Effects of Aging on the Neural Networks Underlying Visuomotor Adaptation

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ABSTRACT

Visuomotor adaptation is the ability to correct movements in response to an error and becomes increasingly important during the aging process when assistive devices may become necessary. Neuroimaging has observed age-related atrophy in several brain regions implicated with visuomotor adaptation, and the integrity of white matter connections between these regions is also known to decline. The present research is a three-part study that assessed age-related changes in brain function and structure during healthy aging. Functional magnetic resonance images (fMRI) and diffusion tensor images (DTI) were acquired from 37 neurologically healthy, right handed participants from three age groups: young (N = 12, age range = 22-39), middle-aged (N = 13, age range = 41-58), and older (N=12, age range = 65-80). During two fMRI scans, participants completed a novel moving-target task in which visual feedback of a cursor on a computer screen was manipulated in order to elicit a visuomotor response.

In the first paper of this thesis, the behavioural and neural differences between the first fMRI scan (early adaptation trials) and second scan (late adaptation trials) were analyzed for the young age group. This study aimed to outline the visuomotor transformations associated with a novel task that incorporates more natural behaviours. Visuomotor behaviour was examined through measurements of the mean cursor velocity and number of reversals in cursor direction. Although the interaction between scan number and cursor type was found to be insignificant for cursor velocity along with an insignificant main effect of scan number, a repeated-measures analysis of variance (ANOVA) found a significant main effect of cursor type. Pairwise comparisons revealed significant differences between normal and x-flip cursor conditions, and x- and y-flip conditions. Following an insignificant interaction between scan and condition, a

significant main effect of cursor condition (normal, x-flip, or y-flip) for the number of reversals was determined. Pairwise comparisons revealed that participants made fewer reversals during the normal cursor condition when compared to either the x- or y-flip conditions. Areas of neural activity related to visuomotor transformations were subsequently identified through fMRI using contrast to examine regions of greater signal change for distorted vs. normal cursor conditions. A random-effects General Linear Model (GLM) was then performed to examine differences in neural activity between the two fMRI scans. Frontal regions and the postcentral and anterior cingulate gyri were activated for the early adaptation trials, while the superior temporal, inferior frontal and parahippocampal gyri, as well as the putamen and parietal regions were activated for the late trials.

In a second paper, age-related differences in neural correlates of visuomotor adaptation were investigated using a random-effects GLM with a distorted versus normal condition contrast applied to examine between-groups differences across three age groups. Middle and superior frontal, and transverse and superior temporal gyri as well as the inferior parietal lobule, putamen, cuneus and anterior cerebellum were engaged to a greater extent in the middle group compared to the young age group. Extensive parietal, temporal, frontal and cingulate regions were observed to be more active in the older age group than the middle or young age groups. These findings suggest more widespread activation with increased age, which has been observed in previous fMRI studies. Furthermore, in conjunction with the first study of this thesis, the findings suggest that older age groups remain in an early phase of adaptation longer than younger age groups as more motor and frontal regions are activated with advancing age.

In a third paper, tract-based spatial statistics were used to compute fractional anisotropy (FA) and examine changes in white matter integrity between groups. This study aimed to assess

the anatomical differences in white matter between three age groups that could facilitate changes in function. Following independent t-test analyses, decline in mean FA was found in the uncinate fasciculus between young and middle aged groups and in the inferior longitudinal fasciculus between the middle and older aged groups. An examination between young and older aged groups revealed decline in mean FA of a greater number of structures including the fornix, posterior limb of internal capsule and cingulum, suggesting largest differences occur between greater age differences. Further strengthening the findings from the fMRI study, the mean FA in anterior-posterior tracts that anatomically connect functional regions used in visuomotor adaptation differed most between younger and older age groups.

In conclusion, this research assisted in mapping the changes in behaviours and neural networks of visuomotor adaptation and anatomical connections facilitating these networks across the natural aging process. Although further investigation of the changes in visuomotor behaviour and underlying neural correlates between early and late phases of adaptation, the current study confirms that changes in performance and neural activity do occur as manual actions are learned. In addition, the current study partially confirms that older adults may remain in an early stage of learning longer than young adults, and use more regions of the brain to carry out the same functions as younger adults. Finally, further confirming previous literature, this study has determined that the integrity of white matter connections declines in the brain as it ages. Future analysis of the functional and effective connectivity between these regions will further our understanding of the mechanisms of neural aging.

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GLOSSARY OF TERMS

3D Motion Correction: The correction of a participant's head movement from a functional MRI image by performing rigid-body realignment of all volumes to a single volume of a scan. This includes displacement in the x, y, and z planes, and rotation in pitch, roll and yaw but no stretching or skewing of the data is done.

Activity: The neural responses identified by changes in blood flow that occur in neuronal tissue.

Anatomical Connectivity: Structural links of white matter tracts between spatially separated brain structures.

Anterior Commissure-Posterior Commissure Line: A reference line drawn between two bands of white matter that connect the two temporal lobes (anterior commissure), and the left and right midbrain (posterior commissure).

Blood-Oxygenation Level-Dependent (BOLD) Effect: The source of signal change in T_2*-weighted MRI images, which is sensitive to excess amounts of oxygenated blood sent to functional brain areas, that allows for non-invasive identification of areas of neural activity.

Cluster Threshold: The minimum number of adjacent voxels that can be used to define a brain area as significantly activated.

Design matrix: A matrix of independent variable data values used to model and analyze statistical designs.

Diamagnetic: Materials having a weak repulsion from a magnetic field by inducing a magnetic field in the opposite direction to the applied magnetic field.

Diffusion Tensor Imaging: A neuroimaging technique that compiles images that contain information regarding the magnitude, anisotropy and orientation of molecular diffusion.

Echo-Planar Imaging: A rapid MRI technique that is performed by sending a single electromagnetic pulse in order to acquire many echoes from one phase step to develop a two-dimensional image.

Fractional Anisotropy: A calculated scalar value that measures the degree of non-random diffusion of water molecules through white matter tracts in the brain.

Gradient Echo Imaging: A MRI technique that is performed by changing the external magnetic field after a single radiofrequency wave has been sent, then again in the opposite direction.

Haemodynamic Response: A vascular dilation due to increased neuronal metabolism leading to a localized increase in blood flow and blood oxygen. Due to differences in magnetic susceptibilities of oxygenated and deoxygenated blood, a change in signal is detectable by T_2*-weighted MRI.

Linear Trend Removal: The removal of a line fit to estimate the slope and intercept of the signal over time if it is thought that the trend is a type of noise.

Magnetic Susceptibility: The degree of magnetization of an object or substance when in contact with a magnetic field.

Montreal Neurological Institute (MNI) Coordinate Space: A standardized three-dimensional coordinate system used to map brain regions, based on an average of 305 T_1-weighted MRI volumes.

Paramagnetic: Materials having one or more unpaired electrons whose magnetic dipole moments cause an attraction to a magnetic field.

Slice-Scan Time Correction: Correction used to account for time differences between the acquisitions of two-dimensional slices that make up a volume, which can take several seconds to acquire.

Statistical Parametric Map: A statistical technique used to identify significantly activated voxels in a brain image.

Talairach Coordinate Space: A standardized three-dimensional coordinate system used to map brain regions, based on post-mortem dissection of a single human brain.

Temporal Filtering: Attempts to increase the signal-to-noise ratio in fMRI images by removing low-frequency drifts within a raw signal which may be attributed to physiological and scanner noise.

Volume: One three-dimensional whole-brain image generated in the MRI; all volumes from an MRI scan add up to a four-dimensional image used for analysis.

Voxel: A three-dimensional element of volume, comparable to a three-dimensional pixel.

CHAPTER I: INTRODUCTION

Preamble

In this thesis, I aim to investigate the underlying neural correlates associated with visuomotor adaptation behaviour in an aiming task and how these responses change in aging. Functional magnetic resonance imaging (fMRI) will be used to reveal localized areas of signal change associated with task-related visuomotor transformations. Age-related changes in anatomical connectivity will also be assessed through diffusion tensor imaging (DTI). To frame what the reader will encounter, I will first outline the objectives and research hypotheses in the current chapter. In chapter two, a background of current literature and a rationale to the methodology are laid out. Chapter three summarizes two pilot studies using the novel task in a purely behavioural setting (i.e., outside the MRI). Chapters four through six are individual manuscripts for three specific aims, which I have laid out in the next section of this chapter. Chapter four, titled "Neural correlates underlying visuomotor adaptation in typically-functioning adults during a novel dynamic point-to-point task: a fMRI study" examines the areas of neural activation during a novel visuomotor adaptation task performed by young adults, and assesses how behaviours and brain regions change between the early and late phases of adaptation. Chapter five, titled "Age-related changes in the underlying neural correlates of a novel visuomotor adaptation task" examines how these areas change between young, middle, and older-aged adults to assess how neural activation of visuomotor adaptation changes over the aging process. Chapter six, titled "Effects of aging on anatomical connectivity: a DTI study" examines how white matter connections change between young, middle, and older-aged adults to

assess how anatomical connectivity differs between age groups. Finally, the results from the three specific studies come together with a general discussion of overarching themes in chapter seven.

Specific Aim 1

Objective. The purpose of the first study was to determine changes in visuomotor behaviour and neural activity from the early trials of visuomotor transformations to the late trials for the young age group being studied.

Hypothesis. The hypothesis was that activation would be observed in the inferior frontal and medial frontal gyri, posterior parietal cortex, inferior parietal lobule, basal ganglia, and cerebellum during the early trials. It was also hypothesized that the parietal, temporal and cerebellar regions would be involved during the late trials.

Approach. Participants completed an adaptive dynamic point-to-point task using an fMRI paradigm to determine possible changes in brain activity between the early and late trials of the task.

Specific Aim 2

Objective. The purpose of the second study was to determine differences in neural activity underlying visuomotor adaptation between different stages of aging with fMRI.

Hypothesis. The hypothesis of the fMRI study was that activation would be observed in brain regions consistent with previous studies of visuomotor adaptation such as the posterior

parietal cortex, inferior parietal lobule, pre- and post-central gyri, supramarginal gyrus, superior and inferior frontal gyri, precuneus, cingulate gyrus, and insula. In the young age group, it was anticipated that fMRI activity would be present in these regions. It was hypothesized that larger cluster sizes, with more voxels significantly correlated with the paradigm, would be associated with greater recruitment of cognitive strategies during the task that come naturally with advancing age. For the middle age group, the level of activity was anticipated to have more widespread and bilateral activation associated with increased difficulty performing the visuomotor adaptation task compared to young, healthy participants. As such, the older participants were expected to have a similar result, unless the task was too difficult for this age group. If so, a decrease in activity can be expected, however this decrease will likely be associated with the lack of cognitive strategy rather than increase in performance behaviour.

Approach. Participants from three age groups completed an adaptive dynamic point-to-point task using an fMRI paradigm to determine possible between-groups differences in brain activity during this task.

Specific Aim 3

Objective. To determine changes in anatomical connectivity of brain regions during different stages of aging using DTI.

Hypothesis. It was hypothesized that there would be a decline in the rate of water diffusion along white matter tracts in older-aged groups when compared to younger groups, which

would be evident by a decline in fractional anisotropy seen in the mean FA images of each group.

Approach. DTI images of each participant from the three age groups were acquired to determine possible differences in FA and therefore white matter integrity between groups.

CHAPTER II: BACKGROUND & RATIONALE

Motor Control

Visuomotor Adaptation

Motor control is the neural process of receiving sensory inputs to coordinate and execute a desired motor output (Willingham, 1998; Wolpert & Kawato, 1998). The motor control system must be able to provide accurate motor commands for a multitude of distinct functions, and as such depends on a successful interaction with one's surroundings. Motor learning is the process of improving the accuracy of motor movements with practice. It is the part of motor control associated with the relatively permanent acquisition of novel skills and re-acquisition of previously learned movements.

One form of motor learning is visuomotor adaptation. Visuomotor adaptation is the ability to improve spatial and temporal accuracy of movements with practice of motor tasks (Contreras-Vidal & Buch, 2003; Willingham, 1998) and allows for individuals to interact successfully with their environment (Wolpert & Kawato, 1998). It is dependent on visuomotor transformations, which rely on the closed-loop motor control system. Manual actions in particular are intricate behaviours in nature which require coordination between the awareness of these environments and one's intended movement. This coordination is achieved by the integration of sensory information into meaningful movements based on visual feedback of minute distortions. Multiple conscious and unconscious mechanisms of recalibration are used in visuomotor adaptation. The largest movement errors are seen in the early phase of visuomotor adaptation and accuracy improves as the brain transitions from a conscious mode to an

unconscious mode in the late phase when adaptation occurs (Anguera, Seidler, & Gehring, 2009). The visuomotor adaptation system can be estimated by the development of an internal model (Wolpert & Kawato, 1998), which is a neural representation of the natural connections used in motor responses and commands (Imamizu et al., 2000).

Neural Systems of Motor Control

Motor control of hand movements can be achieved through a closed-loop system based on visual feedback (Heuer & Hegele, 2008). Closed-loop control mechanisms require continuous visual feedback during movement execution in order to make the correct transformations of sensory information. Motor outputs can be estimated through the involvement of an internal model, which contains many components: input, executive, effector, output, and comparator (Figure 2 – 1).

The sensory system is important in motor control by collecting proprioceptive and visual information about one's environment. Proprioception is one type of sensory feedback that provides information about the location of the hand in space with or without visual information (Willingham, 1998). Ascending sensory information from the limbs, such as proprioceptive, tactile, and pain, propagates through the spinal cord to the primary somatosensory cortex and cerebellum (Figure 2 – 2; Shumway-Cook & Woollacott, 2012). Visual feedback is another type of sensory information (Rohde, van Dam, & Ernst, 2014). The position of objects in space and of an individual's body in space are important for correct selection of movements, and this can be achieved through acquiring visual information about one's environment. The visual cortex lies at the rear of the brain in the occipital lobe (Kandel, Schwartz & Jessel, 2000). The primary visual

cortex receives visual information from the eyes and this information is passed through neural networks to secondary visual areas.

The executive component of closed-loop motor control is composed of a complex network of neural regions. The posterior parietal cortex, which is situated between the somatosensory and visual cortices, is involved in transforming sensory information and identifying stimuli. The motor system is involved in the coordination of hand movements in response to information provided by sensory systems (Willingham, 1998). The premotor cortex selects how to respond to the stimuli. Information is then propagated to the supplementary motor area (SMA) which determines an action through a network composed of the striatum, basal ganglia, and thalamus (Kandel et al., 2000). Finally, the effector performs this desired action through the lateral corticospinal pathway that propagates motor information from the primary motor cortex to the spinal cord onto the target muscles, and the resultant output is the movement of the hand. The comparator then detects errors in comparison to the desired movement, allowing for online improvement of the movement, and for the next movement to be more accurate.

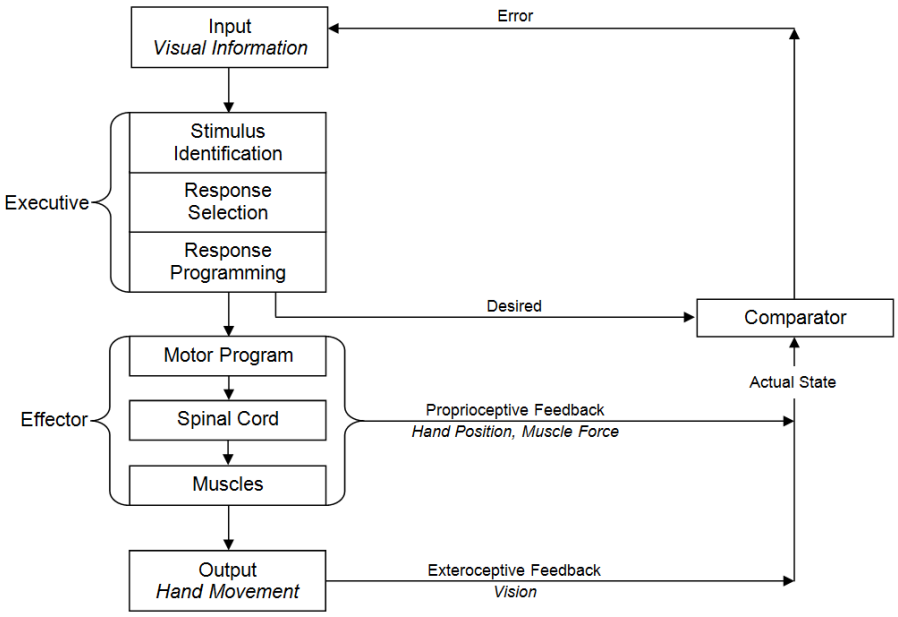

Figure 2 - 1. Closed-loop model of motor control.

