Brain plasticity and behavioural improvement in visuomotor learning: MRI study

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List of key abbreviations

MR	magnetic resonance
MRI	magnetic resonance imaging
fMRI	functional magnetic resonance imaging
DTI	diffusion tensor imaging
RT	response time
MFD	mean fixation duration
TNF	total number of fixations
VBM	voxel-based morphometry
WM	white matter
GM	grey matter
FA	fractional anisotropy
MD	mean diffusivity
AD	axial diffusivity
RD	radial diffusivity
BOLD	blood-oxygen-level-dependent
DWI	diffusion weighted imaging
ADC	apparent diffusion coefficient
CSF	cerebral spinal fluid
V3d	dorsal visual area (3)
FOR	fastigial oculomotor region
OC	oculomotor cerebellum

FEF	frontal eye field
VPL	visual perceptual learning
Min	minute
S	second
MS	millisecond
MM	millimetre
TR	repetition time
TI	inversion time
TE	echo time
3T	3 tesla
EPI	echo-planar
FOV	field of view
SPM	statistical parametric mapping
MNI	montreal neurological institution
GLM	general linear model
ROI	region of interest
FSL	FMRIB software library
TBSS	tract-based spatial statistic
ANTs	advanced normalization tool
SPSS	statistical package for social sciences
HH	homonymous hemianopia
LI	Laterality index

Abstract

Study 1

A better understanding of practice-induced functional and structural changes in our brains can help us design more effective learning environments that provide better outcomes. Although there is growing evidence from human neuroimaging that experience-dependent brain plasticity is expressed in measurable functional and structural brain changes that are correlated with behavioural performance, the relationship between behavioural performance and structural or functional brain changes, and particularly the time course of these changes, is not well characterised.

To understand the link between neuroplastic changes and behavioural performance, 15 healthy participants in this study followed a systematic eye movement training programme (30 training sessions) for 30 minutes daily at home, 5 days a week and for 6 consecutive weeks. In lab task sessions, behavioural performance statistics and eye tracking data were captured throughout the training period to evaluate learning outcomes. Imaging data (DTI and fMRI) were collected at baseline, after two and six weeks of continuous training, and four weeks after training ended.

Participants showed significant behavioural performance improvements (faster response time, lower fixation number and fixation duration) at the end of the training period compared to the baseline level.

Spatially overlapping reductions in microstructural diffusivity measures (MD, AD and RD) and functional activation increases (BOLD signal) were observed in two main areas (atlas-based): extrastriate visual cortex (V3d) and the frontal part of the cerebellum/Fastigial Oculomotor Region (FOR), which are both involved in visual processing. An increase of functional activity was also recorded in the right frontal eye field.

Behavioural, structural and functional changes were correlated. Microstructural change is a better predictor for long-term behavioural change than functional activation is, whereas the latter is superior in predicting instantaneous performance. Structural and functional changes at week 2 of the training programme also predict the behavioural performance improvement at week 6 and 10, which suggests that imaging data at an early stage of training may be useful in optimising practice environments or rehabilitative training programmes.

Study 2

To investigate the impact of the proposed eye movement training programme in patient population, seven hemianopic participants in this study followed a systematic eye movement training programme for 30 minutes daily at home, 5 days a week and for 6 consecutive weeks. In lab task sessions, Behavioural performance statistics and eye tracking data were captured throughout the training period to evaluate learning outcomes. Imaging data (DTI and fMRI) were collected at baseline, after two and six weeks of continuous training.

Similar to the healthy group (study 1), hemianopic participants showed significant improvements in behavioural performance (faster response time, lower fixation number and fixation duration). In particular, the response time in affected visual field was decreased over the training period in all behavioural performance tests (lab test, voluntary fMRI test and involuntary fMRI test), and this reduction reached the significant level at the end of the training period.

The intact visual cortex (contralateral lesion area) showed a greater number of active voxels during the fMRI trained task at all three scanning visits (week 0, 2 and 6) compared to the stroked visual cortex (ipsilateral lesion area), and the degree of the laterality index (LI) which assess hemispheric dominance of the functional tasks was increased at the end of the training period compared with the baseline. A significant increase of functional activity was recorded in the right frontal eye field.

The results, therefore, suggest that the current eye movement training facilitates the development of specific compensatory eye movement strategies in patients with homonymous visual field defects by adopting a more advantageous strategy of more rapid switching of hemifields as a result of training. This improvement is associated with brain plasticity in the visuomotor brain areas.

Declaration

No portion of this work has been submitted in support of any other application for degree or qualification at this or any other University or institute of learning.

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0.0 General overview and aims of the thesis

Many human neuroimaging studies (Collins, 2015; Tucker & Luu, 2012; Zatorre et al., 2012; Fields, 2015; Wang et al., 2014; Sampaio & Johansen, 2017) have provided clear evidence that learning-dependent neural plasticity is reflected in observable brain structural changes, and this anatomical change is usually associated with functional changes in individual neurones, causing behavioural change (Sampaio & Johansen, 2017). In particular, longitudinal learning studies have improved our understanding of the relationship between learning and plasticity in the structural and functional aspects of the human brain (Wang et al., 2014; Sampaio & Johansen, 2017). Understanding the link between brain plasticity and behavioural performance improvement offers useful insights into the learning process (Baker et al., 2015; Lövdén et al., 2013). For instance, a better understanding of learning mechanisms may improve the rehabilitative programme efficiency for stroke survivors (Baker et al., 2015), especially if potential outcomes can be predicted from neural markers at the early stages of intervention.

Logically, if the observed microstructural changes are causally related to behavioural changes, brain water diffusivity tests should correlate with behavioural performance (Sagi et al., 2012) as well as functional brain stimulation measures (Straathof et al., 2019). To test the hypothesis that microstructural MR, functional MR, and behavioural data during training will display associated changes, it important to choose a well-controlled task to investigate the possible association between multiple outcome measures that provides clearly defined outcome measures. Ideally, this task should be novel for all potential participants to make a better control for previous experience.

Rowe et al. (2017) proposed an eye-movement training programme for patients with hemianopia (people with visual field impairment, usually caused by strokes in visual areas), with a substantial change in vision-related quality of life recorded as a direct effect of the training (Rowe et al., 2017). In this intervention, over six weeks the participants learn to make systematic bilateral eye movements to scan an experimental environment. This task provides precisely measurable data on behavioural performance and eye-movement parameters

(Mannan et al., 2010; Pambakian et al, 2004; Wang, 2001), which can be directly correlated with MR imaging parameters.

While the task has been previously used in neurorehabilitation, it can be conducted on healthy participants to provide insights into the underlying neural mechanisms of visual perceptual learning, which is characterised after visual experience as long-term visual performance changes, and is thought to reflect brain plasticity in the adult population (Dong et al., 2018). This visual-scanning training should be novel for all potential participants to make a better control for previous experience and may allow us to investigate the learning mechanism appropriately. In addition, using a learning task that is carried out over a relatively extended period means that we can scan participants several times during the training and these repeated scans will enable us to test how early parameter changes may predict the potential long-term brain changes or behavioural outcomes. Therefore, the previous visual training task has been chosen in this project, and the key research question is: does this intervention cause measurable functional and structural changes in the brain?

Aim of the thesis

The main aim of this thesis is to investigate the learning mechanism when applying visuomotor learning to test the hypothesis that structural MR, functional MR, and behavioural data during training will display associated changes. In this thesis, it is expected to see significant behavioural performance changes associated with functional and/or structural parameters derived from advanced Magnetic resonance imaging (MRI) brain scans throughout an extended period of the visuomotor learning programme. Specific hypotheses are detailed in Chapters 2 and 3 (introduction sections).

Methods to test the hypothesis

For this PhD thesis, behavioural and imaging methodology have been developed to test the thesis hypotheses (see specific hypotheses in Chapter 2). Both behavioural and imaging methodology are explained in more detail in Chapters 2 and 3 (method sections).

In general, all participants in this research will follow eye-movement training developed for hemianopia neurorehabilitation: VISION visual scanning training (Rowe et al., 2017). The basic training paradigm will remain unchanged, except that the visual targets in this project will be presented on a computer screen (digital version designed especially for the current project) instead of an A4 landscape card, used by Rowe and colleagues (Rowe et al., 2017), to enable us to measure behavioural performance and eye-tracking data, such as correct eye fixation points and gaze latency.

Training paradigm

The participants will be asked to continually train at home for 30 minutes daily, five days a week and for six consecutive weeks. The training performance data, such as the response accuracy and training duration per day, will be recorded automatically and checked by the PhD student (Abdulrahman Aloufi) every week.

Behavioural performance data

In addition to the performance monitoring that will be carried out while participants are training at home, each participant will be assessed in the laboratory (before, during and after the training period), using an eye tracker. The data gathered at home will be used to check compliance with the training regime while the data recorded in the lab, using the same equipment and a controlled environment for all participants, will be the basis of the performance data that will be used to compare to imaging data. Three behavioural performance variables were measured: (1) Response Time (RT) – the average time taken by participants to respond to each stimulus in the experiment; (2) Mean Fixation Duration (MFD) – fixation durations were estimated from the eye-tracking data as periods where the eye position varied less than 0.5º over a minimum of 60 ms (Mannan et al., 2010); (3) Total Number of Fixations (TNF) – the number of fixations (gazes) required to complete the task session of 379 stimuli.

Imaging Data

Each participant will have multiple MRI scan visits: pre-training, during training and following training. In each MRI scan, functional magnetic resonance imaging (fMRI) and Diffusion tensor imaging (DTI) data will be collected routinely. More details about the data collection protocol and data analysis for behavioural and imaging data will explained in Chapters 2 and 3 (methods sections).

Applying this methodology on a healthy group with normal vision (in Chapter 2) was a precursor to a neurological evaluation of learning-induced training in hemianopia patients (in Chapter 3).

Chapter one

Brain plasticity and behavioural improvement during learning

1.1 Introduction

Acquisition of information and the ability to learn new skills or knowledge is usually considered as learning (Collins, 2015). Although there is no clear definition of learning, a permanent behavioural change as a consequence of experience or practice is a generally accepted definition (Haselgrove, 2016). From a scientific perspective, motor and perceptual learning take place between a stimulus and a response (Holland, 2008; Vleugels et al., 2020; Klotz et al., 2012; Tucker & Luu, 2012). Simply, being slower to respond to a particular task stimulation is not adaptive (Perez et al., 2013; Klotz et al., 2012) and practice (learning) may lead to rapid response (Vleugels et al., 2020; Tejas et al., 2014; Tucker & Luu, 2012). Thus, it is important to incorporate measurable behaviours into a definition of learning.

There is substantial empirical evidence that learning leads to measurable behavioural performance changes. People respond differently depending on what they have learned and this may link the measurable responses to different experiences or abilities (Haselhuhn et al., 2012; T. J. Bosch et al., 2018). This means that it is possible to design appropriate experiments to discover how learning could take place.

Changes in behavioural reactions are based on perception. For instance, improvements in our ability to distinguish between triangles and squares is involved in perceptual learning (Connolly, 2019). People may see the same thing differently due to the stable change from the past perceptual learning. This means the long-term perceptual changes that result from practice or experience are defined as perceptual learning, and short-term perceptual change is not such learning at all (Connolly, 2019).

1.1.1 Brain plasticity and learning

Learning is a form of information processing which occurs in the brain, and the basic information processing unit in the brain is the neurone. The study of the brain and nervous system is known as neuroscience, which may help us to have a better understanding about the changes that happen in the brain when people learn. Learning changes the brain structure that helps people build on what they already know, and changes their behaviours depending on what they already do (Collins, 2015). This means that learning may change how people behave and respond to surrounding stimulation in particular ways, as a consequence of creating new neural connections and disconnecting some of the older ones that are no longer useful (Zatorre et al., 2012; Fields, 2015).

Creating neural networks in the brain is a complicated process that connects, disconnects and reconnects neurones as one learns, unlearns and relearns (Collins, 2015). This demonstrates the concept of neuroplasticity, when the neural synaptic connections and neural pathways change as a result of responding to the world around us (Fusi & Abbott, 2005). During learning, neurones are connected up and that reorganises brain structures to establish stronger and faster efficient connection pathways to allow neurones to interact differently to each other (Collins, 2015; Fusi & Abbott, 2005).

An increase in the number of synaptic connections is not the only structural brain change that may be associated with learning to enhance brain plasticity. Myelination processing could also be involved, together with synaptic remodelling during learning by myelination of the unmyelinated neural axons or repair and modification of existing myelin sheaths (Zatorre et al., 2012; Fields, 2015). Neural functional activity that happens as a consequence of responding to stimulations from the surrounding environment modifies myelin regulation in appropriate brain regions and that may coincide with the development of specific cognitive functions or behaviours (Zatorre et al., 2012; Fields, 2015). Myelin sheath is present only in vertebrates, and myelin regulation seems relevant to the human brain (Fields, 2015). Glial cells in the human brain produce fatty phospholipid proteins to insulate neurones within myelin sheaths, hence less electrical energy is wasted (Collins, 2015). The fatty myelin sheaths cover the axons

of neurones and have been proposed to modulate signal processing by changing the relative speed of axonal transmission (Collins, 2015; Zatorre et al., 2012; Fields, 2015).

Surprisingly, neurogenesis can happen with learning in adult brains. There is empirical evidence of the role of learning in neural maturation to promote the functional neural networks in the hippocampus (Piatti et al., 2011; Pedro and José, 2018). Another possibility for brain structural change during learning is the increase of the non-neural cells number. Unlike neurones, astrocytes and oligodendrocytes (non-neural brain cells) have the ability to divide in the adult brain, and this structural plasticity of non-neuronal cell and gliogenesis happens in response to learning and experiences (Zatorre et al., 2012). Moreover, vasculature changes in the brain and an increase in blood volume is defined as angiogenesis processing that could be a consequence of gliogenesis processing that occurs during learning (Pereira et al., 2007).

Changes at different levels of microstructural brain tissue (such as neurogenesis, gliogenesis and myelination) occur to establish stronger, faster and more efficient connections between neurones when people learn. Importantly, people need to pay attention to the stimuli that can change or rewire human brains in order to change or add some behaviours, or to improve skills and gather knowledge (Collins, 2015). The repetition of a stimulus is the simplest form of learning that may strengthen the nerve impulses along the same pathways until the brain cells wire together (Collins, 2015; Haselgrove, 2016). Therefore, repetition may be the key to learning.

As learning is a complex biological mechanism, there have been different theories and a body of research about learning over the past years that usually remain under debate with new theories frequently superseding the old ones. However, it is fairly clear that learning is a process of changes in the brain and affects behaviour and thus performance. Therefore, it could be better to talk about learning on the basis of what actually happens in people's brains, rather than try to explain the learning mechanism based on vague hypotheses and the latest theoretical trends (Collins, 2015).

Learning has always been considered as a psychological process that is merely supported by biological mechanisms, therefore a better understanding of the mechanisms of neuroplasticity may add more concrete interpretations to modern learning theory (Tucker & Luu, 2012). Perhaps a better understanding of learning-induced functional and structural changes in our brains can help us to create more effective learning environments that may provide better outcomes. For example, it may help us to design and deliver more effective training sessions, rehabilitative programmes and learning environments. This may help to add a professional standing for those working in any learning field and will help to understand what form of learning they are dealing with, and hence how to produce the best results. In other words, a better understanding of learning mechanisms at the level of neuroplasticity is important because this supports the development of a theoretical framework and may help to optimise learning outcomes.

Merely studying behavioural changes is not enough to understand in detail human development processes. MR imaging methods are biologically specific methods that greatly help to non-invasively probe brain tissue microstructure and may lead us to a more comprehensive understanding of the link between learning and brain plasticity. Instead of conventional or qualitative MRI imaging techniques, advanced MRI methods are able to measure quantitative maps of the brain tissue's magnetic resonance properties. By using advanced MRI techniques, we will be able to get a more specific brain characterisation of plasticity-related behavioural change (Tardif et al., 2016; Tomoyo et al., 2016).

1.1.2 Neuroimaging and brain plasticity during learning

Over the last two decades, numerous neuroimaging studies of human brain plasticity have provided convincing evidence for rapid and extensive experience-induced neuroplasticity in vivo. Therefore, it has become widely accepted that the human brain is plastic with lifelong capacity to change its structure and function as a necessary mechanism for essential development, learning and recovery from brain damage or disease. After a stroke, for instance, the brain undergoes various stages of regeneration, where the central nervous system can reorganise neural circuitry both naturally and with the aid of behavioural therapy and non-invasive brain stimulation (Angela et al., 2015).

Results from a wide variety of human brain imaging studies over the last decade have found that the structure of white and grey matter can change after learning and functional experience (Wang et al., 2014). While most studies consider the long-term impact of learning, recent studies have reported rapid changes in grey and white matter (Hofstetter & Assaf, 2017; Sagi et al., 2012). However, although there is evidence from human neuroimaging studies that experience-dependent neural plasticity is expressed in measurable brain changes, the relationship between behavioural performance and structural or functional brain changes is not well understood (Fields et al., 2013). Undoubtedly, better understanding of the relationship between brain plasticity and behavioural performance change will provide a valuable insight into the learning process (Baker et al., 2015; Lövdén et al., 2013). For example, a deeper understanding of learning mechanisms may improve the efficiency of rehabilitative programmes (Baker et al., 2015), especially if outcomes can be predicted from neural markers at early stages of rehabilitative interventions.

Advanced structural MRI images can provide information to describe the size, shape, and integrity of white and grey matter structures in the brain. These advanced MRI methods also enable non-invasive longitudinal investigation of the entire brain by providing the big picture of neural change in space and time, which could be associated with measures of behavioural performance or training.

1.1.3 Learning-induced macrostructural changes in cross-sectional studies

Non-invasive investigation of experience-induced brain plasticity started with classical cross-sectional MRI studies that showed brain structure variations in populations that have been through extensive experience relative to controls. For example, MRI techniques such as voxel-based morphometry (VBM) showed enlargement of the corpus callosum, a white matter (WM) structure, in musicians compared with non-musicians (Schlaug et al., 1995). Similarly, significant grey matter (GM) volume increase was reported in the hippocampi of people working for many years as taxi drivers in London compared with those of controls (Maguire et al., 2000). Moreover, the differences were not only observed in the thickness or the surface of brain structures. A study using a DTI (diffusion tensor imaging) technique showed differences in WM architecture in the brains of professional musicians as greater fractional anisotropy (FA)

in the corpus callosum compared with non-musicians (Schmithorst & Wilke, 2002). More recently, structural alterations in WM in pianists (Bengtsson et al., 2005), and between professional musicians, amateur musicians, and non-musicians (Gaser & Schlaug, 2003), have been characterised in cross-sectional studies using DTI imaging techniques.

One of the possible limiting factors of the cross-sectional VBM studies comparing a trained group with controls is that since such studies (Maguire et al., 2000; Schmithorst & Wilke, 2002; Sato & Tanaka, 2015; Steele et al., 2013) are mostly focused on single scans, which are reported after several years of training, it is difficult to create consistent evidence that structural variations in the target group are induced by training rather than by other confounding factors. The same limitation, of one single scan, also applies to other cross-sectional studies that used DTI techniques to compare trained groups with controls in MRI neuroplasticity studies (Bengtsson et al., 2005; Gaser & Schlaug, 2003). Probably, therefore, the best approach to assessing purely the impact of learning on brain plasticity is to conduct a longitudinal study, in which one can observe the shift in the same individuals over time (for example, Jason et al., 2012).

1.1.4 Learning-induced macrostructural changes in longitudinal studies

After cross-sectional studies, subsequent longitudinal MRI studies have shown evidence for learning-induced brain plasticity. Over the last decade, many longitudinal MRI studies have shown evidence for learning-induced brain plasticity in both white and grey matter (Wang et al., 2014). One of the first longitudinal MRI studies used VBM methods to show increased density of GM in the visual motion region bilaterally as people learn to juggle over a three-month period (Draganski et al., 2004), and the same researchers later indicated that the changes (that can be measured using volumetric imaging) become noticeable after as little as seven days of training (Driemeyer et al., 2008). More recently, some longitudinal neuroimaging studies have shown that volumetric data quantifying change in brain structures can predict subsequent behavioural performance measures (Gryga et al., 2012; Sampaio et al., 2014; Kaustubh et al., 2013; Voss & Zatorre, 2012).

Although most longitudinal studies look at the long-term effects of learning (Gryga et al., 2012; Sampaio et al., 2014; Kaustubh et al., 2013; Voss & Zatorre, 2012; Scholz et al., 2009; Lövdén et al., 2010; Huber et al., 2018), some studies have reported rapid changes in both grey and white matter (Driemeyer et al., 2008; Taubert et al., 2010). Training on a complex whole-body balancing task, for example, results in increased GM in the frontal and parietal cortex after just two days of training, and altered FA over six weeks of training in corresponding white matter regions (Taubert et al., 2010). Even shorter, some studies using DTI methods have reported significant neural plasticity alterations in white and grey matter, which were expressed as water diffusivity changes, in the same cases within 24 hours (Hofstetter & Assaf, 2017; Sagi et al., 2012). Previous research using DTI (Hofstetter & Assaf, 2017; Sagi et al., 2012) successfully linked behavioural performance improvement with significant microstructural alteration to demonstrate that neural plasticity is directly related to behavioural performance improvements.

1.1.5 VBM limitations

VBM was the one of the earliest imaging techniques that was used for automatic volumetric analysis and this technique is still in wide use today. VBM measures morphological changes, for example volume increases in specific brain areas. This means that subtle changes, for example microstructural changes, may not be measurable using this technique. Though the VBM approach in classical cross-sectional studies has been under debate for several years (Tardif et al., 2016), it is still common in existing brain plasticity studies. Many recent cross-sectional studies (Maguire et al., 2000; Schmithorst & Wilke, 2002; Sato & Tanaka, 2015; Steele et al., 2013) used VBM methods to identify volumetric variations in brain structure thickness or the surface of different brain regions. Another limitation is that while changes in GM volume and thickness following learning were observed using morphometric analysis (VBM) of T1-weighted MRI imaging, the non-quantitative nature of T1-weighted contrast makes it more sensitive to several confounding factors, which are not specific to the underlying microstructural brain biology.

Changes in GM volume and thickness were postulated to be correlated mainly with one or more of the following events: synaptogenesis, myelination, dendritic branching or pruning,

neurogenesis (mainly in the hippocampus), gliogenesis and angiogenesis (Tardif et al., 2016). Unlike VBM, changes in DTI parameters represented successful microstructural changes during learning in many brain plasticity studies (Zatorre et al., 2012; Sampaio & Johansen, 2017; Egger et al., 2016). DTI methods, for example, helped in association of a higher degree of intracortical myelination with greater performance during a speeded task (Grydeland et al., 2013).

1.1.6 DTI and learning

DTI can generate structural maps of the fibre orientation and size of the white matter. DTI measures water diffusivity along multiple directional axes and is able to detect microstructural changes in grey and white matter (Zatorre et al., 2012; Sampaio et al., 2014; Cao et al., 2016). The fractional anisotropy, or FA, is the most widely used anisotropy DTI measure and is often considered a measure of "white matter integrity" (O'Donnell & Westin, 2011). Diffusivity of water molecules in a parallel direction to the tracts of white matter is detectable by a DTI marker called axial diffusivity (AD), while the DTI radial diffusivity (RD) is defined as perpendicular diffusivity (Pawel et al., 2018). The mean diffusivity (MD) is defined as the average amount of water diffusion across all directional axes within a voxel (O'Donnell & Westin, 2011). See supplementary materials (section A) for more details about the DTI sequence.

Changes in DTI parameters (FA, AD, RD and MD) were associated with microstructural alterations during learning (Wang et al., 2014; Sampaio & Johansen, 2017; Egger et al., 2016). Increasing FA or decreasing MD measures, for example, have been shown to be associated with neurogenesis or myelination increases during training in a number of brain imaging studies (Wang et al., 2014; Sampaio & Johansen, 2017; Madden et al., 2009). Similarly, training-induced changes in AD or RD have been suggested as indices of myelination or microstructural brain alteration (Cao et al., 2016; Egger et al., 2016). Unfortunately, the effect of training and the relationship between the different DTI parameters is not well understood (Cao et al., 2016). Longitudinal studies, which include multiple scans, may provide the necessary data to better understand how learning induces change in DTI measures (Zatorre et

al., 2012; Wang et al., 2014; Sampaio & Johansen, 2017; Jason et al., 2012). More literature about the role of DTI in learning studies is detailed in chapter 2 (introduction section).

Aside from the brain's structural images, the brain's functional images can also be visualised using MRI. This technology, called fMRI, can calculate the level-dependent blood oxygenation (BOLD) signal, which is well associated with the ability of the local synaptic activity (Tomoyo et al., 2016). See supplementary materials (section B) for more details about the fMRI technique.

1.1.7 fMRI and learning

The behavioural performance change that characterises brain plasticity caused by training or experience is usually the result of neural functional change in the local brain area. While part of this brain activation adjustment arises from structural alterations that support local function, variations in neuronal encoding and neurovascular coupling can also lead to functional response alterations. In the fMRI technique, transient physiological changes in the volume and/or flow of the blood, or more permanent changes from angiogenesis, can cause the observed brain activation signal change (Tardif et al., 2016). For example, during learning, oligodendrocyte cells need more metabolic requirements to produce the myelin sheath and must first ensure proper access to the blood supply (Yuen et al., 2014).

Over recent years, changes in neural activity have been the key to functional research into learning-induced brain plasticity in human brains, and a large number of fMRI studies have used the blood-oxygen-level-dependent (BOLD) signal to understand the brain functional learning process. Multiple human imaging learning studies have shown both localised increase and decrease in the fMRI signal (Albouy et al., 2012; King et al., 2013; Steele & Penhune, 2010). More literature about the role of fMRI in learning studies is detailed in chapter 2 (introduction section).

As the BOLD signals suffer from considerable physiological ambiguity, the interpretation of these signals is not straightforward (Buxton, 2010). Indeed, brain functional changes may

only take their full meaning when coupled with behavioural measures and the underlying structural, vascular, and metabolic environment (Tardif et al., 2016). Unfortunately, very few previous neuroimaging studies have incorporated imaging data from fMRI and DTI (Cao et al., 2016; Olesen et al., 2003). Some of these studies have suggested that a combination of these advanced MRI methods may provide more information of how brain structure and brain function can alter new brain development hypotheses and models, which should be tested by behavioural research (Tomoyo et al., 2016).

In summary, MRI studies on experience-dependent and learning-induced plasticity in human brains have contributed significantly to our understanding of the characteristic spatial and temporal patterns of structural and functional brain changes, but their biological meaning remains unclear (Tardif et al., 2016). Many human neuroimaging studies (Collins, 2015; Tucker & Luu, 2012; Zatorre et al., 2012; Fields, 2015; Wang et al., 2014; Sampaio & Johansen, 2017) have provided clear evidence that learning-dependent neural plasticity is reflected in observable brain structural changes, and this anatomical change is usually associated with functional changes in individual neurones, causing behavioural change (Sampaio & Johansen, 2017). Indeed, while many longitudinal studies have explored the link between time spent on training and structural brain changes (Lövdén et al., 2013), there is no consistent outcome pattern suggesting a single particular neural mechanism underlying training (Everts et al., 2007). A wide variety of neuroimaging studies (Zatorre et al., 2012; Sagi et al., 2012; Scholz et al., 2009; Madden et al., 2009; Thomas et al., 2009) link learning to brain alterations, however brain plasticity mechanisms are still not fully understood (Fields et al., 2013).

To date, a few longitudinal studies have performed behavioural and imaging assessments before, during and after training periods (Lövdén et al., 2013). Perhaps the best approach to assess purely the impact of learning on brain plasticity is to perform a longitudinal study, in which one can observe the shift in the same individuals over time (for example, Jason et al., 2012). Moreover, although the widely use of the fMRI and DTI in the brain plasticity studies, a few previous studies have combined data from DTI and fMRI (Cao et al., 2016; Olesen et al., 2003), and some of these studies demonstrate that a combination of these advanced MRI techniques can provide additional knowledge about brain organisation and brain function that

can modify new hypotheses and models of brain development, which can be tested by behavioural studies (Tomoyo et al., 2016). Therefore, importantly, DTI imaging should be paired with other advanced imaging techniques (e.g., fMRI) to explore the underlying learning process in longitudinal studies (Cao et al., 2016).

Future research may use these advanced neuroimaging methods to address these fundamental questions: how do we learn, why do some people learn more quickly than others, and how can we develop and enhance our learning? (Tardif et al., 2016). Therefore, in this project it was aimed to use advanced MRI techniques (such as DTI and fMRI) to enhance our understanding of the learning mechanisms in order to design and deliver more effective training sessions, rehabilitative programmes and learning environments.

In this thesis, a longitudinal study will be conducted to collect empirical behavioural data together with imaging data while groups of participants follow daily training sessions for a reasonably extended period. The data will be collected before, during and after the project's training intervention in order to investigate the correlation between behavioural performance, brain functional data and brain structural data. More details about the aims, hypotheses and methods of this thesis are provided in Chapters 2 and 3.

Chapter two

This chapter was published as a journal article in NeuroImage:

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Behavioural performance improvement in visuomotor learning correlates with functional and microstructural brain changes

2.1 Introduction

There is growing evidence from human neuroimaging studies (Zatorre et al., 2012; Fields, 2015; Collins, 2015; Tucker et al., 2012; Wang et al., 2014; Sampaio-Baptista & Johansen, 2017) that learning is associated with measurable structural brain changes. This alteration in structure supports the corresponding changes in the functional properties of individual neurones, giving rise to behavioural change (Sampaio-Baptista & Johansen, 2017).

Practice-induced structural changes of cortical and subcortical areas have been reported to occur in grey and white matter (Wang et al., 2014). While most studies consider the long-term effect of practice, some recent studies have demonstrated measurable changes at much faster time scales (Hofstetter et al., 2017; Sagi et al., 2012). Understanding the relationship between brain plasticity and behavioural performance change provides a valuable insight into the learning process (Baker et al., 2015; Lövdén et al., 2013). Better knowledge of how the brain is altered by practice and experience is also important for neurorehabilitation, for example for outcome prediction or to optimise behavioural or cognitive interventions used in rehabilitation (Baker et al., 2015; Kelly & Garavan, 2005; Dayan & Cohen, 2011).

Training-related structural brain plasticity has been studied in volumetric studies for a number of skills that combine perceptual and motor skills, such as juggling, computer games, sports, typing, phonetics and music making (Draganski et al., 2004; Draganski et al., 2006; Bezzola et al., 2011; Boyke et al., 2008; Cannonieri et al., 2007; Golestani et al., 2011; Schmithorst & Wilke, 200; Maguire, 2000; Sato et al., 2015). These classical studies consistently show larger local brain volume in task-relevant brain areas in skilled participants compared to untrained controls. Significant positive correlations between grey matter volume and the duration of practice are commonly reported and support the claim that the observed differences are training-induced (Draganski et al., 2006; Cannonieri et al., 2007; Eleanor et al., 2000).

2.1.1 Diffusivity changes in response to short duration perceptual and motor training

In addition to the volumetric brain structure changes discussed above, brain microstructure, as measured by DTI, has been shown to be a good predictor for skills, such as musical aptitude (Spray et al., 2017), musical performance (Oechslin et al., 2010), gymnastics (Deng et al., 2018), reading skills (Horowitz-Kraus et al., 2014), or working memory (Takeuchi et al., 2010), as well as in clinical diagnosis in a wide range of areas, ranging from hallucination proneness (Spray et al., 2018) to multiple sclerosis (Roosendaal et al., 2009).

Plasticity studies can broadly be split into studies that compare groups that received extensive training with control groups, and studies that measure rapid learning-induced microstructural changes within subjects. Studies that compare groups commonly show that extensive training is linked to increased fractional anisotropy (FA) and decreased diffusivity measures (e.g. Steele et al., 201; Moore et al., 2017 (motor training), Salminen et al., 2016 (n-back memory), and Cao et al., 2016 (cognitive training)). Increases in FA and decreases in diffusivity measures, however, are not reported in all training studies: Imfeld et al. (2009), for example, showed that diffusivity measures in the corticospinal tract of early onset musicians was higher and FA lower than in controls. Oechslin et al. (2010), presumably using the same imaging data, showed that mean FA in the superior longitudinal fasciculus was negatively correlated with pitch identification performance. Similar data was reported by Vandermosten et al. (2016) who showed that, for a group of trained phoneticians, the FA in auditory areas was reduced compared to controls.

Golestani et al. (2011), also for phoneticians, showed systematic gross morphological difference in the transverse gyri of the trained group vs controls. These structures are thought to be established in utero, highlighting that influences of domain-specific predispositions cannot be distinguished from training related morphological differences when comparing controls with groups that received specialist training (and may well have been selected for this training because of specific predispositions). This significant confound can be avoided by looking at the effect of training on a novel task within groups although this approach precludes

the study of very long term training effects since the same participants have to be scanned at least twice, before and after training.

A number of recent studies have shown diffusivity reduction and/or FA increases in task-relevant brain areas after very short training periods. Hofstetter et al. (2017), for a lexical training task, showed rapid diffusivity reduction in language-related brain areas, while Tavor et al. (2020) showed that short duration (45 mins) keyboard training causes significant MD reduction in motor areas. Similarly, training on memory tasks cause rapid changes in the hippocampus: Daria Antonenko et al. (2016) showed that reductions in diffusivity and increases in FA are seen in older participants (mean age 69 years), suggesting that observed changes are not age-limited. Sagi et al., (2012) and Tavor et al. (2013), showed significant changes to hippocampal microstructure in participants trained to navigate in a car racing game. Interestingly, in Tavor et al.'s (2013) study, the transient changes returned to baseline after approximately a week. This is consistent with data by Blumenfeld-Katzir et al., (2011) that link DTI changes observed in rats trained to perform a navigation task over five days to structural plasticity in astrocytes. The involvement of these glial cells suggests that the rapid microstructural changes seen in rats and humans may not be the results of direct changes to neural processes, but perhaps instead reflect changes that are precursors to more long-term neural changes. Furthermore, at least in the short term and in rats, rapid diffusivity changes appear to depend on the nature of the novel experience rather than exposure time (Hofstetter and Assaf, 2017).

In summary, while long term DTI training studies show conflicting changes in DTI parameters with learning, which may be explained by group differences, short term studies show more consistent increases in FA and/or reductions in diffusivity measures, even after very short training on novel tasks. These changes often are correlated with performance and do not appear to be limited by the age of the participants (Daria et al., 2016; Madden et al., 2009; Antonenko et al., 2016; Nichols & Joanisse, 2016; Bennette et al., 2011). These changes may reflect transient changes in supporting tissue, for example astrocytes (Sagi et al., 2012; Theodosis et al., 2008), rather than directly reflect neural plasticity.

Functional and structural changes to neural tissue can be caused by a number of mechanisms and affect grey matter, white matter, and extra-neuronal structures (review: Zatorre et al., 2012). Unfortunately, the effect of training on these structures and the relationship between the different DTI parameters is not well understood (Golestani et al., 2011). Longitudinal studies that include multiple scans may provide the necessary data to better understand how practice induces change in DTI measures of microstructure in the human brain (Zatorre et al., 2012; Wang et al., 2014; Sampaio-Baptista & Johansen, 2017).

To explore the underlying learning mechanisms during longitudinal studies (Kelly & Garavan, 2005; Cao et al., 2016), DTI needs to be combined with other imaging modalities (e.g. fMRI). If the observed microstructural changes have a causal relationship to behavioural changes, then one would expect diffusivity measures to correlate not only with behavioural performance (Sagi et al., 2012), but also with functional brain activation measures (Straathof et al., 2019). Moreover, if microstructural changes are apparent within days (Hofstetter et al., 2017; Sagi et al., 2012) rather than months of the onset of a new practice task, then this offers the possibility to directly measure brain micro-structural change before, during and after training.

2.1.2 fMRI activation changes in response to short duration motor and perceptual training

In general, reports of fMRI activation changes with learning are not entirely consistent (Kelly & Garavan, 2005). Some authors report an increase in activation (Yi et al., 2013) (Larcombe et al., 2018) others a decrease over time (Schneiders et al., 2011; Kirk et al., 2007; Farrar & Budson, 2017), yet others show simultaneous increase in some areas and decrease in other areas, consistent with functional reorganisation (Kelly & Garavan, 2005). A possible explanation for these inconsistent results is that there are distinct mechanisms and temporal phases in the time course of learning, related to differential dynamics of blood oxygen level-dependent (BOLD) activity (Yotsumoto et al., 2008). The following review will focus on motor and perceptual learning, which is at the core of the task we use.

One of the earliest reports of fMRI experiments that provide evidence of experience-dependent reorganisation of task relevant areas was provided by Karni et al. (1995) who showed that motor learning results in persistent and task-specific BOLD response increases in motor cortex. Later work on motor sequence learning and motor adaptation confirmed these findings and emphasized the role of sleep dependent consolidation (Debas et al., 2010; Karen et al., 2010); review (Doyon and Benali, 2005)).

A substantial amount of fMRI data supports proposals that perceptual training, like motor training, also leads to changes in local connections within task relevant areas. In the visual domain this has been shown for tasks ranging from texture (Sophie et al., 2002) or curvature discrimination (Maertens & Pollmann, 2005) to motion perception (Shibata et al., 2012) (Shibata et al., 2016). Similar effects have been demonstrated in other sensory modalities: short term discrimination training leads to neural activation increases, for example for auditory pitch discrimination (de Souza et al., 2013), or tactile grating orientation discrimination training (Hodzic et al., 2004) that were correlated to behavioural performance gains.

While perceptual learning necessarily modifies mostly sensory brain areas, similar effects have been shown in non-perceptual tasks. One example is mental practise, the cognitive rehearsal of movements, which, in stroke patients, led to simultaneous improvements in clinical motion measures and increased functional activation in bilateral motor cortex and ipsilateral superior parietal cortex (Page et al., 2009). Karabanov et al. (2019) using an endoscopic motor skill training task show task specific bilateral activation in task relevant motor areas were positively correlated with individual skill improvement. Censor et al. (2012) argue that perceptual and motor learning show similar characteristics in terms temporal dynamics and the interactions between primary cortical and higher-order brain areas that are suggestive of a common learning mechanism for both types of tasks.

In visual perceptual learning (VPL), initial functional activation increases are consistently reported with learning (Yotsumoto et al., 2008; Frank et al., 2018; Hadjikhani et al., 2001; Furmanski et al., 2004; Kourtzi et al., 2005), the further time course of functional activation changes with learning is much less clear. Yotsumoto and colleagues (Yotsumoto et al., 2008),

for instance, found that functional activation in the primary visual cortex (V1) initially increased, but returned to the level observed before training while behavioural performance still improved. The authors hypothesize that there are distinct temporal phases in the time course of perceptual learning, which are expressed in differential dynamics of BOLD activity. The initial activation increase can be explained in terms of an early encoding phase, while the drop in activation as learning progresses is explained by the consolidation in a later retention phase.

The reduction in functional activity to baseline levels, however, is not seen in other studies: Most strikingly, Frank and colleagues (Frank et al., 2018) measured behavioural performance and functional activation during a VPL task that required participants to discriminate complex motion patters and found that performance and task specific functional activation increases were still measurable three *years* after participants completed the initial VPL training.

A possible explanation of these differential results is that functional activation changes can be explained by different models: if learning leads to neuroplastic changes that make pre-existing task-relevant neural circuitry more efficient, then a *reduction* of activity would be expected. More efficient neural circuitry might enable participants to direct attentional resources better to task relevant areas, leading to more local *increases* of activation in relevant areas (Büchel & Friston, 1997). Another, partial, explanation for activation increases, particularly in self-paced tasks, are rate effects (Nyberg et al., 2006; Nyberg et al., 2006): increased activation may be caused by an increase in the number of stimuli participants can process in a given time (Liu et al., 2005), or by attending to task-relevant aspects, such as the modality, of the signals.

Functional activation changes in many VPL studies (Yotsumoto et al., 2014; Frank et al., 2016; Dong-Wha et al., 2018) are reflected in structural changes. Cortical thickness measures, for example, were associated with successful behavioural improvement in two VPL training studies (Bi et al., 2014; Frank et al., 2016) that also reported increase of functional activation with learning. Similarly, FA increases have been shown to accompany functional activation increases with training, and these FA increases were correlated significantly with behavioural

improvement (Dong-Wha et al., 2018). A better understanding of the time course of functional activation patterns, in particular when combined with microstructural data, may therefore shed light on the dynamics of learning induced neuroplastic changes.

The aim of this study is to test the hypothesis that training induces correlated changes in microstructural MR parameters, functional activation measures and behavioural data. To investigate the potential correlations between multiple outcome measures we chose a task which has clearly defined outcome measure, is novel for all participants to control for previous experience, and is relevant for clinical applications (Rowe et al., 2017). The task we chose is a 'visual search' task that is used for rehabilitation of patients with hemianopia (visual field loss, typically caused by injury to visual cortex) (Rowe et al., 2017). Indeed, for clinical and rehabilitative purposes, several studies have explored the impact of scanning eye movements into the affected visual field for hemianopia patients (Hanna et al., 2017). The training aims to compensate for visual field defects by improving the speed and accuracy of eye movements into the defective visual field portion (Aimola et al., 2014; Jacquin-Courtois et al., 2013; Lane et al., 2010; Ong et al., 2015; Pambakian et al., 2004).

Rowe et al. (2017) proposed a specific eye movement training program for stroke survivors with hemianopia and show an improvement in vision-related quality of life with training. In this intervention, stroke survivors learn to make systematic bilateral eye movements to scan the environment over six weeks. The task provides precisely measurable data on performance and eye movement parameters (Mannan et al., 2010; Pambakian et al., 2004; Wang, 2001), which can be directly correlated with MR imaging parameters. While the task has previously been used in neuro-rehabilitation, it can be applied to healthy participants and provides insights into the underlying neural mechanisms of perceptual and motor learning that reflect general principles of brain plasticity in adults (Dong-Wha et al., 2018).

Using a visuomotor learning task that is carried out over a relatively extended period means that we can scan participants multiple times during the training and these repeated scans enable us to test how early parameter changes predict longer-term changes or behavioural outcomes.

2.1.3 Specific Hypotheses

In this novel visuomotor learning task, we expect to see significant performance improvements over time in terms of processing speed, in terms of the required number of gazes to perform the task and in terms of gaze fixation duration.

1) Most fMRI studies in motor or visual perceptual learning, as discussed previously, report early increases of fMRI signal as a consequence of training. We therefore hypothesize that BOLD activation in functionally relevant areas should increase.

2) In addition to testing participants on the trained task, data was collected for an untrained, involuntary, eye movement task. We expect this task to activate broadly similar brain areas in fMRI, but do not expect to see significant performance or functional activation changes for this control task.

3) As discussed in the introduction, many learning studies show a reduction in diffusivity measures (MD, AD and RD) and an increase in FA with training. We therefore expect to see an increase in FA and/or a reduction in water diffusivity measures (MD, AD and RD) in the functionally relevant brain areas.

4) One of the aims of this study is to characterise the time course of behavioural, functional and structural change. Being able to demonstrate correlations between these parameters would strengthen the argument that the observed changes are directly or indirectly related and have predictive value.

2.2 Methods

2.2.1 Participants

To determine the number of participants required for the experiment, a power analysis (g-power, V3.1.9.4 (Faul et al., 2020)) was carried out. The effect size was estimated from previous results published by Sagi et al. (2012) who conducted a similar learning study (Cohen's d = 0.95). For the DTI analysis we have a clear a-priori hypothesis: decreased diffusivity measures and increased FA. The minimum participant number for a one-tailed, paired samples (comparing pre-and post-training data) analysis with α error probability (0.05) and power (1-β error prob = 0.95) was estimated as 14 (actual power 0.956).

