrained motion direction) may induce transfer of learning across such parameters in the trained part of the visual field (Zhang et al., 2010; Zhang & Yang, 2014). Easier tasks are more likely to show transfer of learning across stimulus parameters, such as motion direction (Liu, 1999) and orientation (Wang et al., 2013), and this transfer effect disappears if the training task is very difficult (Hung & Seitz, 2014). When the basic stimulus elements are comparable, perceptual learning can transfer even to distinct tasks (McGovern et al., 2012). These transferable properties indicate that higher level cortical areas may play a role in perceptual learning.

Mechanisms of visual perceptual learning

In order to bring together evidence that VPL is mediated at early as well as higher cortical regions, the learning process has been modelled as a two-part process (Chen et al., 2015). It has been proposed that changes in early visual cortex reflect a sharpened tuning of sensory neurones to the trained stimulus (Bejjanki et al., 2011; Poggio et al., 1992). The model also suggests that changes in extrastriate areas may reflect a reweighted connectivity between sensory and decision-making areas (Dosher & Lu, 1998; Law & Gold, 2008; Law & Gold, 2009). Therefore, VPL induces task-specific changes in the connectivity between sensory neurones tuned to the stimulus, and areas which integrate that information to provide an appropriate response.

The explanation for why some studies have found such variation in the role of early versus higher cortical areas in VPL is perhaps explained by the specifics of the training task (Sasaki et al., 2010). For instance, if a task requires very fine sensory discrimination, such as for a difficult orientation discrimination task, then there are likely to be changes in the early visual cortex where neurones have small receptive fields and are already tuned in a way that facilitates such discrimination. However, if a task requires a global integration of sensory signals, such as for the extraction of

coherent motion amongst noise, then higher visual areas with larger receptive fields and broader sensory tuning are more likely to be involved.

1.2 Visual processing in individuals with visual field defects

1.2.1 Introduction to visual field defects

Visual field defects (VFDs) are a type of partial cortical blindness: a loss of vision caused by damage to the vision areas of the brain. The extent and pattern of field loss is dependent upon where in the visual system the lesion occurs (Figure 5). Most commonly, lesions leading to VFDs occur in the occipital cortex (Fujino 1986; Zhang et al., 2006b), resulting in damage to the primary visual cortex or its afferents. Depending on the extent of the lesion, such damage can result in homonymous hemianopia, which is the loss of one half of the visual field in both eyes, or homonymous quadrantopia, which is a binocular loss of a quarter of the visual field. Macular sparing, which is where the central few degrees of visual field are left intact, is often observed following damage to the striate cortex caused by occlusion of the posterior cerebral artery. Sparing in the macula frequently occurs in this circumstance because the cortical regions representing the central vision are supplied with blood from a collateral projection of the middle cerebral artery.

Homonymous hemianopia can also result from damage to the optic radiation between the thalamus and the cortex, or from damage to the LGN. Other types of VFD include the loss of all information from one eye (monocular blindness), caused by optic nerve lesion or damage to the eye, and loss of the temporal half of the visual field in both eyes (bitemporal hemianopia), caused by damage to the optic chiasm (Figure 5).

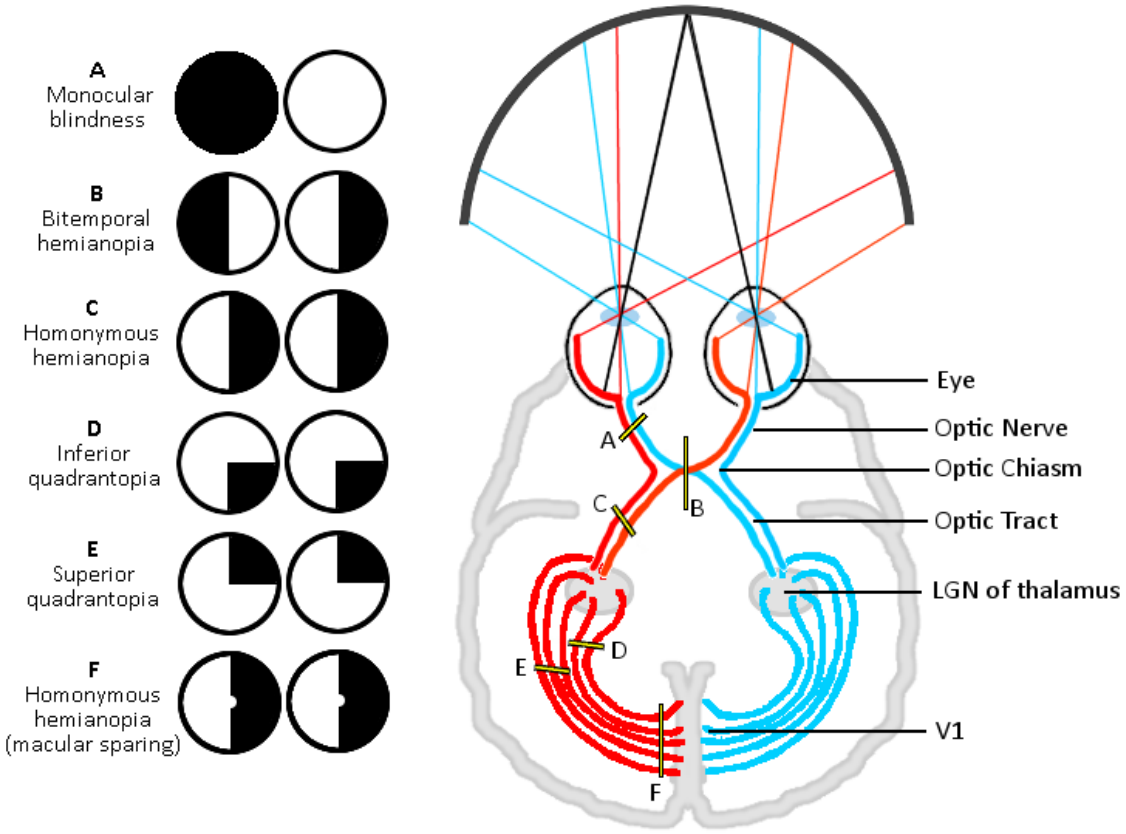


Figure 5: Visual field defects resulting from damage to visual pathways. Lesions affecting one eye are pre-chiasmic and all post-chiasmic lesions are homonymous. The extent of the visual field loss varies depending on where in the brain the damage occurs. On the left, the diagram shows a representation of the visual field in each eye, with the shaded region indicating cortical blindness in the corresponding area of visual field. On the right, the locations of corresponding lesions in the brain are illustrated with yellow bars. LGN = Lateral geniculate nucleus, V1 = Primary visual cortex. Image adapted from OpenStax CNX, 2016 and Allwright, 2016.

1.2.2 Aetiology of visual field defects

Transient VFDs are sometimes reported following stroke (Gray, 1989), migraine, seizure and transient ischaemic attack (Goodwin, 2014). A persistent VFD is a loss of visual field that does not spontaneously recover within the initial days or months following insult. The leading cause of persistent VFDs in adult patients is stroke, with an 8.3-46% incidence of VFD in stroke patients (Gilhotra, 2002; Gray, 1989). The range in reported incidence is likely a result of variable population demographics, measurement techniques, and reporting biases (Ajina & Kennard, 2012).

Further reports corroborate cerebrovascular disease as a major cause of VFD (Aldrich et al., 1987), with a reported 63-89% of VFDs being vascular in origin (Fujino 1986; Trobe, 1973). Less common causes of VFD include trauma, tumour, surgery, and demyelination (Aldrich et al., 1987; Bruce et al., 2006; Zhang et al., 2006b). In children, perinatal hypoxia and prematurity are the leading causes of VFD, with less common origins being hydrocephalus, structural central nervous system abnormalities, and seizures (Khetpal & Donahue, 2007).

1.2.3 Visual field defects and disability

The presence of a VFD can have a significant negative impact on quality of life. Impairment of the visual field can affect important everyday life skills, such as the ability to drive and the ability to read. Understanding how VFDs affect the daily life of patients is an important component in developing effective rehabilitative and compensatory strategies.

In the UK, in order to drive legally, individuals must have a total horizontal visual field of at least 160°, which should extend a minimum of 70° to the left and right of central vision, and 30° above and below central vision. If any defects are present within the central 30° of vision, then driving is not allowed (Driver and Vehicle Licensing Agency UK, 2015). These strict guidelines prevent nearly all patients with VFDs from driving. Prohibition from driving can significantly decrease independence and employment opportunities and is associated with an increased likelihood of depression (Ragland et al., 2005). Due to the negative impact of driving cessation on quality of life, many patients with VFDs continue to drive illegally (Goodwin, 2014).

Drivers with VFDs have been shown in driving simulators to make smaller head scans toward the blind side of their visual field, compared to the seeing field, and this can impair their ability to detect pedestrians and other hazards (Alberti et al., 2014). One study demonstrated that patients with VFDs detected pedestrians in a simulator only 46% of the time (Bowers et al., 2014). Furthermore, drivers with

VFDs demonstrate an impaired ability to control vehicle position, adjust speed for traffic conditions, and respond to unexpected events (de Haan et al., 2014; Elgin et al., 2010).

Another major issue identified in patients with VFDs is an impaired reading ability (hemianopic alexia). The group worst affected are patients who read from left to right and have a defect in the right visual hemifield which involves the macular region. Such patients are impaired because reading text requires the ability to see 3-4 letters to the left of fixation, and 7-11 letters to the right of fixation (Kerkhoff, 2000). Patients reading left to right with left-sided deficits are also impaired, due to difficulties with locating the next line of text (Trauzettel-Klosinski & Brendler, 1998). A further cause of reading difficulty in patients with VFDs is that such patients typically show disordered eye scanning behaviours. Those with field loss tend to fixate for longer, have smaller saccade sizes and make more frequent maladaptive regressive saccades (Zihl, 1995).

Other difficulties encountered by patients with VFDs include "disorientation, trouble crossing the street in traffic, bumping into objects, inability to detect hazards, and increased risk of falling" (Goodwin, 2014). These are mostly caused by problems with visually scanning and evaluating the environment.

1.2.4 Residual visual abilities in patients with VFDs

Within the cortically blind portion of the visual field following V1 damage, it has been shown that some visual function can remain. This function was originally termed 'blindsight', which is defined as the ability to successfully complete visual tasks despite a lack of conscious awareness of the stimulus (Weiskrantz et al., 1974). As such vision function was further investigated, the terms 'Type I blindsight' and 'Type II blindsight' were introduced (Weiskrantz, 1997). These terms reflected the discovery that as well as the original blindsight phenomenon (type 1 blindsight), some patients have partial awareness of the presence of visual stimuli in their blind

field (type 2 blindsight).

More recently, it has been established that some patients may retain even conscious visual processing of certain types of stimuli in their blind field (Sahraie et al., 2010b). As a result, retention of function in the scotoma is now commonly referred to using the broader term of 'residual vision'. There is evidence in humans of a residual ability to detect motion within blind visual regions, as well as evidence for form and wavelength sensitivity in the blind field (Weiskrantz et al., 1974; Weiskrantz, 1986). These findings have been supported by evidence in macaque monkeys (Stoerig & Cowey, 1997).

It is interesting to consider the potential pathways in the brain involved in residual vision, following damage to V1. Although spared islands of V1 may play a role in residual vision, there is evidence in humans that pathways that bypass V1 and project directly to the extrastriate cortex may also be involved (Kentridge et al., 1997). Two such pathways which bypass V1 have been proposed. The first projects from the retina to the superior colliculus, then directly to extrastriate area V5/MT (Bittar et al., 1999; Leh et al., 2010; Pegna et al., 2005; Ptito et al., 1999) and the second projects from the retina to the LGN of the thalamus, then directly to V5/MT (Schmid et al., 2010).

Collicular-pulvinar-extrastriate pathway for residual vision

It has been proposed that there is a direct pathway connecting the superior colliculus to V5/MT+, which bypasses the primary visual cortex (REFs).

Previous research in the macaque monkey has demonstrated that the superior colliculus does not receive inputs from retinal ganglion cells which are associated with activity of short-wavelength sensitive (S-) cone photoreceptor cells. S-cone cells detect blue stimuli, and therefore a lack of such projections to the collicular region indicates that this area may be blind to blue stimuli (Marrocco & Li, 1977; Schiller

& Malpeli, 1977; Sumner et al., 2002). Information about S-cone isolating stimuli therefore can only reach extrastriate areas, such as V5/MT+, via primary visual cortex (Warner et al., 2010). Since achromatic stimuli and stimuli of other colours activate the superior colliculus, such stimuli may activate extrastriate areas even in the absence of V1. Leh et al. (2010) investigated the role of a collicular pathway in human blindsight. The functional brain activity of a hemispherectomised patient with blindsight ability was monitored using fMRI, whilst the individual observed S-cone-isolating visual stimuli and achromatic stimuli. It was shown that the subject had increased neural activity in the extrastriate area V5/MT+ following achromatic stimuli, but no change in activity when observing S-cone isolating stimuli. This finding demonstrated that blindsight may be mediated by a collicular pathway.

Further evidence of the role of the superior colliculus in human blindsight is provided by investigation of the structural connectivity of the brains of hemispherectomised patients. Comparison of hemispherectomised individuals with blindsight to those without blindsight demonstrated that those with blindsight had ipsilateral and contralateral connections from the superior collusions to visual association areas, primary visual areas, parietal areas, prefrontal areas, and to the posterior part of the internal capsule. In contrast, the patients without blindsight did not show projections from the superior colliculus to the hemispherectomised side (Leh et al., 2006).

'Affective blindsight' describes the ability of patients with VFD to react to the emotional content of stimuli presented in their blind field, in the absence of conscious awareness of the stimuli. Research in humans has demonstrated that fear-related stimuli presented in the blind field can cause activation of the amygdala, via a collicular visual pathway that bypasses V1 (Morris et al., 2001). Diffusion tensor imaging (DTI) tractography has also been used to demonstrate increased connectivity between the pulvinar and amygdala, as well as between the superior colliculus and amygdala, in a patient with damage to V1 (Tamietto et al., 2012). This gives further evidence that subcortical pathways to the extrastriate cortex, which bypass V1, are involved in residual vision in patients with V1 damage.

Geniculo-extrastriate pathway for residual vision

There is strong evidence for a direct pathway between the LGN and extrastriate region V5/MT in the macaque monkey cortex (Sincich et al., 2004). The homologous area in humans is thought to play a key role in residual visual processing in patients with damage to V1.

Schmid et al. (2010) studied macaques with V1 lesions using fMRI. Two macaque monkeys with surgical removal of V1 were exposed to a visual stimulus presented in the scotoma. Neural activity monitored using fMRI indicated that there was significant activity in extrastriate visual regions during exposure to the visual stimulus. This indicates a neural correlate of residual visual processing in the scotoma. An injection of a GABA-A agonist drug into the LGN of the thalamus was carried out, in order to cause temporary inactivation of the LGN. Visual stimuli presented in the scotoma following LGN activation in V1-lesioned monkeys did not cause activation of extrastriate visual areas. This demonstrated that visual information reached the extrastriate cortex via a direct projection from the LGN. This important finding provides strong evidence that the LGN is an important node in the mediation of residual vision which bypasses V1.

The anatomical connectivity of GY, a well-studied patient with damage to V1 who exhibits residual vision in the blind field, was carried out by Bridge et al. (2008). DTI tractography was used to measure the structure and connectivity of white matter in the brain of GY. This individual had a tract connecting the LGN with ipsilateral V5/MT, which was also present in healthy control subjects. However, in contrast to subjects with an intact visual system, GY showed connections between LGN and contralateral V5/MT, as well as a transcallosal connection between V5/MT bilaterally. These connections not only demonstrate the structural plasticity that can occur following lesion to V1, but also support the hypothesis that residual vision may be mediated by a direct geniculostriate visual pathway (Rees, 2008).

1.2.5 Spontaneous recovery of VFD

Spontaneous recovery of VFD following vascular brain damage occurs in only a minority of cases (Gray, 1989), and is theorised to be an effect of recovery from inflammation following the insult. Therefore, recovery is probably mediated by reorganisation of function of cells that were perturbed but not destroyed around the lesion site (Eysel et al., 1999; Eysel & Schweigart, 1992). Spontaneous recovery after the initial 3-6 months following stroke is highly unlikely (Tiel & Kolmel, 1991; Zhang et al., 2006a). Rehabilitation of visual field defects presents a challenge, since patients are frequently of an aged population, which makes relearning more of a difficulty (Peszczynski, 1961). Despite this, there are several compensatory, substitution and restitutive strategies which have been employed to successfully rehabilitate persistent VFDs.

1.2.6 Substitution and compensatory therapies for VFDs

Prism therapy is a type of substitution therapy for rehabilitating VFDs. Prism therapy involves the use of distorting prisms, which are attached to spectacles. The most modern version of prism therapy involves the attachment of prism lenses such that the prism covers the entire width of a section of the spectacles. This allows objects in the blind visual field to be detected without eye movements towards the blind region. The distorting lens is applied over a single eye, so that there is expansion of the visual field, rather than the simple relocation, which would occur with binocular prism application. Studies of patients using such prisms show that the therapy can improve specific activities such as obstacle avoidance as well as having a positive impact upon reported quality of life measures (Giorgi et al., 2009; O'Neill et al., 2000). Furthermore, prism therapy has a good rate of long-term use (Bowers et al., 2008).

Eye movement training is a compensatory therapy applied for the rehabilitation of VFDs. The eye movement behaviour of individuals with VFDs is often impaired

(Bergsma et al., 2011). Repeated practice of large saccadic eye movements towards the scotoma, aiming to give the patient a better overview of the visual scene as a whole, can increase the area of visual search (Kerkhoff et al., 1992; Zihl, 1995). Such training can transfer to real-life tasks (Kerkhoff et al., 1994). This therapy is also low-cost and portable (Mannan et al., 2010; Pambakian et al., 2004).

1.2.7 Restitutive therapies for VFDs

Compensatory therapies for VFDs offer strategies which may help patients to better accommodate their visual impairment. Another focus of research has been to investigate the influence of inducing neuroplasticity, in order to improve visual function in the blind visual field. These restitutive strategies aim to directly train the region of visual field affected by the scotoma.

Early research in macaque monkeys demonstrated that repeated exposure to visual stimuli within the scotoma could eventually increase the size of the seeing visual field (Cowey, 1967; Mohler & Wurtz, 1977). This research was then applied in humans, and found success in the reduction of scotoma size in a majority of patients (Zihl & von Cramon, 1979; Zihl & von Cramon, 1985). However, subsequent studies determined that after controlling for additional variables (Balliet et al., 1985), recovery is likely only possible in a minority of patient cases (Pambakian & Kennard, 1997). More recently, Sabel et al. produced a vision restitution training protocol (VRT). VRT involves the detection of lights at the border of and within the blind field. After extensive daily training, enlargement of the visual field was reported (Kasten et al., 2000). However, controversy regarding VRT has persisted in the literature due to the impact of confounding eye movements upon claimed benefits (Horton, 2005b; Sabel et al., 2005; Sabel, 2006), and the effects of VRT remain unproven.

Flicker stimulation training as a therapy for VFD involves repeated exposure to a flickering stimulus in the blind field. Following training, there is a significant improvement in the rate of successful identification of flickering letters positioned in

the blind field (Raninen et al., 2007). Imaging determined that there was functional reorganisation at the cortical level as a result of the training (Henriksson et al., 2007). However, extensive training was required (sessions twice weekly for a year) in order to observe such effects.

In patients with damage to V1, residual vision in the scotoma has been shown to be optimally sensitive to stimuli with a narrow spatial and temporal bandwidth (Barbur et al., 1994; Sahraie et al., 2003; Sahraie et al., 2010a). Sahraie and colleagues have developed a perceptual training protocol which aims to target residual vision by exploiting this finding. Repeated training in the detection of circular patches of sinewave gratings led to an increased ability to detect and discriminate the gratings (Sahraie et al., 2006). Furthermore, there was an expansion of the visual field border and participants reported a subjective improvement in vision.

In the blind field of patients with VFDs, there is often considerable residual motion perception (Moore et al., 2001; Morland et al., 1999; Schenk & Zihl, 1997). Huxlin et al. trained patients with VFDs on a complex motion perception task, which required participants to be able to extract a global motion direction vector by integrating multiple different dot directions (Huxlin, 2008). Training resulted in significantly improved direction integration thresholds in the blind field (Huxlin et al., 2009). Training effects also improved contrast sensitivity and the extraction of coherent motion from noise motion, both of which were not trained directly. Perimetric analysis of the visual field border also indicated a modest reduction in the size of the scotoma.

1.3 Synopsis of thesis

The overall aim of this thesis is to investigate perceptual learning of motion in a healthy population, with a view to designing a motion perception training programme for patients with visual field defects (VFDs) caused by damage to the primary visual cortex (V1).

In the first data chapter (Chapter 3), a motion perception training programme is tested in a healthy population, in order to verify if the task design is appropriate for initiating improvement in motion perception. The programme involves training participants every day for five consecutive days, on a motion direction discrimination task. The training stimulus is delivered in a single visual hemifield offset from central gaze fixation. Before and after training, performance in both visual hemifields is assessed in order to determine the transferability of training to untrained regions of the visual field. A second group of participants is trained on a non-motion orientation discrimination task, so that any attentional learning effects of the training can be separated out from motion perception learning.

In the second data chapter (Chapter 4), the impact of training timecourse on learning is examined. Participants complete the same number of trials of the motion perception task or orientation task as in the previous chapter, however, the training is condensed down into a single day rather than spread over five days. The impact of learning timecourse upon magnitude of learning effects and transferability of learning effects across the visual field is determined.

In the next chapter (Chapter 5), fMRI methods were applied in order to localise and quantify any functional changes in brain activity induced by the motion perception training programme. Participants complete the motion perception task inside an MRI scanner, before and after the motion perception training programme spread over five consecutive days, as in the first data chapter.

In the fourth data chapter (Chapter 6), the impact of combining brain stimulation with the motion perception training programme is investigated. Participants complete the five days of motion perception training while undergoing transcranial direct current stimulation (tDCS) of the extrastriate cortex. This study determines if the learning effects of the programme could be increased with the combination of electrical brain stimulation of the visual cortex.

In the final data chapter (Chapter 7), the motion perception training programme is

piloted in a patient with a VFD caused by damage to V1. The aim of this study is to determine if learning can be demonstrated when the task is applied in a patient, and to discover what modifications may be required to make the task more appropriate for those with VFDs.

An overall discussion summarising the main findings and future directions following the results of this thesis is presented in Chapter 8.

2 General Methods

2.1 Introduction

Psychophysics has been defined as "the analysis of perceptual processes, by studying the effect on a subject's experience or behavior of systematically varying the properties of a stimulus along one or more physical dimensions" (Bruce et al., 2006). Psychophysical methods have been used consistently in this thesis to determine performance on visual tasks. Such basic methods have a strong history of providing rigorous, accurate and objective measurements of perceptual experience (Read et al., 2015).

All experiments collated in this thesis shared common psychophysical methods, and therefore they are detailed here rather than repeated within each individual chapter. Minor variations on the psychophysical methods are highlighted and detailed in each chapter as appropriate. Further additional methods such as brain imaging and brain stimulation are explained in full in their respective chapters.

2.2 General methods

2.2.1 Participants

Participants with self-reported normal or corrected-to-normal vision participated in the experiments (breakdown of numbers, age, and gender are provided within each chapter). All participants were inexperienced in visual psychophysical experiments. Each study was approved individually by the local Inter Divisional Research Ethics Committee (IDREC) at The University of Oxford and all subjects gave written, informed consent. All research adhered to the Declaration of Helsinki (v7, 2008).

2.2.2 Visual tasks

The aim of this project was to investigate motion perception, and motion perception learning, in a variety of different ways. As such, a task was designed which required participants to discern direction of motion, therefore engaging motion perception processing, the focus of the study. In order to extract motion-specific task effects, a separate non-motion task was also designed. This non-motion task required participants to discern the orientation of Gabor patches (sinusoidal gratings). Thus, there were two tasks used in this project: a motion direction perception task (sometimes abbreviated in this thesis to 'motion task') and a Gabor orientation perception task (sometimes abbreviated to 'orientation task').

Initial performance on each task was assessed prior to any task training, to determine baseline ability to complete the task. Once all training sessions of the appropriate task had been carried out, the performance assessment was repeated. Performance in the second assessment could then be compared against the first assessment to determine whether any changes had taken place after the training period. This allowed the inference of the effect of training on task performance.

In all pre-training and post-training visual assessments, stimuli were presented individually to the left and the right visual hemifields. This allowed separate assessment of each visual hemifield. During the training sessions, participants were shown stimuli in a single visual hemifield. Therefore, there was always a 'trained' and an 'untrained' visual hemifield. This was instigated so that effects of transfer of learning across the visual field could be determined.

The number of trials in the assessments and training, and the timings of the sessions, were varied across experiments, and so are detailed in the Methods sections of later chapters.

Motion direction perception task

For the motion direction perception task (Figure 6), participants were asked to identify whether a group of coherently-moving dots had leftwards or rightwards motion, when displayed amongst randomly-moving distractor dots ('noise'). Participants were told to keep their eyes on a fixation cross presented in the centre of the screen, during presentation of the stimulus in the periphery (500ms). Instructions further detailed that the direction of the coherent motion would vary up to 45° offset from the horizontal plane (coherent motion direction was variable but restricted to within a 90° angle centred around the horizontal plane). Subjects were only required to extract leftwards or rightwards motion. Responses were provided by a left arrow or right arrow keyboard press. Participants were also informed that the task difficulty would be varied depending on their performance and that this would happen by a change in the proportion of randomly-moving distractor dots presented on the screen. Subjects were told feedback would be provided visually on a trial-by-trial basis, with the fixation cross changing green or red briefly (for 200ms) following a correct or incorrect answer respectively. The task was self-paced, as participants were allowed as long as required to complete each trial. It was emphasised that accuracy at the task was more important than speed.

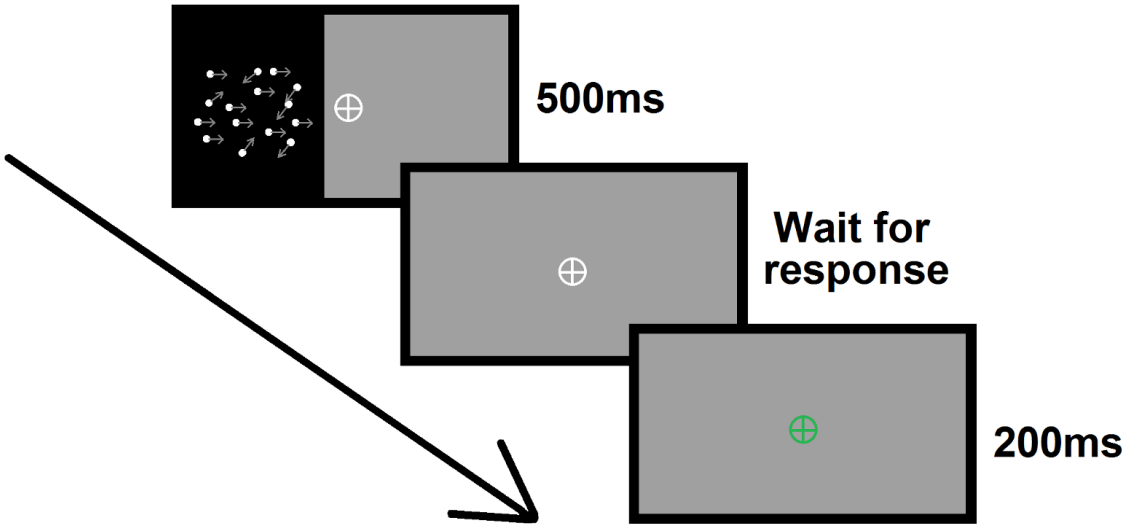


Figure 6: Stimuli and timing for the motion direction perception task. The stimulus was offset from central gaze fixation, either in the left or right visual hemifield. The stimulus was presented for 500ms before disappearing. The response window opened immediately, and the program paused until the participant gave a response using keyboard input (left or right arrow key). Once a response had been recorded, the fixation cross flashed either red or green for 200ms, to signal an incorrect or correct response respectively.

Gabor orientation perception task

For the Gabor orientation perception task (Figure 7), participants were instructed to identify whether the overall orientation of an area of Gabor patches was vertical or horizontal. Coherent Gabor patches were vertically/horizontally-oriented and the remaining patches were oriented randomly ('noise'), with the noise having a net orientation of zero. This stimulus was chosen for its similarities to the motion task (extraction of coherence amongst noise), but without any motion element. The parameters were chosen so that task difficulty was similar to the motion task. Other than being required to determine orientation instead of motion, the instructions given to participants were similar to those for the motion task. Participants used an up arrow to indicate vertical orientation and a right arrow for horizontal orientation.

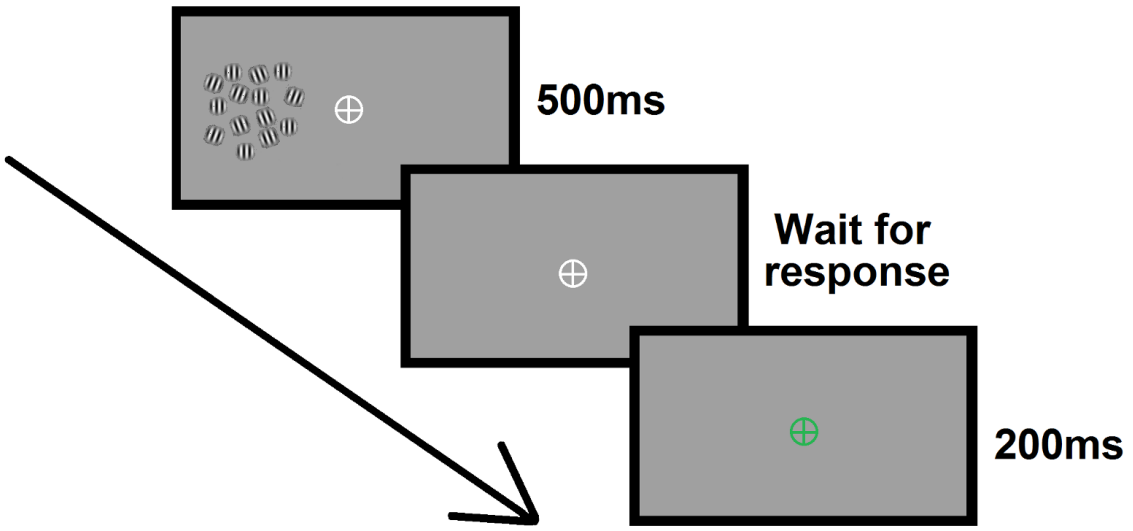


Figure 7: Stimuli and timing for the Gabor orientation perception task. The stimulus was offset from central gaze fixation, either in the left or right visual hemifield. The stimulus was presented for 500ms before disappearing. The response window opened immediately, and the program paused until the participant gave a response using keyboard input (up or right arrow key). Once a response had been recorded, the fixation cross flashed either red or green for 200ms, to signal an incorrect or correct response respectively.

Modulation of task difficulty

For both tasks, participants started with a coherence level of 80% to ensure detection of the stimulus. The difficulty of both tasks was then varied adaptively, following a two-up one down staircase procedure, using the implementation of García-Pérez (1998). Two consecutive correct responses resulted in coherence being changed by a factor of 0.8, while an incorrect response resulted in a change of 1.458. For the motion stimulus, the ratio of coherently-moving dots to randomly-moving dots was altered. For the orientation stimulus, the ratio of coherent (vertical or horizontal) to randomly-oriented Gabor patches was altered. This staircase procedure was used so that thresholds for the detection of the stimulus for each session could be calculated, and also to provide scope for learning and improvement in each task.

Task timings

In both tasks a single trial took 700ms, plus response time. The stimulus was presented for 500ms, in line with previous literature estimating 500ms is sufficient for temporal integration of dot motion (Watamaniuk & Sekuler, 1992). Once the stimulus had disappeared, the program paused until participants gave a button press response. The fixation cross changed colour for 200ms to provide the participant with trial feedback; it turned green if the response recorded was correct, or red if incorrect. This period was chosen as it was brief enough to keep each trial face-paced, while being long enough that the participant could determine their performance.

After every 20 trials, a pause screen was displayed. This was optional, so participants could skip past the screen immediately if they preferred, or could pause for up to 2 minutes. Censor et al. (2006) found that the number of trials per block in a session affected the performance on a visual texture discrimination task. Despite the number of trials overall being kept constant, if participants completed a task in 50-trial blocks, performance was significantly worse compared to those completing the session in 26-trial blocks. Therefore, fewer trials per block improved performance on a visual perception task. Accordingly, 20-trial blocks were used here to maximise the learning effect.

2.2.3 Visual stimuli

Visual stimuli were programmed using Processing Java v2.0b6 (MIT) and Matlab (vR2012a) with functions from the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007), and were presented on a laptop computer (Acer Aspire 5733, 1366x768 pixel resolution, 60Hz refresh rate, 15-inch display) or CRT monitor (ViewSonic E70fSB, 1280x1024 pixel resolution, 75Hz refresh rate, 17-inch display) in a darkened room. Participants were positioned 56cm from the screen and used a chin-rest to minimise head movements.

Moving dots were presented within a circular area offset from fixation. The number of dots, as well as diameter and offset of the stimulation area varied depending on the experiment and exact setup, and are therefore detailed fully in the Methods section of the relevant chapters. Across all experiments, the dot diameter was 0.15°, and dots moved with a speed of 6°/s for a limited lifetime of 200ms (1/12th of the dots died each frame), at a density of 1.5 dots/degree^2. These parameters were chosen because they have been shown to be largely effective at targeting the motion system (Moo et al., 2008). On a trial-by-trial basis, spawning dots were generated at random, non-overlapping locations within the stimulus aperture to prevent the participant from tracking individual dots. During each block, the number of trials where the coherent motion was leftwards was equal to the number of trials where the coherent motion was rightwards. The initial stimulus was set such that 80% of the dots had coherent motion. This initial stimulus was always above the detection threshold for participants and ensured they could see the stimulus and perform the task correctly.

The allocation of noise dot motion direction was carried out in a paired manner. For half of the noise dots, the direction of movement was allocated at random. In order to ensure noise dots had a net direction of zero, the other half of the dots were allocated such that each was in opposition to a noise dot in the first set. For example, if a dot had been allocated a vector of 045° then its pair was allocated a vector of 225°. This occurred on a trial-by-trial basis.

Three different coloured stimuli could be used: blue dots on a yellow background, red dots on a green background and white dots on a black background. The luminance and chromaticity measures (SpectraScan PR-650) were blue: 15cd/m^2 (x=0.168, y=0.080), yellow: 29.5cd/m^2 (x=0.387, y=0.497), red: 11.2cd/m^2 (x=0.579, y=0.327), green: 18.3cd/m^2 (x=0.276, y=0.565), white: 96.8cd/m^2 (x=0.289, y=0.312), and black: 0.92cd/m^2 (x=0.236, y=0.247).

In the Gabor orientation task, Gabor patches of 90% contrast were presented within a circular area offset from fixation. The number of Gabor patches, as well as

diameter and offset of the stimulation area varied depending on the experiment and exact setup and are therefore detailed fully in the Methods section of the relevant chapters. Gabor diameter was always 1° and spatial frequency was 5 cycles/°. These values were chosen because the percentage of correct responses prior to any training had a similar average and variation of performance, compared to the motion task. Gabors appeared in a non-overlapping, randomly jittered locations to prevent nearby patches combining to form long lines. During each block, the number of trials where the coherent orientation was vertical was equal to the number of trials where the coherent orientation was horizontal. The initial stimulus was set such that 80% of the patches were coherence. This initial stimulus was always above the detection threshold for participants and ensured they could see the stimulus and perform the task correctly.

The allocation of noise Gabor patches was carried out in a paired manner. For half of the patches, the orientation was allocated at random from a range of 0° oriented (vertical) to 90° oriented (horizontal). In order to ensure noise patches had a net orientation of zero, the other half of the patches were allocated such that each was rotated 90° clockwise from a patch in the first set. For example, if a patch had been oriented 10° from vertical then its pair was allocated an orientation 100° from the vertical. This occurred on a trial-by-trial basis.

2.2.4 Data analysis

Statistical analyses of behavioural data were carried out using SPSS Statistics (IBM, v19). Exact statistical tests carried out are further detailed in the relevant chapters.

For each block of visual task assessment or training, a coherence threshold at which the participant was predicted to be correct 80% of the time was calculated. For all tasks, the difficulty was modulated according to participant performance using a two-down one-up protocol (see above). The coherence threshold was produced by

calculating the mean of the coherence percentages for each trial in which a reversal occurred (a reversal is where the stimulus changed from increasing in difficulty to decreasing in difficulty, or vice versa). An example calculation is demonstrated in Figure 8.

The first 10 reversal values were always discarded because the initial stimulus was always set at 80% coherence, which was far above detection threshold. The discarding also reduced the impact of initial errors unrelated to the stimulus (for example, pressing the wrong button), which may be most likely to occur at the start of each block. For each assessment, an average of 77.4 reversals (SD=8.8) were used to calculate the coherence threshold. For each training session, an average of 97.7 reversals (SD=8.5) were used to calculate the coherence threshold.

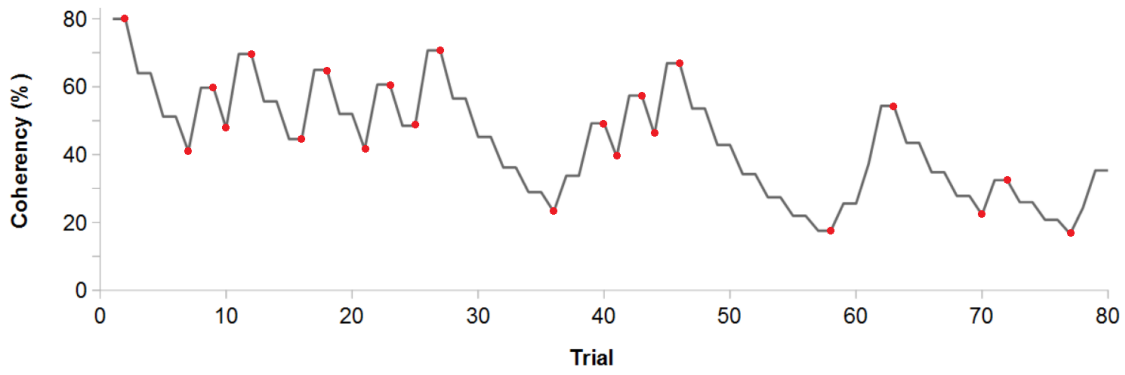


Figure 8: Example staircase calculation. The data show an example 80 trials of a participant completing a task where the difficulty (percentage of dots moving coherently, or percentage of Gabor patches oriented vertically/horizontally) is modified according to a two-down one-up staircase protocol. To calculate the motion coherence threshold for this block, the reversal values (peaks and troughs) marked in red are averaged. This outputs a single number, which represents a statistical estimate for the amount of coherence required for the participant to get the task correct 80% of the time (García-Pérez, 1998).

To quantify change in threshold from the pre-training assessment to the post-training assessment, a learning index was calculated using the following formula:

$$LearningIndex = \frac{\left(T_{preTrain} - T_{postTrain}\right)}{\left(T_{preTrain} + T_{postTrain}\right)}$$

where $T_{preTrain}$ and $T_{postTrain}$ are the thresholds for the pre- and post-training assessments respectively.

This index was chosen over the simple ($T_{postTrain}$ - $T_{preTrain}$) as the result of this calculation only gives the magnitude of change, irrespective of the proportion of change relative to the starting threshold (e.g. it cannot differentiate between a change in coherence from 80% to 40% or 70% to 30%). An alternative value which compares two values but accounts for this is the ratio of change: ($T_{postTrain}$ / $T_{preTrain}$). However, this calculation outputs a large range of numbers.

The learning index described above outputs the ratio of change, scaled to a range between -1 (a decrease at the post measure) and +1 (an increase at the post measure), with 0 indicating no change.

3 Investigation of the learning effects of motion perceptual training in healthy individuals

3.1 Introduction

Visual perceptual learning (VPL) describes the improvement in performance of a vision perception task with repeated practice (Gibson, 1953; Gibson, 1963). Over recent years, the use of VPL to augment visual function, both in healthy individuals and in those with specific visual disorders, has increased considerably. In the healthy visual system, positive benefits of VPL have been documented for vernier acuity (Fahle, 1994; McKee & Westheimer, 1978), motion perception (Fahle & Skrandies, 1994; Zhang & Yang, 2014), speed of visual processing (Lev et al., 2014), reading speed (Chung et al., 2004), and contrast sensitivity (De Valois, 1977; Deveau et al., 2014). One condition for which VPL has been particularly effective is amblyopia, in which one eye shows decreased visual function, often leading to deficits in binocular vision. Following extensive training, a number of studies have shown an enhancement in stereoscopic vision (Astle et al., 2011; Ding & Levi, 2011) and contrast sensitivity (Polat et al., 2004), in addition to both spatial and stereo acuity (Xi et al., 2014). In patients with visual cortical damage, VPL may be applied to boost residual visual function, either by recruiting neighbouring cortical tissue or by increasing visual activity in weaker pathways. Indeed, there have been initial reports of some visual recovery following extended VPL of around 3 months in such patients (Henriksson et al., 2007; Huxlin et al., 2009; Sahraie et al., 2006). However, an effective short-term protocol would make such treatments more attractive.

The transferability of visual improvements following VPL remains the subject of considerable debate. Initially, VPL was considered specific to the trained task, and not transferable to untrained retinal locations (Karni & Sagi, 1991), stimulus orientations (Poggio et al., 1992), or other parameters (Ahissar & Hochstein, 1993;

Fahle & Morgan, 1996; Fiorentini & Berardi, 1980). However, more recent data suggest that learning can be transferable, both spatially and across tasks. Learning transfer to a different region of the visual field has been demonstrated specifically when those areas have been trained on a different visual task (Mastropasqua et al., 2015; Xiao et al., 2008). Furthermore, simultaneous or subsequent passive exposure to untrained stimulus attributes (such as an untrained motion direction) may induce transfer of learning across such parameters in the trained part of the visual field (Zhang et al., 2010; Zhang & Yang, 2014). Easier tasks are more likely to show transfer of learning across stimulus parameters (Liu, 1999; Wang et al., 2013), and this transfer effect disappears if the training task is very difficult (Hung & Seitz, 2014). When the basic stimulus elements are comparable, perceptual learning can transfer even to distinct tasks (McGovern et al., 2012).

The aim of this experiment was to determine whether five days of motion perception training in healthy individuals is sufficient to elicit an improvement in motion perception in the peripheral visual field. To apply VPL as a therapy for patients with visual cortex damage to boost residual vision, the effects should be as transferable as possible. Thus in this study, we aimed to quantify the extent to which effects of a simple five-day training protocol transferred across stimulus attribute (colour), spatial location (hemifield) and stimulus elements (moving dots compared to oriented Gabor patches).

3.2 Methods

Further information about the setup of this experiment can be found in Chapter 2.

3.2.1 Participants

Twenty-four subjects (12 female and 12 male; M=21.8 years; SD=2.91 years) participated in this study. Four participants produced pilot data ('pilot' group), ten participants were assigned to the full version of the motion direction perception training protocol ('motion training' group), and the remaining ten participants to a Gabor orientation training protocol ('control' group).

3.2.2 Visual tasks and stimuli

There were two tasks used in this project: a motion direction perception task and a Gabor orientation perception task.

For the motion direction perception task, participants identified whether a group of coherently-moving dots had leftwards or rightwards motion when displayed amongst randomly-moving distractor dots ('noise'). The direction of coherent motion was variable and restricted to within a 90° angle centred around the horizontal plane. In the motion direction perception task, moving dots (n=212) were presented within a circular area 13° in diameter centred 9.9° to the left or right of fixation (the edge was 3.4° from fixation). For the assessments (see below), three different coloured stimuli were used: blue dots on a yellow background, red dots on a green background, and white dots on a black background. For the training, blue dots were presented on a yellow background. For the pilot group, the conditions were presented in a fixed order as stated above. Otherwise, the conditions were presented pseudorandomly on a trial-by trial basis.

Participants completing the Gabor orientation perception task were instructed to identify whether Gabor patches were vertically-orientated or horizontally-oriented.

The patches were displayed amongst randomly-oriented patches ('noise'). The overall orientation of the noise Gabor patches was always zero. In the Gabor orientation perception task, Gabor patches (n=50) of 90% contrast were presented within a circular area 13° in diameter centred 9.9° to the left or right of fixation (the edge was 3.4° from fixation).

3.2.3 Assessment and training paradigms

All participants undertook a five-day training protocol that consisted of two assessment sessions (Days 1 and 5, before and after training respectively), and ten training sessions at a frequency of two per day (Figure 9). All participants completed motion direction perception task assessments, and then fourteen participants were trained for five days on the motion direction perception task (pilot group plus motion-trained group) while the other ten were trained on the Gabor orientation perception task (control group). Participants in the control group also completed the Gabor orientation perception task during the assessment sessions.

In all assessments delivered to non-pilot subjects, stimuli were presented to the left or right visual hemifield pseudorandomly, with 200 trials per hemifield. (Assessments were delivered to pilot subjects in a fixed order, see above). During the training sessions, participants in the pilot and motion training groups performed the motion direction perception task, but only in a single hemifield (half of the participants trained the left hemifield, whilst half trained the right). Each training session (two sessions per day) consisted of 400 trials and participants were offered an optional break screen every 20 trials to reduce fatigue. Similarly, the control group performed the Gabor orientation perception task in a single hemifield with the same protocol.

All participants received visual feedback on their task performance following every trial of either task during training sessions and assessment sessions. A red cross was displayed for an incorrect response and a green cross was displayed for a correct response.

Group	Day 1	Day 2	Day 3	Day 4	Day 5
Pilot group	- Motion coherence assessment *(Fixed block order)* - Motion coherence training	- Motion coherence training	- Motion coherence training	- Motion coherence training	- Motion coherence training - Motion coherence assessment *(Fixed block order)*
Motion training group	- Motion coherence assessment - Motion coherence training	- Motion coherence training	- Motion coherence training	- Motion coherence training	- Motion coherence training - Motion coherence assessment
Control group	- Motion coherence assessment - Gabor orientation assessment - Gabor orientation training	- Gabor orientation training	- Gabor orientation training	- Gabor orientation training	- Gabor orientation training - Gabor orientation assessment - Motion coherence assessment

Figure 9: Experimental protocol followed by the motion training and control participants. Each participant completed assessments on Day 1 and Day 5. Training was performed twice per day across the 5 days. The motion-trained participants were assessed on the motion direction perception task only. The control participants were assessed on the motion direction perception and Gabor orientation perception tasks.