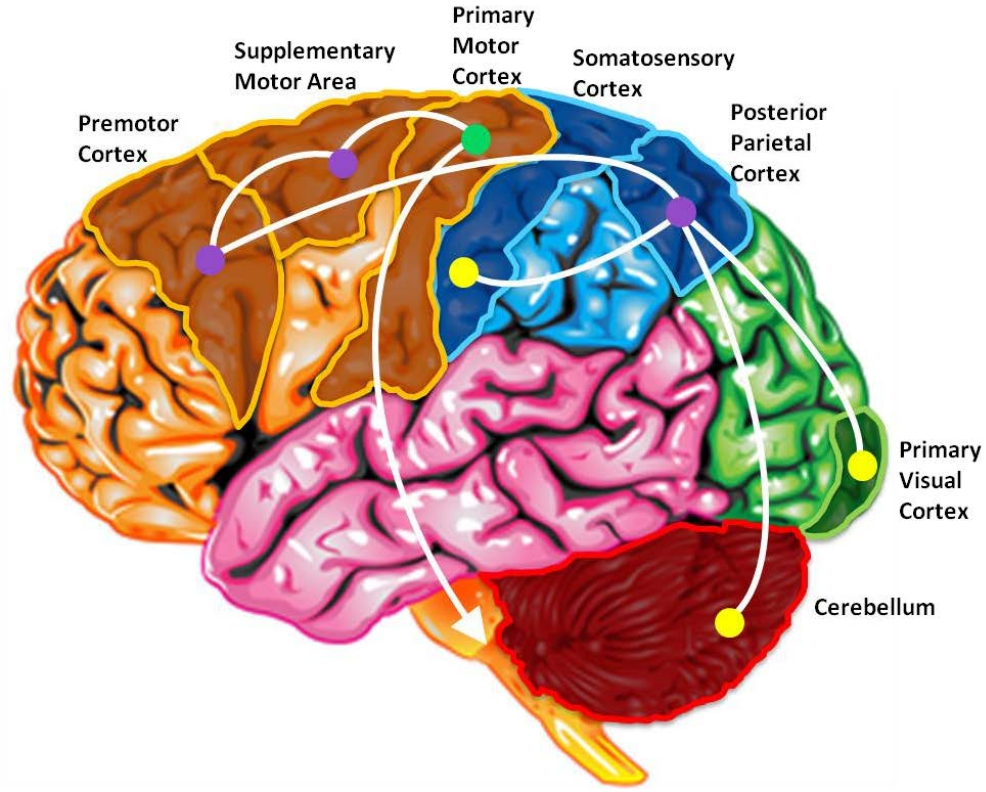

Figure 2 - 2. Closed-loop motor control neural network. Visual information is received in the primary visual cortex and proprioceptive information in the somatosensory cortex and cerebellum. The posterior parietal cortex then integrates this information, the premotor cortex plans a motor response, the supplementary motor area coordinates the motor response, and the primary motor cortex executes the motor response, in this case movement of the hand and arm. Yellow dots indicate input components; purple dots indicate executive components; and green dots indicate effector components

Visuomotor Adaptation Tasks

Complex adjustments to errors in movement can be achieved through an internal model which can be built through the practice of a visuomotor adaptation task (Wolpert & Kawato, 1998). A visuomotor adaptation task can be performed by distorting the mapping between visual and motor space (Anguera, Russell, Noll, & Seidler, 2007). These tasks typically involve reaching, pointing or grasping toward a target with normal and distorted visual feedback for comparison between these conditions (Anguera et al., 2009). Reaching for a target requires integration of visual information for motor output (Ingram et al., 2000). An introduction of a visually distorted environment leads to an interruption in visuomotor performance (Abeele & Bock, 2003). Practice of a visuomotor adaptation task is needed to strengthen an internal model under distorted conditions in order to improve visuomotor performance (Contreras-Vidal & Buch, 2003).

Classically, prism lenses have been used to study visuomotor adaptation. In these experiments, lenses are distorted with an optical shift and participants complete a repeated pointing exercise to a visual target (Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013). Participants often point in the opposite direction to the target when prism lenses are initially removed. Prismatic lenses offer methodological limitations in the magnetic bore of an MRI scanner. Specifically, the addition of prisms between experimental trials to induce adaptation and subsequent removal of prisms to measure aftereffects could potentially lead to participant movement during the scan or distraction from the task (Danckert, Ferber, & Goodale, 2008). One study placed a prism over one eye and a neutral lens over the other in an effort to avoid participant motion (Chapman et al., 2010). An occluding patch was transferred over the neutral

lens in adaptation trials then over the prism in de-adaptation trials. Although scans were uninterrupted, occlusion shifts visual feedback into one visual field during different trial types.

The use of computer-based tasks offers several advantages over prism lenses. Conventional computer-based point-to-point tasks are visual tasks that involve movement of a cursor toward a specific target, and can be used with any volume coil that allows for vision of stimuli. The relationship between the intended cursor movement and actual movement of the participant's hand is a function of the internal model built for visuomotor responses (Imamizu, Kuroda, Miyauchi, Yoshioka, & Kawato, 2003), and induces transformations much like prism lenses. Usually, point-to-point tasks use a static target, with one direction of intended movement. The static point-to-point tasks conventionally seen in visuomotor adaptation studies lack multidirectional movements and limit the ability of individuals to strengthen the necessary internal model for adaptation.

While our interactions with stationary targets have been well studied, visuomotor adaptation behaviour towards moving or dynamic targets have received less attention. Prism adaptation has been used during dynamic stimuli while participants pointed at moving targets (Field, Shipley, & Cunningham, 1999). Field et al (1999) dropped targets from a predetermined height and the participants, trained with prism lenses, were instructed to point to where they expected the ball to land. The vision of the ball was blocked from the participant to different extents. It was determined that better vision of the target led to better adaptation, in which the magnitude of adaptation increased over testing trials. The greatest aftereffects were seen closest to the training point during the dynamic events when compared to static events. From their findings, it can be concluded that dynamic events are more complex than static events, and require sensitivity to the speed and trajectory of the moving object for effective interactions.

Computer-based tasks have been developed to investigate the effects of moving targets on visuomotor transformations (Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005; Foulkes & Miall, 2000; Miall, Reckess, & Imamizu, 2001). Foulkes and Miall (2000) used a manual-tracking task where participants were instructed to follow continuously moving targets that unexpectedly jumped to change locations. Improvements in performance were measured after a set of perturbation trials, where cursor movements were distorted, to show that human movements can be controlled by visual feedback. However, no trends were determined between perturbed and unperturbed trials because participants used varying strategies to overcome the jumping target. Diedrichsen et al (2005) used a disappearing and reappearing point-to-point target task to assess the transformations involved in multidirectional movements. They determined less adaptive responses for the jumping target when compared to a standard visual rotation, which left participants in a constant state of early visuomotor adaptation. These two studies similarly conclude that a disappearing target is not optimal for visuomotor adaptation studies involving closed-loop motor control because it does not allow participants to follow the target movement with continuous visual feedback.

More recently, a computer-based viewing window task has been developed for visuomotor adaptation studies, where an image of an everyday object is blurred out on a computer screen and participants have control of a small, clear "window" which they can move around the image to identify what the object is (Baugh & Marotta, 2007). Viewing window tasks produced activity in a novel brain area called the claustrum (Baugh, Lawrence, & Marotta, 2011), which has a relatively unknown function (Crick & Koch, 2005). The recruitment of claustrum activity in this visuomotor task could be due to the permission of natural exploration for the participant through multidirectional movements, which may aid in the development of a

better internal model than static point-to-point tasks. In addition, the task takes longer to complete than a conventional static point-to-point task which may facilitate activity in more brain regions. However, the presence of familiar objects introduces a perceptual component, which may explain the novel brain region engaged during the task. To determine whether multidirectional movements induce better adaptation with continuous visual feedback and without the perceptual component, a moving target point-to-point task may answer any questions.

Visuomotor Adaptation and Aging

With aging many different systems in the body are naturally affected, yet the rate of change occurring in each is non-linear. Neural systems are one component of the human body known to be affected by aging, however the location and extent of atrophy is still not fully understood (Mattson & Magnus, 2006). In addition, age-related changes in neural systems are heterogeneous in that cognitive, sensory and motor functions may decline at different rates within an individual and between individuals. Motor system decline associated with aging is dependent on structural neuromuscular (Lexell, 1997) and cerebral changes (Madden et al., 2009). Evidence of this degeneration can be observed through changes in motor performance, which is thought to decrease in relation to age in individuals older than 60 years (Loibl, Beutling, Kaza, & Lotze, 2011).

Investigation of the age-related changes in visuomotor adaptation is important for determining the average underlying degradation of neural connections for a population (Baugh & Marotta, 2009; Buch, Young, & Contreras-Vidal, 2003). The effects of aging on visuomotor adaptation are continually being examined through behavioural and imaging studies, but results

have been inconsistent (Buch et al., 2003). This is likely due to the heterogeneity of age-related change in neural systems. Decline in neural function could be as a result of a decrease in the visual system's ability to properly identify stimuli (Shumway-Cook & Woollacott, 2012). Changes could also be due to declining function of the motor system or due to central processing limitations (amount of time taken to make decisions about a movement). The results from different studies vary in that some find no behavioural deficits in visuomotor adaptation (Roller, Cohen, Kimball, & Bloomberg, 2002) and some find reduced adaptation (Seidler, 2006). There are also studies that have not determined changes in behaviour after a visual distortion is removed, and studies that have determined larger after-effects in healthy older populations when compared to young populations. Buch et al. (2003) suggest that this high level of controversy could be due to the way participants are instructed to perform the different tasks used, as well as the difficulty of the task, and differing cognitive abilities of the different aging populations.

Age-related decline in visuomotor adaptation has been observed during a task where visual perturbations were introduced suddenly rather than gradually (Buch et al., 2003). These sudden distortions may recruit cognitive areas of the brain for strategic movement plans, suggesting that cognitive strategies are affected in the aging process. In a study on the effects of aging on tool use, Heuer & Hegele (2010) investigated participants' performance while reaching targets using a sliding lever. It was determined that the younger age group was more efficient at using closed-loop control systems than were the older age group. They suggest that the processing of visual feedback in order to optimize closed-loop control and thus improve performance is more efficient in younger than older adults (Heuer & Hegele, 2010). The more limited use of closed-loop control in older participants indicates an age-related decline in visual information processing. A reduction in the velocity of reaching movements has also been seen in

aging studies involving hand movement coordination (Fradet, Lee, & Dounskaia, 2008). Fradet et al. (2008) determined in a study involving movement towards targets that older adults spent more time in the target approach phase of the task than younger adults. This is a contributing factor of the sensory system where processing of the visual targets has reduced accuracy. They suggest that this could also be due to an increase in submovements, which are velocity fluctuations and movement adjustments that are factors of the motor system.

In 2011, 14.4 percent of Canada's population was 65 years of age or older (Statistics Canada, 2011). This percentage is projected to increase to 23.7 percent by 2036, meaning that studies of aging effects on visuomotor adaptation performance are increasingly important. The growing need for visuomotor adaptation ability for older adults is associated with the need for assistive devices to aid in the performance of daily activities. Each new motor movement associated with beginning to use an assistive device will effectively be taught and learned through the neural mechanism of visuomotor adaptation in order for the transition into using assistive devices to be successful. For these reasons, further investigation of the behaviours and neural mechanisms associated with visuomotor adaptation and how these are affected by age is necessary.

Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a powerful, non-invasive method used to assess brain structure. Functional MRI (fMRI) indirectly identifies areas of activity in the brain through localized changes in blood flow and oxygen called the blood oxygenation level-dependent (BOLD) effect (Ogawa, Lee, Kay, & Tank, 1990). In an area of BOLD activity, neurons are being recruited from that region to perform a specific function resulting in increased metabolism and demand for oxygen, initiating a haemodynamic response. During the haemodynamic response, excess oxyhemoglobin is transported to active neuronal tissue. Oxyhemoglobin is a diamagnetic molecule whereas deoxyhemoglobin is a paramagnetic molecule, so the magnetic susceptibility of these regions are different (Buxton, Uludağ, Dubowitz, & Liu, 2004). The difference in magnetic susceptibility of the proton signal of blood vessels in the brain and its surrounding tissue after a change in blood oxygenation creates the BOLD contrast. By comparing changes in BOLD signal change associated with the delivery of a stimulus, or performance of a task, fMRI allows researchers to uncover task-related areas of activity in the brain. Furthermore, this imaging technique has been very useful in determining areas of the brain that are used in visuomotor adaptation. Using this method, it is hoped that changes in neural activity during the aging process can be determined. To determine differences in neural activity between age groups, areas of signal change are identified first on a single-subject level by performing a GLM using a modelled time course of the participants behaviour in the task (such as response time) predicting the time of signal change. Areas that are different between groups of subjects are then identified in a second, group-level random-effects GLM.

fMRI and Visuomotor Adaptation

A variety of cortical and subcortical brain regions have been determined to be involved in the visuomotor adaptation process through functional neuroimaging (Anguera et al., 2007; Sakai et al., 1998; Seidler, Noll, & Chintalapati, 2006). Proprioception, visual and motor commands involved in visuomotor adaptation are practiced in the somatosensory and primary visual cortices (the areas of the brain where sensory and visual information are perceived), and the primary motor cortex (the area that signals the body to move in response to sensory information). The posterior parietal cortex is situated between these areas of the brain and is believed to be involved in receiving sensory and visual input for the integration into motor movements due to its extensive connections with these areas. More specifically, the parietal lobe is involved in visuomotor adaptation based on previous functional MRI studies of the brain (Culham, Cavanagh, & Kanwisher, 2001). Initial contributions of neural activity have also been observed in the premotor cortex, dorso-lateral prefrontal cortex, supplementary motor area (SMA), precuneus, basal ganglia, cerebellum, and striatum from fMRI studies of the early phase of visuomotor adaptation when greater cognitive strategies are evoked for action selection and movement planning (Anguera et al., 2007; Sakai et al., 1998; Seidler et al., 2006). FMRI studies of the late phase of visuomotor adaptation reported activity in the cerebellum and temporal cortex when movements have become more automatic (Imamizu et al., 2000; Miall et al., 2001). It has been proposed that the frontal areas are more active during the early stages while the parietal areas and cerebellum are more active during the late stages (Sakai et al., 1998). The cerebellum is thought to be an important neural component in hand-eye coordination in reaching, pointing or tracking (Miall et al., 2001). Activation and blood flow to the cerebellum is typically seen with fMRI studies early in visuomotor adaptation as well and weakens into the late

adaptation (Imamizu et al., 2000; Miall et al., 2001). Closed-loop control mechanisms are thought to infer communication between the cerebellum and prefrontal cortex (Heuer & Hegele, 2008).

During a novel visuomotor adaptation task mentioned previously in this chapter (the viewing window task), activity in the claustrum was identified through fMRI studies (Baugh et al., 2011). The claustrum is located in the limbic lobe, lateral to the putamen and medial to the insula. Three divisions of the claustrum have been proposed to be connected to cerebral cortices: the anterior-dorsal area (somatosensory and motor cortices), the posterior dorsal area(visual cortex), and the ventral area (auditory cortex) (Smythies, Edelstein, & Ramachandran, 2012). Crick and Koch (2005) proposed that the claustrum is associated with the integration of visual and sensory information. Although its function is still not well understood, they hypothesized that the claustrum binds these separate information processes into a unity which connects the many characteristics of real life objects (Crick & Koch, 2005). For example, the smell, touch, size, and colour of a flower can be sensed at the same time by the perceptual binding of visual and sensory processes.

fMRI and Aging of the Motor System

Many studies have assessed how natural, healthy aging affects task-related functions in the brain. In general, the pattern of activation normally seen in young adults shifts toward a more bilateral activation pattern in older adults (Ward & Frackowiak, 2003). Typically in motor task studies, contralateral activation is observed in the primary motor, premotor and posterior parietal cortices as well as the supplementary motor area for young and older individuals (Hutchinson et al., 2002), with more widespread and bilateral activation in the primary motor and premotor

cortices and SMA for older individuals (Naccarato et al., 2006). Other studies have demonstrated that these differences are greater when the motor task is more challenging, thus requiring a greater recruitment of cognitive strategies (Heuninckx, Wenderoth, & Swinnen, 2008). To further understand how these mechanisms of age-related change occur for motor tasks, it must be determined whether the bilateralization and increase in activated brain regions is compensatory, associated with movement adaptation, or due to increased difficulty of the task for older adults (Loibl et al., 2011).