In the current study, 15 healthy participants (7 female, 8 male) with normal vision were recruited (mean age = 35.9 years, range 21 – 60). All participants gave informed consent and the study was approved by University of Liverpool Ethics Committee (reference number: 1596).

2.2.2 Training design

All participants followed an eye movement training programme developed for hemianopia neurorehabilitation: *VISION visual scanning training* (Rowe et al., 2017). The basic training paradigm remained unchanged, except that the visual targets were presented on a computer screen instead of an A4 landscape card to enable us to measure behavioural performance and eye tracking data, such as correct eye fixation points and gaze duration.

The digital version of the VISION visual scanning training card (Fig.2.1) was created using *PsychoPy2 (v1.82.01)* (Peirce et al., 2019), and consists of numbered circles radiating out from a central fixation target along three axes, one horizontal, the other two spanning the diagonals of the screen. The participants learn to move their gaze quickly between a sequence of permanently visible and numbered targets as indicated in the diagram. Participants start just to the right of the fixation point (target 1, right) then move to the left hemifield (1, left), then to target (2) on the right etc.

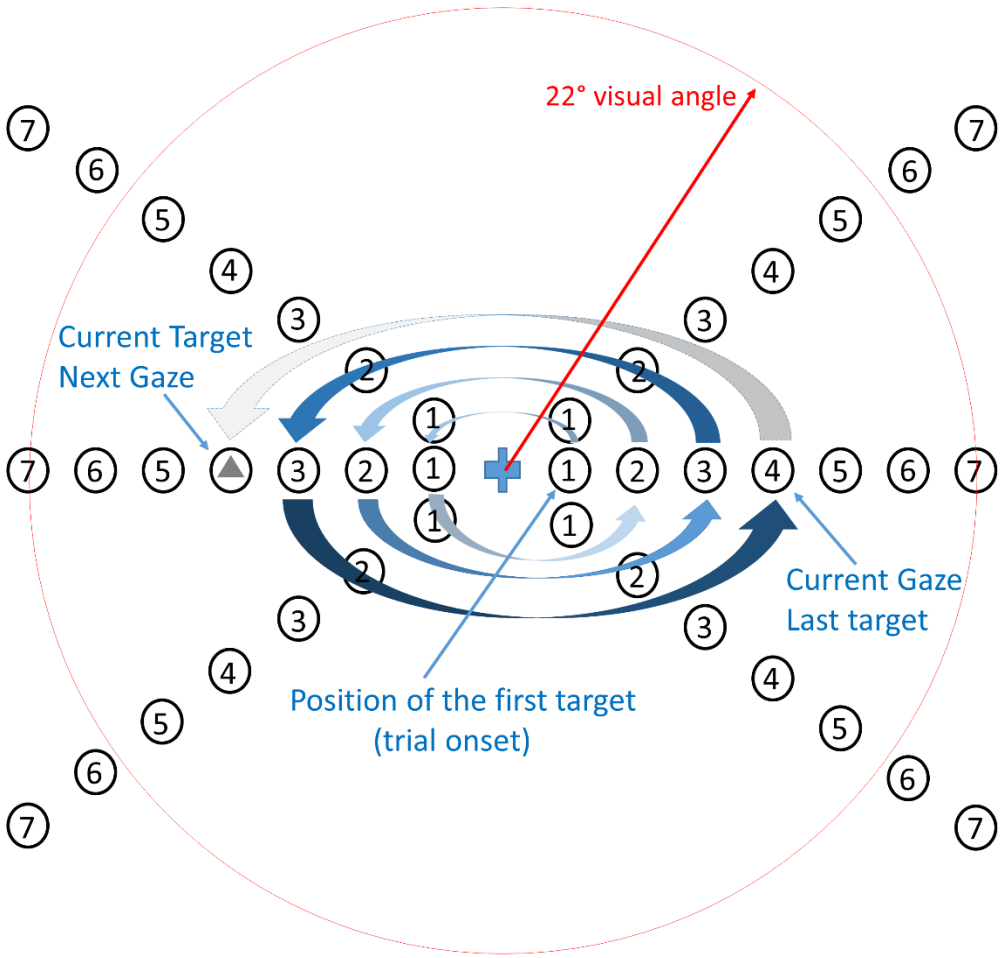

Fig.2.1 Schematic representation of the digital VISION visual scanning training: *the diagram shows the target gaze positions that participants are asked to look at during the task. The numbered circles and fixation point are permanently visible, participants systematically look at all numbered targets, alternating left and right. The next target always contains a small shape (circle or triangle), which participants have to identify. As soon as a response is given the current target disappears and a random shape is presented at the next target position. The targets are repetitively represented (379 stimuli) on three different axes (horizontal and two oblique axes). The digital version was used for training at home (30 minutes daily), lab testing and for the voluntary fMRI task.*

2.2.2.1 Training task and stimuli

Participants were asked to identify a small (0.45° visual angle, grey colour) symbol at the fixation target positions by pressing an appropriate button on a custom key-pad (left for triangle, right for circle). The first target appeared at the first numbered position near the centre of the screen at the beginning of each training session. Subsequent stimuli were presented in predictable positions but with a random shape (triangle or circle), systematically alternating between hemifields along the horizontal as well as oblique planes to ensure stimulation of a wide visual area. Only one target shape was visible at a time; the next target was presented in the opposite hemifield as soon as participants responded to the current stimulus. The three axes

of targets were always fixated in the same order: horizontal, then bottom-left to top-right, and then top-left to bottom-right.

As in the original training paradigm, participants were instructed to minimise head movements and keep at a fixed distance from the computer screen to achieve at least a 30-degree field of vision to the right and left sides. Participants were asked to respond as rapidly and accurately as possible. A minimum performance criterion of > 75% correct (the midpoint between chance and ceiling performance) was defined for all behavioural and functional tasks to ensure participants were attending to the stimuli.

2.2.2.2 Training paradigm

Participants were asked to continually train at home for 30 minutes daily, five days a week and for six consecutive weeks. Performance data (response times, accuracy, and overall training duration) were recorded automatically and checked every week (results: Table 2.2).

2.2.3 Behavioural performance data

In addition to the performance monitoring that was carried out while participants were training at home, each participant was assessed in the laboratory, using an eye tracker, every week. The data gathered at home were used to check compliance with the training regime while the data recorded in the lab, using common equipment and a controlled environment for all participants, is the basis of the performance data reported here.

2.2.3.1 Testing procedure

Behavioural performance was measured for each subject at the baseline (week 0), once every week for six weeks of training and at a follow-up test, one month after the training ended, to quantify visuomotor learning gains (Table 2.1).

All participants performed a session of the same 379 targets at each data collection point. The test session was performed on a laptop screen of 38.3 x 21.6 cm (width x height) at a viewing distance of 50 cm. A chin rest was used to minimise head movements. A display mounted eye tracker (*The EyeTribe – Model: ET1000),* individually calibrated for each test session, was used to record gaze position data.

Data collection	week 0	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9	week 10
Behavioural Data	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit				8th visit
Functional Data	1st scan		2nd scan				3rd scan				4th scan
Structural Data	1st scan		2nd scan				3rd scan				4th scan
		Training Period									

Table.2.1 Data collection protocol*: table shows behavioural performance measures in lab (baseline, six visits during the training period and a follow up visit after a month of training period), and MRI scans visits (baseline, two weeks later, end of the training period and a follow up visit after a month of training period). During the MRI scan visits the fMRI data (voluntary and involuntary), DTI data and in-scanner behavioural performance data were collected.*

2.2.3.2 Behavioural performance measurement

The principal behavioural performance measure was the mean response time (RT): the average time taken by participants to respond to each stimulus in the experiment. For experiments conducted in the lab and training runs at home, the number of targets in each run was fixed. The fMRI experiment was a block design, with alternating 'task' and 'rest' conditions, here the total execution time (task block duration) was fixed so that the number of targets processed varied between participants and MRI sessions.

In addition to the behavioural RT measure, two sets of eye tracking data were recorded: the Mean Fixation Duration (MFD); fixation durations were estimated from the eye tracking data as periods where the eye position varied less than 0.5º over a minimum of 60 ms (Mannan et al., 2010), and the total number of fixations (TNF); the number of fixations (gazes) required to complete the task.

Learning-related behavioural changes in this study were expected for eye movement parameters rather than for response accuracy, where we expect near ceiling performance, see also tables 2S1, 2S2 and 2S3 in the supplementary material (section D).

2.2.3.3 Stimulus presentation in the scanner

Participants were asked to lie still in the MRI scanner in a low light environment. The stimuli were presented via an MRI compatible monitor (NordicNeuroLab, model LCD 3.0.4, https://www.nordicneurolab.com). Participants saw the stimuli through a small mirror mounted on the head coil, providing a visual field of 45° degrees. PsychoPy2 *(v1.82.01)* (Peirce et al., 2019) was used for stimulus presentation and to record participants' responses via NordicNeuroLab fMRI Response Grips (using right index finger for circle targets and left index finger for triangle targets).

2.2.4 Image Data Analysis: General approach

Our image analysis is split into three parts. Firstly, we identify regions of significant change in functional and diffusivity measures over the six-week course of training. This analysis was limited to task-relevant brain regions, i.e. areas that show significant functional activation at any time during training. Following on from this analysis, we analyse the time course of change in the functional and diffusivity measures, focussing on the regions identified in the previous step. The final analysis tests whether neuroimaging measures correlate with behavioural performance and whether it is possible to extrapolate (predict) measures in time.

2.2.5 Functional Imaging Data Analysis

2.2.5.1 Functional imaging tasks

Two functional task sessions, voluntary and involuntary eye movement, were run for each participant at each MRI scan visit. For the voluntary eye movement task, stimulus presentation and participant instructions were identical to those used during training. For the involuntary eye movement task, serving as a control task, participants were asked to respond to circle or triangle targets (grey colour, size varied randomly between 0.92° and 1.14° visual degrees), which were presented in random positions to create involuntary saccades which means that the saccade has to be programmed each time afresh.

A standard block-design of 15 blocks, 32 seconds block duration (Maus et al., 2010), alternating 16 seconds of rest and 16 seconds of activity, was applied to measure the fMRI contrast changes for both tasks. Each functional task took 8 minutes (160 volumes) to complete. All sessions started with 16 seconds of rest and participants were requested to fixate a central fixation point during the rest periods.

The response accuracy and the total number of responses to the targets were recorded using PsychoPy2 (Peirce et al., 2019). Both tasks were performed at each of four fMRI scan visits (week 0, 2, 6 and 10, Table 2.1) that coincided with DTI scans and performance tests. Global activation patterns elicited during the training task are compared with those seen during the control task to demonstrate learning specific changes.

2.2.5.2 fMRI data acquisition

Anatomical, T1-weighted images (mprage, voxel size: 1.0×1.0×1.0 mm, TR = 2000.0 ms, TE = 2.25 ms, TI = 912 ms) and functional, T2*-weighted MR images were acquired with a 3T Siemens Magnetom Prisma using a 32-channel receiver head-coil. Functional imaging data were acquired using an echo-planar (EPI) pulse sequence (a T2*-weighted gradient-echo). Forty-eight interleaved transverse slices (voxel size = 3.0 × 3.0 × 2.7 mm, inter-slice gap = 2.97 mm) to cover the whole brain volume were acquired with EPI acceleration factor set to 2 and repetition time TR = 3000 ms (TE = 30 ms, flip angle = 90°, FOV 192 × 192 mm^2).

2.2.5.3 fMRI statistical analysis

Analysis of the functional data was performed with SPM12 (Statistical Parametric Mapping software, https://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2016a. Pre-processing of the functional data was performed using the SPM12 default batch (preproc_fMRI.m) starting with slice time correction, before realignment of all functional scanning sessions to a common image. For each participant, the EPI volumes for all eight sessions, voluntary and involuntary task at each of the four visits, were processed at the same time. All images within each session were spatially realigned to the first volume of the session, unwarped and corrected for motion artefacts.

The T1 weighted (mprage) structural image, collected during the baseline scan, was segmented into white matter, grey matter and cerebrospinal fluid for spatial normalization. All EPI images for each individual were realigned to this single, high resolution structural scan.

To complete the preprocessing, all EPI images were normalised to the Montreal Neurological Institution (MNI) space, resampled (1×1×1 mm^3 voxels using trilinear interpolation) and spatially smoothed with a 6 mm Gaussian kernel (full-width at half-maximum) for the group analysis.

2.2.5.4 First level fMRI data analysis

Data were analysed using a random-effect model (Friston et al., 1999), implemented in a two-level procedure. In the first level, fMRI signals for individual subjects were modelled in a General Linear Model (GLM) by a design-matrix, modelling the onsets and the durations of each block in the voluntary and involuntary task. In addition to the four regressors that were used for further analysis, rest_voluntary, act_voluntary, rest_involuntary and act_involuntary, six motion parameters, representing translational and rotational motion in three dimensions each, computed at the realignment stage, were modelled as nuisance regressors. From the four task-related regressors, two contrasts were created (act_voluntry vs rest_voluntary and act_involuntary vs rest_involuntary) for each visit. These contrasts form the basis of the ROI definition because they enable us to restrict further analysis to task-relevant brain regions in the fMRI and DTI data.

2.2.5.5 Second level fMRI Analysis 1: ROI definition

In fMRI and DTI analysis, it is common to define independent regions of interest (ROI) to increase sensitivity to small changes of the parameters of interest, here relatively subtle changes in fMRI or DTI parameters over six weeks of training (Froeling et al., 2016).

For DTI analysis, in particular for white matter tracts, it is common to use anatomically or functionally defined ROIs to extract white matter tracts that connect these regions (Anon, 2007; Revill et al., 2014; Beer et al., 2013) while in functional imaging independent functional scans are commonly used to define ROIs (Poldrack, 2007).

Training effects in DTI data are not restricted to white matter, but have also been shown to modulate grey matter diffusivity (Fields, 2011; Kühn et al., 2014; Noppeney et al., 2012; Blumenfeld-Katzir et al., 2011). Functionally relevant grey matter areas should therefore be included in the DTI analysis.

We expect relatively small structural or functional learning-induced changes over time but expect these neuroplastic changes to be restricted to task-relevant grey-matter regions, or in white matter tracts that connect relevant regions. To enhance the specificity of our analysis we therefore define a ROI that is used in fMRI and DTI analysis: group-wise fMRI activation maps (voluntary eye movement vs rest, thresholded pTFCE < 0.05) (Spisák et al., 2019), were computed separately for each of the four visits. These four maps were combined using a logical union (OR) operation to ensure that *any* clusters that were significantly active at *any* time of the training were included in the resulting ROI.

The DTI and fMRI used different image acquisition sequences and were processed independently. To allow for any inaccuracies in the alignment of the two modalities, the fMRI-based ROI masks were further smoothed using a 6 mm Gaussian kernel. The resulting mask consequently extends significantly into white matter adjacent to functionally defined regions: 55.9% of voxels in the global mask are located in white matter tracts identified from the DTI FA map (FA ≥ 0.15) (Dellani et al., 2007); see supplementary material (section C, Fig. 2S1)

2.2.5.6 Second level fMRI Analysis 2: training-induced functional activation change

For the second-level analysis (group analysis), contrast images from the first level analysis were entered into flexible ANOVA (repeated measures) analysis (Friston et al., 2002). This

analysis was performed separately for the two functional experiments (voluntary and involuntary) and consisted of four contrasts: two contrasts characterise the activation contrasts at baseline (week 0) and the end of training (week 6) relative to rest: ACTw0 > RESTw0 and ACTw6 > RESTw6. The remaining two contrasts compare activation post-training (week 6) with the baseline (week 0): ACTw0 > ACTw6 and ACTw0 < ACTw6). Cluster level probability values, thresholded at pFWE < 0.05, were computed from a voxel-level threshold of *p*-unc < 0.001. The cutoff for the cluster size used in the analysis was 845 voxels. All analyses were limited to the ROI.

2.2.6 Structural imaging data

2.2.6.1 DTI data acquisition

Diffusion-weighted images were collected immediately following the fMRI scans at each of the four visits (see Table 1). An EPI sequence with the following parameters was applied: repetition time/TR = 3200 ms, echo time/TE = 90 ms, flip angle = 90 degree, slice thickness = 2.5 mm, FOV = 220 × 220 voxels, 50 slices. As DTI sequences suffer from spatial distortions along the phase encoding direction (Thakkar et al., 2002), two diffusion-weighted sequences were acquired with reverse encoding directions, resulting in pairs of images with distortions in opposite directions. The principal DTI sequence (posterior/interior) consisted of a non-diffusion weighted T2 (b-value = 0s/mm^2) followed by a 64-direction diffusion weighted (b-value = 1000s/mm^2) images.

2.2.6.2 DTI data analysis

DTI data were analysed using FMRIB Software Library (FSL 5.0.9, http://www.fMRIb.ox.ac.uk/fsl/) (Woolrich et al., 2009) in a pipeline (Burzynska et al., 2010), including: (1) topup, to estimate and correct susceptibility induced distortions (Andersson et al., 2003), (2) eddy, to correct for eddy currents and motion artefacts in diffusion data (Andersson & Sotiropoulos, 2016), (3) BET (brain extraction tool) to remove the skull and non-brain tissue (Pechaud et al., 2006), and (4) DTIFIT for voxel-by-voxel calculation of the diffusion tensors (Basser et al., 1994). The following DTI parameters were computed: axial

diffusivity (AD = $\lambda 1$), radial diffusivity, RD = $(\lambda 2 + \lambda 3)/2$, mean diffusivity MD = $(\lambda 1 + \lambda 2 + \lambda 3)/3$, and fractional anisotropy FA = $\sqrt{((\lambda 1 - \lambda 2)2 + (\lambda 2 - \lambda 3)2 + (\lambda 1 - \lambda 3)2) / 2(\lambda 12 + \lambda 22 + \lambda 32)}$).

Instead of TBSS (tract-based spatial statistic) (Smith et al., 2006), the conventional DTI analysis consisting of nonlinear registration, followed by projection onto an alignment-invariant tract representation, the "mean FA skeleton", we followed the work of Schwarz et al. (Schwarz et al., 2014), who showed that ANTs (Advanced Normalization Tool) (Avants et al., 2011) groupwise registration methods enable more sensitive detection of the true structural changes and greater specificity in resisting false positives, which may occur from misregistration. As diffusion gradients are specified in the native space (Thakkar et al., 2002), DTI analysis was also carried out in the native space for each participant. In order to perform voxel-based analysis (VBA) we used ANTs (*antsMultivariateTemplateConstruction2.sh*) (Klein et al., 2010) to generate a FA template images for each individual subject. All DTI maps (FA, MD, AD and RD), then, were realigned in native space, using this FA template. DTI parameter changes between visits were computed in native space as a first level of analysis. To transform the DTI maps into a common space, transformation matrices mapping the individual FA templates into a common space (FMRIB58_FA_1mm.nii.gz) were computed using *antsRegistrationSyNQuick.sh.* The same transformation was then applied to all DTI maps using *antsApplyTransforms* (Avants et al., 2011).

The group analysis (as a second level of analysis) was then conducted after transforming the results of individual calculations into a common space. To increase the signal to noise ratio (SNR) (Schwarz et al., 2014), all computed images were smoothed with a 5 mm Gaussian kernel after transformation to the common space. The FSL-randomise script (*https://fsl.fMRIb.ox.ac.uk/fsl/fslwiki/Randomise*) (Winkler et al., 2014) was applied with default settings ($z = 2.3$ and $p = 0.05$) and by running 5000 permutations for statistical inference.

In a joint functional and DTI analysis, it is common to consider white matter tracts that connect functionally relevant grey matter areas. We performed a separate TBSS analysis to identify changes located in white matter tracts and found that all clusters of significant changes

in the TBSS analysis were included in the main ROI mask. Instead of duplicating the material in the main text, we therefore cover the TBSS analysis in the supplementary materials (section C, Fig. 2S2).

2.2.7 fMRI and DTI data extraction for time course analysis

The basis of the time-course analysis are brain areas that showed significant functional or structural change at week 6 (the end of training) compared to baseline.

2.2.7.1 fMRI data extraction

The MarsBar ROI toolbox for SPM (release 0.42) (Brett et al., 2002) and REX (http://web.mit.edu/swg/rex) were used to extract the mean activation in those areas that exhibited significant change at week 6 for all other time points. The labels of these regions were obtained using SPM-Anatomy toolbox v.1.7 (atlas-based). All clusters fell into occipital (v3d), cerebellar (OC) regions (see Fig. 2.5a, in the results section) and the right frontal eye field (FEF); see Fig.2.4 in results section. Where more than one activation cluster was located within a single anatomical region the clusters were combined.

2.2.7.2 DTI data extraction

Analogous to the fMRI processing, mean DTI parameters (AD, RD, MD and FA) were calculated over all voxels showing significant change. Clusters for each of the four DTI parameters were extracted and analysed separately because the size and shape of regions of change differed across DTI parameters. This means that each parameter mean is based on a mask that is specific to the parameter under consideration (see Fig. 2.5b for MD mask for time course data extraction; supplementary material, Fig.2.S6a for AD mask data extraction, 2.S6b for RD mask data extraction; Fig. 2.S4 for FA mask data extraction). Where more than one activation cluster was located within a single anatomical region the clusters were combined into a single data extraction mask (for time course analysis) to mirror the fMRI analysis.

2.2.8 Statistical analysis for all variables

To evaluate performance gains during training, paired samples t-tests, using Statistical Package for Social Sciences (SPSS V 16.0) for windows, were computed.

For further analysis testing whether changes in behavioural performance, functional activation patterns, and structural measures are coincident, we correlated these measures.

We expect an improvement in performance measures (decrease in RT, MFD and TNF), a decrease in all diffusivity measures (MD, AD, RD) and an increase in fractional anisotropy (FA) with training. For this reason (Ruxton & Neuhaeuser, 2020), one-sided statistical tests were used for these parameters.

Similarly, the existing literature (Yotsumoto et al., 2008; Hadjikhani et al., 2001; Furmanski et al., 2004; Kourtzi et al., 2005; Little et al., 2004) shows consistent functional activation increases in motor and perceptual learning tasks. We therefore used one-sided t-tests, hypothesizing an *increase* in mean functional activity with training, in all direct comparisons of fMRI data.

Behavioural performance data (RT and TNF) and DTI measures for the correlational analysis were expressed as change relative to the first measure recorded for each participant to minimise inter-subject variability:

$\Delta P_t = \frac{P_t}{P_0}$ where the relative performance change at time *t*, ΔP_t, is the ratio of the absolute performance *Pt* and the performance at the baseline *P0*.

The functional imaging data are proportional signal change estimates, β, already, so that they were used as they were recorded. The significance level for all correlation analyses was set at $p \leq 0.05$. The measures are highly correlated with each other, therefore violate the

independence assumption that is the basis for multiple comparison correction (see Fig.2.7 for summary data), we therefore present uncorrected p values for the correlation analysis.

2.3 Results

All 15 participants completed the training period with the minimum daily training session (30 minutes daily) and exceeded the minimum performance requirement (75% correct target identification in each task session). Thus, all behavioural and imaging data were included in the data analysis. Table 2 and section D in supplementary materials (Table 2.S1, Table 2.S2 and Table 2.S3) contain more details about behavioural performance accuracy of the participants during the training and tasks session.

Training and Tasks Performance results

Training and Tasks	Results (mean and standard deviation)
Daily training duration at home	31.44 minutes (5.4 minutes)
Accuracy of target detection at home	91.9% (5.1%)
Accuracy of target detection at lab	92.9% (3.0%)
Accuracy of target detection in scanner (voluntary task)	90.6% (2.0%)
Accuracy of target detection in scanner (involuntary task)	91.5% (2.0%)

Table.2.2 Results of training durations at home and behavioural performance accuracies: *the table shows the mean and standard deviation of the participants' daily training at home and the accuracy of target detection (home task, lab task and fMRI task).*

2.3.1 Impact of training – behavioural data

Behavioural performance improved significantly over the training period (Fig.2.2 and supplementary material, section E, Fig. 2.S3a and 2.S3b). In the group analysis, there is a significant main effect of training week in a repeated measures (subject) ANOVA $F_{(7,14)} = 11.50$, $p = 0.0013$). The mean response time (RT) decreased significantly from 0.80 (± 0.19) s

at week 0 to 0.47 (± 0.10) s at week (t(14) = 10.89, $p < 0.001$). The number of fixations (TNF) and mean fixation duration (MFD) measures also reduced significantly: the TNF reduced from 666 (± 132) to 485 (± 69), t(14) = 7.00, $p < 0.001$, while MFD reduced from 0.335 (± .053) s to 0.221 (± .041) s, t(14) = 8.02 , $p < 0.001$.

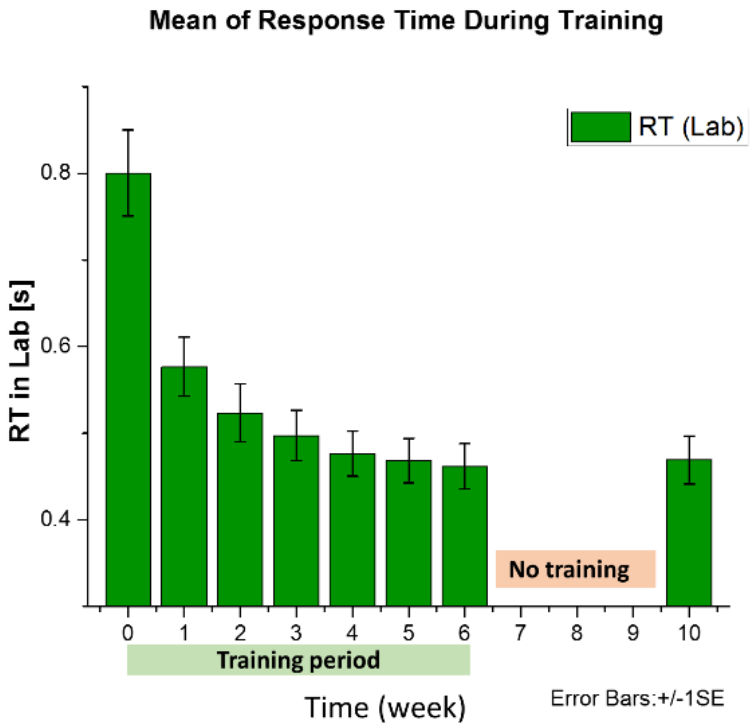

Fig.2.2 Training effects on behavioural performance: *the chart shows impact of the training on the average response time during the lab tests over the training period and one month after training (rightmost bar in the graph).*

Behavioural performance improvements were maintained one month after the training ended in all behavioural measures. The mean RT at week 10 was significantly lower than at baseline (0.47 s (± 0.10s) vs 0.80 s ± (0.19s), t(14) = 10.542, p < 0.001) but not different to the RT measured at week 6, Fig.2.2. See supplementary material, section E, for the other behavioural measures.

2.3.2 Impact of training – imaging data

Our participants were instructed to execute a complex sequence of alternating speeded voluntary eye movements. To show that behavioural and functional changes were the result of

training we asked all participants to carry out an involuntary eye movement (control) task to show the dissociation of training effects between the two tasks. We hypothesize that we will see an increase in functional activation and the DTI FA measure and a decrease in mean diffusivity measures (MD, RD, AD) in task-relevant brain areas for the training task only.

Both MRI functional tasks (voluntary and involuntary eye movement) cause similar global brain activation patterns (Fig. 2.3a and 2.3b). A significant increase in fMRI signal with training, however, was only shown in the voluntary (trained) task, Fig. 2.3c. No systematic training induced functional changes were shown for the involuntary (control) eye movement task, Fig. 2.3d.

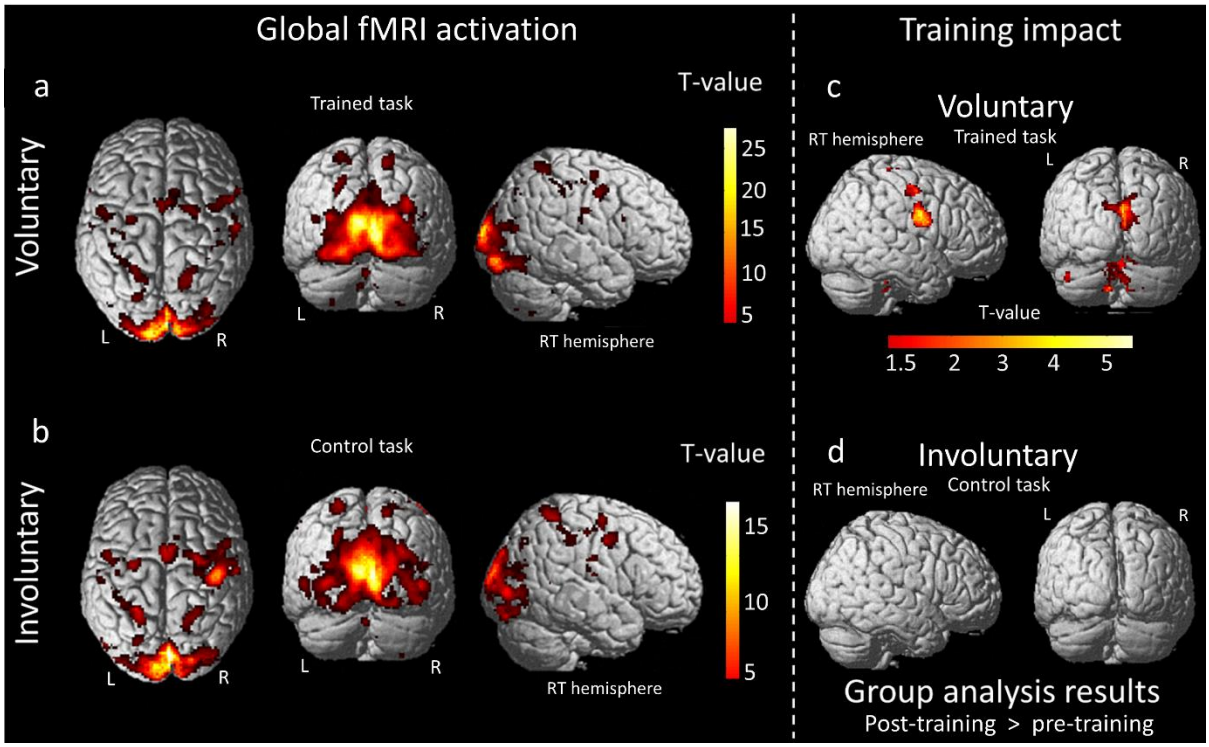

Fig.2.3 Global functional activation for the trained (voluntary) and control (involuntary) task*: Panel (a) and (b) show the average global activation (P_{FWE} < 0.05 cluster level) at baseline (week 0) for the voluntary and involuntary task. Significant activation changes between baseline and the end of training (week 6) are seen in occipital cortex, cerebellum and FEF (P_{FWE} < 0.05 cluster level) for the trained task in panel (c), but not for the control (involuntary eye movements) task in panel (d).*

At the end of the training period, significant fMRI activation changes were observed in the frontal eye field (FEF), the occipital lobe and cerebellum (Fig.2.4 and Fig.2.5a), $p_{(FWE)} < .05$ while participants performed the trained task.

Significant MD reductions were also observed in matching regions, the occipital lobe and cerebellum ($p_{(FWE)} < .05$, see Fig. 2.5b). The functional and structural brain changes overlapped mainly in extrastriate area (v3d) and Oculomotor Cerebellum region (OC), Fig. 2.5c.

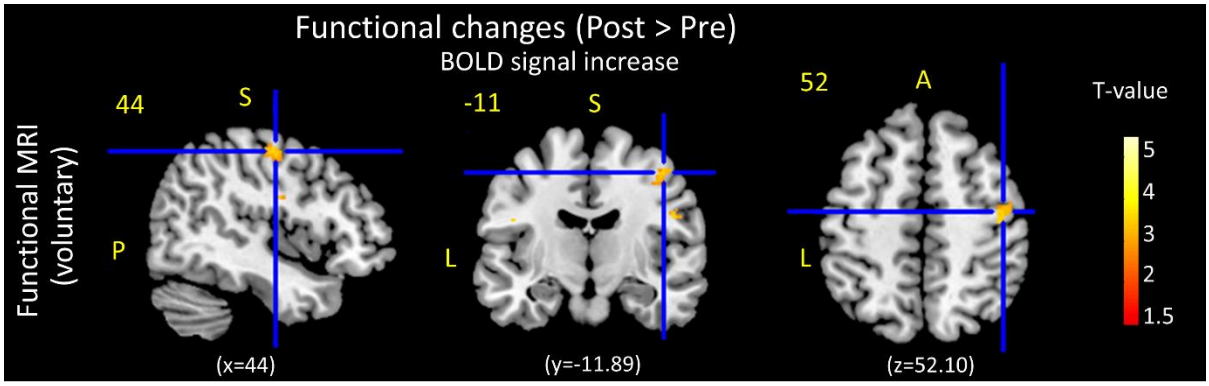

Fig.2.4 Functional activation change in the frontal eye field: *Post-Pre contrast shows functional activation ($P_{FWE} < 0.05$ cluster level) in the right FEF (x = 44, y = -11.89, z = 52.10) as a result of training. No significant activation changes were seen for the control task in the same area.*

We hypothesized that at the end of the training period, significant increases in fMRI activation, FA and a simultaneous reduction in diffusivity measures would be seen. Our data shows overlapping functional and structural changes in two functionally relevant areas. These changes are seen only for the trained, not the control task. No structural, but functional changes are seen in FEF. Fractional Anisotropy, FA, one of the key DTI measures, did not show significant change in any region (Fig. 2.S4, section F in supplementary materials). The pattern of change for the three diffusivity measures, AD, RD and MD are similar. As the MD measure is a composite of AD and RD the discussion below will focus on MD changes. Additional details are provided in the supplementary materials, including maps showing AD and RD data (section F, Fig. 2.S6), and more details about the affected functional and structural brain areas (section F, Fig. 2.S7).

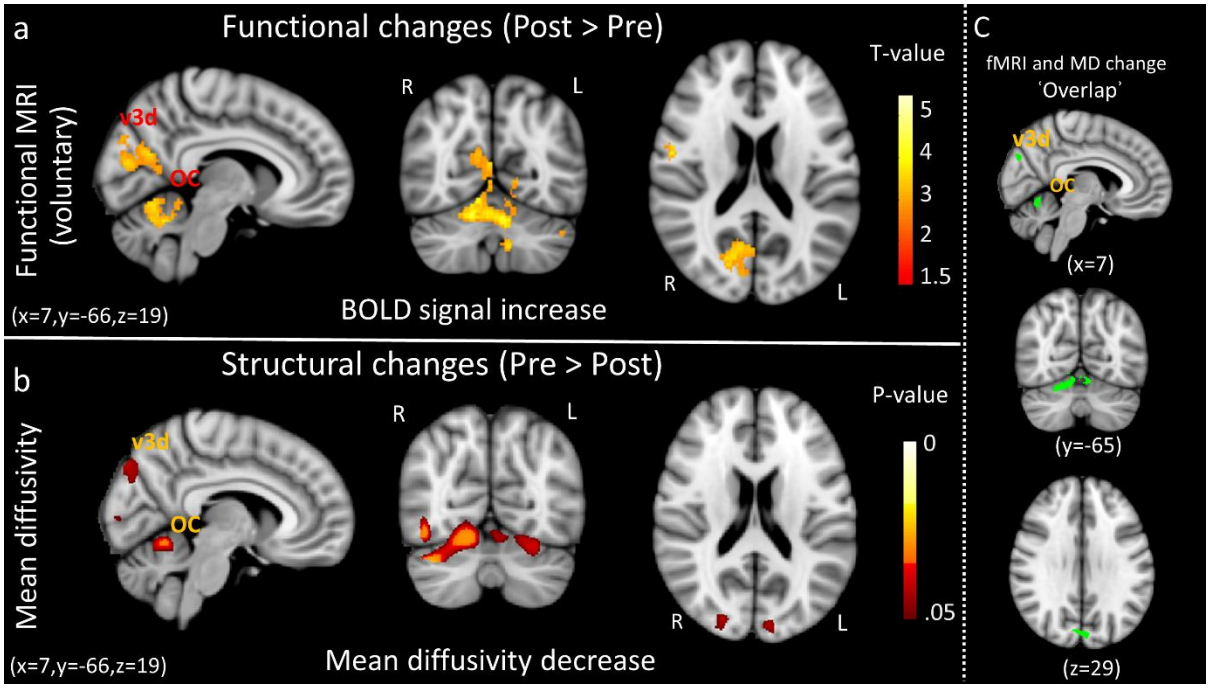

Fig.2.5 Direct comparison of the effect of training on functional and structural parameters*: Panel (a) shows significant increases in fMRI signal ($P_{FWE} < 0.05$ cluster level), while panel (b) presents significant reduction in the DTI MD measure. Functional and structural changes co-occur in extrastriate area (v3d) and oculomotor cerebellum (OC). The background images are T1-weighted Montreal Neurological Institute (MNI) standard templates (fsl standard/MNI152_T1_1mm) for orientation. Sections intersect at MNI coordinates [x = 7, y = -66, z = 19]. Panel (c) shows areas where fMRI and DTI changes overlap. Note that the spm fMRI images (panel a) are 'flipped' to facilitate comparison with the fsl representation of the MD images (panel b). All analyses were limited to the ROI area, which mean that all significant functional and structural clusters changes are located in the ROI mask (supplementary material, Fig. 2.S1a).*

2.3.3 Time course of functional and structural change

Behavioural measures (Fig.2.2 and Fig.2.S3) show the typical exponential performance improvement that was first described a century ago (Thurstone, 1919). The extracted micro-structural imaging data show matching gradual MD reductions in both visual and cerebellum MD target regions (Fig. 2.6b and 2.6d) over the six weeks of training. At week 6, MD was reduced significantly in the both target regions (MD visual, $t(14) = 5.93$, $p < 0.001$; MD cerebellum, , $t(14) = 8.08$, $p < 0.001$).

Functional activation changes were measured for the trained, voluntary eye movement task as well as for a control task involving involuntary eye movements (voluntary: Fig. 2.6a, Fig. 2.6c and Fig. 2.S8; involuntary: Fig 2.S9). Separate repeated measures ANOVAs with the factors time, (week 0,2, 6 and 10), condition (voluntary, involuntary) and participant as the repeated measure were conducted for each of the three regions of interest (visual cortex,

cerebellum and FEF). All three analyses showed significant main effects of training duration (factor 'Time': week 0, 2, 6 and 10) and significant interactions between duration and factor 'Condition' (voluntary, involuntary) consistent with differential learning effects for the two conditions. Significant main effects of 'Condition' were seen in visual cortex and cerebellum, but not in the FEF region. Post-hoc, paired t-tests show that the activation increases between week 0 and week 6 are significant in all three areas for the voluntary eye movement task but not for the control task (Table 3).

Region	*ANOVA*			*One-sided Post-hoc paired t-test (baseline pre training vs week 6)*	
	Condition	**Time**	**Interaction**	**voluntary**	**involuntary**
Visual cortex	**$F_{3,14} = 31.52$, $p < 0.001$**	**$F_{3,14} = 5.73$, $p = 0.011$**	**$F_{3,14} = 14.4$, $p < 0.001$**	**$t(14) = -4.22$, $p < 0.001$**	**$t(14) = 0.23$, $p = 0.41$**
cerebellum	**$F_{3,14} = 49.2$, $p < 0.001$**	**$F_{3,14} = 4.85$, $p = 0.02$**	**$F_{3,14} = 10.6$, $p < 0.001$**	**$t(14) = -4.17$, $p < 0.001$**	**$t(14) = -0.22$, $p = 0.41$**
FEF	**$F_{3,14} = 0.02$, $p = 0.87$ (n.s.)**	**$F_{3,14} = 5.94$, $p = 0.010$**	**$F_{3,14} = 7.34$, $p < 0.004$**	**$t(14) = -4.86$, $p < 0.001$**	**$t(14) = -1.02$, $p = 0.15$**

Table.2.3 Summary statistics of the ANOVA main training effects*: The table shows main effect of condition (voluntary vs involuntary), time (week 0,2,6, and 10) and their interaction for three separate ANOVAs that were computed for the three brain areas where significant change was seen. Significant interactions and a main effect of test time are seen in all three data extracted areas.. Post-hoc paired t-tests, comparing the mean BOLD response after training with the baseline measure in each area are shown on the right. A significant main effect of condition is seen in visual cortex and cerebellum, but not in FEF. Post-hoc tests show significant activation increases in all extracted data areas for the trained, but not for the control task.*

Functional activations and mean diffusivity changes in the visual and cerebellar target areas, as shown in Fig.6, partially reverted to baseline after the cessation of training. MD values in the visual area at week 10 remained significantly below baseline, $t(14) = 1.72$, $p < 0.05$, whereas the MD in cerebellum was no longer significantly different from the baseline, $t(14) = 1.2$, $p < 0.12$, Fig. 2.6b and 2.6d)

Functional activation during the voluntary task, which was increased significantly relative to baseline at weeks 2 and 6 during training, reduced at the week 10 test to a point where it was no longer significantly different from baseline (visual cortex $t(14) = -1.50$, $p = 0.07$, cerebellum $t(14) = -1.27$ $p = 0.11$, and FEF $t(14) = -1.55$, $p = 0.7$), Fig. 6a and 6c.

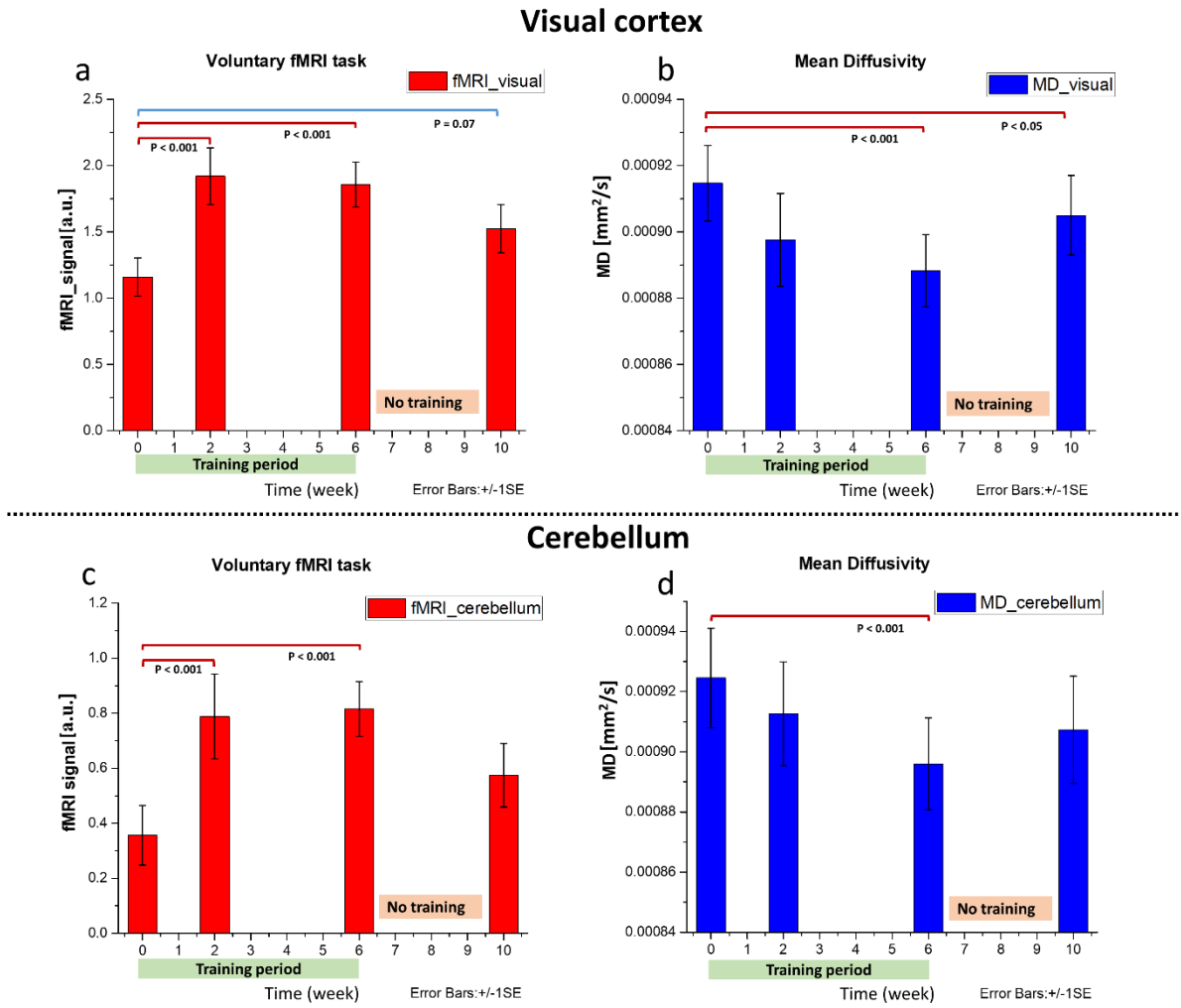

Fig.2.6 Time course data extraction for functional and structural measures from the areas that showed significant changes at week 6*: the charts show impact of the training on imaging data; fMRI data is shown on the left (red), MD data is shown on the right (blue). The extracted imaging data represent, separately, the mean measures (fMRI beta and MD) of all significant clusters in the visual cortex and cerebellum where significant changes are seen after six weeks of training. Both metrics follow roughly exponential behaviour during training, but then revert back towards baseline during the month after training ceases while behavioural performance remains static.*

2.3.4 Correlations between behavioural, functional and structural changes

If structural and functional adaptation supports behavioural adaptation, then the degree of this change should be related to behavioural performance changes at the individual level. The following sections describe correlations between measures, but also between neuroimaging measures recorded at week 2 and behavioural outcome measures recorded at weeks 6 and 10 to test whether early structural or functional change predicts longer term outcomes.