3.3 Results

3.3.1 Timing has an effect on consecutively-presented task conditions

Data from the pilot group were analysed separately from the main data. Participants in the pilot group were assessed on six different motion conditions in a fixed order (i.e. trials of blue dots in training hemifield, then blue dots in opposite hemifield, followed by red dots in training hemifield etc.). A one-way ANOVA showed a significant effect of timing on participant performance on the motion task (Figure 10: F=3.429; df=5; p=0.024). Since this effect occurred so rapidly, it is likely due to participants simply learning how to do the task, rather than an improvement in perception. The next iteration of this experiment (affecting the motion-training and control groups) presented the conditions in an interleaved pseudorandom order during assessments to prevent this confound.

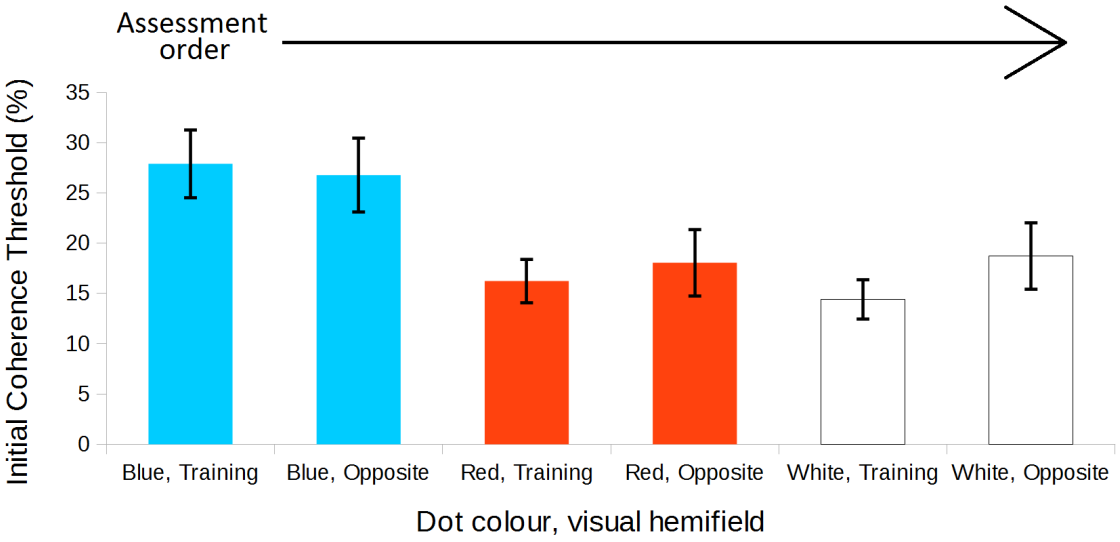


Figure 10: Timing has an effect on initial task performance. Participants in the pilot group (n=4) were assessed on performance of a motion task for six different stimulus conditions prior to task training. Calculation of initial coherence threshold demonstrated that the participants improved over the 6 assessments (thresholds get lower from left to right) and therefore the conditions should be presented interleaved for a more accurate assessment. These data were only used for pilot purposes, and were not included in the main analysis described later in this chapter. Error bars show $\pm SEM$.

3.3.2 There is variability in the initial ability of participants to complete the motion direction perception task

The initial motion coherence thresholds varied considerably across the 20 participants, ranging from thresholds of 7.1% to 90.4% of dots moving coherently, with a mean of 37.2% for the motion training group and 44.2% for the control group. A repeated measures ANOVA (factors: group, colour, hemifield) showed no significant effect of group ($F=0.548$; $df=1$; $p=0.478$) or stimulus colour ($F=2.728$; $df=1$; $p=0.125$), but a significant effect of hemifield in which the stimulus was presented ($F=6.604$; $df=1$; $p=0.030$) indicating slightly lower thresholds in the right hemifield (corresponding to the left hemisphere).

3.3.3 Five days is sufficient for perceptual learning to occur

Performance in the daily training sessions was quantified to determine the change in performance over the five-day protocol. The motion training group showed a significant improvement in coherence thresholds, with the mean reducing from 14.45% at Session 1 to 10.23% at Session 10 (one-way ANOVA with post-hoc Dunnett: $F=3.321$; $df=9$; $p=0.002$). Given the considerable variability between participants, the daily coherence threshold was normalised to the threshold obtained in Session 1. This normalised improvement for the motion training group is shown in Figure 11A. Figure 11B shows the improvement on the Gabor orientation perception task in the control group. Again, there was a significant improvement in coherence threshold from 22.60% at Session 1 to 16.18% at Session 10 (one-way ANOVA with post-hoc Dunnett: $F=3.489$; $df=9$; $p=0.001$). Note that training thresholds are lower than assessment thresholds because the participant is aware of the hemifield in which the stimulus will occur. This is not the case for the assessment sessions where attention must be divided across the two hemifields.

To support the hypothesis that learning involved a perceptual component and was not just procedural learning, a paired t-test including both groups of data was carried

out to compare performance at Session 6 (where participants had completed 2000 trials of the task during training) with Session 10. Participants were significantly better at the final training session compared to at Session 6 (Session 6: M=0.98, SD=0.56; Session 10: M=0.65, SD=0.14; t=2.889; df=19; p=0.009), even though such a high number of trials had already been competed at Session 6.

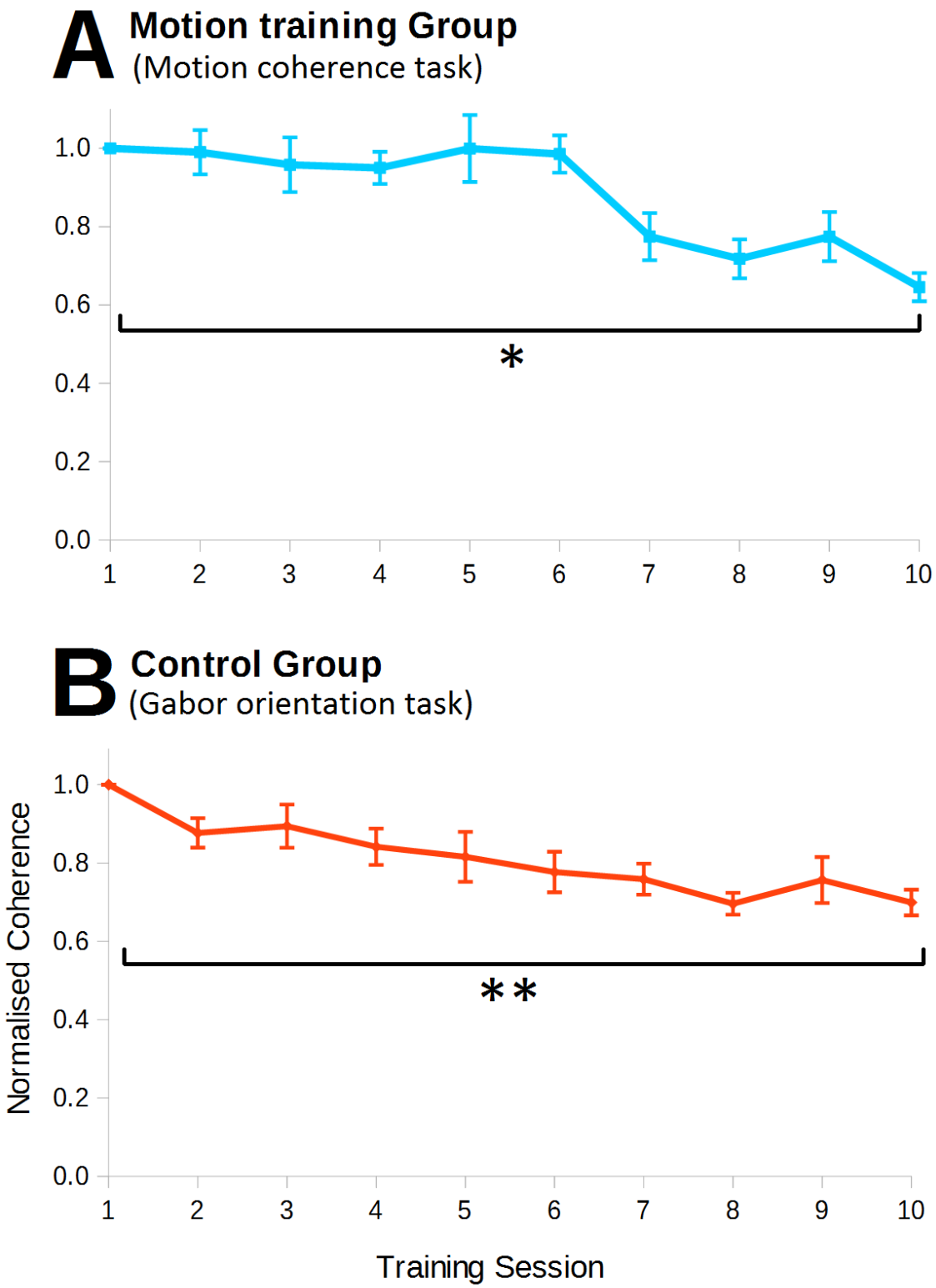


Figure 11: Participants in both groups showed significant improvement in performance of the trained task across the 5 days. **(A)** The improvement in motion coherence thresholds for the motion training group. **(B)** The improvement in orientation coherence thresholds for the control group. Thresholds were normalised to performance in the initial training session. Significant improvement between the first and final session, measured with a post-hoc Dunnett test, is indicated by *p<0.01 and **p<0.001. Error bars show $\pm SEM$.

Figure 12 shows the mean thresholds for the motion task assessments (at pre-training and post-training), for the motion training (A) and control group (B). A repeated measures ANOVA was used to assess the effect of training, colour and hemifield for each group separately. As can be seen from the graphs, there was a highly significant effect of training in both groups (Motion training: F=9.885; df=1; p=0.012 and Control: F=12.304; df=1; p=0.007). There was no overall effect of hemifield (Motion training: F=0.069; df=1; p= 0.799 and Control: F=0.050; df=1; p=0.829) or colour (Motion training: F=2.958; df=2; p=1.109 and Control: F=2.858; df=2; p=0.116) in either group. This indicates a comparable improvement of the trained and untrained hemifields and across the different stimulus colours. There were no significant interactions.

Figure 12C demonstrates the mean thresholds for the orientation task assessments at pre-training and post-training for the control subjects (these data were not acquired in the motion training group). A 2-way ANOVA demonstrated a significant effect of training on this task (F=8.116; df=1; p= 0.007) but no overall effect of hemifield (F=1.222; df=1; p=0.276) and no significant interaction.

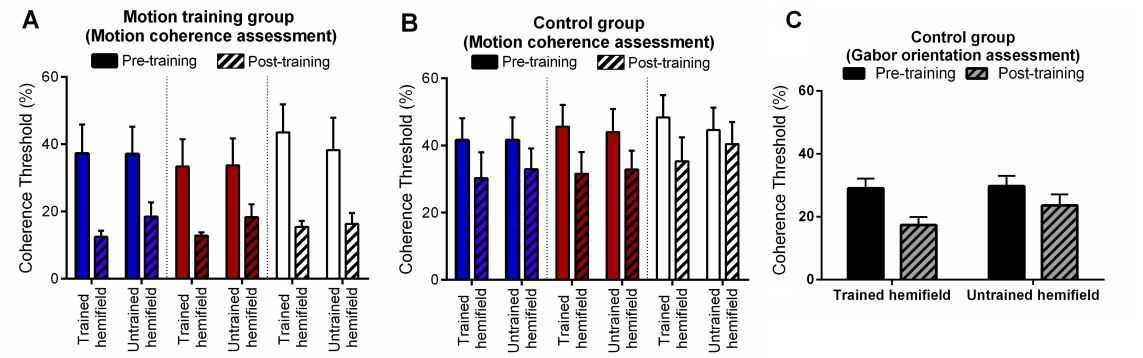


Figure 12: Training led to a significant decrease in coherence thresholds. (A) The decrease in absolute threshold for motion coherence between the baseline and post-training assessments for participants trained on the motion task. **(B)** Control participants trained on the orientation task also improved on the motion task between assessments, although to a considerably lesser extent that those who had been trained. **(C)** The control participants trained on the Gabor orientation task also improved their thresholds on that task at assessment. Blue bars represent coherence thresholds for the blue dots presented on a yellow background, red bars represent red dots presented on a green background, and white bars represent white dots shown on a black background. Error bars show $\pm SEM$.

To quantify the change in threshold between the two assessments, a learning index was calculated from the motion coherence thresholds before and after training, using the following formula:

$$LearningIndex = \frac{\left(T_{preTrain} - T_{postTrain}\right)}{\left(T_{preTrain} + T_{postTrain}\right)}$$

where $T_{preTrain}$ and $T_{postTrain}$ are the thresholds for the pre- and post-training assessments respectively.

Given that stimulus colour had no effect on performance (Figure 12), the motion task assessment data were collapsed across stimulus colour to investigate the effects of training group on motion coherence thresholds following training. Figure 13 shows the mean learning index across the two groups and both hemifields. An independent t-test demonstrated the motion training group showed a significantly greater learning index than the control group for the motion task in the training hemifield (Motion training group: M=0.36, SD=0.05; Control group: M=0.17, SD=0.04; t=10.216; df=18; $p=1x10^{-5}$). Furthermore, paired t-tests showed both training groups showed a significantly higher learning index for the motion task in the trained hemifield compared to the untrained hemifield (Motion: t=5.014; df=9; p=0.001 and Control: t=4.027; df=9; p=0.003).

The control group showed significant learning of the orientation task in both hemifields (Figure 12). Figure 13 indicates there was more learning in the trained hemifield (M=0.26, SD=0.19) compared to the untrained hemifield (M=0.13, SD=0.16), confirmed statistically with a paired t-test (t=10.083; df=9; $p=1x10^{-5}$). Although the learning index is higher for the control group when performing the orientation task in the trained hemifield (M=0.26, SD=0.19) compared to the motion task in the trained hemifield (M=0.16, SD=0.04), the difference is not significant (paired t-test: t=1.514; df=9; p=0.164). However, this may be due to a single participant who performed worse in the post-training assessment compared to the pre-training (co-

herence thresholds 31.4% and 22.2% respectively). If this participant is excluded, the trend for the group improving more in the Gabor orientation assessment than the motion direction perception assessment is stronger, however still not significant following Bonferroni correction (paired t-test: t=2.721; df=8; p=0.026).

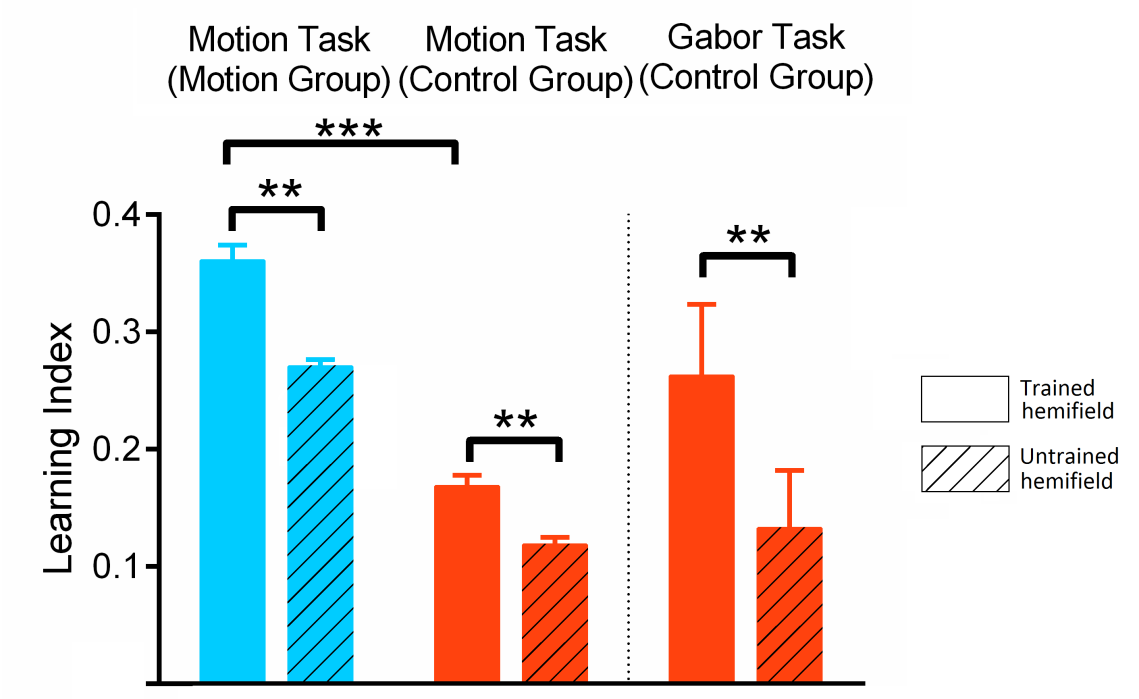


Figure 13: Learning index for both groups calculated from the visual assessment tasks. There was a significantly higher learning index in the motion training group than the control group performing the motion task. The data from the different colour conditions were collapsed, since there were no significant differences in either group. Both groups showed greater learning in the trained hemifield, compared to the untrained hemifield. Control participants also showed significantly more learning in the trained hemifield, compared to the untrained hemifield, for the orientation task. **p<0.001, ***p<0.0001. Error bars show $\pm SEM$.

In addition to the overall decrease in thresholds between the pre- and post training assessments, there was also a significant correlation between the initial direction discrimination threshold and the learning index for the motion trained group (Figure 14: Pearson's r=0.819; p=0.004). This suggests that the participants with the highest initial thresholds improved the most on task performance. This is perhaps unsurprising, as there is likely to be minimum amount of coherence required to perceive the direction of motion with a 500ms exposure.

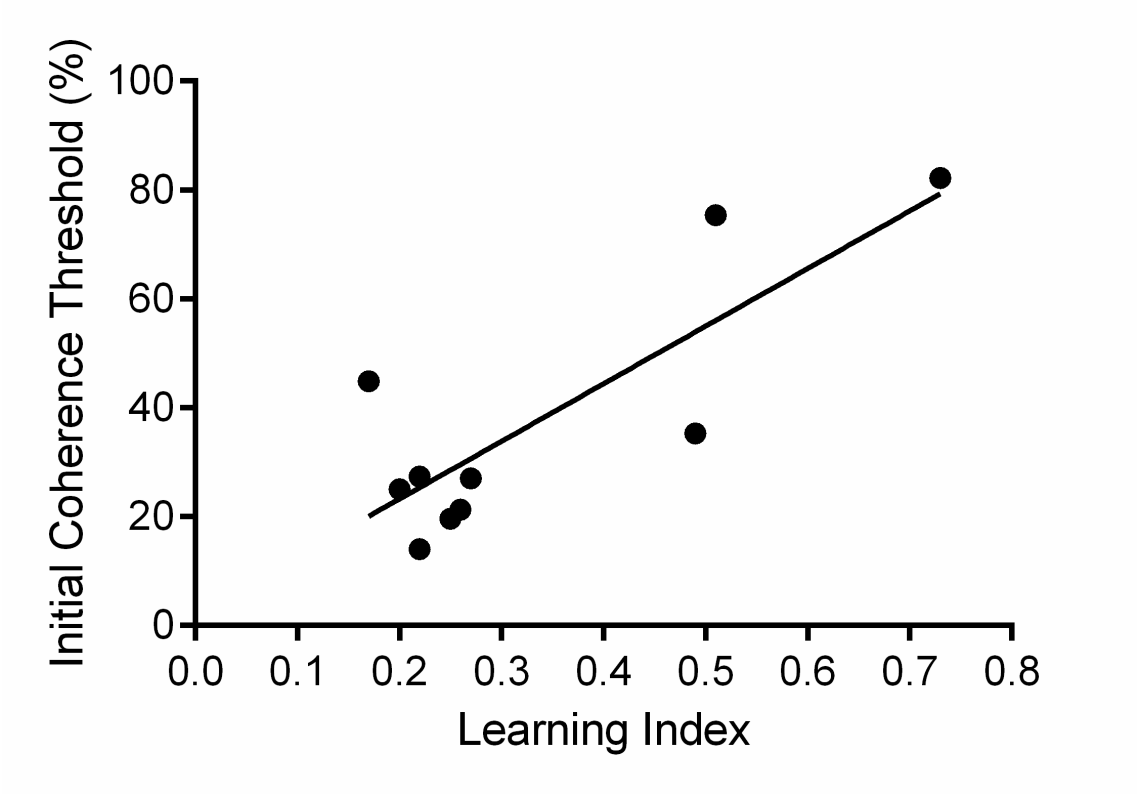


Figure 14: Learning index as a function of initial motion coherence threshold. The participants with the highest initial motion coherence thresholds showed large learning indices. In contrast, those with low thresholds at the initial assessment showed lower indices. There was a significant correlation between these metrics (Pearsons r=0.819; p=0.004).

3.4 Discussion

Participants in the current experiment undertook a five-day visual training protocol to determine the extent to which improvements in visual performance could transfer across stimulus parameters (colour), spatial location (trained visual hemifield compared to untrained hemifield) and task (motion compared to orientation). Motion training using blue dots on a yellow background improved performance on stimuli composed of red dots on green background and white dots on black background. There was also considerable, although not complete, transfer of learning to the untrained visual hemifield. In contrast, training on a control condition with different stimuli and task resulted in considerably less improvement in motion coherence thresholds.

3.4.1 Overall effect of training

Both motion-trained and control participants showed improvement in the trained tasks at the post-training assessment compared to the pre-training assessment. To confirm that learning had a perceptual component, and was not purely procedural, an additional analysis was carried out to compare performance at training Session 6 with performance at Session 10 (the final training session). By Session 6, the participants had completed 2000 trials of the task, so it is unlikely that there was much task learning past this point. Subjects performed significantly better at Session 10 compared to Session 6, indicating the learning contained a perceptual element.

3.4.2 Transfer across colours

Motion trained subjects were trained on blue dots with a yellow background, but when tested in the assessment performed equally well on red/green and white/black stimulus presentations. Furthermore, the control group also showed significant learning in all colour combinations that were assessed. Unfortunately, because the

coloured stimuli were not isoluminant, luminance contrast was a confound in this experiment. Therefore, the results are most likely explained by participants ignoring colour information since luminance information could be used to complete the task. Thus, further investigation is required using isoluminant stimuli to establish whether there is any transfer of learning of the motion direction perception task across colours.

3.4.3 Transfer of learning between tasks

There was some improvement in the motion direction perception task in the control group, even though subjects were trained on a task with no motion element. It is possible this could have been a result of the 're-test' effect, rather than perceptual learning, since the task was novel in the first assessment and because participants received feedback about performance following every trial. However, the control group showed significantly greater improvement in the motion direction perception task in the hemifield trained on the Gabor orientation perception task compared to the untrained hemifield. This strongly suggests that training on the Gabor orientation perception task also improved performance on the motion direction perception task. The most obvious common parameter between the two tasks was covert attention, which is known to improve performance on visual tasks (Posner, 1980; Yeshurun & Carrasco, 1998), and therefore it is likely there was some attentional learning component of the training. Furthermore, both tasks involved coherence detection, so the improvement could be a transfer of noise-filtering ability. Nonetheless, this result is consistent with previous results showing that visual perceptual learning is most likely to transfer spatially when there has been previous training or exposure of the second location (Zhang & Yang, 2014).

Subjects trained on the motion direction perception task showed significantly more improvement in the motion task assessment compared to control subjects. This indicates that there was not complete transfer of learning across tasks, and that motion direction perception training is somewhat specific. Since the ultimate aim is

to improve residual vision in patients with cortical damage to the primary visual cortex, visual motion area hMT+ is a good region to target for perceptual learning, since this cortical area is often spared following primary visual cortex lesions.

3.4.4 Transfer between hemifields

For both the training groups, there was significant improvement for stimuli presented in the untrained hemifield following training. The training index averaged across all the colour conditions clearly shows that there is less learning in the untrained hemifield in both the motion training and control groups. Thus, there is not complete transfer across spatial location. A number of stimulus conditions have been shown to facilitate the transfer of training effects, including low task precision (Jeter et al., 2009; Liu, 1999) or difficulty (Hung & Seitz, 2014). In the current experiment, the stimulus area was large and the coherently moving dots spanned a range of different directions, leading to low task precision. In addition, the step size of the adaptive coherence change was large, so that each time a participant gave an incorrect response, the task became much easier to resolve. Previous research has demonstrated that too many training trials can lead to overspecialisation (Jeter et al., 2010). Here, the trials were not too numerous, and therefore overspecialisation was not induced.

Thus, this experimental design brought together multiple elements suggested by the literature to evoke the transfer of perceptual learning (Jeter et al., 2009; Jeter et al., 2010; Mastropasqua et al., 2015; Xiao et al., 2008). Some motion sensitive areas, such as area MST, have receptive fields that cover large portions of the visual field spanning both hemifields (Huk et al., 2002). Therefore, it would perhaps not be surprising if there were some transfer of the learning across hemifields in the case of the motion direction perception task.

3.4.5 Location of learning effect

The main protocol in this study was a motion direction perception task, likely to evoke activation in hMT+ (Ajina et al., 2015; Braddick et al., 2001), and requiring summation across regions of the visual field. In contrast, the Gabor orientation perception task was more targeted towards receptive field properties of early visual areas such as V1 and V2. Thus, the difference in performance for participants trained on the motion task and orientation tasks is perhaps unsurprising. Motion perception is often preserved following cortical damage to V1, and in these cases, there is significant activation in hMT+ measured with functional magnetic resonance imaging (Ajina et al. 2015; Bridge et al. 2010; Leh et al., 2010). It is for this reason that a task involving motion was selected for the current experiment. In the healthy subjects used in this study, improvement in performance occurred for both stimulus types. However, it would be interesting to determine whether there was a difference between these two stimulus training types in patients with cortical damage to early visual cortex, as one might predict that only training on the hMT+ targeted task might lead to improvement.

3.4.6 Eye movements

No eye tracking data was analysed for this study, and therefore the impact of eye movements on the results cannot be determined. It is possible that participants made eye movements during stimulus presentation, therefore altering where in the visual field the stimulus was actually delivered. Therefore, the behavioural data described here may have been confounded by eye movements. Future studies must control for this confound more tightly by monitoring gaze position during stimulus presentation.

3.5 Conclusions

To conclude, these data support the notion that perceptual learning can take place after only five days of training, and is transferable across stimulus attributes and spatial locations under certain conditions. It would be interesting to develop this training protocol for application as a potential rehabilitative therapy for people with visual field defects resulting from cortical damage.

4 Investigation of the impact of timecourse on learning effects of motion perceptual training in healthy individuals

4.1 Introduction

4.1.1 Translational potential of single-day perceptual learning protocol

The overall aim of this thesis is to understand and develop a motion perception training programme appropriate for application as a rehabilitative therapy in patients with visual problems. If a rehabilitative therapy could be delivered in a single day, rather than being spread across multiple days as described in Chapter 3, it would be highly advantageous. For instance, if training is to be delivered in a laboratory setting, then multiple meetings could be prohibitive for patients travelling from afar, or for patients with mobility problems (either related or unrelated to visual damage). Furthermore, single-day training would be easier to deliver in an acute hospital setting compared to multi-day training, permitting the effect of learning immediately following visual damage to be determined. Thus, it would be useful to know if repeated visits are necessary.

Perceptual learning is defined as an improvement in perception resulting from practice of a task (Gibson, 1953). In general, increased practice results in increased perceptual learning (Fahle & Poggio, 2002). However, too much practice of a task, or practice with insufficient breaks for learning consolidation can reduce or prevent perceptual learning (Mednick et al., 2002). This phenomenon is called overtraining and is explored in more detail below. To understand if a single-day application of a perceptual learning paradigm could be applied in a patient population, it is important to first determine whether the amount of perceptual learning reduces when training intensity is increased, as this will inform the optimal training protocol

design. Furthermore, it is crucial to establish whether breaks including sleep are required for perceptual learning to occur in case this is necessary for learning to occur with this training task.

4.1.2 The role of overexposure in perceptual learning

If participants are trained on the same task repeatedly during the same day, performance can worsen due to overexposure (Censor et al., 2006; Mednick et al., 2002; Ofen et al., 2007). For instance, Ofen et al. (2007) found that if participants were continually tested on a visual task, in which they initially gave correct responses around 90% of the time, performance at the task progressively decreased over time. This deterioration in performance was abolished if the task was relocated to a different retinal location, indicating that the deterioration effect is not due to just fatigue or loss of participant motivation (Deliens et al., 2014; Mednick et al., 2002).

Evidence from macaque monkeys indicated that early visual areas such as the primary visual cortex (V1) are highly retinotopic and orientation selective (Hubel & Wiesel, 1968; Rosa, 2002). In humans, overtraining has been shown to be specific to the trained visual field and target orientation (Mednick et al., 2002), but transferable to the untrained eye and to untrained background orientations (Mednick et al., 2005; Ofen et al., 2007) and therefore not a general fatigue effect. Thus, overexposure of a stimulus is thought to lead to saturation or fatigue of neuronal activity in early visual areas, which can produce the observed overtraining effects (Mednick et al., 2008).

4.1.3 The role of sleep in perceptual learning

Perceptual learning is initially fragile until consolidation of the learning has occurred (Sasaki et al., 2010). It appears that at least six hours of sleep may be required for formation of new synapses and other structural and functional changes associated with perceptual learning (Karni et al., 1994; Plihal & Born, 1997; Stickgold et al.,

2000b). Perceptual learning has been shown to be correlated with the amount of slow wave sleep (SWS) in the first quarter of the sleep period, and the amount of rapid eye movement (REM) sleep in the final quarter of the sleep session (Gais et al., 2000; Stickgold et al., 2000a). This indicates that sleep plays an important role in perceptual learning.

In contrast, brief perceptual learning (30-60 minutes of training) has been shown to occur in the absence of sleep (Censor et al., 2006). This shows that sleep is not necessary for perceptual learning to occur. If participants are overexposed to a task, learning effects can be completely abolished. Furthermore, sleep does not appear to rescue such overtraining effects (Censor et al., 2006). Therefore, despite the important role of sleep in perceptual learning consolidation, it has been shown to be neither necessary nor sufficient for such learning, and does not necessarily protect against overtraining.

4.1.4 Overtraining of motion perception

The majority of studies of overtraining have used a texture discrimination task (TDT; Karni & Sagi, 1991). This task involves participants determining whether peripherally-presented diagonal bars are closer to a vertical or horizontal orientation. The target bars are displayed amongst horizontally-oriented distractors, and the stimulus is followed by a visual mask. Little research has been done to ascertain whether the findings described above hold true for other visual tasks which could engage different areas of the visual system and therefore yield dissimilar results. However, initial findings show that overtraining effects do still exist for a motion perception task (Ashley & Pearson, 2012). Ashley & Pearson (2012) trained subjects on a motion direction discrimination task, and then tested their performance on the task the following day. It was shown that participants who completed two training sessions separated with a one-hour break improved significantly more than those who completed the two training sessions with no break in between. Furthermore,

it was shown that a group of participants who completed only a single training session on the first day improved signficantly more than those who completed two sessions without a break in between. This study demonstrated that overtraining effects established using a TDT also may apply to motion perception tasks.

4.1.5 Summary and experimental aims

In Chapter 3 of this thesis, the effect of motion perception training across five consecutive days was examined. The aim of the present experiment was to determine the effects of an equivalent amount of motion perception training, condensed down into a single day. Here, we trained participants for several hours on a motion direction perception task in a single visual hemifield. Training was interspersed with three 15-minute breaks. The impact of reducing the time span across which training is delivered was determined for the magnitude and specificity of learning effects. Subjects were assessed on their performance of the motion task in both visual hemifields before and after training. Therefore, the effects of training timespan upon transfer of learning across visual hemifields could also be analysed. An additional group was trained on a Gabor orientation perception task but assessed on the motion task before and after training, so that transfer of learning between visual tasks could also be assessed. The goal is to use the information gained from this study to guide future development of the motion perception protocol as a rehabilitative therapy for patients with visual problems.

4.2 Methods

Further information about the setup of this experiment can be found in Chapter 2.

4.2.1 Participants

Twenty-four subjects (12 female and 12 male; M=23.2 years; SD=3.89 years) participated in this study. Twelve participants were assigned to a motion perception training protocol ('motion training group'), and the remaining twelve participants to a Gabor orientation perception training protocol ('orientation training group').

4.2.2 Visual tasks and stimuli

There were two tasks used in this project: a motion direction perception task and a Gabor orientation perception task.

For the motion direction perception task, participants identified whether a group of coherently-moving dots had leftwards or rightwards motion when displayed amongst randomly-moving distractor dots ('noise'). The direction of coherent motion was variable and restricted to within a 90° angle centred around the horizontal plane. Moving dots (n=150) were presented within a circular area 10° in diameter centred 8.3° to the left or right of fixation (the edge was 3.3° from fixation). The stimulus consisted of high contrast white dots on a black background. During the assessments, the conditions (left or right visual hemifield) were presented pseudorandomly.

Participants completing the Gabor orientation perception task were instructed to identify whether Gabor patches were vertically-orientated or horizontally-oriented. The patches were displayed amongst randomly-oriented patches ('noise'). The overall orientation of the noise Gabor patches was always zero. In the orientation task, Gabor patches (n=50) of 90% contrast were presented within a circular area 10° in diameter centred 8.3° to the left or right of fixation (the edge was 3.3° from fixation).

4.2.3 Assessment and training paradigms

All participants undertook two assessment sessions (400 trials each), and ten training sessions (400 trials each). Twelve participants were trained on the motion direction perception task (motion training group) while the other twelve were trained on the Gabor orientation perception task (orientation training group). All participants completed motion direction perception task assessments before and after training. Participants in the orientation training group additionally completed 400 trials of the Gabor orientation perception task during the assessment sessions.

In all assessments, stimuli were presented to the left or right visual hemifield pseudorandomly, with 200 trials per hemifield. During the training sessions, participants completed their allocated visual task in a single visual hemifield (half of the participants trained the left hemifield and the other half trained the right hemifield). During training, participants were offered an optional break screen every 20 trials to reduce fatigue (maximum pause duration of 1 minute). There was a pause of 2-3 minutes between each training session while the program was restarted. Fifteen minute breaks were implemented on a frequent basis during the experiment (Figure 15). Each task assessment took around 15 minutes, and each training session took approximately 10 minutes. The total duration of participation was 3-4 hours.

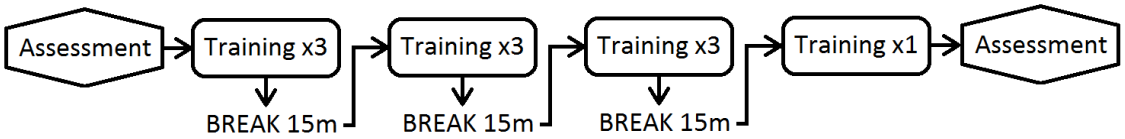


Figure 15: Experimental protocol followed by the participants. Each participant completed assessments of the motion direction perception task in both visual hemifields before and after training. The motion training group were assessed on the motion direction perception task only. The orientation training participants were assessed on the motion directon perception and Gabor orientation perception tasks. Following the baseline assessments, participants completed the training. Training sessions were delivered to a single visual hemifield. The motion training group completed the motion direction perception task during training sessions, whereas the orientation training group completed the Gabor orientation perception task. Each block of three training sessions was followed by a 15-minute break for all participants.

4.3 Results

4.3.1 A single day of behavioural training is sufficient for task learning to occur

Performance in each of the ten daily training sessions was quantified for all participants in the motion training group and orientation training group, to determine the change in overall performance (Figure 16). Groups were analysed separately. Previously, ten training sessions of a perceptual task spread over five days were shown to be sufficient for participants to improve at the trained task (Chapter 3), and this finding was replicated here. The motion training group showed an improvement in motion coherence thresholds across the training sessions, with the mean decreasing from 33.3% coherence at Session 1 (SD=12.76%) to 22.8% coherence at Session 10 (SD=11.85%). A change in coherence threshold was also identified in the orientation training group, with the mean orientation coherence threshold decreasing from 25.8% coherence (SD=7.95%) to 18.7% (SD=5.38%), on average.

Because there was within-subject variability, daily coherence thresholds were normalised to permit further analysis. Performance was normalised to coherence threshold obtained during the initial training session (Session 1). Non-parametric combination (NPC) analysis with post-hoc Fisher test confirmed that overall, sessions subsequent to Session 1 were significantly different compared to Session 1 for both the motion trained group (p=0.0002) and the orientation trained group (p=0.0002). Further analysis showed that for the motion trained group there was significant improvement in performance from Session 2, which remained present across the remainder of the training sessions (one-way ANOVA with unidirectional post-hoc Dunnett: F=11.709; df=9; $p=2.1x10^{-5}$). For the orientation training group, there was a significant improvement from Session 1 by Session 4, which remained for all subsequent sessions (one-way ANOVA with unidirectional post-hoc Dunnett: F=5.778; df=9; $p=1x10^{-5}$).

The amount of learning of each task for the motion training group (M=0.68, SD=0.12) and orientation training group (M=0.74, SD=0.13) was found to be comparable using an independent t-test of normalised performance at final training session (t=-1.202; df=22; p=0.242).

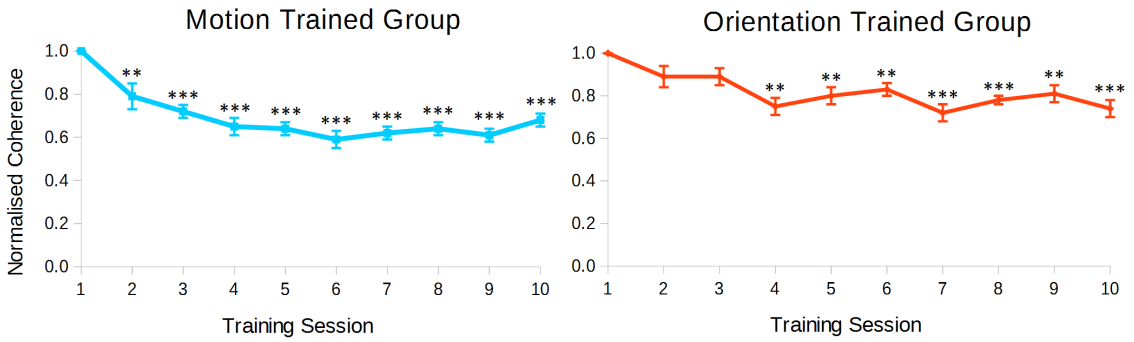


Figure 16: Normalised participant performance during training for the motion task and orientation task. Performance at each training session was quantified and normalised according to participant performance at the initial training session. There is an improvement at the trained task across the 10 training sessions for both groups. **(A)** Improvement in performance by participants in the motion training group. **(B)** Improvement in performance by participants in the orientation training group. **p<0.01, ***p<0.001. Error bars are $\pm SEM$.

4.3.2 No transfer of learning across visual hemifields

Before and after training in a single visual hemifield, participants were assessed on performance at their allocated trained task in both visual hemifields. This allowed analysis of any training-dependent changes of the trained and the untrained visual hemifields.

Figure 17 shows the mean absolute thresholds for the trained task assessments (at pre-training and post-training), for the motion training and orientation training group (B). For the motion training group, coherence threshold was significantly different at post-training (M=30.6, SD=15.91) compared to pre-training (M=55.1, SD=20.18) in the trained visual hemifield (t=7.764; df=11; p=9x10^{-7}) but not in the untrained hemifield (Pre-training: M=52.3, SD=21.29; Post-training: M=49.6, SD=19.19; t=0.512; df=11; p=0.613). This finding was consistent in the orientation

training group, where training significantly improved performance in the trained visual hemifield (Pre-training: M=32.5, SD=14.71; Post-training: M=20.1, SD=6.32; t=3.875; df=11; p=0.003) but not in the untrained hemifield (Pre-training: M=30.4, SD=13.13; Post-training: M=29.6, SD=12.51; t=0.349; df=11; p=0.734). Note the p-values remain significant after Bonferroni correction for four t-tests (p<0.0125).

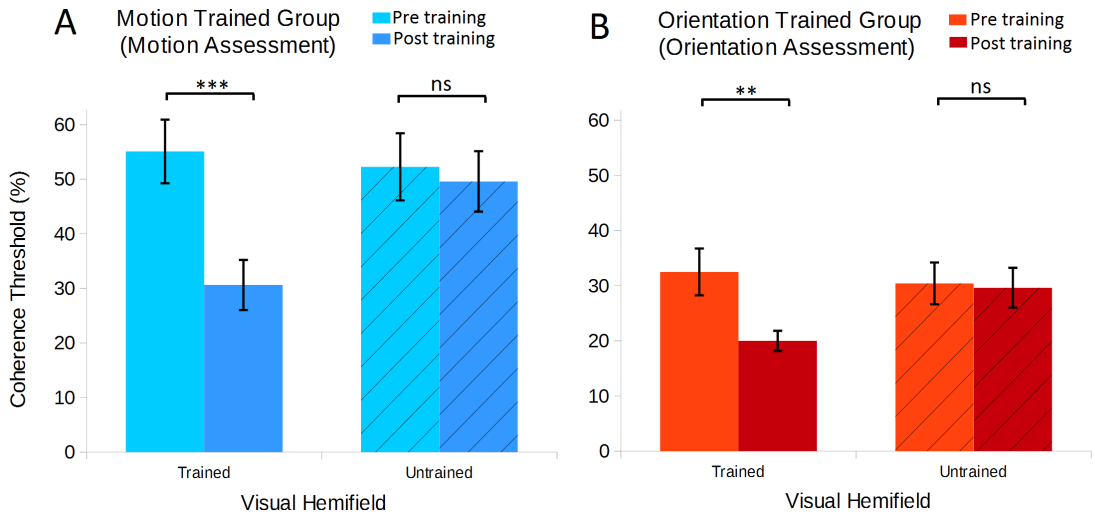


Figure 17: Participants in both groups showed significant improvement in performance of the trained task, specific to trained visual hemifield. (A) The change in absolute motion coherence thresholds for the motion training group, between the pre-training and post-training assessments. **(B)** Improvements in the absolute Gabor orientation coherence thresholds for the orientation training group, at pre-training and post-training. Significant improvement in the trained visual hemifields were identified using paired t-tests: **p<0.01, ***p<0.001, ns=not significant. Error bars show $\pm SEM$.

A learning index (see Chapter 2) was calculated to quantify the magnitude of change in performance from the pre-training to the post-training assessment. Analysis was carried out for the trained task, in both motion training and orientation training groups, and was separated by visual hemifield, to again allow comparison of learning in the untrained versus trained visual hemifield (Figure 18). For the motion trained group, a paired t-test confirmed that there was significantly more learning in the trained hemifield compared to the untrained visual hemifield (Trained: M=0.30, SD=0.13; Untrained: M=0.02, SD=0.18; t=4.096; df=11; p=0.002). This difference in the visual hemifields following training was also significant for the orientation training group (Trained: M=0.22, SD=0.14; Untrained: M=0.01, SD=0.14; t=3.806;

df=11; p=0.003). These findings confirmed that learning was specific to the trained visual hemifield, for both the motion training and orientation training groups.

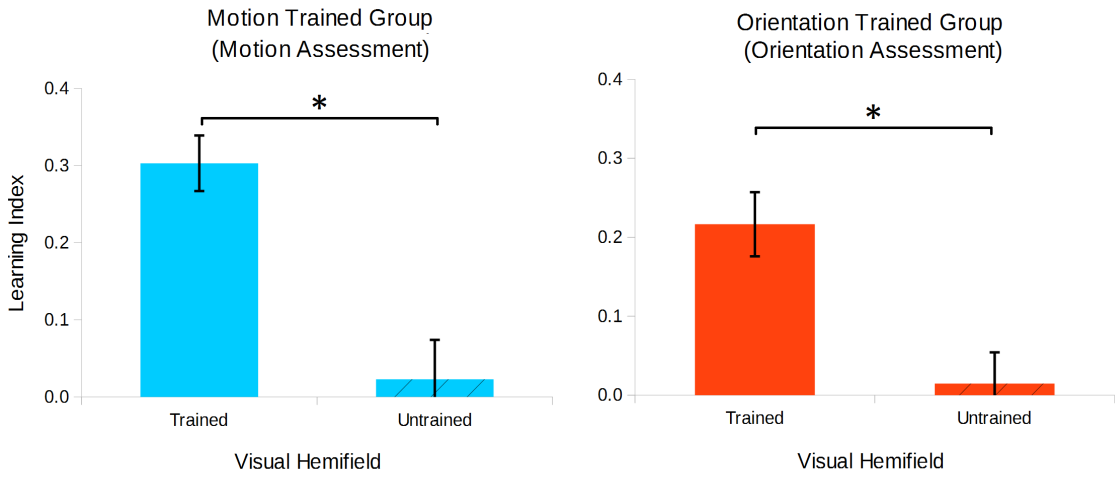


Figure 18: Comparison of visual hemifield learning indices across both training groups, for the trained task. The graphs show the learning index for the motion task (motion training group) or orientation task (orientation training group), for trained and untrained visual hemifields. **(A)** For participants trained on the motion task, the learning appears to be specific to the trained visual hemifield. **(B)** For individuals trained on the orientation task, the learning is also specific to the trained visual hemifield. Significant changes were identified using paired t-tests; *p<0.01. Error bars show $\pm SEM$.

4.3.3 No transfer of learning across visual tasks

The orientation trained group were assessed on their performance of the motion direction perception task, before and after training of the Gabor orientation perception task (Figure 19), to determine any transfer of training effects to an untrained task.

For the orientation training group, paired t-tests comparing pre-training values (Trained: M=51.9, SD=19.64; Untrained: M=50.3, SD=18.01) with post-training values (Trained: M=39.8, SD=15.94; Untrained: M=38.8, SD=14.44) demonstrated that the coherence threshold for the motion task decreased at the post-training measure compared to the pre-training measure in both the trained visual hemifield (t=2.789; df=11; p=0.018) and the untrained visual hemifield (t=2.346; df=11; p=0.039).