Diffusion Tensor Imaging

Diffusion-tensor imaging (DTI) is an advanced MRI technique that is sensitive to the diffusion of water through white matter tracts. Water moves faster along the main pathways of white matter tracts rather than across them, generating contrast in the MRI image along the fast-diffusing tracts against the diffusion of water in tissues oriented in the perpendicular direction (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Kuhnt et al., 2013; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). This directional movement of water, called anisotropic diffusion, is a source of signal that can be measured and used to construct maps of the white matter tracts in the brain. Fractional anisotropy (FA) is a value determined through diffusion imaging that depicts the directionality of anisotropic diffusion, reflecting white matter integrity in the brain. For example, a white matter tract with a high fiber density, large axonal diameter, and significant myelination in comparison to surrounding structures will have a high FA value (maximum value of 1) and be considered having a high integrity. Whereas an area with equal diffusion as its surrounding structures will have a FA value of 0. By calculating FA data from

DTI, hypotheses of changes in anatomical connectivity may be made. This has been useful in mapping functional and structural connectivity to better understand the anatomy of the brain and to help with the early detection of neurological degeneration (Basser et al., 2000; Filler, 2010).

Methods of DTI Analysis

A common method used to analyze changes in white matter microstructure of the brain is voxel-based morphometry (VBM). In VBM, localized differences in white matter and FA images between two groups of participants can be analyzed (Li, Wang, Hu, Liang, & Chen, 2013). This type of analysis, however, comes with limitations such as alignment procedures for FA images (Smith et al., 2006, 2007). For example, two groups may exhibit different ventricular sizes but have the same basic white matter integrity. Due to the difference in ventricular size, the registration of each group's mean FA image may align differently, and statistical analysis will show this misalignment as a group difference in FA when a group difference may not be present.

Another method to examine white matter integrity with DTI is tractography. This approach may overcome alignment and smoothing issues seen with VBM by analyzing individual tractography results (Smith et al., 2006). However, tractography-based analyses do not allow for whole-brain voxel-wise exploration, requiring experimenters to define specific tracts to be analyzed prior to statistics, which may not be known in advance (Smith et al., 2007).

Tract-based spatial statistics (TBSS) minimizes the potential misalignment problems of VBM by determining a white matter skeleton restricted only to the center of major white matter tracts, and mapping FA values from each individual directly onto this standard skeleton for group comparisons (Smith et al., 2006, 2007). It also allows for whole-brain exploratory voxel-wise analyses, therefore offering an advantage over tractography methods.

DTI and Aging

There has been much interest in FA from DTI as a marker for white matter tract integrity studying normal aging (Moseley, 2002). DTI has prevailed as a technique for visualizing the degradation of fibrous tissue connections in eugeric aging (Basser et al., 2000; Filler, 2010; Surova et al., 2013). Age-related declines in white matter microstructure can be identified by detecting and mapping changes in the FA along these tracts between age groups (Madden et al., 2009). A group of researchers studied age-related changes of the white matter integrity in the fibers coursing through the corpus callosum connecting to both the occipital and parietal lobes. Through DTI tractography they determined that parietal fibers, particularly those going to the right hemisphere, are associated with age-related decline. Greater decline was seen in bilateral peripheral segments of the tracts rather than central segments for the older age group compared to younger. Likewise, Inano et al. (2011) determined through TBSS analysis significant decreases in FA of the corpus callosum, fornix, internal capsule, external capsule and cingulum for the older age group compared to the younger. Together, this research demonstrates the value of FA measurement in assessing age-related changes in white matter tract integrity.

CHAPTER III: METHODOLOGICAL PILOT STUDIES

Comparison of Conventional Static and Novel Dynamic Point-to-Point Tasks

Background/Objectives

The ability to correct movements is essential for successfully completing simple day-to-day tasks. While interactions with stationary targets have been well-studied, visuomotor adaptation in a moving-target task has received less attention despite our interaction with moving objects on a daily basis. The present study compared visuomotor behaviour during a computer-based point-to-point task to a novel task in which the target was static or moving in order to determine whether a moving target induces better adaptation to movements. It was hypothesized that a dynamic task would lead to better adaptation than a typical static task.

Method

Twenty-two right-handed healthy young adults (mean = 24.6 ± 4.3 years; 11 males) controlled the movement of a cross-hair cursor from the center of the screen on a desktop computer with a MRI-compatible trackball to a single, square target under four cursor conditions: normal, flip over x-axis, y-axis and both axes. The target was presented randomly in one of the four corners, 400 pixels from center (Figure 3 - 1).

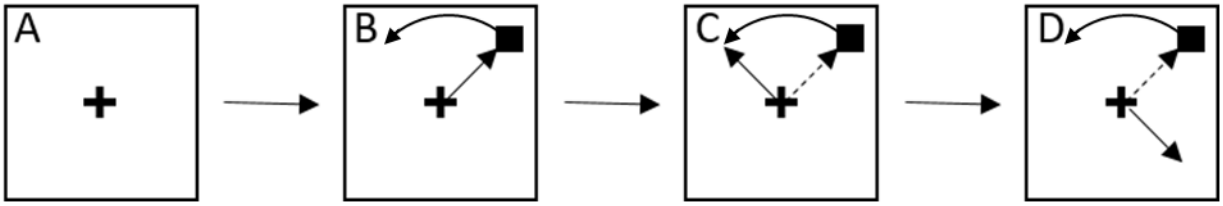

Figure 3 - 1. Visuomotor adaptation task schematic. The start position of the cursor was always the center of the screen (A), with targets appearing in one of the four corners (here with target in the top right quadrant). Participants were instructed to reach a target moving in a counter-clockwise circle with an MRI-compatible trackball as quickly and accurately as possible. During adaptation trials, feedback of the cursor was normal (B), flipped over the x-axis (C), or flipped over the y-axis (D). These conditions are shown with the intended movement as a dashed line and the feedback of movement as a solid line.

Participants were divided into two groups where one group performed the static-target task first while the other completed the dynamic. During the static task, the target remained stationary for the duration of the trial, and during the dynamic task, the target moved in a counter-clockwise direction at 6.25 pixels/s. A trial ended when the cursor intercepted the target. To examine changes in behaviour over the course of the experiment, each set was divided into three phases: pre-distortion, adaptation and post-distortion. The pre and post phases (50 trials each) were presented with normal cursor control while the adaptation phase (150 trials) was presented with all four cursor conditions pseudo-randomly interleaved. This was repeated a second time with the other target condition. For analysis, the adaptation phase was separated into early and late phases (75 trials each). A repeated-measures ANOVA was performed using a 2(target type) x 2(task order) x 4(phase) factorial design to examine significant differences in mean path distance, movement time, and cursor velocity between the static and dynamic tasks.

Results

Significant interactions between target type, phase and group number were observed for path distance ($F(3,60)=3.624$, $p=0.018$), movement time ($F(3,60)=6.712$, $p\leq0.001$), and cursor velocity ($F(3,60)=4.395$, $p=0.007$) (Figure 3 – 2).

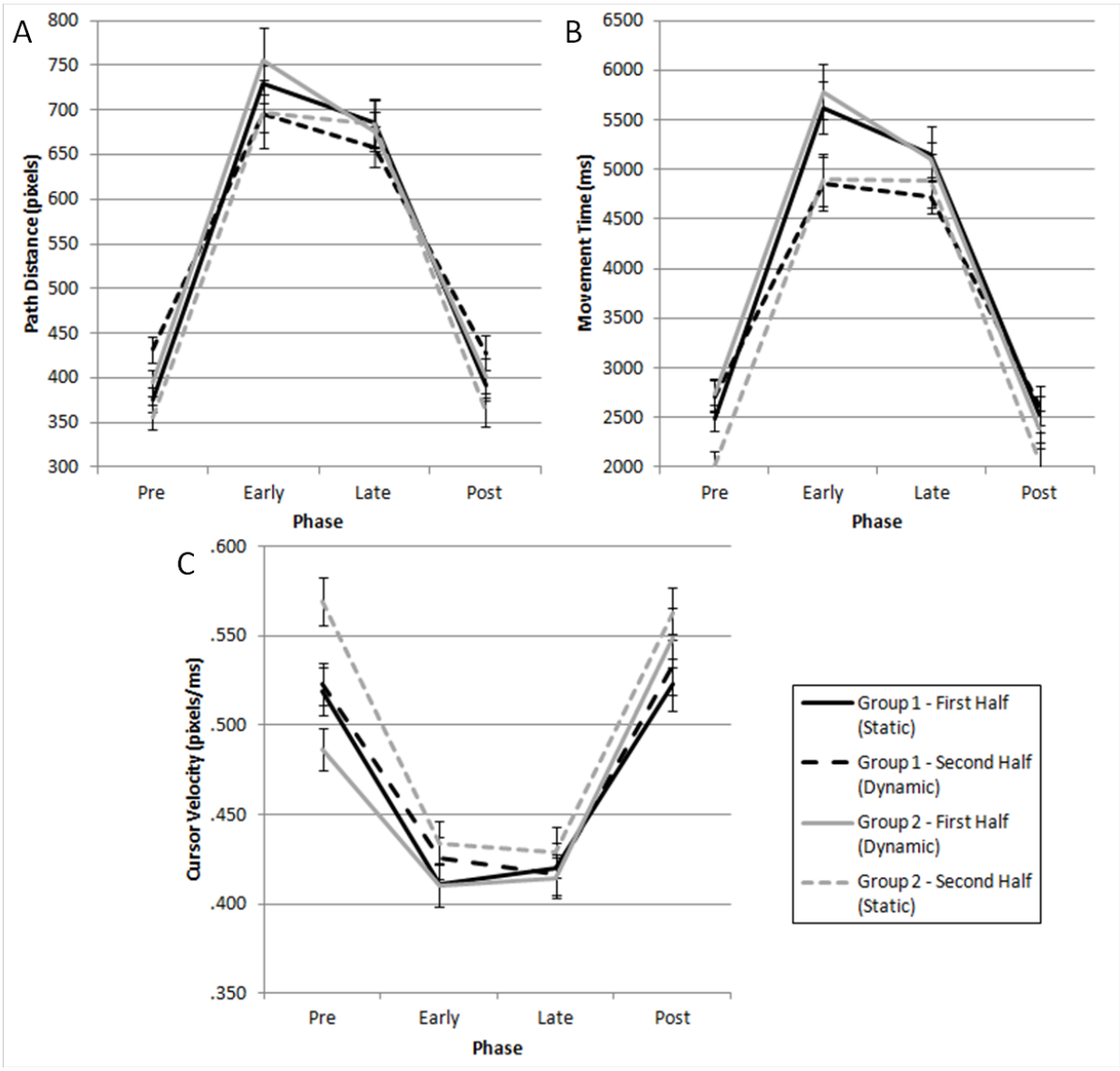

Figure 3 - 2. Mean path distance (A), movement time (B) and cursor velocity (C) observed during static and dynamic trials for both groups over each phase of the study. Group 1 performed the static-target task in the first half, and group 2 performed the dynamic-target task. A significant interaction was observed between target type, phase and group number for all three measures. Error bars represent the standard error of the mean.

A significant interaction between target type and phase indicates better adaptation to the dynamic target over time, as reflected by decreases in distance ($F(3,60)=5.600$, $p=0.002$) and time ($F(3,60)=4.141$, $p=0.004$), and increases in velocity ($F(3,60)=4.858$, $p=0.004$). A significant interaction between target type and group number indicates order effects, with overall better performance observed by group 1, as reflected by faster time ($F(1,20)=27.953$, $p\leq0.001$) and velocity ($F(1,20)=17.694$, $p\leq0.001$). Following an insignificant interaction between phase and group number, a significant main effect of phase was revealed for distance ($F(3,60)=344.625$, $p\leq0.001$), time ($F(3,60)=386.507$, $p\leq0.001$), and velocity ($F(3,60)=164.635$, $p\leq0.001$), indicating that all participants improved performance of the task, as anticipated.

Discussion

The results of this study suggest that moving targets elicit a stronger adaptive response to movement errors than static targets. In the future, functional MRI will be used to determine the underlying neural correlates of visuomotor adaptation to dynamic stimuli.

Differences in Visuomotor Adaptation Behaviour Between Age Groups

Background/Objectives

Visuomotor adaptation is a skill used to adjust movements in order to successfully complete day-to-day motor tasks. During the natural aging process, neural connections begin to weaken, making it more difficult to control and correct movements. The present study compares visuomotor behaviour between young and older participants during a novel dynamic point-to-

point task. It was hypothesized that older adults would demonstrate a lesser visuomotor task performance when compared to young adults.

Method

Twelve young (mean age = 25.6 ± 4.1 years; 5 male), and 12 older (mean age = 58.6 ± 9.9; 6 male) healthy right-handed adults controlled the movement of a cross-hair cursor from the center of the screen on a desktop computer with a MRI-compatible trackball to a single, square target under four cursor conditions: normal, flip over x-axis, y-axis and both axes. The target was presented randomly in one of the four corners, 400 pixels from center (Figure 3 - 1). During the task, the target moved in a counter-clockwise direction at 6.25 pixels/s. A trial ended when the cursor intercepted the target. To examine changes in behaviour over the course of the experiment, the task was divided into three phases: pre-distortion, adaptation and post-distortion. The pre and post phases (50 trials each) were presented with normal cursor control while the adaptation phase (150 trials) was presented with all four cursor conditions pseudo-randomly interleaved. For analysis, the adaptation phase was separated into early and late phases (75 trials each). A repeated-measures ANOVA was performed using a 2(target type) x 2(age group) x 4(phase) factorial design to examine significant differences in mean path distance, movement time, and cursor velocity between the age groups.

Results

Interactions between distortion type, phase and group number were determined to be insignificant. Following insignificant interactions between phase and group number, and between distortion type and phase, a significant interaction between distortion type and group was

observed, as reflected by shorter path distances ($F(3,66)=4.433$, $p=0.007$) and quicker movement times ($F(3,66)=5.067$, $p=0.003$) for the young age group. A main effect of distortion type was also determined for path distance ($F(3,66)=35.079$, $p\leq0.001$) and movement time ($F(3,66)=33.324$, $p\leq0.001$) (Figure 3 – 3).