2.3.4.1 Overall pattern of correlations

The diagram in figure 7 shows an overview of correlations between neuroimaging parameters that changed significantly over the course of training and behavioural performance measures. In each case the change at weeks 2, 6, and 10, relative to baseline, is the basis for the correlation.

The measures are grouped by modality and marked by blue triangles: fMRI, top left, DTI diffusivity measures, middle, and behavioural measures, lower right. In each case the diagram shows that most measures within the two imaging modalities and behaviour are correlated. This confirms that the measures represent systematic, and gradual, changes that coincide over more than one brain region. Correlations across measures are much sparser: the most obvious correlations are between diffusivity measures and behavioural performance, identified by yellow shaded boxes in Fig. 7. AD, RD and MD measured at weeks 2 and 6 in the cerebellum are correlated with behavioural measures recorded at weeks 2-10.

Two further clusters of correlations link diffusivity measures to functional activation in the visual cortex, light blue blocks in Fig.2.7. Correlations between functional activation patterns and behavioural data are very limited (top right corner in Fig.2.7).

We include this data because it illustrates that the measures are highly correlated, especially within imaging modalities and across time. The data shows clear structure, which is incompatible with the random pattern that would be expected if the correlations emerged from type II errors as a result of noisy data. It is important to note that many of the correlations in this bulk analysis, for example across different measures, in different brain areas, or recorded at different times do not represent particularly meaningful comparisons. The detailed data discussed in the following sections represent planned comparisons for a small subset of possible correlations to test whether structural or functional change predicts performance.

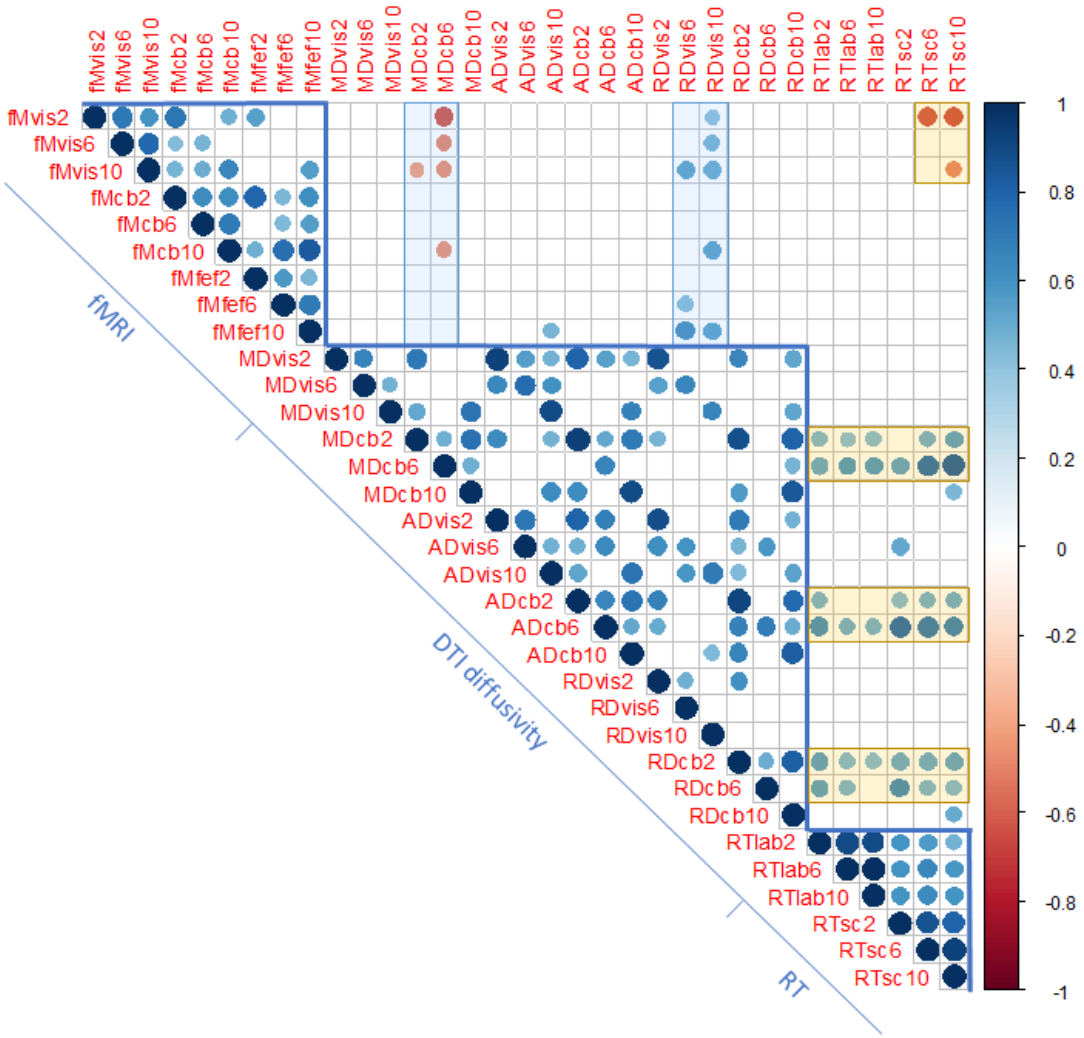

Fig.2.7 Diagram showing overall correlations between parameters showing significant changes at the end of training: *The diagram shows significant correlations (p<0.05, one sided, no correction) between neuroimaging and behavioural parameters. The matrix labels consist of three components: the type of measurement (fM: fMRI, MS, RD, AD: diffusivity measures, and RT: response time), the next letters identify the target area (vis=visual cortex, cb=cerebellum, fef=frontal eye field) for the neuroimaging data, while, for behavioural data, the label indicates where the data was recorded: lab=laboratory, sc=scanner). The final component is a number identifying the week the data was recorded (weeks 2,6,10). All changes are relative to the baseline at week 0. The size of the circle and colour indicates the degree and polarity of correlation, see colourbar on the right.*

2.3.4.2 Structural vs behavioural changes

Performance changes at the end of the training period are correlated with all three diffusivity measures (MD, AD and RD) in the cerebellum, but not in visual areas. Figure 2.8 shows the MD data against mean RT measured in the lab, $r(13) = 0.58$, $p < .01$.

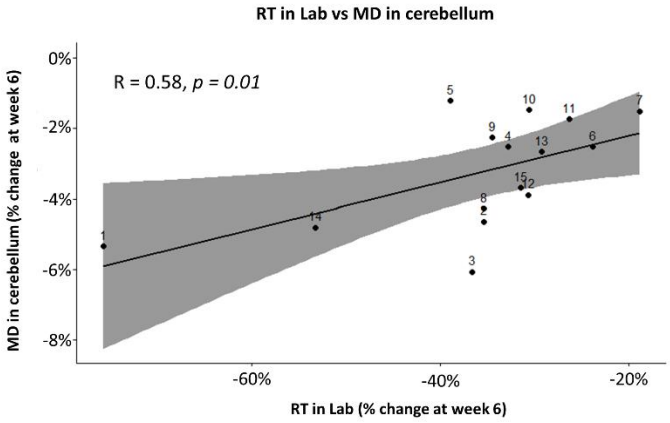

Fig.2.8 Correlation between RT change and MD change in cerebellum: *the graph shows a significant positive correlation between relative RT and MD changes among participants (numbers identify participants) over the six week training periods. All changes are relative to measures recorded at baseline (week 0).*

See supplementary materials (section G, Table 2.S4 and Table 2.S5) for additional correlation analysis between structural and lab behavioural data.

2.3.4.3 Functional vs behavioural changes

A wide range of DTI diffusivity measures were correlated with behavioural performance measures obtained under controlled laboratory conditions; see figure 2.8 and section G, Tables 2.S4 and 2.S5 in supplementary materials. We therefore expected to also see correlations between the functional activation and behavioural performance changes. Our data did not show this correlation at any time point. A possible explanation for this discrepancy is that the structural and performance changes discussed in the previous section are long-term changes, while functional activation reflects short-term behaviour in the scanner that is affected by additional task and environmental constraints. To further investigate this, correlations with performance, measured in the scanner instead of the lab environment, were computed.

The overall performance data in the scanner was similar to that seen in the lab. The mean RT while participants performed the voluntary fMRI task in scanner reduced significantly from 0.69s (± 0.10s) at baseline level to 0.45s (± 0.18s) after six weeks of training, $t(14) = 8.92$, $p < .00$. Similar significant change was shown after two weeks of training ($t(14) = 12.92$, $p < .001$) and also a month after training ceded ($t(14) = 12.05$, $p < .001$) (see also Fig. 2.S8d in supplementary materials, section H).

The functional data for the involuntary eye movement task shows similar overall activation patterns, but no significant activation change during the training period and no correlation of activation with either behavioural or structural change data, as expected for a control task, supplementary material (section H, Fig. 2.S9).

2.3.4.4 Overall functional vs behavioural changes: voluntary vs involuntary task

The correlation analyses presented so far aimed to investigate parameter changes seen at discrete time points. This is important to evaluate to what extent individual data is related and can be used to make outcome predictions. The measure, however, is fragile because it considers parameter changes between baseline and single time points. Using single measures means that the data may be more affected by measurement noise. An alternative approach is to test whether general trends, for example fMRI activation vs RT, are correlated for the population. This data is much more robust because all measurements can be considered at once, but does not allow individual outcome predictions to be made. We present it here because it shows that, overall, functional activation is correlated with RT, particularly for the visual cortex. More importantly the analysis enables us to address one of the potential confounds in the experiment: Both tasks that participants performed in the scanner are self-timed; this means that participants process increasing numbers of targets per unit time as they become more proficient at the task. What if the functional changes we see in the fMRI signal are not a direct result of learning, but simply reflect faster processing? One might, for example, expect activity in circuits controlling eye-movements to increase as participants perform the task faster, but these increases would be possible without direct effects of learning in these areas. The data in figure 9 shows all fMRI data against RT in the voluntary and involuntary tasks. If rate, and not learning, modulated activation, then one would expect to see higher BOLD signals in task relevant areas for shorter average RTs. This is clearly seen for the learned task. The same effect, however, should also be visible for the involuntary task where we see a broad range of mean RTs. The involuntary task does NOT show any link between RT and fMRI signal in any of our target regions, confirming that rate effects do not account for the differences seen.

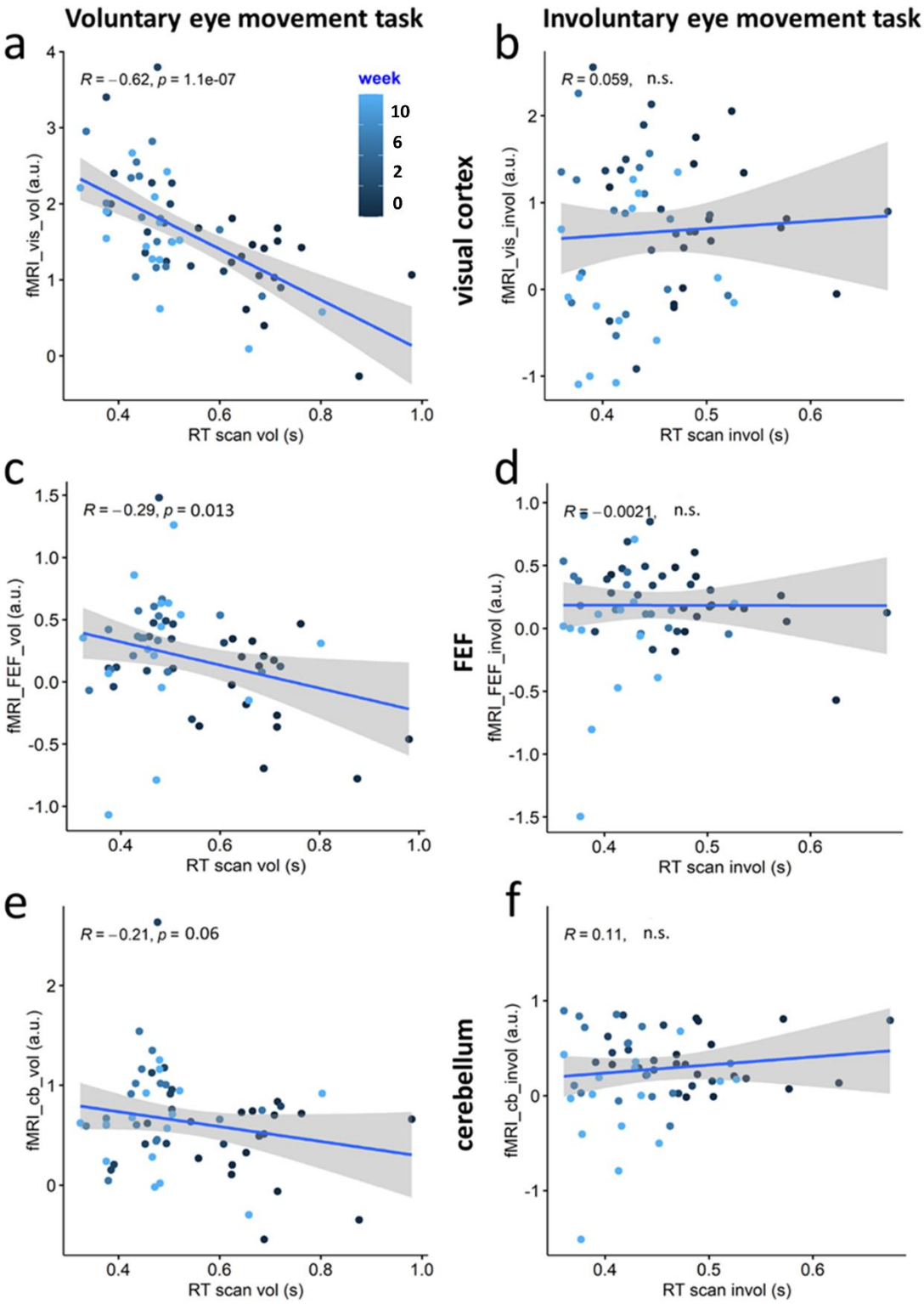

Fig.2.9 Correlation of fMRI activation against RT in scanner over all weeks: *the left column shows fMRI activation against RT for the voluntary (trained) task. Training reduces RT and increases fMRI activation in visual cortex (panel a) and FEF (panel c) significantly while the correlation is marginally significant in cerebellum (panel e). Equivalent changes are not seen for the involuntary eye movement task that served as a control (panels b, d, f).*

2.3.5 Outcome prediction

Cerebellar MD changes (Fig.2.8) as well as AD and RD changes (supplementary material, Table 2.S4) at the end of training were correlated with behavioural performance improvements. One of the key motivations for this research was to test whether early structural change (our week 2 data) can predict future neuroplastic or performance improvements because this would provide the basis for rehabilitative outcome prediction.

Interestingly, as shown in figure 10, the cerebellar MD change at week 2 predicts the changes of both the RT in lab at week 6, $r(13) = 0.43$, $p < .05$ (Fig. 2.10c), and MD at week 6, $r(13) = 0.48$, $p < .03$ (Fig. 2.10d). The other diffusivity measures, AD and RD, showed similar predictive properties as shown in the supplementary materials (section F and J, Fig. 2.S6 and Fig. 2.S11).

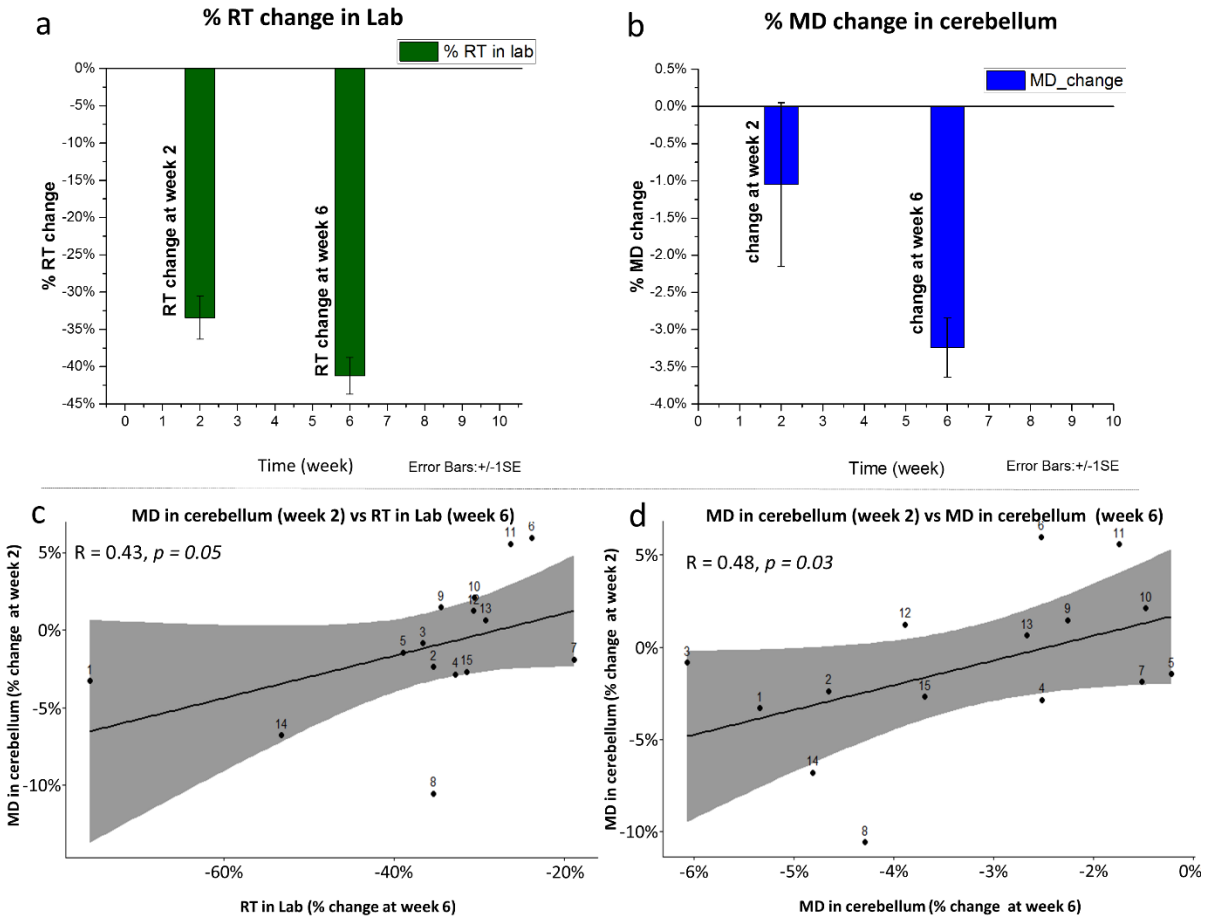

***Fig.2.10 Outcome prediction in lab**: (a) and (b) show the consistency of the percentage changes of the behavioural improvement and microstructural changes in cerebellum over the training period, (c) shows a significant correlation between the improvement in the completion time (at week 6) and the reduction in mean diffusivity after two week of training (week 2), and (d) reveal the correlation among participants when compare the initial stage of MD changes (week 2) vs the later stage of MD change (week 6) during visuomotor learning.*

Functional activation data in visual cortex after two weeks of practice did not predict the behavioural changes in the lab, but surprisingly predicts in-scan performance at the end of training and four weeks after the end of training well (visual fMRI week 2 vs RT in scanner week 6, $r(13) = -0.64$, $p < .005$, Fig. 2.11a; visual fMRI week 2 vs RT in scanner week 10 $r(13) = -0.64$, $p < .004$, Fig. 2.11b).

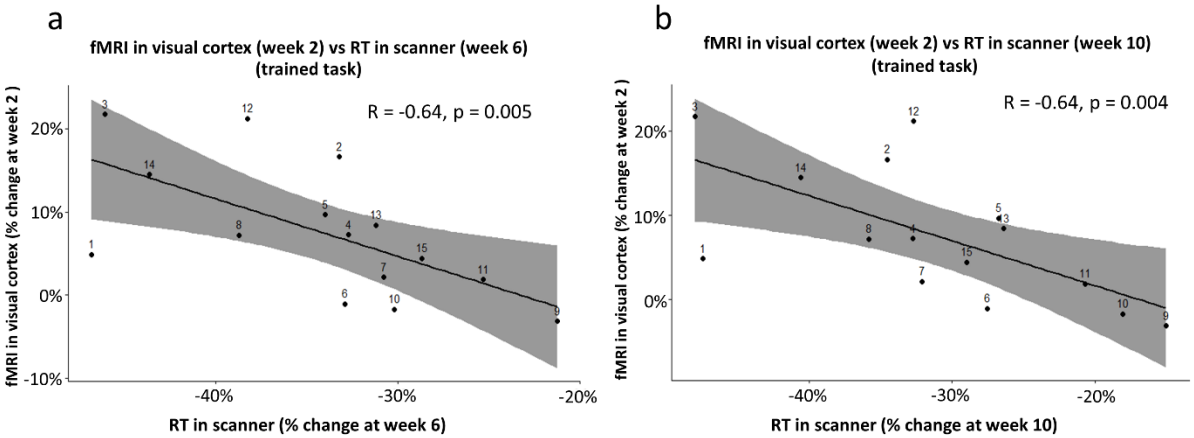

Fig.2.11 Outcome prediction in scanner*: (a) shows a significant correlation between voluntary fMRI increase in the visual area after two weeks of training (week 2) and the reduction in scanner RT at the end of the training period (week 6), (b) shows a significant correlation between voluntary fMRI increase in visual area after two weeks of training (week 2) and the reduction in scanner RT after a month of training ended (week 10).*

2.4 Discussion

The primary aim of the study was to investigate the link between behavioural performance on a visuomotor learning task with functional and structural parameters derived from neuroimaging.

As expected from previous work (Little et al., 2004), all participants showed significant behavioural performance improvements over the course of the training period: the mean response time, the number of fixations required to complete the task, and the mean fixation duration required for individual decisions reduced significantly while response accuracy remained high (>90%). The results are consistent with two previous studies (Mannan et al., 2010; Pambakian et al., 2004), which applied visual search training for rehabilitative purposes on hemianopia patients. Performance was measured four weeks after the cessation of training

and remained at levels seen at the end of the training. This indicates that the training effect was persistent as would be expected for motor and perceptual learning.

2.4.1 Neuroplastic Change

The principal finding is that the current eye movement training leads to significant, bilateral functional activation increases in extrastriate visual cortex (v3d), the frontal part of the Oculomotor Cerebellum (OC) (Amir et al., 2016) and in the right FEF. The functional activation changes in extrastriate visual cortex and cerebellum were accompanied by a significant decrease in DTI mean diffusivity measures in these areas and the underlying connecting white matter tracts. No significant changes in FA were observed.

2.4.1.1 Functional activation during voluntary eye movements

Extrastriate Cortex

Previous fMRI studies (Büchel et al., 1998; Hietanen et al., 2006) highlighted the role of extrastriate area in visual processing. A longitudinal eye movement training study in hemianopia patients also reported an increase of brain activation following the training in this area (Nelles et al., 2010). The current results suggest a key role of extrastriate cortex in visuomotor learning.

Our data shows bilateral (although right-dominant) functional and structural plasticity at the junction between intraparietal and transverse occipital sulcus (IPS/TOS) and bilateral changes at dorsal V3 (v3d). This is consistent with data reported by Corbetta and colleagues (Corbetta et al., 1998) who showed selective activation in the IPS/TOS area when participants performed saccadic shifts to peripheral stimuli. Another fMRI study by (Müller-Plath, 2008), using a visual search task, reported a role of IPS/TOS and dorsal V3 (v3d) in eye movement programming, although the specific role of v3d in the eye movement processing is still not clearly understood.

Cerebellum

Our results showed significant functional and structural alteration in the frontal part of the cerebellum (oculomotor region: the fastigial oculomotor region and central lobule, see Fig. 2.5a and 2.5b in results section), consistent with previous studies (Wang & Jabri 2002; Fuchs et al., 2010; Patel & Zee, 2015; Kheradmand & Zee, 2011; Blurton et al., 2012), that highlight the important role of the cerebellum in eye movement control. The oculomotor cerebellum is, for example, involved in the control of gaze shifting and rapid redirection of gaze from one object to another (Wang & Jabri 2002; Fuchs et al., 2010). The fastigial oculomotor region, which was also changed functionally in the current study, facilitates saccade initiation (Patel & Zee, 2015; Kheradmand & Zee, 2011), and makes them fast, accurate and consistent (Robinson, 2001). Our findings are in line with those of Blurton and colleagues (Blurton et al., 2012), who found a significant reduction in BOLD response following saccadic adaption. This suggests that the cerebellum plays a key role in sequence learning (Hikosaka et al., 2002; Debaere et al., 2004), which is the basis of our scanning task.

Frontal eye field (FEF)

In a functional MRI study, Cornelissen and colleagues (Cornelissen et al., 2002) suggested a protocol that can be used to define FEF, which resulted in mean Talairach coordinates averaged over subjects and hemispheres of x=40.6 (±4.9), y=–8.5 (±3.8), z=55.4 (±4.5) mm. Our functional results show a significant functional activation increase roughly in this anatomical area (MNI x = 44, y = -11.89, z = 52.10, see Fig 2.5). This activation change was significant two and six weeks after training commenced. No significant structural alterations, however, were seen in FEF in the current study. The FEF is known to play a key role in saccade initiation (Alkan et al., 2011), as well as in cognitive processes that require gaze control, such as attentional orienting, visual awareness and perceptual modulation (Vernet et al., 2014).

In addition to FEF an area in right motor cortex, (BA4, MNI coordinates: x = 54, y = -2, z = 26; see supplementary materials, section F, Fig. 2.S7c) showed a significant functional change at the end of training period in the current study, suggesting a role in visuomotor learning.

Despite the crucial role of supplementary eye field (SEF) and dorsolateral prefrontal cortex (dIPFC) in saccadic control, the current data did not show evidence of a selective functional activation increase while participants performed the voluntary and involuntary eye movement tasks. The main roles of SEF and dIPFC are in the inhibition of unwanted reflexive saccades (Vernet et al., 2014; Pouget, 2015). SEF, also, is involved in sequencing saccades with body movements (Pouget, 2015; Pierrot-Deseilligny et al., 2004). A possible explanation for the absence of significant change in both SEF and dIPFC during the current functional tasks may be that the trained task requires systematic/predictive eye movements but does not include antisaccades or saccades combined with body movement.

2.4.2 Linking Neuroplastic to Behavioural Change

A key finding in this study is that changes in diffusivity in the cerebellum, and, to a lesser extent, functional activation changes, are significantly correlated with behavioural performance changes at set time points. Behavioural and functional activation changes were seen for the trained voluntary eye movement task but not while participants performed involuntary eye movements, our control task (Fig. 2.3). These findings are consistent with the interpretation that neuroplastic changes in our target areas support performance improvements.

2.4.2.1 Functional activation changes over time

Although a wide range of neuroimaging studies (Zatorre et al., 2012; Sagi et al., 2012; Cao et al., 2016; Thomas et al., 2009) (Madden et al., 2009; Scholz et al., 2009; Mukai et al., 2007) link learning with brain alterations, the mechanisms underlying brain plasticity are still not fully understood (Fields, 2013) and the results are not entirely consistent. It has been argued that longitudinal learning studies can strengthen our understanding of the link between practice and neuroplasticity (Wang et al., 2014; Sampaio-Baptista & Johansen, 2017). Most studies, as discussed in the introduction, show activation increases during motor or perceptual learning over the course of training (Yotsumoto et al., 2008; Hadjikhani et al., 2001; Furmanski et al., 2004; Kourtzi et al., 2005). Some studies report that this BOLD response increases were maintained for months or years after training ended (Frank et al., 2018; Bi et al., 2014). Frank

et al. (2018), for instance, reported that performance and functional activation changes caused by visual motion patterns training was maintained three years after the completion of training. Others show contradictory data: Thomas et al. (2009), for example, report reduced activation in directly task-relevant areas, but a simultaneous activation increase in middle frontal cortex in a mirroring learning task. Yotsumoto et al. (2008), provide evidence for differential dynamics of BOLD activity during learning. They showed increasing activity and performance improvements in the early stages (day 1 and 10) of training, followed by a decrease of activation to baseline while performance remained unchanged. Similar data, at a much shorter time scale, are reported by Mukai et al. (2007), who scanned participants while training on a contrast discrimination task: while the training group showed overall activation increases compared to a control group in task relevant areas, this activation reduced significantly over the first hour of training. These findings, as Yotsumoto et al. (2008) argue, are consistent with a consolidation model where learning leads to efficiency gains, therefore reduced metabolic demand.

The functional imaging data reported here (Fig.2.6 and Fig. 2.S8 in supplementary materials) shows significant initial increases relative to baseline (week 2), but no significant change in activation while training continued between weeks 2 and 6. This finding is consistent with a model that assumes changing dynamics in the BOLD response as training progresses. We do not, however, observe the activation reduction reported by Yotsumoto et al (2008) while training was ongoing, instead we observed a reduction towards, but not all the way to baseline *after* training ceased while performance was maintained.

The findings that functional activation patterns do not change monotonically during training or linearly with performance further strengthen the case for considering functional activation at multiple time points. They may explain why functional activation in visual cortex, recorded at week 2, but not at later stages, is a good predictor for performance at later stages (Fig.2.6).

2.4.2.2 Microstructural change over time

The current study showed exponential changes in behavioural performance, which were associated with more gradual microstructural alterations. This gradual reduction in diffusivity is consistent with a linear pattern of brain changes over time reported by Erickson and colleagues (Kirk et al., 2011) in a longitudinal study. The rather more gradual change of diffusivity measures, compared to fMRI data, may explain the better correlation with behavioural performance and suggests different time-courses of change in functional and microstructural plasticity measures.

A trend of structural changes to return to the baseline level after the completion of the training course, consistent with our findings, was reported in some longitudinal studies (Scholz et al., 2009; Lövdén et al., 2012). Microstructural alterations resulting from spatial navigation training, for example, reverted to the baseline four months after the completion of the training course (Lövdén et al., 2012). Sagi et al. (2012) showed that the effects of learning modulated DTI activity in humans and rats within 24 hours. They argue that, at least in rats, the measured MD decreases during training are linked to an increase in the number of synaptic vesicles, an increase in the number of astrocytic processes, and an increase in brain-derived neurotrophic factor (BDNF), which they argue is indicative of long term potentiation. It is interesting to note the astrocyte involvement – if glial cell activity is upregulated during active learning phases and affects diffusivity measures, then a full or partial reversion of activity in these cells after training ceases might explain the diffusivity reduction we observed after active learning ceased.

2.4.3 Eye movement processing and fMRI activation

One of the surprising results of this study is the high degree of correlation between mean RT in scanner and mean fMRI activation (Fig. 2.S10 in supplementary materials). This finding raises the important question whether RT *directly* predicts observed fMRI activation, for example via rate effects, rather than neuroplastic change. The reasons underlying the association between reaction times and the fMRI BOLD response are complicated by the fact that we were unable to measure the actual eye movement of the participants while they performed the task in the scanner.

Rate effects that reflect improvements in motor performance can affect the results in studies of learning-related changes in brain activity (e.g., Nyberg et al., 2006; Rao et al., 1996; Riecker et al., 2003). Nyberg et al. (2006) showed that motor training in a finger tapping task increased functional activity in SMA and right cerebellum could be dissociated from pure rate effects.

If one, or all, of our target areas were purely relay areas where activation increases directly reflect more frequent or faster eye movements, then increased metabolism, without any underlying neuroplastic change, might be expected as participants improve over time. This explanation is not plausible for two reasons: the most direct evidence is provided by the fMRI measures during involuntary tasks – here, in contrast to the trained task, raw RT and BOLD response data are *not* correlated, meaning that in our target regions the RT does not directly predict the BOLD signal (Fig.2.9 in results section). A second argument for the hypothesis that the functional activation changes in this region are the result of learning is that the DTI analysis showed diffusivity changes in the same region. These changes, in contrast to fMRI activity, are clearly not task specific.

2.4.4 Structural Changes Supporting Learning

The learning of new skills relies upon changes in brain function, and this functional adaptation depends on the capacity of the nervous system to modify its structure (Scholz et al., 2009). Our correlation analysis, which shows that behavioural performance, functional activation *and* microstructural change are linked in functionally relevant brain areas is consistent with this.

An increase of FA and a reduction in MD, AD and RD are commonly associated with learning (Sampaio-Baptista & Johansen, 2017; Madden et al., 2009), and may represent microstructural alterations (e.g. myelination processing, glio-genesis, angiogenesis and fibre remodelling) (Wang et al., 2014; Sampaio-Baptista & Johansen, 2017; Cao et al., 2016). The present data show a significant reduction in MD and AD during training which is consistent with increased density of cellular membranes, for example of glial cells, that restrict the freedom of water diffusion (Ruxton & Neuhaeuser, 2020). Similarly, RD significantly reduces during training and this is consistent with increased myelination (Wang et al., 2014; Cao et al.,

2016) in white matter tracts because a growing myelin sheath restricts water diffusivity perpendicular to the direction of the axons.

While this study presents robust reductions in MD, AD and RD that are correlated with behavioural data, the increase in FA, which we hypothesized to see, did not come close to significance in any of our target regions. FA changes are consistently reported for long term training studies (Zatorre et al., 2012), it would be interesting to test whether more intense training or longer training periods would change this finding (Wang et al., 2014; Lövdén et al., 2013; Cao et al., 2016).

2.4.5 Outcome prediction and rehabilitation

A key finding of this study was that diffusivity measures (MD, AD and RD), recorded after two weeks, predicted behavioural performance gains and structural change at the end of training. Functional activity at week two predicted performance at later time points *in the scanner* but not performance in the lab (Fig. 2.11a). One possible explanation for this discrepancy may lie in the complex and non-monotonic temporal dynamics that have been reported for functional activation changes during training, which we discuss in previous sections (Yotsumoto et al., 2008). A second consideration is that fMRI activation, like performance, is an instantaneous measure of activity in the scanner. It is well known, and not surprising, that running experiments in the novel, and perhaps threatening, scanner environment has a negative impact on performance (Gutchess & Park, 2006; van Maanen et al., 2016). Our behavioural data is consistent with this: the target detection accuracy in the scanner, for example, was significantly lower than in the lab ($t(14) = 2.197$, $p < 0.01$; see Tables 2.S1 and 2.S2, supplementary material Section D). Environmental changes will affect some participants more than others but are likely to affect functional and behavioural measures simultaneously. One would hope that any detrimental effects of the scanner environment resolve as participants get used to the environment, for example over repeated scans in learning studies. A potential issue here is that any baseline measures are taken at the first scan, where differential effects are likely to be largest and will affect all subsequent outcome measures. It is nevertheless difficult to derive a general recommendation to use ‘in scan’ performance, because these measures are constrained by the total time available for scans.

A possible application of the finding that microstructural data provides early outcome prediction lies in neurorehabilitation. One area of application are specific situations, where overt behavioural performance measures are difficult to obtain because of the patient's condition. An example of this would be very early aphasia interventions, which have shown promise after strokes, but where outcome measures (better fluency) are obtained weeks or months after admission (Godecke et al., 2012). Many patients would not be able to understand instructions or reliably execute them in functional imaging tasks, so that structural scans that do not require active patient participation in cognitive tasks offer a promising alternative. Using structural rather than functional imaging to predict outcomes, however, has potential advantages well beyond the narrow application areas where communication with patients is impaired. Our participants, even though they were healthy volunteers and were scanned repeatedly, showed different performance patterns in the scanner compared to performance in the lab. These performance differences are likely to be exacerbated for patient groups that are scanned infrequently, which is likely in a rehabilitative setting, or are older than our participants because divided attention costs are larger for older than younger adults (Gutchess & Park, 2006; van Maanen et al., 2016). The fMRI environment, therefore, may have a disproportionate effect on cognitive performance of older adults, who are more likely to require neurorehabilitation, than young participants. DTI structural scans therefore offer the prospect of providing data that is easier to capture and more robust than functional imaging, particularly for patients with a range of cognitive issues, and for whom the experience is likely to be novel and frightening.

2.4.6 Age as a factor

Janacsek et al. (2012) measured the effect of age on participant performance using an implicit sequence learning (ASRT) task (Howard & Howard, 1997). This task, like our task, requires participants to identify stimuli presented in a predictable sequence of positions on the screen. The most important finding was that improvements in learning *rate* were seen in adolescents, learning rate was stable between 15 and 59 years, and then gradually reduced for older participants. Reaction times followed a u-shaped pattern with a minimum between 18 and 29 years while accuracy monotonically increased up to very old age. Finding that learning rate does not change until we reach a relatively high age is consistent with reports of rapid learning-

induced DTI changes seen in older participants (average 69 years, Antonenko et al. (2016)), showing that microstructural change is not restricted to younger participants.

Our participants were aged between 18 and 60 years old, and our analysis showed that age was not significantly related to any of the outcome measures, which were expressed as parameter *change* over time. We therefore did not include age as a covariate into our analysis. Age, however, was significantly correlated with the majority (11/17) of the absolute measures. On this basis we argue against the use of absolute neurometrics or performance measures as the basis for systematic evaluation of neuroplastic change in time.

2.4.7 Limitations

Our participants were scanned four times over the course of the experiment. Our data indicate differential time courses of functional, microstructural and behavioural performance measures. It would be interesting to document very early (Sagi et al., 2012; Yotsumoto et al., 2008) neuroplastic changes in response to the task as well as extend the post-intervention period beyond the four weeks we used (Frank et al., 2018).

We show that functional activation measures predict learning outcomes measured in the lab less well than instantaneous performance in the scanner. One reason for this may be that our task was inherently self-paced, so that neural efficiency gains associated with the processing of individual stimuli could be counteracted by increasing numbers of stimuli that participants were able process with training. It would be instructive to consider the effect more systematically in future studies as they may lead to stronger evidence for fMRI activity reduction through consolidation.

The present study was designed to identify co-localised functional and structural changes in a VPL task and to quantify the time course of these changes. While the number of participants we used for these experiments lies within the range typically used for longitudinal studies (Yotusmoto et al. (2008) - 15 participants; Kourtzi et al. (2008) - 19 participants; Frank et al.

(2014) - 26 participants) we would have preferred to use a much larger participant number for the correlational analysis.

2.5 Conclusion

Visuomotor training led to an improvement in visual motor skills: fewer fixations and reduced fixation duration were required to perform the task. The behavioural improvement was associated with significant functional and structural brain plasticity. Microstructural alterations and functional activation changes coincide in two anatomical brain areas; extrastriate area (v3d and IPS/TOS) and cerebellar oculomotor region; both are known to be involved in visual eye movement processing.

The current study shows that microstructural changes can be reliably detected after relatively short durations of training and that these measures correlated well with functional and behavioural measures. We therefore argue these measures should be recorded routinely in learning paradigms because they provide further evidence that practice outcomes and neurometrics are related.

Water diffusivity indices (MD, AD and RD) may provide accurate measures that *predict* long-term learning outcomes at the initial stages of training.

Statement of Data Availability

All data and code are available from the authors upon reasonable request.

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Chapter three

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Behavioural performance improvement in visuomotor learning correlates with functional and microstructural brain changes: hemianopia study

3.1 Introduction

3.1.1 What is hemianopia?

Homonymous hemianopia (HH) is the loss of one half of the visual field (Rowe et al., 2014; Bouwmeester et al., 2007). Ischemic stroke in the posterior visual pathway is the most common cause of HH (Zhang et al., 2006). Unilateral damage of the primary visual cortex causes a perfectly symmetrical loss of vision in both eyes which leads to a loss of visual perception over half the field of vision (Perez et al., 2013; Mannan et al., 2010). Visual field loss is a serious disability and can result in injuries or accidents which may have subsequent cost implications to the National Health Service and the patient (Rowe et al., 2014). After a stroke, patients with hemianopic field defects suffer negative effects on their quality of life and daily activities (Howard et al., 2013; Roth et al., 2009; Jacquin-Courtois et al., 2013).

Approximately 30% of patients who have had a stroke are found to have HH (Rowe et al., 2019). However, according to a recent study with a huge database (11900 cases) (Ali et al., 2013), 60.5% of stroke survivor patients present a cortical visual impairment with HH affecting 35% of the stroke patients. One striking report among 415 stroke patients suspected of having a visual difficulty is that eye-movement impairment was reported in 181 of the patients (43%) (Rowe et al., 2017).

Although cortical visual impairments are common after brain damage, they are rarely considered in neurorehabilitation programmes (Perez et al., 2013). Whereas traditionally, the treatment of motor disorders (Hatem et al., 2016), language and speech (Koyuncu et al., 2016) is systematic, no visual training is usually proposed to patients with cortical visual impairment (Perez et al., 2013). Although efforts have been made to train patients with HH since the beginning of the 20th century (Bouwmeester et al., 2007), the present service provision and treatment for visual field loss is inconsistent and not commonplace, even in stroke units where

orthoptic services are provided (Rowe et al., 2014; Howard et al., 2013). Therefore, further research is required to aid clinicians and improve provision for supporting HH patients along their rehabilitation journey (Howard et al., 2013).

HH leads to specific deficits, which can be the basis for objective evaluation of rehabilitation outcome. Slow and inaccurate performance in functional visual activities is associated with HH (Perez et al., 2013). Numerous visual refixations and inaccurate saccades result in impaired scanning and longer search times (Howard et al., 2013). Furthermore, HH patients exhibit longer fixation times and less consistent oculomotor behaviour (Perez et al., 2013). Consequently, hemianopic patients suffer from impaired visuospatial exploration (Mannan et al., 2010), and inefficient visual search strategies that require a lot of attention to be useful (Bouwmeester et al., 2007; Perez et al., 2013). As a result, HH impacts spatial orientation, reading ability, and educational outcomes, which may lead to a poor quality of life and disable visual functional activities (Roth et al., 2009; Jacquin-Courtois et al., 2013).