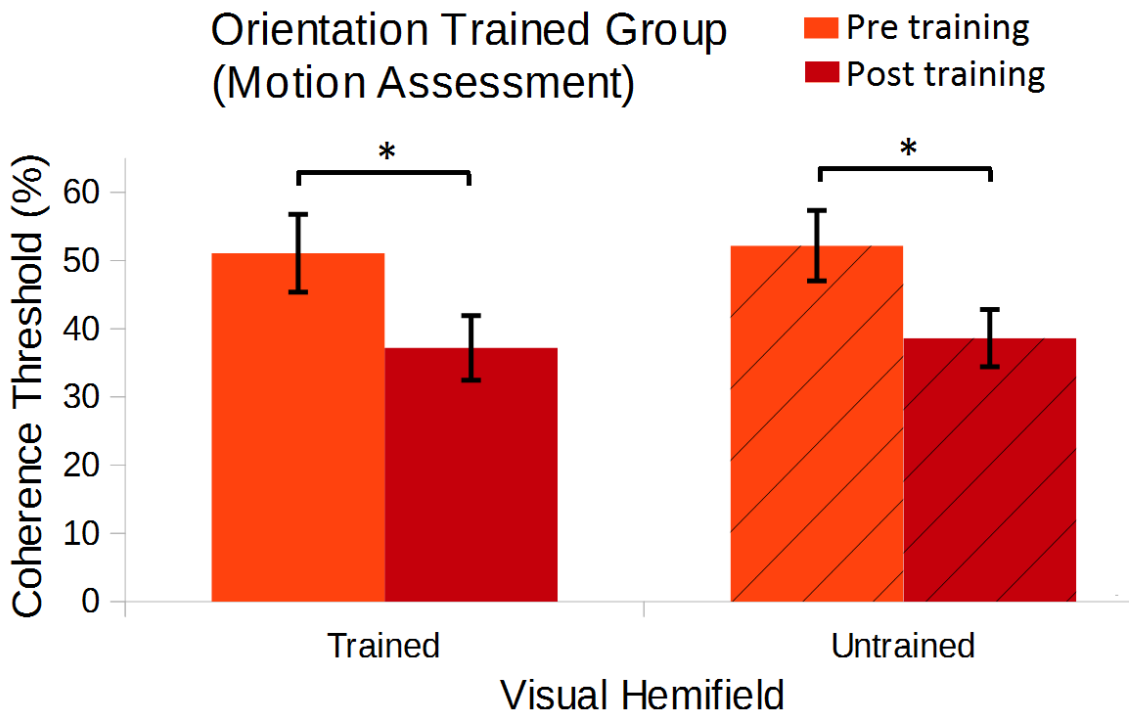


Figure 19: Participants improve in performance of an untrained visual task. The change in absolute motion coherence thresholds for the orientation training group, between the pre-training and post-training assessments is shown here. Significant improvements were identified using paired t-tests; *p<0.05. Error bars show $\pm SEM$.

A learning index was calculated to quantify the magnitude of change in performance from the first to the second assessment of the motion task in each visual hemifield (Figure 20). Paired t-tests supported the findings described above; there was no significant difference in learning between visual hemifields for this performance measure (t=0.155; df=11; p=0.880).

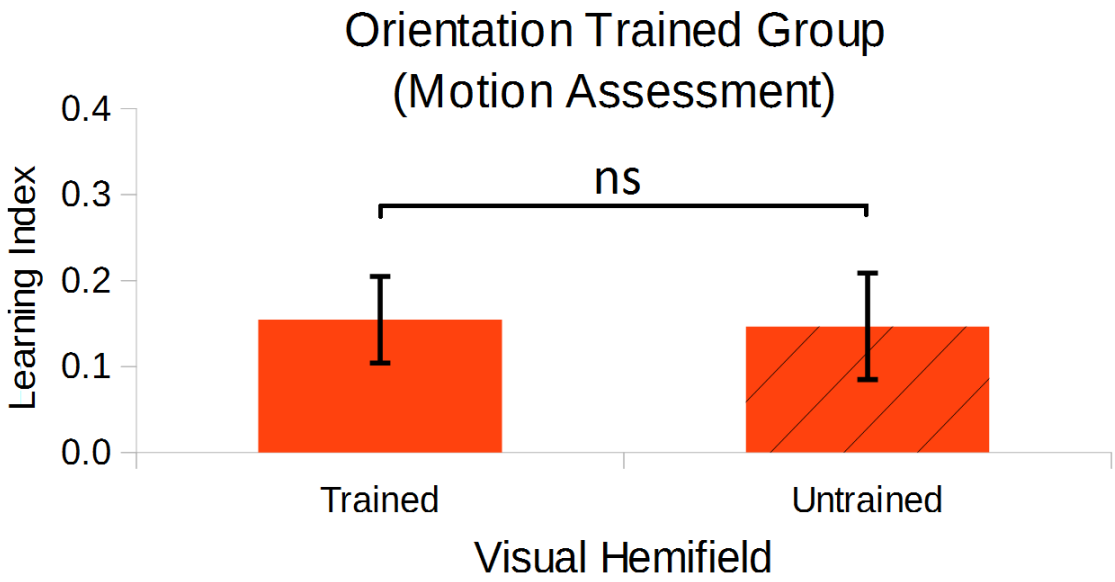


Figure 20: Comparison of visual hemifield learning indices for the untrained motion task, for the orientation training group. The graph shows the learning index for the motion task, for trained and untrained visual hemifields. For individuals trained on the orientation task, there is no significant difference in learning between the visual hemifields. Significant changes were identified using paired t-tests: ns=not significant. Error bars show $\pm SEM$.

4.4 Discussion

This experiment demonstrated that intense perceptual training during a single day was sufficient for learning to occur. Performance improved by a significant amount for both a motion direction perception task and a Gabor orientation perception task, despite a short duration of approximately 3 hours between assessments. Learning was found to be specific to the trained visual hemifield.

4.4.1 Overtraining effects are not apparent using current protocol

Overtraining is a phenomenon by which extended exposure to a perceptual task results in a worsening of performance. Ofen et al. (2007) found that if participants were continually tested on a visual task in which they initially gave correct responses around 90% of the time, performance at the task progressively decreased following overexposure. Performance recovered when subjects were tested at a new location of the visual field; therefore the effects were unlikely to be caused by general fatigue or boredom.

In this experiment, participants completed a total of 4000 training trials of a task over a time period of approximately 3 hours. Across the training sessions (consisting of 400 blocks each), there was no decline in performance for either the motion or the orientation task. In fact, participants demonstrated learning. This indicates that using this protocol, overtraining did not take place.

A key difference between this study and previous literature looking at overtraining effects is the task difficulty. In the study by Ofen et al. described above, the stimulus was at a constant difficulty, which was far above threshold. In this experiment, the difficulty of the task was adaptive. The stimulus was presented at difficulties (coherence percentages) that were near to, below and above threshold, during each training session. The lack of overtraining effects elicited here may therefore be linked to task difficulty. Tasks which are far above discrimination threshold may

overstimulate the cortex, resulting in unwanted neural adaptation and a decrease in learning.

4.4.2 Waking perceptual learning is possible, but may be influenced by task difficulty and trial block size

Previous literature has examined the effect of waking and sleep consolidation on a visual texture discrimination task (TDT). This task involves determining whether stimulus bars are vertically-oriented or horizontally-oriented. Improvements in performance of a TDT have been shown to correlate with early-phase SWS and late-phase REM sleep (Gais et al., 2000; Stickgold et al., 2000a). So, sleep can improve learning, but can learning also occur during wakefulness? In the two studies mentioned above, the researchers found that learning did not occur if there was an absence of sleep between sessions. However, this finding was biased as the waking group were sleep deprived. REM sleep and SWS are known to be required for normal cognitive functioning. In order to investigate the question of wakeful learning, studies within the same day are required.

Censor et al. (2006) carried out a study that showed learning of the TDT can indeed occur in the absence of sleep. Participants performed the TDT during a morning session, and again in the evening of the same day (following 8-10 hours of wakefulness). At the second session, the difficulty of the TDT was modulated depending on performance in the first session, so there were fewer trials far above the discrimination threshold. Using this setup, the group found an improvement in TDT performance. However, if the second session was made as difficult as the first session (and therefore included blocks where the participant had perfect performance), no learning was seen between sessions. Thus, in order for wakeful learning to occur, training trials must not be too easy. This also showed the range of sensory stimuli used can affect the measurement of thresholds directly (Prince et al., 2001). Here, difficulty (coherence) was modulated using a staircase design with large step sizes.

Therefore, consistently correct answers would take the task difficulty down to the minimum possible discrimination threshold for both tasks ($\approx$ 10% coherence) in a single block of 20 trials. The results here provide further evidence that training closer to discrimination threshold can promote learning during a wakeful period. This finding also supports the result described above, showing perceptual deterioration does not occur when training trial difficulty is closer to discrimination threshold.

Censor et al. (2006) also determined the effect of number of trials in training blocks on wakeful and sleep consolidation. Using a similar design to that described above, in addition to the morning and evening TDT sessions, a final session was completed in the morning of the following day (after 8-10 hours, which included sleep). A group which completed the TDT training in 50-trial blocks showed no learning, whereas a 26-trial block group showed overall learning, which occurred in the overnight interval (only after sleep consolidation). These findings suggest that neural adaptation, induced by overexposure to the stimulus without sufficient recovery time, can prevent learning of a TDT, but that this effect is rescued by sleep (Censor et al., 2006).

Here, we showed that performance of a motion direction perception task and a Gabor orientation perception task can improve over a duration of 3 hours. This occurs when the 3-hour duration is filled with training of the task on 20-trial blocks, in 400-block sessions interspersed with 15-minute breaks. For this protocol, the small block size (20 trials) and other additional pauses in training likely contributed to a lack of overtraining. It is theorised that the brief pauses afforded an opportunity for reduced neural adaption of cells involved in the task. This brief return or partial return to baseline during pauses means that reactivation of those cortical networks is more likely, compared to if breaks had been more sparse. These findings imply that small block sizes may be key to ensuring learning occurs during a period without sleep, though need to be parametrically studied for a conclusive result.

4.4.3 No transfer of perceptual learning to untrained visual hemifield

In this study, participants were trained on either a motion direction perception task or a Gabor orientation perception task, in a single visual hemifield. All subjects were assessed on their performance in the trained task before and after training, in both the untrained and the trained visual hemifields. For both groups of participants, perceptual learning was highly specific to the trained visual hemifield and did not transfer to the untrained visual field.

Early areas of the visual cortex show much more stringent retinotopy and smaller receptive fields, compared to later visual areas. Since the learning shown here was specific to the trained visual field, it is an indication of involvement of lower visual cortices, such as V1-5. This finding is in contrast to the training programme described in Chapter 3, when the same amount of training was distributed over five consecutive days, though statistical analysis between these two studies has not been carried out. In the five-day learning protocol, perceptual learning was partially transferred to the untrained visual hemifield. This partial transfer could be an indication that brain areas with large RFs such as MST for motion, or higher occipitotemporal areas for global orientation (Ostwald et al., 2008; Yoshor et al., 2007), were likely involved in mediating the learning effects.

Since the amount of training was identical between the five-day protocol and the one-day protocol presented here, this suggests that the timecourse of perceptual training can influence the amount of transfer between visual hemifields. As such, it is indicated that perceptual learning timecourse can alter the neural level at which perceptual learning occurs. So, if perceptual learning is condensed down into a single day, perceptual learning occurs in lower visual areas (V1-5). If learning is spread across multiple days, it is more likely to engage higher visual areas, such as area MST.

Supporting this finding, previous literature has indicated that higher order brain areas are more activated following sleep-consolidated learning, compared to a sleep-

deprived condition. Maquet et al. (2003) compared the performance of subjects trained on a visuomotor task that involves tracking of a dot presented on a screen by movement of a handheld joystick. Participants were either sleep deprived for the first night following training, or allowed to sleep as normal. It was shown that performance was better in the non sleep-deprived group, and was associated with increased functional activity in the superior temporal sulcus (STS), as well as increased connectivity between STS and the cerebellum and between the supplementary eye fields and frontal eye fields.

Walker et al. trained subjects monocularly on a TDT followed by fMRI scanning to localise changes in brain activity. There was a period of sleep after training of one eye (sleep condition), or a short delay with no sleep (no sleep condition) before the fMRI scan was carried out. The sleep condition showed significantly more activity than the no sleep condition in V1, but also higher areas such as the occipital temporal junction, the medial temporal lobe, and the inferior parietal lobe (Walker et al., 2005).

The lack of transfer of learning across the visual field seen in this one-day training protocol contrasts with the transfer of learning observed when the same amount of training is spread across a five-day protocol. So, the timecourse of perceptual learning affects the amount of transfer of perceptual learning across the visual field. Transfer of learning indicates the involvement of higher order visual areas with large RFs, such as MST, whereas lack of transfer indicates that learning occurs in earlier visual areas. The timecourse of perceptual learning therefore may alter the level of processing at which the perceptual learning effects are mediated.

4.4.4 Improvement of untrained task due to re-test effect

The participants trained on the Gabor orientation perception task showed an improvement in the motion direction perception task that was not specific to the trained hemifield. Since the improvement here was not specific to the trained

hemifield, it is likely that the improvement seen in the orientation trained group was just a re-test effect, indicating no improvement in the motion task induced by Gabor orientation perception training. This lack of transfer to an untrained task is also in contrast to the five-day training programme described in Chapter 3, which showed an elevated improvement in the trained visual hemifield compared to the untrained hemifield. Previous research has demonstrated no transfer of perceptual learning across tasks completed on the same day (Fahle, 1997), but transfer when tasks were spread across multiple days (McGovern et al., 2012), and so adds further credence to the timecourse being important for transfer of learning.

4.4.5 Eye movements

No eye tracking data was analysed for this study, and therefore the impact of eye movements on the results cannot be determined. It is possible that participants made eye movements during stimulus presentation, therefore altering where in the visual field the stimulus was actually delivered. Therefore, the behavioural data described here may have been confounded by eye movements. Future studies must control for this confound more tightly by monitoring gaze position during stimulus presentation.

4.4.6 Future work

In this experiment, performance assessments were carried out immediately following the termination of the perceptual training. Because no investigation was carried out to determine the longevity of learning effects induced during this experiment, no conclusions can be made about learning endurance. If an additional assessment session was added the following day, this could determine if the effects of training last beyond the day of training. Furthermore, it could be used to determine the impact of sleep on the amount of learning demonstrated. An assessment added five days later could be used as a comparison between the five-day protocol and the one-day

protocol, allowing separation of the effects of training timecourse and time alone upon learning.

In this study, significant learning has been demonstrated when a perceptual training programme is condensed into a single day. If learning effects were demonstrated to endure over time, it would be useful to trial such a training programme in a patient population. As described in the introduction of this chapter, a single day of perceptual learning would be useful for application in a patient population who may be physically limited in their capacity to attend multiple laboratory visits.

4.5 Conclusions

In conclusion, it appears that a single, intense day of perceptual learning is sufficient for learning to take place. However, the learning is more specific to the task and area of visual field that is trained than equivalent training spread out over multiple days. This provides further evidence that distributing training over multiple days may be required for the engagement of higher visual areas for the consolidation and transfer of motion perception learning. It is possible that sleep is also required for this process to occur.

It remains to be determined whether an intense one-day motion perception training protocol is likely to be appropriate for influencing visual function in patients with brain injury, as the durability of learning effects have not yet been established. However, since it appears that the learning here is more likely to engage early visual cortices over higher visual cortices, it would be very interesting to determine how patients with damage to the primary visual cortex respond to such training, in comparison to the same amount of training spread over multiple days.

5 Investigation of the changes in neural activity following motion perceptual training in healthy individuals

5.1 Introduction

Visual perceptual learning (VPL) is the ability to improve at a task following repeated practice (Gibson, 1953). In recent years there have been many advances in the understanding of the mechanisms behind such learning (Lu et al., 2011; Sasaki et al., 2010). In this experiment, participants underwent fMRI scanning to determine changes in neural activity following visual motion perceptual learning.

5.1.1 Changes in the visual cortices

Imaging and electrophysiology studies of VPL

Early literature found that the effects of VPL in humans were not transferred to untrained regions of the visual field (Karni & Sagi, 1991; Shiu & Pashler, 1992). As well as location-specificity, the effects of VPL may also show specificity for trained stimulus features such as orientation (Crist et al., 1997; Fiorentini % Berardi, 1980; Poggio et al., 1992) and motion direction (Ball & Sekuler, 1987; Vaina et al., 1998; Watanabe et al., 2002). Since lower regions of the macaque monkey visual cortex tend to be more retinotopic (Rosa, 2002), have smaller receptive fields, and are often more finely tuned for orientation (Vanduffel et al., 2002), early literature concluded that perceptual learning effects in humans were likely mediated by the primary visual cortex (V1) and other early visual areas (Karni & Sagi, 1991). Functional imaging studies in humans, which showed that changes in blood oxygenation level dependent (BOLD) signal can be associated with perceptual learning, supported the importance of V1 (Furmanski et al., 2004; Schwartz et al., 2002; Walker et al., 2005; Yotsumoto

et al., 2008).

Investigation into the neural activity associated with perceptual learning using fMRI has proven a useful way to determine the locus of task improvements. Goldhacker et al. (2014) looked at the change in BOLD signal during and following training of a motion perception task. The stimulus consisted of four patches of motion, at least three of which contained only noise stimuli. The task was to determine if coherent motion was present or absent in the fourth patch. The coherence of the target patch was varied. fMRI results demonstrated that there were changes in V1 and V5/MT+ which correlated with the amount of learning of the motion task, indicating that both primary and extrastriate visual areas were involved in the VPL of this task. Similar findings were demonstrated by another group (Thompson et al., 2013), showing that training of a motion task that consists of locally balanced, motion opponent signals caused suppression of activity in V5/MT+.

Shibita et al. (2012) carried out a study where they participants were trainedon a two-alternative forced choice (2AFC) task. Participants were instructed to determine the interval in which coherent motion was present, rather than noise motion. Training was on a single motion direction. The groups showed that learning effects were specific to the trained motion direction and did not transfer to other motion directions. fMRI scanning carried out before and after training was used to correlate changes in performance of the motion task with changes in BOLD signal. The results showed that of the 8 visual areas assessed (V1, V2, V3, VP, V3A, V4v, V4d, and MT+) only area V3A activity correlated with learning. It is interesting that no changes in V5/MT+ were found to be associated with change in performance of a motion task. Although this finding may be in contrast to earlier research demonstrating V5/MT+ to be important in visual motion learning (Vaina et al., 1998; Zohary et al., 1994), it has been supported by another group (Chen et al., 2015). It is likely that the specifics of the task are important in discerning whether the effects will be at V3A or V5/MT+, since the functional differences between V3A and V5/MT+ have not yet been fully established (Koyama et al., 2005).

Studies carried out in animals, which permit invasive direct recording of cortical neurones not possible in humans, are in line with the human data. Yang & Maunsell (2004) trained macaque monkeys on an orientation discrimination task. It was demonstrated that even when there is location- and orientation-specific learning, there are neural changes outside of V1, such as the altered orientation tuning identified in V4 neurones. This is an indication that despite specificity of learning, it should not be assumed that VPL occurs only in V1. Further investigations in non-human primates, this time rhesus monkeys, have also shown evidence of extrastriate neural changes. VPL of a global motion detection task, where coherent motion must be extracted from a background of randomly-moving noise, was found to be associated with changes in MT (Zohary et al., 1994). There is clear evidence that even when learning is highly specific and retinotopic, higher order visual areas may still be involved in task learning.

Psychophysical and behavioural studies of VPL

In addition to imaging studies, psychophysical and behavioural studies have also provided evidence for the involvement of striate and extrastriate areas in VPL.

Recent visual perception studies have shown that learning can transfer to untrained retinal locations and untrained stimulus parameters under particular conditions (Liu, 1999; Mastropasqua et al., 2015; Xiao et al., 2008; Zhang et al., 2010; Zhang & Yang, 2014). Since higher order visual areas show broader responses to orientation and motion directions than the highly retinotopic V1 (Gegenfurtner et al., 1997), this provides further evidence of the involvement of visual areas outside of primary visual cortex in VPL.

Further behavioural support for extrastriate involvement in VPL is demonstrated by perceptual constancy research. Perceptual constancy describes the ability to recognise an object despite viewing from different angles, distance or under different light conditions (variable sensory input). Constancy-based representations of objects

can be improved upon in perceputal learning tasks (Garrigan & Kellman, 2008). Because this learning occurs despite variable sensory input, it provides evidence for the involvement of higher order visual areas, which are not as sensory-specific, in VPL.

Initial research of stereoscopic visual learning demonstrated that practice effects of a stereoacuity task are specific to trained retinal location, and therefore dependent on V1 (Ramachandran, 1976). However, a study which trained two retinal areas equally using a different stimulus set for each retinal location indicated this may not be the case (Sowden et al., 1996). At one location, depth perception training was of stimuli in front of the fixation plane, at the other location, training was of behind the fixation plane. Following training, there was no difference in the ability of participants to discern depth in front of fixation compared to behind fixation, regardless of location. Since learning of both tasks was found to transfer to the untrained location, this indicates an involvement of cells outside of V1, since primary visual cortex neurones are disparity selective and topographically organised.

5.1.2 Changes in attentional, decision-making and other areas

Research has identified that top-down mechanisms, such as attention and reward, play a key role in VPL during training (Herzog & Fahle, 1998). The role of attention can be explored by a dual-stimuli setup: two simultaneous visual stimuli are presented, where only one of which is attended. It has been shown that the participant can learn the non-attended stimulus, depending on its salience. If the non-attended stimulus is very salient, it will be inhibited by the attentional system and only the attended stimulus will be learnt (Tsushima et al., 2006; Tsushima et al., 2008). However, if the non-attended stimulus is not salient enough to be noticed by the attentional system, there will be improvement in that task during training. This learning can also be facilitated by appropriate feedback (Seitz et al., 2009). The mechanism of action driving these behaviours is thought to be an ongoing top-down influence from

frontal brain regions on the weighting of sensory signals in early visual areas (Seitz & Watanabe, 2005).

Studies of the non-human primate show that following motion direction discrimination training, there are changes in the cells of the lateral intraparietal (LIP) area, which is likely a locus for converting sensation to action (i.e. a decision-making area), being neither sensory nor motor area (Law & Gold, 2008; Shadlen & Newsome, 1996). Further studies have demonstrated that training on a fine depth discrimination task can protect learning of a coarse depth discrimination task against chemical disruption of V5/MT+, providing further evidence that VPL affects decision as well as sensory networks (Chowdhury & DeAngelis, 2008).

5.1.3 Consolidation of VPL

Without consolidation, initial learning is fragile and can be lost (Dudai, 1996). This key component of VPL can occur during wakefulness or during sleep, and may involve different brain mechanisms to those mediating online learning as discussed above.

Wakeful consolidation has been shown to occur in the initial hour following training. Training effects of a hyperacuity task can be disturbed if immediately following training, subjects are trained on a very similar task at the same retinotopic location. However, if the second period of training is delayed by an hour following the first task, then initial learning remains intact (Seitz et al., 2005; Yotsumoto et al., 2009). This indicates that there is a sensitive window up to one hour after training during which VPL can be disrupted, where wakeful consolidation takes place.

Such wakeful consolidation has been shown to be associated with changes in resting state brain activity (Urner et al., 2013). A single session of motion coherence training was found to alter the resting state connectivity between the hippocampus and striatum, immediately after training. The change was still present 24 hours later. This indicates change in functional connectivity associated with wakeful consolidation

of a VPL task can occur rapidly and at the level of the hippocampus.

Sleep consolidation also plays an important role in VPL. Studies have shown that deprivation of rapid eye movement (REM) sleep or slow wave sleep (SWS) can abolish the learning effects of a visual perception task (Gais et al., 2000; Karni et al., 1994). Furthermore, the amount of learning of a perceptual task was shown to be correlated with the amount of SWS during the early sleep phase, and REM sleep during late sleep phase (Stickgold et al., 2000a). These findings point to the important role SWS and REM sleep must play in the consolidation of VPL.

5.1.4 Summary and experimental aims

Visual perceptual learning in the healthy adult visual system engages neural systems at a number of different levels, from V1 to extrastriate visual areas. Decision-making areas and attentional systems also exert a top-down influence on VPL.

Here, healthy adult participants completed five consecutive days of motion direction perception training in a single visual hemifield. Participants were assessed on their performance of the trained motion direction perception task before and after the training in both the trained and untrained visual hemifields. fMRI scans of subjects performing the motion task were completed before and after training. A control group completed both assessments and fMRI scans, with no motion direction perception training between scans. This research aimed to confirm whether this particular motion perception training programme can stimulate involvement of extrastriate (such as hMT+), attentional, and decision-making areas, as well as determining any involvement of V1, as might be expected from the literature. The goal was to elucidate whether this motion perception training programme may be appropriate for application in a patient group with damage to the primary visual cortex.

5.2 Methods

Further information about the setup of this experiment can be found in Chapter 2.

5.2.1 Participants

Twenty-eight subjects (14 female and 14 male; M=24.5 years; SD=4.26 years) participated in this study. Fourteen participants were assigned to the full version of the motion direction perception training protocol (motion training group), and the remaining fourteen participants to a no-training group (control group).

5.2.2 Visual tasks and stimuli

The motion direction perception task was used in this experiment (Chapter 2). Participants identified whether a group of coherently-moving dots had leftwards or rightwards motion, when displayed amongst randomly-moving distractor dots (noise). The direction of coherent motion was variable, and restricted to within a 90° angle centred around the horizontal plane.

Moving dots (n=54) were presented within a circular area 6.6° in diameter centred 8.3° to the left or right of fixation (the edge was 5° from fixation). The hemifield conditions were presented pseudorandomly.

Outside the scanner, stimuli were displayed on a CRT monitor (screen subtended a visual angle of 38°x31° 1280x1024 pixel resolution, 75Hz refresh rate) in a darkened room. Further setup is described in Chapter 2.

Inside the scanner, visual stimuli were presented on a plasma monitor (screen subtended a visual angle of 23°x13° 12801040 pixel resolution, 70Hz refresh rate) at the back of the MRI scanner bore. The stimuli were viewed by the participants using a mirror mounted on the head coil. The luminance and chromaticity measures (SpectraScan PR-650) for white stimuli were 356cd/m^2 (x=0.321, y=0.339). There

was insufficient signal for luminance and chromaticity measures of black stimuli.

5.2.3 Assessment and training paradigms

All participants in the study undertook two assessment sessions (Days 1 and 9) and two fMRI scans (Days 2 and 9). Furthermore, participants in the motion-training group completed a five-day protocol of motion perception training involving ten training sessions (two sessions per day, Days 5-9). Participants in the control group completed no training and did not meet with the research team between MRI scans (Figure 21).

In all assessments, stimuli were presented to the left or right visual hemifield pseudorandomly, with 200 trials per hemifield. During the training sessions, participants in the motion-training group performed the motion direction perception task, but only in a single hemifield (half the participants trained the left hemifield, half trained the right). Each training session (two sessions per day) consisted of 400 trials and participants were offered an optional break screen every 20 trials to reduce fatigue.

A motion coherence threshold was calculated for both assessments (for each visual hemifield) and for every training session. It is a measure of the proportion of coherently-moving dots required for the participant to correct discriminate motion direction 80% of the time. A lower threshold (lower proportion of dots are moving coherently) indicates a better performance at the task. To measure change between the two assessments, a learning index was calculated. Please see Chapter 2 for further explanations.

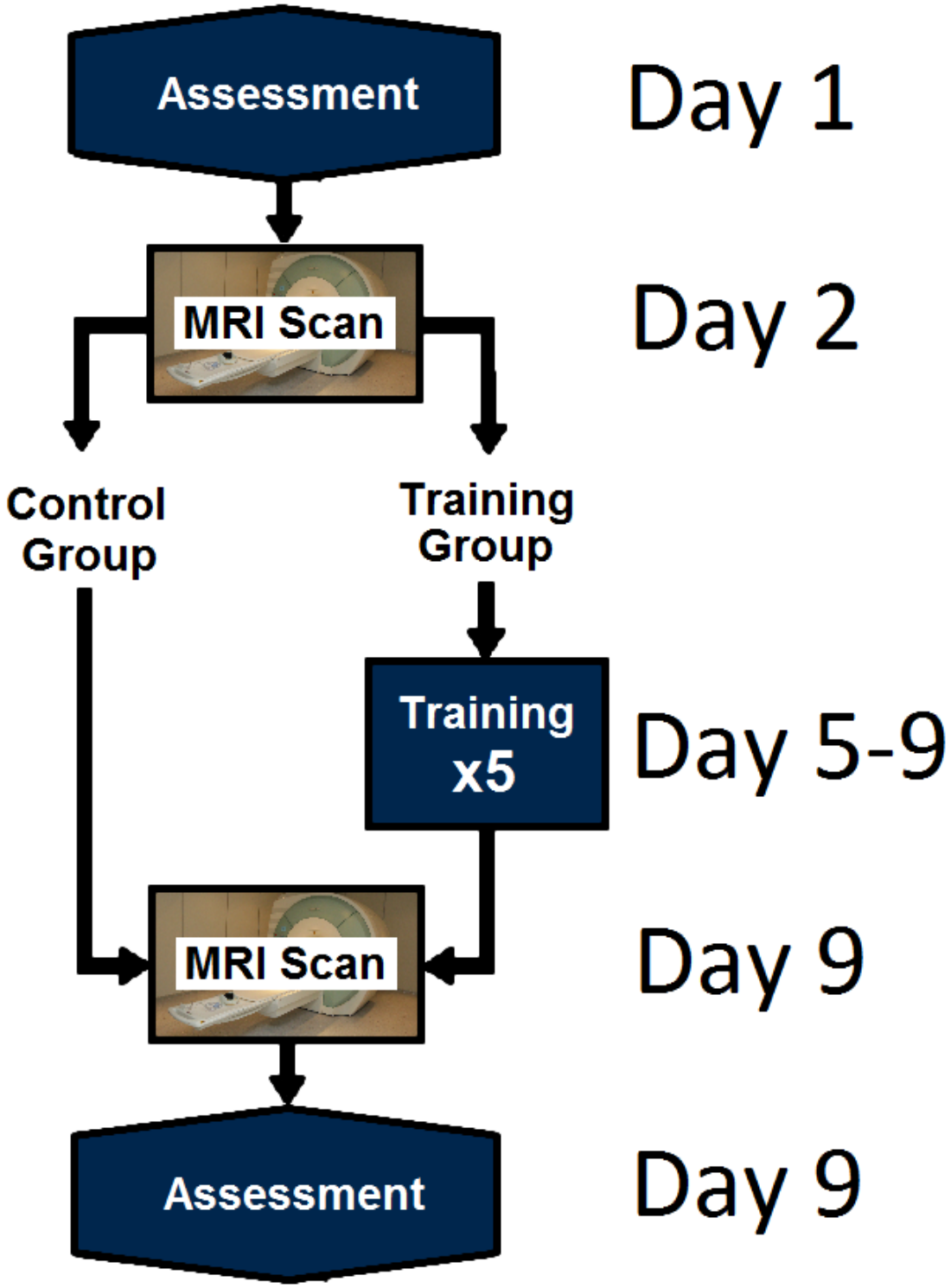


Figure 21: Experimental protocol followed by the motion training and control participants. Each participant completed assessments on Day 1 and Day 9 and an fMRI scan on Day 2 and Day 9. For the motion-training group, training was performed twice per day for 5 days (Days 5-9). The control participants did not meet the researchers between MRI scans.

5.2.4 MRI data acquisition

All MRI data were acquired using a Siemens Verio 3-Tesla MRI scanner with a 32-channel head coil at the Functional Magnetic Resonance Imaging of the Brain Centre (FMRIB), University of Oxford. T1-weighted structural brain images were acquired for each participant at 1mm isotropic resolution (MPRAGE; 192 transverse slices, TR=2040ms, TE=4.7ms, flip angle=8°). A gradient-echo Echo planar imaging (EPI) sequence was used to acquire 312 volumes per scan run (36 transverse slices, 3mm isotropic voxels, TR=2000ms, TE=30ms, flip angle=90°). Three runs of this sequence were acquired per scanner visit.

5.2.5 fMRI task design

The main task in the scanner was to identify if coherent motion was leftwards or rightwards (more details of the task are described above). Participants indicated the perceived direction of motion using a button box inside the scanner. Subjects were instructed to use their right hand index finger on the leftmost button to indicate leftwards motion, and their right hand middle finger on the next button to indicate rightwards motion. Each trial of the task consisted of a 500ms stimulus, 1300ms response window and a 200ms feedback screen. Trials were grouped into 8-trial blocks, each block lasting 16s (Figure 22).

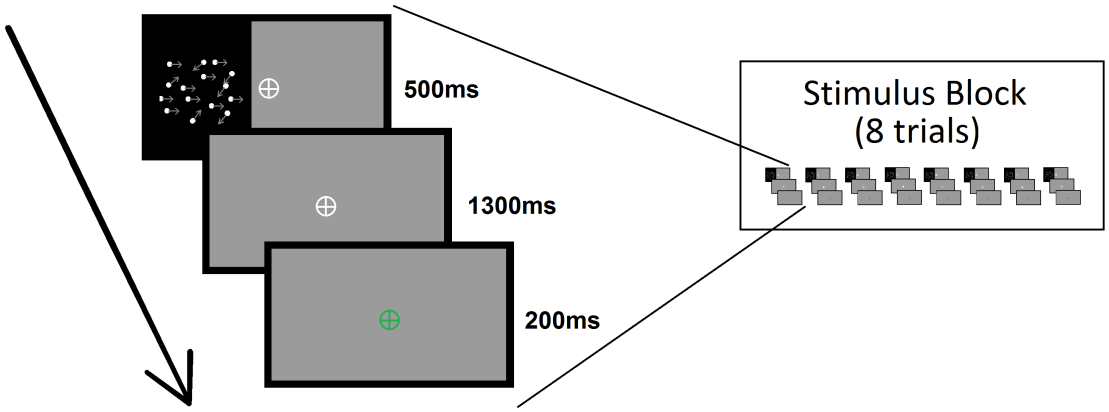


Figure 22: Trial presentation in the scanner. Each trial consisted of a 500ms stimulus screen, 1300ms response window and a 200ms feedback screen. Trials were grouped into 8-trial blocks. Each block lasted 16s.

There were 6 different stimulus types for the motion task in the scanner. These 6 stimuli blocks were:

- baseline coherence in left hemifield
- baseline coherence +10% in left hemifield
- noise motion in left hemifield
- baseline coherence in right hemifield
- baseline coherence +10% in right hemifield
- noise motion in right hemifield.

The stimulus types were were grouped in 8-trial blocks, as described above. Participants were shown 12 blocks (2 repeats each of 6 unique stimulus types) in a pseudorandom order (Figure 23). After every 12 blocks, a rest block of a grey screen with white fixation cross was shown for 16s. There were 39 blocks in total, including rest blocks, during each run. There were three runs per scan session, which were later combined.

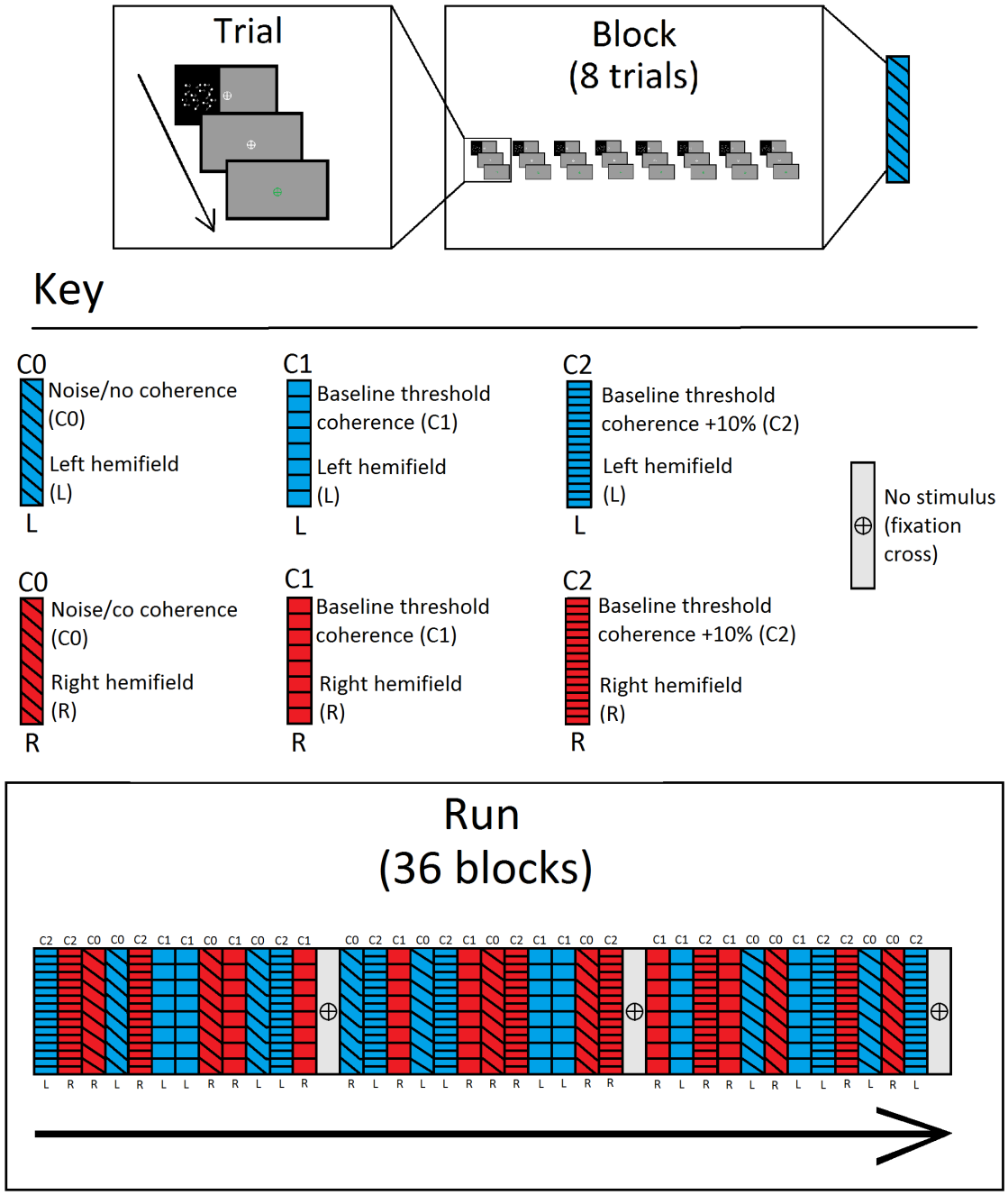


Figure 23: Example of an fMRI run. Participants were asked to complete the motion task inside the scanner. Trials were presented in blocks of 8 trials. Each block is represented in the diagram above by a coloured vertical bar. Each block could be in either the left hemifield (blue bars) or the right hemifield (red bars). Blocks could be of three different difficulties: noise motion (bars with diagonal stripes), motion with coherence at threshold (bars with broad horizontal stripes), or motion with coherence above threshold (bars with narrow horizontal stripes). There were therefore 6 unique stimuli. Participants were shown two repeats of each stimulus block in a pseudorandom order, followed by a rest block of 16s. Rest blocks consisted of the presentation of a fixation cross on the screen, with instructions to just keep the eyes still (grey bars). This design was repeated three times per run, as shown in the visual example. There were three runs per scan session, which were later combined. Participant coherence thresholds were determined prior to each scan session using the task assessment described above. Thresholds were not altered for the second scan according to performance; participants were shown the same stimulus at Scan 1 and Scan 2.

5.2.6 fMRI data analysis

MRI data analyses were carried out using FMRIB's easy analysis tool (FEAT) v6, part of FMRIB software library (FSL; v6, www.fmrib.ox.ac.uk/fsl). Pre-processing of images included motion correction using MCFLIRT (Jenkinson et al., 2002) and spatial smoothing of FWHM 5mm. Magnetic field unwarping (echo spacing=0.56ms, EPI TE=30ms, unwarp direction=-y, signal loss threshold=10%) and slice timing correction (interleaved) were also applied. All MRI data collected from participants receiving training in the right visual hemifield was flipped horizontally. This facilitated analysis of the motion-training group such that all participants effectively trained the left visual hemifield.

T1-weighted images were brain-extracted using FMRIB's brain extraction tool (BET; Smith, 2002). Functional images were registered to T1-weighted structural images for each participant, using FMRIB's linear image registration tool (FLIRT; Jenkinson & Smith, 2001).

Analysis at the whole brain level

Time series statistical analysis was performed using a general linear model (GLM). For whole brain analyses, z (Gaussianised T/F) statistical maps of the change in BOLD activity were thresholded using clusters at $z>2.3$ and a corrected cluster significance threshold of $p=0.05$ (Worsley, 2001). Clusters were projected onto either structural space for each participant, or standard space for group analysis (see below).

A whole brain GLM analysis was performed for each scan run per subject. Each of the 6 block types (see Figure 22) were entered as explanatory variables (EVs) in the design matrix and linear contrasts between the EVs were computed. A higher-level fixed effects analysis was then carried out for each subject, to combine data across the three runs per scanner visit. The contrast for coherent motion compared to noise for each subject for Scan 1 and Scan 2 was extracted for the group stage analysis

(no other contrasts were analysed further).

For group analysis, images were registered to standard space, using the Montreal Neurological Institute (MNI) standard brain with 2mm isotropic voxels, with FMRIB's nonlinear image registration tool (FNIRT; Andersson et al., 2007). A paired t-test was implemented in the higher level FEAT analysis to determine regions activated more in Scan 2 compared to Scan 1 across the motion training and control groups. A further higher level analysis determined the differences between the training and control groups.

Region of interest (ROI) analysis

A region of interest (ROI) analysis was carried out to calculate the percentage BOLD change in visual areas. This analysis was carried out separately for Scan 1 and Scan 2 for every subject, using the mean change in activity when subjects were viewing coherent trials versus motion noise trials. The Juelich atlas (Eickhoff et al., 2005), which contains templates of visual areas based on histological data of 10 individuals, was used to create ROI masks. Masks were created of the Juelich-defined V1, V2, V3, V4 and V5 for each hemisphere. The full-sized Juelich masks indicated where any of the 10 individuals used to generate the atlas showed histological evidence of the region in question. As such, masks were thresholded at 30%. Thresholded masks therefore indicated where at least 7 of the 10 individuals showed histological evidence of the ROI, and so were much more stringent indicators of each region. Within each of the visual area masks, FEATQuery was used to convert COPE values into the percentage BOLD change, for both scan meetings for each subject.

MST was localised in this study using mean MNI co-ordinates established by Fischer et al. (2012) using the fMRI responses of 11 subjects to motion and stationary stimuli. The mean ($\pm SD$) co-ordinates for left MST were (-48$\pm$6, 68$\pm$4, 5$\pm$4) and for right MST were (50$\pm$6, 64$\pm$3, 4$\pm$4).

These values were further supported by evidence that human MST is localised in a sulcus which intersects with the ITS-ALITS junction (inferior temporal sulcus - ascending limb of the inferior temporal sulcus junction; Domoulin et al., 2000).

Correlation analysis

To determine whether changes in BOLD activity in any areas related to the amount of learning, a correlation analysis was carried out across all participants (from both the motion training and control groups). This higher-level analysis correlated change in BOLD signal between scans with the amount of learning from the first to the second assessment. The learning index for change in performance in the motion direction perception task (see Chapter 2) was input as a regressor, for all participants.

5.3 Results

5.3.1 There is variability in the initial ability of participants to complete the motion direction perception task

The initial motion coherence thresholds varied considerably across the 28 participants, consistent with data collected from different healthy populations described in previous chapters (Figure 24). Across all participants, the baseline motion coherence threshold ranged from 17.8% to 86.7% of dots moving coherently. The motion training group had a baseline average of 50.6% coherence (SD=20.59%) and the control group 50.7% (SD=21.97%). A repeated measures ANOVA (factors: group, hemifield) showed no difference in the baseline coherence thresholds for group (F=0.000; df=1; p=0.998), but an effect of hemifield. The hemifield effect corresponded to a statistically significant higher threshold in the left visual hemifield (F=12.883; df=1; p=0.003). The effect magnitude was small (Left hemifield: M=52.4%, SD=20.58%; Right hemifield: M=49.1%, SD=19.58%), but is consistent with previous chapters in this thesis. For the motion training group, there was no significant difference between training and opposite visual hemifield prior to motion perception training (paired t-test: t=-0.702; df=13; p=0.495).

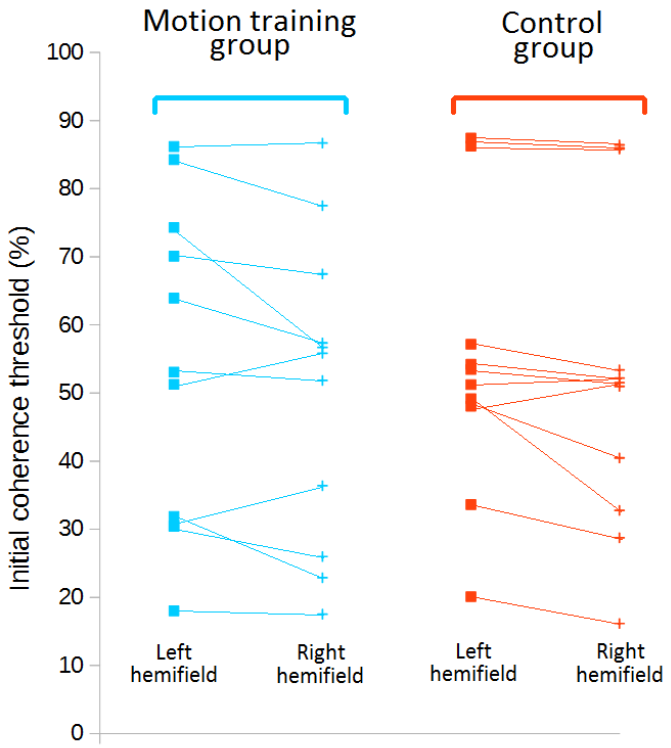


Figure 24: Initial coherence thresholds varied by a large amount. Thresholds are plotted for the motion training group (blue) and the control group (red), for the left visual hemifield (boxes) and the right visual hemifield (crosses). There was no significant difference between groups. Baseline coherence values for the right hemifield were slightly but significantly lower than the left hemifield. Lines pair data from each participant.

5.3.2 Motion-training group show learning of motion direction perception task following five days of training

Performance in the ten daily training sessions (two sessions per day) was quantified for the motion training group, to determine the change in performance over the five-day protocol. Previously, five days of the motion task was shown to be sufficient for participants to improve at the motion task (Chapter 3), and this finding was replicated here. The motion training group showed a significant improvement in coherence thresholds across the training sessions, with the mean decreasing from 35.8% at Session 1 to 22.5% at Session 10.

There was variability in the initial performance of the participants at the first training session (initial coherence thresholds were: mean=35.8%, standard devia-

tion=17.5%, minimum=11.6%, maximum=84.1%). Because of this, daily coherence thresholds were normalised to facilitate further analysis. Performance across the ten training sessions (Session 1 to Session 10) was normalised to the coherence threshold obtained during the initial training session (Session 1). Statistical comparison of performance at each training session with training Session 1 was completed. Analysis using non-parametric combination (NPC) with a post-hoc Fisher analysis confirmed that overall, coherence thresholds were lower after Session 1, for motion trained group (p=0.0002). Further analysis showed that there was significant improvement in performance from Session 2 onwards, which remained significant for all other training sessions (one-way ANOVA with unidirectional post-hoc Dunnett, Session 1 as 'control': F=5.783; df=9; p=9.58x10^{-7}). This learning effect is visualised in Figure 25.