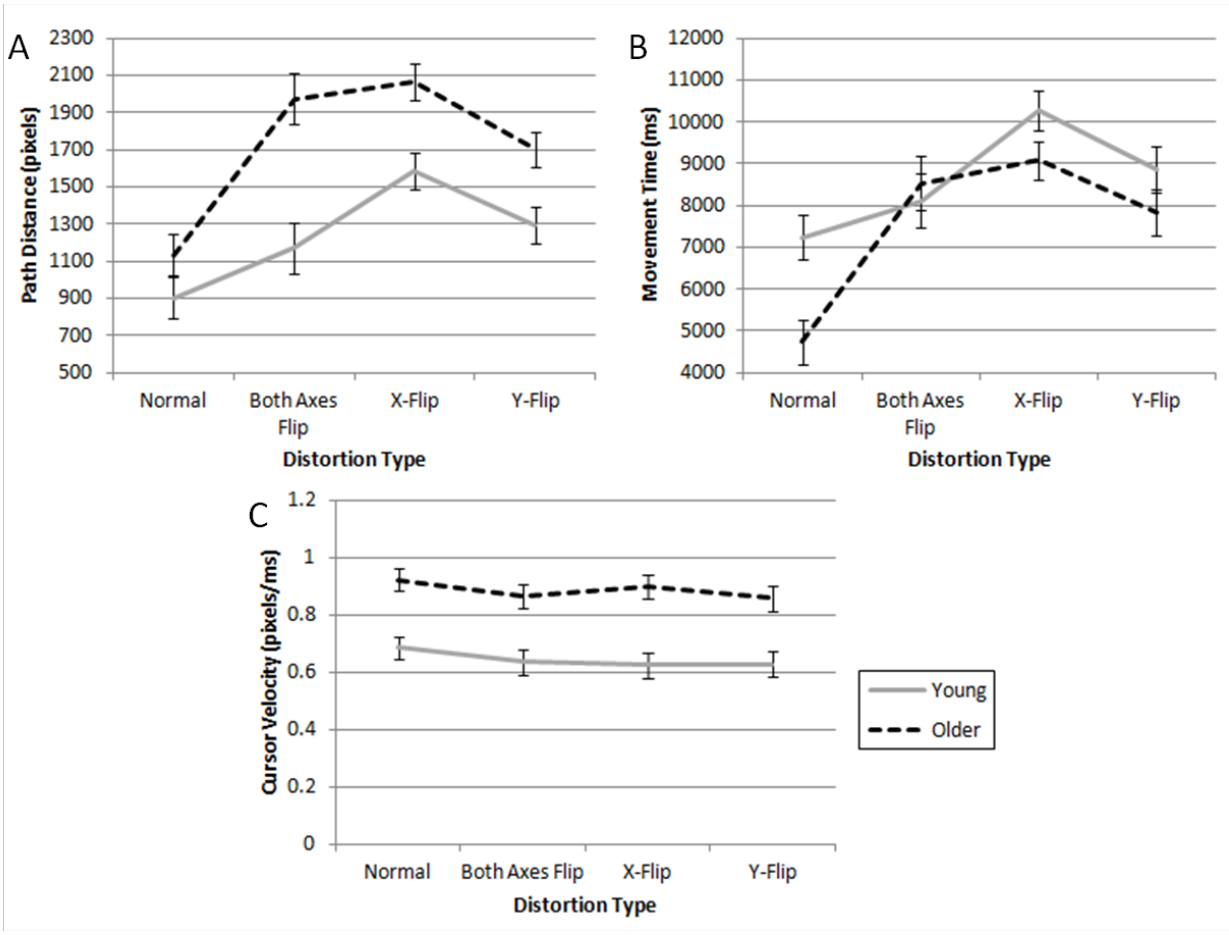

Figure 3 - 3. Mean path distance (A), movement time (B) and cursor velocity (C) observed during the four cursor conditions of the adaptation phase for both groups. A significant interaction was observed between distortion type and group for distance and time. Error bars represent the standard error of the mean.

Discussion

In conclusion, there is a distinction between the young and aging groups, with the aging group exhibiting difficulty adapting to the cursor distortions compared to the young group. The results of this pilot study provided the framework of a computer-based task for future functional MRI investigations of aging.

CHAPTER IV: NEURAL CORRELATES UNDERLYING VISUOMOTOR ADAPTATION IN TYPICALLY-FUNCTIONING ADULTS DURING A NOVEL DYNAMIC POINT-TO-POINT TASK: AN FMRI STUDY

Abstract

Visuomotor adaptation is the ability to integrate sensory information into meaningful motor outputs based on minute visual errors. Neuroimaging studies have focused on adaptation of movements toward stationary targets, and how neural activity changes during the motor learning process from the early phase to the late phase of adaptation. The present study applied functional MRI to reveal the underlying neural correlates of visuomotor adaptation during a novel dynamic-target task, and assesses the regions involved in early and late adaptation trials. Fifteen healthy, right-handed participants (mean = 28.7 ± 5.4 years, 11 males) completed a computer-based point-to-point task by controlling the movement of a cursor to a target while positioned in an MRI. Whole-brain fMRI data were acquired using conventional blood-oxygenation level-dependent (BOLD) imaging techniques. A random-effects general linear model (GLM) was used to determine areas that were significantly more activated during the distorted condition versus the normal condition, and between two consecutive fMRI scans. Frontal regions, areas that are involved in spatial processing and attention in response to movement errors, were activated during the early phase trials. Parietal and temporal regions along with the putamen, parahippocampal gyrus and middle occipital gyrus were activated during the late phase trials. This network may be associated with the perception and directional recoding and ongoing correction of hand movements. These findings suggest a shift from larger

activations in frontal regions in the early phase trials to more widespread regions in the late phase trials, which has been proposed previously in the literature. This information will aid in the development of future investigations of the effects of aging and neural injury on the phases of visuomotor adaptation.

Introduction

Visuomotor adaptation is the ability to integrate sensory information in order to successfully interact with our environment, allowing us to accurately correct movements in response to minute visual errors. This type of learning requires the modification of a well-learned sensorimotor transformation, thought to be based in part on neural networks of the motor control system (Cunningham, 1989), which are thought to predict the sensory inputs following an action (Wolpert & Kawato, 1998). These networks are updated through continuous visual feedback of minute distortions (Shadmehr & Mussa-Ivaldi, 1994), and are commonly studied using visuomotor adaptation tasks (Abeele & Bock, 2003; Anguera et al., 2007). These tasks typically involve movements toward targets under normal and distorted visual feedback to determine how the brain adapts to changes in mapping between visual and motor representations (Anguera et al., 2009; Seidler et al., 2006).

Previous neuroimaging research of visuomotor adaptation in humans using static-target tasks have identified contributions from the posterior parietal (PPC), primary motor (M1), primary visual (V1) and premotor (PM) cortices, as well as the supplementary motor area (SMA), thalamus, basal ganglia, putamen and cerebellum (Baugh et al., 2011; Clower, Hoffman, & Votaw, 1996; Danckert et al., 2008; Inoue et al., 2000; Luauté et al., 2009; R D Seidler, Noll,

& Thiers, 2004). Early in visuomotor adaptation, large errors in movement are made and strategies are utilized to enhance performance (Willingham, 1998). Initial contributions by the M1, PFC, parietal cortex, SMA, cerebellum, basal ganglia and striatum are thought to be involved in cognitive processing and motor execution (Anguera et al., 2007; Seidler et al., 2006). Later in visuomotor adaptation, where improvements in performance have incrementally slowed as movements have become more automatic, activation has been proposed to be involved with ongoing coding of movements (Anguera et al., 2009; Imamizu et al., 2000; Mazzoni & Krakauer, 2006; Miall et al., 2001).

This body of research has greatly contributed to our understanding of the behavioural and neural mechanisms underlying visuomotor adaptation. However, the aforementioned neuroimaging studies used a static target stimuli. Investigation of adaptation of movements toward a dynamic target would allow for identification of brain regions associated with adaptation using multi-directional movements, which may mimic more natural behaviours that are used in day-to-day life. Because behaviour during moving target tasks has received less attention, an examination of whether the regions involved with adaptation in a static environment are also engaged in a dynamic environment is necessary. Miall et al. (2001) used a manual tracking task where participants were instructed to follow continuously moving targets that were unexpectedly displaced to separate the cursor and target. Participants had to overcome this displacement by moving the cursor back to the target. In a motor versus rest fMRI analysis, the SMA, PPC, putamen, globus pallidus, and cerebellum were observed to be involved in the coordination of eye and hand movements and resultant development of an internal model, which has been proposed in other studies (Imamizu et al., 2000; Ingram et al., 2000). In another moving-target task, Diedrichsen et al. (2005) used a point-to-point task with a disappearing and

reappearing target to investigate adaptation behaviour. They found through positron emission tomography (PET), a functional neuroimaging technique, that the PPC, inferior parietal lobule (IPL), postcentral gyrus, and inferior temporal gyrus were involved with errors arising from the target moving to a new location during the reach. These two studies similarly conclude that a displaced target is not optimal for multidirectional visuomotor adaptation studies because the removal of visual information interrupts the use of a closed-loop motor control system (Imamizu et al. 2000). Investigation of how potential changes in the neural correlates evoked during a moving-target task occur between the phases of learning has not been seen previously in the literature, and would be a valuable addition to understanding visuomotor adaptation.

The present study tested the hypothesis that behavioural performance, as assessed by calculated mean cursor velocity and number of cursor reversals per trial, would improve through repetition of the task between two consecutive scans. FMRI was also applied to reveal the underlying neural correlates of the early and late phases of visuomotor adaptation associated with learning of a novel dynamic-target task. It was hypothesized that a moving target task that promotes multi-directional movements would elicit activation in the PPC, IPL, SMA, basal ganglia, cerebellum and frontal regions during the early phase of the study, and temporal, parietal and cerebellar regions during the late phase.

Method

Participants

All procedures were reviewed and approved by the Research Ethics Boards at the Thunder Bay Regional Health Sciences Centre (TBRHSC) and Lakehead University (see

Appendix A). Each participant provided written and informed consent, and was pre-screened for MRI safety prior to their participation in the study. Fifteen participants (mean age = 28.7 ± 5.4 years, 11 males) were recruited from the community and received $25 compensation for their participation. All participants had normal or corrected-to-normal vision, and no history of neurological impairment such as disease or injury. Participants were right-handed, as assessed by an eight-item shortened version of the Edinburgh handedness test, in order to ensure all group data was lateralized to the same side of the body for activity in the same side of the brain. Data from two participants were discarded due to alterations in timing of the stimulus presentation, and one participant's data were removed from analysis due to an incomplete dataset. Thus, analysis was performed on data from twelve participants (mean = 29.5 ± 5.6 years; 9 males).

Experimental Setup and Procedure

Following consent participants practiced ten trials of the computer-based target task to familiarize themselves with basic task requirements, at a desk on a laptop, prior to subsequent testing in the MRI scanner. Task presentation and response collection were accomplished with Presentation software (Neurobehavioural Systems Inc., Berkeley, California). The visuomotor adaptation task required participants to control the movement of a cursor from the center of the screen to a single target using an MRI-compatible trackball (Current Designs, Philadelphia, Pennsylvania) to a target moving in a counter clockwise circle (Figure 4 – 1). A visual fixation cross-hair was presented for a minimum of eight seconds before each target trial. Following the fixation, the next trial would appear. Targets appeared for a maximum of eight seconds beginning randomly in one of the four corners at equal distances from the center of the screen. Participants were asked to move the cursor to the target as quickly and accurately as possible.

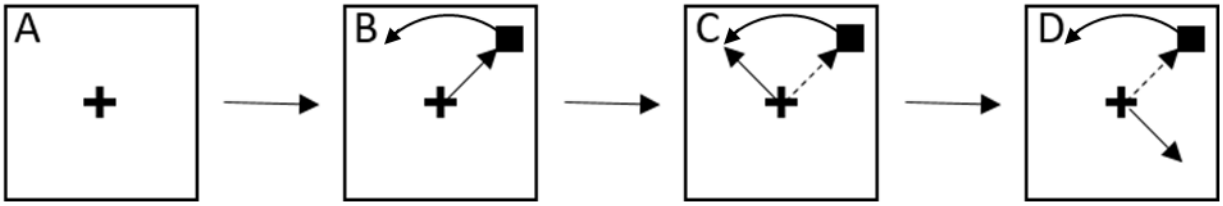

Figure 4 - 1. Visuomotor adaptation task schematic. The start position of the cursor was always the center of the screen (A), with targets appearing in one of the four corners (here with target in the top right quadrant). Participants were instructed to reach a target moving in a counter-clockwise circle with an MRI-compatible trackball as quickly and accurately as possible. During adaptation trials, feedback of the cursor was normal (B), flipped over the x-axis (C), or flipped over the y-axis (D). These conditions are shown with the intended movement as a dashed line and the feedback of movement as a solid line.

During the MRI, participants lay supine in a 3.0 Tesla Philips Achieva (Amsterdam, The Netherlands) with their head comfortably stabilized in an eight-channel Sensory Element (SENSE) head coil (Philips, Amsterdam, The Netherlands) with memory foam padding to prevent head movement. A ten-trial practice task was performed in the MRI to familiarize participants with use of the trackball in the scanner environment. Stimuli were presented from the laptop outside the MRI, through an MRI-compatible projection system onto a projection screen placed behind the participants' head in the bore of the scanner. Participants viewed the projection screen through a mirror attached to the head coil. The MRI-compatible trackball was secured onto a light-weight board and placed on the lap of the participant, allowing for comfortable control of the trackball with the participant's right hand. Data from practice tasks were not included in the analysis.

The difficulty of the task was controlled by the participants' performance, as the target had an adaptive velocity. The target was introduced in the first trial of the practice task with a velocity of 0.55 pixels/ms in the counter clockwise direction. If the participant caught the target in less than six seconds, a fixation appeared until eight seconds elapsed and the next target in the next trial moved 0.05 pixels/ms faster in the same direction. However, if the participant did not reach the target within eight seconds, the next trial began immediately and the target moved 0.05 pixels/ms slower in the next trial.

The velocity of the target movement from the last trial of the practice task was used to determine the starting velocity of the target during the first trial of the first fMRI scan. The target would then move slower or faster according to the timing of the participant's performance as it did during the practice task. Participants completed two runs of this task, one per fMRI scan, consisting of 32 trials within each run (Figure 4 - 2). Sixteen of these trials were presented with

normal cursor control in which the cursor movement directly mimicked the participant's intended movement, eight trials were distorted so that the cursor would move opposite laterally to the participant's intended movement (x-axis flip), and eight trials were distorted so that the cursor would move opposite vertically to the participants' intended movement (y-axis flip). The experimental design was separated into three phases: pre-adaptation, adaptation, and post-adaptation (Figure 4 - 2). The pre and post phases were presented with normal cursor control while the adaptation phase (24 trials) was presented with all three cursor conditions pseudo-randomly interleaved. To ensure unpredictability of the cursor distortion between trials during the adaptation phase, normal cursor control was included. The independent variables in the design are cursor condition (normal, x-flip, or y-flip), and the fMRI scan (1 or 2).

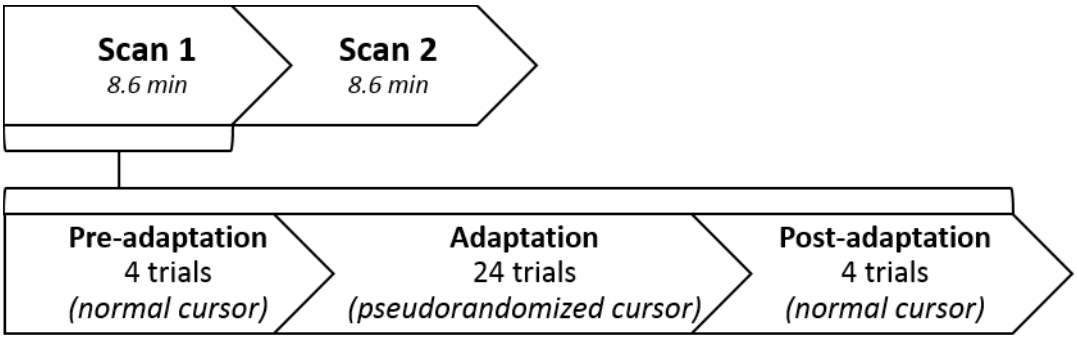

Figure 4 - 2. **Experimental design of the point-to-point task.** Two fMRI scans were acquired, in which participants performed the point-to-point task once per scan. Each fMRI scan lasted 8.6 minutes, with only a few seconds in between to set up the second scan. The task began and ended with normal cursor condition for 4 consecutive trials, in pre- and post- adaptation phases. During the 24 adaptation trials, 8 trials of normal, 8 trials of x-flip, and 8 trials of y-flip were pseudo randomly presented. Independent variables were the cursor condition and fMRI scan.

fMRI Acquisition Parameters

Once participants were positioned in the MRI scanner with their heads at iso-center, structural localizing images were acquired to allow image slice positioning. Two whole-brain T_2*-weighted functional images (one for each run of the task) were acquired consecutively using a single-shot two-dimensional blipped gradient echo-planar pulse sequence (30 slices, FOV = 256 x 256 mm, voxel size = 3.75 x 3.75 x 4.0 mm, TR/TE = 2000/60 ms) while participants performed the task. Each fMRI scan consisted of 258 volumes resulting in a total scan time of 8 minutes 36 seconds. High-resolution three-dimensional structural images were acquired either before or after the fMRI scans using a T_1-weighted gradient echo pulse sequence.