3.1.2 Recovery after stroke

Spontaneous recovery

Some spontaneous recovery from visual field loss following a stroke can occur in roughly 40% of cases (Jacquin-Courtois et al., 2013), and the chance and rate of spontaneous recovery correlates negatively with increasing time since injury. Only around 10% experience full spontaneous recovery within the first two weeks (Rowe et al., 2014), and most recovery is usually completed within the first three months after stroke onset while even small improvement is rarely reported after six months (Perez et al., 2013; Jacquin-Courtois et al., 2013). According to Perez and colleagues (Perez et al., 2013), the rate of partial recovery in HH patients was > 50% in the first month compared to around 20% at six months after the onset of the stroke. Some HH patients learn to compensate for their field loss by spending a greater proportion of the viewing time, and making more fixations, in their blinded half-field (Zihl, 1995; Ishiai et al., 1995). Also, the adverse effects of HH can be mitigated by eye movements that position the target visual image within the intact visual field (Nowakowska et al., 2013). Therefore, spontaneous recovery is most likely to be caused by spontaneous oculomotor compensation (Jacquin-Courtois et al., 2013). This compensation occurs when HH

patients compensate for their visual field loss by adopting more efficient eye-movement strategies (Zihl, 1999; Pambakian et al., 2004), and there is evidence that this compensatory strategy evolves over time (Mannan et al., 2010; Jacquin-Courtois et al., 2013; Nowakowska et al., 2018).

Despite limited spontaneous improvement in visual function, the majority of patients are left with a persistent visual impairment. Even though a degree of recovery may occur in some patients with HH, it is rarely sufficient to remove the disabling consequences of visual field loss (Mannan et al., 2010). Indeed, at least 60% of HH patients continue using ineffective scanning strategies when searching for a target object, with increased reaction times on visual search tasks (Zihl, 1995). Therefore, given the poor rate of spontaneous recovery in HH patients, some logical questions have been asked over the past decades: could specific training simply reinforce the spontaneous adaptive strategies or does it further alter the efficacy of search eye movements (Mannan et al., 2010), or whether the spontaneous compensatory eye-movement strategy could be manipulated advantageously by a specific training in visual search (Pambakian et al., 2004)?

Rehabilitative recovery

There is substantial evidence that HH patients may successfully adapt to visual field loss by training following a stroke (Bouwmeester et al., 2007; Howard et al., 2013; Pambakian et al., 2004). This adaption may improve overall visual functions which can be assessed objectively and subjectively (Pambakian et al., 2004). Several training programmes have been proposed to help HH patients recover. However, compensatory training is the more favourable option according to a Cochrane review in 2019 by Pollock and colleagues (Pollock et al., 2019). As 70% of patients with HH show a spatially disorganised visual search strategy (Zihl, 1999), such training serves to systematically reinforce compensatory oculomotor strategies, thereby fortifying and enlarging their field of search (Pambakian et al., 2004). Visual search training usually leads to an improvement in how HH patients can successfully locate a target with eye movements (the visual search field) with a reduction in response times (Pambakian et al., 2004) (Kerkhoff et al., 1992; Nelles et al., 2001). It can also improve their detection performance (Howard et al., 2013) and encourage patients to make exploratory eye movements into the blind field (Pambakian et al., 2004; Alidz, 2005).

In the optimal search model, eye movements are directed to locations where the greatest possible amount of information is expected to be gained. As HH disrupts normal scanning patterns, some patients make a series of small saccades, with long fixations into their blind field (Meienberg et al., 1981; Zangemeister et al., 2020), which represent disorganised scan paths (Zihl, 1995). In oculomotor training, participants are encouraged to use a particular strategy and are usually trained to make systematic horizontal or oblique scanning saccades into their blind field (Zihl, 1995; Alidz et, 2005; Kerkhoff et al., 1992; Bolognini et al., 2005).

The goal of compensatory treatments is to help patients adjust and adapt to their impairment. Improvement of daily life activities as a consequence of compensatory eye-movement training has been proven empirically, as well as with subjective questionnaires, by many HH studies (Zihl, 1995; Pambakian et al., 2004; Nelles et al., 2001; Rowe et al., 2017). However, still there is a need for more validated instruments that can measure the compensatory treatment outcome objectively (Bouwmeester et al., 2007). Moreover, as repeated visual search training leads to perceptual learning, can improvement in the behavioural performance associated with visual search practice be explained by neuronal changes in response to the learnt stimulus, rather than by changes in eye-movement adaptive strategies (Mannan et al., 2010)?

3.1.3 Outcome measurements and specific hypothesis

According to recent neuroimaging studies, cortical reorganisation after visual system damage can occur any time after a stroke, at all ages and in all types of visual field defects (Perez et al., 2013; Nelles et al., 2010). This change in neuronal activity may facilitate compensation for lost visual function in patients with visual field impairments (Nelles et al., 2010). Recently, cortical reorganisation in HH patients that has been enhanced by rehabilitative visuomotor training has been reported in many fMRI studies (Nelles et al., 2010; Nelles et al., 2009; Lu et al., 2018; Henriksson et al., 2007). However, it still is less well understood (Perez et al., 2013; Nelles et al., 2010) and seems to relate to the visual task performed (Perez et al., 2013). Interestingly, explicit improvement of visual detection performance in the absence of V1 (visual area 1) would imply a degree of neural plasticity (Perez et al., 2013) where the areas adjacent to a lesion can replace the function of the affected area, as may occur after sensory–motor defects (Liepert et al., 2000), or that the undamaged brain hemisphere can reorganised itself to take over part of the damaged hemisphere's functions (Heidi et al., 2002; Rossini et al., 2004). It

would be interesting to investigate if any structural plasticity is associated with any potential improvement in HH visuomotor training recovery.

Therefore, in the current study, visuomotor training (Rowe et al., 2017) will be applied to a group of hemianopia patients to investigate the impact of the task on the potential associated behavioural performance change and the potential associated neural plasticity. This eye-movement training programme was proposed by Rowe and colleagues (Rowe et al., 2017) for stroke survivors with hemianopia with an improvement in vision-related quality of life reported as a direct impact of the training. During this training intervention, HH patients (the target population of the current study) will learn to make systematic bilateral eye movements to scan a digital VISION visual scanning card over six weeks. The task provides precisely empirical measurable data on visual functions (performance and eye-movement parameters) (Mannan et al., 2010; Pambakian et al., 2004; Wang, 2001), which can be directly compared with MR imaging parameters (such as fMRI and DTI data). Subjectively, the positive impact of the task on daily life activities has been investigated (Rowe et al., 2017). However, the explicit empirical visual functions measures such as the effect of this training on response time, number of fixations and fixation duration improvement, has not yet been assessed for HH patients. Moreover, the brain areas that may be enhanced by this task have not been investigated in HH patients. Therefore, the explicit aim of this study is to evaluate the potential change in response time, number of eye fixations and fixation duration over six weeks of this visuomotor training and investigate any associated brain plasticity.

In this study, it is expected to see a reduction in response time over the training period and a reduction in eye-movement parameters (number of fixations and fixation duration). Neural changes (functionally and structurally) in task-relevant brain areas (oculomotor and visual perceptual areas) are expected as consequences of the current eye-movement training. In particular, an increase in FA and a reduction in water diffusivity in the task-relevant brain areas.

3.2 Methods

3.2.1 General behavioural and imaging methodology

In the current study, the same behavioural and imaging methodologies that were applied on the previous study (Chapter 2) were applied identically in terms of training tasks at home, eye tracker behavioural tests in the laboratory, imaging scanning protocol and imaging analysis.

The participants (hemianopic patients) in this study used the same digital VISION visual searching training card that was designed for the healthy group (see Fig. 2.1, in Chapter 2). However, unlike the previous study, all hemianopic participants in the current study were provided with a customised PC for each individual to facilitate training at home and to provide the technical basis for the, on average, more elderly hemianopia patients. The instruction and aims of the training, behavioural and functional tasks and performance measures were the same as those reported in Chapter 2 for the healthy participants.

The hemianopic participants were instructed to do 30 minutes of daily training, five days a week and for six consecutive weeks. Unlike the previous study of healthy participants, there were three data collection visits (scanning and behavioural testing laboratory visits). The imaging and behavioural data were collected pre-training (week 0), two weeks after training onset (week 2) and at the end of the training period (week 6).

3.2.2 Bells task (search and find test)

The current vision training task is actually a search task, so the results of this can be taken into consideration. Therefore, in addition to the behavioural performance measures that were collected from the eye tracker in the laboratory test (RT, TNF and MFD) and RT in the scanner during the fMRI tasks, another objective behavioural performance measure was collected pre- and post-training for each individual by conducting a traditional ‘search and find’ Bells task. The Bells test is traditionally used in the assessment of visual inattention/neglect; not for hemianopia. However, studies of hemianopia (Basagni et al., 2017) have used ‘search and find’ tasks as objective measures for hemianopia subjects. We will substitute the Bells test for this purpose.

The Bells test (Basagni et al., 2017) is a complicated display of small objects (see Fig.3.1) which requires attention and scanning to detect the bells from among the other objects. The Bells chart was expanded and printed as A0 size so that it provided a wide-field assessment.

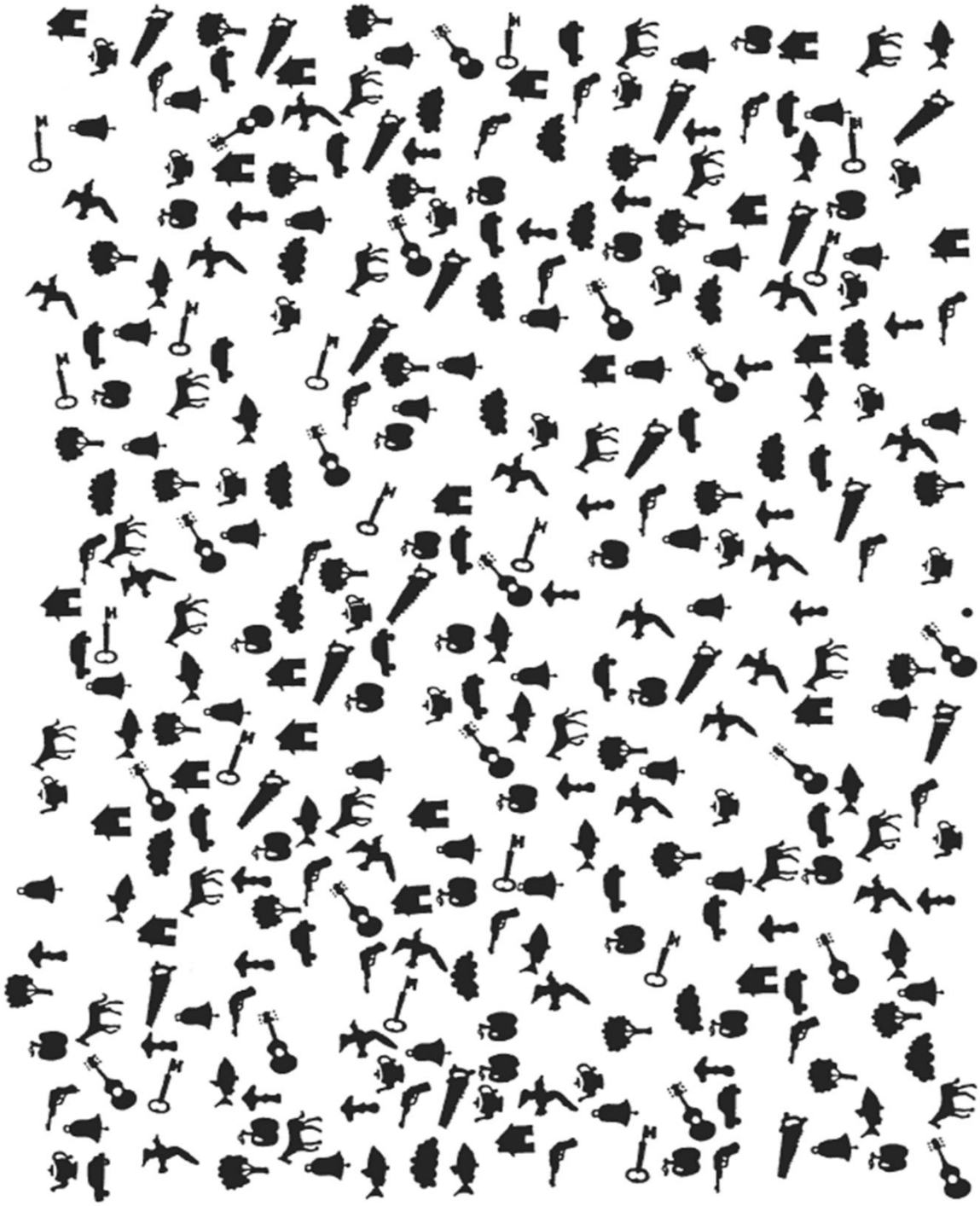


Fig.3.1 Bells task: *The chart contains a number of bells that participants need to search and find; the completion time and number of bells detected were recorded once the participant finished the search.*

3.2.3 Group analysis approach (common space)

For all behavioural and imaging analysis we used the same methods that were applied in the healthy group analysis. However, when the statistical imaging mapping analysis did not show a significant cluster change (perhaps due to the small sample size that was tested) for any fMRI or DTI measures, the PhD student (AA) relied on the results of the previous study (Chapter 2) to use the same significant clusters that were generated from the target brain areas (that showed significant change at the end of the training period). This provides an option to do a group investigation in a common space for particular target areas which may be affected by the eye-movement training. For example, see the binary cluster masks on the images in Fig. 3.10b and Fig. 3.10d for target functional areas or Fig. 3.11 for target structural areas (in the results section).

The hemianopia patients had brain strokes which caused damage in specific areas for each individual – see Fig. 3.5b (results section). The brain damage may negatively affect the transformation of image data from the native space to a common space. Therefore, an additional data extraction method was applied to transform the cluster target masks (the binary masks generated from the study in Chapter 2 for the significant cluster changes in the cerebellum and visual areas) from the common space to the native space for each participant. For example, Fig.3.2 shows the transformation of the binary cluster target mask in the cerebellum from the common space to the native space of subject 1.

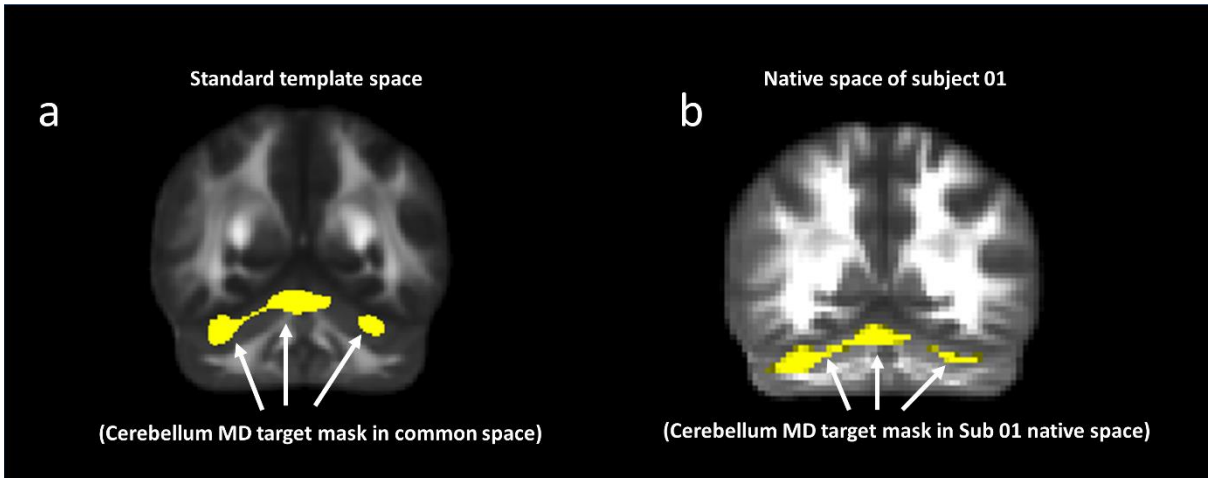


Fig.3.2 Binary mask transformation to extract the DTI data from the native space*: *(a) *shows the binary mask (yellow colour) of the target brain area (MD cerebellum change generated from the healthy study in Chapter 2) which is applied to the standard template to extract the raw DTI data from the participants in the common space;* ***(b)*** *shows the transformed binary target mask (the same mask as in* ***(a)****) to extract the data from the native space for subject 1. A similar transformation technique was applied to each individual participant for both affected brain areas (visual cortex and cerebellum).*

The transformation of a binary mask from the common space to native space for any target brain area makes it possible to extract the data from the native space to be compared with the data of the same area in the common space to check any potential negative impact when transforming brain data with exciting of brain damage areas. The transformation of the binary cluster mask was applied separately for all hemiopia participants.

3.2.4 Individual analysis approach (suggested for clinic)

As shown in Chapter 2, the DTI data provides a reliable method to predict outcomes from the initial stage of learning. This method therefore can be applied to predict outcomes in visuomotor rehabilitation programmes.

The suggested clinical investigation technique relies on individual analysis, instead of group analysis, to define target brain areas where the structural changes are evaluated. Chapter 2 showed that visuomotor training causes neuroplastic change in three main anatomical areas: FEF in the right precentral gyrus, v3d in the extrastriate visual cortex, and OC in the cerebellum (see Fig.3.3).

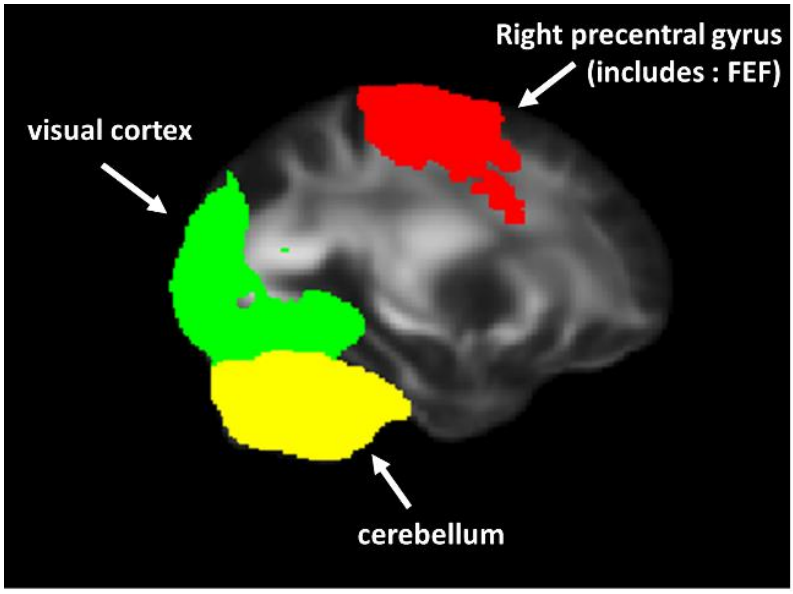


Fig.3.3 The three main ROI areas for potential structural changes during visuomotor learning: *The image shows the three main brain areas that may be affected by the current visuomotor learning, based on the results of the healthy group study (Chapter 2). All three areas showed significant functional changes in the previous study and only the cerebellum and visual areas showed significant structural changes after six weeks of continuous training.*

To apply the clinical technique for the participants in the current study, brain templates for individual participants were generated in the native space of all participants from the three DTI scan visits. Then, all DTI maps (FA, MD, AD and RD) were realigned in the native space for computation purposes to compare the potential changes over the training period (all computation processes were restricted into the three ROIs only). By subtracting the pre-scan visit from the post-scan visit it could be possible to see the areas in the three ROIs that may show any water diffusivity reduction (MD, AD or RD). To investigate the potential increase in the white matter integrity (FA increase) the post-training scan visit was subtracted from the pre-training DTI visit.

In addition to the individual analysis in the native space, the native space data were added together for applied group statistical analysis to investigate the overall pattern of changes.

3.2.5 Blind and intact visual field vs stroke and intact visual cortex

As all participants in the current study suffer from HH, the behavioural performance in the right and left visual fields could be different. This provides an opportunity to investigate the behavioural performance in the intact and blind visual fields separately (see Diagram 3.1). In

addition, the functional activation literalisation can be measured in each scanning visit to investigate the brain activation in the ipsilateral and contralateral lesion areas in the visual cortex. Similarly, the lateralisation of the potential structural changes at the end of the training period can be measured to be compared with the change in the functional lateralisation at the same data point.

RT times in both visual fields (blind and intact) were measured separately to evaluate the behavioural improvement in right and left visual field for all participants. Similarly, voxel count analysis was applied to measure the laterality index (LI) for both functional and structural data. LI was measured to compare the affected visual cortex with the unaffected visual cortex when participants performed the voluntary fMRI task at all scan visits (week 0, week 2 and week 6). The lateralisation of the change was measured at week 6 for DTI data.

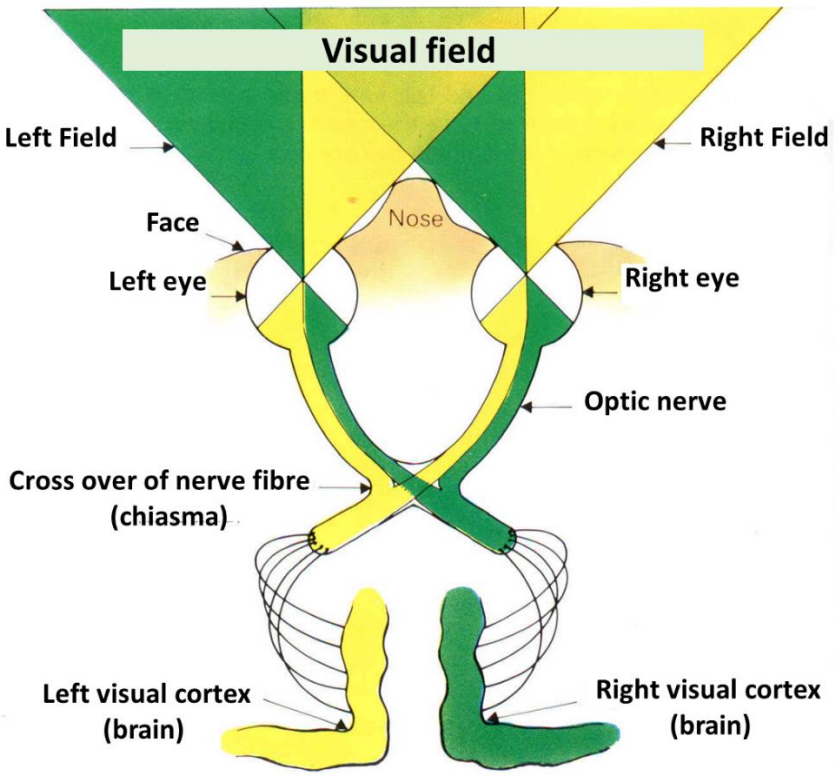


Diagram 3.1 Right and left visual fields: *The diagram shows how the entire visual field can be divided into right and left visual fields. The processing of the visual stimulation in the left visual field occurs in the right visual cortex. The processing of the visual stimulation in the right visual field occurs in the left visual cortex.*

3.3 Results

Seven hemianopia participants (recruited as volunteers from the local stroke association brain charities) completed the training period with the minimum daily training session (30 minutes daily) and exceeded the minimum performance requirement (75% correct target identification) – see Table 3.1. Thus, all behavioural and imaging data of the seven participants were included in the data analysis.

Subject	**Sub01**	**Sub02**	**Sub03**	**Sub04**	**Sub05**	**Sub06**	**Sub07**
Age	72	66	65	62	62	80	55
Gender	F	M	M	F	F	M	M
Affected brain area	Right	Left	Right	Left	Right	Right	Right
Training duration per day (at home)/minutes	32.6	37.9	38.3	32.5	38.73	25.81	51.4
Accuracy of target detection (at home)	99.79%	98.30%	98.75%	96.45%	99.82%	72.56%	83.88%
Accuracy of target detection (in laboratory)	97.17%	98.44%	90.35%	94.64%	98.64%	93.75%	92.88%
Accuracy of target detection (voluntary fMRI task)	91.54%	89.44%	80.17%	75.88%	91.67%	82.00%	86.35%
Accuracy of target detection (involuntary fMRI task)	93.82%	94.67%	92.93%	87.97%	95.16%	91.00%	88.68%

Table3.1 The participants' data: *The table shows age, gender, and affected brain area for each participant. The table also shows the mean of the training duration at home and the mean accuracy of target detection for all tasks (home training task, laboratory task and scanner tasks) for each participant.*

3.3.1 Impact of training – behavioural data

3.3.1.1 Behavioural performance in the laboratory

Behavioural performance improved significantly over the training period, and was shown as a gradual reduction in RT, TNF and MFD (Fig. 3.4a, 3.4b and 3.4c).

In the group analysis, the average response time decreased significantly from 2.22 seconds (week 0) to 1.06 seconds (week 6), $t(6) = 4.059$, $p < 0.003$. Similarly, the average of the total number of fixations required to complete the task and the mean fixation duration also reduced significantly between week 0 and week 6: the mean number of fixations reduced from 1488 at week 0 to 743 at week 6, $t(6) = 3.360$, $p < 0.07$, while the mean fixation duration reduced from

0.449 seconds to 0.3349 seconds, t(6) = 2.115, $p < 0.03$. Unlike the healthy group study (Chapter 2), there was no follow up behavioural test after the training ended.

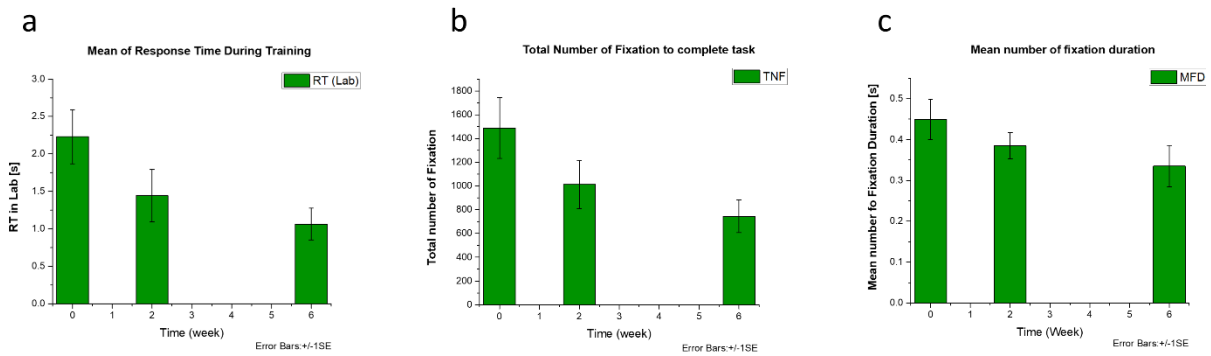


Fig.3.4 Training effects on behavioural performance in the laboratory: *The graphs show the impact of the training on the participants' behavioural performances in the laboratory:* ***(a)*** *shows the reduction of the average response time of the group during the laboratory tests for each week visit over the training period; similarly,* ***(b)*** *and* ***(c)*** *show the average reduction in total number of fixations and mean of fixation duration.*

3.3.1.2 Behavioural performance in the laboratory – Bells task

To measure the outcome following training along with the measurements of the current digital training card, another objective assessment task was applied before and after training. For this purpose, a 'search and find' task was conducted in the current study by introducing the Bells test – see Fig.3.1 (method section).

At the end of the training period (week 6), the mean completion time to detect all bells during the Bells test decreased from 4.82 seconds to 4.01 seconds (Fig.3.5a). This reduction is marginally significant, t(6) = 1.58, p > 0.08. The number of the missing bells at week 0, in Fig. 3.5b, reduced significantly at the end of the training period (week 6), t(6) = 2.750, p = .033.

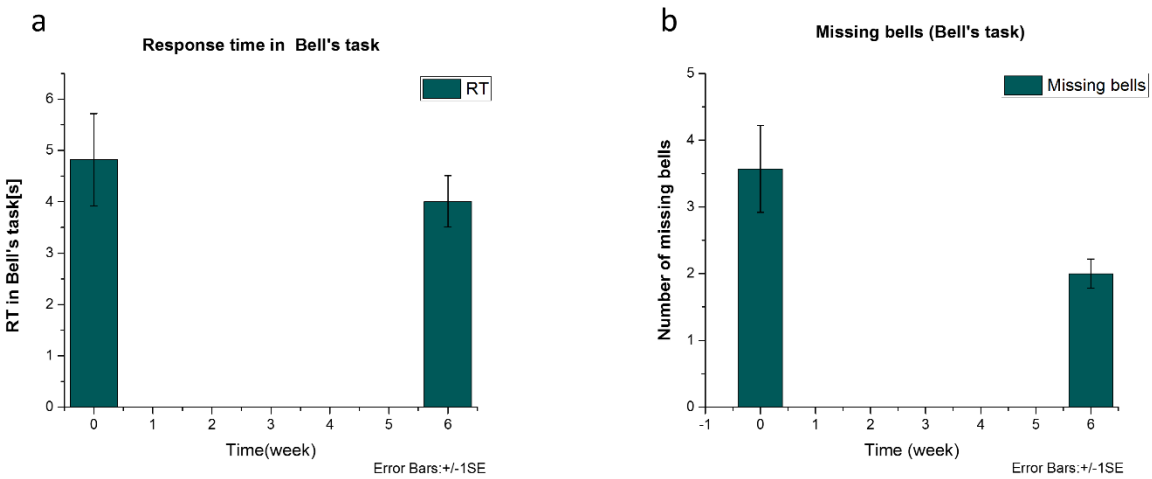


Fig.3.5 Training effects on behavioural performance during Bells task*: *(a) *shows the change in the mean completion time in the post-training (week 6) test compared with the pre-training (week 0) test;* ***(b)*** *shows the change in the number of the missing bells from pre- to post-training tests.*

3.3.1.3 Behavioural performance in fMRI scan

As shown in Fig. 3.6a, the mean response time reduced significantly (when the participants conducting the trained fMRI task) from 2.39 seconds at week 0 to 1.26 seconds at week 6, $t(6) = 2.738$, $p < 0.015$. The control fMRI task (involuntary), in Fig.3.6b, also showed a significant reduction in response time at the end of the training period compared with the pre-training scan, $t(6) = 3.424$, $p < 0.014$.

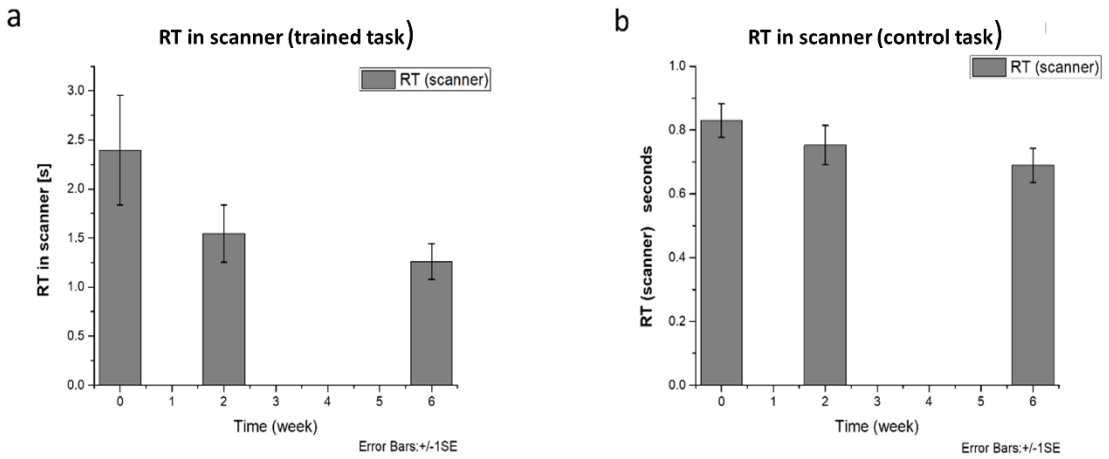


Fig.3.6 Training effects on behavioural performance in the scanner*: *(a) *shows the reduction over the training period in the mean response time during the voluntary eye-movement fMRI task;* ***(b)*** *shows the mean of the response time over the training period during the involuntary eye-movement fMRI task.*

3.3.2 Impact of training – imaging data

3.3.2.1 Functional data – group analysis

Both voluntary and involuntary fMRI tasks cause similar functional brain activation for each individual participant (see Fig. 3.7a). As shown in Fig. 3.7b, the severity of stroke (measured by comparing the white matter integrity between left and right brain hemisphere for each individual) impacted negatively on the size of the global brain activation for some participants. For example, the most severe strokes in the affected brain areas of the *third* and *fourth* participants resulted in less brain activation compared with the rest of the group during both voluntary and involuntary fMRI experimental tasks.

As a result of training, a significant fMRI signal increase was shown only in the voluntary (trained) eye-movement fMRI task. At the end of the training period (week 6), a significant fMRI increase was only seen in the right FEF (Fig. 3.8a) compared with the baseline scan (week 0). No significant increase, however, was reported in the visual cortex and cerebellum where it is expected to see some functional brain changes. The involuntary (control) eye-movement fMRI task showed no training effect in the area that was affected by the trained task (right FEF, Fig. 3.8b) in the current study at the end of the training period (week 6).

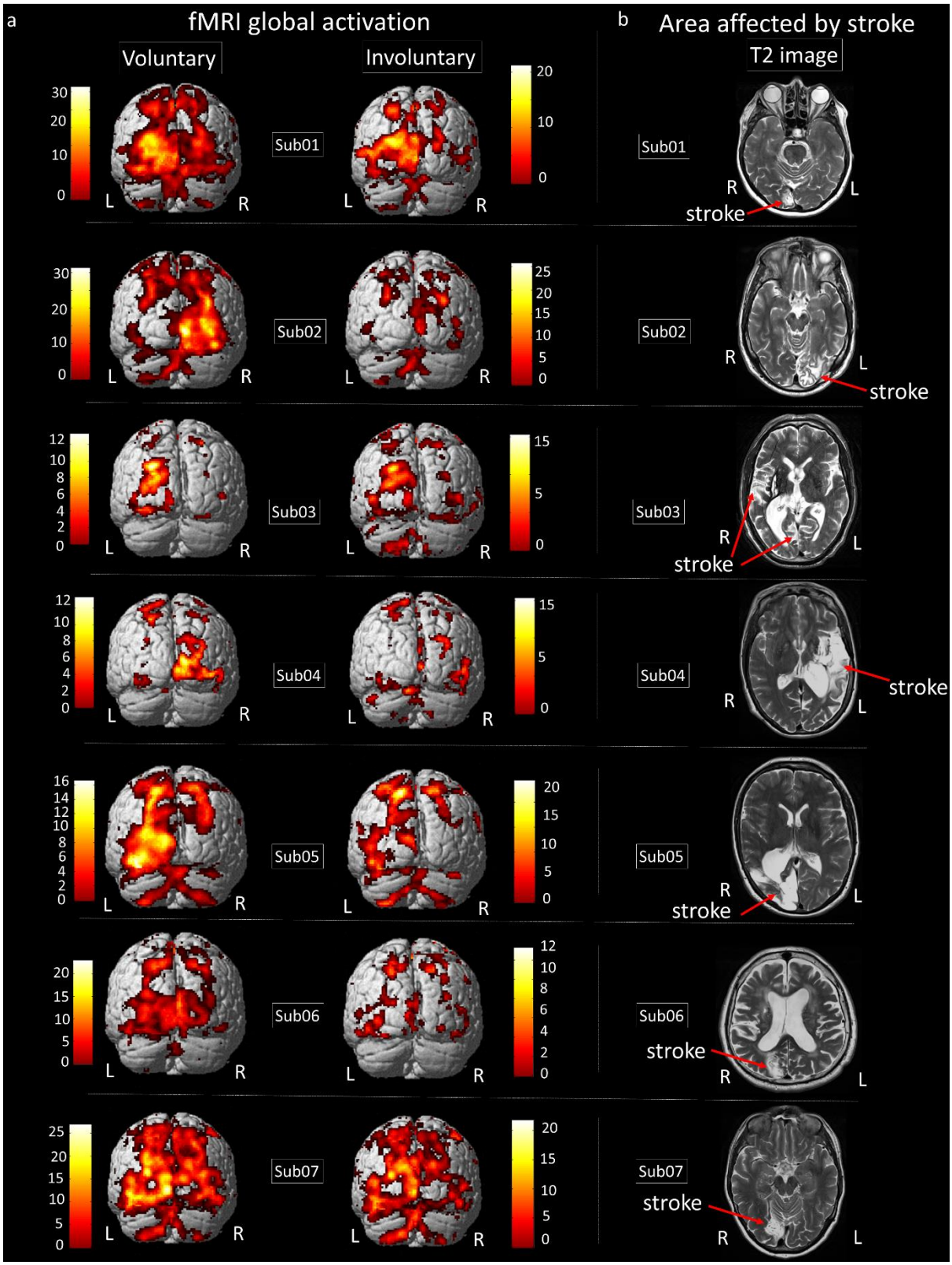


Fig.3.7 The global activation of the functional experiments*: *(a) *shows the global activation of both voluntary and involuntary fMRI tasks at week 0 for all participants ($P_{FEW} < 0.05$, corrected images);* ***(b)*** *shows the strokes in the affected brain areas for all hemianopic participants.*

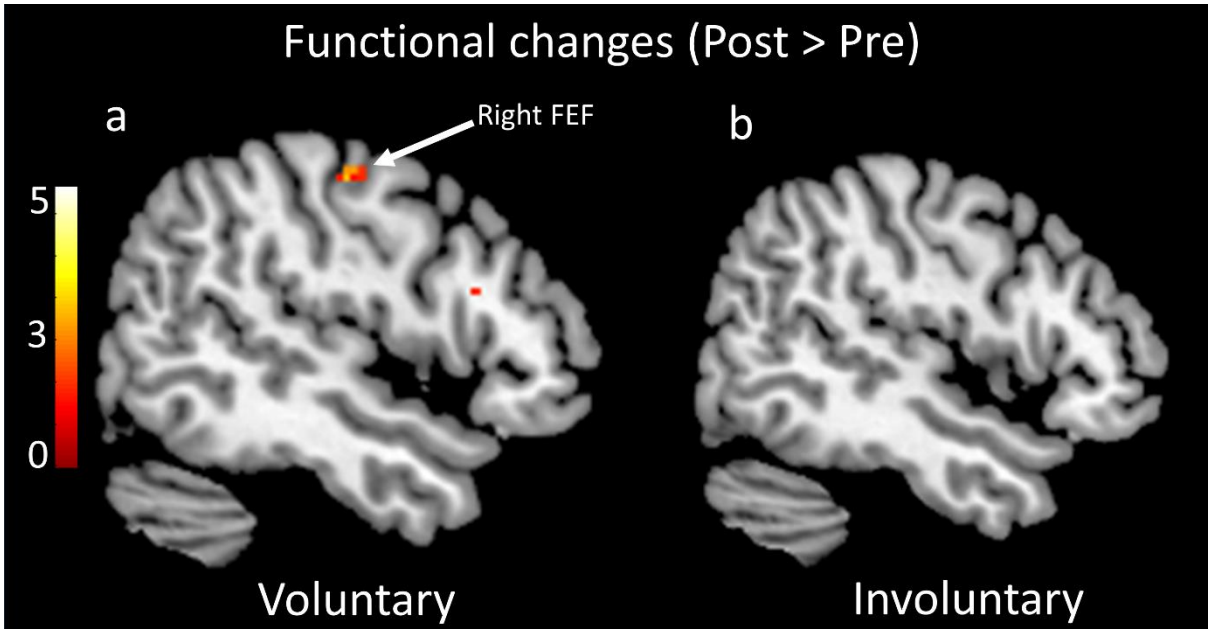


Fig.3.8 Functional activation change in the frontal eye field (FEF): *The figure shows the direct comparison of functional activation (post > pre) for both fMRI tasks (trained and control);* ***(a)*** *shows a significant BOLD signal increase (P_{FWE} < 0.05 cluster level) with visuomotor learning in the right FEF (x = 50, y = -13, z = 51) at the end of the training period (week 6 > week 0);* ***(b)*** *shows no functional activation change as an impact of learning in the same area in image* ***(a)*** *during the control task (involuntary).*

To make a direct comparison of signal intensity and pattern change over the training period in the right FEF, the data were extracted from the same area (right FEF, Fig. 3.8a) for both trained and control fMRI tasks for each individual scan visit (week 0, week 2 and week 6). As expected, the fMRI signals show a gradual increase in change over the training period during the voluntary fMRI task (see Fig. 3.9a). The fMRI activation increased significantly at week 6 compared with baseline at week 0 in the voluntary task, $t(6) = -1.756$, $p < 0.06$. The involuntary fMRI data from the target area (right FEF, Fig. 3.9b) showed no clear increasing pattern change of the BOLD signal over the training period, and the fMRI signal at week 6 did not show a significant increase compared to the baseline at week 0, $t(6) = -.666$, $p > 0.25$.

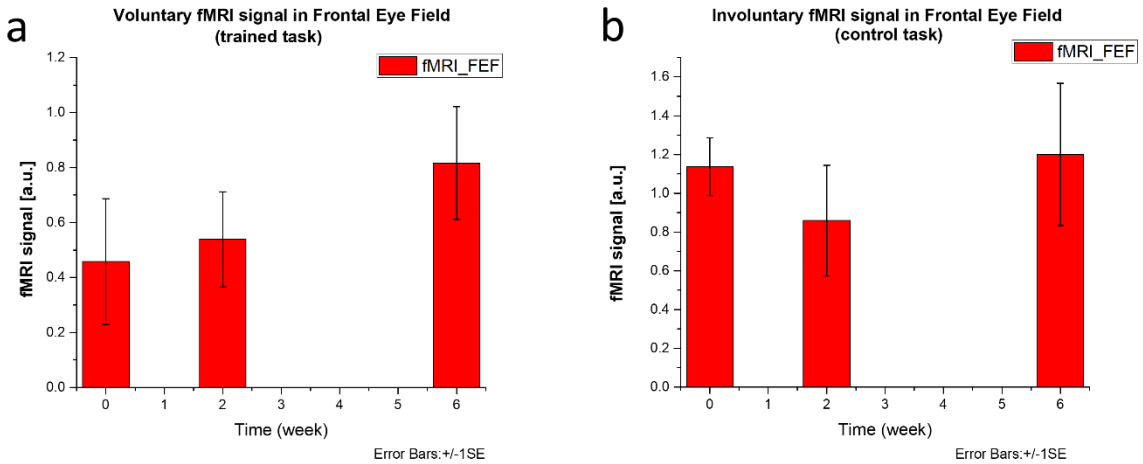


Fig.3.9 Time course analysis of the functional activation change in the frontal eye field*:*(a) *shows the functional change in FEF when participants perform the voluntary (trained) fMRI task over the training period;* ***(b)*** *shows the functional change in FEF when participants perform the involuntary (control) fMRI task over the training period.*

As no significant cluster changes in fMRI were shown in the visual cortex and cerebellum in the hemianopia group study, the binary masks of the cluster change that were generated from the healthy study (Chapter 2) were used to investigate the target brain areas that may be affected by the current visuomotor learning (see Fig. 3.10b for visual cluster mask and Fig. 3.10d for cerebellum cluster mask). These two masks were used to extract data for time course analysis for the particular target areas in the visual cortex and cerebellum.