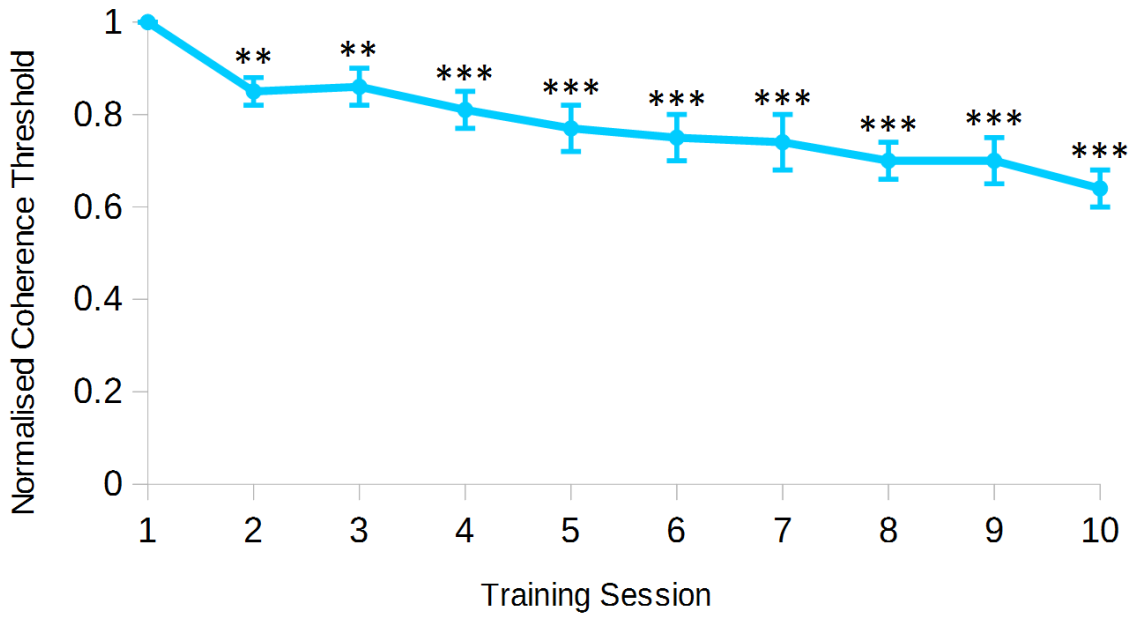


Figure 25: Normalised coherence threshold for the motion-trained participants at each training session. Coherence thresholds gradually decrease over the training sessions, indicating a learning effect. In comparison to performance at Session 1, participants performed significantly better from Session 2 onwards. *p<0.05, **p<0.01, ***p<0.001. Error bars show $\pm SEM$.

5.3.3 Motion-training group show significantly more learning in the trained visual hemifield, compared to the untrained visual hemifield

Motion perception assessments were carried out for all participants on two occasions, one week apart. This corresponded to before and after training for the motion training group, or simply a one-week delay between assessments with no intervening training for the control group. A learning index was calculated to determine the change in performance from the first to second assessment (see Chapter 2). Learning index was calculated separately for each hemifield, for both groups (Figure 26).

The motion training group was trained in a single visual hemifield. Since assessments were carried out for both hemifields, this allowed comparison of trained versus untrained hemifields in the motion-trained group. Analysis comparing the two hemifields showed that participants demonstrated significantly more learning in the trained hemifield compared to the untrained hemifield (paired t-test: t=2.352; df=15; p=0.033). This indicates that there was some specificity of learning effects to the trained location.

The learning indices for the control group was above zero, and this was likely due to a re-test effect (improvement due to the task being non-novel at second encounter). There was no difference in the amount of learning in the left versus right visual hemifields in the control group (paired t-test: t=0.628; df=13; p=0.541). This was expected as no training was carried out in either visual hemifield between assessments.

To further confirm the specificity of learning effects in the motion training group, performance in the untrained visual hemifield for the motion trained group was compared to performance of the control group, averaged across both hemifields. There was no significant difference between groups (independent t-test: t=1.707; df=26; p=0.260), further demonstrating that learning was specific to the trained visual location following motion perception training. It should be noted that there

was a trend towards partial transfer of learning, with the motion trained group performance in the untrained visual hemifield occupying an intermediary value between the performance in the trained hemifield and the performance of the control group, as seen in previous chapters.

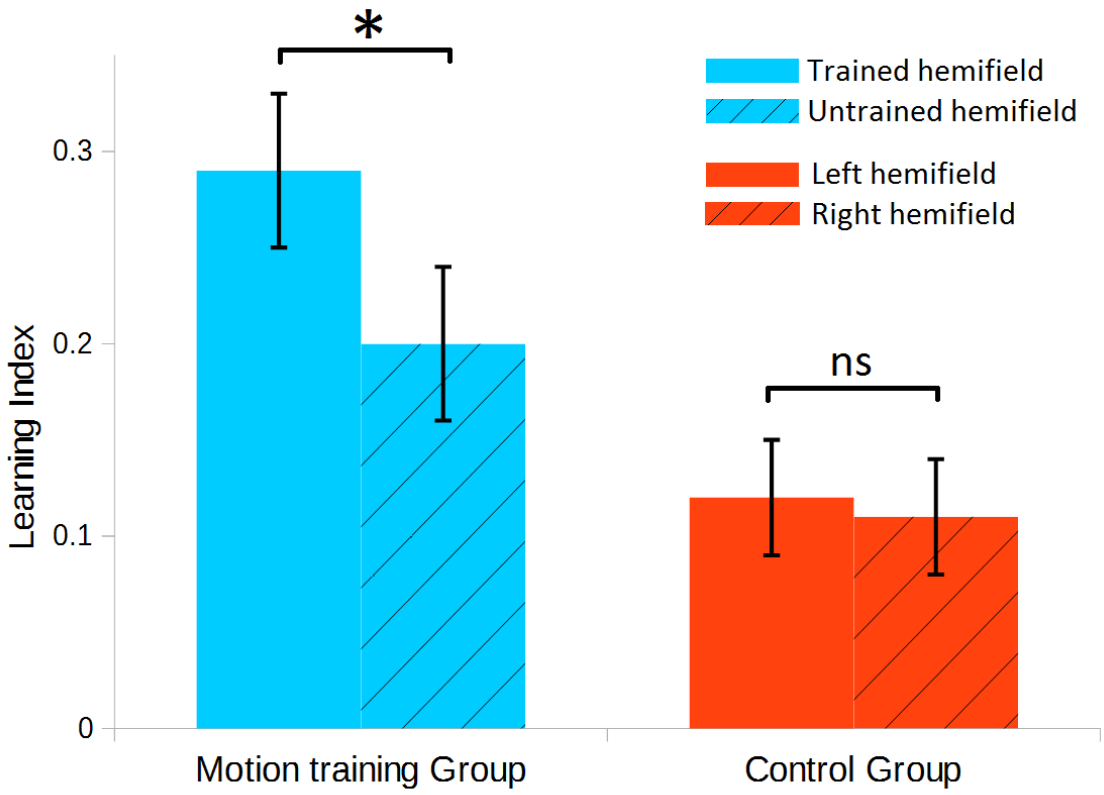


Figure 26: Comparison of learning index across visual hemifields. The motion-training group improved significantly more in the trained visual hemifield compared to the untrained visual hemifield. There were no differences in the hemifields in the control group, where no training was completed. *p<0.05. Error bars show $\pm SEM$.

5.3.4 Motion training group show significantly more improvement on the motion direction perception task compared to the control group

In order to determine if there was a significant amount of learning of the motion task in the training group which was not due to the re-test effect (exposure to a task which is no longer novel) the learning indices for the motion training group were

compared to the control group (Figure 27). The value for the trained visual hemifield was used for the motion training group. The learning index averaged across both hemifields was used for the control group, since there was no difference in learning index between hemifields (see above).

The analysis determined that the motion training group showed significantly more learning on the task compared to the control group (independent t-test: t=3.648; df=26; p=0.001). This supports the evidence presented above, where participants in the motion trained group were shown to demonstrate learning of the motion task beyond the re-test effect.

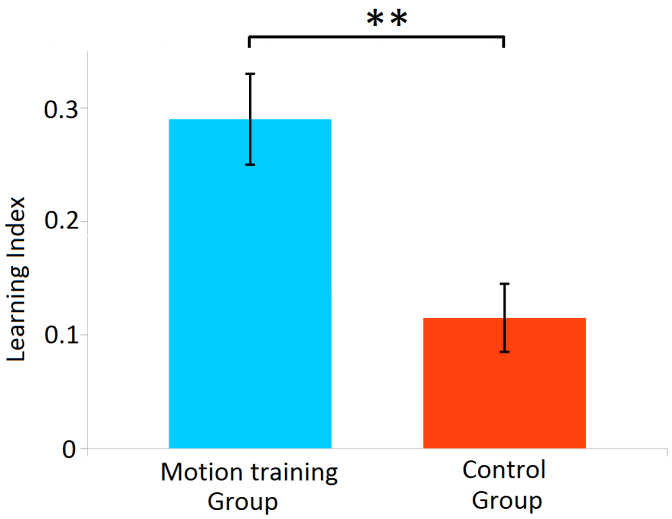


Figure 27: Motion-training group show significantly more improvement on the motion direction perception task compared to control group. The motion-training group had significantly higher learning indices compared to the control group, indicating an effect of motion training. **p<0.01. Error bars show $\pm SEM$.

5.3.5 Functional changes following motion perception training, measured using fMRI

5.3.6 Analysis of the visual cortex

Whole brain analysis showed changes in the visual cortex

The activity map for the motion trained group is presented in Figure 28. In this group, there was an increase in BOLD signal following training in V1, which extended out to further early visual areas, including V2, V3 and V4. Changes appear to be lateralised to the right hemisphere (contralateral to the trained left visual hemifield), although increase in the BOLD signal in V2 of the left hemisphere was also present. There did not appear to be any changes in area hMT+, which is generally considered a centre of visual motion processing.

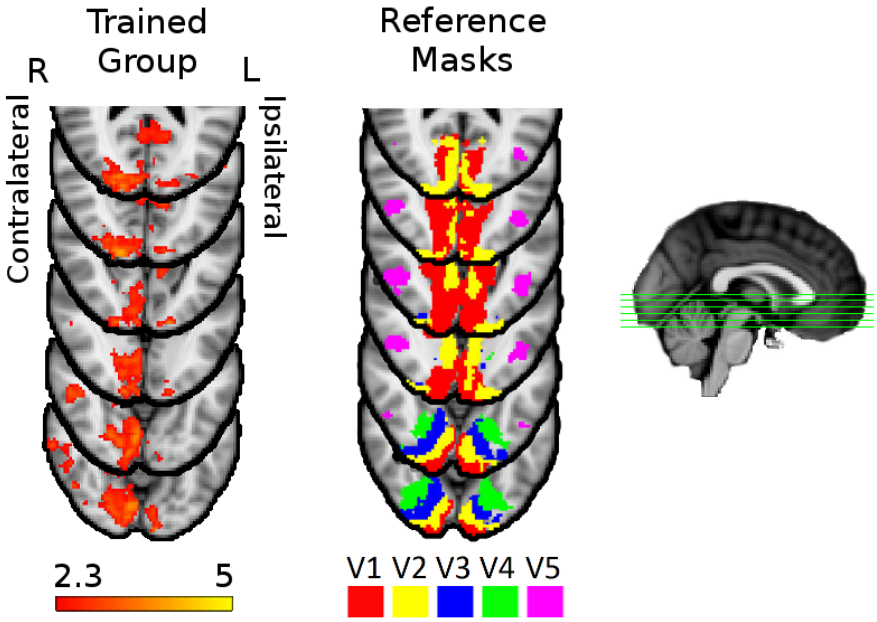


Figure 28: Visual areas show increased activity following training in the motion training group, compared to baseline. **(Left)** Activity is apparently lateralised to the right hemisphere, and is found in early visual areas (V1-V4). Contralateral and ipsilateral are in reference to the trained left visual hemifield. **(Right)** These slices are for reference to illustrate the locations of V1-5. The visual area masks were generated from the Juelich atlas. R=right hemisphere, L=left hemisphere.

For the control subjects, there was a change in the right V2, extending into V3 and V4 (Figure 29). It was surprising that the activity was so lateralised, since there was no difference in the amount of exposure each visual hemisphere had to the motion task.

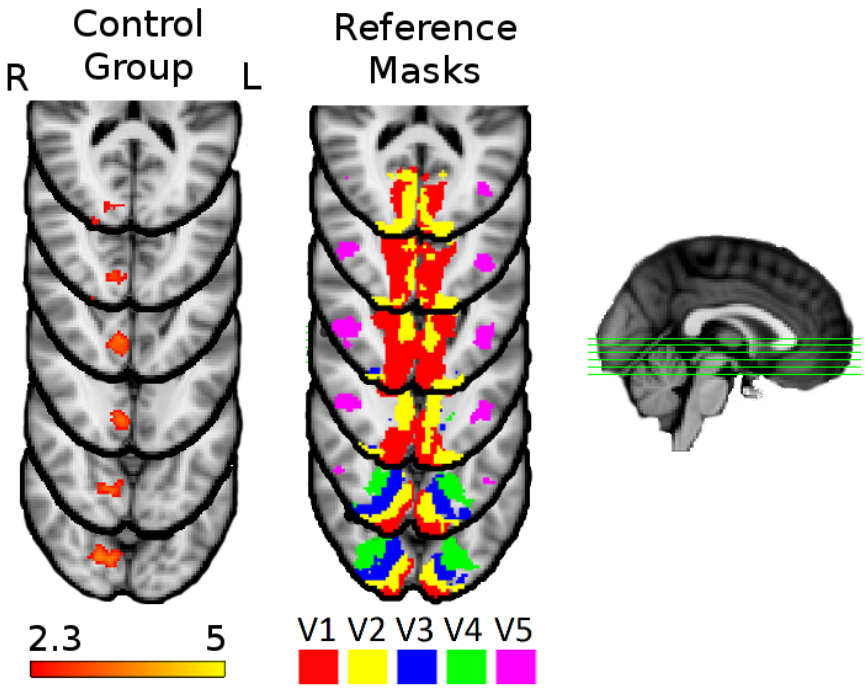


Figure 29: Visual areas show increased activity at Scan 2 compared to Scan 1 in the untrained control group. (Left) Activity is apparently lateralised to the right hemisphere, and found in early visual areas (V1-V2). **(Right)** These slices are for reference to illustrate the locations of V1-5. The visual area masks were generated from the Juelich atlas. R=right hemisphere, L=left hemisphere.

The BOLD signal changes in the control group were compared to changes in the motion training group, in order to isolate the effect of daily motion perception training from the effects of time and task re-exposure (Figure 30). The motion training group showed significantly more activity than the control group in the early visual cortices, emphasising that these changes are likely a result of the training.

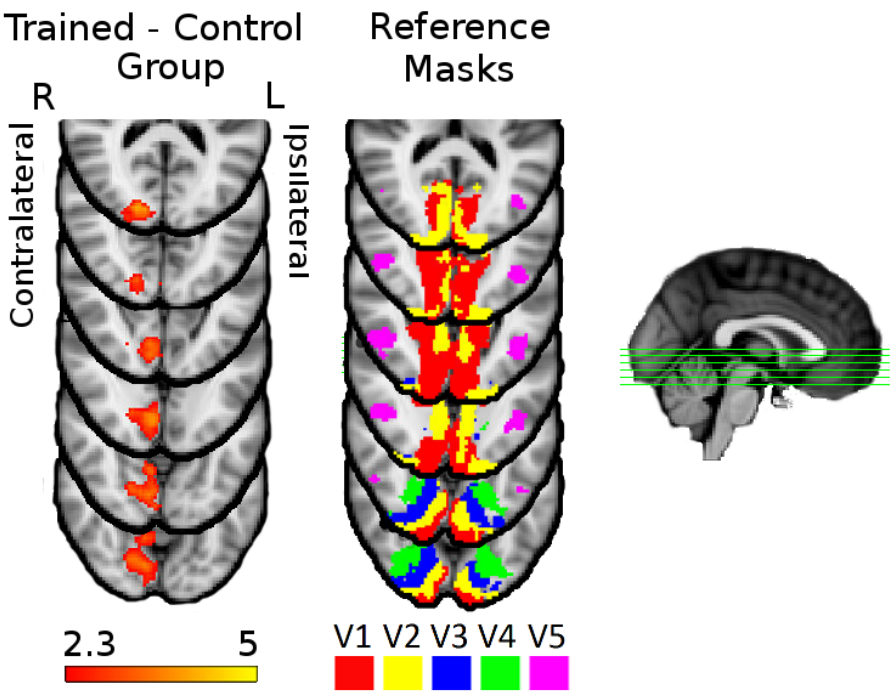


Figure 30: The motion training group show more changes in the visual cortical areas, compared to the control group. (Left) Activity is lateralised to the right hemisphere, and found in early visual areas (V1-V4). Contralateral and ipsilateral are in reference to the trained left visual hemifield. **(Right)** These slices are for reference to illustrate the locations of V1-5. The visual area masks were generated from the Juelich atlas. R=right hemisphere, L=left hemisphere.

ROI analysis of the visual cortex

The data presented above indicate the regions showing statistically significant increases in BOLD across the visual cortex. The next stage of the analysis was to investigate specifically change in activity within defined visual ROIs. Statistical boundary maps (masks) of each visual cortical area V1-5 were created for each hemisphere, using the probabilistic Juelich atlas. For each of these visual area masks, the percentage change in BOLD signal was determined, for trials with coherent motion against trials with only noise motion.

Activity in motion training group is significantly higher in the visual cortex at post-training scan compared to pre-training scan

An ROI analysis was carried out to confirm if motion perception training changed activity in the visual cortex. A repeated measures ANOVA investigated the effect of factors scan number (Scan 1 or Scan 2), visual area (V1-5) and hemisphere (left or right) on the percentage change in BOLD signal. As expected, there was a significant increase in BOLD signal at Scan 2 compared to Scan 1, confirming training had an overall impact on BOLD activity in the visual cortex (RM ANOVA: F=12.866; df=1; p=0.003). Furthermore, there was a significant interaction between scans and visual area (RM ANOVA: F=6.319; df=1; p=0.008), indicating that the change in activity across visual areas was not homogenous.

In order to investigate which visual areas were driving the significant increase in BOLD signal at Scan 2 compared to Scan 1, post-hoc paired-tests were carried out. Pre-training data were compared against post-training at the individual subject level, for each visual cortical area in both hemispheres (paired t-tests: Figure 31). This test indicated that all visual areas showed a significant increase in activity, except V5/MT (Figure 32).

Visual area, hemisphere	Test statistic (t)	Degrees of freedom (df)	Significance (p-value)
V1, left	-3.28	13	0.006
V1, right	-3.99	13	0.002
V2, left	-3.54	13	0.004
V2, right	-4.77	13	3.6×10^{-4}
V3, left	-3.00	13	0.010
V3, right	-3.42	13	0.005
V4, left	-2.84	13	0.014
V4, right	-3.90	13	0.002
V5, left	-0.84	13	0.417
V5, right	-1.66	13	0.120

Figure 31: Paired comparison of pre-training against post-training changes in %BOLD signal. Five visual areas (V1, V2, V3, V4 and V5) were compared for each brain hemisphere. The BOLD signal at post-training was significantly higher (paired t-tests) compared to pre-training for visual areas V1-4 in both hemisphere (highlighted in yellow). There was no change in V5 in either hemisphere.

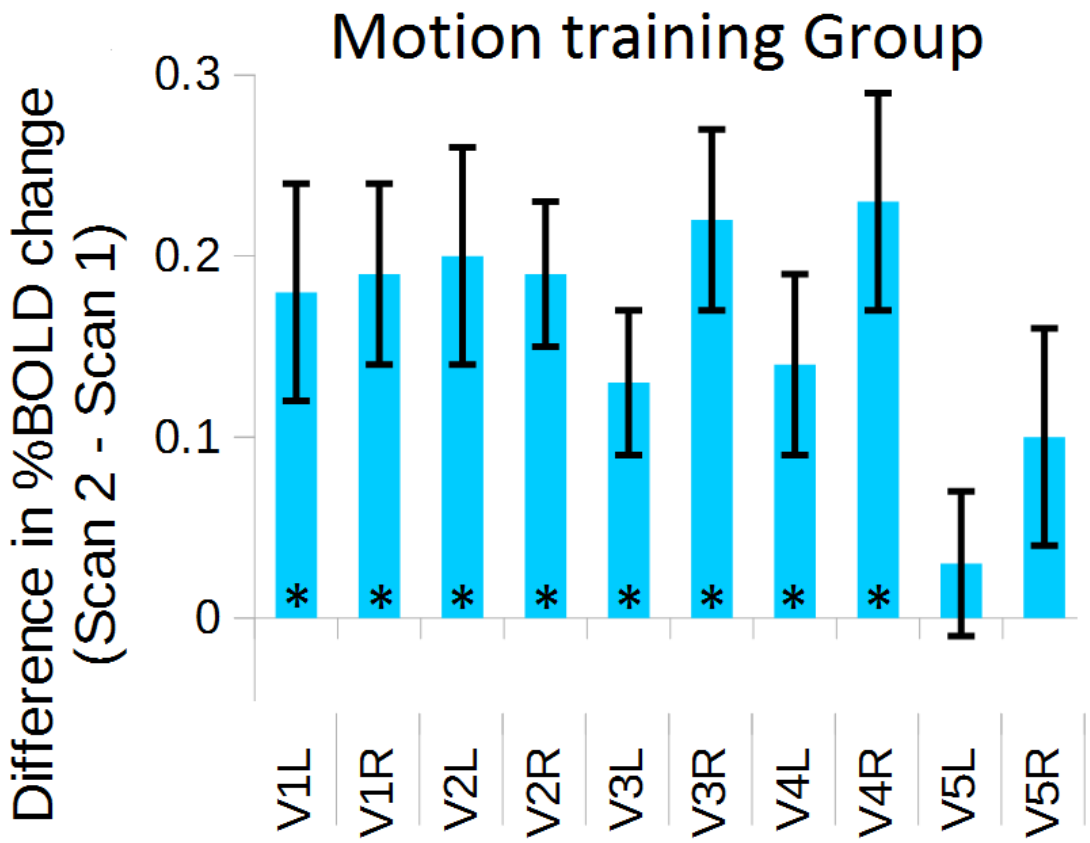


Figure 32: Difference in percentage change BOLD signal for pre-training scan and post-training scan. Five visual areas (V1, V2, V3, V4 and V5) were compared for each brain hemisphere. The BOLD signal at post-training was significantly higher compared to pre-training for visual areas V1-4 in both hemisphere (bars are significantly larger than zero). There was no change in V5 in either hemisphere. R=right hemisphere, L=left hemisphere. *p<0.05 for paired t-test (see Figure 31). Error bars show $\pm SEM$.

Activity in control group is not significantly different in the visual cortex at Scan 1 compared to Scan 2

An analysis carried out for the control group, to investigate if the percentage change in BOLD signal in any of the visual ROIs were different at Scan 2 compared to Scan 1 without training (Figure 33). A repeated measures ANOVA investigated the effect of factors scan number (Scan 1 or 2), visual area (V1-5) and hemisphere (left or right) on the percentage change in BOLD signal. As expected, there was no overall significant difference between scans, showing BOLD activity in the visual

cortex does not change over the space of a week in the absence of motion perception training (F=0.376; df=1; p=0.551).

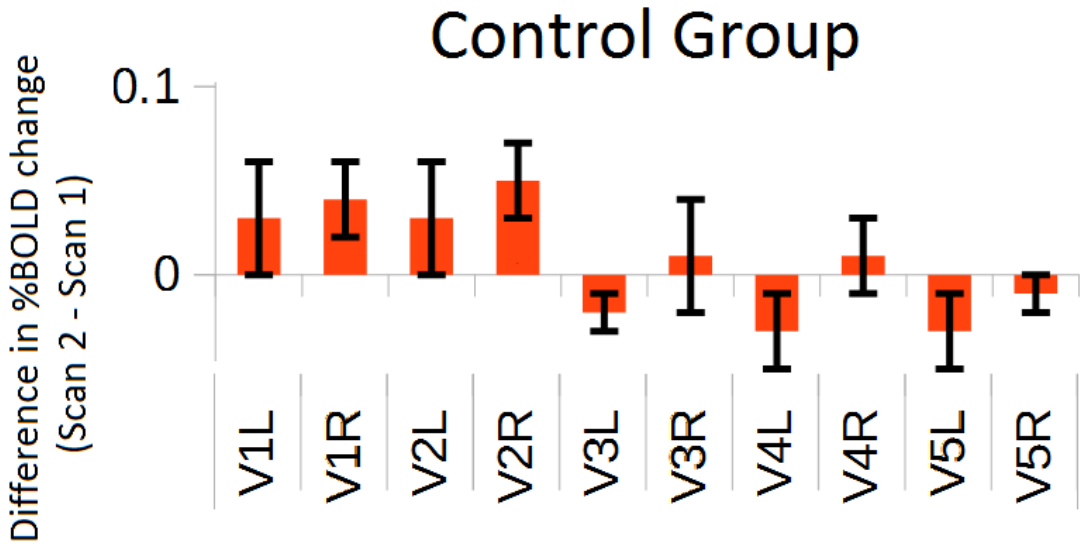


Figure 33: No significant change in BOLD signal between fMRI scans for control group. Five visual areas (V1, V2, V3, V4 and V5) were compared for each brain hemisphere. The BOLD signal at the initial scan was not significantly different compared to the second scan for any of the ROIs. Error bars show $\pm SEM$.

Changes in early visual cortex following motion perception training are not lateralised

The BOLD signal at post-training was significantly higher compared to pre-training for V1, V2, V3 and V4 in both hemispheres for the motion training group. In order to determine if there were differences in hemisphere, values for the right hemisphere (contralateral to the trained visual field) were contrasted against values for the left hemisphere (ipsilateral to the trained visual field) on a subject-by-subject basis. Paired t-tests indicated that there was no effect of hemisphere in V1, V2, V3 or V4 (Figure 34).

Visual area, hemisphere	Test statistic (t)	Degrees of freedom (df)	Significance (p-value)
V1	0.56	13	0.294
V2	-0.19	13	0.424
V3	1.67	13	0.060
V4	2.15	13	0.025

Figure 34: Changes in early visual cortex following motion perception training are not lateralised. Paired t-tests indicated that there was no difference between the change in activity in the left hemisphere compared to the right hemisphere for V1, V2, V3 or V4. Note these values are not significant following Bonferroni correction for multiple comparisons (where $p<0.0125$ for significant effect).

Whole brain correlation analysis showed changes in visual motion area MST

There was a large variation in the amount of learning by the participants, even within each group. Larger changes in motion perception performance are likely to reflect larger neural changes, and smaller changes reflect smaller neural changes. Group-wide averaging does not account for this weighting in signal. Therefore, the next analysis correlated change in BOLD signal with amount of motion perception learning in order to account for the variability in subject learning. Furthermore, this parametric approach meant that participants from both the motion training group and control group could be included in the analysis. The correlation analysis is able to account for any minor perceptual learning that may have occurred in the control group. Furthermore, adding in participants from the control group increased the power of the statistical tests, due to the inclusion of a larger number of participants. It is possible that different mechanisms were involved in small amount of potential perceptual learning resulting from re-test, compared to the perceptual learning resulting from training. This would not confound the results because the re-test effect would be present in both the groups, but the training effect present in

only the motion training group. The difference in BOLD signal between the first and second scan was correlated with the learning index for the trained visual hemifield (motion trained group) or the average of left and right hemifields (control group).

For the initial correlation analysis, there were multiple regions which showed significant correlation with learning (Figure 35). However, these regions were often small, patchy, and quite scattered. A higher-threshold correlation analysis was carried out (z-stat of 3.2) to hone in on the voxels which showed the strongest correlations between motion perception learning and change in BOLD signal. Thus, the analysis clarified which brain regions were most likely to be mediating perceptual learning effects. For the visual cortex, a cluster corresponding to the motion area MST was visualised (Figure 36). This cluster was identified as such due to previous retinotopic mapping reported in the literature (Dumoulin et al., 2000; Fischer et al., 2012).

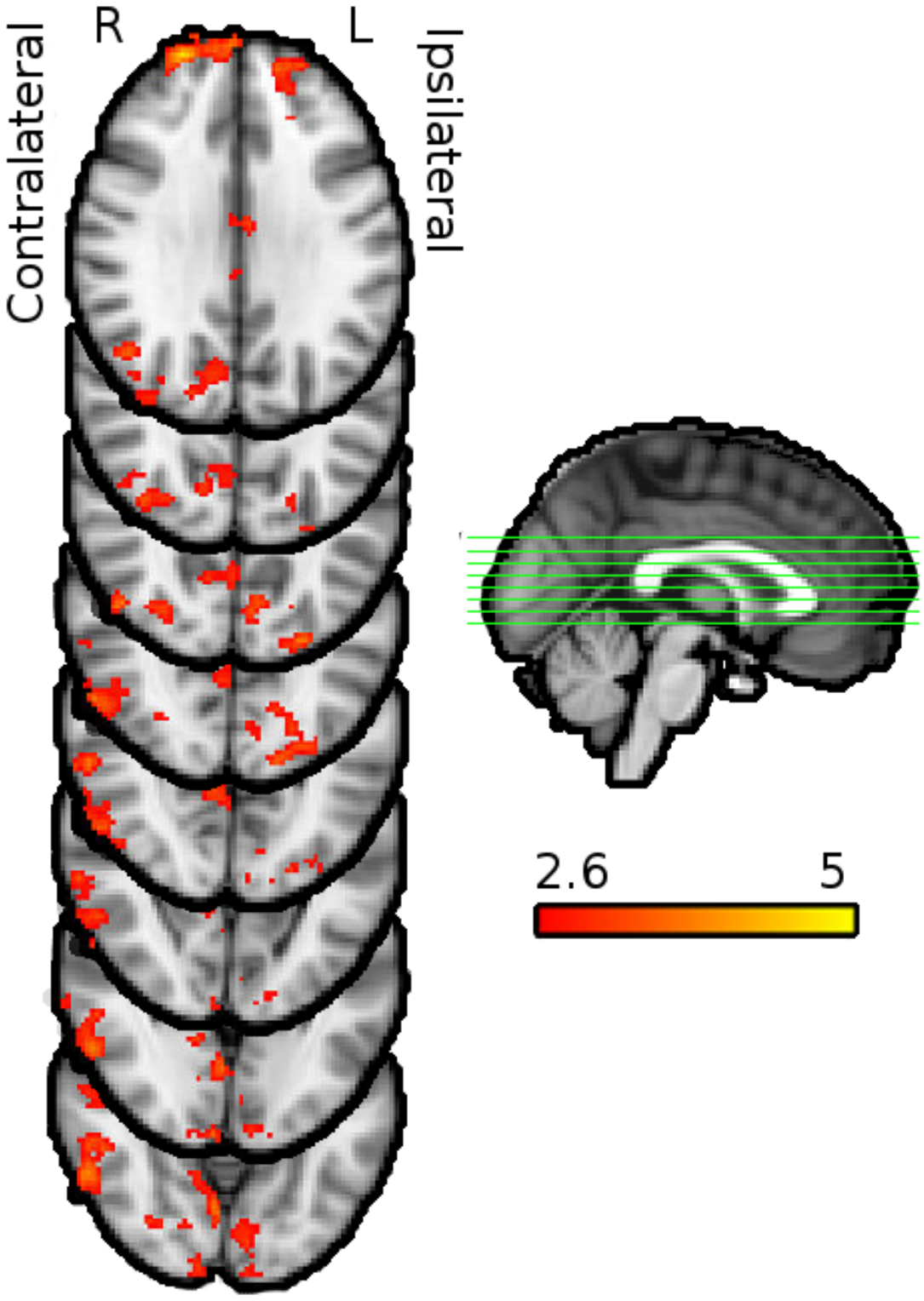


Figure 35: Clusters which show a change in BOLD signal significantly correlated with the amount of task learning. Initial analysis indicated multiple regions which showed significant correlation with learning. However, these regions were often small, patchy, and quite scattered.

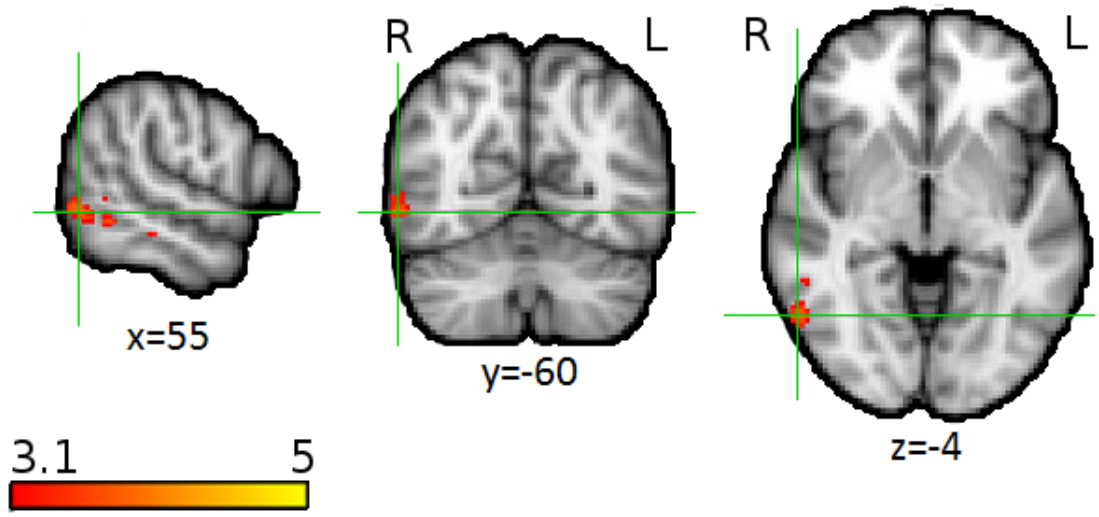


Figure 36: Cluster in MST which shows a change in BOLD signal significantly correlated with the amount of task learning. Right MST motion area has activity significantly correlated with the amount of learning.

5.3.7 Analysis of the non-visual cortex

As well as investigating any changes in the visual cortex, whole brain analyses were inspected to determine whether there were any changes in non-visual areas following motion perception training.

There was a significant increase in the activity in the lateral frontal pole at Scan 2 compared to Scan 1 (Figure 37). In the motion training group, the activity was partially lateralised to the right hemisphere (contralateral to the trained left visual hemifield). There was no change in the BOLD signal in the frontal regions in the control group. When the trained group and control group were contrasted, the changes in frontal regions appeared more lateralised to the right hemisphere. This task required participants to decide on the direction of moving dots, and so required participants to learn to pay attention to a peripheral area of their visual field. It is therefore not surprising there is change in frontal areas associated with decision-making and attention.

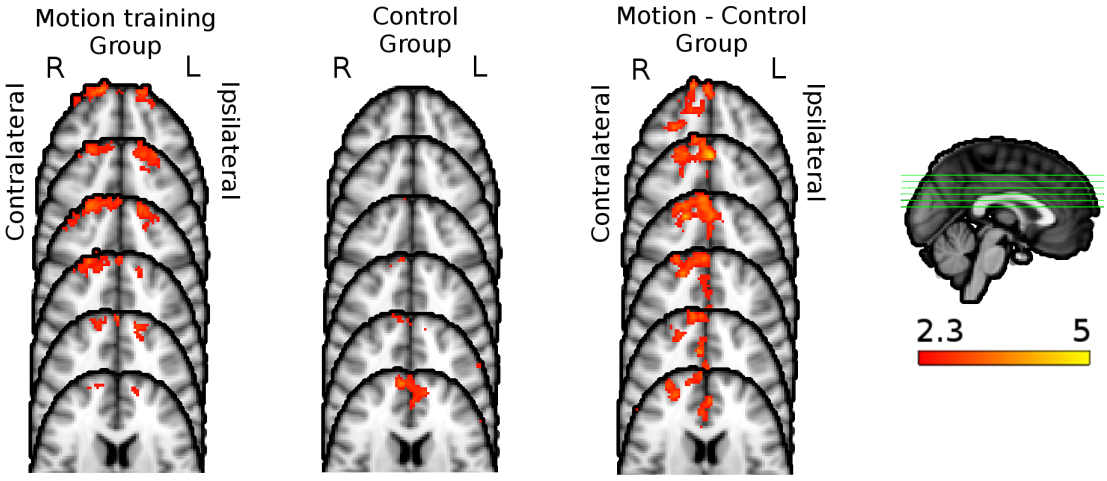


Figure 37: Changes of BOLD signal in frontal regions. There was a significant increase in the BOLD signal in the frontal pole, which was partially lateralised to the right hemisphere, for the motion training group. For the control group, there were no changes in frontal regions. When the trained and control groups were contrasted, the change in BOLD signal appeared more lateralised to the right hemisphere. Contralateral and ipsilateral are in reference to the trained left visual hemifield. R=right hemisphere, L=left hemisphere.

In the motion training group, the right hippocampus was also identified as a location that had an increase in activity at the second scan compared to the first scan (Figure 38). This change was not identified in the control group, and was still present when the motion training group was contrasted against the control group. This finding indicated that there was a lateralised memory component to the learning, and showed that participants were likely recalling previous exposure to the stimulus while completing the task.

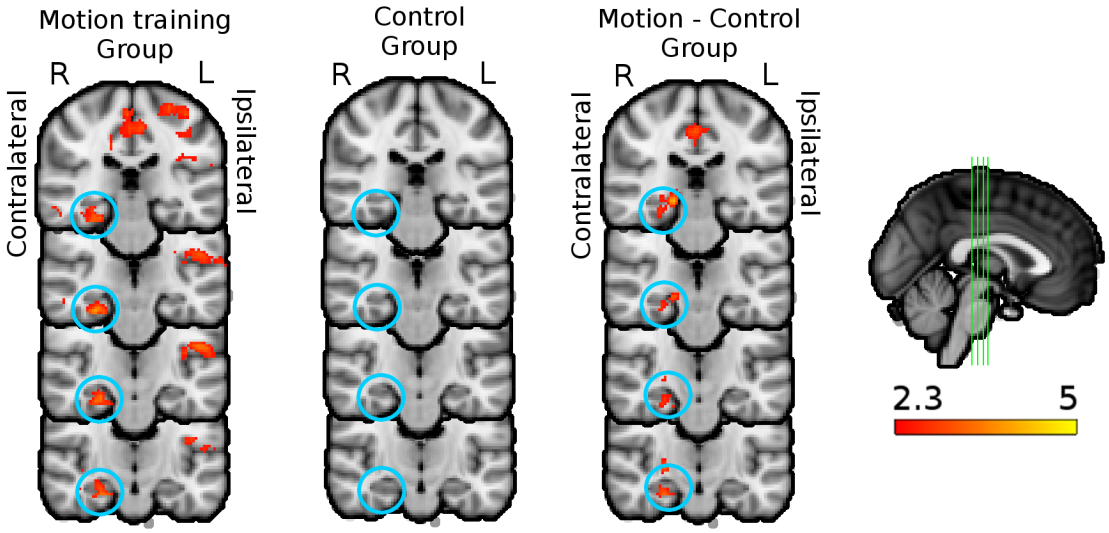


Figure 38: Changes of BOLD signal in hippocampus. There was a significant increase in the BOLD signal in the hippocampus, which was lateralised to the right hemisphere (blue circles), for the motion training group. For the control group, there were no changes in the hippocampus. When the trained and control groups were contrasted, the change in BOLD signal still persisted. Contralateral and ipsilateral are in reference to the trained left visual hemifield. R=right hemisphere, L=left hemisphere.

Changes in BOLD signal correlated with task learning

Following the correlation analysis, the right hippocampus was identified as a region with a change in activity significantly correlated with motion perception learning. This indicated a lateralised memory component to the learning and showed that participants are likely recalling previous exposure to the stimulus while completing the task (Figure 39). The analysis also identified two frontal areas; bilateral dorsal lateral prefrontal cortex (DLPFC) and the right frontal pole (Figure 39).

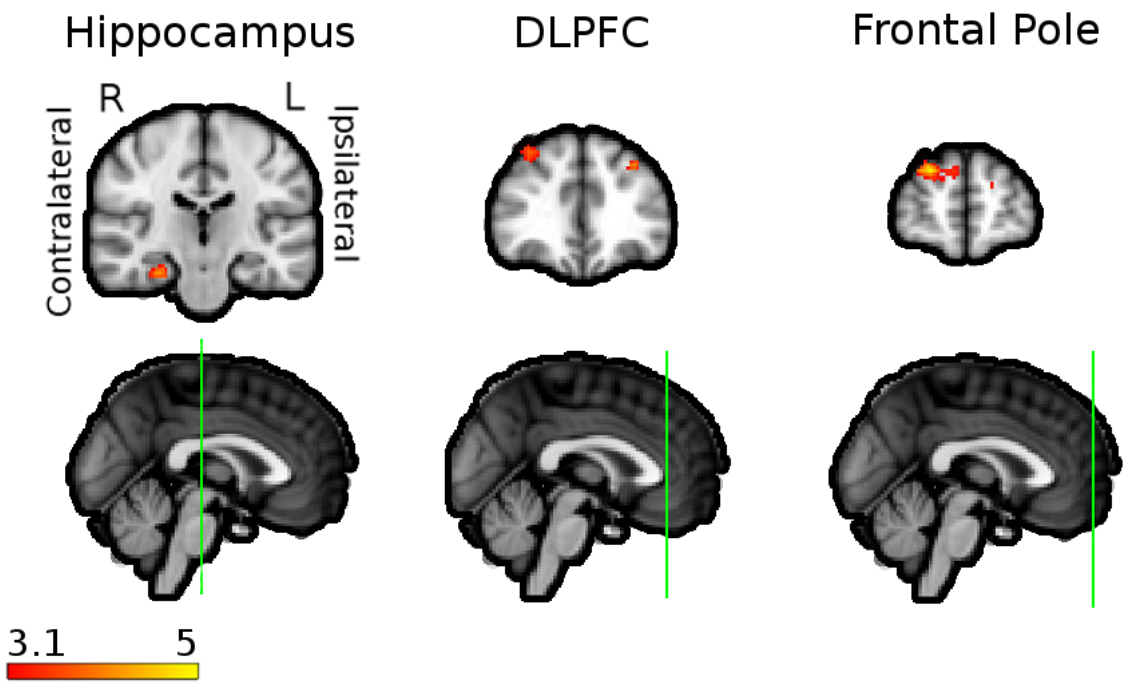


Figure 39: Clusters which show a change in BOLD signal significantly correlated with the amount of task learning. Right hemisphere lateralised activity in the hippocampus was correlated with learning. There was also correlated bilateral activity in the frontal regions. Contralateral and ipsilateral are in reference to the trained left visual hemifield. R=right hemisphere, L=left hemisphere.

5.4 Discussion

In this experiment, participants underwent two fMRI scans and two assessments of their performance on a motion direction perception task in each visual hemifield. There was a one-week delay between the initial and final scans and assessments. A motion training group completed five consecutive days of motion perception training in the intervening week in a single visual hemifield. A control group, where participants performed only assessments and scans and received no training, was included in order to control for the effects of time and for the re-test effect. The aim of this study was to determine and localise the neural effect of motion perception training.

5.4.1 Behavioural effect of training was consistent with previous findings

Participants allocated to the motion training group performed better at the post-training assessment compared to the pre-training assessment, indicating trained participants improved in motion perception in a similar manner to that reported in earlier chapters in this thesis. Control subjects were slightly better at the second assessment compared to the first, however this was likely a result of the task being non-novel at second exposure (re-test effect). The motion training group showed significantly more learning of the motion task compared to the control group. Therefore, it can be concluded five days of motion perception training was sufficient to alter performance at the motion direction perception task.

For the motion training group, change in task performance was higher in the trained visual hemifield compared to the untrained hemifield. The performance of the untrained hemifield was elevated compared to the control group, though not significantly. This indicates that the learning demonstrated was specific to the trained retinal location, although there was perhaps partial transfer of learning effects. For

further discussion on the specificity of learning of this task, please refer to earlier chapters in this thesis.

5.4.2 Eye movements

No eye tracking data was analysed for this study, and therefore the impact of eye movements on the results cannot be determined. It is possible that participants made eye movements during stimulus presentation, therefore altering where in the visual field the stimulus was actually delivered. Therefore, the behavioural data described here may have been confounded by eye movements. Future studies must control for this confound more tightly by monitoring gaze position during stimulus presentation.

5.4.3 Changes in BOLD signal following motion perception training

Participants completed the motion task in an fMRI scanner on two occasions. The BOLD response to trials with a coherent motion element compared to trials with no coherent motion element was contrasted between the two scan sessions.

BOLD signal was elevated in early visual areas following motion perception training

In the motion training group, it was shown that the BOLD signal was increased in early visual areas V1, V2, V3 and V4 at the second scan (post-training) compared to the initial scan (pre-training). For the control group, the participants did not complete any motion perception training between fMRI scans. The changes in the BOLD signal at the second scan compared to the first scan were compared in order to determine the impact of time and repeat exposure to the task, and identified increases in activity of early visual areas. The changes in early visual areas in the control group were significantly smaller than in the motion training group.

It should be noted that the whole brain z-statistic analysis of change in BOLD activity demonstrated a strongly lateralised signal in the lower visual areas. However, ROI analysis of the change in BOLD activity did not indicate any laterality. This difference was a result of averaging the signal across subjects at a different stage of analysis. For the whole brain analysis, data was averaged across group for the pre-training data and for the post-training data, so that pre-training and post-training activity could be compared. For the ROI analysis, change in BOLD was extracted for each individual scan. The pre-training value was then subtracted from the post-training value for each subject, before averaging across group was completed. The apparent laterality in the whole brain analysis is therefore simply an artefact of averaging at an earlier stage in the analysis pipeline.

The motion task was always presented in the peripheral visual field, and participants were instructed to direct their gaze to a central fixation point. Therefore, as well as improving the ability of participants to detect complex motion, exposure to the motion task is likely to also improve the ability of participants to pay attention to the peripheral visual field. These two types of learning may not necessarily be correlated; an improvement in peripheral attention ability may not be required to confer a better ability to extract coherent motion from noise, and an improvement in peripheral visual attention ability does not guarantee increased ability to perceive complex motion. A correlation analysis determined where any changes in BOLD signal were significantly correlated with the amount of learning of the motion task. This analysis showed that the changes in the early visual cortex described above were not correlated in either group with motion perception learning.

It is proposed that the changes in early visual cortices seen here in the motion training group, but not the control group, are an effect of the participants having an improved ability to pay attention to the peripheral visual field. Electrophysiological evidence from single-unit recordings in the macaque cortex have indicated that early visual areas play an important role in modulating visual attention. The cell firing rates in early visual cortical areas V1-4 are elevated when attention is directed to a

stimulus within the cell receptive field (Briggs et al., 2013; Luck et al., 1997; Moran & Desimone, 1985; Motter, 1993). Therefore, increased activity in these areas could indicate improved visual attention. This assertion is backed up by previous studies in this thesis, which have shown that motion perception training in the peripheral visual field can improve performance on a non-motion task presented in the same region of visual space.

Elevation of BOLD signal in MST was correlated with perceptual learning of motion direction perception task

The area of cortex involved in motion perception is termed the human motion complex (hMT+), which can be further subdivided into V5/MT and MST (Huk et al., 2002). MST is the anterior portion of hMT+, and is thought to be involved in optic flow and other complex motion perception tasks (Bremmer et al., 2010; Maloney et al., 2013; Morrone et al., 2000), acting upstream of the more basic motion-sensitive V5/MT (Smith et al., 2006).