Data Analysis

Behavioural Data Analysis

The location of the cursor in regards to the x- and y- axes in pixels and elapsed time in milliseconds (ms) were recorded by the stimulus delivery software Presentation (Neurobehavioural Systems Inc., Berkeley, California) based on the refresh rate of the computer. The mean cursor velocity in pixels per millisecond, and the number of reversals in cursor direction were then calculated for each trial from the raw data using Excel (Microsoft Office, Redmond, Washington). The mean cursor velocity was calculated by dividing the path distance over the movement time for each frame then averaged for each trial. In contrast to previous studies, distance and time were not used as behavioural measures because each trial had a maximum time until the next fixation appeared. Thus, information about the distance and time for the cursor to intercept the target would not be obtainable. The number of reversals in cursor direction over both axes was calculated by first determining the vector of linear displacement for

each frame, then the sum of reversals in direction was calculated for each trial. The data for each participant and each fMRI scan were merged using SPSS Professional 21 (IBM, Chicago, Illinois) for statistical analysis.

To examine the change in participants' performance from the early adaptation trials (scan 1) to the late adaptation trials (scan 2), behavioural measures were statistically analyzed using a repeated-measures analysis of variance (ANOVA) with a 3 (cursor condition) x 2 (fMRI scan number) factorial design, performed in SPSS. Only the adaptation trials were used for this analysis, with eight trials of normal, x-flip, and y-flip conditions per scan (Figure 4 - 2). Statistical analysis was also performed to determine any significant relationships between the cursor conditions and scans for both behavioural measures and compared using a Bonferroni correction method to account for multiple comparisons. The main effects of the scan on the mean behavioural measures were then tested for statistical significance.

fMRI Data Analysis

Functional MRI data were preprocessed and analyzed using BrainVoyager QX v2.6 (BrainInnovation, Maastricht, The Netherlands). The first two volumes of each fMRI scan were discarded to allow the MRI signal to reach a steady state. Preprocessing included motion correction, high-pass temporal filtering, and slice-scan time correction. Functional MRI scans with greater than 2 mm of movement during the motion correction process were discarded and excluded from further analysis. Following preprocessing, the structural image was co-registered to the mean functional image, aligned to the anterior-posterior (AC-PC) line and spatially normalized to the Talairach standard space (Talairach & Tournoux, 1988). These images were

then spatially smoothed with a Gaussian kernel with a full width half maximum (FWHM) of 2 mm.

Design matrices were created based on the time intervals for and between each trial, which were calculated for each run for each participant using Excel (Microsoft Office) from the log data reported by Presentation software. Each time interval was assigned one of four conditions based on the stimulus presented: fixation, normal, x-flip, or y-flip. An estimate of the canonical haemodynamic response function was predicted using this design matrix (Figure 4 - 3).

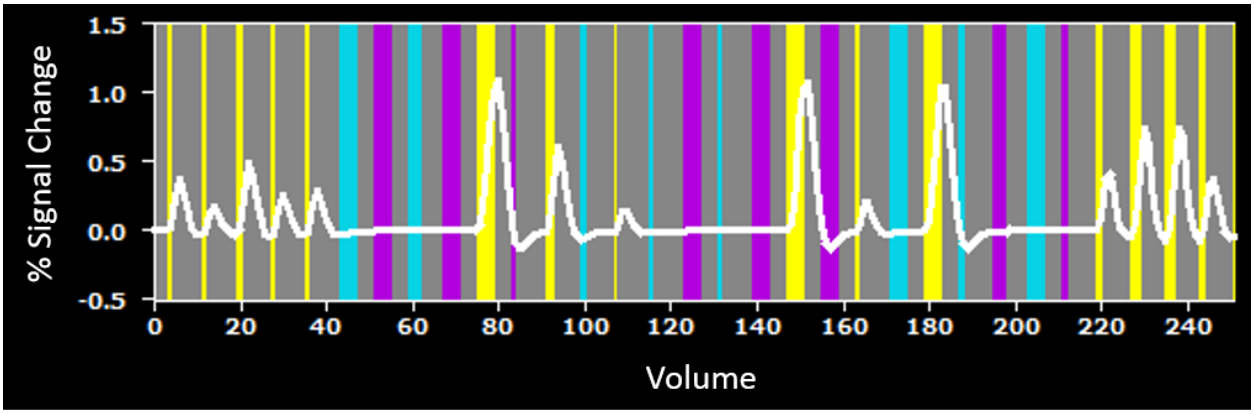

Figure 4 - 3. **Sample design matrix developed for a single participant.** The BOLD signal change is presented on the y-axis, and time (measured by the volume number) presented on the x-axis. The vertical coloured lines represent the trial condition: fixation (grey), normal (yellow), x-flip (purple), and y-flip (blue). The white line represents the hemodynamic response function for the normal cursor trials, where the signal increases at the onset of the condition. The individual timing of the design matrix for each scan of each participant was defined by the behavioural measures recorded by the task software.

Random-effects general linear models (GLMs) were performed at the single participant and group levels through BrainVoyager QX to determine regions significantly activated in association with visuomotor adaptation. A contrast was applied to each individual map to examine regions of statistically greater activation for the distorted cursor conditions (x- and y-flips) in comparison to the normal control condition. The control condition (normal) included all of the components of the visuomotor adaptation task except for the need to change movement based on distorted visual feedback. Thus, the subtraction of images from the control condition should reveal areas actively involved with visuomotor adaptation. A paired t-test was performed on all voxels across the brain for each participant. Voxels whose blood-oxygenation level-dependent (BOLD) signal change is significantly greater than that of surrounding voxels are considered activated. A statistical map of t-tests was developed at the single-participant level using a random-effects GLM to determine whether observed activation was statistically significant. A statistical map is a 3-dimensional representation of the brain in which clusters of activated voxels ($p_{corr}<0.05$) are shown in colour, and the rest of the brain is not depicted. A statistical map can be overlaid onto anatomical images to display which regions of the brain these activated clusters are located.

Images were separated into two groups for analysis based on the time of the trials: early adaptation trials (scan 1: N = 12) and late adaptation trials (scan 2: N = 12). The phase of adaptation trials (scan number) and type of trial (distorted or normal cursor) are the independent variables. The BOLD signal change is the dependent variable. Group-wise statistical maps were developed for both scans of the task again using the random-effects GLM with the statistically significant voxels colour-coded based on their p-value. Cluster threshold estimation was calculated for each cluster of voxels in each map ($p_{uncorr}<0.05$) to correct for multiple

comparisons and eliminate false positives. This correction method incorporates the observation that neighbouring voxels activate in clusters, and calculates the likelihood of obtaining different cluster sizes (Forman et al., 1995). To determine which activated brain regions that are significantly different between the early and late phases, a map of all 24 images was developed with a cluster threshold of 43 voxels. A paired t-test was then applied across voxels for the between-groups map. Significant areas of activation were then localized using the Talairach atlas.

Results

Behavioural Results

Measures of behavioural performance were used to assess learning: cursor velocity, and number of reversals.

Cursor Velocity

A repeated-measures ANOVA with a Bonferroni correction for multiple comparisons was conducted on the mean velocity of cursor movement, calculated in pixels per millisecond for each trial. As anticipated, due to the small number of trials in the task, there was no significant interaction between independent variables (cursor type and scan number). Likewise, no significant main effect of scan number was found. However, a significant main effect of cursor type was determined for cursor velocity ($F(2,44)=6.603$, $p_{corr}=0.003$, $d=1.096$; Figure 4 - 4). Pairwise comparisons revealed significant differences between normal and x-flip cursor conditions ($p_{corr}=0.033$, CI 95%[-0.92,-0.03], $d=2.063$), and x- and y-flip conditions ($p_{corr}=0.013$,

CI 95%[-0.10,0.98], d=1. 697). The pairwise comparisons between normal and y-flip conditions were not found to be significant.

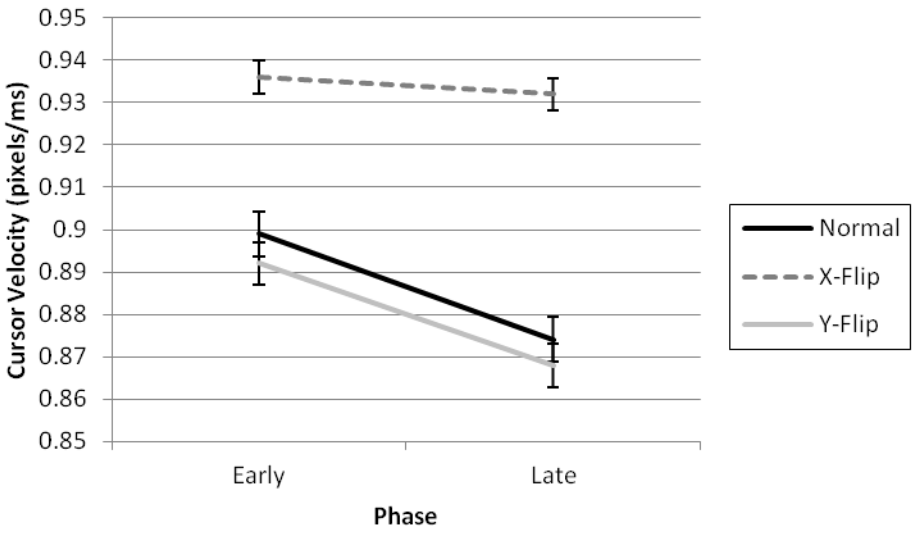

Figure 4 - 4. Mean cursor velocity between fMRI scans, separated by cursor condition. During x-flip conditions, participants had significantly quicker cursor velocities per trial than on trials with normal and y-flip conditions. Error bars represent the standard error of the mean.

Number of Reversals

A repeated-measures ANOVA with a Bonferroni correction for multiple comparisons was conducted on the number of times the cursor reversed direction in movement over both the x- and y-axes per trial, as calculated by the vector of linear displacement on each computer refresh. There was no significant interaction between independent variables (cursor type and scan number). Likewise, no significant main effect of scan number was found. However, a significant main effect of cursor type was determined for number of reversals ($F(2,44)=41.363$, $p_{corr}<0.001$, $d=2.742$; Figure 4 - 5). Pairwise comparisons revealed significant differences between normal and x-flip cursor conditions ($p_{corr}<0.001$, CI 95%[-11.935,-6.112], $d=8.069$), normal and y-flip conditions ($p_{corr}<0.001$, CI 95%[-8.384,-2.974], $d=5.621$) and x- and y-flip conditions ($p_{corr}=0.001$, CI 95%[-1.229,5.460], $d=2.539$).

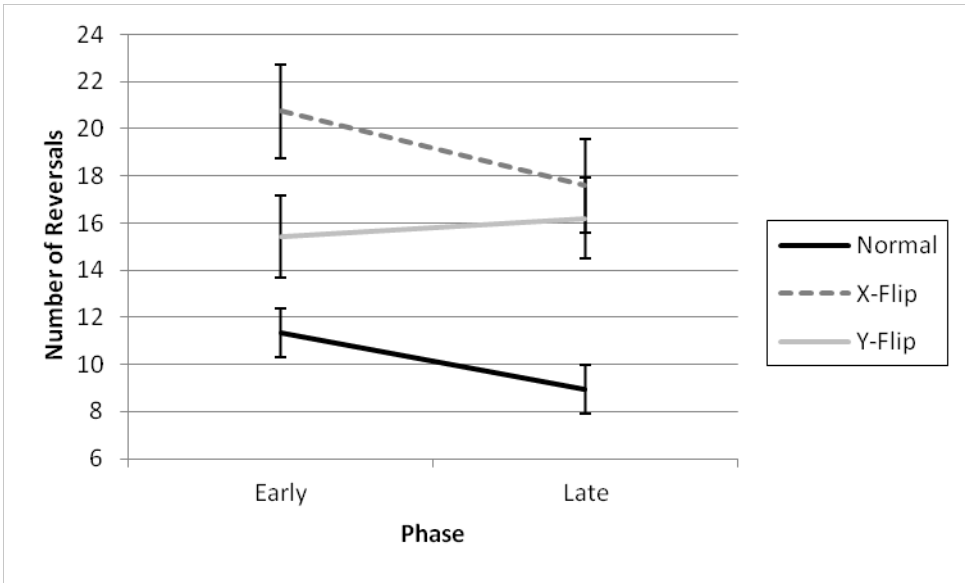

Figure 4 - 5. **Mean number of reversals between fMRI scans, separated by cursor condition.** During x- and y-flip conditions, participants had significantly greater number of reversals per trial than on trials with normal conditions, where no visuomotor transformation was required. Likewise, participants had a significantly greater number of reversals for the x-flip than the y-flip condition. Error bars represent the standard error of the mean.

Sample Movement Paths

Although not statistically analyzed, it was determined upon visual observation of a participant's path of cursor movement that larger errors and greater transformations were made in the first fMRI scan when compared to the second, suggesting a trend in the results. A greater number of trials is necessary to increase the power and determine significance of this trend. Sample spatial trajectories for a single participant are depicted in Figure 4 - 6 at the early stages of adaptation (scan 1) and late in adaptation (scan 2) for the x-axis flip condition. Adaptation to the flipped visual feedback is shown through less distorted trajectories employed in catching the targets in the second scan versus the first.

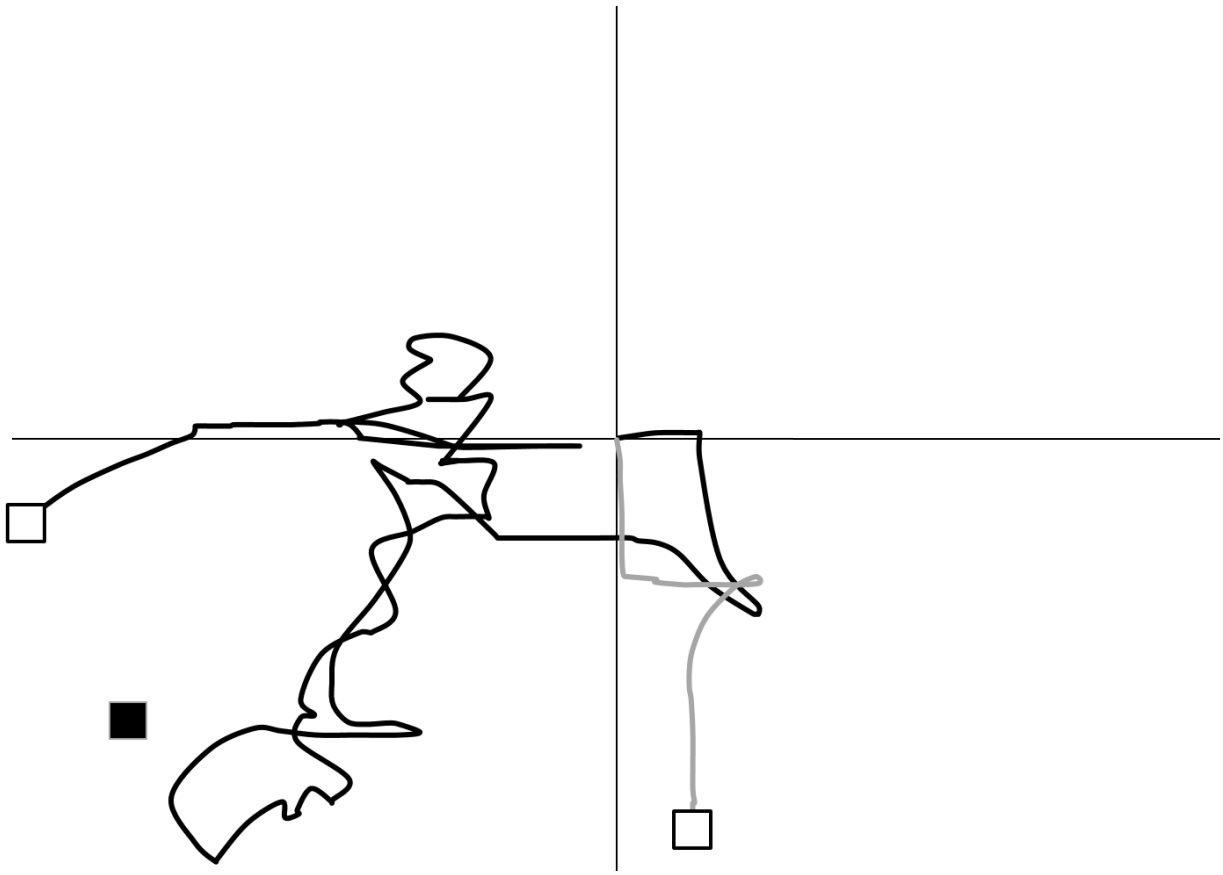

Figure 4 - 6. Example Scan path – Flip in X-Axis. When a visuomotor transformation over the x-axis was required, participants had greater difficulty adapting to the distortions in the first scan (solid black line) than the second scan (solid grey line). The black square represents the starting location of the target, which moved in a counter clockwise direction until the cursor reached the target. During these trials (trial 9 for scan 1 and trial 27 for scan 2), the target was caught before the eight seconds had passed. The white squares represent the end-location of the target, at the point of cursor-target interaction.

fMRI Results

A group-level random-effects GLM was performed ($p_{uncorr}<0.05$, 43 voxel cluster threshold) to determine significantly different regions used for distorted vs. normal conditions between the two scans. Brain regions with significantly greater BOLD signal change for the distorted conditions versus the normal conditions are presented in Table 4 - 1. Activation for the early adaptation trials was observed in right superior, middle and inferior frontal gyri (Figure 4 - 7), and superior temporal gyrus (Figure 4 - 8), as well as the left postcentral gyrus. Activation for the late adaptation trials was observed in the right superior temporal gyrus, putamen, parahippocampal gyrus, posterior parietal cortex and inferior parietal lobule as well as the left middle occipital gyrus. The inferior frontal gyrus was observed to be significantly activated over the whole task.