As shown in Fig. 3.10a and 3.10c, the two target masks for the healthy group were used to extract the functional data from the voluntary fMRI tasks for all hemianopic participants. At the end of the training period, at week 6, the fMRI signals in both target areas (visual and cerebellum) showed levels of increase, but did not reach the significant level in both target brain areas (visual area, $t(6) = -.364$, $p > 0.3$; cerebellum, $t(6) = -1.091$, $p > 0.15$).

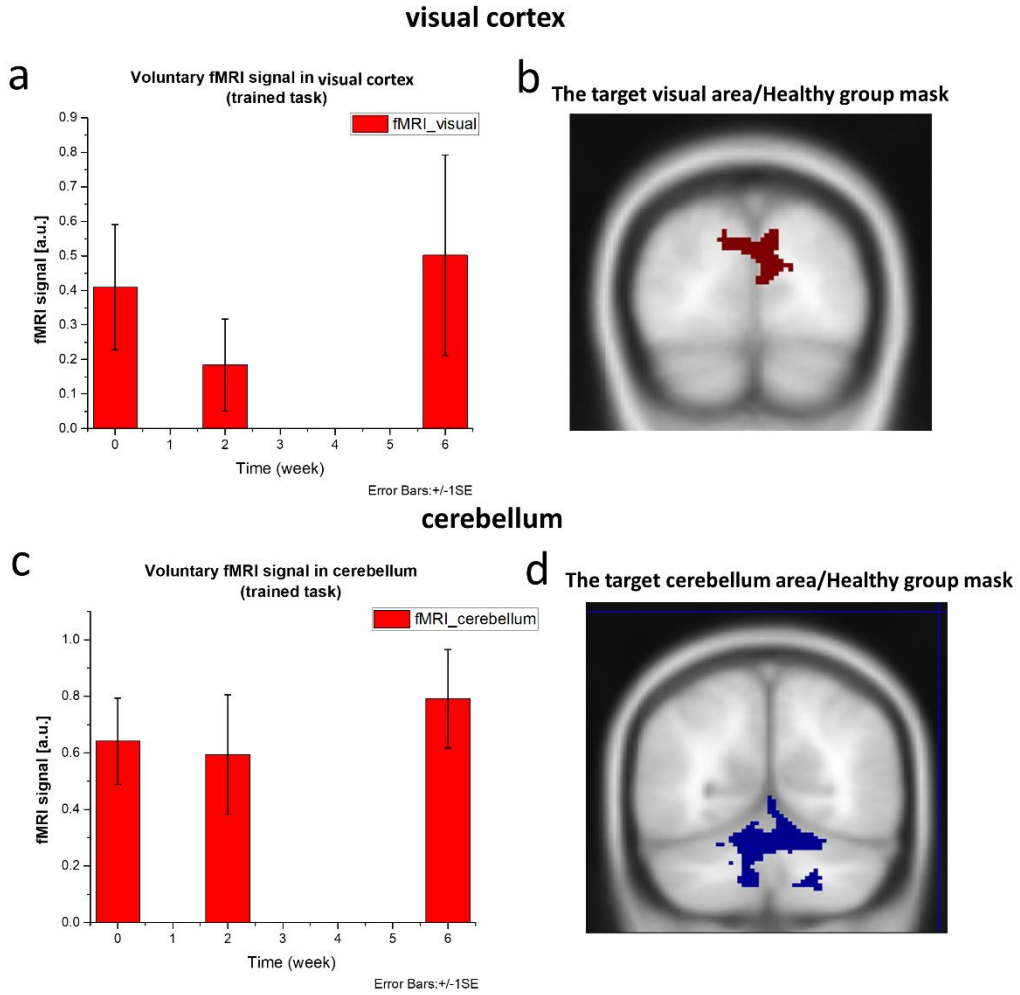


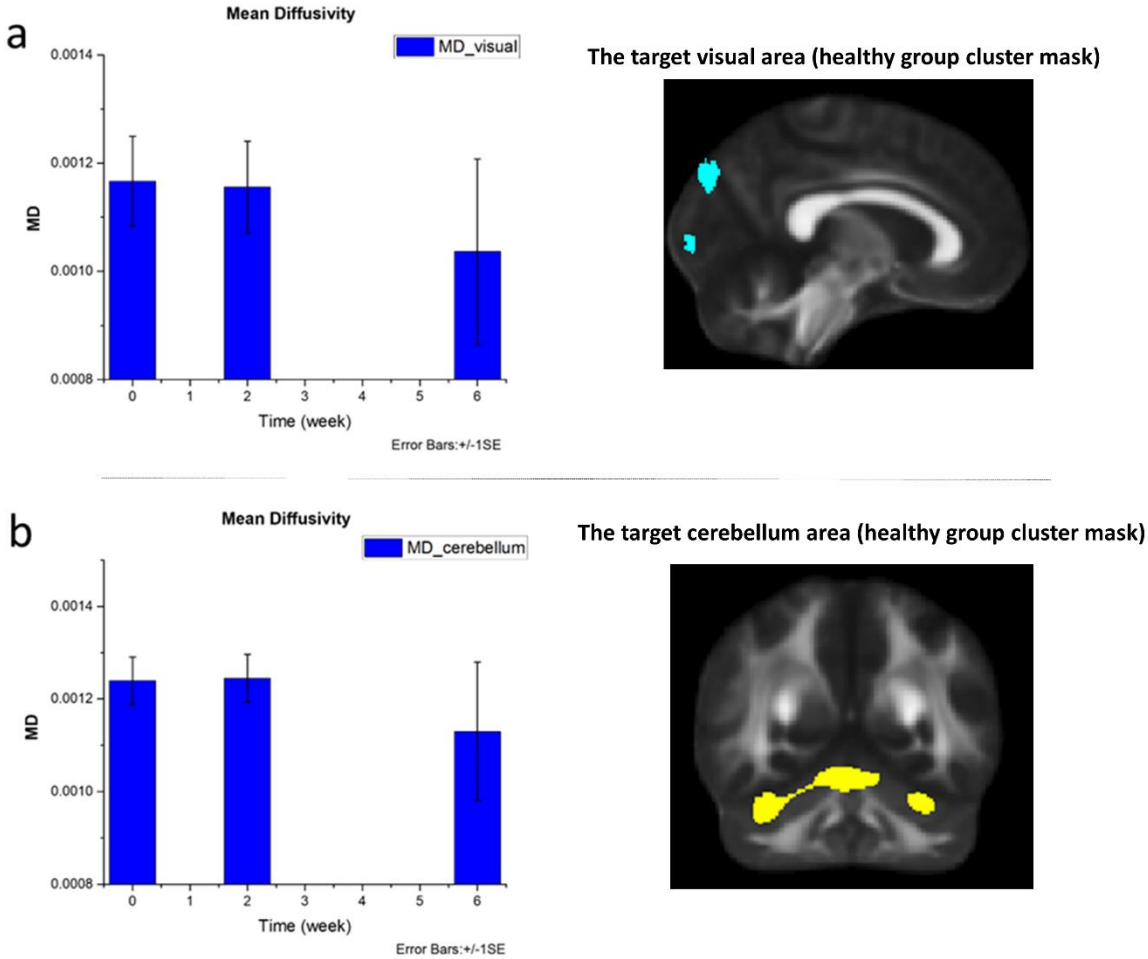
***Fig.3.10 Functional activation change in target visual and cerebellum areas*: (a)** *shows the fMRI signals change over the training period in the visual area of the hemianopic group which was extracted from the target visual mask area in* **(b)** *that represents the visual brain area that is affected by training in the healthy study (Chapter 2). Similarly,* **(c)** *shows the fMRI change over the training period in the cerebellum of the hemianopic group which is extracted from the target cerebellum mask area in* **(d)** *that represents the area in the cerebellum that is affected by training in the healthy study (Chapter 2).*

3.3.2.2 Structural data – group analysis

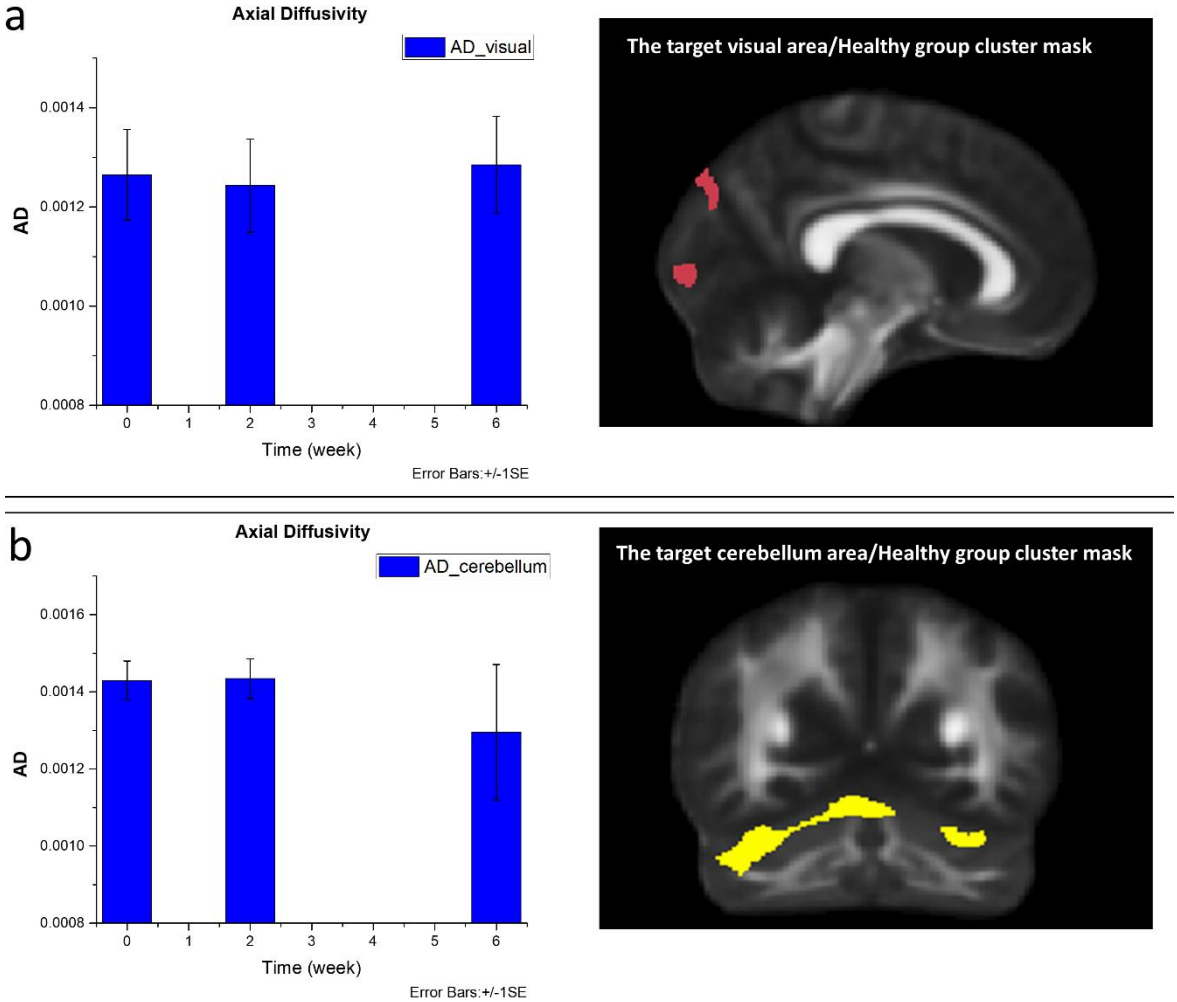
First, the UNION global fMRI mask from the healthy study (Chapter 2) was used to run a statistical parametric mapping for group analysis to investigate any potential structural changes as consequences of the current visuomotor learning in the ROIs anatomical areas which may be involved in the voluntary fMRI task in the hemianopia group. However, no significant DTI measure (FA, MD, AD and RD) changes were reported as an impact of learning at the end of the training period (week 6) compared to the baseline (week 0) in the hemianopia study.

Second, the previous healthy study (Chapter 2) provided target brain areas that showed significant water diffusivity changes in the visual cortex and cerebellum (for example, for MD change, see Fig. 3.11a and 11b). As the same visuomotor learning intervention was applied in the current study in the hemianopia group, those cluster changes were used as cluster frame masks to statistically probe the same target areas in the hemianopic group. The data were extracted from the target areas by using independent frame masks for each water diffusivity measure (MD, AD and RD), as shown in Fig.3.11 for the MD mask, Fig.3.12 for AD and Fig.3.13 for RD.

The water diffusivity measures in the current study show a pattern of gradual reduction over the training period in the target brain areas that were defined from the healthy group study. However, none of the three water diffusivity measures reached the significant level at the end of the training period (week 6) compared with the baseline level at week 0. For example, as shown in Fig.3.11a, the MD in visual target areas reduced gradually over the training duration but did not reach the significant change level at the end of the training period (week 6), $t(6) = .894$, $p > 0.2$.



<u>Fig.3.11 MD change in the target visual and cerebellum areas</u>: ***(a)*** *shows the MD changes over the training period of the hemianopia group in the target visual area that showed significant MD change in the healthy group (top right image);* ***(b)*** *shows the MD changes over the training period of the hemianopia group in the target cerebellum area that showed significant MD change in the healthy group (bottom right image).*



<u>Fig.3.12 AD change in the target visual and cerebellum areas</u>: ***(a)*** *shows the AD changes over the training period of the hemianopia group in the target visual area that showed significant AD change in the healthy group (top right image);* ***(b)*** *shows the AD changes over the training period of the hemianopia group in the target cerebellum area that showed significant AD change in the healthy group (bottom right image).*

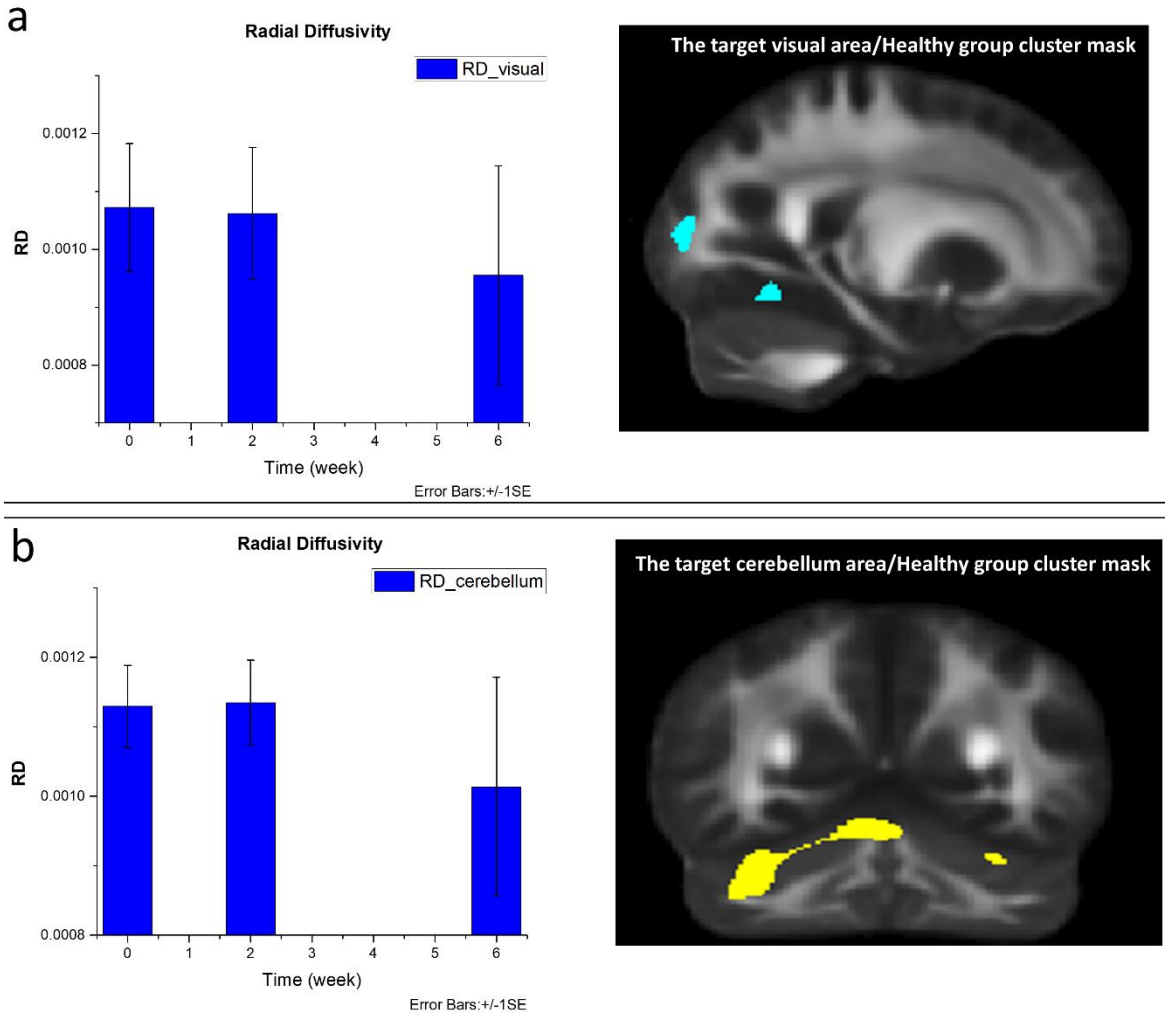


Fig.3.13 RD change in the target visual and cerebellum areas: ***(a)*** *shows the RD changes over the training period of the hemianopia group in the target visual area that showed significant RD change in the healthy group (top right image);* ***(b)*** *shows the RD changes over the training period of the hemianopia group in the target cerebellum area that showed significant RD change in the healthy group (bottom right image).*

Finally, to check the possibility of any negative impact of the brain-damaged areas (stroke areas) during the methodological transformation processing from the native space to common space, the target masks (in Fig. 3.11a and Fig. 3.11b) were transformed to the native space. For example, the cerebellum mask from the common space in Fig. 3.2a (method section) was transformed to the native space of subject 1 (as shown in Fig.3.2b). The results of the extracted data from native space for each individual, in Fig. 3.14a and 3.14b, from the target visual and cerebellum areas showed no difference compared with the common space data in Fig. 3.11a and 3.11b. This means that the brain-damaged areas of the hemianopic participants in this current study did not affect the general analysis approach of the imaging data.

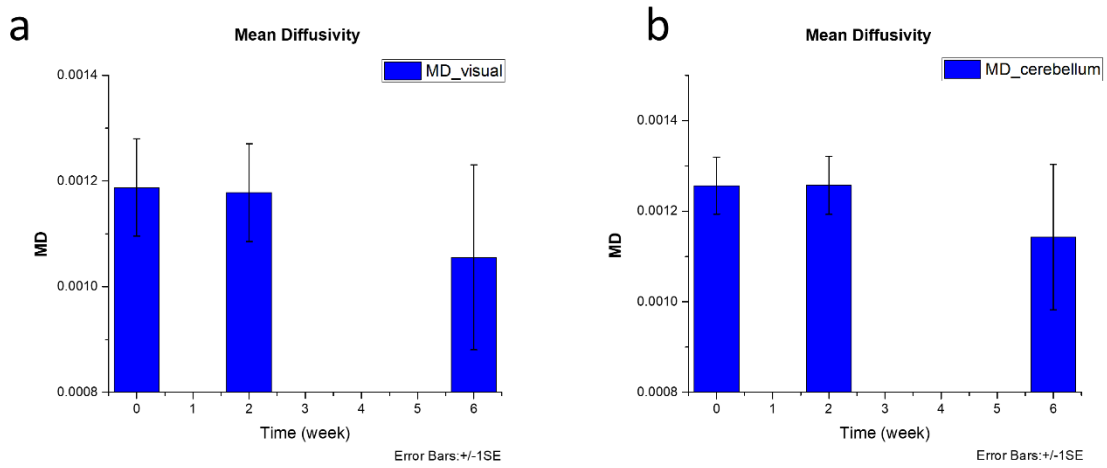


***Fig.3.14 Extraction of DTI data from the native space*: (a)** *shows the MD changes over the training period of the hemianopia group in the target visual area that showed significant MD change in the healthy group;* **(b)** *shows the MD changes over the training period of the hemianopia group in the target cerebellum area that showed significant MD change in the healthy group. The data in both areas were extracted separately from the native space for each individual perspirant, as explained in Fig. 2.S3.*

3.3.2.3 Suggested clinical investigation – individual analysis approach

As shown in Fig.3.15 and Fig.3.16, the areas that were affected by training in all three main suggested ROIs (visual cortex, cerebellum and right FEF area) were defined and investigated over the time course of training to evaluate the potential microstructural brain changes for the first participant. FA in some brain areas (inside the all three ROIs) for subject 1 shows a gradual increase during the training period (see Fig.3.15). Similar gradual changes were reported in all water diffusivity measures as a gradual reduction over the training period in MD, AD and RD for the same subject (subject 1) and approximately in the same brain areas (see Fig.3.16). For the results of the suggested clinical analysis approach for the rest of the hemianopic participants (subjects 2 to 7) in the current study, see the figures from Fig.3.17 to Fig.3.28.

Subject 1

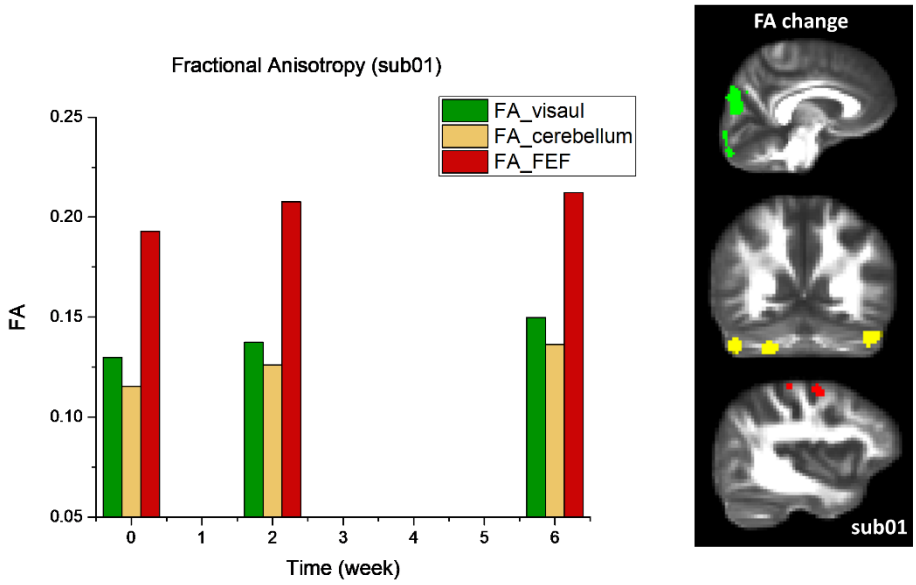


Fig.3.15 FA changes during the training for subject 1: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

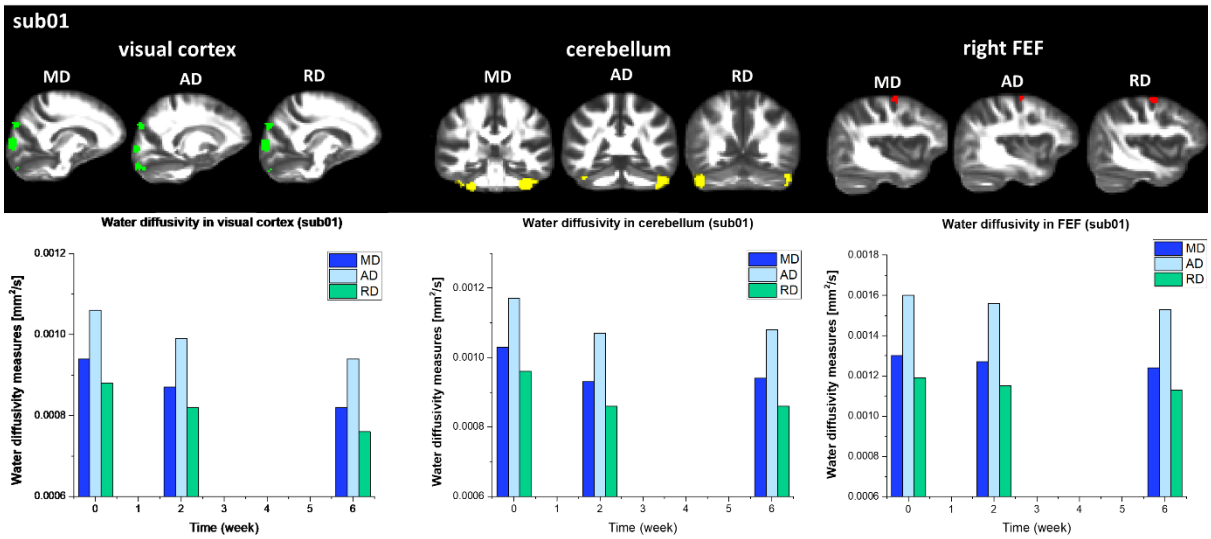


Fig.3.16 Water diffusivity changes in the three ROIs during the training for subject 1: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main ROIs (visual cortex, cerebellum and right FEF area).*

Subject 2

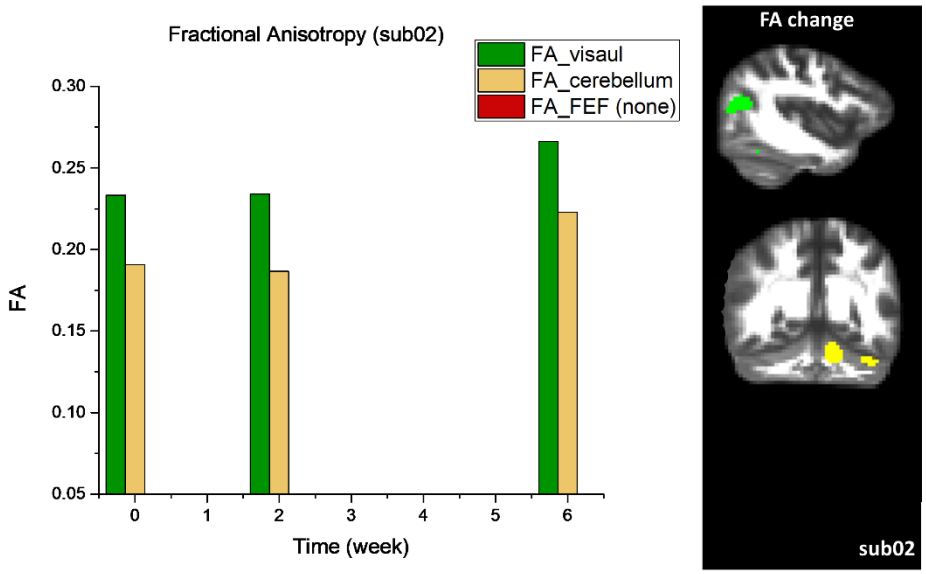


Fig.3.17 FA changes during the training for subject 2: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex and yellow for the affected areas in the cerebellum). The right FEF in subject 2 did show any obvious FA increase, therefore no data was presented in the graph related to the right FEF.*

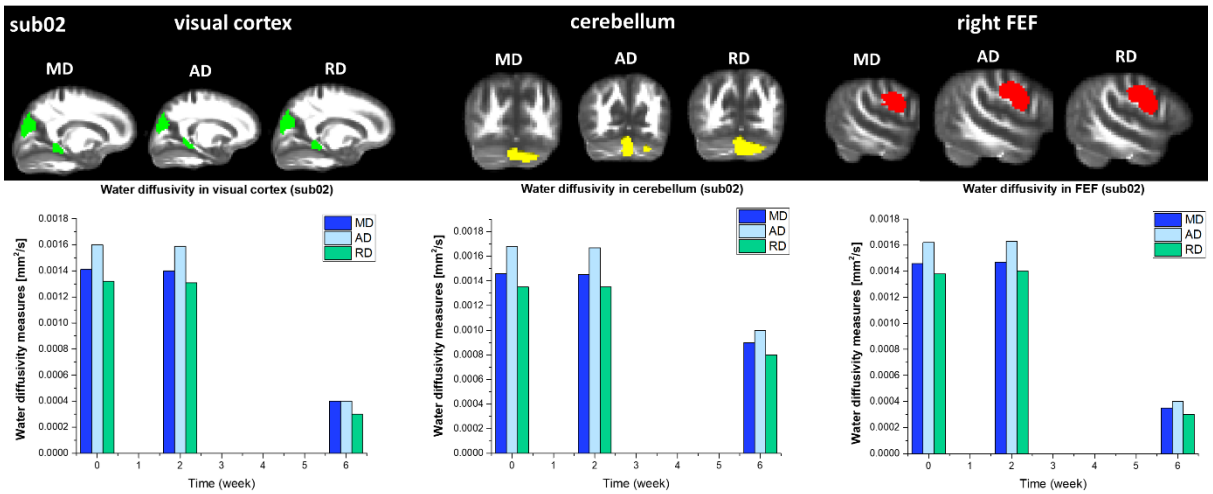


Fig.3.18 Water diffusivity changes in the three ROIs during the training for subject 2: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

Subject 3

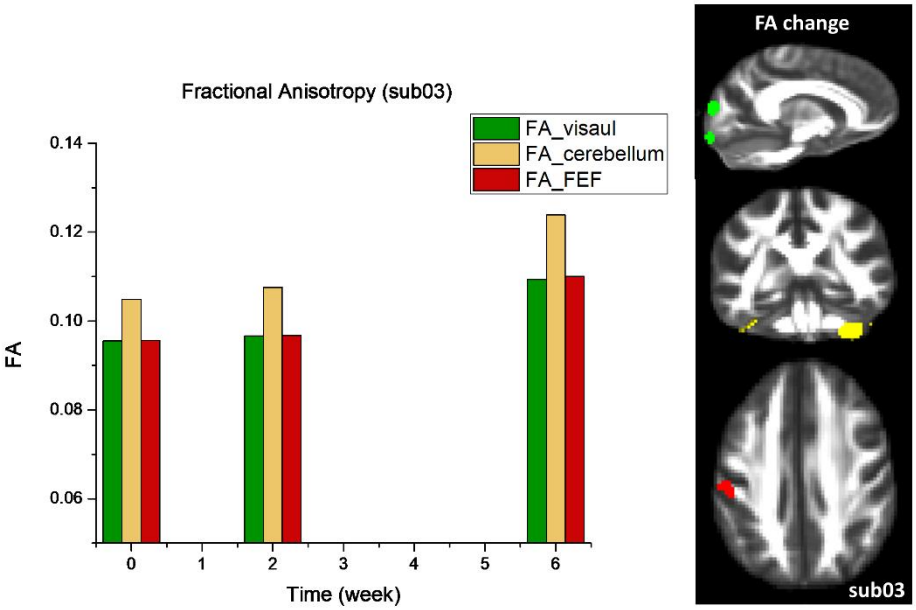


Fig.3.19 FA changes during the training for subject 3: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

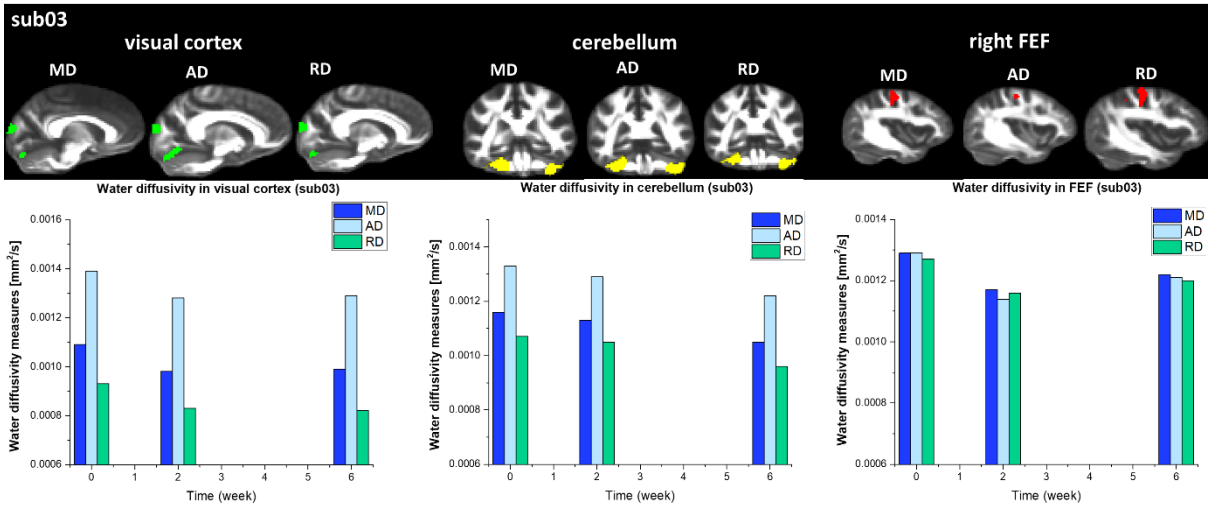


Fig.3.20 Water diffusivity changes in the three ROIs during the training for subject 3: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

Subject 4

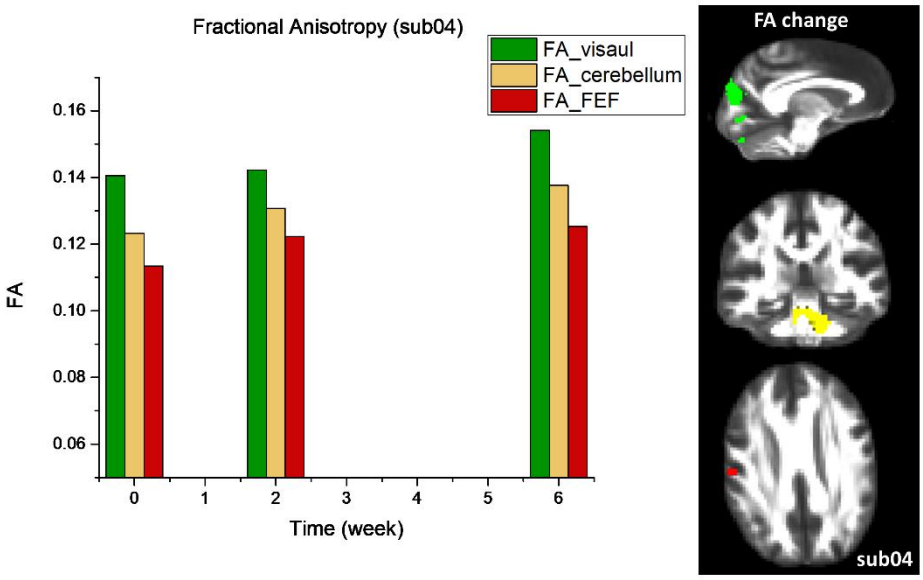


Fig.3.21 FA changes during the training for subject 4: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

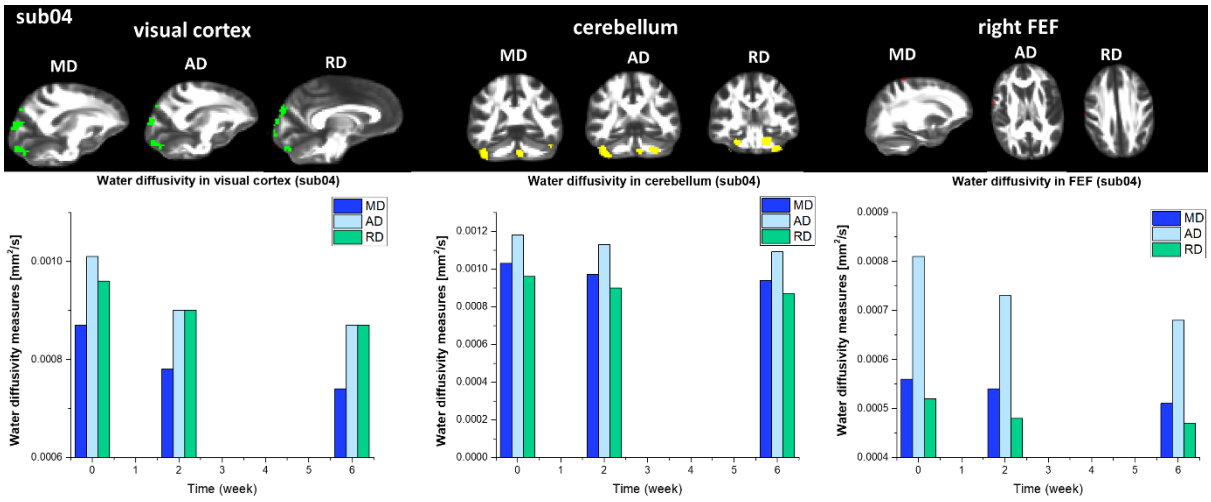


Fig.3.22 Water diffusivity changes in the three ROIs during the training for subject 4: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in the three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

Subject 5

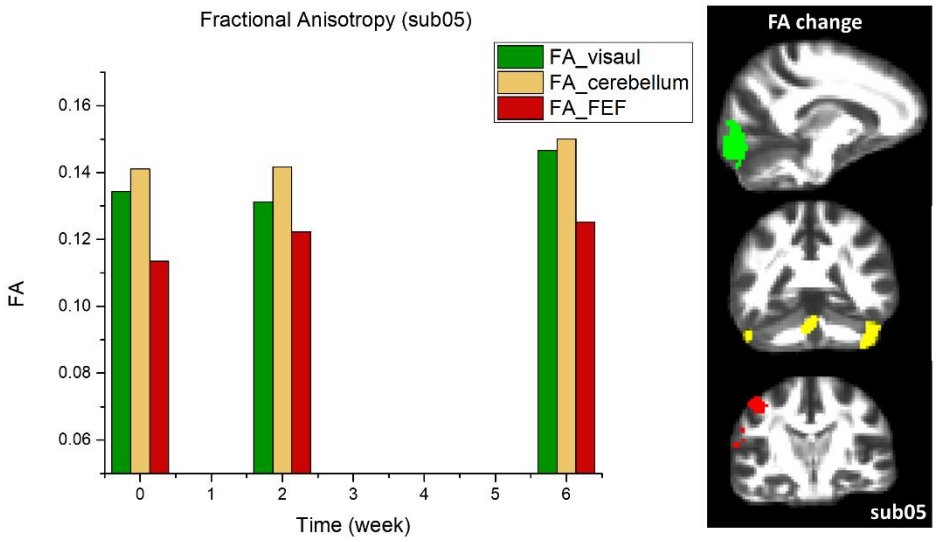


Fig.3.23 FA changes during the training for subject 5: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

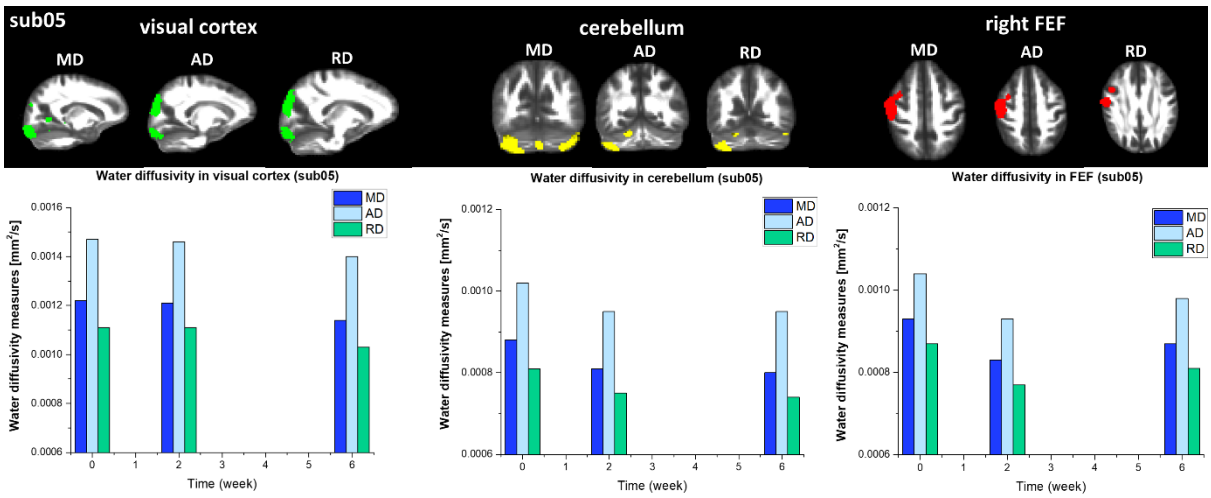


Fig.3.24 Water diffusivity changes in the three ROIs during the training for subject 5: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

Subject 6

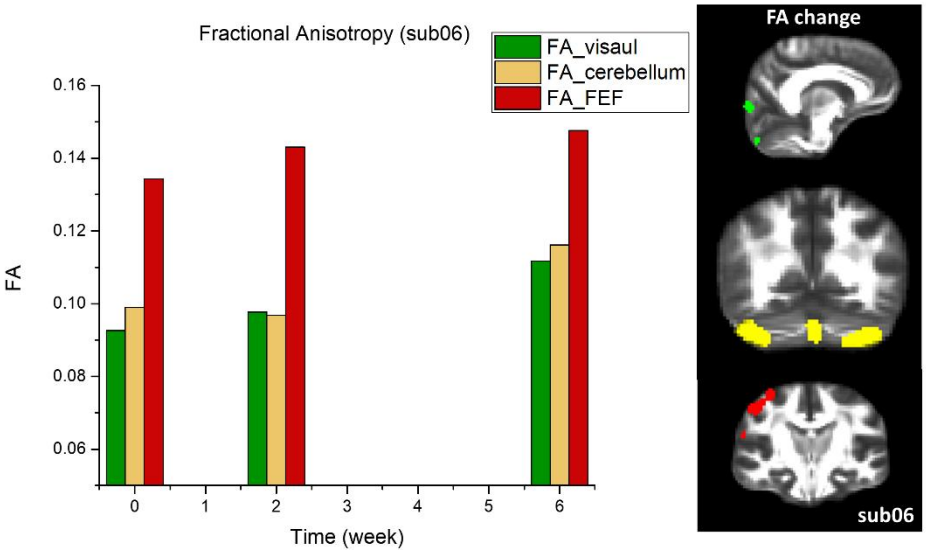


Fig.3.25 FA changes during the training for subject 6: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

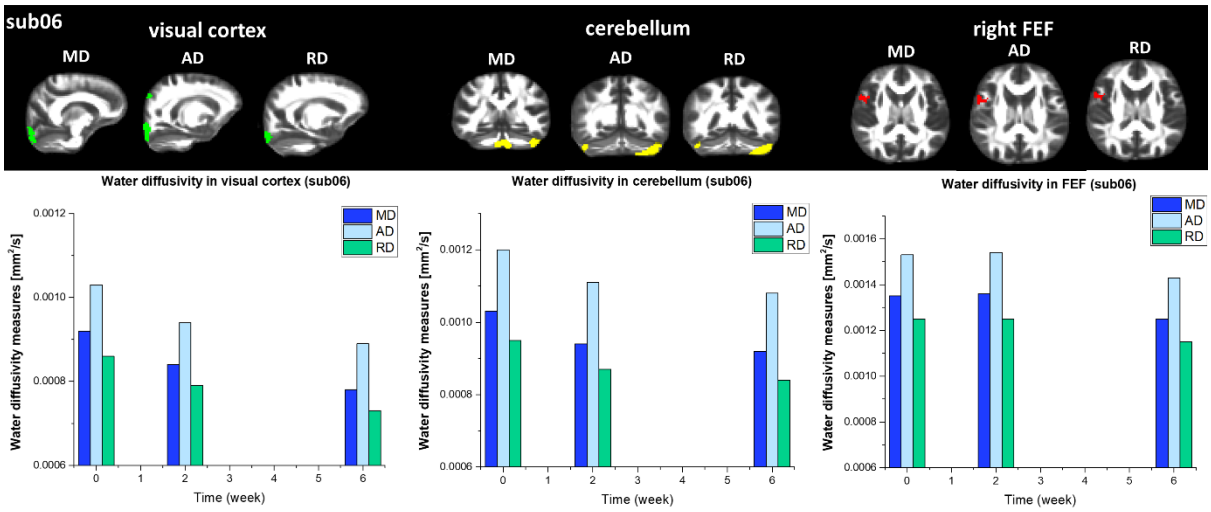


Fig.3.26 Water diffusivity changes in the three ROIs during the training for subject 6: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

Subject 7

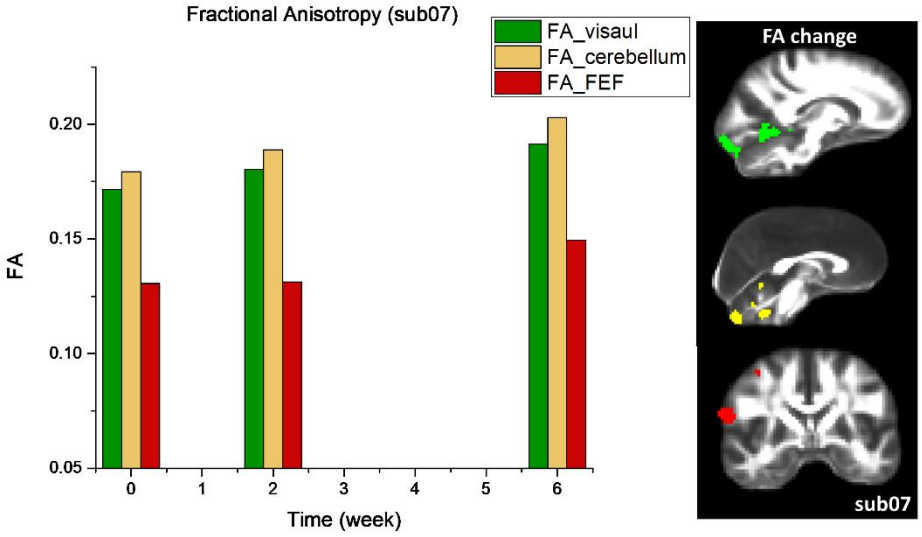


Fig.3.27 FA changes during the training for subject 7: *The graph shows the affected brain areas in the three main ROIs (visual cortex, cerebellum and precentral gyrus/right FEF); each colour in the graph represents the same colour in the images (green for the affected areas in the visual cortex, yellow for the affected areas in the cerebellum and red for the affected areas in the area of the right FEF).*

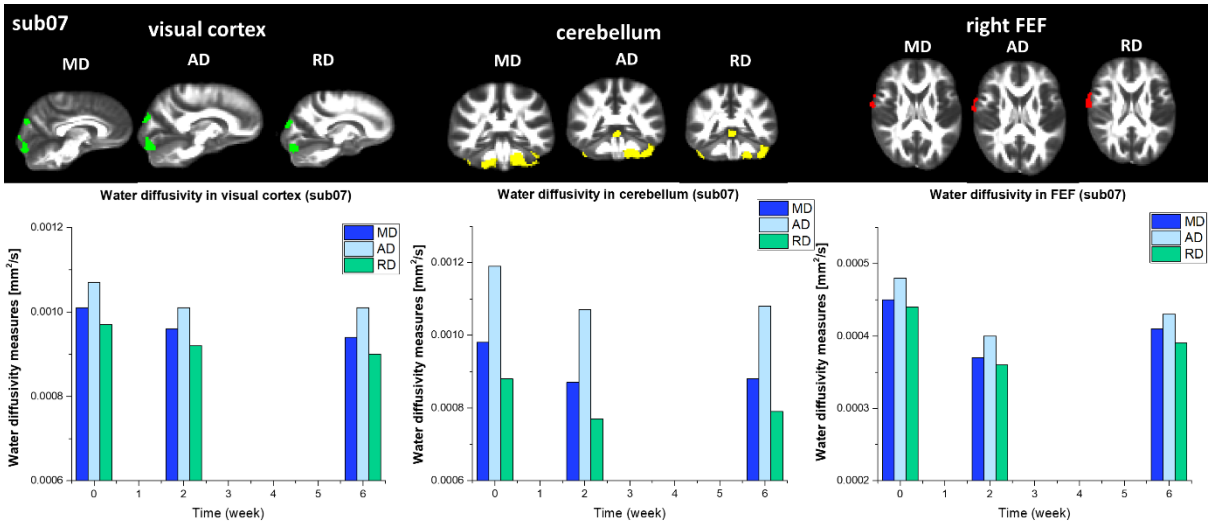


Fig.3.28 Water diffusivity changes in the three ROIs during the training for subject 7: *The graphs show the changes of water diffusivity measures (MD, AD and RD) in the affected brain areas in all three main suggested ROIs (visual cortex, cerebellum and right FEF area).*

3.3.2.4 Group analysis – native space

To understand more deeply the impact of training on hemianopia patients, another group analysis approach was conducted. In this analysis approach, the data that were extracted from the native space (from the three ROIs areas) during the individual analysis were added together for all the seven hemianopic participants to investigate the overall change pattern among participants. In addition, a control area (Heschel's gyrus) which appeared to be unaffected by the current training task was investigated structurally for each participant (in the native space) to be compared with the results of the ROIs data.