Area V5/MT has been shown in humans to be equally responsive to all types of visual motion, regardless of whether coherent motion is present (Smith et al., 2006). In contrast, MST is sensitive to global flow properties, and is most responsive to motion stimuli with flow components. As a result, MST is more responsive to coherent motion in comparison to noise-only motion (Smith et al., 2006). In this study, changes in BOLD signal in area MST were found to be significantly correlated with the amount of motion perception learning of the task. No such changes were identified in area V5/MT. This finding is perfectly in line with the known properties of V5/MT and MST; the training improves the ability of participants to extract coherent motion from background noise motion. This must be mediated by changes at the level of MST, since V5/MT is equally responsive regardless of motion coherence. Furthermore, it has been shown in the macaque monkey that neurones in MST have motion direction selectivity (Tanaka et al. 1986; Van Essen et al., 1981), and activate

preferentially to fields of motion (Komatsu & Wurtz, 1988), both of which were present in the motion task used here, providing further pointers to the involvement of MST in the learning of the task trained in this experiment.

In this experiment, learning targeted the perception of coherent motion amongst noise. After training, participants who demonstrated learning were more effective at extracting coherent motion amongst noise motion. The same coherence thresholds were presented at the first and second fMRI scans. Therefore, for those who showed learning of the task, training could have effectively made it appear as if the trials were more coherent at the second scan compared to the first scan (Liu et al., 2006). Braddich et al. used fMRI to demonstrate that when participants viewed 100% coherent motion versus noise motion, areas V5 and V3A were selectively activated (Braddich et al., 2001). It is interesting that these areas were not found to be correlated with increased perceived coherent motion here. This finding may indicate that perception of amount of coherence is mediated by different neural regions than simply the presence or absence of coherent motion.

Specificity and transfer of behavioural effects of motion perception learning

The behavioural data indicated that improvement in the motion direction perception task was greater in the trained visual hemifield compared to the untrained visual hemifield, in the motion training group. However, the improvement in motion perception of the motion training group in the untrained visual hemifield was higher than the amount of learning seen in the control group. These data therefore indicate that learning was somewhat specific to the trained area of the visual field, but that transfer of learning effects did occur.

Early visual areas V1-4 are retinotopic, and have small receptive fields (Amano et al., 2009), and are therefore likely to mediate learning effects which are local to the region of trained visual field. MST has no retinotopy and very large receptive fields which can extend into the ipsilateral visual hemifield (Duffy & Wurtz, 1991;

Huk et al., 2002). It is likely that factors contributing to improvement at the motion task were mediated at multiple different levels, some of which were retinotopic and some of which were not. Further discussion of the relationship between level of visual processing in the brain and learning specificity has been discussed in Chapter 3.

Increase in BOLD activity correlated with motion perception learning in the hippocampus

The hippocampus is a subcortical area which has been shown to play a key role in the formation of long-term declarative memory (Squire, 1992). In this study, motion perception learning was found to be positively correlated with an increase in the activity of the hippocampus. This indicates that participants were likely recalling previous trials while completing the motion task.

Half of the participants were trained in the right visual hemifield, and half in the left. However, at the analysis stage, the data for all participants trained in the right visual hemifield were flipped horizontally, so all participants effectively trained the left visual hemifield. The change in hippocampal activity correlated with motion perception learning was lateralised to the right hemisphere, contralateral to the trained visual field. No topographic maps have been previously demonstrated in the hippocampus (O'Keefe & Nadel, 1978), however, the right hippocampus receives more inputs from cortical areas in the right hemisphere, and likewise for the left hippocampus. The hippocampus is part of the visual pathway of visual processing, and receives indirect inputs from area MST and other visual areas (Tsanov & Manahan-Vaughan, 2008). The data here therefore confirm the important role of the hippocampus in perceptual learning (Guggenmos et al., 2015; Manns & Squire, 2001).

Increase in BOLD activity correlated with motion perception learning in the

DLPFC and frontal pole

It has been previously proposed that decisions involving perception are completed by the comparison of activity of sensory areas, which are tuned to properties of the different choices (Shadlen et al., 1996). This hypothesis was initially investigated in non-human primates, using a task similar to that used in this experiment. Monkeys were required to make a perceptual decision about the direction of motion of a field of coherently-moving dots, displayed amongst randomly-moving dots. In order to decide the overall direction of motion, the firing rates of pools of neurones tuned to different motion directions are compared (Ditterich et al., 2003; Gold & Shadlen, 2001). This integration is computed by nonsensory areas, such as the lateral intraparietal cortex (LIP) and the dorsolateral prefrontal cortex (DLPFC) (Kim & Shadlen, 1999; Shadlen & Newsome, 2001). In humans, the locus of such sensory integration and perceptual decision-making appears to be the DLPFC (Heekeren et al., 2004). In this study, activity in the DLPFC and the frontal pole was found to be correlated with the amount of motion perception learning. The changes in these areas are likely to be associated with the integration of sensory information, for perceptual decision-making. It is not clear why the activity identified in the frontal pole in this study was lateralised. However, since the right frontal pole receives more inputs from cortical areas in the right hemisphere, and likewise for the left frontal pole, lateralised lower-level stimulation could have produced such a bias in activity.

5.4.4 Future directions

The key areas involved in mediating learning of the motion direction perception task appear to be MST, hippocampus and frontal decision-making regions. Changes in the early visual cortex were not correlated with task learning. Therefore, it would be very interesting to determine the effect of this type of motion perception training on patients with lesioned V1. Such a study could elucidate further the mechanisms involved in perceptual learning of motion. Furthermore, if V1 is not required for

motion perception training to be effective, then such training could perhaps prove directly beneficial as a rehabilitative programme for patients with V1 damage.

5.5 Conclusions

In this experiment, participants completed five days of motion perception training. Subjects completed the trained motion direction perception task inside an fMRI scanner before and after training, so that any changes in neural activity could be localised. There was a significant increase in activity in motion processing area MST, which was found to be positively correlated with the amount of task learning. There were also changes in frontal decision-making areas, and in the hippocampus. Finally, there were increases in activity in the early visual cortices following training, which were not correlated with task learning. Such changes are likely a result of participants learning to pay better attention to a task presented in the peripheral visual field.

Since changes in neural activity following motion perception training are largely in extrastriate, hippocampal and frontal areas, it indicates that motion perception training may be appropriate for rehabilitative application in patients with damage to V1.

6 Investigation of the impact of brain stimulation on motion perceptual training in healthy individuals

6.1 Introduction

Transcranial direct current stimulation (tDCS) is a type of mild electrical brain stimulation. Most commonly, it involves the delivery of a direct current of 1-2mA in 20-minute intervals, using two non-invasive scalp electrodes. tDCS has started to find wider application in recent years (Parent, 2004), and has now been applied in humans in a broad range of neural systems: from the motor system to cognitive and behavioural systems, to disease states such as Alzheimer's, tinnitus, and frontotemporal dementia (Nitsche et al., 2008).

6.1.1 Mechanism of action of tDCS

The two electrodes which deliver the direct current in tDCS are referred to as the anodal (positive) electrode and the cathodal (negative) electrode. Anodal DC stimulation results in cell depolarisation (increased cortical excitability) and cathodal stimulation has the opposite effect (Lang et al., 2005; Purpura & McMurtry, 1965). Current density is a measure of the strength of the electrical field delivered to the brain. It is calculated as the ratio between the delivered current strength and the electrode size. Current density is positively correlated with induced neural excitability under the anode and inhibition under the cathode (Nitsche & Paulus, 2000). Therefore, modifications of delivered current or electrode size can alter the amount of cortical excitability elicited. Unlike other types of brain stimulation, such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS), tDCS does not induce action potentials in neurones by itself. tDCS has been shown to

modulate the resting membrane potential, and can therefore influence the rate of spontaneous cell discharge and evoked potentials (Creutzfeldt et al., 1962).

It is likely that tDCS acts by affecting long-term potentiation (LTP) and long-term depression (LTD) in the brain, which are indicators of learning at the molecular level. LTP describes increased synaptic strength (improved connectivity of neurones at the synaptic level), and LTD is its opposite. Evidence that tDCS can affect LTP has been collected from studies on the rat brain. At the molecular level, LTP is dependent on NMDA-receptor signalling. This initiates a cascade of activity inside the cell, which leads to increased concentrations of cyclic adenosine monophosphate (cAMP). cAMP is an upstream regulator of synaptic protein transcription. Therefore, initiation of this cascade can increase the transcription of proteins involved in improving synaptic efficiency. Studies of cellular mechanisms in the rat cortex have shown that direct current can alter cellular cAMP levels (Hattori et al., 1990). Furthermore, the effects of direct current stimulation can be abolished in the rat by the application of protein synthesis inhibiting drugs (Gartside, 1968) or NMDA-receptor antagonists (Islam et al., 1995). These findings demonstrate that DC cortical stimulation is likely dependent on LTP-mediated protein synthesis, and may interact with neural plasticity mechanisms at the molecular level.

More recent investigations have confirmed that the effects of stimulation are comparable in humans, affecting both glutamatergic (Liebetanz et al., 2002; Nitsche et al., 2003) and GABAergic synapses (Stagg et al., 2009), as well as modulatory neurotransmitters (Stagg & Nitsche, 2011).

6.1.2 Brain stimulation of the visual system

Primary visual cortex

Brain stimulation in the visual system has not been as widely investigated as the application of DC in other neural systems. Very early studies in the cat cortex

showed the occipital lobe is less susceptible to direct current stimulation than the motor cortex (Creutzfeldt et al., 1962), and initial studies in humans have also not yielded straightforward results in the visual domain. In 2001, Antal et al. delivered 7 minutes of 1mA anodal or cathodal stimulation to the occipital lobe, to determine the effect of tDCS on contrast sensitivity. Anodal tDCS did not alter contrast sensitivity, though cathodal stimulation did decrease it (Antal et al., 2001). After-effects were present but brief, returning to baseline after 10 minutes. Using a similar setup in 2003, the same group investigated whether 10 minutes of 1mA anodal stimulation over the occipital pole could alter the threshold for TMS-induced phosphenes. Anodal stimulation of V1 reduced the threshold for both stationary phosphene thresholds induced by TMS over V1, and moving phosphene thresholds induced by TMS over V5/MT+. Cathodal stimulation increased both thresholds. The effect was present immediately and 10 minutes after stimulation, but had returned to baseline after 20 minutes (Antal et al., 2003a; Antal et al., 2003b).

Visual evoked potentials (VEPs) are a measure of the excitability of the visual cortex, measured using electroencephalogram (EEG). The literature looking at the effect of tDCS on VEPs showed that 10 minutes of 1mA anodal occipital stimulation increased the amplitude of the N70 component but decreased the P100 component, with cathodal stimulation having the opposite effects (Antal et al., 2004c). This finding was consistent even when the reference electrode was placed on the neck or back, as opposed to on the vertex (Accornero et al., 2007). Therefore, tDCS can indeed alter neuronal excitability in the visual cortex, as measured by an evoked change in VEPs.

Visual area V5/MT+

Further studies have investigated the effect of tDCS on extrastriate visual areas, however, the results here have been mixed. Early studies applied tDCS to the motion area V5/MT+, to determine its impact on the strength of the 'motion after-effect'

visual illusion. This visual illusion occurs if the same direction of motion is viewed for a period of time, followed by a static stimulus immediately afterwards. The stationary stimulus will appear to move in the opposite direction to the previously observed motion, for a brief duration. The motion after-effect is thought to be a result of selective neural adaptation (Mather & Harris, 1998). Exposure to visual motion causes an imbalance in these interactions, thus resulting in illusory motion.

Antal et al. applied 15 minutes of 1mA tDCS to the motion area V5/MT+ and investigated how it affected the motion after-effect induced by adapting a motion stimulus for 80 seconds. It was shown that either anodal or cathodal stimulation resulted in a reduction in the duration of an induced motion after-effect (Antal et al., 2004d). Antal et al. proposed that tDCS was disturbing normal neural adaptation. Since neural adaptation results in an imbalance of motion direction signalling following exposure to visual motion, disruption of the adaptation mechanism by tDCS resulted in a milder motion after-effect. However, it is not clear why anodal and cathodal stimulation gave the same, rather than opposite, effects.

In a study of visuomotor co-ordination, tDCS applied to V5/MT+ has also not yielded straightforward results. 7 minutes of anodal tDCS had no impact on a visuomotor tracking task involving hand movements, but cathodal stimulation improved performance (Antal et al., 2004b). The authors proposed that the cathodal stimulation produced a 'focusing effect', which by decreasing overall cortical excitability in the region, improved detection of motion patterns. A further study by the same group demonstrated a modest improvement in the initial phase of visuomotor task learning with anodal V5/MT+ stimulation, but no effect with cathodal tDCS (Antal et al., 2004a). It is unclear why the effects found in this study were not consistent with the previous visuomotor experiment described by the same group. One possibility is that the phase of learning in which the stimulation is applied plays a significant role in the effectiveness of tDCS, since it appears the effect of anodal stimulation was only present at the initial phase of learning.

Brain stimulation over V5/MT+ in combination with a motion perception task was first conducted by Antal et al. in 2004 (Antal et al., 2004b). Participants were asked to determine the direction of motion where all of the stimulus dots were moving together, or where coherently-moving dots were presented amongst distractors. Anodal stimulation of 1mA for 7 minutes over V5/MT+ had no effect on performance. Cathodal stimulation improved motion perception when coherence was shown amongst distractors, but worsened it when all dots moved coherently. This finding also supports the focusing effect hypothesis of cathodal stimulation on V5/MT+, as described above. A more recent extension using fMRI demonstrated that 10 minutes of cathodal tDCS over V5/MT+ can induce a change in the BOLD response to coherent motion stimuli in the stimulated region (Antal et al., 2012). These findings point to cathodal stimulation perhaps having a larger effect on motion perception than anodal stimulation, however more detailed studies are required to reach this conclusion.

6.1.3 Application of tDCS as an adjunct therapy

Since tDCS has been shown to modulate the molecular components of learning in the brain, it has the potential to be applied as an adjunct to behavioural or cognitive learning programmes. Adjunct application of tDCS would involve delivery of stimulation while learning is taking place, in order to increase the effectiveness of the learning. There is potential for clinical rehabilitative therapies to be improved by being combined with tDCS. This could decrease the time required for patients to see a positive therapeutic outcome as a result of treatment, or perhaps could increase the maximal impact of rehabilitation therapy itself.

Motor rehabilitation

One area which has shown particular promise for the translational application of tDCS is the rehabilitation of the motor system following brain damage. Application

of tDCS in this field is aimed at correcting brain hemispheric imbalance. It has been proposed that lesions cause an inhibition of the communication between brain hemispheres (Marquez et al., 2015). Reduced output from the lesioned hemisphere leads to overexcitement of the non-lesioned hemisphere. This imbalance then causes overinhibition of the lesioned hemisphere. Rebalance would require excitation of the lesioned hemisphere and inhibition of the non-lesioned hemisphere. Therefore, inhibitory (cathodal) tDCS has been applied to the non-lesioned hemisphere and excitatory (anodal) has been applied to the lesioned hemisphere, in order to upregulate activity of perilesional brain areas during motor rehabilitation (Boggio et al., 2007). Stimulation has been shown to be effective when combined with some motor therapy (Hummel et al, 2008). In a recent review, Marquez et al. summarised fifteen well-controlled tDCS studies for motor rehabilitation following stroke and found that chronic stroke patients with mild or moderate impairments are likely to benefit from tDCS adjunct motor therapy (Marquez et al., 2015), although the treatment effect was modest compared to sham tDCS.

Vision rehabilitation

Following the success of tDCS application in the rehabilitation of motor functions, it has been proposed that brain stimulation may also be a useful adjunct for combination with non-motor rehabilitative therapies. However, there has been limited application of tDCS in visual rehabilitation. A case study of the famous blindsight patient GY attempted to use extrastriate tDCS over V5/MT+ to elevate blindsight ability to conscious visual perception. The stimulation was unsuccessful in its intended capacity, but blindsight-mediated reaction times were improved (Cowey et al., 2013).

Olma et al. investigated the short-term and longer-term impacts of repeated daily sessions of anodal tDCS on motion perception in patients with lesioned primary visual cortex (Olma et al., 2013). They showed that the group that received 20 minutes of 1.5mA anodal tDCS over the lesioned V1 had a modest increase in the

rate of motion perception task improvement compared to a sham-stimulated group. Although these improvements were maintained at later timepoints, it could not be confidently concluded that the anodal group were significantly better at the task than the sham-stimulated group. Furthermore, when previously anodally-stimulated participants were sham-stimulated (and vice versa), the expected impact on learning rate was not reproduced, showing that baseline task ability and previous exposure to the task interacts with the effects of anodal tDCS.

Visual restitution therapy (VRT), a rehabilitation therapy for hemianopia, involves a light detection task at the border zone between the blind and seeing fields. Plow et al. completed a case study with two participants undergoing VRT in combination with sham or anodal tDCS over V1 (Plow et al., 2011). There was a greater improvement in stimulus detection, visual field expansion and reported quality of life of the patient undergoing anodal stimulation, than in the sham patient. The improvement in stimulus detection was particularly marked at the early (first third) of the training programme (Plow et al., 2012a). Furthermore, Halko et al. found that V1 anodal tDCS in combination with VRT affected the fMRI BOLD signal under the anodal electrode and perilesional regions of the cortex, and that these changes were correlated with the stimulating electrical field (Halko et al., 2011). A follow-up study looked at VRT with tDCS in a larger cohort of 8 participants, with 4 participants each for sham and anodal groups (Plow et al., 2012b). A trend was present, but there was no significant difference in visual field border or detection rate of the stimulus identified at post-test period compared to pre-test in either the sham or the anodal group. This is an indication that VRT training effects alone are small, if present at all. The minimal effects of VRT are indeed a known controversy in the vision rehabilitation literature (Horton, 2005). However, when the trends for change in visual field border and stimulus detection were compared between anodal and sham groups, a significant difference was identified. The finding indicates that the study was likely underpowered for the small effect size of VRT. So, VRT may expand visual field and improve stimulus detection at the border of the blind field,

when combined with anodal tDCS.

Further research is required to establish if tDCS in combination with alternative vision rehabilitation therapies (such as prism therapy) may be effective.

6.1.4 Summary and experimental aims

The effect of tDCS in visual brain areas has been inconsistent, and more investigation is required to determine how stimulation can affect visual function and visual learning. The study of visual learning is particularly important for translational purposes, as tDCS has shown strong potential to be applied as a learning adjunct. Successful application of tDCS in the visual system could be adapted to improve the efficacy of rehabilitative therapies in patients with visual defects.

In this experiment, tDCS was applied to the motion processing area of the brain (V5/MT+) in a healthy cohort. Stimulation was applied as an adjunct to motion perception training, each weekday for one week. The aim of the experiment was to determine if anodal DC stimulation could influence the learning effects of motion direction perception training, investigated in earlier chapters of this thesis. From a translational perspective, the results of this study could inform the likelihood that brain stimulation-assisted motion perception training is applied in the future as a visual rehabilitation strategy.

6.2 Methods

Further information about the setup of this experiment can be found in Chapter 2.

6.2.1 Participants

Twenty-four subjects (13 female and 11 male; M=24.7 years; SD=5.81 years) participated in this study. Thirteen subjects were assigned to the anodal stimulation group ('anodal group': 7 female and 6 male; M=23.9 years; SD=6.22 years) and the remaining eleven participants to a sham stimulation group ('sham group': 6 female and 5 male; M=25.5 years; SD=5.43 years). All participants were screened for contraindications to tDCS prior to participation. Three participants were withdrawn before study completion (one from the sham group, two from the anodal group), and were excluded from all analyses.

Data from ten subjects (5 female and 5 male, M=22.3 years; SD=2.21 years) from Chapter 3 who completed the five days of behavioural training without any brain stimulation, were also included in the analysis. Please see Chapter 3 for more information.

6.2.2 Visual tasks and stimuli

The motion direction perception task was used in this experiment. Participants identified whether a group of coherently-moving dots had leftwards or rightwards motion, when displayed amongst randomly-moving distractor dots ('noise'). The direction of coherent motion was variable and restricted to within a 90° angle centred around the horizontal.

Moving dots (n=143) were presented within a circular area 11° in diameter centred 10° to the left or right of fixation (the edge was 4.5° from fixation). Dots were high contrast white dots on a black background. The luminance and chromaticity

measures (SpectraScan PR-650) were white: 96.8cd/m^2 (x=0.289, y=0.312), and black: 0.92cd/m^2 (x=0.236, y=0.247).

6.2.3 Assessment and training paradigms

All participants undertook two assessment sessions (Days 1 and 5), which took 20-30 minutes each, and completed motion perception training every day for five consecutive days (2 training blocks of 400 trials per day, around 10 minutes per block). Sessions were spaced apart by 24 hours ±3 hours.

In all assessments, stimuli were presented to the left or right visual hemifield pseudorandomly, with 200 trials per hemifield. During the training sessions, participants performed the motion direction perception task, but only in a single hemifield (always in the right visual hemifield). Each training session (two per day) consisted of 400 trials and participants were offered an optional break screen every 20 trials to reduce fatigue.

6.2.4 Brain stimulation methods

Prior to each training session, participants were set up with tDCS equipment (HDCkit transcranial direct current stimulation, Magstim). Subjects received either sham or anodal stimulation for 20 minutes during the training. After the 20 minute stimulation run, or after training had finished (whichever was later), the participant was asked to sit with their eyes closed for 5 minutes before the equipment was removed.

For sham stimulation, the current was ramped up to 1mA over a duration of 10 seconds and then switched off. For anodal stimulation, the current was ramped up over a duration of 10 seconds and remained at 1mA for 20 minutes before being ramped down over 10 seconds again at the end of the session.

The experimenter conducting the training and stimulation was blinded as to

whether the participant was receiving sham or anodal stimulation.

Electrodes were placed in sponges (9cm x 8cm and 7cm x 5.5cm) soaked in physiological saline. For placement of the electrodes, the head was measured and marked prior to each round of stimulation. The cathode (8.5cm x 6cm) was placed at the vertex and the anode (5cm x 5cm) was placed 3cm above the mastion-inion line and 6cm left of the midline in the saggital plane (Figure 40). This setup has been used to successfully stimulate left V5/MT+ in published literature (Antal et al., 2004d), and was also guided by previous brain stimulation studies of V5/MT+ (Hotson & Anand, 1999; Walsh et al., 1998). The left V5/MT+ was chosen because previous studies using stimulation of this location with anodal tDCS have shown an improvement in the early stage of visuomotor learning (Antal et al., 2004a).

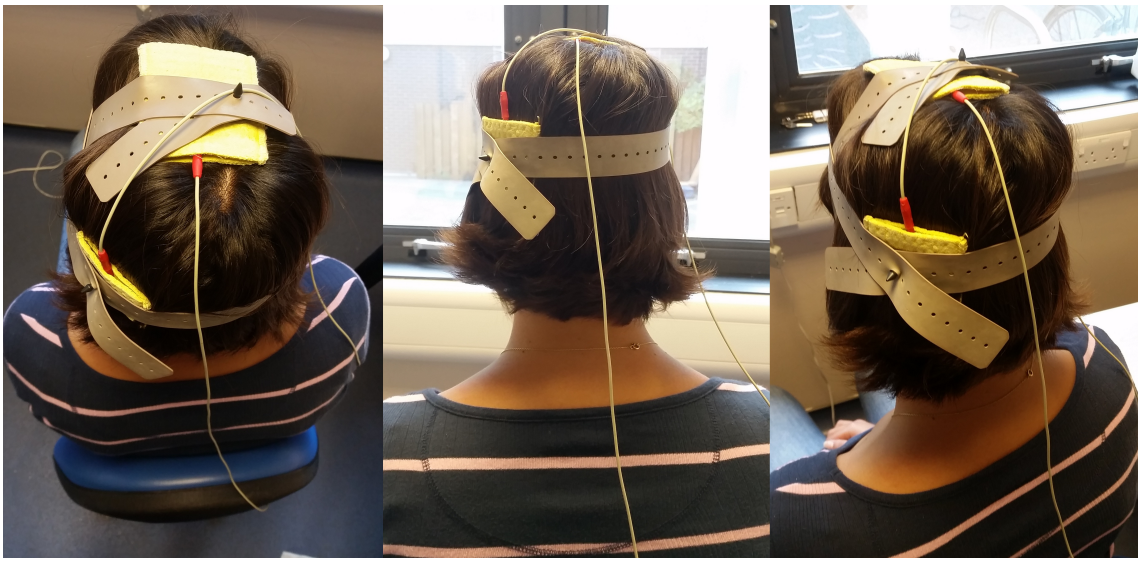


Figure 40: Placement of tDCS electrodes. (Left) Bird's eye view of reference electrode placement. The reference electrode was placed on the vertex. The midline was determined as 50% of the longest distance between the crus of helix for each ear. The vertex was 50% of the distance between the inion and nasion along the midline. **(Middle)** Posterior view of the anodal electrode placement. The anode was centred 3cm above the mastoin-inion line, and 6cm left in the saggital plane. **(Right)** Additional view to aid visualisation of electrode position.

Participants were asked to fill out sensation questionnaires after each stimulation session. Subjects were asked if they experienced any of the following sensations during the stimulation session: headache, neck pain, scalp pain, tingling, itching,

burning, skin redness, sleepiness, fatigue, mood change, trouble concentrating or other. If yes was ticked, participants were asked to rate the intensity of the sensation (mild, moderate or severe) and how likely it was that the sensation was related to the tDCS (not related, remotely, possibly, probably or definitely).

To assess the responses, any sensations which were deemed by the participant to be unrelated to tDCS were discarded. Each related sensation was then given a score per session: 1 point for mild, 2 points for moderate or 3 points for severe. Scores were summed for each participant across their five stimulation sessions, and averaged for each stimulation group, in order to compare the incidence of sensation reporting for sham stimulation compared to anodal stimulation. In a separate analysis, scores were summed for each sensation, across all five sessions and across all participants per group (50 sessions per group). This was to demonstrate which sensations were most commonly reported per type of stimulation.

6.3 Results

6.3.1 Participant withdrawal rate

Three participants withdrew from the study before completion. One participant cited elevated heart rate following sham stimulation, so terminated their participation after a single meeting. Another participant, following a single session of anodal stimulation, terminated their participation without citing a reason. Following two sessions of anodal stimulation, a participant withdrew their participation citing symptoms consistent with a panic attack (dizzy spells, headache, feeling faint, shortness of breath, pins and needles in arms and legs). Since these symptoms are more consistent with anxiety than with hyperexcitation of the cortex, it is likely the effects were psychological in nature and not linked to active tDCS.

6.3.2 Sensation reporting for anodal versus sham stimulation

Following each session of stimulation, participants were asked to complete questionnaires about sensations they experienced in relation to tDCS. Scores were summed for each participant across their five stimulation sessions, and averaged for each stimulation group, in order to compare the incidence of sensation reporting for sham stimulation compared to anodal stimulation (Figure 41A). An independent t-test showed there was no significant difference between groups (Anodal: M=9.9, SD=7.05; Sham: M=7.4, SD=7.24; t=-0.888; df=18; p=0.387). In a separate analysis, scores were summed for each sensation, across all five sessions and across all participants per group (50 sessions for sham, 55 sessions for anodal). There was a significant interaction between sensation and stimulation type delivered (two-way ANOVA: F=2.805; df=11; p=0.002). Further investigation determined that tingling and itching were reported more frequently for anodal stimulation compared to sham stimulation, with no other sensations differing obviously between groups (Figure 41B).

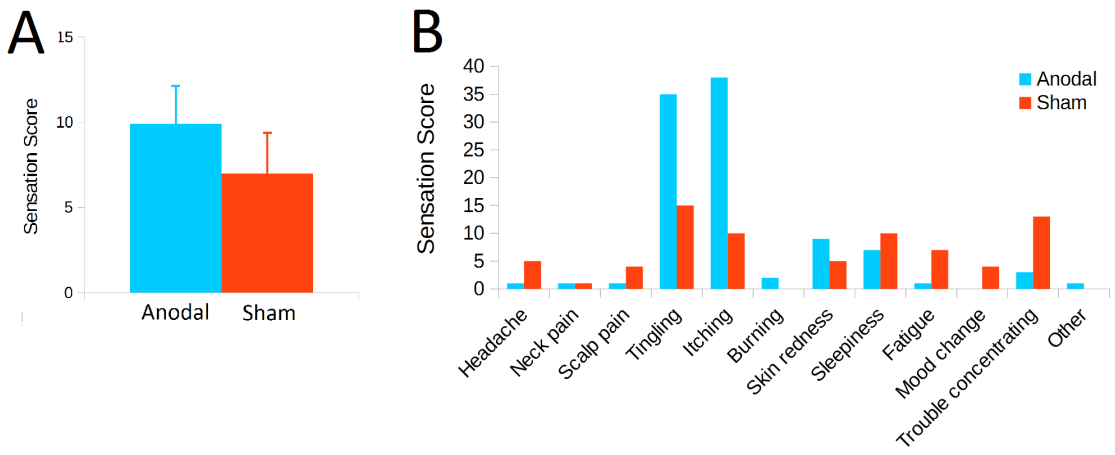


Figure 41: Sensation reporting following tDCS. (A) Average sensation score per subject was not significantly different for sham stimulation compared to anodal stimulation (n=21). **(B)** Incidence of itching and tingling were found to be somewhat more likely to be reported in the group undergoing anodal stimulation compared to the sham stimulation group. No other sensation was compellingly different between groups. Error bars show $\pm SEM$.

6.3.3 Comparison of learning across training sessions for each stimulation group

Participants completed ten sessions of motion perception training, spread over five consecutive days (two sessions per day). Participants underwent anodal or sham tDCS during training sessions. Performance at each session was quantified by determining the motion coherence threshold for that session. Values were then normalised within each subject to performance at the initial training session. Data from ten subjects (5 female, 18-29 years) from Chapter 3 who completed the five days of behavioural training without any brain stimulation, were also included in the analysis. Please see Chapter 3 for more information.

Performance in the daily motion perception training sessions were indistinguishable according to tDCS group (Figure 42). A one-way ANOVA comparing performance in the final training session for the anodal group, sham group and no stimulation group showed there was no difference between groups ($F=1.082$; $df=2$; $p=0.350$).

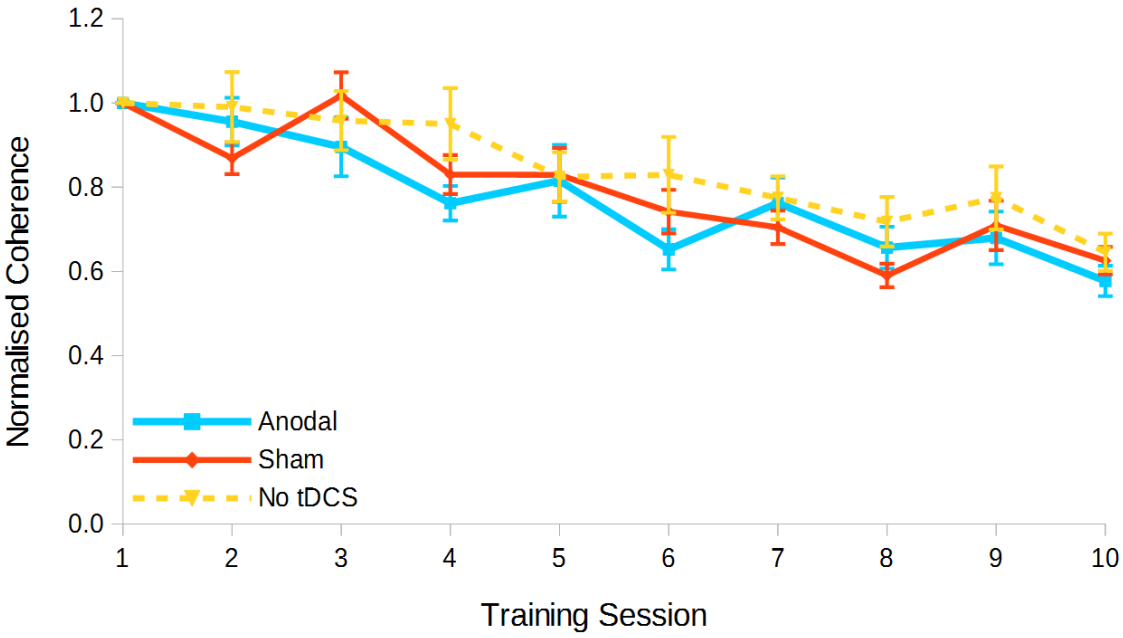


Figure 42: Comparison of sham tDCS group, anodal tDCS group, and no stimulation group across ten training sessions. There was no significant difference between normalised coherence thresholds at the final training session, indicating a similar amount of learning occurred in the anodal, sham and no stimulation groups. Error bars show $\pm SEM$.

6.3.4 Comparison of learning index for motion perception before and after training for each stimulation group

A learning index was calculated (see Chapter 2) to determine changes in the motion perception assessments following training for the untrained and trained visual hemifields (Figure 43). There was no significant difference in this measure between anodal, sham and no tDCS groups for the trained hemifield (one-way ANOVA: F=1.753; df=2; p=0.192) or untrained hemifield (one-way ANOVA: F=2.283; df=2; t=0.121).

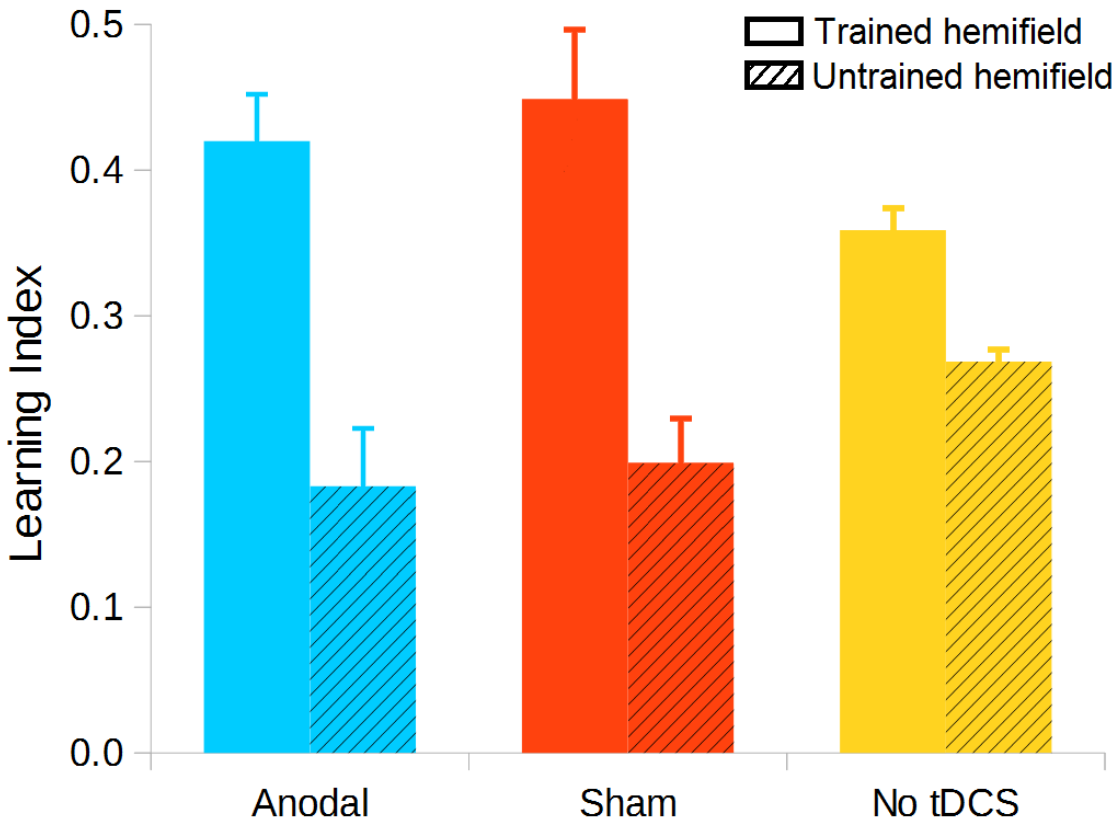


Figure 43: Comparison of learning index for motion perception assessments for each stimulation group. There were no significant differences between stimulation groups for the trained or the untrained visual hemifields. Error bars show $\pm SEM$.

6.4 Discussion

6.4.1 Blinding and safety aspects

Blinding of stimulation type

Although participants and the experimenter delivering the stimulation were blinded as to whether the tDCS was real or sham, itching and tingling were reported with higher frequency in the anodal group compared to the sham stimulation group. This is an indication that it may have been possible to discern the stimulation protocol. For future studies, exit questionnaires will be instigated to verify if this was indeed the case. Previous studies have shown successful blinding with anodal tDCS (Ambrus et al., 2012; Gandiga et al., 2006), although more recent evidence with larger cohorts has called this blinding into question (Fertonani et al., 2015). A large-cohort study of 277 tDCS sessions reported skin sensation effects were significantly higher during anodal compared to sham stimulation (Kessler et al., 2012), supporting the results reported here. Another large cohort study, this time of 693 sessions of transcranial electric stimulation, included transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tNRS) in addition to tDCS sessions (Fertonani et al., 2015). The study demonstrated that anodal tDCS generated marginally more discomfort than sham tDCS, in line with the findings described here. Furthermore, tDCS may cause more sensations than tRNS and tACS, indicating that different types of stimulation may be less distinguishable than tDCS and therefore more appropriate for use.

In this experiment, however, participants undergoing anodal tDCS were not distinguishable from those undergoing sham tDCS in their learning of a motion task. Therefore, there was no apparent placebo effect even if participants were aware of the stimulation.

Safety and side effects of tDCS

No major adverse effects associated with the brain stimulation were reported, providing further evidence that tDCS is a safe and painless technique as previously reported in the literature (Poreisz et al., 2007; Fertonani et al., 2015). However, the withdrawal rate in this study was fairly high (3/24 subjects). Furthermore, one participant showed side effects consistent with high anxiety following brain stimulation, emphasising that in future anxious individuals should be excluded from participation in such a study. The side effect of anxiety following sham or real tDCS has not been previously reported, to the best of the author's current knowledge.

The minor side effects of itching and burning reported here align with previous reports that found mild itching and burning, as well as pinching and tingling, were the most frequently reported side effects of tDCS (Fertonani et al., 2015; Kessler et al., 2012; Poreisz et al., 2007; Russo et al., 2013).

6.4.2 Effect of brain stimulation on motion perception

Motion perception training was completed in combination with anodal or sham tDCS. There were no significant behavioural differences between anodal or sham stimulation groups, nor between either stimulation group in comparison to a no stimulation group reported earlier in this thesis (see Chapter 3). There are a number of possible reasons why no differences were identified between groups in this study.

Failure to stimulate V5/MT+

It is possible that the anodal electrode did not stimulate area V5/MT+ in these participants, since no functional localisation of the brain area was carried out. However, this is highly unlikely. The type of tDCS applied here used large electrodes (active electrode was 5cm x 5cm), which do not provide focal stimulation (Datta

et al., 2009). Area V5/MT+ has been shown to vary only by approximately 2.7cm in the left hemisphere (Watson et al., 1993) and to be on average 0.3cm^3 in size (Malikovic et al., 2007). Therefore it is highly likely that the stimulation at least partially covered V5/MT+. The average location of V5/MT+ (Malikovic et al., 2007) has been overlaid on a simplified image of electrode placement in Figure 44 to facilitate visualisation of V5/MT+ stimulation.

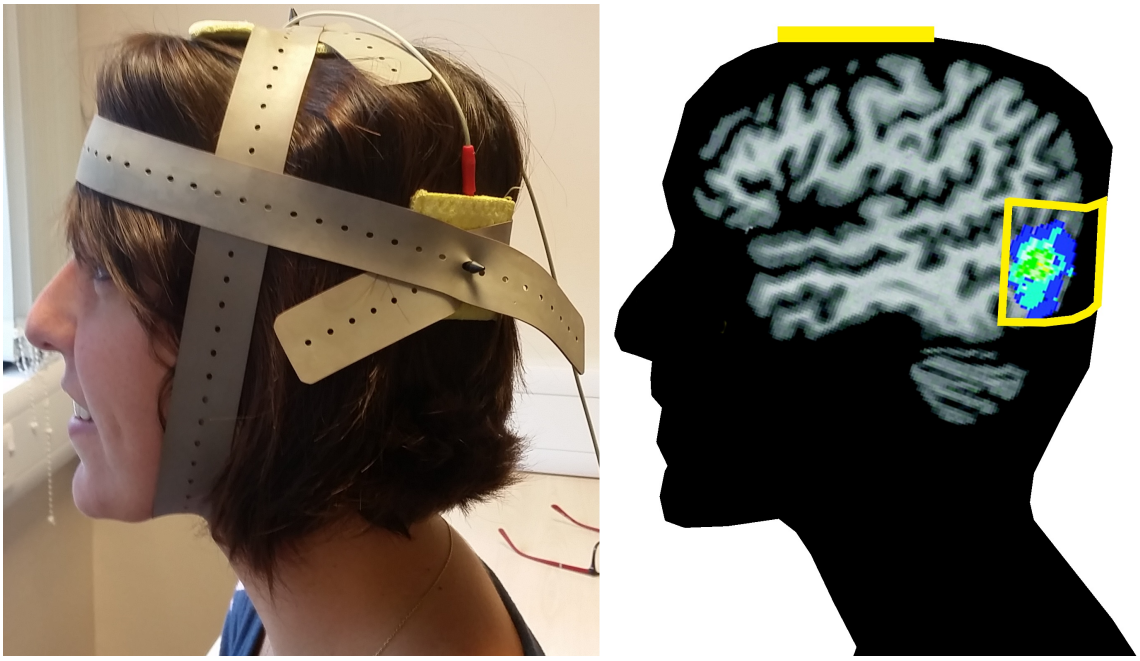


Figure 44: Placement of electrodes likely overlaid V5/MT+. (Left) Image of electrode placement used in this experiment. **(Right)** Simplified diagram of the image shown on the left, with an overlaid image of the average location of V5/MT+ (adapted from Malikovic et al., 2007). This indicates the active electrode was likely to have overlapped, and so stimulated some of V5/MT+.

It is possible that because tDCS has a limited penetration depth, despite the correct localisation of the electrodes over V5/MT+, the targeted brain area was not stimulated due to its sulcal location (Dumoulin et al., 2000). However, this is very unlikely to be the case because tDCS is not focal as described above, and because other groups using a very similar setup to that used in this experiment have shown tDCS to have an effect on motion-related behaviour (Antal et al., 2004d). The findings of Antal and colleagues would not have been possible if V5/MT+ was too deep to be reached with tDCS.

Online versus offline stimulation of V5/MT+

Another explanation for the failure of tDCS to alter motion perception during this experiment could be the timing of tDCS delivery. 'Online' stimulation refers to delivery of tDCS with simultaneous task completion, whereas 'offline' stimulation refers to stimulation before or after task completion. In this experiment, online tDCS stimulation was used. Although online tDCS has been shown to be consistently the most effective approach for the motor and cognitive systems (Martin et al., 2014; Sriraman et al., 2014), there have been indications that this may not be the case for the visual system (Pirulli et al., 2013). It is possible that there was no observed difference between the anodal group and the sham group in this experiment because V5/MT+ activity is not modulated online for this particular task. Online stimulation of the primary visual cortex with anodal tDCS has been shown to alter visual function (Spiegel et al., 2012), however there have been too few studies of extrastriate visual areas to know if this finding may extend to V5/MT+.

6.4.3 Future extensions of this research

This study looked only at the effect of anodal stimulation on a motion direction perception task. It would be interesting to observe if cathodal stimulation of V5/MT+, rather than anodal, would have an impact on motion perception. Previous studies have demonstrated that anodal tDCS in the occipital lobe is not consistently behaviourally excitatory and vice versa for cathodal stimulation. Antal and colleagues (Antal et al., 2004b) found that only cathodal, and not anodal, stimulation over V5/MT+ improved visuomotor co-ordination. In a further study, the group showed that applying either anodal or cathodal stimulation could reduce the motion after-effect (Antal et al., 2004d). These behavioural responses could be due to the anodal stimulation activating inhibitory brain areas, and cathodal stimulation creating disinhibition.

More basic experiments should be completed to further understand why tDCS does

not appear to modulate cortical excitability in a straightforward manner (anodal improves performance, cathodal decreases performance) in the visual cortex, as in the motor cortex. One simple experiment would be to determine the effect of tDCS on a measure of V5/MT+ baseline activity. This could be completed using TMS to stimulate V5/MT+, to induce moving phosphenes. tDCS could then be applied over V5/MT+, to determine if the stimulation is able to modulate the moving phosphene activity threshold. If successful, this would provide evidence that tDCS is indeed able to modulate V5/MT+ activity.

A more direct approach could be used to confirm whether tDCS can affect V5/MT+ activity. Subjects undergoing tDCS inside an fMRI scanner could complete a motion perception-dependent task likely to activate V5/MT+. If this was completed whilst the subjects underwent tDCS, the online changes in BOLD signal could then be determined, which would be a strong indicator of the effect of V5/MT+ stimulation on neural function in the area. Alternatively, positron emission tomography (PET) could be used to directly measure bloodflow changes induced by tDCS over the extrastriate cortex, similar to experiments in the motor cortex (Paquette et al., 2011).

A further extension of this research could be to determine the effect of tACS and tRNS on motion learning compared to tDCS. These more modern types of transcranial electric stimulation have been shown to be potentially more effective than tDCS (Vanneste et al., 2013) and have fewer skin sensation side effects (Fertonani et al., 2015).

6.5 Conclusions

In conclusion, anodal stimulation of left V5/MT+ in healthy participants during motion perception training did not influence motion perception compared to sham stimulation. This is likely because online, anodal stimulation of V5/MT+ is not the most appropriate way to modulate motion perception learning. The effect of tDCS

on area V5/MT+ has not yet been fully established, and this information is required to determine if tDCS can indeed modulate V5/MT+. If it is proven that tDCS can modulate activity of V5/MT+, then modifications could be made to the experiment presented here, to determine if other stimulation types can be used as an adjunct for motion perception learning. Examples include offline stimulation, and/or cathodal stimulation.

7 Investigation of motion perceptual training in an individual with damage to primary visual cortex

7.1 Introduction

Visual field defects (VFDs) are a type of partial cortical blindness: a loss of vision caused by damage to the vision areas of the brain. Homonymous hemianopia describes the loss of one half of the visual field in both eyes, and homonymous quadrantopia is a binocular loss of a quarter of the visual field (Figure 45). Most commonly, lesions leading to VFDs occur in the occipital cortex (Fujino 1986; Zhang et al., 2006b), resulting in damage to the primary visual cortex (V1) or its afferents.