Table 4 - 1. **Anatomical location of regions that are differentially engaged in late adaptation trials compared to early trials when a visuomotor transformation is required (distorted vs. normal conditions).** Bolded regions signify greater activity in late trials compared to early. An asterisk (*) indicates regions activated in both early and late trials. BA = Brodmann's Area, R = Right, L = Left.

Side	Location	BA	Talairach Coordinates			*t*(46)	p_{corr}	Cluster Size (voxels)
			x	*y*	*z*			
Contrast: Early>Late								
R	Middle Frontal Gyrus	46	41	31	11	2.750	0.009	47
R	Inferior Frontal Gyrus	47	38	31	0	2.400	0.020	43
R	Superior Temporal Gyrus	38	35	19	-29	2.743	0.009	85
R	Superior Frontal Gyrus	8	15	13	34	2.887	0.006	52
L	Postcentral Gyrus	1	-52	-26	49	2.245	0.030	43
Contrast: Late>Early								
R	Superior Temporal Gyrus	22	50	-20	3	2.851	0.006	115
R	Superior Temporal Gyrus	22	44	-32	0	4.230	<0.001	279
R	*Inferior Frontal Gyrus	45	48	34	3	2.677	0.010	65
R	Parahippocampal Gyrus	20	41	-29	-9	2.451	0.018	44
R	Inferior Parietal Lobule	40	34	-29	26	2.525	0.015	43
R	Putamen	49	29	-17	12	2.770	0.008	137
R	Posterior Parietal Cortex	5	17	-38	42	2.442	0.019	135
L	Middle Occipital Gyrus	18	-25	-66	11	2.399	0.021	65

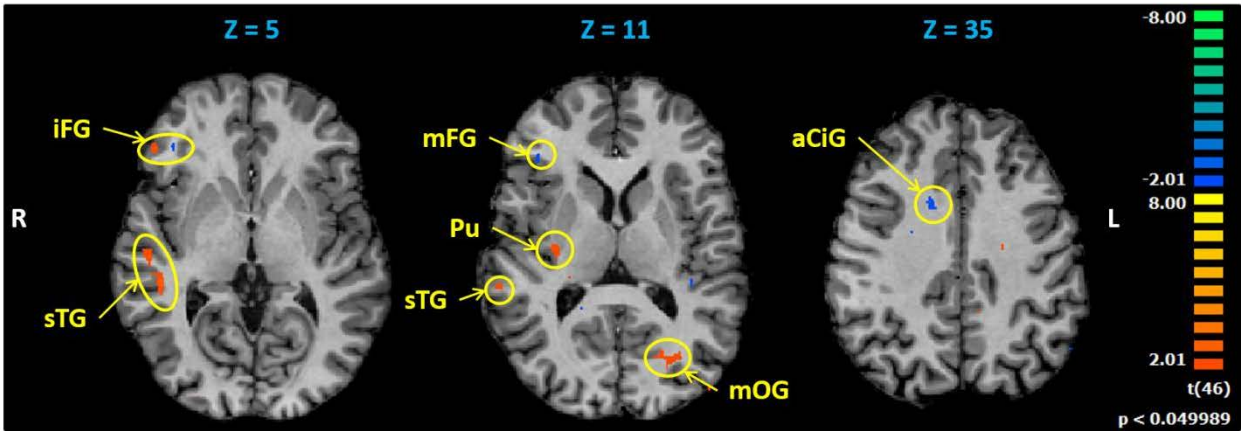

Figure 4 - 7. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal during the early and late trials of the task ($p<0.05$, 43 voxel cluster threshold). Axial slices (Talairach coordinate Z = 5, 11, 35) are presented in radiological orientation with the right side of the brain on the left side of the image. Colour scaling indicates confidence, with regions activated during the late phase in orange and during the early phase in blue. iFG = inferior frontal gyrus, sTG = superior temporal gyrus, mFG = middle frontal gyrus, Pu = putamen, mOG = middle occipital gyrus, aCiG = anterior cingulate gyrus.

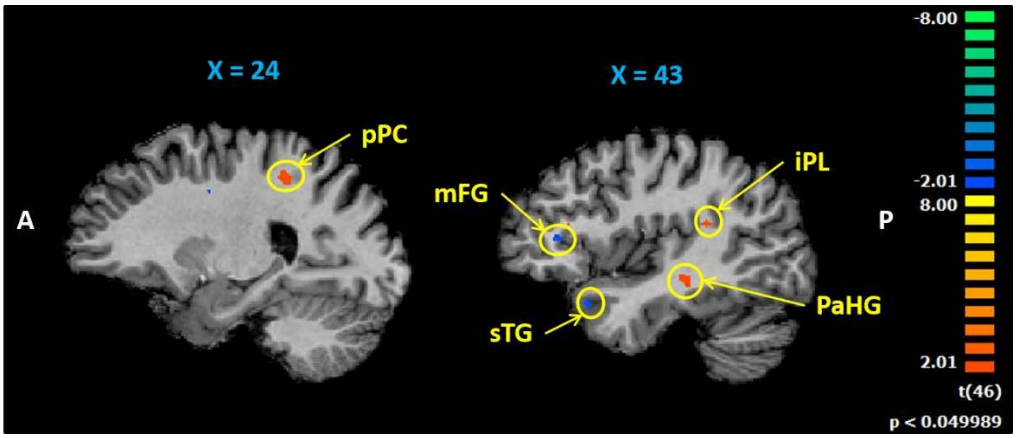

Figure 4 - 8. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal during the early and late trials of the task ($p<0.05$, 43 voxel cluster threshold). Sagittal slices (Talairach coordinate X = 24, 43) of the right hemisphere are presented with the anterior brain is shown on the left side of the image. Colour scaling indicates confidence, with regions activated during the late phase in orange and during the early phase in blue. pPC = posterior parietal cortex, mFG, middle frontal gyrus, sTG = superior temporal gyrus, iPL = inferior parietal lobule, PaHG = parahippocampal gyrus.

Discussion

In an effort to determine behavioural and neural contributions of visuomotor adaptation while interacting with dynamic stimuli, fMRI BOLD activation was measured while participants learned a visuomotor task involving a moving target. The present study tested the hypothesis that behavioural performance, as assessed by calculated mean cursor velocity and number of cursor reversals per trial, would improve through repetition of the task between two consecutive scans. Participants' behavioural performance measures across the experimental period demonstrated that they learned to adapt to distortions in visual feedback. This trend was evident through qualitative analysis of cursor trajectories. Observable, yet statistically insignificant, improvements in cursor velocity and number of reversals between fMRI scans 1 and 2 suggest the possibility that the task was not long enough to reach a stage of late learning. It is important to note that late adaptation was defined in this study relative to the parameters of the fMRI scans, since adaptation over hours or days may lead to more distinct improvements in behavioural performance than the adaptation over minutes presented here.

As anticipated, a significant main effect of cursor condition (normal, x-flip, and y-flip) was observed for both the cursor velocity and number of reversals, indicating significant differences in performance between distorted and normal cursor conditions overall. This phenomenon has been demonstrated in previous studies where an interruption in visual feedback, and subsequent miscalibration of an internal model, causes errors in movement execution (Diedrichsen et al. 2005; Shadmehr & Mussa-Ivaldi 1994). Adaptations to execution errors have been confirmed in studies using randomized distortions in visual feedback (Donchin et al. 2003), resulting in recalibration of an internal model. Interestingly, however, significant differences

were observed between the x- and y-flip conditions. The results for this difference were inconsistent: greater velocities, indicating high performance, and greater number of reversals, indicating low performance for the x-flip condition in comparison to the y-flip condition. This discrepancy could be due to a number of factors, such as participants overshooting the target more on the x-flip condition as a result of moving the cursor faster, requiring more reversals in movement direction. Again, a greater number of trials per condition are needed to properly assess the effects of visuomotor flips on performance.

The contrast applied to fMRI images (distorted cursor condition compared to normal cursor condition) identified the brain areas associated with visuomotor adaptation to dynamic stimuli. Participants were required to develop a new mapping between visual and motor space to compensate for distortions in visual feedback (x- and y-flip conditions), and to compensate for changes in end-movement location. This contrast identified activation during early adaptation trials in the superior, middle and inferior frontal gyri, and superior temporal gyrus, localized in the right hemisphere, and postcentral gyrus, localized in the left hemisphere. Similar to previous work done by Seidler et al. (2006), right lateralized activation in the superior, middle and inferior frontal gyri were observed early in visuomotor learning. It has been proposed that this network contributes to spatial processing involved in adaptation, particularly with working memory and attention (Anguera et al., 2007). Likewise, the frontal operculum (inferior frontal gyrus, BA 47), has been extensively implicated in motor control contributing to visuomotor transformations (Lacquaniti et al., 1997), especially in association with pointing toward memorized target locations.

The distorted versus normal condition contrast identified activation during late adaptation trials in the superior temporal gyrus, putamen, parahippocampal gyrus, posterior parietal cortex

and inferior parietal lobule, localized in the right hemisphere, and the left middle occipital gyrus. These results suggest increased and more widespread activation by the late phase of visuomotor adaptation. During visually-guided tasks with perception of motion of the hand (such as a cursor on a computer screen), a recent positron emission tomography (PET) study determined functional relationships with temporal, posterior parietal, and occipital regions during the movement tasks (Grafton, Fagg, Woods, & Arbib, 1996). Activation of regions within the parietal lobe have also been observed in other visuomotor adaptation studies of hand movements (Clower et al., 1996; Desmurget et al., 1999; Girgenrath, Bock, & Seitz, 2008; Inoue et al., 2000), and specifically in the inferior parietal lobule during prism adaptation (Luauté et al., 2009). Moreover, Desmurget et al. (1999) demonstrated that the PPC plays a critical role in correcting ongoing reaching movements and the inferior parietal lobule (BA 40) has previously been reported in tasks involving directional movements of the arm and visually-guided hand movements (Grafton et al., 1996; Lacquaniti et al., 1997). Activation in the parahippocampal gyrus has been hypothesized to be associated with recoding of visual targets in space when the location of an initial target has changed (Lacquaniti et al., 1997; Sakai et al., 1998). In contrast to the current study, the putamen has been engaged in previous visuomotor studies involving early stages of adaptation to dynamic stimuli (Diedrichsen et al., 2005), and is assumed to be involved in the switching of a movement goal. This finding suggests that a late phase of learning has not been reached with the short task in the present study.

Finally, the inferior frontal gyrus (BA 45) was observed to be significantly activated during the early and late adaptation trials. Frontal regions have been previously reported as active during similar tasks requiring visuomotor transformation to optical rotations (Inoue et al., 2000; Krakauer et al., 2004). These studies did not involve analysis of early and late adaptation,

but the presence of the inferior frontal gyrus in both phases suggest confirmation of its involvement throughout adaptation. It is important to note that early and late trials of adaptation in the current study were defined relative to a learning duration of approximately 17 minutes. Thus, it is unclear whether the current findings can generalize to visuomotor adaptation over multiple learning sessions consisting of hours or days. However, an exact time-point transition from early to late visuomotor adaptation is less likely than a gradual transition.

The contrast applied did not reveal activation in the primary motor, prefrontal, cerebellum, basal ganglia, globus pallidus, or inferior temporal gyrus which have been engaged during other visuomotor studies (Baugh et al., 2011; Clower et al., 1996; Danckert et al., 2008; Mazzoni & Krakauer, 2006; Seidler et al., 2006, 2004). Although not all activated regions previously identified in neuroimaging showed significant levels of activation in the current study, this could be attributed to the variability in size and location of activation observed in previous work. Likewise, since these analyses were made without comparison to the baseline trials (fixation condition), the results in previous studies may instead reflect basic motor execution processes, rather than adaptation.

It is important to acknowledge the asymmetry in sex representation (9 males, 3 females) within the sample of the present study. A typical pattern seen in behavioural studies of visuomotor adaptation is that women tend to be more accurate in their movements, taking longer to reach a target, whereas men tend to make quicker movements and have more errors (Boucher, Denis, & Landriault, 1991). However, investigation of how sex may affect the behavioural results of the current study would require equal representation from both sexes in future research. Previous studies have demonstrated sex-related differences in patterns of brain activity associated with visuomotor adaptation tasks (Gorbet & Sergio, 2007; Gorbet, Staines, & Sergio,

2004). Participants were instructed to move a cursor to a stationary target using a joystick under normal and rotated visual feedback. Greater activation was observed in the left primary sensory and motor cortices, right dorsolateral prefrontal cortex and superior parietal lobule in females. This may explain the lack of activation in the primary motor cortex in the current study, however, this observation occurred during the normal condition trials of the task and not the distorted (Gorbet & Sergio, 2007). Greater activation was observed bilaterally in the lateral sulcus (including the superior temporal gyrus) for males during distorted conditions. The present study observed right superior temporal gyrus activation during distorted trials of both the early and late trials. This activation may be due to the large male representation of the sample, though more exploration is necessary to determine whether this is a sex-related finding or an inherent task-related finding associated with the moving target.

It should be noted that this study is confounded by time, a factor that is independent of the effects of performance. In the present study, it could be argued that differential results between early and late trials may be due to any one of multiple events non-specific to the study, such as subject fatigue. However, this is likely not the case because the presentation of at least an 8-second fixation trial after each task trial would have allowed the participants to rest between trials. Additionally, participants' behavioural performance did not reveal signs of fatigue, which would be evident by decreased performance between scans. Another potential reason for the observed results could be that the participants in the study were young and normally perform well in these tasks to begin with. Perhaps the already well-performing participants reached a state of late learning prior to the second scan.

In summary, significant differences between normal and distorted cursor conditions indicate that visuomotor transformations are being utilized during x- and y-flip conditions.

Consistent with models of motor skill learning, early visuomotor adaptation engages the frontal regions. Based on this study, it is suggested that these regions are involved in spatial processing and attention in response to errors, which would seem appropriate as these skills are required throughout the task. Activation observed in regions for the late adaptation trials may be reflective of perception of motion and recoding of directional reaching hand movements. Together these findings hold promise for a dynamic point-to-point task to assess visuomotor function, however further investigation of a longer task with a greater number of trials is necessary to confirm at which point of learning a late stage is entered.