Fractional anisotropy (visual cortex and cerebellum) – native space group analysis

FA shows a gradual change in both the visual and cerebellum group analysis (see Fig. 3.29a and 29b). At week 6, FA was increased significantly compared with week 0 (FA visual, $t(6) = -4.671$, $p < 0.001$; FA cerebellum, $t(6) = -7.237$, $p < 0.001$).

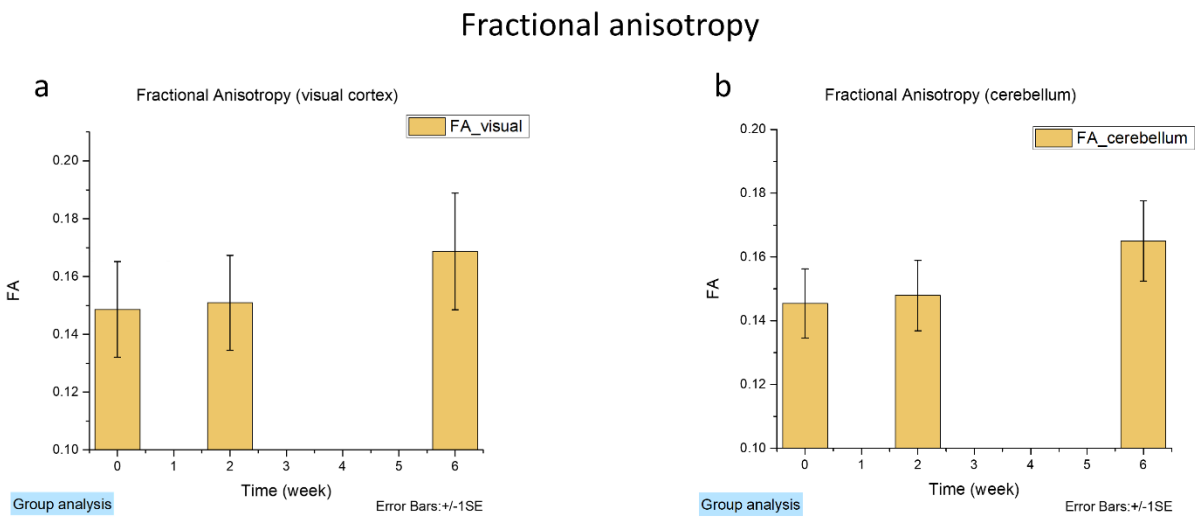


Fig.3.29 Training effect on fractional anisotropy (FA) in the visual cortex and cerebellum (group analysis in native space: *The graphs show an increase of FA during the training period:* ***(a)*** *shows FA increase in the visual cortex, and* ***(b)*** *shows the FA increase in the cerebellum. The data in both graphs were extracted from a specific mask (the area that shows maximum change) for each individual participant in the native space.*

Water diffusivity (visual cortex and cerebellum) – native space group analysis

All water diffusivity measures showed gradual reduction changes over the training period. MD showed gradual reduction in both the visual and cerebellum areas (see Fig. 3.30a and 3.30b). At week 6, MD decreased significantly compared with week 0 in the visual cortex and *marginally*

significantly in the cerebellum (MD visual, $t(6) = 1.687$, $p < 0.07$; MD cerebellum, $t(6) = 1.489$, $p < 0.09$).

Similarly, AD (Fig. 3.30c, 3.30d) and RD (Fig. 3.30e and 3.30f) decreased gradually over the training period. At week 6, AD reduced significantly compared with week 0 in the visual cortex and did not reach the significant level in the cerebellum (AD visual, $t(6) = 1.610$, $p < 0.07$; AD cerebellum, $t(6) = 1.438$, $p < 0.1$). RD at week 6 was significant compared with week 0 in the visual cortex and *marginally* significant in the cerebellum (RD visual, $t(6) = 1.731$, $p < 0.067$; RD cerebellum, $t(6) = 1.527$, $p < 0.08$).

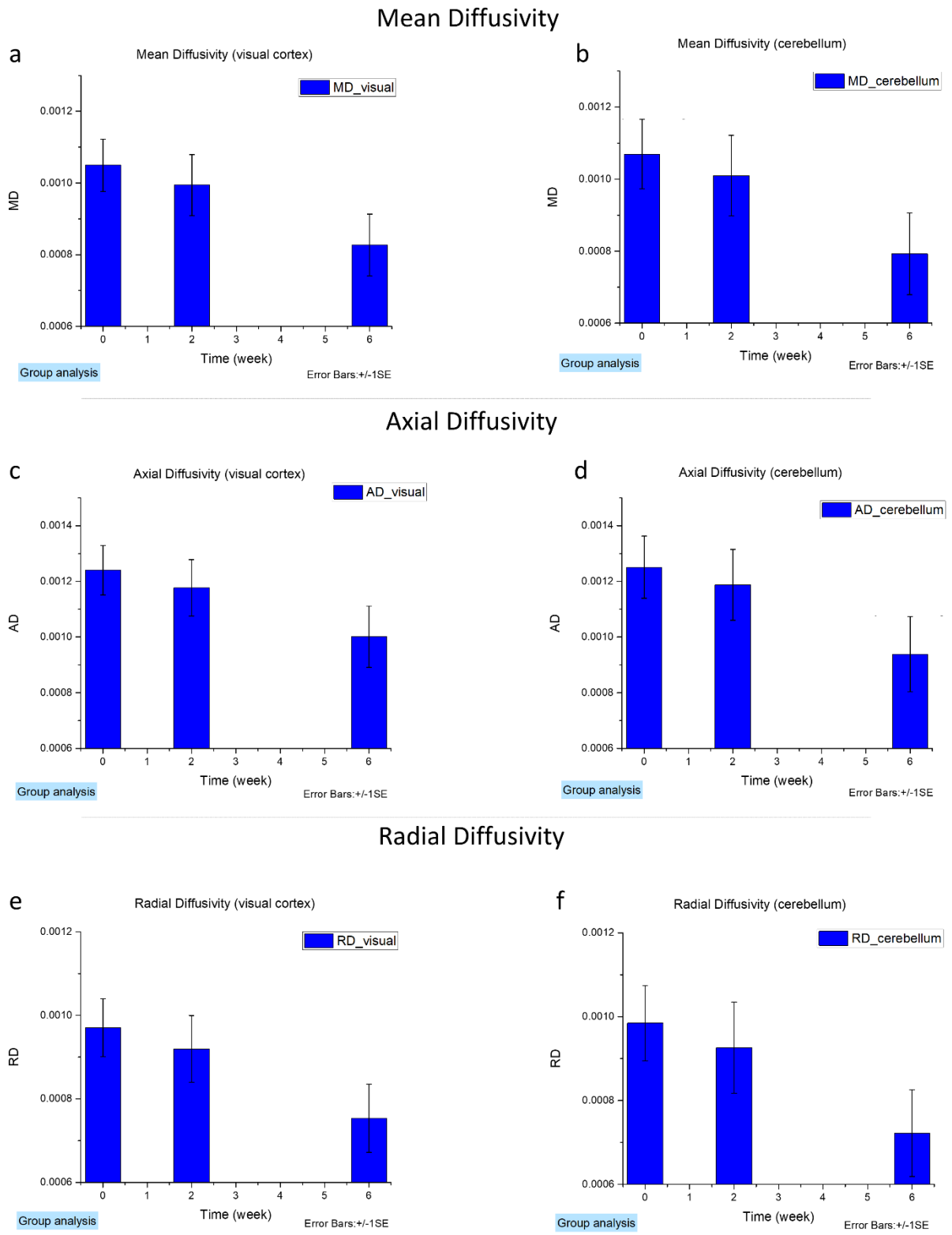


Fig.3.30 Water diffusivity changes during the training period in the visual cortex and cerebellum (group analysis in native space): *The graphs show the impact of training on water diffusivity: MD (top), AD (middle) and RD (bottom) during the training period (weeks 0–6). The data in all graphs were extracted from a specific mask for each individual participant from the native space.*

Fractional anisotropy and water diffusivity (FEF) – native space group analysis

FA in the FEF areas shows the same gradual increase over the training period for the native space group analysis approach, and also reached the significant level at the end of the training period compared with the baseline, $t(6) = -4.37$, $p < 0.007$ (see Fig. 3.31a).

All diffusivity measures (MD, AD and RD) in FEF areas showed the same gradual reduction over the training period for the native space group analysis approach. However, none of them reached the significant level at the end of the training period compared with the baseline (MD, $t(6) = 1.326$, $p = 0.115$; AD, $t(6) = 1.36$, $p = 0.10$; RD $t(6) = 1.356$, $p = 0.11$) (see Fig. 3.31b, 3.31c and 3.31d).

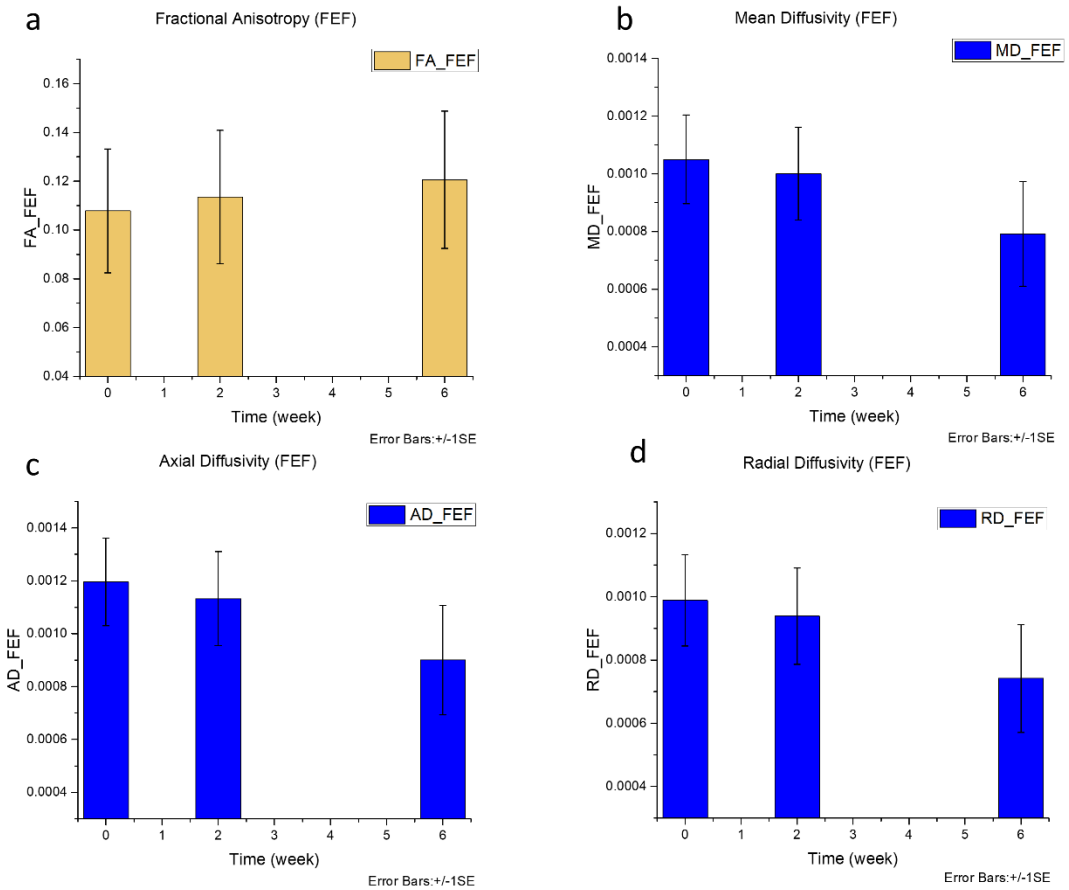
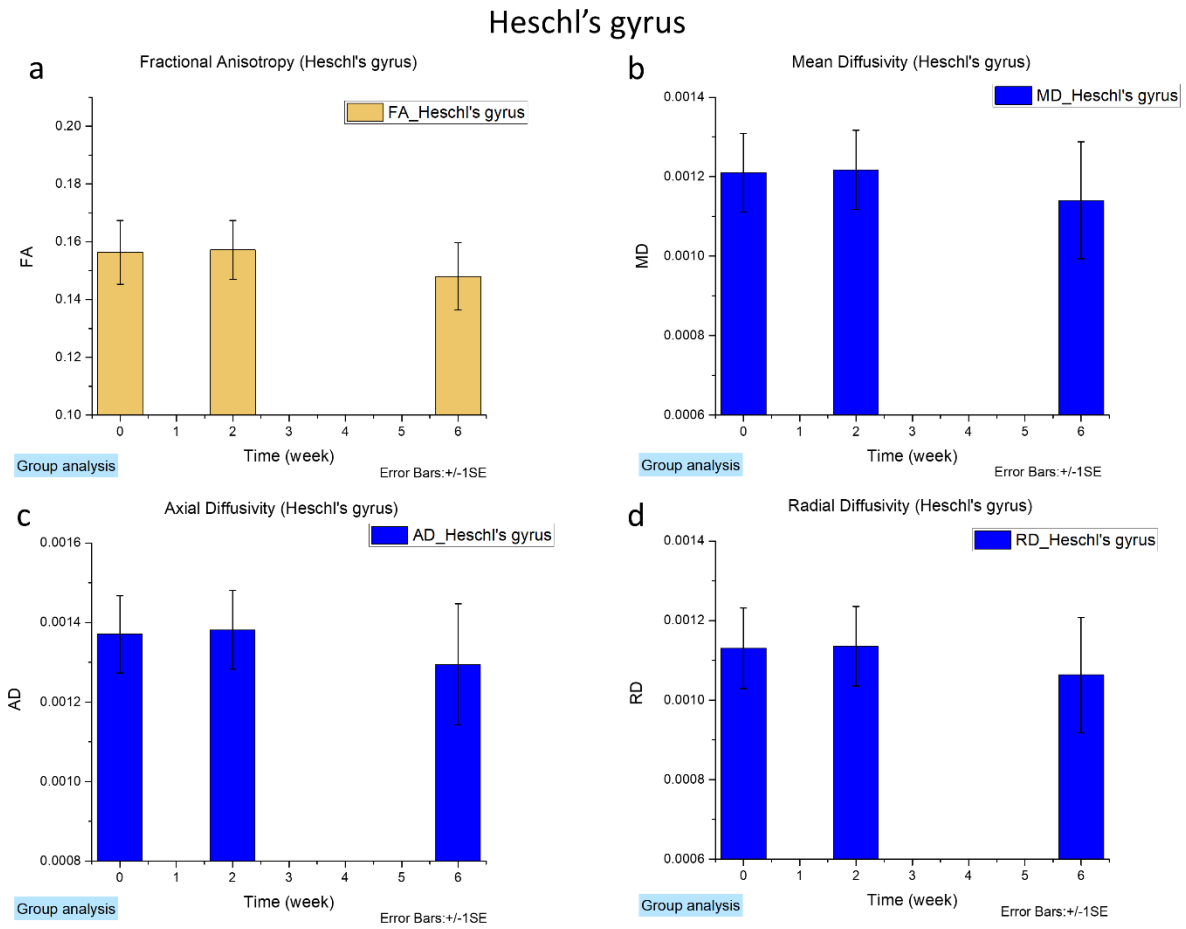


Fig.3.31 Training effect on DTI measures in the FEF (group analysis in native space): *The graphs show a gradual increase in FA and a gradual reduction in all diffusivity measures during the training period:* ***(a)*** *shows FA increase in the FEF, and* ***(b)****,* ***(c)*** *and* ***(d)*** *show reductions in MD, AD and RD in the FEF. The data in all graphs were extracted from a specific mask (the area that shows maximum change) for each individual participant in the native space.*

Control area (Heschel's gyrus) – native space group analysis

No structural significant changes were reported in the control area (Heschel's gyrus) (see Fig.3.32) at the end of the training period in all DTI measures compared with the baseline level (FA, $t(6) = .729$, $p > 0.24$; MD, $t(6) = 0.872$, $p > 0.20$; AD, $t(6) = 0.836$, $p > 0.21$; RD, $t(6) = 0.891$, $p > 0.20$).



<u>Fig.3.32 FA and water diffusivity changes during the training period in Heschel's gyrus (the control area)</u>: *The graphs show group analysis in native space:* ***(a)*** *shows the FA values over the training period (weeks 0, 2 and 6) and* ***(b)***, ***(c)*** *and* ***(d)*** *show the values of the water diffusivity during the training period (weeks 0, 2 and 6). The data in all graphs were extracted from the Heschel's gyrus mask for each individual participant from the native space.*

3.3.2.5 Blind visual field vs intact visual field

As shown in Fig.3.33, the RTs in both the intact and blind visual fields were reduced over the training period in all behavioural performance tests (laboratory, Fig. 3.33a; voluntary fMRI task, Fig. 3.33b; involuntary fMRI task, Fig. 3.33c). At week 0, the RTs in the blind visual field in all three tasks were longer compared with the RTs in the intact visual field. At week 6, very similar behavioural performance in both visual fields was shown in both systematic eye-movement tasks (laboratory task and voluntary fMRI task).

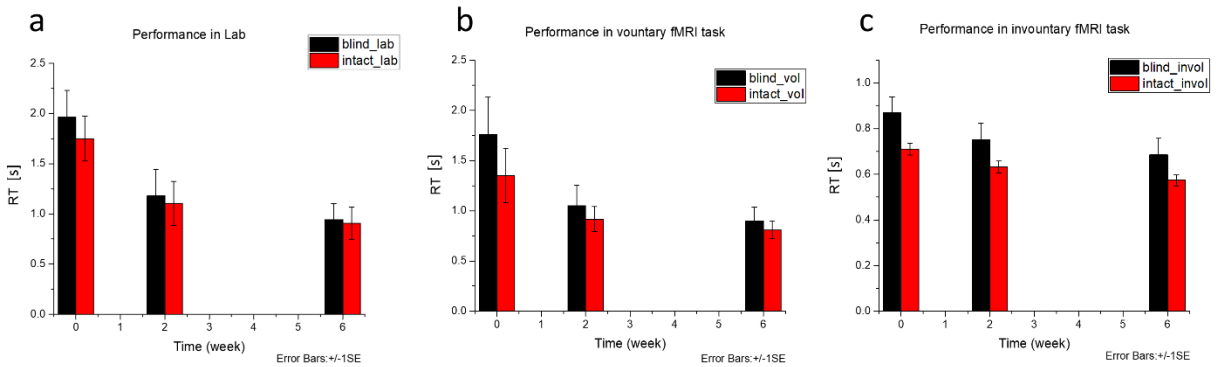


Fig.3.33 Training effects on behavioural performance in the blind and intact visual fields: *The graphs show the impact of the training on the participants' behavioural performances in the blind and intact visual fields:* ***(a)*** *shows the reduction of the average response time (in the intact and blind visual fields) of the group during the laboratory tests for each visit over the training period;* ***(b)*** *shows the reduction of the average response time (in the intact and blind visual fields) of the group during the voluntary fMRI tasks for each visit over the training period;* ***(c)*** *shows the reduction of the average response time (in the intact and blind visual field) of the group during the involuntary fMRI tasks for each visit over the training period.*

RT changes were measured for the intact as well as for the blind visual field (Fig.3.33). Separate repeated measures ANOVAs with the factors time (weeks 0, 2 and 6), condition (intact, blind) and participant as the repeated measure were conducted for each of the three behavioural performance tasks (laboratory, voluntary and involuntary). Laboratory and involuntary analyses showed significant main effects of learning duration and factor 'Time' (weeks 0, 2 and 6) but no significant interactions between duration and factor 'Condition' (intact, blind) were seen in all tasks. No significant main effects of 'Condition' were seen in all tasks. Post-hoc paired t-tests show that the RT reductions between week 0 and week 6 are significant in both visual field (intact and blind) in all three tasks (Table 3.2).

Test	*ANOVA*			*One-sided post-hoc paired t-test (week 0 vs week 6)*	
	Condition	**Time**	**Interaction**	**Intact (VF)**	**Blind (VF)**
Laboratory	**F(6) = 2.41, p = 0.17**	**F(6) = 15.17, p < 0.007**	**F = 1.71, p = 0.27**	**t(6) = 5.15, p < 0.001**	**t(6) = 5.47, p < 0.001**
Voluntary	**F(6) = 4.66, p = 0.09**	**F(6) = 3.25, p = 0.12**	**F(6) = 2.99, p = 0.13**	**t(6) = 2.36, p < 0.02**	**t(6) = 2.85, p < 0.01**
Involuntary	**F(6) = 4.95, p = 0.06**	**F(6) = 10.5, p = 0.01**	**F(6) = 1.39, p = 0.33**	**t(6) = 5.34, p < 0.001**	**t(6) = 4.28, p < 0.002**

Table 3.2 Summary statistics of the ANOVA main training effects (intact and blind visual fields)*: The table shows the main effects of condition (intact visual field vs blind visual field), time (weeks 0, 2 and 6) and their interaction for three separate ANOVAs that were computed for the three behavioural performance tests (laboratory, voluntary fMRI and involuntary fMRI). Post-hoc paired t-tests, comparing the mean RT after training with the baseline measure in each task, are shown on the right. A significant main effect of test time is seen in laboratory and involuntary behavioural tasks. No significant interactions are seen in all three tasks. No significant main effect of condition is seen in all three tasks. Post-hoc tests show significant reduction in RT for all tasks.*

3.3.2.6 Ipsilateral lesion vs contralateral lesion (visual cortex)

fMRI lateralisation

During the voluntary fMRI task (trained task) the intact hemisphere was the dominant visual cortex showing a greater number of active voxels in all three scanning visits (weeks 0, 2 and 6), and the degree of the laterality index (LI) was increased at the end of the training period compared with the baseline, $t(6) = 1.68$, $p < 0.07$ (see Fig.3.34).

DTI change lateralisation

At the end of the training period more structural changes (FA and MD) were seen in the intact visual cortex compared with the affected visual cortex (see Fig.3.35).

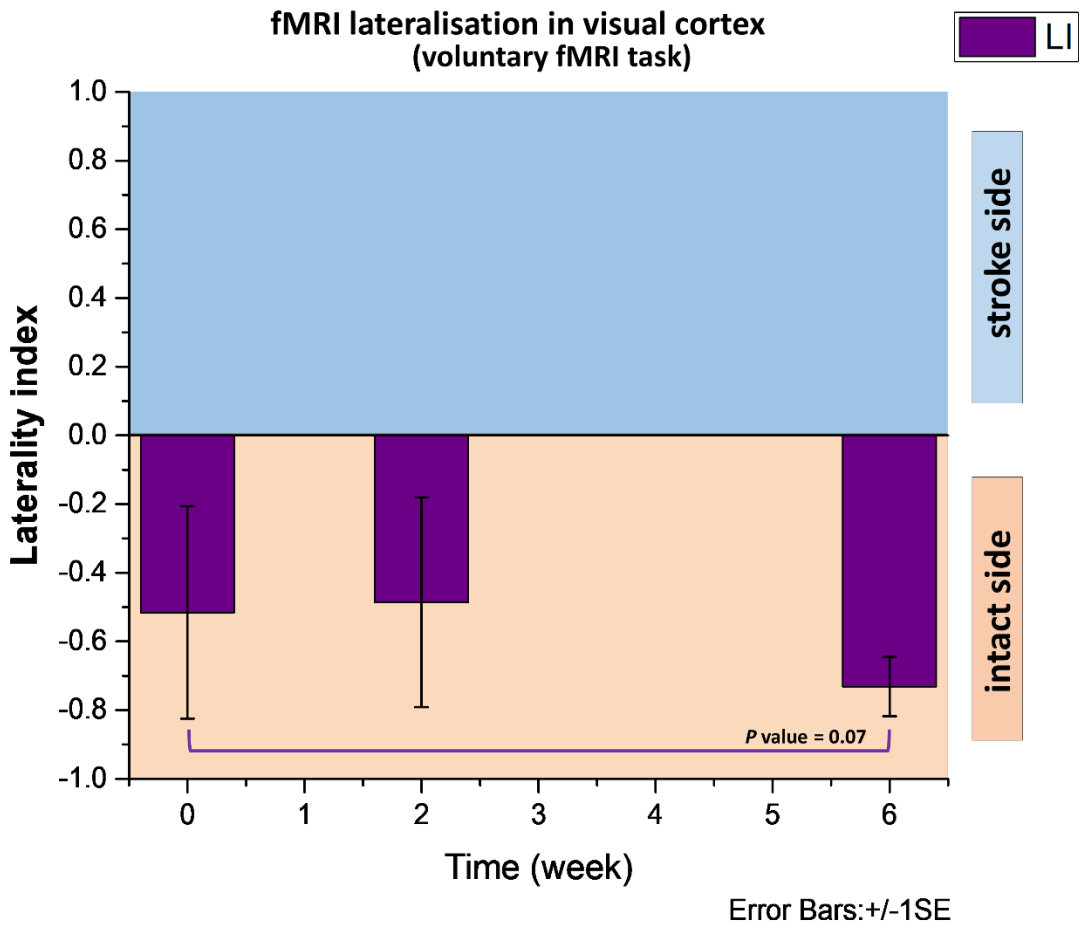


Fig.3.34 Laterality index in the visual cortex (voluntary fMRI task): *The graph shows the contralateral lesion area as the dominant visual cortex during the voluntary fMRI task compared with the ipsilateral lesion (affected visual cortex).*

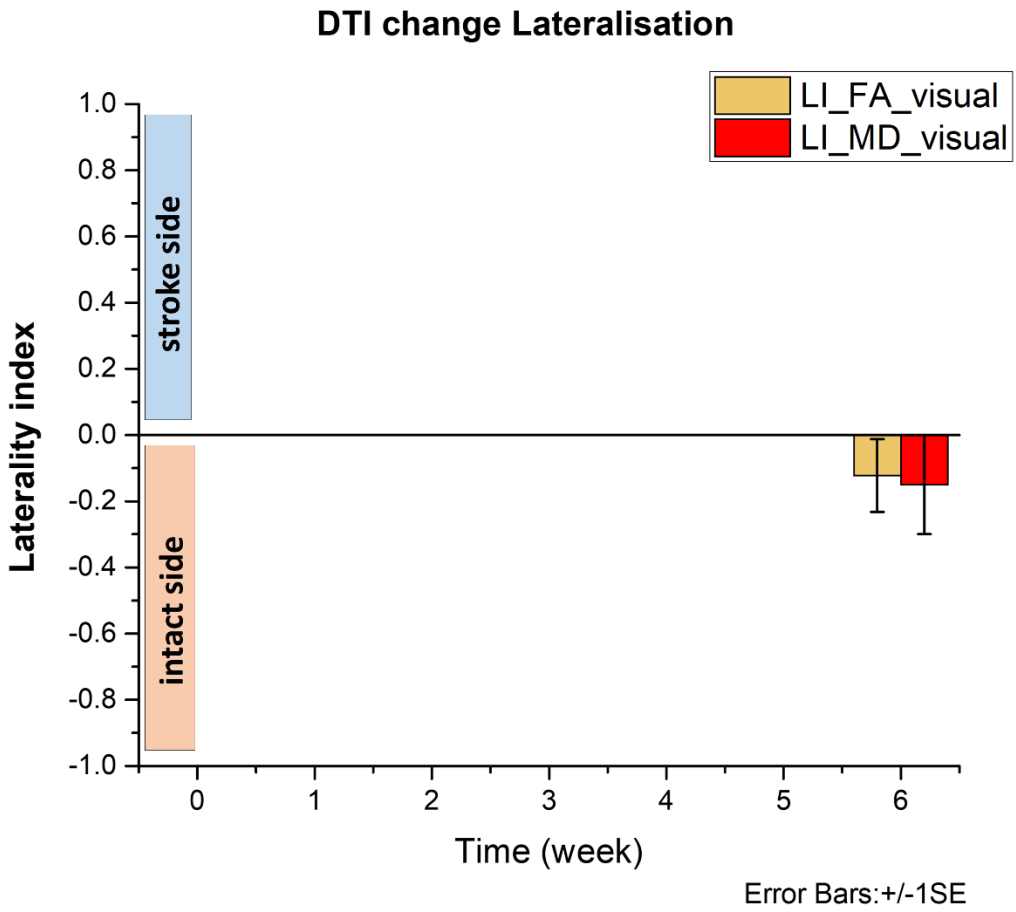


Fig.3.35 Laterality index of the microstructural changes at week 6 in the visual cortex: *The graph shows more structural changes (FA and MD) in the contralateral lesion (intact visual area) compared with the ipsilateral lesion (stroke visual cortex) at the end of the training period.*

3.4 Discussion

The first aim of the study was to assess the expected empirical visual function improvement for a group of the target population (stroke survivors with HH) when performing a proposed visuomotor task over six weeks of daily training. The second aim was to collect imaging data over the training period to investigate the potential associated neural plasticity in the task-relevant brain areas.

3.4.1 Behavioural performance measures

As expected (Howard et al., 2013; Pambakian et al., 2004; Nelles et al., 2001; Kerkhoff et al., 1992; Little et al., 2004), all participants showed significant behavioural performance improvement in visual function over the training period. All empirical behavioural performance measures (response time, total number of eye-movement gazes and the mean fixation duration) reduced significantly, while the response accuracy remained above 90% for all participants.

Intact and blind visual fields

Before training, the HH patients in the current study required a longer response time in both the blind and intact visual fields compared with the after-training assessment visit at week 6 which may indicate more and longer fixations. This demonstrates numerous refixations or inaccurate saccades with the possibility of making a series of small saccades with long fixations into their blind field (Meienberg et al., 1981; Zangemeister et al., 2020), which may indicate the existence of disorganised scanning and the omission of target stimuli prior to training (Zihl, 1995; Pambakian et al., 2004).

The design of the rehabilitative task for HH

The primary aim of visual search rehabilitation programmes that were designed to treat deficits in visual exploration was to improve the disorders of visuospatial disorganisation apparent in some patients with HH. Therefore, these training programmes require HH patients to search for a number of target stimuli over an extended time period and the patients usually are

explicitly instructed to make saccades into the hemianopic hemifield, and to search in a systematic manner (Zihl, 1995; Kerkhoff et al., 1992; Nelles et al., 2001; Kerkhoff et al., 1992; Passamonti et al., 2009). Indeed, it appears that strategic guidance of eye movements is task specific. As the eye-movement task of the current study requires participants to search for a target equally likely to appear in either hemifield, the HH participants found the ipsilesional targets more difficult to detect, and thus adopted a more advantageous strategy of more rapid switching of hemifields as a result of training. Therefore, the design of the current eye-movement training encourages patients to make exploratory eye movements into the blind field (the neglected visual field area). Hence, this leads to an improvement in the way in which HH patients could successfully locate a target with eye movements (the visual search field).

Behavioural outcome measures

Researchers usually record RT, given that an inefficient search strategy will lead to longer RTs (Perez et al., 2013). Our results show a significant reduction in RT after six weeks of training. This result of the reduction in RT was consistent with many visual search training studies that have been applied to the same target population (HH patients) (Mannan et al., 2010; Jacquin-Courtois et al., 2013; Pambakian et al., 2004; Nowakowska et al., 2018). Moreover, being quicker at detecting target locations with fewer fixations required to reach the target has been reported in other HH visual training studies (Mannan et al., 2010; Roth et al., 2009). Consistently, in the current study we reported the gradual reduction of the total number of fixations and the mean fixation duration over the training period which both reached the significant change level at the end of the training.

To conclude, the improvement in all three empirical measurements (RT, TNF and MFD) in the current study may simply reflect more efficient placement of the eyes after training, allowing HH patients to saccade to the probable location of the target. Our results, therefore, suggest that the current eye-movement training facilitates the development of specific compensatory eye-movement strategies in patients with homonymous visual field defects. Importantly, the results of this study complement an earlier study (Rowe et al., 2017) in which Rowe and colleagues demonstrated the transfer of this search training programme to activities of daily living and substantial subjective improvements in the HH patients (Rowe et al., 2017).

3.4.2 Transfer of behavioural performance gains to other tasks

Other objective improvements in HH participants in different environments were reported in the current study. The HH patients in this study showed significant reduction in scanner response time during both fMRI tasks (intentional and attentional eye movement) at the end of the training period. Similarly, HH patients showed significant improvement in target detection (the number of detected bells) and marginally significant improvement in RT during the Bells task at the end of the training period. An improvement in attentional networks was reported by Lu and colleagues (Lu et al., 2018) in hemianopia patients after visual rehabilitation training, which may explain the significant reduction in RT when our participants performed the involuntary eye-movement fMRI task. As a result, it is probably fair to suggest that the learning could transfer from the trained task into the real world.

3.4.3 Brain plasticity and behavioural improvement

Change in some measures of oculomotor behaviour may result from perceptual learning (Mannan et al., 2010). For example, RTs in the current study were shorter after training. One interpretation of this finding is that visual search training results in perceptual learning, facilitating target detection prior to – and during – fixation on target. This leads to lower fixation durations. Thus, as repeated visual search practice leads to perceptual learning, can the improvement in the empirical visual functions associated with visual search training be explained by neuronal changes (functionally and/or structurally), rather than by changes in eye-movement strategies (Perez et al., 2013; Mannan et al., 2010)? Therefore, prospective serial studies that correlate neural activity with quality of explorative eye-movement task in hemianopic patients are necessary to better interpret patterns of neuroplastic changes over time, and understand more deeply their role in recovery of function (Nelles et al., 2010). Functional MRI and DTI data were measured during the training period in the current study to investigate the potential functional and structural brain plasticity that may associate with learning.

fMRI change

A study by Nelles and colleagues (Nelles et al., 2010) used fMRI to study the training effects of eye-movement training on cortical representation of visual hemifields in HH patients. In this

study, the differences in fMRI activation between rest and hemifield stimulation, as well as before and after the training period, were assessed. A significant activation at baseline was found bilaterally in extrastriate cortical areas, with the strongest increases in the contralesional hemisphere. As a result of training, HH patients showed increased activity in the unaffected extrastriate cortex after training in Nelles and colleagues' study (Nelles et al., 2010). Our results, consistent with this, show that brain activation as a response to the visual stimulation when participants performed the eye-movement tasks (both voluntary and involuntary), was reported bilaterally in extrastriate areas in all participants, with the strongest activation in the unaffected areas. This degree of laterality index was greater at week 6 compared with week 0. However, after training, unlike Nelles and colleagues' results (Nelles et al., 2010), no brain activation changes were reported in extrastriate areas when statistical parametric mapping analysis was undertaken with seven hemianopia participants in the current study.

In terms of the training effect on functional activation in the current study, a significant fMRI increase was found in the right FEF during the voluntary eye-movement task. This change occurred gradually over the training period and the patients showed gradual improvement in the RT in the same task. At the end of the training period, the target brain areas (the areas that showed significant fMRI change in the healthy study) in the cerebellum and visual cortex showed a fMRI increase in the current study, but this did not reach the significant level. This is perhaps because of the small sample size in this study or the variety of damaged visual brain areas among participants (five patients with right stroke and two with left stroke). A previous eye-movement study on HH patients reported functional activation changes following training in oculomotor brain areas (Nelles et al., 2009). Other studies reported fMRI changes in the extrastriate cortex (Nelles et al., 2009), prestriate cortex (Lu et al., 2018), the right inferior and lateral temporal, right dorsolateral frontal, bilateral anterior cingulate, and bilateral basal ganglia (Marshall et al., 2008), or were found to induce a stronger activation in the intact visual brain area (Henriksson et al., 2007).

Structural change

As to whether cortical structure changes have a restorative role in enhancing brain activity, the data from all previously investigated fMRI studies (Nelles et al., 2009; Lu et al., 2018; Henriksson et al., 2007; Marshall et al., 2008) that have applied to HH patients have not

answered this question. So far, there is no eye-movement study that has investigated microstructural change following training in HH patients. The current study is a multi-modal MRI imaging study, where both functional and structural imaging data were collected to measure any structural or functional plasticity that may be associated with the expected eye-movement improvement. In group analysis, no structural changes were detected in the ROI areas in the current study. The extracted data from target areas inside the ROI (the areas that showed significant DTI changes in the healthy study (Chapter 2) in the visual cortex and cerebellum), showed a pattern of gradual reduction of water diffusivity in the visual cortex, but the reduction in diffusivity did not reach the significant level in both target areas (visual cortex and cerebellum) at the end of the training period.

Individual analysis approach (suggested for clinic)

As the structural group analysis did not show consistent structural changes and in response to clinical need, a clinical analysis approach was suggested in the current study, to be applied to each individual participant. Therefore, a separate data extraction method for each participant was applied to investigate the three main areas (visual cortex, cerebellum and right FEF) (Fig.3.1 in methods section, 3.2.4). Previously, these areas were determined as the most likely areas to be affected by the current systematic eye-movement interventions based on the data from the healthy group (Chapter 2). The computation of the training effect was performed in native space to investigate the increase (post > pre) in FA or decrease (pre > post) in water diffusivity measures (MD, AD and RD) in all three areas. Then, further analysis was restricted to areas that showed maximal changes in diffusivity measures.

The results from the proposed clinical approach showed changes in all three investigated areas in all HH patients. However, in all participants, the extrastriate area (v3d) showed changes in similar locations. Interestingly, all DTI metrics showed a gradual change pattern over the training period. Therefore, it could be possible to suggest two investigation steps: (1) collection of DTI images during the initial stage of practice (two or three weeks from the training onset) to detect potential structural changes which may predict rehabilitation outcomes; (2) a follow-up imaging analysis (multiple scan visits) may provide a good opportunity to model the time course of changes to optimise the overall training period or

intensity to achieve the best outcome. The current suggested individual analysis approach should be tested in clinical practice as the sample size is very low. The findings of research and clinical study together may allow clinicians to target interventions effectively to ensure people adapt as efficiently as possible to visual field loss following a stroke.

3.4.4 Limitations

HH participants were scanned three times over the course of the experiment. Our data indicates differential time courses of functional, microstructural and behavioural performance measures. It would be interesting to document very early (Sagi et al., 2012; Yotsumoto et al., 2008) neuroplastic changes in response to the task as well as to extend the post-intervention evaluation (Frank et al., 2018).

The present study was designed to identify co-localised functional and structural changes in a VPL task and to quantify the time course of these changes. The number of participants in the current study was below the range typically used for longitudinal studies because of patient access limitations due to COVID-19 (Yotsumoto et al. 2008 – 15 participants; Kourtzi et al. 2008 – 19 participants; Frank et al. 2014 – 26 participants). We would have preferred to use a much larger participant number, especially for the correlational analysis.

Finally, the suggested clinical approach which relies on individual analysis instead of the group analysis has not been tested in clinic yet.