7.1.1 Visual field defects and disability

VFDs have been shown to negatively impact upon quality of life (Gall et al., 2010; Papageorgiou et al., 2007), increase disability (Sand et al., 2016) and reduce the ability to successfully carry out activities of daily living (De Luca et al., 1996; Gall et al., 2010; Glen et al., 2015). VFDs often go unreported by patients and are frequently overlooked or under-prioritised by clinicians (Zhang et al., 2006b), perhaps because patients are often unaware of visual field loss (Peszczynski, 1961).

Spontaneous recovery of VFD following stroke occurs in only a minority of cases (Gray, 1989), and is limited to the first 3-6 months following damage (Zhang et al., 2006a). Rehabilitation of visual field defects presents a challenge, since patients are frequently of an aged population, which makes re-learning more of a difficulty (Peszczynski, 1961). Despite this, there are multiple strategies which have been employed to successfully rehabilitate VFDs.

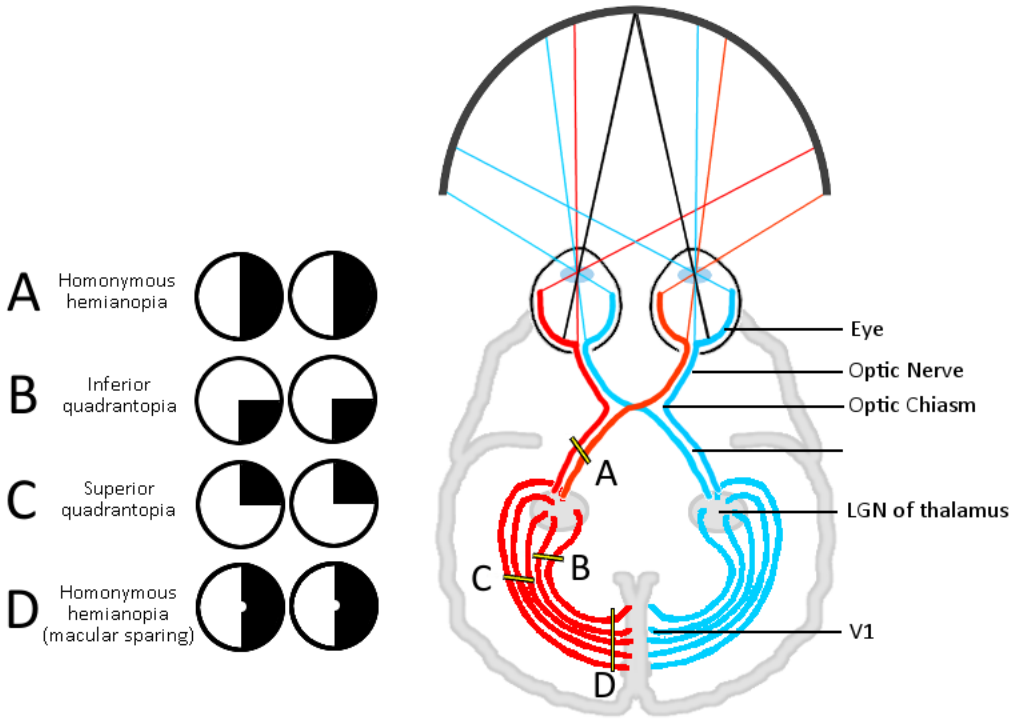


Figure 45: Lesions of the visual system. The extent of the visual field loss varies depending on where in the brain the damage occurs. On the left, the diagram shows a representation of the visual field in each eye, with the shaded region indicating cortical blindness in the corresponding area of visual field. On the right, the locations of corresponding lesions in the brain are illustrated with yellow bars. Post-chiasmic lesions of the visual system may lead to homonymous hemianopia **(A, D)** or quadrantopia **(B, C)**. LGN = Lateral geniculate nucleus, V1 = Primary visual cortex. Image adapted from OpenStax CNX, 2016 and Allwright, 2016.

7.1.2 Substitutive and compensatory therapies for VFDs

Prism therapy

Prism therapy utilises glasses with distorting prisms to expand or relocate the affected area of the visual field. Initially, prisms were applied to glasses such that the prism sector overlapped with the blind part of the visual field in both eyes (Woo & Mandelman, 1983). When gaze is directed through the prisms, the field-of-view is shifted so that the blind field of view can be visualised. There is no effect on vision when the patient looks elsewhere since the prisms are located entirely in the scotoma. This presents a circular problem: the patient will not be able to detect objects in the blind field without first making self-directed eye movements in that direction,

but they would not know an eye movement is required, since the object appears in their scotoma. Furthermore, when the patient looks through the prisms, because the scotoma will be relocated into the seeing field, a problematic central scotoma manifests (Pambakian et al., 2005). As a result of these issues, initial applications of prism therapy were shown to improve visual perception test scores, but not activities of daily living in patients with VFD (Rossi et al., 1990).

In order to attempt to bypass these problems, monocular prisms were trialled (Gottlieb, 1988). By applying the prism to only one of the eyes, the central region of vision is still visible when gaze is directed into the prism, thereby creating visual field expansion rather than relocation. However, this application has been shown to result in central diplopia (double vision) and confusion, which has prevented its clinical application (Cohen, 1993; Gottleib et al., 1996).

In order to overcome all the issues discussed above, a novel application of prism lenses in was developed in 2000 (Peli, 2000). The prism is applied monocularly so that there is visual field expansion and not just relocation as described above. However, the prism also covers the width of the lens in order to be effective no matter where the patient is looking, so self-directed eye movements are not required. The effect of these prisms is to produce extropia (outwards deviation of the eyes) in the periphery, which causes a peripheral, rather than central, diplopia. The peripheral diplopia causes less confusion and is much more acceptable to patients (Bowers et al., 2008), since it occurs in normal vision functioning (Bishop, 1981).

Studies where patients use such prisms show an improvement in obstacle avoidance, and the therapy has a good rate of long-term use (Bowers et al., 2008; Giorgi et al., 2009). A small study of two individuals with VFD showed that these prism glasses may also improve driving ability (Moss et al., 2014). Most importantly, these prisms show a positive impact upon reported quality of life measures (O'Neill et al., 2000).

Eye movement therapy

The eye movement behaviour of individuals with VFDs is often impaired (Bergsma et al., 2011). The majority of patients with such vision loss show a disorganised visual scanning pattern, extending into the intact hemifield on occasion, which drastically increases visual search duration (Zihl, 1995). The increased search time is characterised by an excessive number of fixations and a repetitive scanpath. Such patients struggle to appreciate the visual scene as a whole. Initial studies showed that practice of large saccadic eye movements towards the scotoma, aiming to give the patient a better overview of the visual scene, can increase the area of visual search (Kerkhoff et al., 1992; Zihl, 1995). Furthermore, such training can transfer to a real-life search task of visually identifying objects on a table, and the effects are maintained for least 3 months following training (Kerkhoff et al., 1994).

An improved system for eye movement training, which was low-cost and portable, also showed consistent effects of reduced visual search duration and improved scanpath efficiency (Mannan et al., 2010; Pambakian et al., 2004). More recently, this system has been translated into a free, web-based tool, where its effectiveness is still maintained (Jacquin-Courtois et al., 2013; Ong et al., 2015).

7.1.3 Restitutive therapies for VFDs

Despite the success of the substitutive and compensatory therapies described above, such treatments only offer ways to better cope with the blind area of the visual field. Another area of research within VFD rehabilitation adopts a different strategy of attempting to directly train the blind visual field, in order to restitute visual function within the scotoma.

Neuroplasticity in the visual cortex

Neuroplasticity refers to the changes which can occur in the structure and function of the brain with experience. To fulfill its role as the controller of behaviour, the brain must be able to adapt to environmental pressures and physiological changes. This drive results in neuroplasticity; changes at the molecular and cellular level of the brain which can eventually impact at the behavioural level. It is well-established that there is neuroplasticity in the adult visual cortex at a range of processing levels (Smallman et al., 2001; Zohary et al., 1994).

In the healthy visual system, neuroplastic changes can occur in response to perceptual training, leading to perceptual learning (Ball & Sekuler, 1987; Ramachandran & Braddick, 1973). The role of primary visual cortex (V1) has been well established in perceptual learning (Fiorentini & Berardi, 1980; Karni & Sagi, 1991), however, more recent research has also identified that higher visual areas, such as V4 and hMT+, can also play a role in perceptual learning (Liu, 1999; Yang & Maunsell, 2004).

These findings beg the question; is perceptual learning possible when V1 is damaged? And can such learning contribute to the rehabilitation of VFDs?

Perceptual learning and residual vision

Within the cortically blind portion of the visual field following V1 damage, it has been shown that some visual function remains. This function is frequently referred to as 'blindsight' or as 'residual vision'. For patients with VFDs, the amount of conscious visual awareness within the scotoma is variable (Sahraie et al., 2010b). Where there is no visual awareness of the stimulus, the phenonenom is referred to as 'Type I blindsight'. If the patient has partial conscious awareness (often described by patients as a "feeling" that something is present), then the behaviour is referred to as 'Type II blindsight' (Weiskrantz, 1997).

Initial attempts at visual restitution

Early studies carried out in non-human primates with VFDs indicated that training in the blind field could expand the size of the seeing visual field. Such training consisted of the presentation of lights in the scotoma, where the task was to detect and make saccades towards the lights (Cowey, 1967; Mohler & Wurtz, 1977). This research was then applied in humans, and demonstrated success in expansion of the seeing visual field into the scotoma in a majority of patients (Zihl & von Cramon, 1979; Zihl & von Cramon, 1985). However, subsequent studies failed to replicate such success after controlling for additional variables (Balliet et al., 1985). Further discussion confirmed that reduction of the scotoma size is possible in humans with this type of therapy, however is likely only possible in a minority of patient cases who have reversible damage (Pambakian & Kennard, 1997).

Vision restitution training (VRT)

In the mid nineties, a computerised training programme was developed by Sabel and colleagues to further investigate the findings of Zihl and von Cramon (Kasten & Sabel, 1995). This therapy, termed vision restitution training (VRT), involves the detection of lights at the border of and within the blind field. Spots of bright light appear at one of 500 positions along the border of the scotoma on a dark screen, and the patient must respond when light is detected (Kasten et al., 2000). After 6 months of daily training with VRT, there was an average visual field enlargement of 5° of visual angle, and 72% of patients reported subjective improvements in vision function (Kasten et al., 2000).

Following criticism that the apparent expansion of visual field may be a result of eye movements, in particular because the perimetric data were collected using the same device used for the training (Horton, 2005a), Sabel and colleagues repeated VRT therapy using a scanning laser opthalmoscope to control for eye movements.

Unfortunately, under such conditions, the effects of VRT on visual field expansion were abolished (Reinhard et al., 2005). Further controversy has persisted (Horton, 2005b; Sabel et al., 2005; Sabel, 2006), and the effects of VRT remain unproven. The most recent published literature indicating that changes in visual field border may only occur in combination with mild electrical brain stimulation (Gall et al., 2015).

Flicker stimulation

Flicker stimulation is another type of rehabilitative therapy for VFDs. Training involves exposure to a flickering stimulus in the blind field. Despite no changes in recorded perimetry, significant improvement in detection of flickering stimuli was evoked 25° and 30° into the scotoma. The rate of successful identification of flickering letters positioned in the blind field was comparable to performance in the seeing field, following training (Raninen et al., 2007). Imaging determined that there was ipsilateral representation of the trained visual hemifield in the cortex, indicating functional reorganisation at the cortical level (Henriksson et al., 2007). However, extensive training was required (twice weekly for a year) in order to observe such effects.

The effect of flicker training and compensatory saccadic eye movement training for rehabilitation of VFDs were compared by Roth et al. (2009). Following 6 weeks of eye movement training, patients showed improved visual search ability in their blind field. No such effect was identified for flicker training. However, neither training group showed any change in the size of visual field, likely due to the briefer duration of the training regime.

Optimally-tuned sinewave gratings / NeuroEye Therapy

Residual vision in patients with VFDs has been shown to be optimally sensitive to stimuli with a narrow spatial and temporal bandwidth (Barbur et al., 1994; Sahraie et

al., 2003; Sahraie et al., 2010a). Sahraie and colleagues have developed a perceptual training protocol which aims to target residual vision by exploiting this finding. The training involves detection of circular patches of sinewave gratings, which are spatially and temporally optimally tuned for detection in the blind field of VFD (Sahraie et al., 2006). The training is carried out daily over a 3-month period. It was found that such training can improve the discrimination ability and awareness of sinewave gratings across a range of spatial frequencies and contrasts, expanded the visual field border and lead to subjective improvements in vision. Furthermore, the training progressively led to blindsight performance (type I blindsight detection without awareness), followed by detection with reported awareness (type II blindsight), developing eventually to conscious vision, suggesting that blindsight ability and conscious vision lie on a spectrum (Sahraie et al., 2013).

Research demonstrated that training with optimally-tuned sinewave gratings can be successful with even bilateral cortical damage to V1 (Trevethan et al., 2012), but that if lesions extend to the thalamus the training is less likely to be successful (Sahraie et al., 2010a).

The main issue with the tuned sinewave grating training programme is that successful detection of such a narrow bandwidth of stimuli may be unlikely to transfer to activities of daily living, and an improvement in quality of life, though the decrease in scotoma size is promising. Further investigation is required to determine the wider applicability of this exciting research.

Motion perception training

In the blind field of patients with VFDs, there is often considerable residual motion perception (Morland et al., 1999; Schenk & Zihl, 1997). This phenomenon is also seen in macaque monkeys (Moore et al., 2001). Motion is mediated by activity at V5/MT+, which due to its distal location from V1 is often left intact following damage that results in VFD. Furthermore, there is evidence from macaque monkeys

that V5/MT+ may receive direct inputs from the thalamus, as well as indirect inputs which flow through the superior colliculi, thereby bypassing the lesioned area of the brain (Sincich et al., 2004). More direct evidence has been collected that indicates residual visual functions may be mediated by activity in V5/MT+ in macaques (Schmid et al., 2010).

Huxlin et al. trained patients with VFDs on a complex motion perception task designed to engage area V5/MT+. Participants were required to discriminate left or right motion of a moving dot stimulus. The task difficulty was adaptively modulated by changing the range of displayed motion directions. For example, in the easiest version of the task, all dots moved along the same vector. A harder version of the task involved motion direction discrimination where the dots moved along a range of vectors around the target direction. Correct responses required participants to be able to extract the global direction vector by integrating all dot directions displayed in the stimulus (Huxlin, 2008). Training resulted in direction integration thresholds in the blind field being improved. The extent of improvement meant that after training, thresholds in the blind field were equivalent to thresholds measured in the seeing field (Huxlin et al., 2009). Training effects also improved contrast sensitivity and the extraction of coherent motion from noise motion, both of which were not trained directly. Luminance detection as assessed by perimetry was also altered by training, though only to a very limited extent.

An extension of this research was continued by Huxlin and colleagues in 2014, to determine if training effects could be mediated by stimulation outside of typical blindsight channels. Subjects were trained to discriminate the orientation of static gratings presented in their blind field. Prior to training, subjects were unable to discriminate orientation significantly above chance level. However, following 20-40 daily training sessions, subjects were better able to discriminate orientation. In fact, their performance became comparable to their performance in the intact visual hemifield. Training with the static orientation stimulus also improved the ability of patients to perform a simple motion discrimination task of high-contrast moving

gratings, but the ability to perceive complex motion of moving dots showed only partial recovery (Das et al., 2014).

A further group of participants was trained at two locations in their blind hemifield. At the first location, the static grating orientation task was carried out. At the second location, the motion task described above was trained. Training was completed daily, for 20-40 days. Performance on both tasks, at both locations, was assessed following training. Performance at the trained task in the trained location demonstrated significant learning, with performance levels comparable with those in the seeing hemifield. Further, it was demonstrated that learning of each task was almost completely transferred to the area of the blind field trained in the other task. Unfortunately, no untrained area of the blind field was included for comparison with a trained area (Das et al., 2014). There were no quality of life assessments, so it is not clear if such training may be transferable to daily life for patients.

7.1.4 Summary and experimental overview

Previous research has demonstrated that it is possible to rehabilitate VFD in patients with damage to V1 by encouraging the development of compensatory strategies, or even by direct stimulation of the scotoma by extensive perceptual training in order to enhance residual vision in the blind area of the visual field. The most successful therapies delivered stimuli tuned to blindsight channels, such as motion-based stimuli, at the border of and within the scotoma. However, such therapies typically require many months of training for any effect to be mediated, and show only modest changes in visual field size.

In this experiment, one patient with a homonymous quadrantopia VFD was trained to discriminate horizontal (left or right) motion direction of moving dots, against a background of randomly-moving noise moving dots (extraction of signal against noise). The participant was trained for a total of 2000 trials, spread across three meetings with a large stimulus aperture (30°). The stimulus was moved progressively further

into the blind region with each session. Changes on psychophysically measured motion perception thresholds and perimetric measures of visual field defect size were determined following training.

7.2 Methods

Further information about the setup of this experiment can be found in Chapter 2.

7.2.1 Participant case history

This study was carried out on an adult male patient, aged 73, with a stable lower right quadrantopia. The quadrantopia was caused by a stroke affecting left V1, confirmed by MRI (Figure 46), which occurred at least 16 months prior to the participation in this experiment. The subject declared that there was a little improvement of visual field in the initial months following the stroke, however the scotoma had since stabilised.

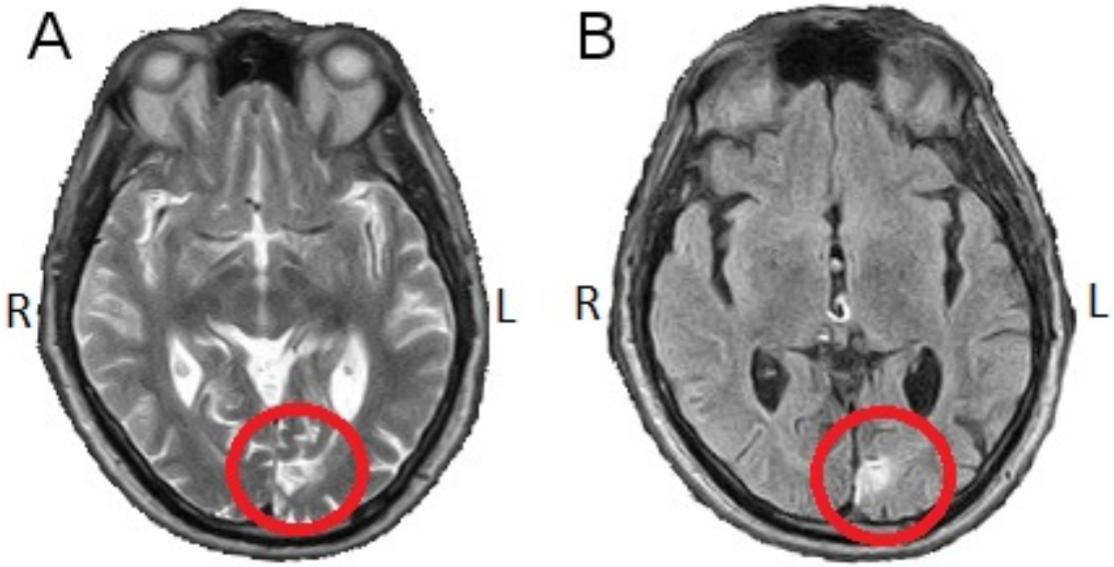


Figure 46: Structural MR scan of participant. Images showing the location and extent of the patient's lesion in the left primary visual cortex. The lesion is shown as a hyperintense region in the images, which has been highlighted with a red circle. **(A)** T2-weighted image. **(B)** T2-weighted FLAIR image.

7.2.2 Perimetry

Perimetry information was collected several weeks before the first session, and immediately following the final session. Data were collected using the Kowa automatic

visual field plotter standard test (AP-340, Kowa Company Ltd.). Light duration was 0.8s with an interval of 0.9s. The background luminance was set to 0.1 candela per square metre (cd/m^2; 31.5 asb). Lights were displayed at different luminances: 14cd/m^2 (43 asb), 42cd/m^2 (133 asb), 135cd/m^2 (435 asb), and 1082cd/m^2 (3400 asb). If the patient could detect a light that was equal to or dimmer than 135cd/m^2 (425 asb), it was categorised as being seen for the purpose of this study. If the patient could detect a light 1083cd/m^2 (3400 asb), it was categorised as partially seen. Where 1083cd/m^2 (3400 asb) points were not detected, the area was classified as blind. 310 points were assessed for each eye in the pre-training session, and 281 points in the post-training session. The baseline visual field is illustrated in Figure 47.

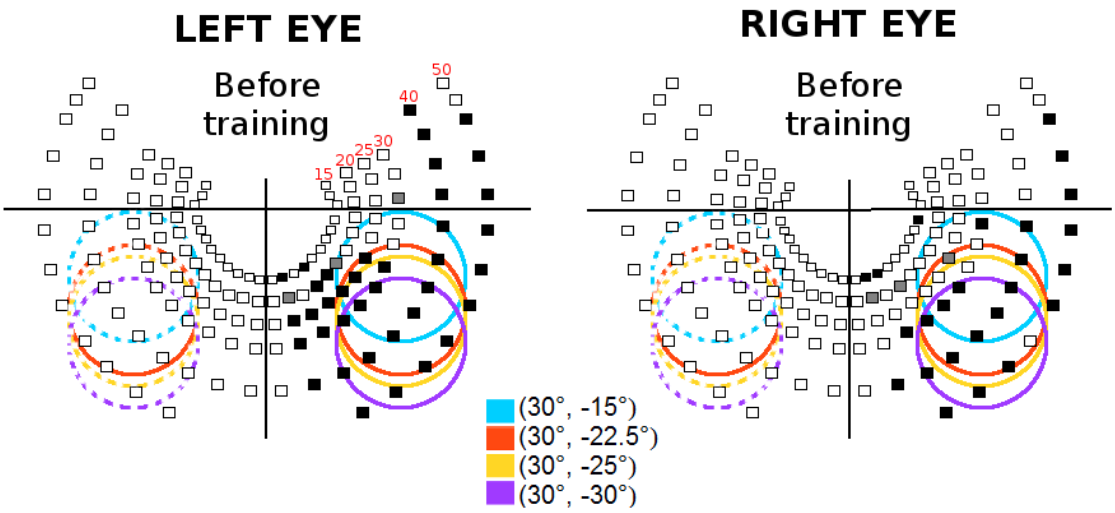


Figure 47: Visual fields visualised using perimetry prior to training. Black boxes denote points not visible at 1083cd/m^2. Grey boxes denote points visible at 1083cd/m^2 or brighter. White boxes denote points visible at 135cd/m^2 or dimmer. Circles show the three training locations and an additional location tested in the blind field (solid lines) and seeing field (dashed lines). All points not shown were successfully detected at 135cd/m^2 by the patient. The blind spot is not visualised.

7.2.3 Visual task and stimuli

The motion direction perception task was used in this experiment (see Chapter 2 for more information). The participant identified whether a group of coherently-moving

dots had leftwards or rightwards motion, when displayed amongst randomly-moving distractor dots ('noise'). The direction of coherent motion was variable and restricted to within a 90° angle centred around the horizontal plane. The stimulus was presented for 500ms within a circular area 30° in diameter, at eight different locations in the visual field. The stimulus locations have been defined here according to the distance (measured in visual degrees) from the centre of the stimulus to the fixation cross. Locations use the format (X°, Y°), with the fixation cross set as (0°, 0°). Positive values denote upwards/rightwards offset and negative values denote downwards/leftwards offset from fixation. Figures 47 and 48 visualise all eight of the stimulus locations.

Motion perception training used the standard two-down one-up staircase described in Chapter 2. However, in assessment blocks, the stimulus difficulty was instead modulated using QUEST (Watson & Pelli, 1983), a different type of adaptive psychometric method, which can obtain a measure of motion perception performance using fewer trials. The stimulus duration was also reduced to 250ms during assessments, as this shorter duration would reduce, although not eliminate, saccadic eye movements towards the stimulus (Carpenter, 1977). It is important to reduce the possibility of saccadic eye movements towards the stimulus during assessments, to provide an accurate measure of performance for the blind field.

Stimuli were presented using Psychtoolbox (v3.0.8) for Matlab (v7.4.0.287, Mathworks) on a widescreen plasma monitor (75Hz, 1360x1024, 50 PDP-503MXE, Pioneer).

Eye tracking data were recorded for all training sessions using EyeLink II (SR Research). Due to technical issues, data for analysis was only available for the first training session. Data were analysed by plotting gaze position and by determining the number of trials where eye position deviated by more than 8° from fixation during presentation of the stimulus.

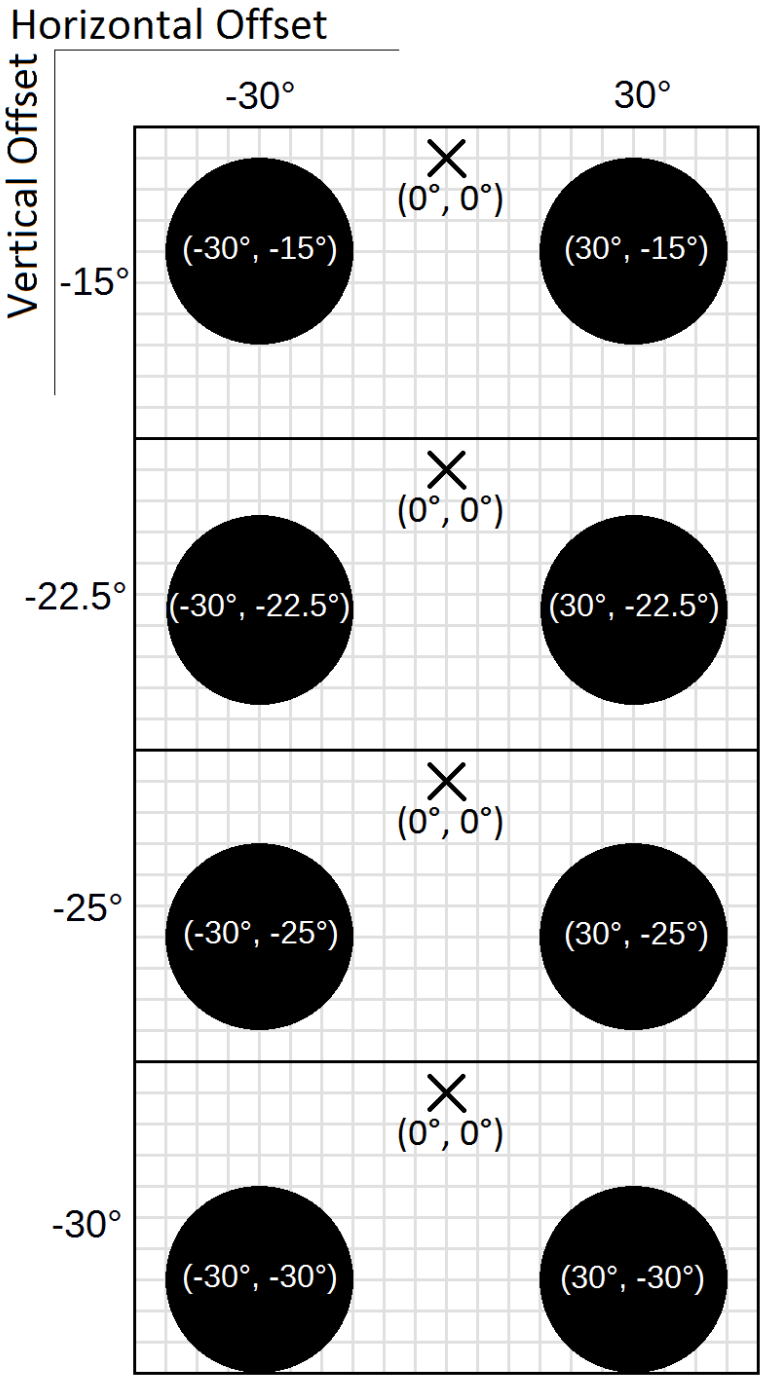


Figure 48: Stimulus locations. The diagram demonstrates where each of the eight stimuli were delivered, with reference to the centre of the stimulus relative to the fixation cross at (0°, 0°). Each square of the grid corresponds to 5°. Note: The left and right stimuli were never presented together; this figure is for illustration purposes only.

7.2.4 Assessment and training paradigms

The participant met with the research team on three occasions. At the first meeting, the participant completed one 400-trial block of motion perception training at the border of the blind field, with the centre of the stimulus at location (30°, -15°). At the second meeting, the participant completed two 400-trial blocks of training deeper into the blind field, at location (30°, -22.5°). On the third and final meeting, the participant completed two 400-trial blocks of the motion direction perception task offset slightly further again into the blind field, at location (30°, -25°).

Across the three sessions, the participant was repeatedly assessed using the motion direction perception task at the three training locations (30°, -15°), (30°, -22.5°) and (30°, -25°), as well as equivalent locations in the seeing field of (-30°, -15°), (-30°, -22.5°) and (-30°, -25°). In addition, the patient was assessed at an extra location deep in the blind field of (30°, -30°), and its equivalent in the seeing field of (-30°, -30°). The training locations are visualised in Figures 47 and 48. The order of training and assessment tasks is summarised in Figure 49.

15

VISIT 1		VISIT 2		VISIT 3	
	Stimulus locations (X°, Y°) from fixation		**Stimulus locations (X°, Y°) from fixation**		**Stimulus locations (X°, Y°) from fixation**
Assessment	(30°, -15°) ; (-30°, -15°)	Assessment	(30°, -30°) ; (-30°, -30°)	Assessment	(30°, -30°) ; (-30°, -30°)
Training	(30°, -15°)	Assessment	(30°, -22.5°) ; (-30°, -22.5°)	Assessment	(30°, -25°) ; (-30°, -25°)
Assessment	(30°, -15°) ; (-30°, -15°)	Training	(30°, -22.5°)	Training	(30°, -25°)
Assessment	(30°, -30°) ; (-30°, -30°)	Break		Break	
		Training	(30°, -22.5°)	Training	(30°, -25°)
		Assessment	(30°, -30°) ; (-30°, -30°)	Assessment	(30°, -30°) ; (-30°, -30°)
		Assessment	(30°, -22.5°) ; (-30°, -22.5°)	Assessment	(30°, -25°) ; (-30°, -25°)
				Assessment	(30°, -22.5°) ; (-30°, -22.5°)
				Assessment	(30°, -15°) ; (-30°, -15°)

Figure 49: Order and locations of assessments and training blocks across the three visits. Locations are given as horizontal and vertical offset from fixation to the centre of the stimulus, in visual degrees. Positive values denote upwards/rightwards offset and negative values denote downwards/leftwards offset from fixation. Training sessions are highlighted in yellow.

7.2.5 Data analysis

In order to determine whether motion perception changed during training, performance was quantified for each training session to give a coherence threshold. The coherence threshold is defined as the percentage of dots required to be moving coherently for the participant to be correct 80% of the time. More information can be found in Chapter 2.

Each block of 400 trials was split into 200-trial sections so within-session analysis could be facilitated. Where 800 trials were completed in a session, the performance in the first 200 trials was compared to the average performance across the remaining 600 trials.

7.3 Results

Throughout each of the three meetings, the participant was assessed on performance of the motion direction perception task at different locations. The stimuli in the assessments were briefer in duration than the training stimuli (250ms instead of 500ms), reducing the possibility of eye movements. As well as assessments in the three training locations, assessments were also carried out at a location deep in the blind field (30°, -30°), and at all equivalent locations in the seeing field.

7.3.1 Learning at the border of the blind field

In the first of the three training sessions, 400 trials of the motion direction perception task were delivered at location (30°, -15°). This means the stimulus, which was 30° in diameter, was positioned so the upper edge was in line with fixation and the leftmost edge was offset 15° to the right of fixation. According to the perimetry (Figure 47), the stimulus was therefore delivered partially in the seeing field with the remainder in the blind field. During this first training session, the coherence threshold decreased from 46.5% to 38.5% coherence (Figure 50), indicating improvement on the task and learning at this location.

Assessments were carried out for area (30°, -15°), and a coherence threshold determined (Figure 51). The improvement in performance seen during training was confirmed, with the assessment threshold decreasing from 85.7% coherence to 44.8% coherence following training. Furthermore, an additional assessment completed at the end of the third session indicated the learning effect was maintained over several days, with a threshold value of 30% coherence.

At the second training session (trials 400-1200), training was moved to location (30°, -22.5°), so a larger proportion of the training was delivered to the blind field compared to the first session (Figure 47). The pattern of response to this training was similar to that for (30°, -15°) described above. Firstly, there was overall learning

during training, with the coherence threshold decreasing from 73.0% in the first 200 trials to an average of 63.6% in the remaining 600 trials (Figure 50). This learning was confirmed by a change in performance between pre-training and post-training assessments, which improved from 100% coherence (chance level) to 72% coherence (Figure 51). This threshold was maintained at 56% when measured at a later date.

The amount of learning seen in the second training session was smaller in magnitude overall compared to the amount of training seen in the first session, despite the number of trials being doubled (800 instead of 400). The smaller magnitude of learning effects was consistent across the training and assessment measures. Furthermore, the starting threshold for the second session was higher than the starting threshold for the first session. This indicates that the participant found the task more difficult at the second location, compared to the first location. This is likely because the stimulus was moved further into the blind field, making it less visible. It is unlikely that the effect was caused by the task being presented more peripherally, because the patient performed equally well at the two equivalent locations in the seeing field (data presented later in this chapter).

7.3.2 Learning within the blind field

At the third and final training session (trials 1200-2000), the task was delivered at location (30°, -25°). The pattern of learning effects at (30°, -25°) looked different to the first two training locations. The participant was still able to successfully complete the task at this location, and even showed improvement in the task over the duration of the training. Performance varied but ultimately improved. The threshold changed from 83.0% coherence in the first 200 trials to an average of 69.0% coherence in the final 600 trials.

However, the assessments determined the coherence threshold as 100% (chance level) at location (30°, -25°). It is possible that the task was too difficult at assessment, and therefore not sensitive enough to detect the learning effects seen in the training. The

QUEST assessment loses power if the participant finds the task difficult, as it uses only 40 trials to determine detection threshold. Further analysis of the pre-training and post-training QUEST assessments at (30°, -25°) was completed for when the stimulus was presented at 100% coherence (the easiest difficulty). The patient was correct 20/38 (52.6%) trials before training, and was correct 24/38 (63.2%) trials after training.

There was no training of area (30°, -30°), and repeated assessments of this blind area showed no change over time. The participant was consistently unable to determine direction of motion above chance level at this location, even when all presented dots moved coherently.

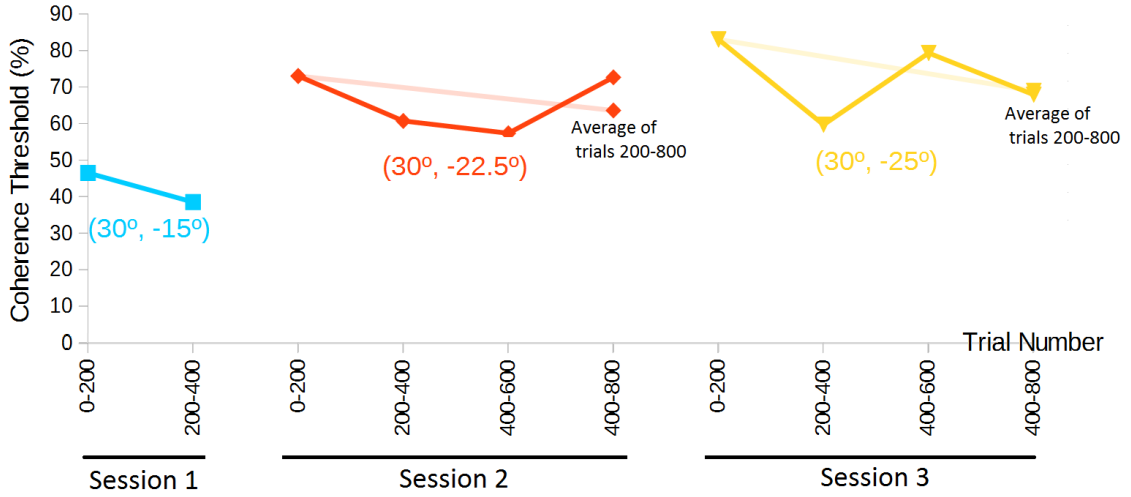


Figure 50: Performance in the three training sessions, broken down into 200-trial blocks. Within each session, performance was on average better than performance in the first 200 trials. Performance in the initial 200 trials of each session was progressively worse, as the stimulus was moved deeper into the blind field with values of 46.5%, 73.0% and 83.0% for (30°, -15°), (30°, -22.5°) and (30°, -25°) respectively.

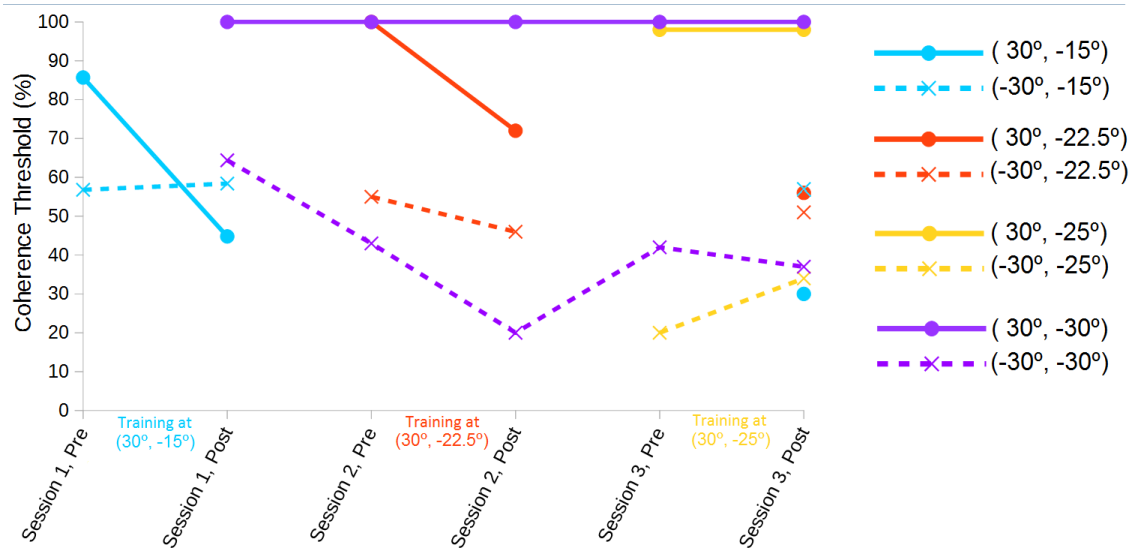


Figure 51: Assessment of coherence thresholds for eight different stimulus locations. The blind field is denoted by solid lines and circle markers, and the seeing field is denoted by dashed lines and cross markers. In the blind field, there was a maintained improvement for two of the training locations (30°, -15°) and (30°, -22.5°), but no change in the third trained location (30°, -25°) or deep in the blind field (30°, -30°). For the seeing field, there was no maintained change at (-30°, -15°) or (-30°, -22.5°), and a decrease in performance at (-30°, -25°). There was a gradual improvement in performance at (-30°, -30°).

7.3.3 Changes in the seeing visual field

Assessments were carried out in the seeing field in locations with the same vertical offset and opposite horizontal offset as the trained areas of the blind visual field. If learning was transferable across the visual field, it would be expected that performance in the motion task would improve at the untrained locations, following improvement at trained locations. In order to compare the change in performance across different locations, a learning index was calculated (see Chapter 2) using the initial and final assessments, for each area of the visual field that was exposed to the stimulus (Figure 52).

For the location trained in the first training session (30°, -15°), the assessment of the equivalent location in the seeing field (-30°, -15°) showed no improvement following training, nor was the performance better at the final assessment several days later. This indicates that the perceptual learning at location was (30°, -15°) was specific

to the hemifield trained. For the seeing field location associated with the second training session (-30°, -22.5°), there was also little-to-no change in performance, indicating again no transfer of learning.

The pattern was different for the third training location. For seeing field location (-30°, -25°), there was a worsening in the performance of the participant. The facile explanation is the result could have been caused by a fatigue effect or had been a performance anomaly caused by noise, since there were limited data collection points.

There was no training of area (30°, -30°), and consistent repeated assessments of this blind area showed no change over time. A very interesting finding was that equivalent seeing area (-30°, -30°) improved across assessment sessions. This was the only area of the seeing field where performance improved. It is not clear why there would be transfer of learning to location (-30°, -30°) from the areas trained. It is possible that the learning effects mediated are simply a result of repeated practice at the assessment task, which can lead to perceptual learning in its own right. An alternative explanation is that it is a noise effect (variation in performance resulting from measurement noise), since (-30°, -30°) is close to (-30°, -25°), where the opposite effect was mediated.

There was no change in motion perception performance at locations (-30°, -15°) or (-30°, -22.5°) and there were opposite changes at positions (-30°, -25°) and (-30°, -30°). Given that the pattern of results presented here is not consistent, and the fact that very minimal data were collected, no firm conclusions can be drawn from this dataset. In future, all locations should be assessed in a randomised manner at each timepoint. This would have generated more data and therefore more solid conclusions could be drawn from the information gathered.

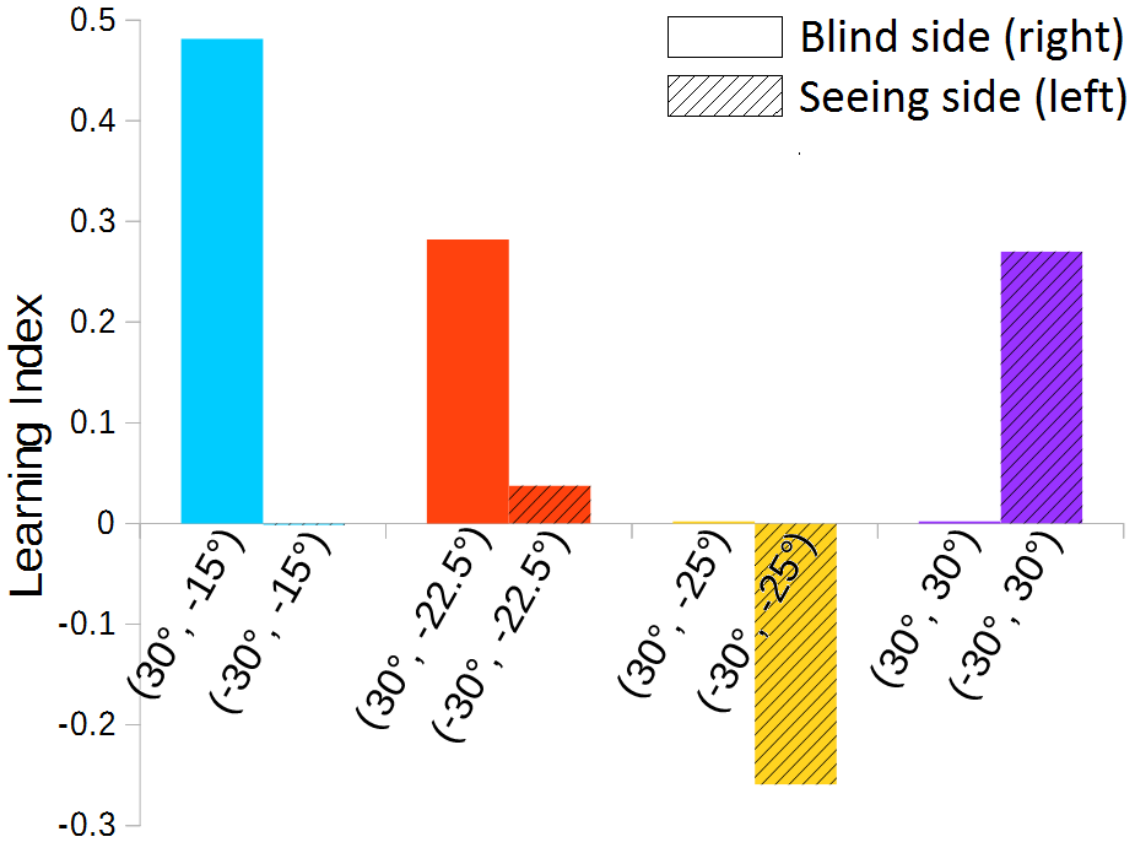


Figure 52: Learning index for all assessed areas of the visual field. For the blind side (plain bars), there were quantifiable improvements at (30°, -15°) and (30°, -22.5°), with no reported change in other areas assessed. For the seeing field (hatched bars), there were no changes in (-30°, -15°) and (-30°, -22.5°) and a decrease in performance at location (-30°, -25°). The only location in the seeing field that showed an improvement was (-30°, -30°).

7.3.4 Changes in visual field following training

Perimetry is used to determine the extent of the visual field, and therefore with patients is used to determine the size and density of any scotoma present. In this experiment, perimetry was completed prior to training, and again immediately after the final training session to determine if there were any changes in visual field (Figures 53 and 54). Before training, the participant missed 64/309 (20.7%) points in the left eye and 51/310 (16.5%) points in the right eye. After training, the participant missed 29/281 (10.3%) points in the left eye and 24/281 (8.5%) points in the right eye (not all points displayed). The changes in both eyes were located both inside and outside of the regions of visual field stimulated by the motion task.

The data in the right eye were not straightforward. Firstly, there were several points that the participant previously reported seeing, but was unable to detect in the second assessment. These points were located just above the horizontal midline, and also in an area between the vertical midline and the motion perception stimulus region (close to the midline). However, there was an improvement in several points which overlapped with the regions of visual field stimulated by the motion direction perception task. These points were spread vertically, and corresponded to the top and middle of the first training stimulus location, or the upper parts of the later training stimulus locations.

The data in the left eye gave a clearer picture. There were improvements in light detection just above the horizontal midline and just next to the stimulus locations, between the vertical midline and the stimuli. Furthermore, there were improvements overlapping with the stimuli. These were clustered in the first training area and upper section of second training area, as well as deep in the blind field; the lower section of the first training area, the middle of the second and third training areas.

It is important to note that there are reliability issues with perimetry measurements. Patient data can be very variable and performance can be strongly impacted by fatigue (Gardiner et al., 2014). In order to conclude whether there were genuine changes in perimetry, repeated pre-training and post-training measurements would be required to overcome measurement noise.