CHAPTER V: AGE-RELATED DIFFERENCES IN THE UNDERLYING NEURAL CORRELATES OF A NOVEL VISUOMOTOR ADAPTATION TASK

Abstract

Normal aging is associated with the recruitment of additional brain regions in older adults as compared to younger adults when performing motor tasks. A consistent finding from functional neuroimaging studies is an age-related increase and expansion in frontal activity and decline in occipitotemporal activity. This posterior-anterior shift in aging (PASA) theory has been typically attributed to functional compensation for cognitive decline. The present study uses functional magnetic resonance imaging (fMRI) to test the differences in neural correlates underlying the visuomotor transformations involved in a moving-target task between age groups. Forty four young, middle and older aged participants (mean = 48.8 ± 17.6, 25 males) were scanned while performing a dynamic point-to-point task. To induce distortions in visual feedback, the movement of the cursor was either normal or manipulated in one of two distortions: a flip over the x- or y-axis. Age-related differences in neural activity involved in the distorted versus normal cursor conditions were identified, and demonstrate increased activations in frontal, parietal, temporal and cingulate regions with advancing age. Premotor, supplementary motor, and primary motor regions were identified to have greater activity in the older age group likely associated with an increased need for motor preparation, while greater temporal and parietal regions associated with spatial attention and coordination were engaged in young and middle age groups, respectively. Supporting the hypothesis of PASA, observations of greater

frontal activity were associated with lesser temporal and parietal activity in older age groups when compared to younger.

Introduction

The ability to acquire new motor skills and adjust movements in response to errors enables us to maintain motor performance. Much research on this ability, visuomotor adaptation, has revealed that these behaviours degrade with advancing age (Pratt & Abrams, 1996; Pratt, Chasteen, & Abrams, 1994; Seidler, 2006; Seidler-Dobrin & Stelmach, 1998). The cause of this reduced learning is variable, with many factors, such as cognition, attention, perception and strategic implementation, relating to the decline in motor learning capability (Langan & Seidler, 2011; Ward & Frackowiak, 2003).

Studies evaluating the effects of aging on visuomotor adaptation performance have found mixed results, with some suggesting no decline (Roller et al., 2002), but the majority demonstrating that aging reduces a person's capacity to adapt movements in response to an error (Buch et al., 2003; Naccarato et al., 2006). Age-related variations of motor performance can be expected to be less pronounced for simpler motor tasks, for example when moving a cursor to a single, stationary target, than in more difficult tasks, for example if the target was moving. This is likely due to the need for more cognitive strategy to make successful movements in older adults than in younger adults.

In recent years, functional neuroimaging techniques have been used to measure brain activity while younger and older adults perform visuomotor tasks. From behavioural and neuroimaging studies, it can be assumed that the neural activity associated with simpler motor

tasks is similar between young and elderly (D'Esposito, Zarahn, Aguirre, & Rypma, 1999), and it is only on tasks of increasing complexity that age-related differences are detected (Vallesi, McIntosh, & Stuss, 2011). These differences are believed to reflect compensatory changes required for older individuals to perform the task at the same level as younger individuals (Hutchinson et al., 2002). The consequence of these age-related changes appears to be that task-related brain activity becomes more wide-spread and increased with advancing age (Heuninckx et al., 2008; Hutchinson et al., 2002; Naccarato et al., 2006; Van Impe, Coxon, Goble, Wenderoth, & Swinnen, 2011; Ward & Frackowiak, 2003). It has been suggested in this compensatory model that the greater activations observed may only be the case when a difference in motor performance between young and older age groups is negligible (Reuter-Lorenz, Stanczak, & Miller, 1999).

Patterns of increased brain activation in the premotor cortex (PMC), supplementary motor area (SMA), and dorso-lateral prefrontal cortex (DLPFC) reflect an increased need for task-related motor preparation and executive attention (Vallesi et al., 2011). Increased activation in frontal regions with age follow the "posterior-anterior shift with aging" or PASA theory (Roski et al., 2014). PASA was first reported by Grady et al. (1994) in a positron emission tomography (PET) study that investigated participants' perceptions of faces and locations. In both conditions, older adults showed weaker activity than younger adults in occipitotemporal regions but greater activity in frontal regions. They suggest that older adults recruited anterior regions to compensate for sensory processing deficits in posterior regions. More recently, PET and fMRI studies have identified the PASA pattern in attention (Cabeza et al., 2004; Madden et al., 2002), visual perception (Grady, 2000; Huettel, Singerman, & McCarthy, 2001), visuospatial

processing (Meulenbroek, Petersson, Voermans, Weber, & Fernández, 2004; Nyberg et al., 2003), and working memory (Cabeza et al., 2004).

The present study aimed to determine the age-related differences in neural activity underlying visuomotor adaptation during a novel dynamic point-to-point task. In younger age groups, activation is anticipated to be observed in the primary motor cortex, supplementary motor area (SMA), and premotor cortex along with the superior and inferior parietal lobules, the pre- and post-central gyri, the supramarginal gyrus, the superior and inferior frontal gyri, the precuneus, the cingulate gyrus, and the insular cortex. For middle-aged groups, the areas of activity are expected to be similar to the young age group, however the level of signal change may increase due to difficulty of the task. Elderly adults are expected to have decreased activity in posterior regions with increased activity in the premotor cortex, SMA and inferior parietal lobule.

Methods

Participants

All procedures were reviewed and approved by the Research Ethics Boards at the Thunder Bay Regional Health Sciences Centre (TBRHSC) and Lakehead University (see Appendix A). Each participant provided written and informed consent, and was pre-screened for MRI safety prior to their participation in the study. Forty-four healthy participants (age range = 22-80 years, mean = 48.8 ± 17.6, 25 males) were recruited from the community and received $25 compensation for their participation. All participants had normal or corrected-to-normal vision, and no history of neurological impairment such as disease or injury. Participants were right-

handed as assessed by an eight-item shortened version of the Edinburgh handedness test. Data from two participants were discarded due to alterations in stimulus presentation, one participant's data were lost due to technical difficulties, one participant's data were discarded because the task was terminated halfway, and three participants' data were removed from analysis due to excessive motion. Thus, analysis was performed on data from 37 participants (mean = 49.7 ± 17.5 years; 23 males). Images were separated into three groups for analysis based on participants' age: young (N = 12, range = 22-39 years, mean = 29.5 ± 5.6, 9 males); middle (N = 13, range = 41-58 years, mean = 49.4 ± 6.5, 8 males); and older (N = 12, range = 65-80 years, mean = 70.1 ± 4.5, 6 males).

Experimental Setup and Procedure

Following consent participants practiced ten trials of the computer-based target task to familiarize themselves with basic task requirements, at a desk on a laptop, prior to subsequent testing in the MRI scanner. Task presentation and response collection were accomplished with Presentation software (Neurobehavioural Systems Inc., Berkeley, California). During the visuomotor adaptation task, participants were required to control the movement of a cursor from the center of the screen to a single target using an MRI-compatible trackball (Current Designs, Philadelphia, Pennsylvania) to a target moving in a counter clockwise circle (Figure 5 - 1). A visual fixation cross-hair was presented for a minimum of eight seconds before each target trial. Following the fixation, the next trial would appear. Targets appeared for a maximum of eight seconds beginning randomly in one of the four corners at equal distances from the center of the screen. Participants were asked to move the cursor to the target as quickly and accurately as possible.

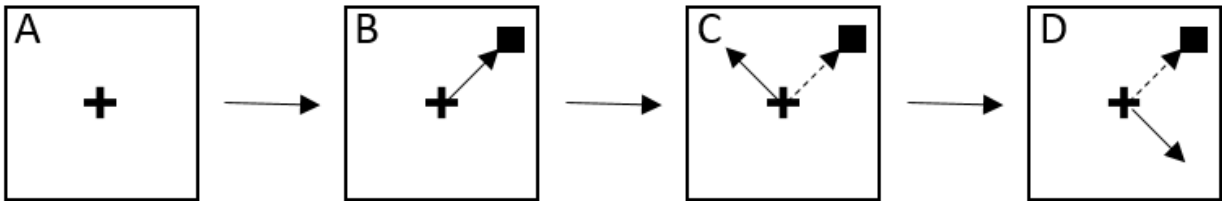

Figure 5 - 1. Visuomotor adaptation task schematic. The start position of the cursor was always the center of the screen (A), with targets appearing in one of the four corners (here with target in the top right quadrant). Participants were instructed to reach a target moving in a counter-clockwise circle with an MRI-compatible trackball as quickly and accurately as possible. During adaptation trials, feedback of the cursor was normal (B), flipped over the x-axis (C), or flipped over the y-axis (D). These conditions are shown with the intended movement as a dashed line and the feedback of movement as a solid line.

During the MRI, participants lay supine in a 3.0 Tesla Philips Achieva (Amsterdam, The Netherlands) with their head comfortably stabilized in an eight-channel Sensory Element (SENSE) head coil (Philips, Amsterdam, The Netherlands) with memory foam padding to prevent head movement. A ten-trial practice task was performed in the MRI to familiarize participants with use of the trackball in the scanner environment. Stimuli were presented from the laptop outside the MRI, through an MRI-compatible projection system onto a projection screen placed behind the participants' head in the bore of the scanner. Participants viewed the projection screen through a mirror attached to the head coil. The MRI-compatible trackball was secured onto a light-weight board and placed on the lap of the participant, allowing for comfortable control of the trackball with the participant's right hand. Data from practice tasks were not included in the analysis.

The difficulty of the task was controlled by the participants' performance, as the target had an adaptive velocity. The target was introduced in the first trial of the practice task with a velocity of 0.55 pixels/ms in the counter clockwise direction. If the participant caught the target in less than six seconds, a fixation appeared until eight seconds elapsed and the next target in the next trial moved 0.05 pixels/ms faster in the same direction. However, if the participant did not reach the target within eight seconds, the next trial began immediately and the target moved 0.05 pixels/ms slower in the next trial.

The velocity of the target movement from the last trial of the practice task was used to determine the starting velocity of the target during the first trial of the first fMRI scan. The target would then move slower or faster according to the timing of the participant's performance as it did during the practice task. Participants completed two runs of this task, one per fMRI scan, consisting of 32 trials within each run (Figure 4 - 2). Sixteen of these trials were presented with

normal cursor control in which the cursor movement directly mimicked the participant's intended movement, eight trials were distorted so that the cursor would move opposite laterally to the participant's intended movement (x-axis flip), and eight trials were distorted so that the cursor would move opposite vertically to the participants' intended movement (y-axis flip). The experimental design was separated into three phases: pre-adaptation, adaptation, and post-adaptation (Figure 5 - 2). The pre and post phases were presented with normal cursor control while the adaptation phase (24 trials) was presented with all three cursor conditions pseudo-randomized. The independent variables in the design are cursor condition (normal, x-flip, or y-flip), and the fMRI scan (1 or 2).

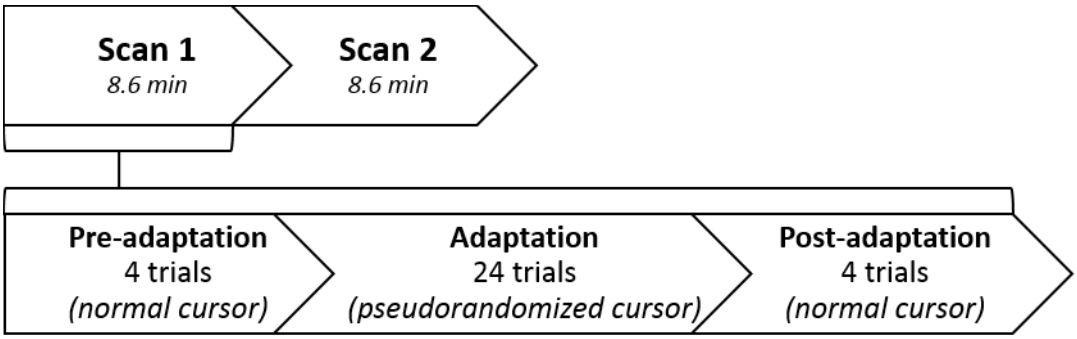

Figure 5 - 2. Experimental design of the point-to-point task. Two fMRI scans were acquired, in which participants performed the point-to-point task once per scan. Each fMRI scan lasted 8.6 minutes, with only a few seconds in between to set up the second scan. The task began and ended with normal cursor condition for 4 consecutive trials, in pre- and post- adaptation phases. During the 24 adaptation trials, 8 trials of normal, 8 trials of x-flip, and 8 trials of y-flip were pseudo randomly presented. Independent variables were the cursor condition and fMRI scan.

fMRI Acquisition Parameters

Once participants were positioned in the MRI scanner with their heads at iso-center, structural localizing images were acquired to allow image slice positioning. Two whole-brain T_2*-weighted functional images (one for each run of the task) were acquired consecutively using a single-shot two-dimensional blipped gradient echo-planar pulse sequence (30 slices, FOV = 256 x 256 mm, voxel size = 3.75 x 3.75 x 4.0 mm, TR/TE = 2000/60 ms) while participants performed the task. Each fMRI scan consisted of 258 volumes resulting in a total scan time of 8 minutes 36 seconds. High-resolution three-dimensional structural images were acquired either before or after the fMRI scans using a T_1-weighted gradient echo pulse sequence.

Data Analysis

Functional MRI data were preprocessed and analyzed using BrainVoyager QX v2.6 (BrainInnovation, Maastricht, The Netherlands). The first two volumes of each fMRI scan were discarded to allow the MRI signal to reach a steady state. Preprocessing included motion correction, high-pass temporal filtering, and slice-scan time correction. Functional MRI scans with greater than 2 mm of movement during the motion correction process were discarded and excluded from further analysis. Following preprocessing, the structural image was co-registered to the mean functional image, aligned to the anterior-posterior (AC-PC) line and spatially normalized to the Talairach standard space (Talairach & Tournoux, 1988). These images were then spatially smoothed with a Gaussian kernel with a full width half maximum (FWHM) of 2 mm.

Design matrices were created based on the time intervals for and between each trial, which were calculated for each run for each participant using Excel (Microsoft Office) from the log data reported by Presentation software. Each time interval was assigned one of four conditions based on the stimulus presented: fixation, normal, x-flip, or y-flip. An estimate of the canonical haemodynamic response function was predicted using this design matrix (Figure 5 - 3).

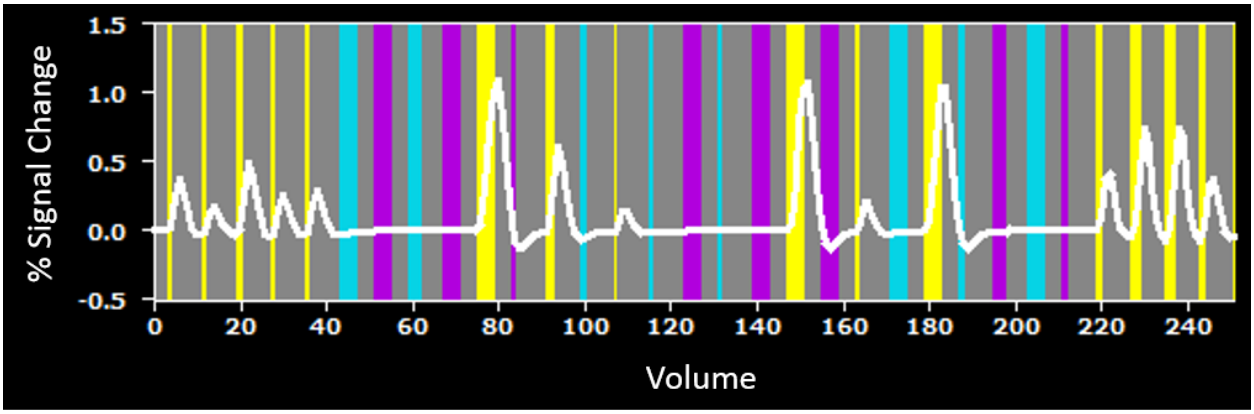

Figure 5 - 3. **Sample design matrix developed for a single participant.** The BOLD signal change is presented on the y-axis, and time (measured by the volume number) presented on the x-axis. The vertical coloured lines represent the trial condition: fixation (grey), normal (yellow), x-flip (purple), and y-flip (blue). The white line represents the hemodynamic response function for the normal cursor trials, where the signal increases at the onset of the condition. The individual timing of the design matrix for each scan of each participant was defined by the behavioural measures recorded by the task software.

Random-effects general linear models (GLMs) were performed at the single participant and group levels through BrainVoyager QX to determine regions significantly activated in association with visuomotor adaptation. A contrast was applied to each individual map to examine regions of statistically greater activation for the distorted cursor conditions (x- and y-flips) in comparison to the normal control condition. The control condition (normal) included all of the components of the visuomotor adaptation task except for the need to change movement based on distorted visual feedback. Thus, the subtraction of images from the control condition should reveal areas actively involved with visuomotor adaptation. A paired t-test was performed on all voxels across the brain for each participant. Voxels whose blood-oxygenation level-dependent (BOLD) signal change is significantly greater than that of surrounding voxels are considered activated. A statistical map of t-tests was developed at the single-participant level using a random-effects GLM to determine whether observed activation was statistically significant. A statistical map is a 3-dimensional representation of the brain in which clusters of activated voxels ($p_{corr}<0.05$) are shown in colour, and the rest of the brain is not depicted. A statistical map can be overlaid onto anatomical images to display which regions of the brain these activated clusters are located.