3.5 Conclusion

Objectively, the current eye-movement task led to an improvement in visuomotor skills in hemianopic participants: fewer fixations and reduced fixation duration were required to perform the task. Subjectively, the results of our study complement an earlier study (Rowe et al., 2017) in which Rowe and colleagues demonstrated the transfer of this search training programme to activities of daily living and substantial subjective improvements in the same target group (HH patients).

The improvement in all three empirical measurements (RT, TNF and MFD) in the current study may simply reflect more efficient placement of the eyes after training, allowing HH patients to saccade to the probable location of the target. Our results, therefore, suggest that the current eye-movement training facilitates the development of specific compensatory eye-movement strategies in patients with homonymous visual field defects by adopting a more advantageous strategy of more rapid switching of hemifields as a result of training. Moreover, the design of current eye-movement training encourages patients to make exploratory eye movements into the blind field (the neglected visual field area). Hence this led to an improvement in how HH patients can successfully locate a target with eye movements in the blind visual field.

The behavioural improvement was consistent with significant functional changes in the right FEF. The gradual functional and structural brain plasticity in all three ROIs (visual cortex, cerebellum and FEF) was consistent with gradual behavioural improvement over the training period. Therefore, for the current eye-movement training, the previously-stated three ROIs could be the best areas to measure brain plasticity in order to predict the outcome from the imaging data.

Chapter four

General discussion

4.1 Research aims

As a deeper understanding of the relationship between brain plasticity and behavioural performance change provides a valuable insight into the learning mechanism (Baker et al., 2015; Lövdén et al., 2013), a better understanding of how the brain responds to practice and experience becomes very important for learning and neurorehabilitation. In this project, a visuomotor rehabilitative task was investigated to assess the potential empirical visual function improvement and associated neural plasticity in task-relevant brain areas. The main aim of this PhD thesis was to investigate the link between behavioural performance improvement and potential brain plasticity, expressed as changes in functional and/or structural parameters, while participants learn to perform a novel visuomotor task. Moreover, using a visuomotor learning task that is carried out over a relatively extended period of time allowed us to scan participants multiple times during the training and these repeated scans enabled us to test how early parameter changes could predict longer-term changes or behavioural outcomes. Therefore, one of the objectives of this study was to characterise the time course of behavioural, functional and structural change which may be useful for outcome prediction or to optimise behavioural or cognitive interventions used in clinical rehabilitation (Baker et al., 2015; Kelly & Garavan, 2005; Dayan & Cohen, 2011).

4.2 Methodological aspects

Behavioural and imaging data were collected at baseline, after two and six weeks of continuous training in both studies, and in one follow-up visit (four weeks after training ended) in the healthy group study only. The principal behavioural performance measure (RT) was the average time taken to process each stimulus in the experimental sequence and was measured in laboratory and in scanner experiments. In addition, eye tracking data (MFD and TNF) were captured, also, throughout the training period. Similar to the behavioural data, two functional task sessions, voluntary (trained task) and involuntary (controlled task) eye movements, were run for each participant at each MRI scan visit (week 0, week 2, week 6 and week 10). Diffusion-weighted images were collected immediately following the fMRI scans at all scan visits.

Explicitly, collecting behavioural performance (RT) and empirical visual functions measures (MFD and TNF) from the current eye-movement task provides precisely measurable data on performance and eye-movement parameters (Mannan et al., 2005; Pambakian et al., 2004; Wang, 2001), which can be directly correlated with MR imaging parameters.

In VPL, initial functional activation increases are consistently reported with learning (Yotsumoto et al., 2008; Frank et al., 2018; Hadjikhani et al., 2001; Furmanski et al., 2004; Kourtzi et al., 2005), however the further time course of functional activation changes with learning is much less clear (Yotsumoto et al., 2008). Therefore, in the current research, the imaging data collection was designed to consider the time course of functional activation over the extended period of training. As functional activation changes in many VPL studies (Bi et al., 2014; Yotsumoto et al., 2014; Frank et al., 2016; Dong-Wha et al., 2018) are reflected in structural changes, the microstructural data (for example, FA as an index of white matter integrity and MD, AD or RD as water diffusivity measures) which are driven from the DTI sequence were combined with the fMRI data with the current research to shed light on the dynamics of learning-induced neuroplastic changes.

4.3 Key findings of behavioural, functional and structural data

4.3.1 Behavioural results

As expected (Mannan et al., 2005; Pambakian et al., 2004; Howard & Rowe, 2018; Little et al., 2004; Nelles et al., 2001; Kerkhoff et al., 1992), all healthy and hemianopic participants showed significant performance improvements over the course of the training period. All empirical behavioural performance measures (RT, MFD and TNF) reduced significantly while the response accuracy remained high (> 90%) for all participants in both studies (healthy and hemianopic). Moreover, the performance improvement remained at levels seen at the end of the training in the healthy study four weeks after the cessation of training. This indicates that the training effect was persistent.

The findings showed exponential changes in behavioural performances, and these gradual improvements reached the significant change levels at end of the training (week 6) in both groups (healthy and hemianopic). This improvement in all three empirical measurements (RT, TNF and MFD) may simply reflect more efficient placement of the eyes after training, allowing healthy participants and HH patients to saccade to the probable location of the target. Similarly, the reduction in RT in our findings is consistent with many visual search training studies with HH patients (Mannan et al., 2005; Pambakian et al., 2004; Jacquin-Courtois et al., 2013; Nowakowska et al., 2018). These studies typically report faster response times and fewer fixations required to reach the target (Mannan et al., 2005; Roth et al., 2018). Visual search training usually leads to an improvement in the way in which HH patients can successfully locate a target with eye movements (the visual search field) with a reduction in RT (Frank et al., 2016; Howard & Rowe, 2018; Little et al., 2004), and improvement in their detection performance (Pambakian et al., 2004) and encourages patients to make exploratory eye movements into the blind field (Frank et al., 2016; Nelles et al., 2001). Our results, therefore, suggest that the current eye-movement training facilitates the development of specific eye-movement strategies. Importantly, the behavioural improvements in our results complement an earlier study (Rowe et al., 2017) in which Rowe and colleagues demonstrated the transfer of this search training programme to activities of daily life and substantial subjective improvements in the same target population (HH patients). Moreover, showing other objective improvements in HH participants with different environments (Bells task and involuntary fMRI task) may suggest that the learning could transfer from the trained task into the real world.

4.3.2 fMRI results

The principal fMRI finding is that eye-movement training leads to significant, bilateral increases in functional activity in the extrastriate visual cortex (v3d) and the frontal part of the oculomotor cerebellum (OC) in the healthy group, and in the right FEF in both healthy and hemianopic groups.

The role of the extrastriate area in visual processing has been highlighted in previous fMRI studies (Büchel et al., 1998; Hietanen et al., 2006; Corbetta et al., 1998; Müller-Plath, 2008). Our data from the healthy group shows bilateral functional plasticity at the junction between

the intraparietal and transverse occipital sulcus (IPS/TOS) and bilateral changes at dorsal V3 (v3d). This finding is consistent with data reported by Corbetta and colleagues (Corbetta et al., 1998) who show selective activation in the IPS/TOS area when participants performed saccadic shifts to peripheral stimuli. Similarly, an fMRI study by (Müller-Plath, 2008), using a visual search task, reported a role of IPS/TOS and dorsal V3 (v3d) in eye-movement programming. Unfortunately, our data from the hemianopia study did not report any clear functional plasticity in the visual cortex when applying a group statistical mapping on seven subjects whereas some previous fMRI studies (Henriksson et al., 2007; Nelles et al., 2010; Nelles et al., 2009) (with larger sample sizes) reported clear functional plasticity following eye-movement training in the extrastriate area.

The results of the study 1 (healthy study) showed a significant fMRI increase in the frontal part of the cerebellum which is consistent with previous studies (Wang et al., 2002; Fuchs et al., 2010; Patel et al., 2015; Kheradmand & Zee, 2011; Robinson, 2001) that highlight the crucial role of the cerebellum in eye-movement control. OC controls gaze shifting and rapid redirection of gaze from one object to another (Wang et al., 2002; Fuchs et al., 2010). In particular, the fastigial oculomotor region in the cerebellum, which changed functionally in the current study, has been shown to facilitate saccade initiation (Patel et al., 2015; Kheradmand & Zee, 2011), and makes them fast, accurate and consistent (Robinson, 2001). Similarly, to our functional findings, a reduced in BOLD response in the cerebellum following saccade adaption training was reported in an fMRI study by Blurton and colleagues (Blurton et al., 2012). Indeed, the cerebellum plays a key role in sequence learning (Hikosaka et al., 2002; Debaere et al., 2004), which is the foundation of the task that our participants learnt.

In terms of functional activation increases in FEF, our functional results showed a significant functional increase at the end of the training period in both groups (healthy and hemianopic). FEF has a key role in saccade initiation (Alkan et al., 2011), as well as cognitive processes that require gaze control, such as attentional orienting, visual awareness and perceptual modulation (Vernet et al., 2014).

4.3.3 DTI results

In the healthy group, functional activation changes in the extrastriate visual cortex and cerebellum were accompanied by a significant decrease in DTI mean diffusivity measures in these areas and the underlying connecting white matter tracts. In addition, the suggested clinical approach analysis for DTI measures (in the hemianopia study) showed microstructural changes in all three ROIs (visual cortex, cerebellum and FEF areas) in all participants.

4.4 The current PhD project's novelty

First, a digital version from the original VISION visual search card (Rowe et al., 2017) was adapted for the current research. This digital card provided precisely measurable data on performance and eye-movement parameters (Mannan et al., 2005; Pambakian et al., 2004; Wang, 2001), which were directly correlated with MR imaging parameters, thus allowing the investigation of brain plasticity in adults. Using computer-based training not only enables precise capture of performance data but also enables adaptive stimulus presentation or the 'gamification' of the task, which could be very monotonous and requires high levels of commitment from the participants. Sharing performance gains among groups of 'learners' or the use of games that employ similar mechanisms offers the possibility of making the task more attractive or improving outcomes.

Second, behavioural and functional and structural imaging methodologies were developed in this research to complement an earlier study (Rowe et al., 2017) in which Rowe and colleagues demonstrated the transfer of this search training programme to activities of daily living and substantial subjective improvements in HH patients. These methods helped to evaluate the empirical visual function improvement and defined three main brain areas (visual cortex, cerebellum and FEF) which may demonstrate functional or structural plasticity as consequences of applying the current visuomotor training for an extended period of the time.

Finally, to the best of our knowledge, structural plasticity has not been investigated using DTI data in HH patients in an eye-movement training programme. Therefore, in response to the clinical need, a suggested clinical approach analysis for individual structural data analysis

was proposed and applied in the current project which may help to fill in the gap between knowledge and practice. This suggested clinical approach assessment could be applied and tested in clinic, and could provide an opportunity to consider learning on the basis of what actually happens in HH patients' brains, rather than explain a learning mechanism based on vague hypotheses and the latest theoretical trends. Additionally, this may help to add a professional standing for those working in any learning field and may help to understand what forms of learning they are dealing with, and hence how to produce better outcomes.

4.5 Conclusions

The current visual search training led to an improvement in visuomotor skills: fewer fixations and reduced fixation duration were required to perform the task in both groups. The behavioural improvement was associated with significant functional and structural brain plasticity in three main areas (visual cortex, cerebellum and FEF).

The main finding of the current study is that microstructural changes can be reliably detected after relatively short durations of training and that these measures correlate well with functional and behavioural measures.

The improvement in all three empirical measurements (RT, TNF and MFD) may simply reflect more efficient placement of the eyes after training, allowing healthy participants and HH patients to saccade to the probable location of the target. Our results, therefore, suggest that the current eye-movement training facilitates the development of specific eye-movement strategies, especially for HH patients. Importantly, the explicit empirical visual functions improvements in our results complement an earlier study (Rowe et al., 2017) in which Rowe and colleagues demonstrated the transfer of this search training programme to activities of daily living and substantial subjective improvements in the same target population (HH patients).

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Supplementary materials

Section A: Diffusion Weighted Imaging (DWI)

Diffusion weighted imaging (DWI) is an MRI sequence based on signals measured from water molecule motion (water diffusivity in the brain). It indicates the white and grey matter organisation. DWI is a widely used imaging technique in clinic (e.g. in early stroke diagnosis) and research (Jenkinson & Chappell, 2018; McRobbie, 2017).

Water molecules normally diffuse randomly inside the brain (Brownian motion), however this normal diffusion motion can be restricted by biological barriers, such as axon bundles or by the bodies and branches of non-neuronal cells. Water molecules are diffused in an axial direction or perpendicular to the main axonal direction (Jenkinson & Chappell, 2018) (see Fig. S1).

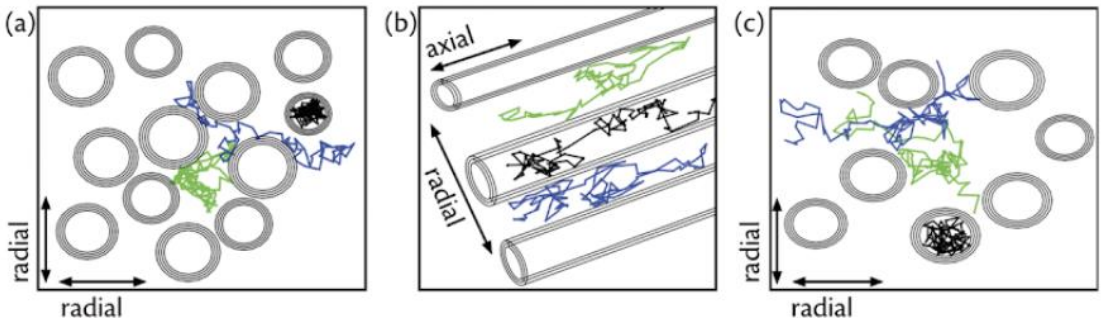

Fig.1.S1 Water diffusivity*: *(a) *Axons are packed the water diffusion in extra-cellular and intra-cellular space which restrict the water motion mainly in radial direction compared with axial water diffusivity in* ***(b)***. ***(c)*** *Water molecules in the extracellular area diffuse more freely in the absence of more barriers.*

Under a strong MRI magnetic field, water molecules move in multiple directions (Jellison et al., 2004), and the main direction of diffusivity is aligned with the direction of the main WM fibre tract. This occurs due to the presence of axonal membranes and myelin sheaths as barriers (Moseley et al., 1990). Thus, the water diffusivity within the WM fibre is considered as anisotropic (directionally dependent) (Jellison et al., 2004).

To determine the main orientation of the direction of diffusion inside a voxel, diffusion along thousands of axes should be calculated and this is unpractical. Basser and colleagues, therefore, introduced the "diffusion tensor" model which can estimate perfectly anisotropic directions (Basser et al., 1994). Diffusion tensor imaging (DTI) is a 3D mathematical model of diffusion, and is represented as a 3 × 3 matrix which involves eigenvalues (λ1, λ2, and λ3) and eigenvectors (ε1, ε2, and ε3) which are measured from diffusion measurements along six spatial directions (see Fig. S2). Therefore, this tensor model can be applied to quantify the degree of diffusivity and the dominant direction of water diffusion across each single voxel (Jellison et al., 2004).

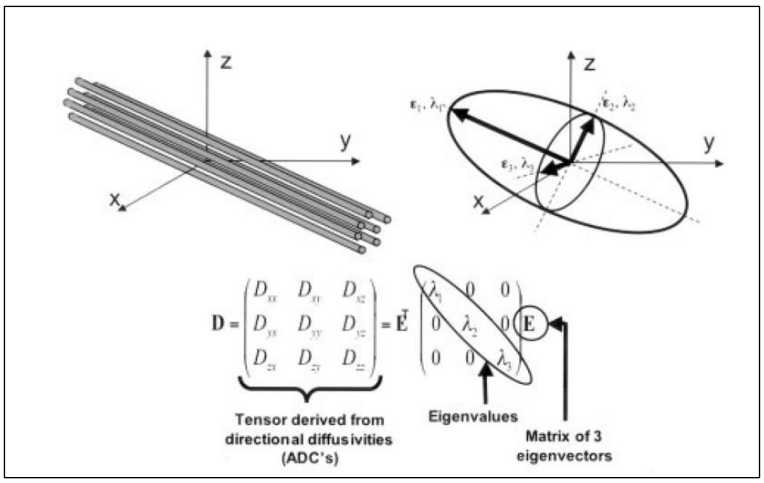

Fig.1.S2 An arbitrary orientation and directional dependence (anisotropy) on diffusion measurements: *Top left diagram shows fibre tracts in an arbitrary alignment with respect to scanner geometry (x, y, z axes) and placed directional dependence on diffusion measurements (anisotropy). Top right diagram shows the 3D diffusivity as ellipsoid which is characterised by three eigenvalues (λ1, λ2, λ3) and three eigenvectors (ε1, ε2, and ε3). The diffusion tensor matrix, bottom, involves six noncollinear diffusion measurements. The eigenvalues reflect diffusivity along three axes and the eigenvectors represent the maximum diffusivity direction.*

DTI can characterise tissue microstructure therefore it is widely used to provide various physical quantities, including the main following brain maps: fractional anisotropy (FA) and mean diffusivity (MD). MD is known as the "apparent diffusion coefficient" (ADC), which represents the average diffusivity across voxels (equation 3.2, Fig. S3). MD is derived from axial diffusivity (AD) and radial diffusivity (RD). AD measures water diffusivity that occurs along the strongest direction (longitudinal) (equation 3.3, Fig. S3), and RD measures the diffusion that occur in the transverse direction (equation 3.4, Fig. S3), which is perpendicular

to the main fibre tract direction. FA describes the white matter integrity and is obtained from equation 3.5 (Fig. S3). Low FA, such as the scalar value of 0, means diffusion is relatively similar in all directions (isotropic) and high FA indicates that there is a dominant diffusion direction (anisotropic) (Basser et al., 1994).

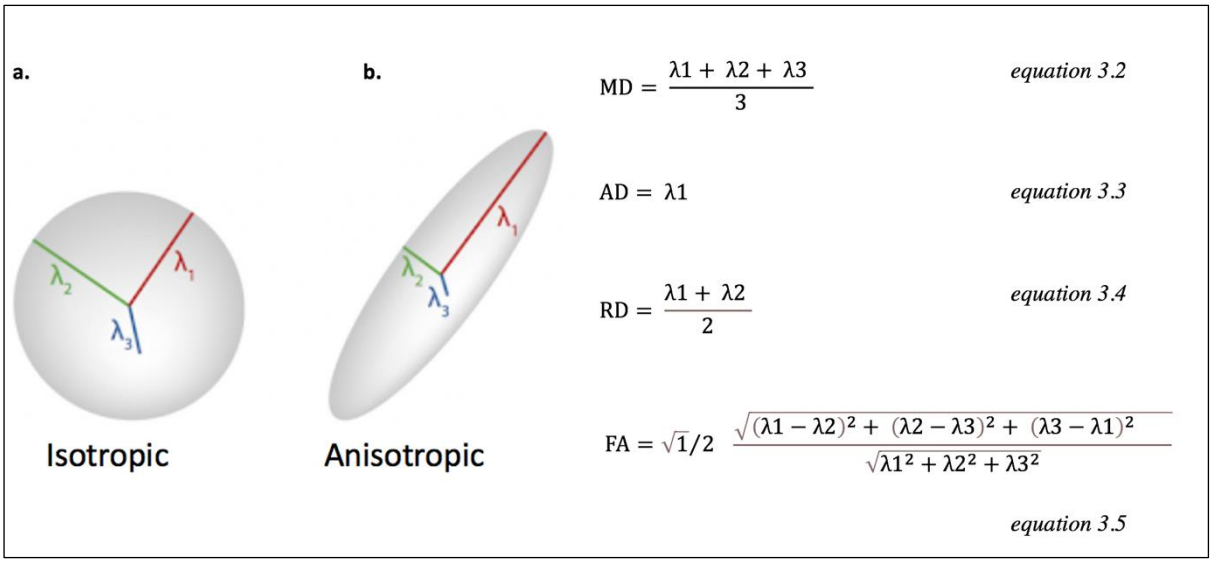

Fig.1.S3 Water diffusivity tensor shapes and measures*: *(a) *is "**isotropic**" diffusion where eigenvalues are roughly equal across main vectors.* ***(b)*** *represents the shape of "**anisotropic**" diffusion where diffusion is primarily in one direction. Equations for the diffusivity measures include: mean diffusivity (MD), axonal direction (AD), radial diffusivity (RD), and fractional anisotropy (FA).*

To extract DTI measures, it's important to conduct appropriate DTI fitting analysis by providing two sets of diffusion-encoded MRI images: the first set with no diffusion (b=0), which is considered as a baseline for DTI model fitting; the second set with a b-value that varies between 700 to 1300 s/mm^2. 1000 s/mm^2 is the most commonly used in research studies (Jenkinson & Chappell, 2018).

Water molecules diffuse differently through brain tissues depending on tissue type, hence different voxel intensities are observed. For example, cerebral spinal fluid (CSF) appears dark because the water is freely and equally diffused in all directions, and GM voxels have a higher intensity than CSF. WM, comparatively, is observed with the brightest voxels, because the water diffusion is restricted by the direction of the axonal fibre bundle (McRobbie, 2017; Jenkinson & Chappell, 2018) (see Fig. S4).

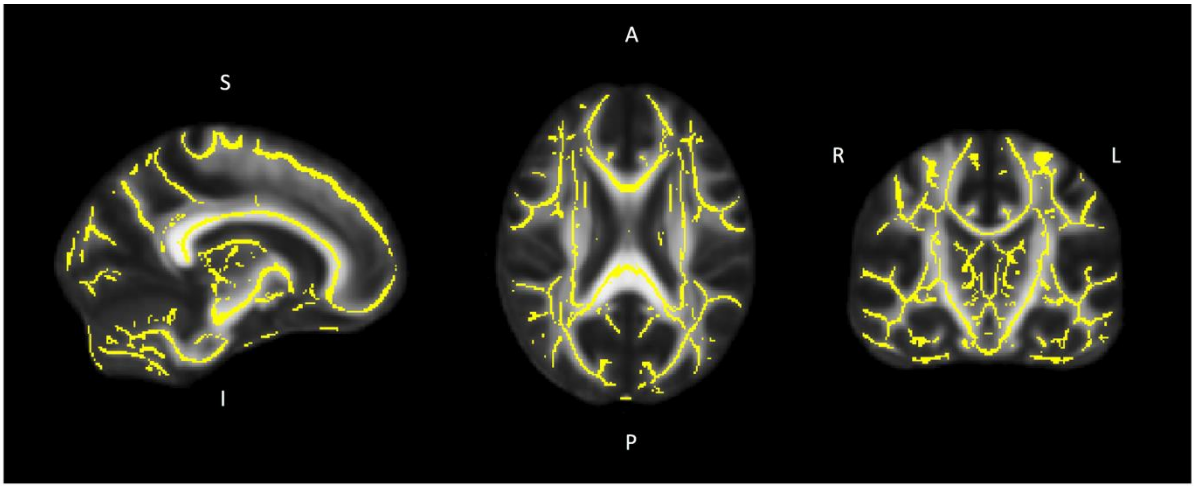

Fig.1.S4 DTI-weighted image: *White areas represent the skeleton of the WM and the yellow areas highlight the fractional anisotropy skeleton (FA map). S (superior), I (inferior), A (anterior), P (posterior), R (right) and L (left).*

Section B: fMRI and Blood Oxygenation Level Dependent (BOLD)

Brain function information can be characterised by MR imaging by measuring blood oxygenation level dependent (BOLD). An MRI scan is sensitive to the changes within the oxygenation level of blood haemoglobin (Ogawa et al., 1990). Blood has different magnetic properties: oxyhaemoglobin describes the high oxygen level which acts as a diamagnetic substance; deoxyhaemoglobin (low oxygen level) gives blood paramagnetic behaviour under an MRI field. BOLD signal in a particular area is detected if that area has a higher oxyhaemoglobin ratio than the surrounding areas (Amaro & Barker, 2006). BOLD signals, therefore, have been considered as natural contrast agents which reflect haemodynamic changes associated with brain activities (Ogawa et al., 1990).

BOLD images are real-time tools that indirectly demonstrate in vivo neuronal activity during task execution and rest status (Amaro & Barker, 2006). When specific brain areas are excited by stimuli, neurones within these areas consume more oxygen, which causes an elevation in blood flow to feed the excited neurones and an increased oxyhaemoglobin level while the deoxyhaemoglobin level decreases significantly. This metabolic demand provides an opportunity to detect the BOLD signal changes over time which may occur in particular functional brain areas as a consequence of a specific control task or in some functional brain areas during the resting state (see Fig. S5).

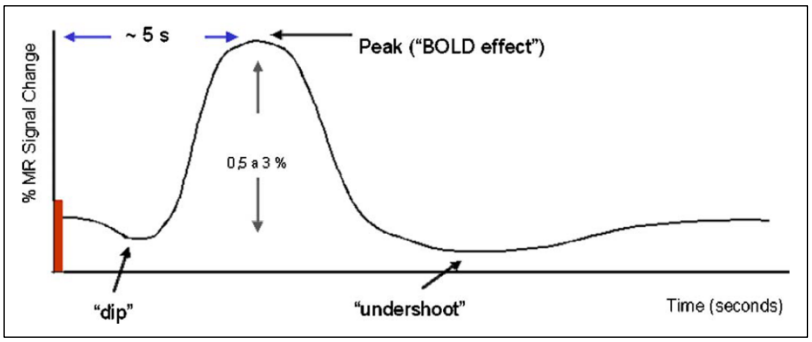

Fig.1.S5 BOLD signal: *The initial dip results from a temporary rise in the deoxyhaemoglobin level when particular brain areas are excited by stimuli. After the 3s of presenting stimulus, the BOLD effect peak is recorded. Stop the stimulation, return the MR signal to the baseline again, and this what is called the "undershoot" effect.*

BOLD signals suffer from considerable physiological ambiguity and the interpretation of these signals is not straightforward (Buxton, 2010). Low temporal resolution is a clear limitation in fMRI (Glover, 2011). Another problem is signal dropout or spatial distortion caused by magnetic susceptibility at interfaces between air and brain tissue (Cho, 1992). Other weaknesses include the scanner's loud noise associated with switched magnetic fields and some loss of flexibility in experimental design.

Section (C) ROI definition

pTFCE

Threshold free cluster enhancement methods (TFCE (Smith and Nichols, 2009) and pTFCE (Spisak et al., 2019)) boost neuroimaging signals compared to conventional voxel-wise analysis by exploiting spatial neighbourhood information to trade spatial signal localisation against sensitivity. Spisak et al. (2019) argue that, because of the inherent smoothness (and additional smoothing) of neural activation patterns, the lost localisation capacity is "unutilised" in real, smoothed, images. The practical implication of this approach is that, compared to conventional processing, pTFCE, results in substantial increase in the number of detected "true positive" voxels, forming contiguous clusters.

We argue that this approach is ideal for the definition of ROIs that use contrasts, which are independent of the primary test, and where therefore a precise overlap of activation peaks may not be expected, while the definition of a 'reasonable' candidate area for analysis is important.

While pTFCE was used for the ROI definition, the conventional, and more conservative, SPM analysis was used in the main fMRI analysis where spatial localisation of the activation pattern was a key objective.

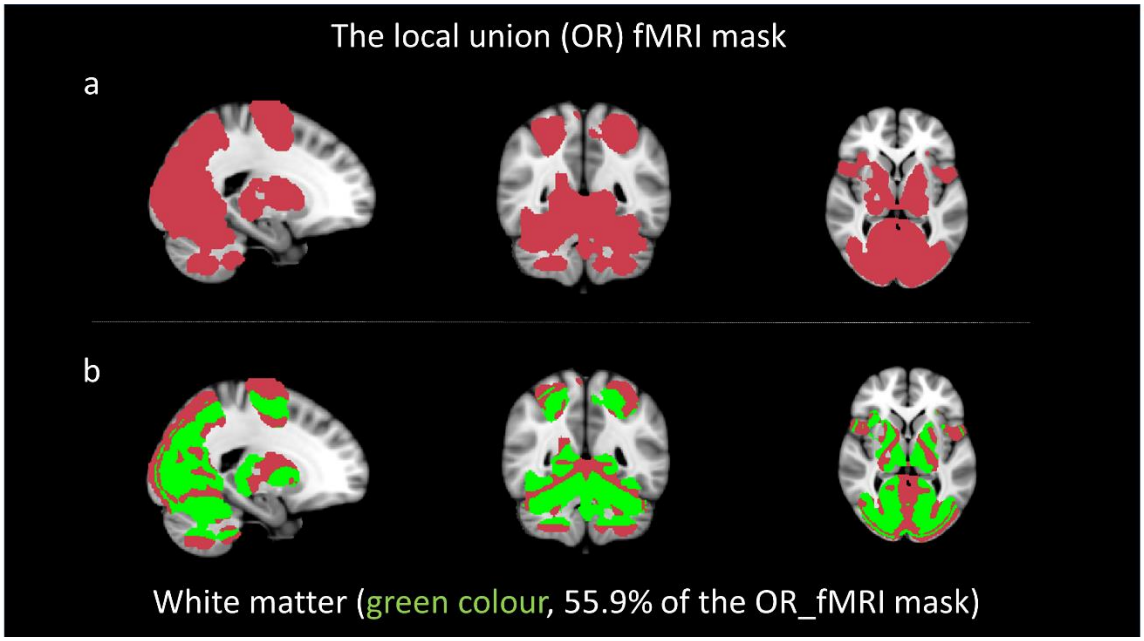

Fig.2.S1 The global union fMRI mask and the percentage of white matter included: *(a) shows a logical union (OR) of the masks extracted for each of the four visits that used to define the ROI for functional and structural group analysis. (b) shows the percentage of white matter that included in the (UNION) fMRI mask. The percentages of voxels lying in white matter were computed using the average FA map [FA ≥ 0.15] for segmentation.*

ROI mask vs TBSS analysis

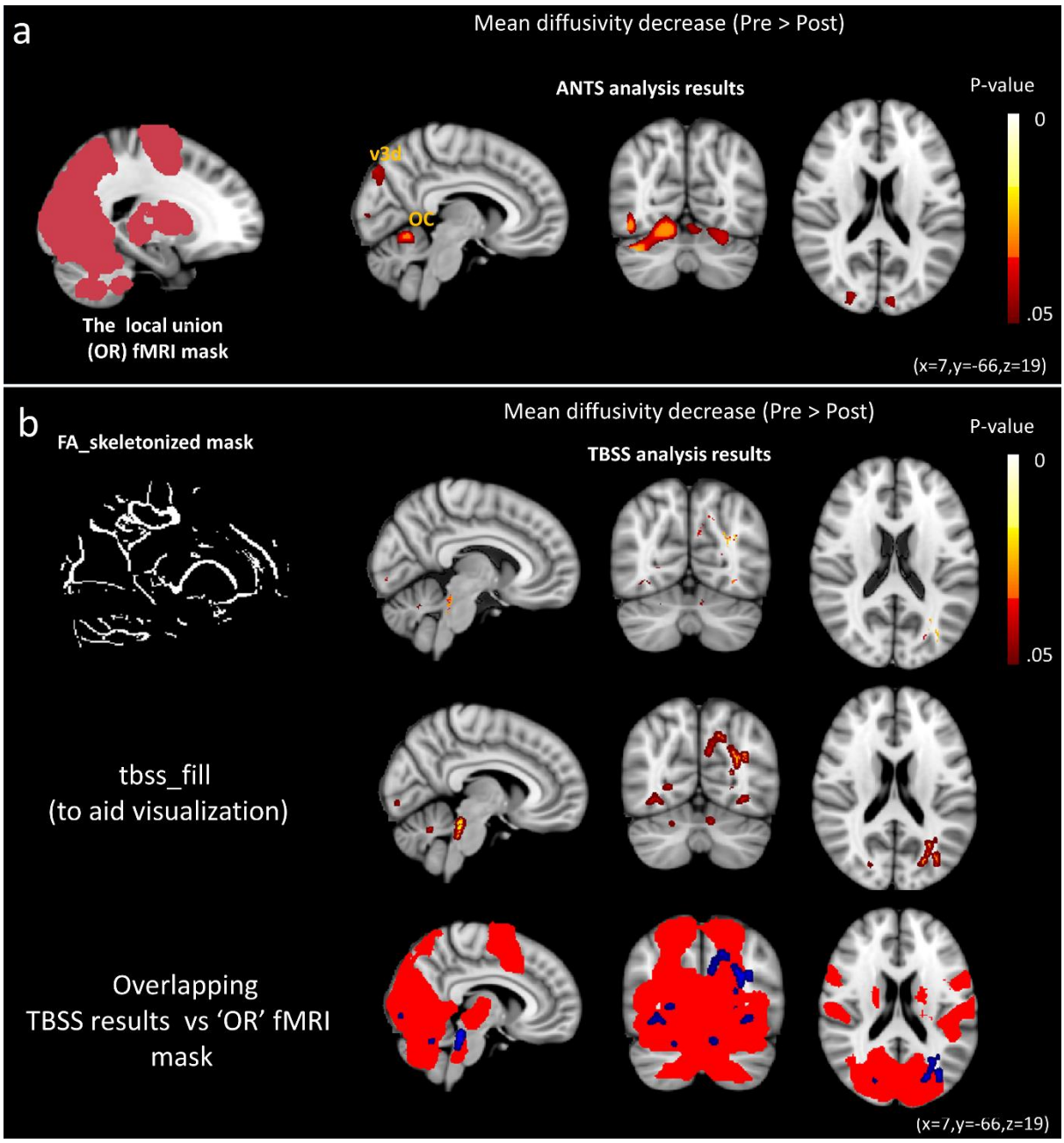

Fig.2.S2 Comparing TBSS result with the study's approach analysis for DTI data: *(a) shows the study's analysis approach: a ROI mask, representing any area of significant functional activation at any of the four scans, covers grey matter and adjoining white matter areas. Panel (b) shows the results of the TBSS analysis for the DTI data, which reported similar structural changes in visual cortex and cerebellum (top row), the images in the middle row show the same data, but were filled using the tbss_fill routine to aid visualization. The bottom row of images shows he overlap between ROI mask and TBSS results.*

Section (D) Behavioural Performance

Performance accuracy (Lab experiment) over the time

Performance over time (lab)	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 10	Mean (SD)
Sub01	92%	94%	95%	95%	96%	95%	97%	96%	93.7% (2.5%)
Sub02	88%	92%	86%	90%	90%	93%	92%	94%	90.6% (2.6%)
Sub03	97%	96%	95%	96%	96%	93%	93%	95%	95.1% (1.4%)
Sub04	97%	94%	91%	90%	92%	94%	96%	96%	93.7% (2.5%)
Sub05	99%	98%	97%	97%	91%	80%	83%	86%	91.3% (7.5%)
Sub06	97%	96%	95%	93%	94%	86%	87%	87%	91.8% (4.4%)
Sub07	94%	93%	94%	86%	81%	89%	92%	86%	89.3% (4.7%)
Sub08	99%	96%	94%	95%	95%	90%	99%	94%	95.2% (2.9%)
Sub09	97%	96%	95%	92%	93%	91%	92%	94%	93.7% (2.1%)
Sub10	94%	98%	98%	98%	99%	100%	100%	98%	98.1% (1.8%)
Sub11	85%	91%	90%	90%	83%	87%	82%	78%	85.7% (4.5%)
Sub12	99%	96%	96%	96%	98%	96%	96%	97%	96.7% (1.1%)
Sub13	97%	96%	89%	89%	92%	91%	88%	87%	91.1% (3.6%)
Sub14	99%	96%	92%	95%	90%	89%	92%	93%	93.2% (3.2%)
Sub15	93%	96%	96%	93%	91%	93%	94%	90%	93.2% (2.1%)
Mean (SD)	95.13% (4.2%)	95.2% (2%)	93.5% (3.2%)	93% (3.4%)	92% (4.9%)	91.1% (4.7%)	92.2% (5.3%)	91.4% (5.5%)	92.9% (3.0%)

Table.2.S1 Accuracy of the participants' performances over the time (in lab): *The table shows the percentage of the correct answers for test carried out in the lab. The overall accuracy was 92.9% (3.0%).*

Performance accuracy (*voluntary fMRI experiment*) over the time

Performance over time (fMRI-voluntary)	Week 0	Week 2	Week 6	Week 10	Mean (SD)
Sub01	80%	92%	94%	90%	89.0% (6.2%)
Sub02	82%	87%	87%	91%	86.7% (3.6%)
Sub03	95%	96%	92%	96%	94.7% (1.8%)
Sub04	92%	92%	91%	95%	92.5% (1.5%)
Sub05	94%	93%	91%	90%	92.0% (1.8%)
Sub06	93%	90%	84%	86%	88.2% (4.0%)
Sub07	915%	88%	90%	93%	90.5% (2.0%)
Sub08	91%	90%	87%	90%	89.5% (1.7%)
Sub09	92%	93%	90%	91%	91.5% (1.2%)
Sub10	89%	94%	92%	91%	91.5% (2.0%)
Sub11	92%	91%	88%	84%	88.7% (3.5%)
Sub12	91%	90%	91%	90%	90.5% (0.5%)
Sub13	92%	91%	89%	92%	91.0% (1.4%)
Sub14	91%	92%	91%	90%	91.0% (0.8%)
Sub15	94%	94%	90&	92%	92.5% (1.9%)
Mean (SD)	90.6% (4.1%)	91.5% (2.3%)	89.8% (2.4%)	90.7% (2.9%)	90.6% (2.0%)

Table.2.S2 Response accuracy (voluntary): *The table shows the mean correct response percentage for the voluntary fMRI task. The overall mean accuracy is 90.6% (2.0%).*

Performance accuracy (*Involuntary fMRI experiment*) over the time

Performance over time (fMRI-involuntary)	Week 0	Week 2	Week 6	Week 10	Means (SD)
Sub01	94%	92%	92%	92%	92.5% (1.0%)
Sub02	88%	82%	83%	90%	85.7% (3.8%)
Sub03	94%	91%	90%	89%	91.0% (2.1%)
Sub04	95%	92%	90%	92%	92.2% (2.0%)
Sub05	96%	93%	90%	89%	92.0% (3.1%)
Sub06	95%	94%	90%	90%	92.2% (2.6%)
Sub07	91%	90%	90%	91%	90.5% (0.5%)
Sub08	96%	91%	88%	91%	91.5% (3.3%)
Sub09	95%	94%	94%	92%	93.5% (1.2%)
Sub10	94%	93%	96%	94%	94.2% (1.2%)
Sub11	95%	93%	88%	86%	90.5% (4.2%)
Sub12	96%	95%	93%	91%	93.7% (2.2%)
Sub13	92%	90%	90%	90%	90.5% (1.0%)
Sub14	94%	92%	89%	84%	89.7% (4.3%)
Sub15	95%	93%	93%	90%	92.7% (2.0%)
Means (SD)	94.0% (2.1%)	91.6% (3.0%)	90.4% (3.4%)	90.0% (2.4%)	91.5% (2.0%)

Table.2.S3 Response accuracy (voluntary): *The table shows the mean correct response percentage for the voluntary fMRI task. The overall mean accuracy is 91.5% (2.0%).*

Section (E) Behavioural Data

The impact of training-behavioural data

Fig.2.S3 Training effects on behavioural performance: *the charts show impact of the training on behavioural performance during the lab experiments; Panel (a) shows a gradual reduction in the number of gazes required to complete the task by test week, panel (b) shows the mean fixation duration over the training period. One month after training (rightmost bar in both graphs) there is little change in performance compared to week 6.*

Maintenance of training performance

Participants required significantly fewer fixations (TNF) at the last visit (week 10) compared with the pre-training visit, $t(14) = 4.869$, $p < 0.001$. The reduction in the fixation duration (MFD) was, also, significantly below baseline one month after the training ended, $t(14) = 7.076$, $p < 0.001$.

Section (F) Additional Imaging Data

The increase of Fractional Anisotropy (FA), in areas where significant diffusivity decreases were recorded, did not reach the level of significance after training (Fig. S4).