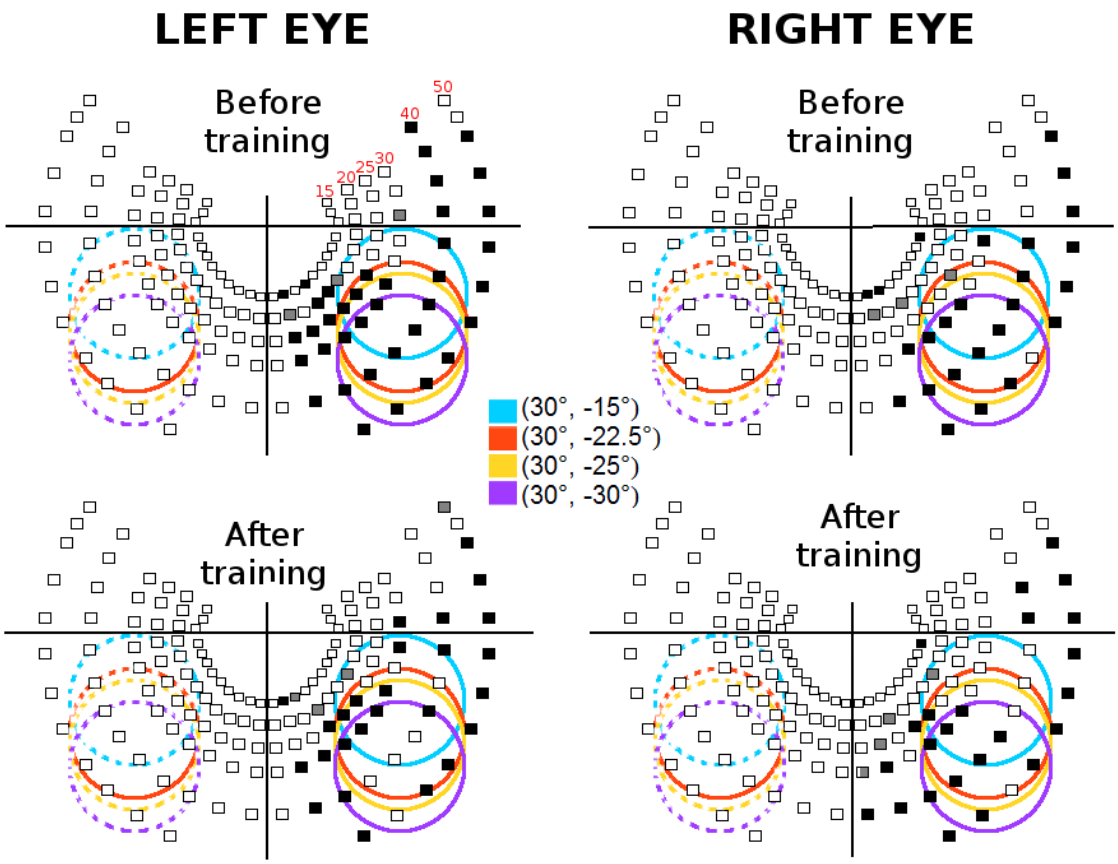


Figure 53: Perimetry before and after training. There was an overall decrease in the percentage of missed points following training. There is a large patch of visual field which became visible in the left eye, which overlaps with the stimulus location. Some points also improved in the right eye overlapping with the stimulus. There were also improvements outside of the stimulated parts of the visual field. Black boxes denote points not visible at 1083cd/m^2. Grey boxes denote points visible at 1083cd/m^2 or brighter. White boxes denote points visible at 135cd/m^2 or dimmer. Circles show the three training locations and an additional location tested in the blind field (solid lines) and seeing field (dashed lines). All points not shown were successfully detected at 135cd/m^2 by the patient. The blind spot is not visualised.

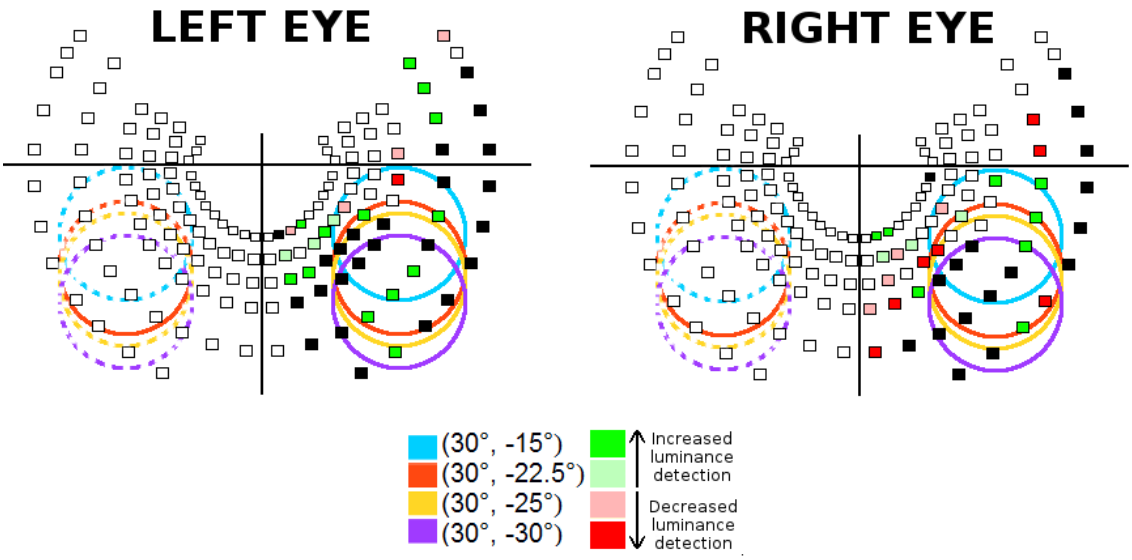


Figure 54: Changes in perimetry measures following training. There was an overall decrease in the percentage of missed points following training. There is a large patch of visual field which became visible in the left eye, which overlaps with the stimulus location. Some points also improved in the right eye overlapping with the stimulus. There were also improvements outside of the stimulated parts of the visual field. Green boxes indicate an increase in luminance detection and red boxes represent a decrease. White boxes indicate that the point was detected both before and after training, and black boxes indicate that the point was not detected either before or after training. Circles show the three training locations and an additional location tested in the blind field (solid lines) and seeing field (dashed lines). All points not shown were successfully detected at 135cd/m^2 by the patient. The blind spot is not visualised.

7.3.5 Eyetracking data

Eyetrack data were collected successfully for the first training session only. Analysis demonstrated that the participant failed to fixate on 55/400 trials. All deviations were to the right and downwards, towards the stimulus. Gaze position for a selection of trials is shown in Figure 55. It appeared that the eye movements occurred mostly at the start of training, with 49/55 gaze deviations occurring in the first 150 of 400 trials (Figure 56).

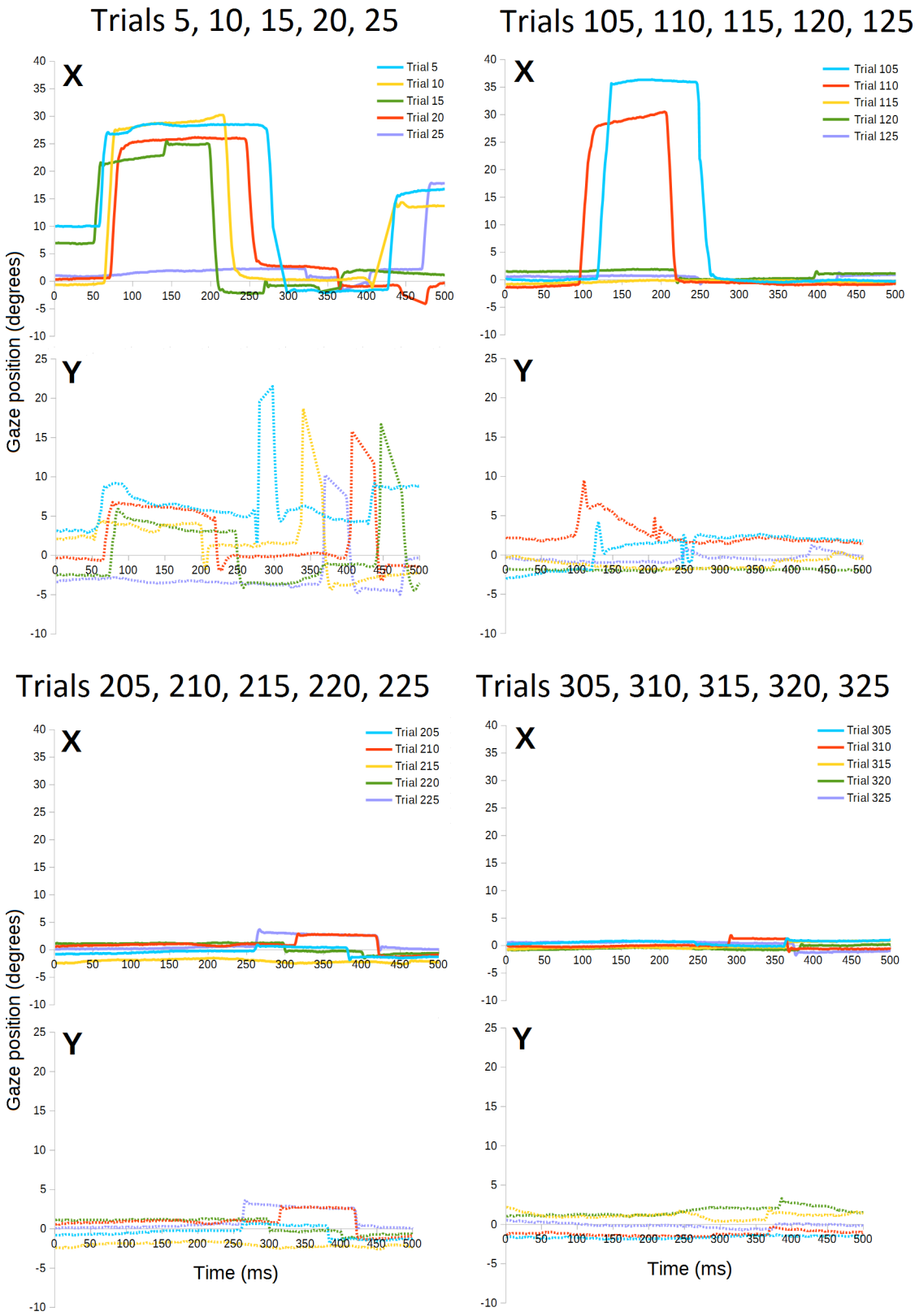


Figure 55: Fixation of gaze position improved during training. The participant completed 400 trials during the first training session. This figure shows the gaze position during stimulus presentation for 20 example trials (trials 5, 10, 15, 20, 25, 105, 110, 115, 120, 125, 205, 210, 215, 220, 225, 305, 310, 315, 320, and 325). Initially, the participant made eye movements to the right (upward deviation of solid line) and downwards (upwards deviation of dotted line), towards the stimulus. However, during later trials, the participant was able to maintain fixation. Solid line = X-axis of gaze; dotted line = Y-axis of gaze.

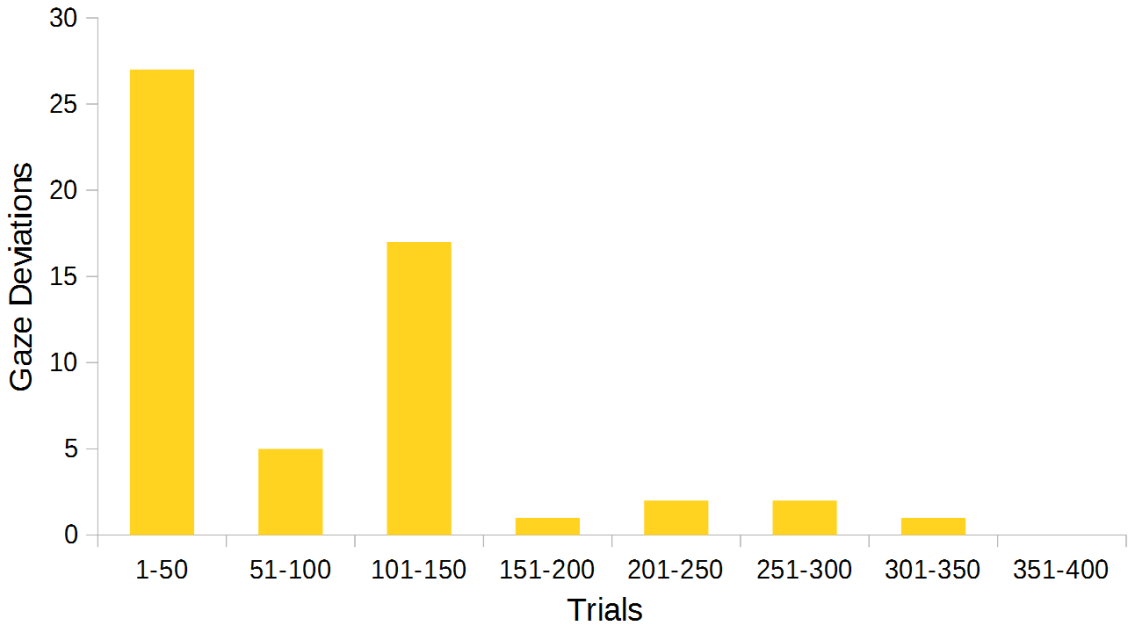


Figure 56: Number of gaze deviations was highest at the start of the training session. The number of gaze deviations (defined as an eye movement exceeding 8° in any direction) was highest during the first 50 trials. As the training progressed, the participant was better able to maintain fixation.

7.4 Discussion

In this experiment, a patient with a lower right quadrantopia was trained on a motion direction perception task across three sessions, which involved discriminating the direction of coherently-moving dots presented against a background of randomly moving dots. The large stimulus area was moved progressively further into the blind area of the visual field across the three training sessions. In addition to training, assessments of motion perception performance were also carried out. Assessments differed to the training by being shorter in duration (250ms instead of 500ms), and using a different adaptive method (QUEST instead of two-down one-up staircase). Assessments were carried out for the three trained areas and an additional location deeper in the blind field, plus matched equivalent areas in the seeing field.

7.4.1 Motion perception learning in the blind field following training

Residual vision refers to the ability of patients with VFDs to perform visual tasks within their blind field (Weiskrantz et al., 1974). One of the retained visual abilities frequently reported is the ability to detect motion (Barbur et al., 1980; Blythe et al., 1987). In this experiment, the patient was able to successfully complete a motion direction perception task above chance level, in all three of the training areas tested. This included a region which was deep in the blind field, indicating that residual vision was engaged in this study. Not only was there simple detection of motion, but the patient was able to successfully discriminate the direction of motion of coherently-moving stimuli amongst randomly-moving noise. With repeated exposure to the task, the amount of coherent motion required for successful discrimination of direction of motion. by the patient was decreased. This potentially indicated the possibility of perceptual learning of complex motion stimuli, deep within the blind field. The result is backed up by previous research that indicates similar patients can indeed improve motion perception performance with repeated practice (Huxlin et al., 2009). Huxlin et al. showed that repeated practice of a motion direction

discrimination task, where the range of motion directions was increased following training of global integration, can be improved following practice. However, training here was delivered over only three sessions, whereas many months were required in previous studies. There is further discussion of this point below.

Was learning confounded by light scatter?

It is possible that any learning shown here was a result of light scatter effects. If a bright stimulus is presented in the blind field, there may be light which scatters to stimulate areas of the retina corresponding to intact areas of the visual field. Therefore, the patient may use these cues, rather than responding to information actually presented in the blind field. It is unlikely that light scatter was an issue here. A similar setup was applied in the literature previously, with white dots on a dark background being presented to healthy individuals in the blind spot (Huxlin et al. 2009). It was shown that participants were unable to discern the direction of motion under such conditions, even with training. Regardless, in future experiments, stimuli would be presented as dark dots on a white background to reduce any potential light scatter effect.

Was learning confounded by eye movements?

Although the participant was able to perform the motion task at the third training location (30°, -25°), the subject was unable to successfully perform the assessment at this location. The main difference between the training and assessment session was that the duration of the stimulus was reduced from 500ms to 250ms. One explanation for why the participant found the shorter task duration more difficult could be that there is less time for the visual system to integrate the motion stimulus. Previous studies have indeed shown that shorter exposure time to a stimulus makes the task more challenging. For instance, an electrophysiology study in non-human

primates demonstrated that activity in a decision-making area increased, potentially indicating an increased cognitive demand, when task duration was longer. It was shown that as time elapsed following the onset of a moving stimulus, the firing rate of cells increased (Roitman & Shadlen, 2002). Therefore, the longer the stimulus exposure, the more reliable the behavioural decision. However, for the areas trained in the first and second sessions, post-training assessment thresholds were similar to thresholds obtained during training. This indicates that stimulus duration is unlikely to alter task difficulty in this manner.

An alternative, more troublesome explanation is that training performance was confounded by eye movements. If the patient was making eye movements towards the stimulus during training, but not during assessments, this could account for the difference in performance as the stimulus would be brought further into the seeing field during the training. The brief duration of stimulus presentation at assessments compared to the training stimuli could indeed have facilitated this possibility. Saccadic eye movements take 20-150ms depending on amplitude (De Brouwer et al., 2002; Leigh & Kennard, 2004), and the stimulus was only presented for 250ms at assessments, compared to 500ms at training. Therefore if an eye movement was made, it would have had a more deleterious effect on determining direction of motion at the assessment trials compared to the longer training trials.

Eye tracking was successfully carried out in only the first of the three training sessions, and indicated that although the participant was improving their ability to fixate over time, there were still eye movements towards the stimulus on a frequent basis. It is important to state here that the behavioural data described may have been confounded by eye movements. Future studies must control for this confound more tightly. Despite this, the perimeter used an automatic eye tracker that did not deliver stimuli without proper fixation, and therefore the effects on visual field are not confounded.

7.4.2 Changes in visual field driven by attentional improvements

In this study, there may have been changes in the border of the participant's scotoma, following motion perception training. The perimetry data were collected using an automated perimeter, and therefore the changes cannot be accounted for by eye movements, since the perimeter will only deliver luminance stimuli once appropriate eye fixation has been detected.

There was a clear difference in improvement between eyes, and it is not obvious why this should be the case for a binocular task. It is possible that the differences were caused by left eye dominance, or different visual acuity in the eyes. Eye dominance and acuity were not assessed in this experiment, but will be followed up in this participant at a later stage.

The improvements in the visual field are possibly a result of improved visuospatial attention, which led to improved detection of luminance stimuli across the visual field, both within and outside the areas in which the motion stimulus was delivered.

Previous research showed that attentional training can improve visual field size as measured using perimetry, in patients with VFDs (Lane et al., 2010). Lane et al. trained patients to complete a visual attention task close to fixation over 15 sessions, and demonstrated a resultant expansion in the size of the visual field, in both the seeing and damaged visual hemifields. It was recently shown that an expansion in visual field following vision restoration therapy was correlated with increased spatial attention and altertness (Kasten et al., 2007), further implicating improved visuospatial attention as an important modulator of performance on perimetry assessments. Moreover, expansions in the visual field have been reported following compensatory eye movement training (Kerkhoff et al., 1992; Kerkhoff et al., 1994). These findings support the claim that the motion training delivered here may have expanded the visual field by improving visuospatial attention, though future experiments would benefit from directly testing this hypothesis with attentional assessments.

7.4.3 Fast rate of learning and recovery

The rate of learning and recovery seen here was much faster than that previously described for restitution therapies. Other therapies require many months of daily training to mediate effects on behaviour and visual field (Huxlin et al., 2009; Sahraie et al., 2006), however, a change was observed here after only three training sessions.

It is possible that this effect was determined by the patient. The exact parameters that determine the responsiveness of patients to rehabilitative treatments has not yet been established, and would benefit from further investigation. Previous studies have shown a huge variability in improvement within groups of patients with VFDs (Poggel et al., 2010). It is likely a result of the heterogeneity of the cortical lesions which cause the field loss. Here, the lesion size was small and localised to V1, therefore more of the visual system was likely intact, increasing the chance of positive effects following rehabilitation. Furthermore, evidence has demonstrated that when the field border is not sharp, as was the case for this patient, there is a significantly increased likelihood of recovery (Green et al., 2011). The heterogeneity of patients with brain lesions frequently leads to therapies which are only applicable in a subset of individuals.

7.4.4 Future work

The findings here have demonstrated that motion perception training may lead to improved motion perception and partial recovery of visual field loss, in a patient with a homonymous quadrantopia. However, it is not clear whether the behavioural effects were genuine or confounded by eye movements. In future studies, trials will control for eye fixation by preventing the initiation of a trial without correct fixation, and sounding an alarm if fixation is broken during stimulus presentation. If such fixation breaks occur, the trial will be repeated until the stimulus can be delivered to the correct area of visual field.

Despite the potentially confounded behavioural findings, there was still a detected change in the patient's visual field, which may have been a result of a visuospatial learning component of the training. Future studies will directly assess visuospatial attention to further elucidate its role in rehabilitation of VFDs.

This research was carried out on a single patient, and is therefore preliminary. A repeat of this experiment in a larger cohort would determine how generalisable the training effects might be to other patients with VFDs.

A further extension to this research would be to include a longer-term follow-up. The effects here were not re-tested after a quiescent period, and therefore no conclusions can be drawn regarding the longevity of the training effects. In future, a follow-up assessment of motion perception performance and scotoma size will be carried out several months following training.

The validity of applying this motion perception training as a treatment requires there to be a demonstrable effect on the quality of life of the patient. Therefore, quality of life assessment questionnaires and assessments of activities of daily living need to be assessed before and after training to determine any impact the training might have in future studies. An assessment of the patient's subjective report on their scotoma size would also prove relevant and useful, as an indicator for how debilitating the patient finds their scotoma.

7.5 Conclusions

This case study comprised motion perception training of a patient with a lower right homonymous quadrantopia. The training consisted of three sessions of a motion perception task, which were delivered progressively further into the blind field. The results indicated that learning of a motion direction perception task may occur in the blind field, but were potentially confounded by eye movements. Perimetry data indicated that the patient may have showed a change in the size of visual fields, which could have been mediated by improved visuospatial attention. However, further

perimetry data should be collected to overcome measurement noise confounds.

The preliminary results presented here demonstrate motion perception training remains a promising avenue for future research studies. The time dedicated to this research programme was approximately 6 hours in total, spread across 3 meetings. This represents a significant reduction in time required compared to other similar rehabilitative therapies, which require many months of daily training lasting 30-60 minutes each, in order to induce visual field expansion.

8 General Discussion

The overall aim of this thesis was to investigate perceptual learning of motion in a healthy population, with a view to designing a motion perception training programme for patients with visual field defects (VFDs) caused by damage to the primary visual cortex (V1).

8.1 Thesis overview

The training delivered throughout this thesis involved participants determining the horizontal direction of moving dots, presented against a background of randomly-moving dots. This complex motion task required extraction of motion signal from noise. The task was adaptive, so the ratio of coherent to noise dots was modulated depending on performance of the subject. The 500ms stimulus was always delivered in the peripheral visual field, offset horizontally from fixation.

The main goal of the first study (Chapter 3) was to simply determine whether five days of motion perception training was sufficient for learning of the motion direction perception task to occur, in order to confirm whether the timing and difficulty of the task were appropriate. A secondary aim was to investigate whether any learning effects were transferable to an untrained area of the visual field. It was shown that the training protocol was indeed sufficient for learning of the task to take place following five days of exposure, as significant improvement in the motion task was demonstrated. The improvement in the motion task was shown to be partially transferable to an untrained region of the visual field. There were also indications that there was an attentional component to the learning, but that this component could not explain all of the learning effects.

The aim of the second study (Chapter 4) was to discover how the timecourse of training delivery could influence learning. Healthy participants completed a condensed

motion perception training protocol, over several hours in a single day. The same number of trials were delivered compared to when the training was distributed over five days in Chapter 3. A similar amount of learning was demonstrated, but in the case of the shorter timecourse, the effects were shown to be highly specific to the trained area of the visual field. Therefore, if the timecourse of training is reduced from five days to one day, perceptual learning of a motion task appears to become more retinotopic. This indicates that the neural mechanisms of learning may differ depending on the training timecourse.

In order to investigate the neural structures involved in mediating learning of the motion direction perception task following five days of training, a functional MRI study was completed (Chapter 5). This experiment required participants to complete the motion task inside an fMRI scanner, before and after a five-day training protocol (Chapter 3). A key area involved in perceptual learning of motion for this task is the extrastriate area MST. Other important regions identified in this experiment are frontal decision-making areas and the hippocampus.

In the next chapter (Chapter 6), the effect of transcranial direct current stimulation (tDCS) of hMT+ on learning of the motion direction perception task over five days was investigated. The aim of this study was to determine whether learning effects could be maximised by increasing the excitability of the brain region involved in mediating learning of the task. There was no difference in learning between the group stimulated with anodal tDCS and the group receiving sham stimulation. Therefore, it was concluded that this setup of 20 minutes of anodal tDCS over hMT+ in healthy participants has no effect on learning of the trained motion direction perception task.

The goal of the final data chapter (Chapter 7) was to pilot the motion perception training protocol in a patient with a VFD caused by damage to V1. The patient completed three sessions of the motion perception training, which were delivered progressively further into the blind field. There appeared to be some learning of the task, however, due to eye movement confounds towards the stimulus, strong

conclusions about learning effects could not be drawn. This study highlighted that for applying this learning paradigm, a tighter control for eye movements must be integrated. This is particularly key in patients to ensure stimulation of the region of visual field which includes the scotoma. However, eye fixation monitoring should be included in all studies using this paradigm, including in healthy participants, in order to verify that stimulation is being delivered in the intended region of the visual field.

8.2 Summary of key findings

Overall, it appeared that learning of the motion direction perception task implemented in these studies was consistent and robust. In all studies where motion perception learning was distributed across five days in a healthy population, the amount of learning was similar, with partial transfer of learning effects to the untrained visual hemifield. Timecourse of learning was found to be the most important modulator of learning effects. Specifically, when training is condensed down into a single day, the overall magnitude of the learning is not altered, however transfer of learning to untrained regions of the visual field was completely abolished.

These findings possibly indicate that learning across multiple days may be mediated by extrastriate areas rather than early visual regions. Early visual area such as V1 have small receptive fields and are highly retinotopic. Therefore, if learning was mediated by V1, the effects of training would likely be highly specific to the area of visual field where the stimulus was delivered. In contrast, higher visual areas such as hMT+ have large receptive fields, and therefore if learning was mediated by cells in this area, transfer of learning outside of the stimulus region would be predicted. This assertion was confirmed directly in the MRI experiment, which showed learning effects were strongly correlated with changes in the anterior portion of hMT+, likely corresponding to MST, but not in V1 or other early visual areas.

8.3 Future work

8.3.1 Expanded investigation of the healthy visual system

These experiments have not investigated the long-term effect of motion perception training. Future studies of such learning in the healthy visual system could determine whether improvement in motion perception is short-lived, or if it may last for an extended period of time. This would involve re-testing participants on motion perception performance at a timepoint several weeks or months after training has been completed. This information will be important if a motion perception training programme is to be applied as a rehabilitative therapy, where short-term effects would be of limited use to the patient.

In this thesis, it was shown that motion perception learning effects are partially transferable to untrained regions of the visual field. Furthermore, it was shown that some training effects can transfer to an untrained visual task. An open question is whether training effects may be able to transfer across different-coloured stimuli, when the stimuli are not defined by luminance. Such second-order motion perception may engage different brain mechanisms to first-order (luminance-defined) motion (O'Keefe & Movshon, 1998). Information about transfer of learning effects across colours could further elucidate brain pathways involved in motion perception learning, since different coloured stimuli are processed by different pathways in the brain. It is proposed that future experiments determine the magnitude and specificity of motion perception learning of colour-defined, isoluminant stimuli.

An open question about the application of tDCS in the healthy visual system remains. It is not clear from the literature whether tDCS is able to modulate function of visual tasks. As discussed in Chapter 6, more basic investigations into the effect of tDCS in the visual system is required. One simple experiment would be to determine the effect of tDCS on a measure of hMT+ baseline activity. This could be completed using TMS to stimulate hMT+, to induce moving phosphenes. tDCS could then

be applied over V5/MT+, to determine if the stimulation is able to modulate the moving phosphene activity threshold. If successful, this would provide evidence that tDCS is indeed able to modulate V5/MT+ activity.

8.3.2 Expanded investigation of the visual system when V1 is damaged

Potential application of motion perception training as a rehabilitative therapy

Since the learning effects here were very robust and likely mediated by neural regions outside of V1, it is proposed that a rehabilitative programme incorporating such motion perception training may be appropriate for patients with visual problems following damage to V1.

The hMT+ compex is often left intact by lesions which cause damage to V1, due to its distal location from the striate cortex. This brain region is particularly interesting from a rehabilitative perspective since it has been proposed as a site which may mediate residual vision. Residual motion perception frequently remains present in the blind field of patients with VFDs. There is evidence that the motion areas of the brain may receive direct inputs from the thalamus, as well as indirect inputs which flow through the superior colliculi, thereby bypassing the lesioned V1 region of the brain. It is proposed that these pathways may mediate the residual motion processing frequently observed (Leh et al., 2006; Sincich et al., 2004).

Indeed, Huxlin et al. have previously investigated the effect of motion perception training on patients with V1 damage. Participants were required to discriminate left or right motion of moving dots in the blind visual field. The task difficulty was adaptively modulated by altering the range of displayed motion directions. Participants were instructed to extract the global motion direction vector by integrating all dot motion directions displayed in the stimulus (Huxlin, 2008). Training resulted in a large improvement in direction integration threshold in the blind field (Huxlin et al., 2009).

The exact visual areas involved in the motion perception training carried out

by Huxlin et al. have not been fully established. Huxlin et al. did not complete functional imaging and so any neural changes were not directly measured. Although there were changes which transferred across visual tasks to different trained areas of the visual field, learning did not transfer to untrained regions. This may indicate that learning effects were not mediated at extrastriate areas with large receptive fields, such as hMT+. However, direct measures of changes in brain activity are required to make firmer conclusions.

It would be advantageous to be able to engage an area of the brain with large receptive field for a rehabilitative therapy. This would be because if training effects could transfer to untrained visual areas, then it is possible training completed partially or fully in the seeing field could transfer to the blind field. If this was possible, it would be a significant advantage with regard to patient application. Patients will be more motivated to complete a task in the seeing field, compared to the blind field. With the training task used here, there was some transfer of perceptual learning to untrained regions of the visual field. This indicated that the area of the brain that mediating the learning is not primary visual cortex, where cell RFs are smaller than the stimulus size.

Targeting training to areas of the brain with large receptive fields is also advantageous

Another advantage of targeting rehabilitation to the hMT+ complex is that MST is involved in optic flow. Many patients with V1 damage have collisions resulting from the VFD. An improved ability to process optic flow information could translate to improved object avoidance. This could decrease collision frequency and therefore improve quality of life.

A major criticism of the previous literature on motion perception training for VFD rehabilitation is the time taken for improvements to occur. Previous studies have required daily training over several months in order for an effect on visual behaviour to be observed. In healthy individuals, the motion perception training

paradigm applied here initiates learning in a rapid manner. The case study of a single patient indicates that this may also be the case for patients with damage to V1. Improvement over the course of weeks instead of months is likely to increase the number of patients able to complete sufficient training sessions to observe an effect. Furthermore, a briefer protocol is significantly easier to implement with regard to practicality and expense.

Potential application of motion perception training combined with tDCS in patients

In this series of experiments, tDCS was applied over the extrastriate visual cortex to determine whether stimulation could improve visual perceptual learning in healthy individuals. Interestingly, there was no difference between a group that underwent real stimulation and a sham stimulation group. It is not clear whether this may also be the case for a patient population.

The connectivity in the visual system of an individual with damage to V1 is likely to look different to that in the healthy visual system. For example, Bridge et al. demonstrated in a case study of a patient with V1 damage that there was strengthening of a pathway from the LGN to V5/MT+ in the opposite hemisphere, and of a bilateral cortico-cortical connection between both V5/MT+ areas (Bridge et al., 2008). The aim of rehabilitation is to train residual pathways involving hMT+, which may bypass V1. However, in the healthy system, such connections are likely to be small and underused, since V1 connections will dominate. Stimulation of V5/MT+ by tDCS would have a very different effect on the visual system in a patient population, compared to healthy individuals, since V5/MT+ may play a different functional role for vision in the absence of primary visual cortex.

Furthermore, the learning effects of the training on healthy individuals may already be at ceiling without brain stimulation. As a result, application of tDCS may not be able to further increase learning. It is likely that a patient population will show more learning capacity due to worse initial task performance. Therefore, this provides

more scope for tDCS application as a learning adjunct.

Previous studies have looked at the effect of tDCS on visual rehabilitation of patients with V1 damage. However, stimulation has always been delivered over the occipital lobe with the intention to stimulate perilesional areas of the visual cortex (Gall et al., 2015; Plow et al., 2012). The application of tDCS in order to improve residual visual processing is novel and has not been previously attempted.

8.4 Final Conclusions

In conclusion, it appears that the motion perception training paradigm applied in these experiments produces robust improvement of motion perception in healthy participants. Learning is mediated by extrastriate visual areas, and is not modulated by direct current stimulation of such regions.

Motion perception training shows promise, with further development, as an avenue for rehabilitation of the visual system and visual perception, following damage to the primary visual cortex.

9 Bibliography

Accornero N, Li Voti P, La Riccia M, Gregori B. (2007). Visual evoked potentials modulation during direct current cortical polarization. Exp Brain Res 178(2):261-6.

Ahissar M, Hochstein S. (1993). Attentional control of early perceptual learning. Proc Natl Acad Sci U S A 90(12):5718-22.

Ajina S, Kennard C, Rees G, Bridge H. (2015). Motion area V5/MT+ response to global motion in the absence of V1 resembles early visual cortex. Brain 138(1):164-78.

Ajina S, Kennard C. (2012). Rehabilitation of damage to the visual brain. Rev Neurol 168(10):754-61.

Alais D, van der Smagt MJ, van den Berg AV, van de Grind WA. (1998). Local and global factors affecting the coherent motion of gratings presented in multiple apertures. Vision Res 38(11):1581-91.

Alberti CF, Peli E, Bowers AR. (2014). Driving with hemianopia: III. Detection of stationary and approaching pedestrians in a simulator. Invest Ophthalmol Vis Sci 55(1):368-74.

Albright TD, Desimone R, Gross CG. (1984). Columnar organization of directionally selective cells in visual area MT of the macaque. J Neurophysiol 51(1):16-31.

Aldrich MS, Alessi AG, Beck RW, Gilman S. (1987). Cortical blindness: etiology, diagnosis, and prognosis. Ann Neurol 21(2):149-58.

Allwright, F. (2016). ONLINE: [https://www.studyblue.com/flashcard/view/10805286]. Last accessed 03/03/16.

Altman J. (1962). Are new neurons formed in the brains of adult mammals? Science 135(3509):1127-8.

Amano K, Wandell BA, Dumoulin SO. (2009). Visual field maps, population receptive field sizes, and visual field coverage in the human MT+ complex. J Neurophysiol 102(5):2704-18.

Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. (2012). The fade-in short stimulation fade-out approach to sham tDCS - reliable at 1mA for naive and experienced subjects, but not investigators. Brain Stimul 5(4):499-504.

Andersson JLR, Jenkinson M, Smith S. (2007). Non-linear registration, aka spatial normalisation. FMRIB technical report TR07JA2.

Antal A, Kincses TZ, Nitsche MA, Paulus W. (2003a). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res 150(3):375-8.

Antal A, Kincses TZ, Nitsche MA, Paulus W. (2003b) Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. Neuropsychologia 41(13):1802-7.

Antal A, Kovcs G, Chaieb L, Cziraki C, Paulus W, Greenlee MW. (2012). Cathodal stimulation of human MT+ leads to elevated fMRI signal: a tDCS-fMRI study. Restor Neurol Neurosci 30(3):255-63.

Antal A, Nitsche MA, Kincses TZ, Kruse W, Hoffmann KP, Paulus W. (2004a). Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. Eur J Neurosci 19(10):2888-92.

Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann KP, Paulus W. (2004b). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 16(4):521-7.

Antal A, Nitsche MA, Paulus W. (2001). External modulation of visual perception in humans. Neuroreport 12(16):3553-5.

Antal A, Varga ET, Kincses TZ, Nitsche MA, Paulus W. (2004c). Oscillatory brain activity and transcranial direct current stimulation in humans. Neuroreport 15(8):1307-10.

Antal A, Varga ET, Nitsche MA, Chadaide Z, Paulus W, Kovcs G, Vidnynszky Z. (2004d). Direct current stimulation over MT+/V5 modulates motion aftereffect in humans. Neuroreport 15;15(16):2491-4.

Ashley S, Pearson J. (2012). When more equals less: overtraining inhibits perceptual learning owing to lack of wakeful consolidation. Proc Biol Sci 279(1745):4143-7.

Astle AT, McGraw PV, Webb BS. (2011). Recovery of stereo acuity in adults with amblyopia. BMJ Case Reports pii: bcr0720103143.

Baker CL Jr, Hess RF, Zihl J. (1991). Residual motion perception in a motion-blind patient, assessed with limited-lifetime random dot stimuli. J Neurosci 11(2):454-61.

Ball K, Sekuler R. (1987). Direction-specific improvement in motion discrimination. Vision Res 27(6):953-65.

Balliet R, Blood KM, Bach-y-Rita P. (1985). Visual field rehabilitation in the cortically blind? J Neurol Neurosurg Psychiatry 48(11):1113-24.

Barbur JL, Harlow AJ, Weiskrantz L. (1994). Spatial and temporal response properties of residual vision in a case of hemianopia. Philos Trans R Soc Lond B Biol Sci 343(1304):157-66.

Barbur JL, Ruddock KH, Waterfield VA. (1980). Human visual responses in the absence of the geniculo-calcarine projection. Brain 103(4):905-28.

Barrett NA, Large MM, Smith GL, Michie PT, Karayanidis F, Kavanagh DJ, Fawdry R, Henderson D, O'Sullivan BT. (2001). Human cortical processing of colour and pattern. Hum Brain Mapp 13(4):213-25.

Bear MF, Kirkwood A. (1993). Neocortical long-term potentiation. Curr Opin Neurobiol 3(2):197-202.

Bejjanki VR, Beck JM, Lu ZL, Pouget A. (2011). Perceptual learning as improved probabilistic inference in early sensory areas. Nat Neurosci 14(5):642-8.

Bergsma DP, Leenders MJ, Verster JC, van der Wildt GJ, van den Berg AV. (2011). Oculomotor behavior of hemianopic chronic stroke patients in a driving simulator is modulated by vision training. Restor Neurol Neurosci 29(5):347-59.

Bishop PO. (1953). Synaptic transmission; an analysis of the electrical activity of the lateral geniculate nucleus in the cat after optic nerve stimulation. Proc R Soc Lond B Biol Sci 141(904):362-92.

Bishop PO. (1981). Binocular vision. In: Kaufman PL, Alm A, Adler FH (Eds.). Adlers physiology of the eye: Clinical application. Mosby.

Bittar RG, Ptito M, Faubert J, Dumoulin SO, Ptito A. (1999). Activation of the remaining hemisphere following stimulation of the blind hemifield in hemispherectomized subjects. Neuroimage 10(1):339-46.

Blake R, Sekuler R, Grossman E. (2003). Motion processing in human visual cortex. In: Kaas JH, Collins C (Eds.). Primate Visual System. CRC Press.

Bliss TV, Lomo T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232(2):331-56.

Blythe IM, Kennard C, Ruddock KH. (1987). Residual vision in patients with retrogeniculate lesions of the visual pathways. Brain 110 (4):887-905.

Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosc 25(2):123-9.

Bowers AR, Ananyev E, Mandel AJ, Goldstein RB, Peli E. (2014). Driving with hemianopia: IV. Head scanning and detection at intersections in a simulator. Invest Ophthalmol Vis Sci 55(3):1540-8.

Bowers AR, Keeney K, Peli E. (2008). Community-based trial of a peripheral prism visual field expansion device for hemianopia. Arch Ophthalmol 126(5):657-64

Braddick OJ, O'Brien JM, Wattam-Bell J, Atkinson J, Hartley T, Turner R. (2001). Brain areas sensitive to coherent visual motion. Perception 30(1):61-72.

Brainard DH. The psychophysics toolbox. Spatial Vision 1997;10:433-6.

Bremmer F, Kubischik M, Pekel M, Hoffmann KP, Lappe M. (2010). Visual selectivity for heading in monkey area MST. Exp Brain Res 200(1):51-60.

Bridge H, Hicks SL, Xie J, Okell TW, Mannan S, Alexander I, Cowey A, Kennard C. (2010). Visual activation of extra-striate cortex in the absence of V1 activation. Neuropsychologia 48(14):4148-54.

Bridge H, Thomas O, Jbabdi S, Cowey A. (2008). Changes in connectivity after visual cortical brain damage underlie altered visual function. Brain 131(6):1433-44.

Briggs F, Mangun GR, Usrey WM. (2013). Attention enhances synaptic efficacy and the signal-to-noise ratio in neural circuits. Nature 499(7459):476-80.

Britten KH, Shadlen MN, Newsome WT, Movshon JA. (1992). The analysis of visual motion: a comparison of neuronal and psychophysical performance. J Neurosci 12(12):4745-65.

Bruce BB, Zhang X, Kedar S, Newman NJ, Biousse V. (2006). Traumatic homonymous hemianopia. J Neurol Neurosurg Psychiatry 77(8):986-8.

Bruce V, Green PR, Georgeson MA. (1996). Visual perception. Psychology Press.

Buffalo EA, Fries P, Landman R, Liang H, Desimone R. (2010). A backward progression of attentional effects in the ventral stream. Proc Natl Acad Sci U S A 107(1):361-5.

Cajal RS. (1991). Degeneration and regeneration of the nervous system. May RM, DeFelipe J, Jones EG (Eds.). Oxford University Press.

Carpenter, RHS. (1997). Movements of the eyes. Pion.

Cavanagh P, Mather G. (1989). Motion: the long and short of it. Spat Vis 4(2-3):103-29.

Censor N, Karni A, Sagi D. (2006). A link between perceptual learning, adaptation and sleep. Vision Res 46(23):4071-4.

Censor N, Sagi D. (2008). Benefits of efficient consolidation: short training enables long-term resistance to perceptual adaptation induced by intensive testing. Vision Res 48(7):970-7.

Chen N, Bi T, Zhou T, Li S, Liu Z, Fang F. (2015). Sharpened cortical tuning and enhanced cortico-cortical communication contribute to the long-term neural mechanisms of visual motion perceptual learning. Neuroimage 115:17-29.

Chowdhury SA, DeAngelis GC. (2008). Fine discrimination training alters the causal contribution of macaque area MT to depth perception. Neuron 60(2):367-77.

Chubb C, Sperling G. (1988). Drift-balanced random stimuli: a general basis for studying non-Fourier motion perception. J Opt Soc Am A 5(11):1986-2007.

Chung ST, Legge GE, Cheung SH. (2004). Letter-recognition and reading speed in peripheral vision benefit from perceptual learning. Vision Res 44(7):695-709.

Cohen JM. (1993). An overview of enhancement techniques for peripheral field loss. J Am Optom Assoc 64(1):60-70. cortex. PLoS One 7(5):e36220.

Cowey A, Alexander I, Ellison A. (2013). Modulation of cortical excitability can speed up blindsight but not improve it. Exp Brain Res 224(3):469-75.

Cowey A, Stoerig P, Bannister M. (1994). Retinal ganglion cells labelled from the pulvinar nucleus in macaque monkeys. Neuroscience 61(3):691-705.

Cowey A. (1967). Perimetric study of field defects in monkeys after cortical and retinal ablations. Q J Exp Psychol 19(3):232-45.

Creutzfeldt OD, Fromm GH, Kapp H. (1962). Influence of transcortical DC currents on cortical neuronal activity. Exp Neurol 5:436-52.

Crist RE, Kapadia MK, Westheimer G, Gilbert CD. (1997). Perceptual learning of spatial localization: specificity for orientation, position, and context. J Neurophysiol 78(6):2889-94.

Culham J, He S, Dukelow S, Verstraten FA. (2001). Visual motion and the human brain: what has neuroimaging told us? Acta Psychol (Amst) 107(1-3):69-94.

Das A, Tadin D, Huxlin KR. (2014). Beyond blindsight: properties of visual relearning in cortically blind fields. J Neurosci 34(35):11652-64.

Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2(4):201-7.

Davidson RM, Bender DB. (1991). Selectivity for relative motion in the monkey superior colliculus. J Neurophysiol 65(5):1115-33.

De Brouwer S, Missal M, Barnes G, Lefvre P. (2002). Quantitative analysis of catch-up saccades during sustained pursuit. J Neurophysiol 87(4):1772-80.

de Haan GA, Melis-Dankers BJ, Brouwer WH, Bredewoud RA, Tucha O, Heutink J. (2014). Car driving performance in hemianopia: an on-road driving study. Invest Ophthalmol Vis Sci 55(10):6482-9.

De Luca M, Spinelli D, Zoccolotti P. (1996). Eye movement patterns in reading as a function of visual field defects and contrast sensitivity loss. Cortex 32(3):491-502.

De Valois KK. (1977). Spatial frequency adaptation can enhance contrast sensitivity. Vision Res. 1977;17(9):1057-65.

Deliens G, Schmitz R, Peigneux P. (2014). Interocular transfer of perceptual skills after sleep. J Vis 14(1) pii:23.

Derrington AM, Badcock DR. (1985). Separate detectors for simple and complex grating patterns? Vision Res 25(12):1869-78.

Deveau J, Lovcik G, Seitz AR. (2014). Broad-based visual benefits from training with an integrated perceptual-learning video game. Vision Res 99:134-40.

DeYoe EA, Van Essen DC. (1988). Concurrent processing streams in monkey visual cortex. Trends Neurosci 11(5):219-26.

Diamond IT, Hall WC. (1969). Evolution of neocortex. Science 164(3877):251-62.

Ding J, Levi DM. (2011). Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. Proc Natl Acad Sci U S A. 108(37):E733-41.

Ditterich J, Mazurek ME, Shadlen MN. (2003). Microstimulation of visual cortex affects the speed of perceptual decisions. Nat Neurosci 6(8):891-8.

Dosher BA, Lu ZL. (1998). Perceptual learning reflects external noise filtering and internal noise reduction through channel reweighting. Proc Natl Acad Sci U S A 95(23):13988-93.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. (2004). Neuroplasticity: changes in grey matter induced by training. Nature 427(6972):311-2.

Driver and Vehicle Licensing Agency. (2015). Driving eyesight rules. Retrieved 14/10/15 from: [https://www.gov.uk/driving-eyesight-rules].

Dubner R, Zeki SM. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. Brain Res 35(2):528-32.

Dudai Y. (1996). Consolidation: fragility on the road to the engram. Neuron 17(3):367-70.

Duffy CJ, Wurtz RH. (1991). Sensitivity of MST neurons to optic flow stimuli. I. A continuum of response selectivity to large-field stimuli. J Neurophysiol 65(6):1329-45.

Dumoulin S, Wandell BA. (2008). Population receptive field estimates in human visual cortex. Neuroimage 39(2):647-60.

Dumoulin SO, Bittar RG, Kabani NJ, Baker CL Jr, Le Goualher G, Bruce Pike G, Evans AC. (2000). A new anatomical landmark for reliable identification of human area V5/MT: a

Dunwiddie TV, Lynch G. (1979). The relationship between extracellular calcium concentrations and the induction of hippocampal long-term potentiation. Brain Res 169(1):103-10.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25(4):1325-35.

Elgin J, McGwin G, Wood JM, Vaphiades MS, Braswell RA, DeCarlo DK, Kline LB, Owsley C. (2010). Evaluation of on-road driving in people with hemianopia and quadrantanopia. Am J Occup Ther 64(2):268-78.

Eriksson PS, Perfilieva E, Bjrk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. (1998). Neurogenesis in the adult human hippocampus. Nat Med 4(11):1313-7.

Essen DC, Zeki SM. (1978). The topographic organization of rhesus monkey prestriate cortex. J Physiol 277:193-226. excitability. Brain 125(10):2238-47.

Eysel UT, Schweigart G, Mittmann T, Eyding D, Qu Y, Vandesande F, Orban G, Arckens L. (1999). Reorganization in the visual cortex after retinal and cortical damage. Restor Neurol Neurosci 15(2-3):153-64.

Eysel UT, Schweigart G. (1992). Increased receptive field size in the surround of chronic lesions in the adult cat visual cortex. Cereb Cortex 9(2):101-9.

Fahle M, Edelman S. (1993). Long-term learning in vernier acuity: effects of stimulus orientation, range and of feedback. Vision Res 33(3):397-412.

Fahle M, Morgan M. (1996). No transfer of perceptual learning between similar stimuli in the same retinal position. Current Biology 6(3), 292297.

Fahle M, Poggio T. (2002). Perceptual Learning. MIT Press.

Fahle M, Skrandies W. (1994). An electrophysiological correlate of learning in motion perception. Ger J Ophthalmol 3(6):427-32.

Fahle M. (1994). Human pattern recognition: parallel processing and perceptual learning. Perception 23(4):411-27.

Fahle M. (1997). Specificity of learning curvature, orientation, and vernier discriminations. Vision Res 37(14):1885-95.

Felleman DJ, Van Essen DC. (1987). Receptive field properties of neurons in area V3 of macaque monkey extrastriate cortex. J Neurophysiol 57(4):889-920.

Felsten G, Benevento LA, Burman D. (1983). Opponent-color responses in macaque extrageniculate visual pathways: the lateral pulvinar. Brain Res 288(1-2):363-7.

Fertonani A, Ferrari C, Miniussi C. (2015). What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol 126(11):2181-8.

Fiorentini A, Berardi N. (1980). Perceptual learning specific for orientation and spatial frequency. Nature 287(5777):43-4.

Fischer E, Bülthoff HH, Logothetis NK, Bartels A. (2012). Visual motion responses in the posterior cingulate sulcus: a comparison to V5/MT and MST. Cereb Cortex 22(4):865-76.

Fox K. (2002). Anatomical pathways and molecular mechanisms for plasticity in the barrel cortex. Neuroscience 111(4):799-814.

Fujino T, Kazuki K, Yamada R. (1985). Homonymous hemianopia: A retrospective study of 140 cases. Neuroophthalmology 6(1):17-21.

Furmanski CS, Schluppeck D, Engel SA. (2004). Learning strengthens the response of primary visual cortex to simple patterns. Curr Biol 14(7):573-8.

Gais S, Plihal W, Wagner U, Born J. (2000). Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 3(12):1335-9.

Gall C, Franke GH, Sabel BA. (2010). Vision-related quality of life in first stroke patients with homonymous visual field defects. Health Qual Life Outcomes 8:33.

Gall C, Silvennoinen K, Granata G, de Rossi F, Vecchio F, Brsel D, Bola M, Sailer M, Waleszczyk WJ, Rossini PM, Tatlisumak T, Sabel BA. (2015). Non-invasive electric current stimulation for restoration of vision after unilateral occipital stroke. Contemp Clin Trials 43:231-6.

Gall C, Wagenbreth C, Sgorzaly S, Franke GH, Sabel BA. (2010). Parafoveal vision impairments and their influence on reading performance and self-evaluated reading abilities. Graefes Arch Clin Exp Ophthalmol 248(6):863-75.

Gandiga PC, Hummel FC, Cohen LG. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 117(4):845-50.

García-Pérez MA. (1998). Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. Vision Res 38(12):1861-81.

Gardiner SK, Swanson WH, Goren D, Mansberger SL, Demirel S. (2014). Assessment of the reliability of standard automated perimetry in regions of glaucomatous damage. Ophthalmology 121(7):1359-69.

Garrigan P, Kellman PJ. (2008). Perceptual learning depends on perceptual constancy. Proc Natl Acad Sci U S A 105(6):2248-53.

Gartside IB. (1968). Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. Nature 220(5165):383-4.

Gattass R, Gross CG, Sandell JH. (1981). Visual topography of V2 in the macaque. J Comp Neurol 201(4):519-39.

Gattass R, Gross CG. (1981). Visual topography of striate projection zone (MT) in posterior superior temporal sulcus of the macaque. J Neurophysiol 46(3):621-38.

Gegenfurtner KR, Kiper DC, Levitt JB. (1997). Functional properties of neurons in macaque area V3. J Neurophysiol 77(4):1906-23.

Gibson EJ. (1953). Improvement in perceptual judgments as a function of controlled practice or training. Psychol Bull 50(6):401-31.

Gibson EJ. (1963). Perceptual learning. Annu Rev Psychol 14:29-56.

Gilhotra JS, Mitchell P, Healey PR, Cumming RG, Currie J. (2002). Homonymous visual field defects and stroke in an older population. Stroke 33(10):2417-20.

Giorgi RG, Woods RL, Peli E. (2009). Clinical and laboratory evaluation of peripheral prism glasses for hemianopia. Optom Vis Sci 86(5):492-502.

Glen FC, Smith ND, Crabb DP. (2015). Impact of superior and inferior visual field loss on hazard detection in a computer-based driving test. Br J Ophthalmol 99(5):613-7.

Gold JI, Shadlen MN. (2001). Neural computations that underlie decisions about sensory stimuli. Trends Cogn Sci 5(1):10-16.

Goldhacker M, Rosengarth K, Plank T, Greenlee MW. (2014). The effect of feedback on performance and brain activation during perceptual learning. Vision Res 99:99-110.

Goodale MA, Milner AD. (1992). Separate visual pathways for perception and action. Trends Neurosci 15(1):20-5.

Goodwin D. (2014). Homonymous hemianopia: challenges and solutions. Clin Ophthalmol 8:1919-27.

Gooley JJ, Lu J, Chou TC, Scammell TE, Saper CB. (2001). Melanopsin in cells of origin of the retinohypothalamic tract. Nat Neurosci 4(12):1165.

Gottlieb DD, Allen CH, Eikenberry J, Ingall-Woodruff S, Johnson M. (1996). Living with Vision Loss. Atlanta, GA (Eds.). St. Barthelemy Press.

Gottlieb DD. (1988). Method of using a prism in lens for the treatment of visual field loss. U.S. Patent 4,779,972.

Gould E. (2007). How widespread is adult neurogenesis in mammals? Nat Rev Neurosci 8(6):481-8.

Gray CS, French JM, Bates D, Cartlidge NE, Venables GS, James OF. (1989). Recovery of visual fields in acute stroke: homonymous hemianopia associated with adverse prognosis. Age Ageing 18(6):419-21.

Green AM, Chapman CE, Kalaska JF, Leport F. (2011). Enhancing performance for action and perception: Multisensory integration, neuroplasticity and neuroprosthetics, part II.

Guggenmos M, Rothkirch M, Obermayer K, Haynes JD, Sterzer P. (2015). A hippocampal signature of perceptual learning in object recognition. J Cogn Neurosci 27(4):787-97.

Haerer AF. (1973). Visual field defects and the prognosis of stroke patients. Stroke 4(2):163-8.

Halko MA, Datta A, Plow EB, Scaturro J, Bikson M, Merabet LB. (2011). Neuroplastic changes following rehabilitative training correlate with regional electrical field induced

Harvey JA, McIlwain H. (1968). Excitatory acidic amino acids and the cation content and sodium ion flux of isolated tissues from the brain. Biochem J 108(2):269-74.

Hattori Y, Moriwaki A, Hori Y. (1990). Biphasic effects of polarizing current on adenosine-sensitive generation of cyclic AMP in rat cerebral cortex. Neurosci Lett 116(3):320-4.

Hawken MJ, Parker AJ, Lund JS. (1988). Laminar organization and contrast sensitivity of direction-selective cells in the striate cortex of the Old World monkey. J Neurosci 8(10):3541-8.

Heekeren HR, Marrett S, Bandettini PA, Ungerleider LG. (2004). A general mechanism for perceptual decision-making in the human brain. Nature 431(7010):859-62.

Henriksson L, Raninen A, Näsänen R, Hyvärinen L, Vanni S. (2007). Training-induced cortical representation of a hemianopic hemifield. J Neurol Neurosurg Psychiatry 78(1):74-81.

Herzog MH, Fahle M. (1998). Modeling perceptual learning: difficulties and how they can be overcome. Biol Cybern 78(2):107-17.

Hess RH, Baker CL Jr, Zihl J. (1989). The "motion-blind patient: low-level spatial and temporal filters. J Neurosci 9(5):1628-40.

Holmes G. (1918). Disturbances of vision by cerebral lesions. Br J Ophthalmol 2(7): 353384.

Horton JC. (2005a). Disappointing results from Nova Vision's visual restoration therapy. Br J Ophthalmol 89(1):1-2.

Horton JC. (2005b). Vision restoration therapy: confounded by eye movements. Br J Ophthalmol 89(7):792-4.

Hotson J, Braun D, Herzberg W, Boman D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. Vision Res 34(16):2115-23.

Hotson JR, Anand S. (1999). The selectivity and timing of motion processing in human temporo-parieto-occipital and occipital cortex: a transcranial magnetic stimulation study. Neuropsychologia 37(2):169-79.

Howard RJ, Brammer M, Wright I, Woodruff PW, Bullmore ET, Zeki S. (1996). A direct demonstration of functional specialization within motion-related visual and auditory cortex of the human brain. Curr Biol 6(8):1015-9.

Hubel DH, Wiesel TN. (1968). Receptive fields and functional architecture of monkey striate cortex. J Physiol 195(1):215-43.

Hubel DH, Wiesel TN. (1974). Uniformity of monkey striate cortex: a parallel relationship between field size, scatter, and magnification factor. J Comp Neurol 158(3):295-305.

Hubel DH. (1988). Eye, brain and vision. Scientific American Library.

Huk AC, Dougherty RF, Heeger DJ. (2002). Retinotopy and functional subdivision of human areas MT and MST. J Neurosci 22(16):7195-205.

Huk AC, Ress D, Heeger DJ. (2001). Neuronal basis of the motion aftereffect reconsidered. Neuron 32(1):161-72.

Hummel FC, Celnik P, Pascual-Leone A, Fregni F, Byblow WD, Buetefisch CM, Rothwell J, Cohen LG, Gerloff C. (2008). Controversy: Noninvasive and invasive

cortical stimulation show efficacy in treating stroke patients. Brain Stimul 1(4):370-82.

Hung SC, Seitz AR. (2014). Prolonged training at threshold promotes robust retinotopic specificity in perceptual learning. J Neurosci 34(25):8423-31.

Huxlin KR, Martin T, Kelly K, Riley M, Friedman DI, Burgin WS, Hayhoe M. (2009). Perceptual relearning of complex visual motion after V1 damage in humans. J Neurosci 29(13):3981-91.

Huxlin KR. (2008). Perceptual plasticity in damaged adult visual systems. Vision Res 48(20):2154-66.

Islam N, Moriwaki A, Hattori Y, Hayashi Y, Lu YF, Hori Y. (1995). c-Fos expression mediated by N-methyl-D-aspartate receptors following anodal polarization in the rat brain. Exp Neurol 133(1):25-31.

Jacquin-Courtois S, Bays PM, Salemme R, Leff AP, Husain M. (2013). Rapid compensation of visual search strategy in patients with chronic visual field defects. Cortex 49(4):994-1000.

Jayakumar J, Roy S, Dreher B, Martin PR, Vidyasagar TR. (2013). Multiple pathways carry signals from short-wavelength-sensitive ("blue') cones to the middle temporal area of the macaque. J Physiol 591(1):339-52.

Jenkinson M, Bannister P, Brady J, Smith S. (2002). Improved optimisation for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17(2):825-841

Jenkinson M, Smith SM. (2001). A global optimisation method for robust affine registration of brain Iimages. Medical Image Analysis 5(2) 143-156.

Jeter PE, Dosher BA, Liu SH, Lu ZL. (2010). Specificity of perceptual learning increases with increased training. Vision Res 50(19):1928-40.

Jeter PE, Dosher BA, Petrov A, Lu ZL. (2009). Task precision at transfer determines specificity of perceptual learning. J Vis 9(3):1.1-13.

Karni A, Sagi D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. Proc Natl Acad Sci U S A 88(11):4966-70.

Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265(5172):679-82.

Kasten E, Bunzenthal U, Mller-Oehring EM, Mueller I, Sabel BA. (2007). Vision restoration therapy does not benefit from costimulation: A pilot study. J Clin Exp Neuropsychol 29(6):569-84.

Kasten E, Poggel DA, Sabel BA. (2000). Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. J Cogn Neurosci 12(6):1001-12.

Kasten E, Sabel BA. (1995). Visual field enlargement after computer training in brain-damaged patients with homonymous deficits: an open pilot trial. Restor Neurol Neurosci 8(3):113-27.

Kentridge RW, Heywood CA, Weiskrantz L. (1997). Residual vision in multiple retinal locations within a scotoma: Implications for blindsight. J Cogn Neurosci 9(2):191-202.

Kerkhoff G, Mninger U, Haaf E, Eberle-Strauss G, Stgerer E. (1992). Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. Restor Neurol Neurosci 4(4):245-54.

Kerkhoff G, Münssinger U, Meier EK. (1994). Neurovisual rehabilitation in cerebral blindness. Arch Neurol 51(5):474-81.

Kerkhoff G. (2000). Neurovisual rehabilitation: recent developments and future directions Am J Ophthalmol 130(5):687-8.

Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. (2012). Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul 5(2):155-62.

Khetpal V, Donahue SP. (2007). Cortical visual impairment: etiology, associated findings, and prognosis in a tertiary care setting. J AAPOS 11(3):235-9.

Kim JN, Shadlen MN. (1999). Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. Nat Neurosci 2(2):176-85.

Kleiner M, Brainard DH, Pelli D. What's new in psychtoolbox-3? Perception. 2007. 36: ECVP Abstract Supplement.

Komatsu H, Wurtz RH. (1988). Relation of cortical areas MT and MST to pursuit eye movements. I. Localization and visual properties of neurons. J Neurophysiol 60(2):580-603.

Koyama S, Sasaki Y, Andersen GJ, Tootell RB, Matsuura M, Watanabe T. (2005). Separate processing of different global-motion structures in visual cortex is revealed by FMRI. Curr Biol 15(22):2027-32.

Kyriakareli A, Cousins S, Pettorossi VE, Bronstein AM. (2013). Effect of transcranial direct current stimulation on vestibular-ocular and vestibulo-perceptual thresholds. Neuroreport 24(14):808-12.

Lüscher C, Malenka RC. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harb Perspect Biol 4(6).

Lømo T. (2003). The discovery of long-term potentiation. Philos Trans R Soc Lond B Biol Sci 358(1432):617-20.

Lane AR, Smith DT, Ellison A, Schenk T. (2010). Visual exploration training is no better than attention training for treating hemianopia. Brain 133(6):1717-28.

Laties AM, Sprague JM. (1966). The projection of optic fibers to the visual centers in the cat. J Comp Neurol 127(1):35-70.

Law CT, Gold JI. (2008). Neural correlates of perceptual learning in a sensory-motor, but not a sensory, cortical area. Nat Neurosci 11(4):505-13.

Law CT, Gold JI. (2009). Reinforcement learning can account for associative and perceptual learning on a visual-decision task. Nat Neurosci 12(5):655-63.

Leh SE, Johansen-Berg H, Ptito A. (2006). Unconscious vision: new insights into the neuronal correlate of blindsight using diffusion tractography. Brain 129(7):1822-32.

Leh SE, Ptito A, Schönwiesner M, Chakravarty MM, Mullen KT. (2010). Blindsight mediated by an S-cone-independent collicular pathway: an fMRI study in hemispherectomized subjects. J Cogn Neurosci 22(4):670-82.

Leigh RJ, Kennard C. (2004). Using saccades as a research tool in the clinical neurosciences. Brain 127(3):460-77.

Lelkens AM, Koenderink JJ. (1984). Illusory motion in visual displays. Vision Res 24(9):1083-90.

Lev M, Ludwig K, Gilaie-Dotan S, Voss S, Sterzer P, Hesselmann G, Polat U. (2014). Training improves visual processing speed and generalizes to untrained functions. Sci Rep 4:7251.

Lewis TL, Maurer D. (2009). Effects of early pattern deprivation on visual development. Optom Vis Sci 86(6):640-6.

Liebetanz D, Nitsche MA, Tergau F, Paulus W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex

Liu T, Fuller S, Carrasco M. (2006). Attention alters the appearance of motion coherence. Psychon Bull Rev 13(6):1091-6.

Liu Z. (1999). Perceptual learning in motion discrimination that generalizes across motion directions. Proc Natl Acad Sci U S A 96(24):14085-7.

Luck SJ, Chelazzi L, Hillyard SA, Desimone R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J Neurophysiol 77(1):24-42.

Luu S, Lee AW, Daly A, Chen CS. (2010). Visual field defects after stroke–a practical guide for Gps. Aust Fam Physician 39(7):499-503.

Malikovic A, Amunts K, Schleicher A, Mohlberg H, Eickhoff SB, Wilms M, Palomero-Gallagher N, Armstrong E, Zilles K. (2007). Cytoarchitectonic analysis of the human extrastriate cortex in the region of V5/MT+: a probabilistic, stereotaxic map of area hOc5. Cereb Cortex 17(3):562-74.

Maloney RT, Watson TL, Clifford CW. (2013). Human cortical and behavioral sensitivity to patterns of complex motion at eccentricity. J Neurophysiol 110(11):2545-56.

Mannan SK, Pambakian AL, Kennard C. (2010). Compensatory strategies following visual search training in patients with homonymous hemianopia: an eye movement study. J Neurol 257(11):1812-21.

Manns JR, Squire LR. (2001). Perceptual learning, awareness, and the hippocampus. Hippocampus 11(6):776-82.

Maquet P, Schwartz S, Passingham R, Frith C. (2003). Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging. J Neurosci 23(4):1432-40.

Marcar VL, Cowey A. (1992). The effect of removing superior temporal cortical motion areas in the macaque monkey: II. Motion discrimination using random dot displays. Eur J Neurosci 4(12):1228-1238.

Marquez J, van Vliet P, McElduff P, Lagopoulos J, Parsons M. (2015). Transcranial direct current stimulation (tDCS): does it have merit in stroke rehabilitation? A systematic review. Int J Stroke 10(3):306-16.

Marrocco RT, Li RH. (1977). Monkey superior colliculus: properties of single cells and their afferent inputs. J Neurophysiol 40(4):844-60.

Mastropasqua T, Galliussi J, Pascucci D, Turatto M. (2015). Location transfer of perceptual learning: passive stimulation and double training. Vision Res 108:93-102.

Mather G, Harris J. (1998). Theoretical models of the motion aftereffect. In: Mather G, Verstraten F, Anstis S (Eds). The motion aftereffect. The MIT Press.

McGovern DP, Webb BS, Peirce JW. (2012). Transfer of perceptual learning between different visual tasks. J Vis 12(11):4.

McKee SP, Westheimer G. (1978). Improvement in vernier acuity with practice. Percept Psychophys 24(3):258-62.

McLennan H. (1983). Receptors for the excitatory amino acids in the mammalian central nervous system. Prog Neurobiol 20(3-4):251-71.

Mednick SC, Arman AC, Boynton GM. (2005). The time course and specificity of perceptual deterioration. Proc Natl Acad Sci U S A 102(10):3881-5.

Mednick SC, Drummond SP, Arman AC, Boynton GM. (2008). Perceptual deterioration is reflected in the neural response: fMRI study of nappers and non-nappers. Perception 37(7):1086-97.

Mednick SC, Nakayama K, Cantero JL, Atienza M, Levin AA, Pathak N, Stickgold R. (2002). The restorative effect of naps on perceptual deterioration. Nat Neurosci 5(7):677-81.

Miller MW, Nowakowski RS. (1988). Use of bromodeoxyuridine-immunohistochemistry to examine the proliferation, migration and time of origin of cells in the central nervous system. Brain Res 457(1):44-52.

Mishkin M, Ungerleider LG. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. Behav Brain Res 6(1):57-77.

Mishkin M. (1972). Cortical visual areas and their interactions. In: Karczmar AG, Eccles JC (Eds.). Brain and human behaviour. Springer-Verlag.

Mohler CW, Wurtz RH. (1977). Role of striate cortex and superior colliculus in visual guidance of saccadic eye movements in monkeys. J Neurophysiol 40(1):74-94.

Montminy MR, Bilezikjian LM. (1987). Binding of a nuclear protein to the cyclic-AMP response element of the somatostatin gene. Nature 328(6126):175-8.

Moo LR, Emerton BC, Slotnick SD. (2008). Functional MT + lesion impairs contralateral motion processing. Cogn Neuropsychol 25(5):677-89.

Moore T, Rodman HR, Gross CG. (2001). Direction of motion discrimination after early lesions of striate cortex (V1) of the macaque monkey. Proc Natl Acad Sci U S A 98(1):325-30.

Moran J, Desimone R. (1985). Selective attention gates visual processing in the extrastriate cortex. Science 229(4715):782-4.

Morland AB, Jones SR, Finlay AL, Deyzac E, L S, Kemp S. (1999). Visual perception of motion, luminance and colour in a human hemianope. Brain 122(6):1183-98.

Morris JS, DeGelder B, Weiskrantz L, Dolan RJ. Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. Brain 124(6):1241-52.

Morrone MC, Tosetti M, Montanaro D, Fiorentini A, Cioni G, Burr DC. (2000). A cortical area that responds specifically to optic flow, revealed by fMRI. Nat Neurosci 3(12):1322-8.

Moss AM, Harrison AR, Lee MS. (2014). Patients with homonymous hemianopia become visually qualified to drive using novel monocular sector prisms. J Neuroophthalmol 34(1):53-6.

Motter BC. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. J Neurophysiol 70(3):909-19.

Movshon JA, Newsome WT. (1996). Visual response properties of striate cortical neurons projecting to area MT in macaque monkeys. J Neurosci 16(23):7733-41. Neurol Neurosci 15(2-3):153-64.

Newsome WT, Paré EB. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). J Neurosci 8(6):2201-11.

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A. (2008). Transcranial direct current stimulation: State of the art 2008. Brain Stimul 1(3):206-23.

Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553(1):293-301.

Nitsche MA, Paulus W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527(3):633-9.

Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. (1984). Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307(5950):462-5.

O'Keefe J, Nadel L. (1978). The Hippocampus as a cognitive map. Clarendon.

O'Keefe LP, Movshon JA. (1998). Processing of first- and second-order motion signals by neurons in area MT of the macaque monkey. Vis Neurosci 15(2):305-17.

O'Neill EC, Connell PP, O'Connor JC, Brady J, Reid I, Logan P. (2011). Prism therapy and visual rehabilitation in homonymous visual field loss. Optom Vis Sci 88(2):263-8.

Ofen N, Moran A, Sagi D. (2007). Effects of trial repetition in texture discrimination. Vision Res 47(8):1094-102.

Olma MC, Dargie RA, Behrens JR, Kraft A, Irlbacher K, Fahle M, Brandt SA. (2013). Long-term effects of serial anodal tDCS on motion perception in subjects with

occipital stroke measured in the unaffected visual hemifield. Front Hum Neurosci 7:314.

Ong YH, Brown MM, Robinson P, Plant GT, Husain M, Leff AP. (2012). Read-Right: a "web app" that improves reading speeds in patients with hemianopia. J Neurol 259(12):2611-5.

Ong YH, Jacquin-Courtois S, Gorgoraptis N Bays PM, Husain M, Leff AP. (2015). Eye-Search: A web-based therapy that improves visual search in hemianopia. Ann Clin Transl Neurol 2(1):74-8.

OpenStax CNX. (2016). Figure 4, Sensory Pathways.
ONLINE: [https://cnx.org/contents/FPtK1zmh@6.17:KcreJ7oj@5/Central-Processing]. Last accessed 03/03/16.

Ostwald D, Lam JM, Li S, Kourtzi Z. (2008). Neural coding of global form in the human visual cortex. J Neurophysiol 99(5):2456-69.

Pambakian A, Currie J, Kennard C. (2005). Rehabilitation strategies for patients with homonymous visual field defects. J Neuroophthalmol 25(2):136-42.

Pambakian AL, Kennard C. (1997). Can visual function be restored in patients with homonymous hemianopia? Br J Ophthalmol 81(4):324-8.

Pambakian AL, Mannan SK, Hodgson TL, Kennard C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. J Neurol Neurosurg Psychiatry 75(10):1443-8.

Panizza B. (1855). Osservazioni sul nervo ottico. Giornale, Ist Lombardo di Sei e Let , 7: 237-252.

Papageorgiou E, Hardiess G, Schaeffel F, Wiethoelter H, Karnath HO, Mallot H, Schoenfisch B, Schiefer U. (2007). Assessment of vision-related quality of life in patients with homonymous visual field defects. Graefes Arch Clin Exp Ophthalmol 245(12):1749-58.

Paquette C, Sidel M, Radinska BA, Soucy JP, Thiel A. (2011). Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement. J Cereb Blood Flow Metab 31(10):2086-95.

Parent A. (2004). Giovanni Aldini: from animal electricity to human brain stimulation. Can J Neurol Sci 31(4):576-84.

Pegna AJ, Khateb A, Lazeyras F, Seghier ML. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. Nat Neurosci 8(1):24-5.

Peli E. (2000). Field expansion for homonymous hemianopia by optically induced peripheral exotropia. Optom Vis Sci 77(9):453-64.

Peszczynski, M (1961). Prognosis for rehabilitation of the older Adult and the aged hemiplegic patient. Am J Cardiol 7:365-369.

Pirulli C, Fertonani A, Miniussi C. (2013). The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. Brain Stimul 6(4):683-9.

Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. (1997). J Cogn Neurosci 9(4):534-47.

Plow EB, Obretenova SN, Fregni F, Pascual-Leone A, Merabet LB. (2012b). Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical

Plow EB, Obretenova SN, Halko MA, Kenkel S, Jackson ML, Pascual-Leone A, Merabet LB. (2011). Combining visual rehabilitative training and noninvasive brain stimulation to enhance visual function in patients with hemianopia: a comparative case study. PM R 3(9):825-35.

Plow EB, Obretenova SN, Jackson ML, Merabet LB. (2012a). Temporal profile of functional visual rehabilitative outcomes modulated by transcranial direct current stimulation. Neuromodulation 15(4):367-73.

Poggel DA, Mueller I, Kasten E, Bunzenthal U, Sabel BA. (2010). Subjective and objective outcome measures of computer-based vision restoration training. NeuroRehabilitation 27(2):173-87.

Poggio T, Fahle M, Edelman S. (1992). Fast perceptual learning in visual hyperacuity. Science 256(5059):1018-21.

Polat U, Ma-Naim T, Belkin M, Sagi D. (2004). Improving vision in adult amblyopia by perceptual learning. Proc Natl Acad Sci U S A. 101(17):6692-7.

Posner MI. (1980). Orienting of attention. Q J Exp Psychol 32:3-25.

Prince S, Offen S, Cumming BG, Eagle RA. (2001). The integration of orientation information in the motion correspondence problem. Perception 30(3):367-80. Prog Brain Res 192:219-20.

Ptito M, Johannsen P, Faubert J, Gjedde A. (1999). Activation of human extrageniculostriate pathways after damage to area V1. Neuroimage 9(1):97-107.

Purpura DP, McMurtry JG. (1965). Intracellular activities and evoked potential changes during hyperpolarisation of motor cortex. J Neurophysiol 28:166-85. quantitative analysis of sulcal patterning. Cereb Cortex 10(5):454-63.

Ragland DR, Satariano WA, MacLeod KE. (2005). Driving cessation and increased depressive symptoms. J Gerontol A Biol Sci Med Sci 60(3):399-403.

Rakic P. (1985). Limits of neurogenesis in primates. Science 227(4690):1054-6.

Rall TW, Sutherland EW. (1962). Adenyl cyclase. II. The enzymatically catalyzed formation of adenosine 3',5'-phosphate and inorganic pyrophosphate from adenosine triphosphate. J Biol Chem 237:1228-32.

Ramachandran VS, Braddick O. (1973). Orientation-specific learning in stereopsis. Perception 2(3):371-6.

Ramachandran VS. (1976). Learning-like phenomena in stereopsis. Nature 262(5567):382-4.

Raninen A, Vanni S, Hyvärinen L, Näsänen R. (2007). Temporal sensitivity in a hemianopic visual field can be improved by long-term training using flicker stimulation. J Neurol Neurosurg Psychiatry 78(1):66-73.

Read JC. (2015). The place of human psychophysics in modern neuroscience. Neuroscience 296:116-29.

Rees G. (2008). The anatomy of blindsight. Brain 131(6):1414-5.

Reichardt W. (1961). Autocorrelation, a principle for the evaluation of sensory information by the central nervous system. In: Rosenblith WA (Ed.) Sensory communication. MIT Press.

Reinhard J, Schreiber A, Schiefer U, Kasten E, Sabel BA, Kenkel S, Vonthein R, Trauzettel-Klosinski S. (2005). Does visual restitution training change absolute

homonymous visual field defects? A fundus controlled study. Br J Ophthalmol 89(1):30-5.

Rodman HR, Albright TD. (1989). Single-unit analysis of pattern-motion selective properties in the middle temporal visual area (MT). Exp Brain Res 75(1):53-64.

Roitman JD, Shadlen MN. (2002). Response of neurons in the lateral intraparietal area during a combined visual discrimination reaction time task. J Neurosci 22(21):9475-89.

Rosa MG. (2002). Visual maps in the adult primate cerebral cortex: some implications for brain development and evolution. Braz J Med Biol Res 35(12):1485-98.

Rossi PW, Kheyfets S, Reding MJ. (1990). Fresnel prisms improve visual perception in stroke patients with homonymous hemianopia or unilateral visual neglect. Neurology 40(10):1597-9.

Roth T, Sokolov AN, Messias A, Roth P, Weller M, Trauzettel-Klosinski S. (2009). Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study. Neurology 72(4):324-31.

Russo R, Wallace D, Fitzgerald PB, Cooper NR. (2013). Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. Brain Stimul 6(6):946-51.

Sabel BA, Kenkel S, Kasten E. (2005). Vision restoration therapy. Br J Ophthalmol 89(5):522-4.

Sabel BA. (2006). Vision restoration therapy and raising red flags too early. Br J Ophthalmol 90(5):659-60.

Sahraie A, Hibbard PB, Trevethan CT, Ritchie KL, Weiskrantz L. (2010b). Consciousness of the first order in blindsight. Proc Natl Acad Sci U S A 107(49):21217-22.

Sahraie A, Macleod MJ, Trevethan CT, Robson SE, Olson JA, Callaghan P, Yip B. (2010a). Improved detection following Neuro-Eye Therapy in patients with post-geniculate brain damage. Exp Brain Res 206(1):25-34.

Sahraie A, Trevethan CT, MacLeod MJ, Murray AD, Olson JA, Weiskrantz L. (2006). Increased sensitivity after repeated stimulation of residual spatial channels in blindsight. Proc Natl Acad Sci U S A 103(40):14971-6.

Sahraie A, Trevethan CT, Macleod MJ, Weiskrantz L, Hunt AR. (2013). The continuum of detection and awareness of visual stimuli within the blindfield: from blindsight to the sighted-sight. Invest Ophthalmol Vis Sci 54(5):3579-85.

Sahraie A, Trevethan CT, Weiskrantz L, Olson J, MacLeod MJ, Murray AD, Dijkhuizen RS, Counsell C, Coleman R. (2003). Spatial channels of visual processing in cortical blindness. Eur J Neurosci 18(5):1189-96.

Saito H, Yukie M, Tanaka K, Hikosaka K, Fukada Y, Iwai E. (1986). Integration of direction signals of image motion in the superior temporal sulcus of the macaque monkey. J Neurosci 6(1):145-57.

Salzman CD, Britten KH, Newsome WT. (1990). Cortical microstimulation influences perceptual judgements of motion direction. Nature 346(6280):174-7.

Salzman CD, Murasugi CM, Britten KH, Newsome WT. (1992). Microstimulation in visual area MT: effects on direction discrimination performance. J Neurosci 12(6):2331-55. Sand KM, Wilhelmsen G, Naess H, Midelfart A, Thomassen L, Hoff JM. (2016). Vision problems in ischaemic stroke patients: effects on life quality and disability. Eur J Neurol 23 1:1-7.

Sano M, Kitajima S. (1992). Activation of microtubule-associated protein kinase in PC12D cells in response to both fibroblast growth factor and epidermal growth factor and concomitant stimulation of the outgrowth of neurites. J Neurochem 58(3):837-44.

Sasaki Y, Nanez JE, Watanabe T. (2010). Advances in visual perceptual learning and plasticity. Nat Rev Neurosci 11(1):53-60.

Schenk T, Zihl J. (1997). Visual motion perception after brain damage: I. Deficits in global motion perception. Neuropsychologia 35(9):1289-97.

Schiller PH, Finlay BL, Volman SF. (1976). Quantitative studies of single-cell properties in monkey striate cortex. V. Multivariate statistical analyses and models. J Neurophysiol 39(6):1288-374.

Schiller PH, Malpeli JG. (1977). Properties and tectal projections of monkey retinal ganglion cells.J Neurophysiol 40(2):428-45.

Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS, Kasner SE. (2003). Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke 34(1):134-7.

Schmid MC, Mrowka SW, Turchi J, Saunders RC, Wilke M, Peters AJ, Ye FQ, Leopold DA. (2010). Blindsight depends on the lateral geniculate nucleus. Nature 466(7304):373-7.

Schneider KA, Kastner S. (2005). Visual responses of the human superior colliculus: a high-resolution functional magnetic resonance imaging study. J Neurophysiol 94(4):2491-503.

Schoups A, Vogels R, Qian N, Orban G. (2001). Practising orientation identification improves orientation coding in V1 neurons. Nature 412(6846):549-53.

Schwartz S, Maquet P, Frith C. (2002). Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. Proc Natl Acad Sci U S A 99(26):17137-42.

Seitz A, Watanabe T. (2005). A unified model for perceptual learning. Trends Cogn Sci 9(7):329-34.

Seitz AR, Kim D, Watanabe T. (2009). Rewards evoke learning of unconsciously processed visual stimuli in adult humans. Neuron 61(5):700-7.

Seitz AR, Yamagishi N, Werner B, Goda N, Kawato M, Watanabe T. (2005). Task-specific disruption of perceptual learning. Proc Natl Acad Sci U S A 102(41):14895-900.

Shadlen MN, Britten KH, Newsome WT, Movshon JA. (1996). A computational analysis of the relationship between neuronal and behavioral responses to visual motion. J Neurosci 16(4):1486-510.

Shadlen MN, Newsome WT. (1996). Motion perception: seeing and deciding. Proc Natl Acad Sci U S A 93(2):628-33.

Shadlen MN, Newsome WT. (2001). Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey. J Neurophysiol 86(4):1916-36.

Shibata K, Chang LH, Kim D, Nez JE Sr, Kamitani Y, Watanabe T, Sasaki Y. (2012). Decoding reveals plasticity in V3A as a result of motion perceptual learning. PLoS One 7(8):e44003.

Shiu LP, Pashler H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. Percept Psychophys 52(5):582-8.

Sincich LC, Park KF, Wohlgemuth MJ, Horton JC. (2004). Bypassing V1: a direct geniculate input to area MT. Nat Neurosci 7(10):1123-8.

Smallman HS, MacLeod DI, Doyle P. (2001). Vision. Realignment of cones after cataract removal. Nature 412(6847):604-5.

Smith AT, Singh KD, Williams AL, Greenlee MW. (2001). Estimating receptive field size from fMRI data in human striate and extrastriate visual cortex. Cereb Cortex 11(12):1182-90.

Smith AT, Wall MB, Williams AL, Singh KD. (2006). Sensitivity to optic flow in human cortical areas MT and MST. Eur J Neurosci 23(2):561-9.

Smith SM. (2002). Fast robust automated brain extraction. Human Brain Mapping 17(3):143-155.

Sowden P, Davies I, Rose D, Kaye M. (1996). Perceptual learning of stereoacuity. Perception 25(9):1043-52.

Spiegel DP, Hansen BC, Byblow WD, Thompson B. (2012). Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual

Spitzyna GA, Wise RJ, McDonald SA, Plant GT, Kidd D, Crewes H, Leff AP. (2007). Optokinetic therapy improves text reading in patients with hemianopic alexia: a controlled trial. Neurology 68(22):1922-30.

Squire LR. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99(2):195-231.

Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, Morris PG, Matthews PM, Johansen-Berg H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci 29(16):5202-6.

Stagg CJ, Nitsche MA. (2011). Physiological basis of transcranial direct current stimulation. Neuroscientist 17(1):37-53.

Stickgold R, James L, Hobson JA. (2000b). Visual discrimination learning requires sleep after training. Nat Neurosci 3(12):1237-8.

Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. (2000a). Visual discrimination task improvement: A multi-step process occurring during sleep. J Cogn Neurosci 12(2):246-54. stimulation. Neurorehabil Neural Repair 26(6):616-26.

Stoerig P, Cowey A. (1997). Blindsight in man and monkey. Brain 120 (3):535-59.

Sumner P, Adamjee T, Mollon JD. (2002). Signals invisible to the collicular and magnocellular pathways can capture visual attention. Curr Biol 12(15):1312-6.

Tamietto M, Pullens P, de Gelder B, Weiskrantz L, Goebel R. (2012). Subcortical connections to human amygdala and changes following destruction of the visual cortex. Curr Biol 22(15):1449-55.

Tanaka K, Hikosaka K, Saito H, Yukie M, Fukada Y, Iwai E. (1986). Analysis of local and wide-field movements in the superior temporal visual areas of the macaque monkey. J Neurosci 6(1):134-44.

Thompson B, Tjan BS, Liu Z. (2013). Perceptual learning of motion direction discrimination with suppressed and unsuppressed MT in humans: an fMRI study. PLoS One 8(1):e53458.

Thurston SE, Leigh RJ, Crawford T, Thompson A, Kennard C. (1988). Two distinct deficits of visual tracking caused by unilateral lesions of cerebral cortex in humans. Ann Neurol 23(3):266-73.

Tiel K, Kolmel HW. (1991). Patterns of recovery from homonymous hemianopia subsequent to infarction in the distribution of the posterior cerebral artery. Neuro-ophthalmology 11:3339.

Trauzettel-Klosinski S, Brendler K. (1998). Eye movements in reading with hemianopic field defects: the significance of clinical parameters. Graefes Arch Clin Exp Ophthalmol 236(2):91-102.

Trauzettel-Klosinski S. (2011). Current methods of visual rehabilitation. Dtsch Arztebl Int 108(51-52):871-8.

Trevethan CT, Urquhart J, Ward R, Gentleman D, Sahraie A. (2012). Evidence for perceptual learning with repeated stimulation after partial and total cortical blindness. Adv Cogn Psychol 8(1):29-37.

Trobe JD, Lorber ML, Schlezinger NS. (1973). Isolated homonymous hemianopia. A review of 104 cases. Arch Ophthalmol 89(5):377-81.

Tsanov M, Manahan-Vaughan D. (2008). Synaptic plasticity from visual cortex to hippocampus: systems integration in spatial information processing. Neuroscientist 14(6):584-97.

Tsushima Y, Sasaki Y, Watanabe T. (2006). Greater disruption due to failure of inhibitory control on an ambiguous distractor. Science 314(5806):1786-8.

Tsushima Y, Seitz AR, Watanabe T. (2008). Task-irrelevant learning occurs only when the irrelevant feature is weak. Curr Biol 18(12):R516-7.

Turner AM, Greenough WT. (1985). Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron. Brain Re 329(1-2):195-203.

Urner M, Schwarzkopf DS, Friston K, Rees G. (2013). Early visual learning induces long-lasting connectivity changes during rest in the human brain. Neuroimage 77:148-56.

Vaina LM, Belliveau JW, des Roziers EB, Zeffiro TA. (1998). Neural systems underlying learning and representation of global motion. Proc Natl Acad Sci U S A 95(21):12657-62.

Van Essen DC, Anderson CH, Felleman DJ. (1992). Information processing in the primate visual system: an integrated systems perspective. Science 255(5043):419-23.

Van Essen DC, Maunsell JH, Bixby JL. (1981). The middle temporal visual area in the macaque: myeloarchitecture, connections, functional properties and topographic organization. J Comp Neurol 199(3):293-326.

Van Essen DC, Newsome WT, Maunsell JH. (1984). The visual field representation in striate cortex of the macaque monkey: asymmetries, anisotropies, and individual variability.

Vanduffel W, Tootell RB, Schoups AA, Orban GA. (2002). The organization of orientation selectivity throughout macaque visual cortex. Cereb Cortex 12(6):647-62.

Vanneste S, Fregni F, De Ridder D. (2013). Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front Psychiatry 4:158.

Vidnyánszky Z, Blaser E, Papathomas TV. (2002). Motion integration during motion aftereffects. Trends Cogn Sci 6(4):157-161. Vision Res 24(5):429-48.

Volkmar FR, Greenough WT. (1972). Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science 176(4042):1445-7.

Wald G. (1968). Molecular basis of visual excitation. Science 162(3850):230-9.

Walker MP, Stickgold R, Jolesz FA, Yoo SS. (2005). The functional anatomy of sleep-dependent visual skill learning. Cereb Cortex 15(11):1666-75.

Walsh V, Ellison A, Battelli L, Cowey A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. Proc Biol Sci 265(1395):537-43.

Wandell BA, Smirnakis SM. (2009). Plasticity and stability of visual field maps in adult primary visual cortex. Nat Rev Neurosci 10(12):873-84.

Wandell BA, Winawer J. (2011). Imaging retinotopic maps in the human brain. Vision Res 51(7):718-37.

Wandell BA. (1999). Computational neuroimaging of human visual cortex. Annu Rev Neurosci 22:145-73.

Wang LY, Salter MW, MacDonald JF. (1991). Regulation of kainate receptors by cAMP-dependent protein kinase and phosphatases. Science 253(5024):1132-5.

Wang X, Zhou Y, Liu Z. (2013). Transfer in motion perceptual learning depends on the difficulty of the training task. J Vis 13(7):5.

Warner CE, Goldshmit Y, Bourne JA. (2010). Retinal afferents synapse with relay cells targeting the middle temporal area in the pulvinar and lateral geniculate nuclei. Front Neuroanat 4:8.

Wässle H1, Boycott BB. (1991). Functional architecture of the mammalian retina. Physiol Rev 71(2):447-80.

Watamaniuk SN, Sekuler R. (1992). Temporal and spatial integration in dynamic random-dot stimuli. Vision Res 32(12):2341-7.

Watanabe T, Náñez JE Sr, Koyama S, Mukai I, Liederman J, Sasaki Y. (2002). Greater plasticity in lower-level than higher-level visual motion processing in a passive perceptual learning task. Nat Neurosci 5(10):1003-9.

Watson AB, Pelli DG. (1983). QUEST: a Bayesian adaptive psychometric method. Percept Psychophys 33(2):113-20.

Watson JD, Myers R, Frackowiak RS, Hajnal JV, Woods RP, Mazziotta JC, Shipp S, Zeki S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cereb Cortex 3(2):79-94.

Weiskrantz L (1997). Consciousness lost and found: A neuropsychological exploration. Oxford University Press.

Weiskrantz L, Warrington EK, Sanders MD, Marshall J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. Brain 97(4):709-28.

Weiskrantz L. (1986). Blindsight: A case study and implications. Oxford University Press.

Wiesel TN, Hubel DH. (1963). Single-cell responses in striate cortex of kitten deprived of vision in one eye. J Neurophysiol 26:1003-17. with tDCS. Neuroimage 57(3):885-91.

Woo GC, Mandelman T. (1983). Fresnel prism therapy for right hemianopia. Am J Optom Physiol Opt 60(8):739-43.

Worsley KJ. (2001). Statistical analysis of activation images. In: Jezzard P, Matthews PM, Smith SM (Eds.). Functional MRI: An introduction to Methods. Oxford University Press.

Xi J, Jia WL, Feng LX, Lu ZL, Huang CB. (2014). Perceptual learning improves stereoacuity in amblyopia. Invest Ophthalmol Vis Sci 55(4):2384-91.

Xiao LQ, Zhang JY, Wang R, Klein SA, Levi DM, Yu C. (2008). Complete transfer of perceptual learning across retinal locations enabled by double training. Curr Biol 18(24):1922-6.

Yang T, Maunsell JH. (2004). The effect of perceptual learning on neuronal responses in monkey visual area V4. J Neurosci 24(7):1617-26.

Yeshurun Y, Carrasco M. (1998). Attention improves or impairs visual performance by enhancing spatial resolution. Nature 396(6706):72-5.

Yoshor D, Bosking WH, Ghose GM, Maunsell JH. (2007). Receptive fields in human visual cortex mapped with surface electrodes. Cereb Cortex 17(10):2293-302.

Yotsumoto Y, Chang LH, Watanabe T, Sasaki Y. (2009). Interference and feature specificity in visual perceptual learning. Vision Res 49(21):2611-23.

Yotsumoto Y, Watanabe T, Sasaki Y. (2008). Different dynamics of performance and brain activation in the time course of perceptual learning. Neuron 57(6):827-33.

Zeki S, Watson JD, Lueck CJ, Friston KJ, Kennard C, Frackowiak RS. (1991). A direct demonstration of functional specialization in human visual cortex. J Neurosci 11(3):641-9.

Zeki SM. (1974). Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. J Physiol 236(3):549-73.

Zhang JY, Yang YX. (2014). Perceptual learning of motion direction discrimination transfers to an opposite direction with TPE training. Vision Res 99:93-8.

Zhang JY, Zhang GL, Xiao LQ, Klein SA, Levi DM, Yu C. (2010). Rule-based learning explains visual perceptual learning and its specificity and transfer. J Neurosci 30(37):12323-8.

Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. (2006a). Natural history of homonymous hemianopia. Neurology 66(6):901-5.

Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. (2006b). Homonymous hemianopias: clinical-anatomic correlations in 904 cases. Neurology 66(6):906-10.

Zihl J, von Cramon D, Mai N. (1983). Selective disturbance of movement vision after bilateral brain damage. Brain 106(2):313-40.

Zihl J, von Cramon D. (1979). Restitution of visual function in patients with cerebral blindness. J Neurol Neurosurg Psychiatry 42(4):312-22.

Zihl J, von Cramon D. (1985). Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. Brain 108 (2):335-65.

Zihl J. (1995a). Eye movement patterns in hemianopic dyslexia. Brain 118 (4):891-912.

Zihl J. (1995b). Visual scanning behavior in patients with homonymous hemianopia. Neuropsychologia 33(3):287-303.

Zohary E, Celebrini S, Britten KH, Newsome WT. (1994). Neuronal plasticity that underlies improvement in perceptual performance. Science 263(5151):1289-92.