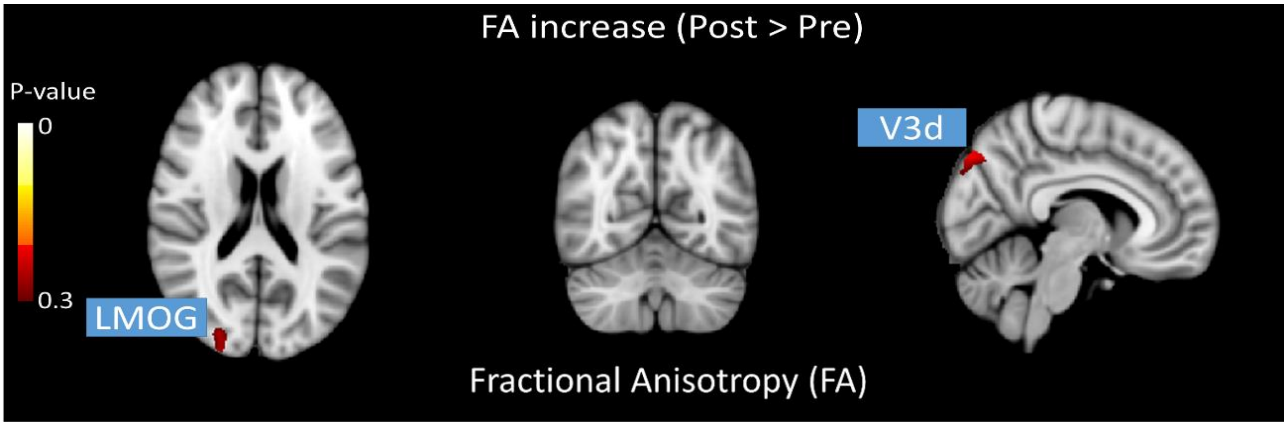

Fig.2.S4 Affected brain areas (Fractional anisotropy/FA): *FA increases were observed, but did not reach significance after training in two areas; V3D (L Cuneus/hOc3d [v3d]); LMOG (L middle Occipital Gyrus/ hOc4d [v3a], MNI: - 25 -89 9). All areas were defined by SPM-Anatomy toolbox (v.1.7).*

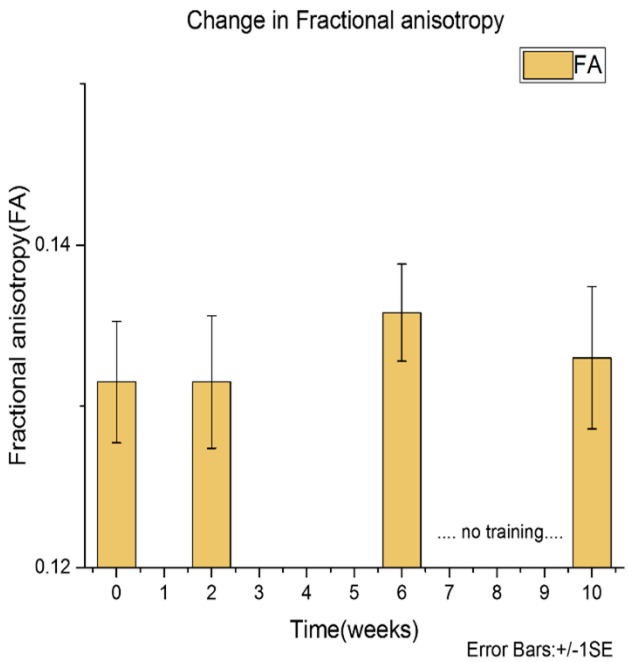

Fig.2.S5 Training effect on Fractional Anisotropy: *the graph shows the change in FA, during the training period, in extrastriate area/ v3d (see Fig. S4, above).*

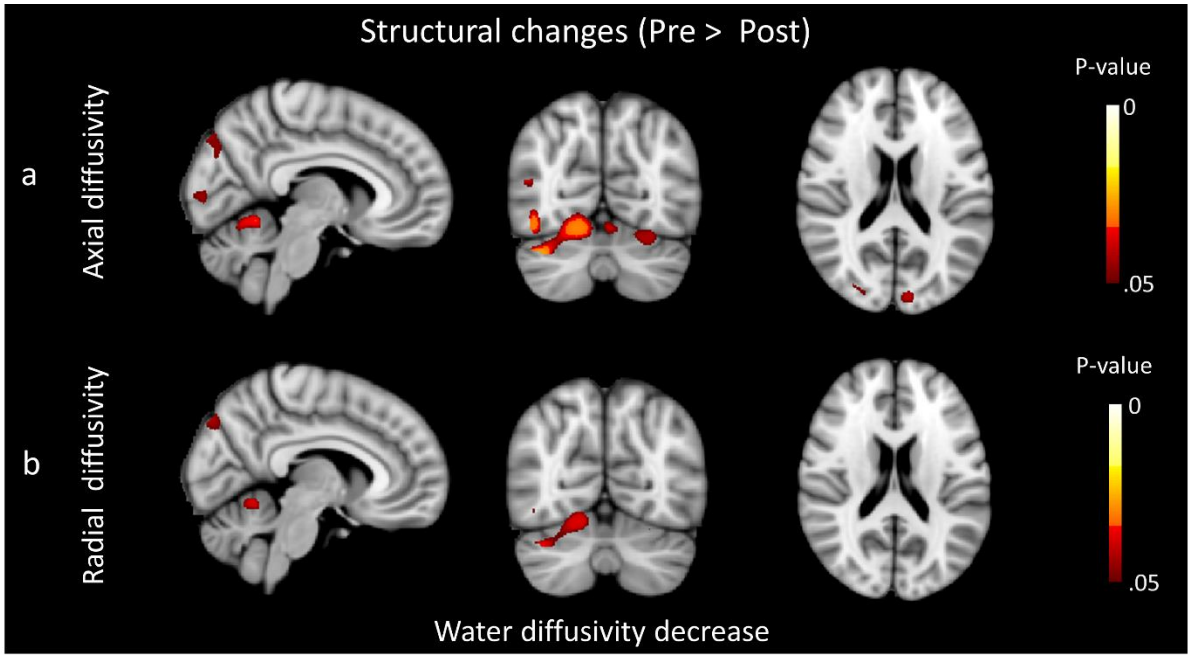

***Fig.2.S6 Significant reductions in Axial and Radial diffusivity following training*: Panel** *(a) shows significant reduction in axial diffusivity at week 6 compared to baseline, panel (b) shows significant reduction in radial diffusivity at week 6 compared to baseline.*

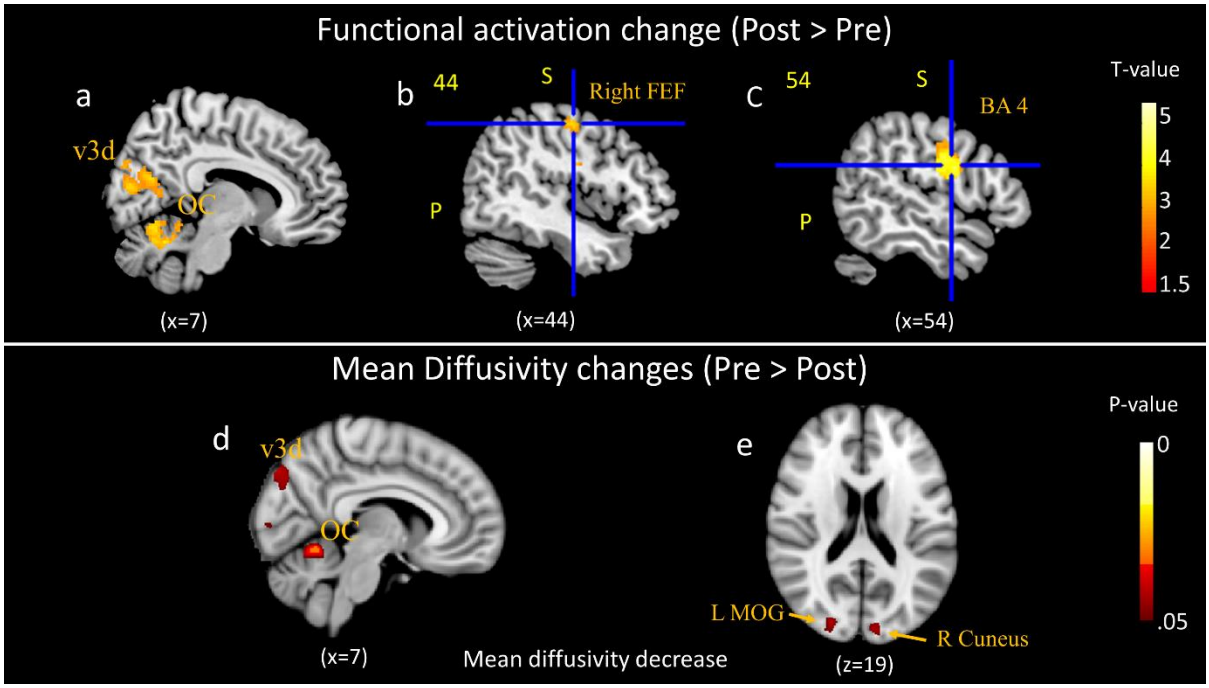

***Fig.2.S7 Affected brain areas*:** *Panels (a) and (d) show overlapping changes in fMRI and MD in two main areas: extrastriate area (L Cuneus/hOc3d [v3d]) and oculomotor cerebellum (L cerebellum-crus 1). Panel (b) shows the significant fMRI increases ($P_{FWE} < 0.05$ cluster level) in right Frontal Eye Field (x = 44, y = -11, z = 52) while panel (c) shows the significant fMRI activation increase ($P_{FWE} < 0.05$ cluster level) in Brodmann area 4 (x = 54, y = -2, z = 26). These activation changes were not colocalised with significant diffusivity changes. Panel (e) shows the significant reduction in mean diffusivity in two visual areas (L middle Occipital Gyrus/ hOc4d [v3a], MNI: -27 -89 9; and 6 R Cuneus/hOc3d [v3d]. All areas were defined by SPM-Anatomy toolbox (v.1.7). All changes compare metrics between baseline and the end of training.*

Section (G) Correlation Analysis

Changes in ***lab*** measures vs changes of ***DTI*** measures in cerebellum

Variables	RT in lab			MFD		
	week 2	week 6	week 10	week 2	week 6	week 10
MD cerebellum week 2	r = 0.47 *p* = 0.039	r = 0.47 *p* = 0.05	-/-	-/-	-/-	-/-
MD cerebellum week 6		r = 0.58 *p* = 0.011	-/-		-/-	-/-
MD cerebellum week 10			-/-			-/-
AD cerebellum week 2	r = 0.49 *p* = 0.032	r = 0.39 *p* = 0.07	-/-	r = 0.35 *p* = 0.1	-/-	-/-
AD cerebellum week 6		r = 0.47 *p* = 0.038	-/-		-/-	-/-
AD cerebellum week 10			-/-			r = 0.38 *p* = 0.08
RD cerebellum week 2	r = 0.57 *p* = 0.013	r = 0.45 *p* = 0.04	-/-	-/-	-/-	-/-
RD cerebellum week 6		r = 0.47 *p* = 0.037	-/-		-/-	-/-
RD cerebellum week 10			-/-			r = 0.47 *p* = 0.039

Table.2.S4 Correlations between behavioural performance changes in lab vs water diffusivity changes in cerebellum: *The table represents the significant correlations across time in the dataset. The symbol '-/-' means the is no significant correlation. Yellow highlights indicate marginally significant correlations.*

Changes in ***lab*** measures vs changes of ***DTI*** measures in visual area

Variables	RT in lab			MFD		
	week 2	week 6	week 10	week 2	week 6	week 10
MD visual cortex week 2	r = 0.38 *p* = 0.08	-/-	-/-	r = 0.43 *p* = 0.055	-/-	-/-
AD visual cortex week 2	r = 0.43 *p* = 0.032	-/-	-/-	r = 0.47 *p* = 0.038	-/-	-/-

Table.2.S5 Correlations between behavioural performance changes in lab vs water diffusivity changes in visual cortex: *The table represents the significant correlations across time in the dataset. The symbol '-/-' means the is no significant correlation. Yellow highlights indicate marginally significant correlations.*

Section (H) Voluntary vs involuntary-eye movement fMRI tasks

Voluntary eye movement task

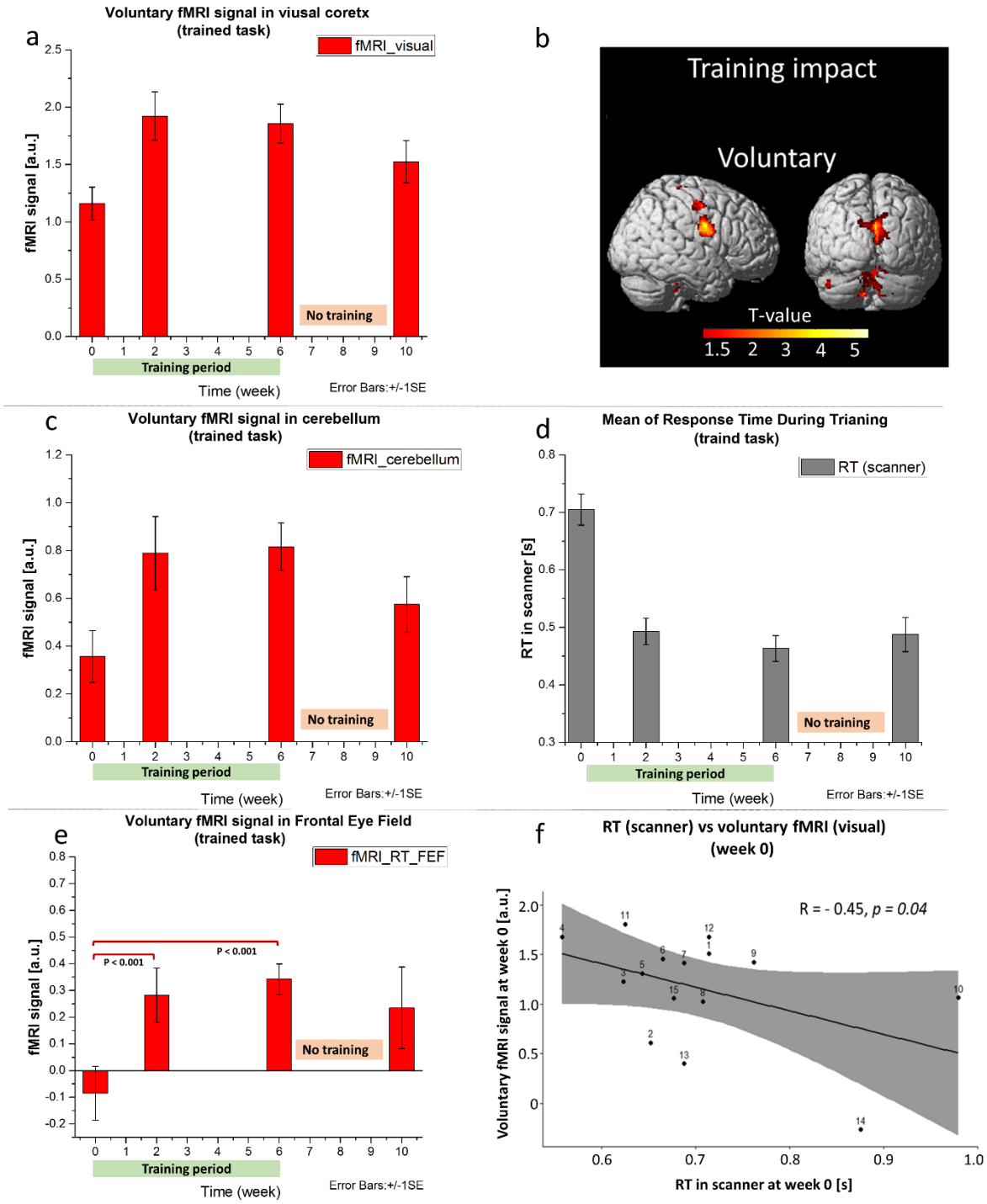

Fig.2.S8 Voluntary eye movement task performance and fMRI data: *fMRI signal change in visual cortex ROI (panel a), cerebellum (panel c), and FEF (panel c). Panel (b) shows a render of significant fMRI increases (P_{FWE} < 0.05 cluster level) after six weeks of training. Behavioural performance (panel d) and correlation with activation in the visual Roi are shown in panel (f).*

Involuntary eye movement task

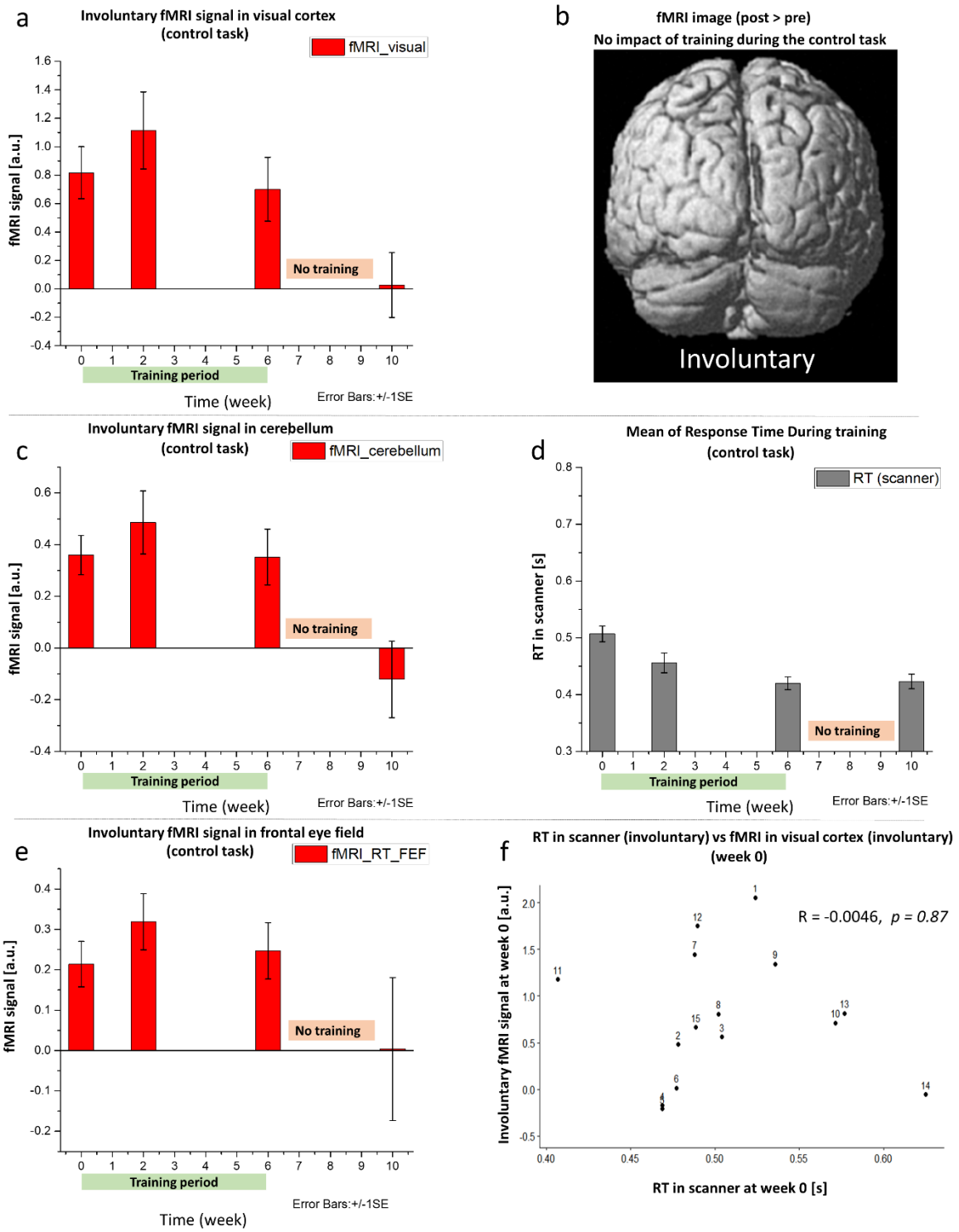

Fig.2.S9 Involuntary eye movement task performance and fMRI data: *eye movement task performance and fMRI data: fMRI signal change in visual cortex ROI (panel a), cerebellum (panel c), and FEF (panel c). Panel (b) shows a render of (no) significant fMRI increases (P_{FWE} < 0.05 cluster level) after six weeks of training. Behavioural performance (panel d) is not correlated with activation in the visual ROI (panel f).*

fMRI signals T-test results for trained and control tasks

Data collection time points	*Voluntary (trained task)*	*Involuntary (control task)*
fMRI visual change (week 2)	t(14) = -3.72, p = 0.001	t(14) = -1.462, p = 0.082
fMRI visual change (week 6)	t(14) = -4.22, p = 0.00042	t(14) = .23, p = 0.41
fMRI visual change (week 10)	t(14) = -1.50, p = 0.072	t(14) = -.28, p = 0.36
fMRI cerebellum change (week 2)	t(14) = -3.04, p = 0.0045	t(14) = -1.82, p = 0.045
fMRI cerebellum change (week 6)	t(14) = -4.17, p = 0.00045	t(14) = -.22, p = 0.41
fMRI cerebellum change (week 10)	t(14) = -1.27, p = 0.112	t(14) = -.38, p = 0.35
fMRI FEF change (week 2)	t(14) = -3.04, p = 0.0045	t(14) = -1.75, p = 0.0501
fMRI FEF change (week 6)	t(14) = -4.86, p < 0.00011	t(14) = -1.024, p = 0.15
fMRI FEF change (week 10)	t(14) = -1.55, p = 0.07	t(14) = -.497, p = 0.31

Table.2.S6 Comparison t-test between voluntary and involuntary fMRI signal changes in all significant change areas: *the table shows the significant fMRI signals changes (green colour), marginally significant change (yellow) and insignificant changes (red) during voluntary and involuntary eye movement tasks. All data collection points compared to the baseline level (week 0).*

Section (I) fMRI of voluntary eye movement tasks vs Voluntary eye movement processing

To test whether mean fMRI activation was directly linked to the mean RT (or number of signals processed in the fixed duration scanning blocks), these values, as shown in Fig. S10, were significantly correlated at each time point (week 2, $r(13) = -58$, $p < .01$, Fig S10b; week 6, $r(13) = -6$, $p < .009$, Fig. S10c; week 10, $r(13) = -65$, $p < .004$, Fig. S10d,). The fMRI activation also was correlated significantly with the scanner mean RT before any training session at the baseline visit (week 0), $r(13) = -45$, $p < .02$.

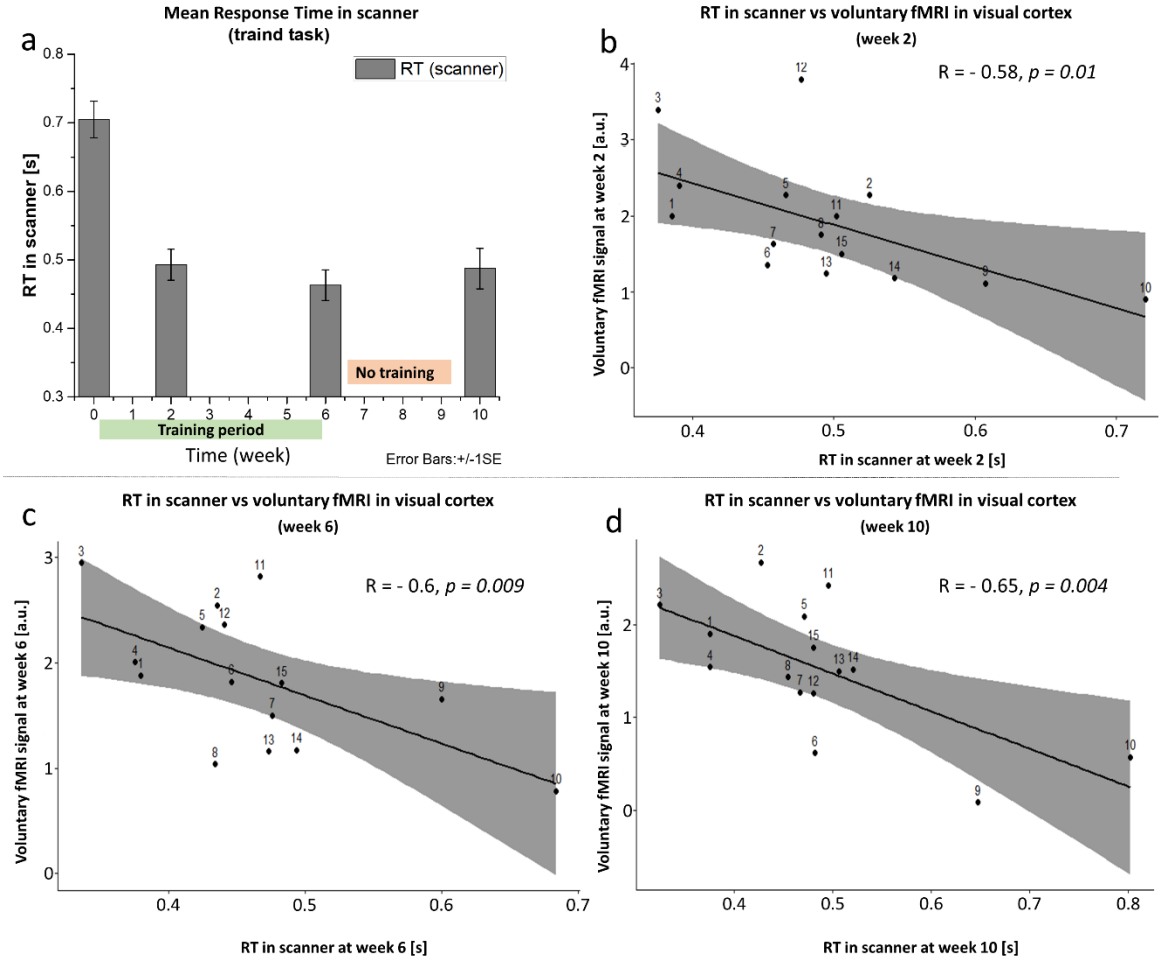

Fig.2.S10 fMRI activation in the visual area during the voluntary behavioural task: *Panel (a) shows the mean response time (error bars SEM) at each visit. Panels (b), (c) and (d) show the mean fMRI signal against mean RT for individual participants at weeks 2,6 and 10. Activity in the visual area and RT are significantly correlated in all cases.*

Section (J) Outcome prediction-AD and RD

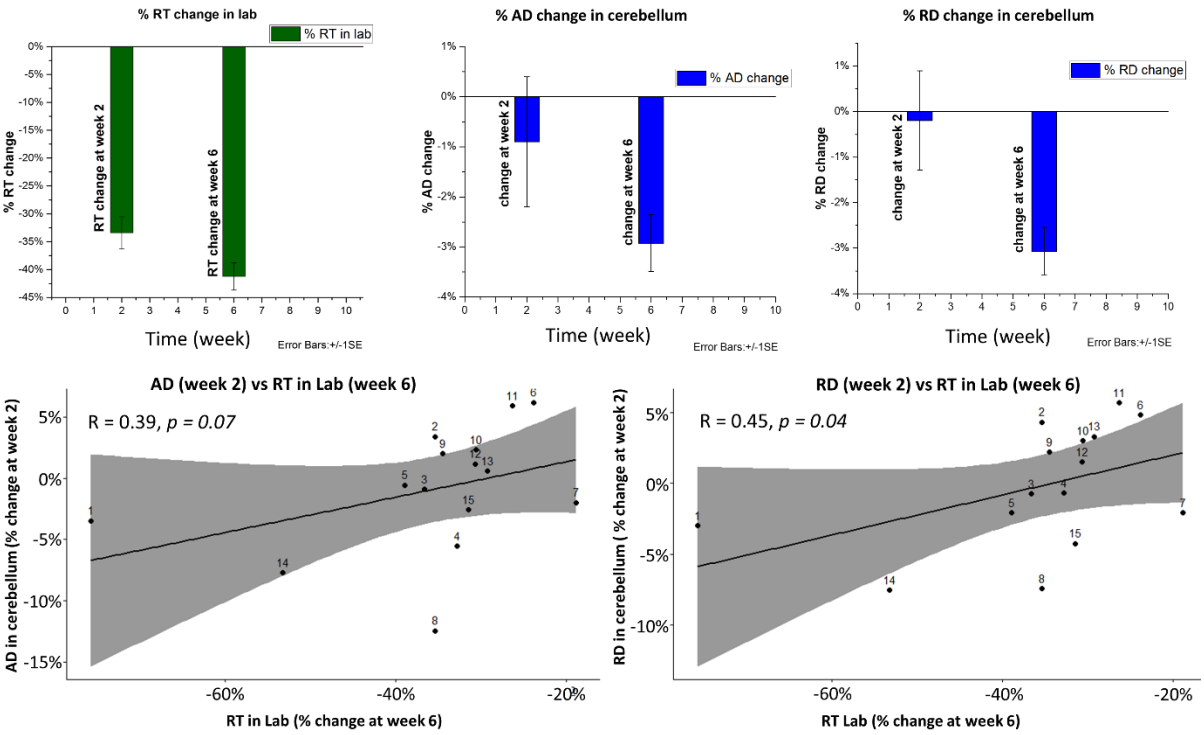

Fig.2.S11 Outcome prediction*: panels (a), (b) and (c) show percentage change of behavioural and microstructural measures (AD and RD) in the cerebellum over the training period. Panel (d) shows a significant correlation between the behavioural performance change at week 6 and the reduction in axial diffusivity at week 2. Panel (e) shows similar data for radial diffusivity (RD).*

General Appendices

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Behavioural performance improvement in visuomotor learning correlates with functional and microstructural brain changes

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ABSTRACT

A better understanding of practice-induced functional and structural changes in our brains can help us design more effective learning environments that provide better outcomes. Although there is growing evidence from human neuroimaging that experience-dependent brain plasticity is expressed in measurable brain changes that are correlated with behavioural performance, the relationship between behavioural performance and structural or functional brain changes, and particularly the time course of these changes, is not well characterised.

To understand the link between neuroplastic changes and behavioural performance, 15 healthy participants in this study followed a systematic eye movement training programme for 30 min daily at home, 5 days a week and for 6 consecutive weeks. Behavioural performance statistics and eye tracking data were captured throughout the training period to evaluate learning outcomes. Imaging data (DTI and fMRI) were collected at baseline, after two and six weeks of continuous training, and four weeks after training ended.

Participants showed significant improvements in behavioural performance (faster task completion time, lower fixation number and fixation duration).

Spatially overlapping reductions in microstructural diffusivity measures (MD, AD and RD) and functional activation increases (BOLD signal) were observed in two main areas: extrastriate visual cortex (V3d) and the frontal part of the cerebellum/Fastigial Oculomotor Region (FOR), which are both involved in visual processing. An increase of functional activity was also recorded in the right frontal eye field.

Behavioural, structural and functional changes were correlated. Microstructural change is a better predictor for long-term behavioural change than functional activation is, whereas the latter is superior in predicting instantaneous performance. Structural and functional measures at week 2 of the training programme also predict performance at week 6 and 10, which suggests that imaging data at an early stage of training may be useful in optimising practice environments or rehabilitative training programmes.

1. Introduction

There is growing evidence from human neuroimaging studies (Zatorre et al., 2012; Fields, 2015; Collins, 2015; Tucker and Luu, 2012; Wang et al., 2014; Sampaio-Baptista and Johansen-Berg, 2017) that learning is associated with measurable structural brain changes. This alteration in structure supports the corresponding changes in the functional properties of individual neurones, giving rise to behavioural change (Sampaio-Baptista and Johansen-Berg, 2017).

Practice-induced structural changes of cortical and subcortical areas have been reported to occur in grey and white matter (Wang et al., 2014). While most studies consider the long-term effect of practice, some recent studies have demonstrated measurable changes at much faster time scales (Hofstetter et al., 2017; Sagi et al., 2012). Understanding the relationship between brain plasticity and behavioural performance change provides a valuable insight into the learning process (Baker et al., 2015; Lövdén et al., 2013). Better knowledge of how the brain is altered by practice and experience is also important for neurorehabilitation, for example for outcome prediction or to optimise behavioural or cognitive interventions used in rehabilitation (Baker et al., 2015; Kelly and Garavan, 2005; Dayan and Cohen, 2011).

Training-related structural brain plasticity has been studied in volumetric studies for a number of skills that combine perceptual and motor skills, such as juggling, computer games, sports, typing, phonetics and music making (Draganski et al., 2004, 2006; Bezzola et al., 2011; Boyke et al., 9; Cannonieri et al., 2007; Golestani et al., 2011;

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Version 2.0

06.11.2015

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INFORMATION FOR VOLUNTEERS (study 1)

fMRI Pattern Classification – **Structural and functional brain imaging as an early predictor of rehabilitative success in 'scanning training' for patients with hemianopia (visual field defects).**

You are being invited to take part in a research study. Before you decide whether to take part, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take your time to decide whether you wish to take part.

What is the purpose of the study?
The study aims to examine functional brain activity in individuals while encode actions, which can be visual stimulation, body actions and eye movement training.

Why have I been chosen to take part?
We have chosen you to take part in the study because you are healthy, have normal or corrected to normal hearing and vision and are willing to learn to adapt new eye movement strategies.

Do I have to take part?
Your participation in this study is completely voluntary, and you are free to withdraw from taking part at any time.

What will happen to me if I take part?
.
We will run many scans at different time points to study structural and functional changes in your brain while you learn to do an eye movement tanning. We will scan you one before training, and then up to five times during and after training to measure how your brain changes as you learn new skills.

Before the scan you will be asked to fill in a short safety screening form to make sure there are no reasons why you would not be suitable for magnetic resonance scanning. You will be asked

to wear a gown (changing rooms are provided) and remove items which are affected by the magnetic field (e.g. hearing aids, mobile phones, keys, coins, pens, credit cards (secure lockers are provided). MR scans are noisy (so you will need to wear disposable earplugs that will be provided) but cause no pain, harm or long-term effects. Some people may experience slight feelings of claustrophobia in the scanner. If you do feel uncomfortable, you will be able to notify us immediately and we will remove you from the scanner without delay.

For this study, there will be at least two scanning session; you will lie in the MRI scanner while observing a sequence of short human actions and asked to press a button when an action repeats. The actions can be visual stimulations and each of the actions is 3 seconds long.

During the scanning session, you will be asked to press a button when you see the same action in direct succession. We will also run two structural scans where you just must remain still.

Each of the two scanning sessions will take less than an hour to complete. It is important to minimise head movements during the scans, we will therefore ask you not to speak during or between experiments, although we can hear you if necessary.

Subsequent scans will be short (less than 15 minutes) scans that will be scheduled at regular points during the training procedure.

What are the possible disadvantages and risks of taking part?
The MRI scanner is noisy, but otherwise there are no reported long-term effects. High quality disposable earplugs will be provided to protect against the possibility of hearing loss. Some people may experience slight feelings of claustrophobia in the scanner. If you do feel uncomfortable you will be able to notify us immediately and we will remove you from the scanner without delay.

There are no known risks in properly conducted magnetic resonance scanning. As it involves a strong magnetic field, certain standard precautions will be observed. Most importantly, we will NOT study you if you are fitted with a heart pacemaker, mini-defibrillator or a neurostimulator; if you have surgical clips in your head; if you have suffered injuries that may have left metal particles in your eye or head, or elsewhere in your body; or if you have an artificial heart valve. We will also ask about other kinds of surgery and metal implants that might affect your suitability.

Occasionally research studies using magnetic resonance imaging reveal significant unexpected abnormalities that require medical follow-up, either for further investigation or (more rarely) treatment. The scans we do are for research purposes, but we review them carefully to avoid missing such an abnormality. We will spend a few extra minutes taking high-quality images that will be reviewed by a consultant radiologist. If any significant abnormality is found, we will send the report to your GP, who will be able to take it further with you. Please note that this is not a substitute for a 'medical' magnetic resonance scan that a doctor might order to make a diagnosis. It should therefore not be a 'health check'.

Will information about me be kept confidential?
All information that is collected about you during the research will be kept strictly confidential by the researchers. Your data related to the MR study will be treated anonymously. Your personal information that is collected on the safety screening form will be kept for up to 15 years, and then will be confidentially destroyed. You have a legal right to view your personal

information stored with us. If you wish to view your personal information, please write to the University of Liverpool Data Protection Officer, Computing Services Department, University of Liverpool.

Will my taking part be covered by an insurance scheme?
Participants taking part in University of Liverpool ethically approved study will have an insurance cover.

What will happen to the results of the study?
The results of the research study will be presented at research meetings and published in scientific literature, so that other researchers can also benefit from the sharing of information. The study will take at least three months to conduct and longer to analyse fully, but we would be happy to supply you with our conclusive results after this time.

What will happen if I want to stop taking part?
During the study, you are able to withdraw at any time without explanation. Your results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and that no further use is made of them.

What if I am unhappy or if there is a problem?
If you are unhappy, or if there is a problem, please feel free to let us know by contacting Dr Georg Meyer, and we will try to help. If you remain unhappy or have a complaint that you feel you cannot come to us with, then you should contact the Research Governance Officer on 0151-794-8290 (ethics@liv.ac.uk). When contacting the Research Governance Officer, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

Who can I contact if I have further questions?
If you wish to take part in this study or if you require more information, please contact:

Dr Georg Meyer,
Department of Psychological Sciences,
Eleanor Rathbone Building
Telephone: +44 0151 7942579
Email: georg@liverpool.ac.uk

Thank you for taking the time to read this.

Systematic Eye movement training for Hemianopia people (Study to predict the outcome of a visual training rehabilitation program)

Participant Information Sheet (study 2)

You are being invited to take part in a research study.

Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take a part.

Thank you for reading this.

Part 1

What is the purpose of the study?

Visual impairment can be caused by problems with eye movements and eyesight not working properly. Visual problems can occur in nearly three quarters of stroke survivors and can be complex.

Visual impairment can impact on quality of life through loss of confidence, being unable to move around properly, having difficulty with judging distances and increased risk of falls.

Visual impairment may impact on a patient's ability to take part in rehabilitation and to return to independent living.

- In this study we aim to measure the impact of 6 weeks of eye movement training on the behavioural performance of the participants during and following the training period.

- We expect improvement in the behavioural of eye movement and we aim to link this improvement with functional and structural brain changes.

- We aim to understand deeply the potential changes (improvements) to help general rehabilitation.

Why have I been chosen to take part?

You are being invited to take part because you have been identified as having a visual problem. Your participating could

help to understand the visual impairment deeply in order to make a good rehabilitation strategy for stroke survivors who are suffering from visual problems. In addition, you may get some visual improvement which could impact positively on your daily life activates.

Do I have to take part?

Your participation in this study is completely voluntary, and you are free to withdraw from taking part at any time.

What will happen if I take part?

You will be asked to sign a consent form before taking a part in this study. If you have difficulty writing, someone independent can witness your agreement to take part and sign the form instead.

You will visit the imaging centre at The University of Liverpool Five times.

The times and dates of all visits will be made to be convenient for the participant. The duration time between first visit and second visit will be one week. The time duration between second visit and third visit will be one week as well. However, the time between visit 3 and visit 4 will be Five weeks. Finally, the last visit will be a month after visit number 4.

After visit 2 the participant will start to do eye movement training at home for six weeks. The training should be 30 minutes every day for Five days per week.

The training will be done on computer and the researchers will support the participant to do the task easily at home.

Part 2

What happens during the assessment?

- In each visit the researcher will ask you to do an eye movement task on the computer which will be explained how you can do the task before starting. The purpose of this task to measure the behavioural performance of the participant and will take around 5 minutes only.

- Immediately, after the behavioural task the participant will do brain imaging scanning and the scan will take around 40 minutes. During the scanning the participants will response by pressing left and right button to some visual targets which will appear on the screen inside the scanner.

- Before the scan you will be asked to fill in a short safety screening form to make sure there are no reasons why you would not be suitable for magnetic resonance scanning.

- You will be asked to wear a gown (changing rooms are provided) and remove items which are affected by the magnetic field (e.g. hearing aids, mobile phones, keys, coins, pens, credit cards (secure lockers are provided).

- MR scans are noisy (so you will need to wear disposable earplugs that will be provided) but cause no pain, harm or long-term effects.

- Some people may experience slight feelings of claustrophobia in the scanner. If you do feel uncomfortable, you will be able to notify us immediately and we will remove you from the scanner without delay.

- We will ask you not to speak during or between experiments, although we can hear you if necessary.

Expenses and / or payments

The study will cover the transportation costs for all visits.

What are the possible disadvantages and risks of taking part?

The MRI scanner is noisy, but otherwise there are no reported long-term effects. High quality disposable earplugs will be provided to protect against the possibility of hearing loss. Some people may experience slight feelings of claustrophobia in the scanner. If you do feel uncomfortable you will be able to notify us immediately and we will remove you from the scanner without delay.

There are no known risks in properly conducted magnetic resonance scanning. As it involves a strong magnetic field, certain standard precautions will be observed. Most importantly, we will NOT study you if you are fitted with a heart pacemaker, mini-defibrillator or a neurostimulator; if you have surgical clips in your head; if you have suffered injuries that may have left metal particles in your eye or head, or elsewhere in your body; or if you have an artificial heart valve. We will also ask about other kinds of surgery and metal implants that might affect your suitability.

Occasionally research studies using magnetic resonance imaging reveal significant unexpected abnormalities that require medical follow-up, either for further investigation or (more rarely) treatment. The scans we do are for research purposes, but we review them carefully to avoid missing such an abnormality. We will spend a few extra minutes taking high-quality images that will be reviewed by a consultant radiologist. If any significant abnormality is found, we will send the report to your GP, who will

be able to take it further with you. Please note that this is not a substitute for a ‘medical’ magnetic resonance scan that a doctor might order to make a diagnosis. It should therefore not be a ‘health check’.

Will my taking part be covered by an insurance scheme?

Participants taking part in University of Liverpool ethically approved study will have an insurance cover.

What will happen to the results of the study?

The results of the research study will be presented at research meetings and published in scientific literature, so that other researchers can also benefit from the sharing of information. The study will take at least three months to conduct and longer to analyse fully, but we would be happy to supply you with our conclusive results after this time.

What will happen if I want to stop taking part?

During the study, you are able to withdraw at any time without explanation. Your results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and that no further use is made of them.

What if I am unhappy or if there is a problem?

If you are unhappy, or if there is a problem, please feel free to let us know by contacting Dr Georg Meyer, and we will try to help. If you remain unhappy or have a complaint that you feel you cannot come to us with, then you should contact the Research Governance Officer on 0151-794-8290 (ethics@liv.ac.uk). When contacting the Research Governance Officer, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

Will my participation be kept confidential?

All information will be kept private, confidential and secure. Only people involved in this study or in making sure it is run correctly will be able to look at your records.

Will my taking part be covered by an insurance scheme?

There are no special compensation arrangements in place for this study. The normal NHS complaints mechanisms will still be available to you.

What will happen if I want to stop taking part?

Anybody taking part can withdraw at any time, without explanation. Results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and no further use is made of them.

Who can I contact if I have further questions?

If you wish to take part in this study or if you require more information, please contact:

Dr. Georg Meyer,

Department of Psychological Sciences,

Eleanor Rathbone Building

Telephone: +44 0151 7942579

Email: georg@liverpool.ac.uk

Or, you may contact the **Principal Investigator.**

Dr Fiona Rowe, Department of Health Services Research,

Whelan Building, University of Liverpool, Brownlow Hill,

Liverpool L69 3GB

T: 0151 7944956

E: rowef@liverpool.ac.uk

CONSENT FORM

Title of Research Project:	Structural and functional brain imaging as an early predictor of rehabilitative success in 'scanning training' for patients with hemianopia (visual field defects).	
Researcher(s):	Dr Georg Meyer, Dr Vanessa Sluming, Prof Fiona Rowe	**Please initial box**

1. I confirm that I have read and have understood the information sheet (Version 1, dated 15/05/2018) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I agree that, should an incidental abnormality be picked up on my scan, it will be dealt with through the procedure described in the information sheet. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my rights being affected. ☐

4. I agree to take part in the above study. ☐

Participant Name Date Signature

Name of Person taking consent Date Signature

Researcher Date Signature

The contact details of lead Researcher (Principal Investigator) are:
Dr Georg Meyer,
Department of Psychological Sciences,
Eleanor Rathbone Building
Telephone: +44 0151 7942579
Email: georg@liv.ac.uk

Ethics Letter (study1)

UNIVERSITY OF LIVERPOOL

Health and Life Sciences Committee on Research Ethics (Psychology, Health and Society)

20 July 2017

Dear Dr Meyer,

I am pleased to inform you that your application for research ethics approval has been approved. Details and conditions of the approval can be found below:

Reference:	1596
Project Title:	Structural and functional brain imaging as an early predictor of rehabilitative success in 'scanning training' for patients with hemianopia (visual field defects).
Principal Investigator/Supervisor:	Dr Georg Meyer
Co-Investigator(s):	Mr Abdulrahman Aloufi, Miss Molly Day
Lead Student Investigator:	-
Department:	Psychological Sciences
Approval Date:	20/07/2017
Approval Expiry Date:	Five years from the approval date listed above

The application was **APPROVED** subject to the following conditions:

Conditions

- All serious adverse events must be reported via the Research Integrity and Ethics Team (ethics@liverpool.ac.uk) within 24 hours of their occurrence.
- If you wish to extend the duration of the study beyond the research ethics approval expiry date listed above, a new application should be submitted.
- If you wish to make an amendment to the research, please create and submit an amendment form using the research ethics system.
- If the named Principal Investigator or Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore it will be necessary to create and submit an amendment form using the research ethics system.
- It is the responsibility of the Principal Investigator/Supervisor to inform all the investigators of the terms of the approval.

Kind regards,

Health and Life Sciences Committee on Research Ethics (Psychology, Health and Society)

Ethics Letter (study2)

UNIVERSITY OF LIVERPOOL

Central University Research Ethics Committee for Physical Interventions

14 September 2018

Dear Dr Meyer

I am pleased to inform you that your application for research ethics approval has been approved. Application details and conditions of approval can be found below. Appendix A contains a list of documents approved by the Committee.

Application Details

Reference:	3430
Project Title:	Systematic Eye movement training for Hemianopia people (Study to predict the outcome of a visual training rehabilitation program)
Principal Investigator/Supervisor:	Dr Georg Meyer
Co-Investigator(s):	Mr Abdulrahman Aloufi
Lead Student Investigator:	-
Department:	Psychological Sciences
Approval Date:	14/09/2018
Approval Expiry Date:	Five years from the approval date listed above

The application was **APPROVED** subject to the following conditions:

Conditions of approval

- All serious adverse events must be reported to the Committee (ethics@liverpool.ac.uk) in accordance with the procedure for reporting adverse events.
- If you wish to extend the duration of the study beyond the research ethics approval expiry date listed above, a new application should be submitted.
- If you wish to make an amendment to the study, please create and submit an amendment form using the research ethics system.
- If the named Principal Investigator or Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore it will be necessary to create and submit an amendment form within the research ethics system.
- It is the responsibility of the Principal Investigator/Supervisor to inform all the investigators of the terms of the approval.

Kind regards,

Central University Research Ethics Committee for Physical Interventions

ethics@liverpool.ac.uk

0151-795-8355

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