Images were separated into three groups for analysis based on participants' age: young (N = 12, range = 22-39 years, mean = 29.5 ± 5.6, 9 males); middle (N = 13, range = 41-58 years, mean = 49.4 ± 6.5, 8 males); and older (N = 12, range = 65-80 years, mean = 70.1 ± 4.5, 6 males). Age and type of trial (distorted or normal cursor) are the independent variables. The BOLD signal change is the dependent variable. Group-wise statistical maps were constructed using a random-effects GLM with the statistically significant voxels colour-coded based on their p-value. Cluster threshold estimation was calculated for each cluster of voxels in each map

($p_{uncorr}<0.05$) to correct for multiple comparisons and eliminate false positives. To analyze the regions of activity that are significantly different between the young and middle age groups, a map of all 25 images was developed with a cluster threshold of 41 voxels. A random-effects GLM was then applied across voxels for the between-groups map. This analysis was repeated to compare the middle and older age groups (25 images, 47 voxel cluster threshold) and the young and older age groups (24 images, 46 voxel cluster threshold). Significant areas of activation were then localized using the Talairach atlas.

Results

Young vs. Middle-Aged

A group-level random-effects GLM of each voxel was performed between young and middle-aged groups ($p_{uncorr}<0.05$, 41 voxel cluster threshold) to determine significantly different regions used for distorted vs. normal conditions. Brain regions with significantly greater BOLD signal change are presented in Table 5 - 1. Bilateral activation for the young age group was observed in the inferior frontal gyrus (Figure 5 - 4). Activation was also observed in the right superior and middle temporal gyri, fusiform gyrus, posterior parietal cortex (Figure 5 - 5), as well as the left hippocampus. Bilateral activation for the middle age group was observed in the anterior cerebellum. In addition, the right superior and middle frontal gyri, and cuneus as well as the left putamen, superior and transverse temporal gyri, and inferior parietal lobule.

Table 5 - 1. **Anatomical location of regions that are differentially engaged in young and middle age groups when a visuomotor transformation is required (distorted vs. normal conditions).** BA = Brodmann's Area, YA = young age group, MA = middle age group..

Side	Anatomical Location	BA	Talairach Coordinates			*t*(48)	p_{corr}	Cluster Size (voxels)
			x	*y*	*z*			
Contrast: YA>MA								
Right	Superior Temporal Gyrus	22	50	-17	3	2.365	0.022	46
	Fusiform Gyrus	37	53	-44	-13	3.379	0.001	89
	Inferior Frontal Gyrus	45	48	34	6	2.601	0.012	50
	Middle Temporal Gyrus	21	44	-38	3	2.566	0.013	78
	Superior Temporal Gyrus	38	38	10	-9	2.917	0.005	96
	Posterior Parietal Cortex	5	24	-38	45	2.472	0.017	62
Left	Hippocampus	54	-28	-29	-6	2.827	0.007	47
	Inferior Frontal Gyrus	45	-48	34	3	2.510	0.016	69
Contrast: MA>YA								
Right	Middle Frontal Gyrus	46	41	31	11	2.733	0.009	114
	Superior Frontal Gyrus	8	19	25	32	3.022	0.004	66
	Cuneus	17	11	-59	12	2.930	0.005	90
	Anterior Cerebellum		2	-44	-12	2.334	0.023	57
Left	Anterior Cerebellum		-7	-35	-30	3.797	<0.001	158
	Putamen	49	-22	7	10	2.748	0.008	42
	Superior Temporal Gyrus	22	-49	-2	0	2.933	0.005	82
	Inferior Parietal Lobule	40	-55	-38	27	2.501	0.016	56
	Transverse Temporal Gyrus	41	-61	-11	9	2.929	0.005	126

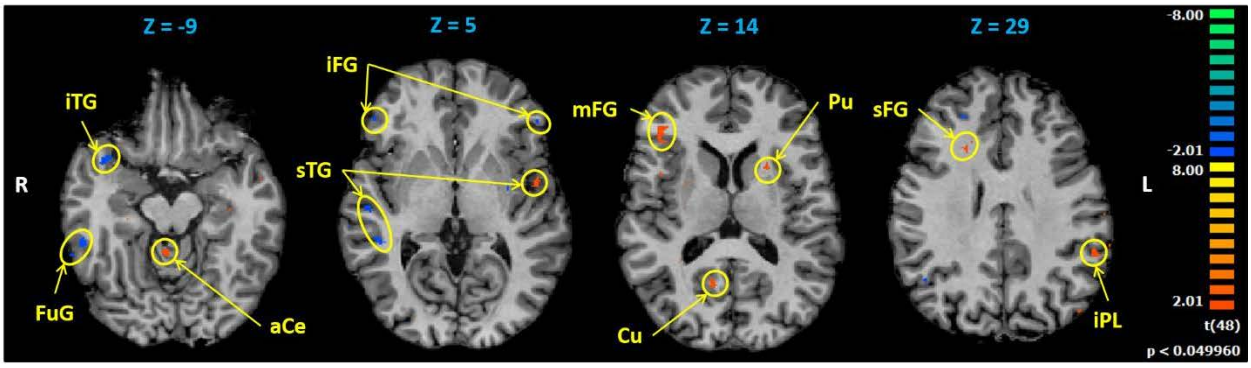

Figure 5 - 4. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for young and middle age groups ($p<0.05$, 41 voxel cluster threshold). Axial slices (Talairach coordinate Z = -9, 5, 14, 29) are presented in radiological orientation with the right side of the brain on the left side of the image. Colour scaling indicates confidence, with regions activated for the middle age group in orange and the young age group in blue. iTG = inferior temporal gyrus, FuG = fusiform gyrus, iFG = inferior frontal gyrus, sTG = superior temporal gyrus, mFG = middle frontal gyrus, Cu = cuneus, Pu = putamen, sFG = superior frontal gyrus, iPL = inferior parietal lobule.

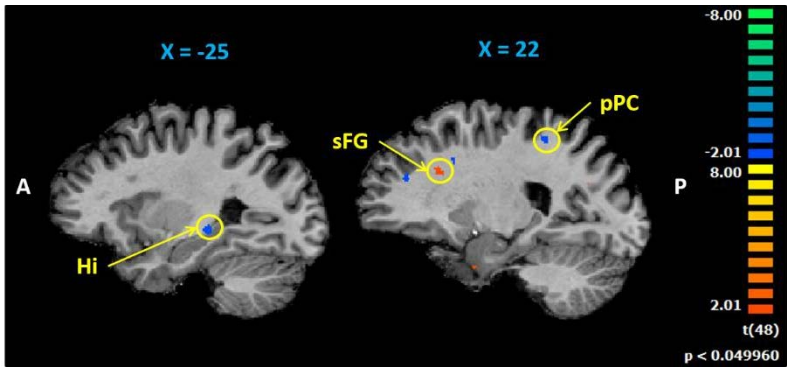

Figure 5 - 5. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for young and middle age groups ($p<0.05$, 41 voxel cluster threshold). Sagittal slices (Talairach coordinate X = -25, 22) are presented in the left (left image) and right (right image) hemispheres of the brain. The anterior brain is shown on the left side of the image. Colour scaling indicates confidence, with regions activated for the middle age group in orange and the young age group in blue. Hi = hippocampus, sFG = superior frontal gyrus, pPC = posterior parietal cortex.

Middle vs. Older Aged

A group-level random-effects GLM of each voxel was performed between middle and older aged groups ($p_{uncorr}<0.05$, 47 voxel cluster threshold) to determine significantly different regions used for distorted vs. normal conditions. Brain regions with significantly greater BOLD signal change are presented in Table 5 - 2. Bilateral activation was observed for the middle age group in the posterior cingulate gyrus (Figure 5 - 6). Right inferior parietal lobule and inferior frontal gyrus, as well as the left inferior temporal gyrus were also observed (Figure 5 - 7). Bilateral activation for the older age group was observed in the fusiform gyrus, inferior temporal gyrus and middle frontal gyrus. In addition, the right superior, medial and inferior frontal gyri, middle temporal and postcentral gyri and anterior cerebellum, as well as the left precuneus, anterior cingulate gyrus, lingual gyrus, posterior cerebellum, and precentral gyrus were observed.

Table 5 - 2. **Anatomical location of regions that are differentially engaged in middle and older age groups when a visuomotor transformation is required (distorted vs. normal conditions).** BA = Brodmann's Area, MA = middle age group, OA = older age group.

Side	Anatomical Location	BA	Talairach Coordinates			*t*(48)	p_{corr}	Cluster Size (voxels)
			x	*y*	*z*			
Contrast: MA>OA								
Right	Inferior Parietal Lobule	40	41	-32	21	3.174	0.003	105
	Inferior Frontal Gyrus	46	38	34	12	2.977	0.005	84
	Posterior Cingulate Gyrus	23	11	-50	24	2.548	0.014	56
Left	Posterior Cingulate Gyrus	30	-10	-41	17	2.643	0.011	69
	Posterior Cingulate Gyrus	30	-22	-50	18	2.661	0.011	227
	Inferior Temporal Gyrus	38	-40	-2	-33	2.721	0.009	50
Contrast: OA>MA								
Right	Postcentral Gyrus	1	60	-11	24	2.745	0.009	167
	Fusiform Gyrus	37	59	-50	-12	3.013	0.004	943
	Inferior Temporal Gyrus	21	60	-8	-12	3.001	0.004	121
	Middle Frontal Gyrus	6	41	1	45	2.937	0.005	639
	Inferior Frontal Gyrus	6	57	4	27	2.235	0.030	82
	Inferior Frontal Gyrus	45	53	23	12	3.487	0.001	133
	Middle Temporal Gyrus	21	56	-17	-11	2.606	0.012	72
	Middle Frontal Gyrus	46	44	32	18	2.778	0.008	108
	Middle Frontal Gyrus	9	35	28	24	2.677	0.010	50
	Anterior Cerebellum		32	-47	-21	2.625	0.012	94
	Superior Frontal Gyrus	9	14	52	27	2.660	0.011	408
	Medial Frontal Gyrus	8	12	25	45	2.793	0.008	103
	Middle Frontal Gyrus	10	15	58	21	2.933	0.005	56
Left	Lingual Gyrus	18	-4	-83	-6	2.764	0.008	117
	Precuneus	31	-10	-62	27	2.444	0.018	65
	Anterior Cingulate Gyrus	32	-13	42	6	2.718	0.009	100
	Middle Frontal Gyrus	9	-22	31	33	2.913	0.005	70
	Posterior Cerebellum		-22	-68	-33	3.197	0.003	142
	Precentral Gyrus	4	-43	-8	30	2.888	0.006	103
	Inferior Temporal Gyrus	21	-58	-32	-15	2.275	0.027	51
	Fusiform Gyrus	20	-56	-14	-27	2.418	0.020	69

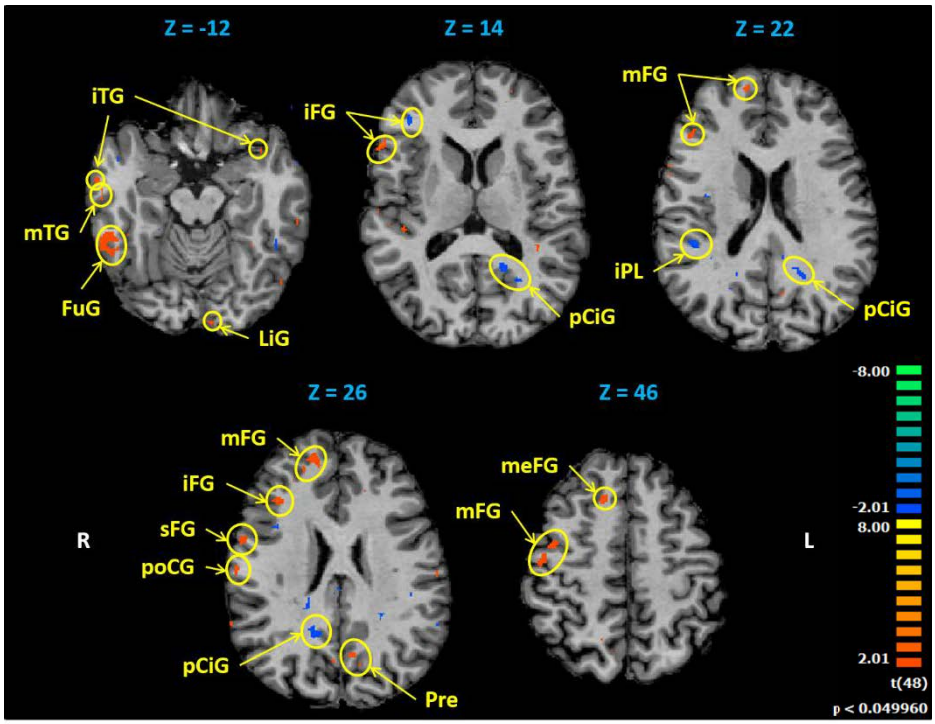

Figure 5 - 6. **Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for middle and older age groups** ($p<0.05$, 47 voxel cluster threshold). Axial slices (Talairach coordinate Z = -12, 14, 22, 26, 46) are presented in radiological orientation with the right side of the brain on the left side of the image. Colour scaling indicates confidence, with regions activated for the older age group in orange and the middle age group in blue. iTG = inferior temporal gyrus, mTG = middle temporal gyrus, FuG = fusiform gyrus, LiG = lingual gyrus, iFG = inferior frontal gyrus, oCiG = posterior cingulate gyrus, iPL = inferior parietal lobule, sFG = superior frontal gyrus, poCG = postcentral gyrus, Pre = precuneus, meFG = medial frontal gyrus.

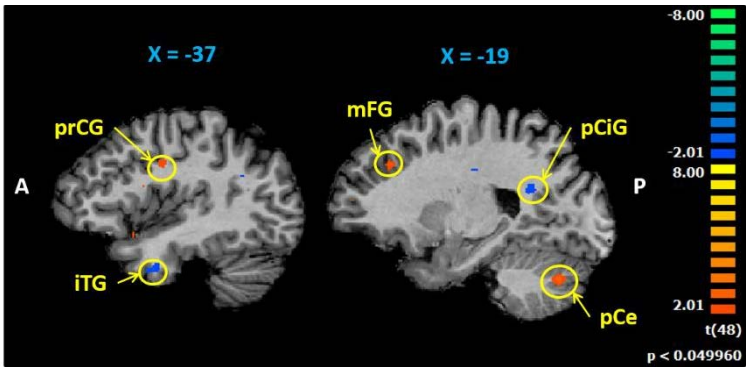

Figure 5 - 7. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for middle and older age groups ($p<0.05$, 47 voxel cluster threshold). Sagittal slices (Talairach coordinate X = -37, -19) are presented in the left hemisphere of the brain. The anterior brain is shown on the left side of the image. Colour scaling indicates confidence, with regions activated for the older age group in orange and the middle age group in blue. prCG = precentral gyrus, iTG = inferior temporal gyrus, mFG = middle frontal gyrus, pCiG = posterior cingulate gyrus, pCe = posterior cerebellum.

Young vs. Older Aged

A group-level random-effects GLM was performed between young and middle-aged groups ($p_{uncorr}<0.01$, 45 voxel cluster threshold) to determine significantly different regions for distorted vs. normal conditions. Brain regions with significantly greater BOLD signal change are presented in Table 5 - 3. Activation for the young age group was observed in the right angular gyrus and medial globus pallidus (Figure 5 - 8), as well as the left superior temporal gyrus. Bilateral activation for the older age group was observed in the medial frontal, postcentral, lingual, superior temporal and anterior cingulate gyri as well as the inferior parietal lobule (Figure 5 - 9). Activation was also observed in the right inferior frontal gyrus and caudate, and left middle frontal, precentral and inferior temporal gyri as well as the posterior parietal cortex, hippocampus, and anterior cerebellum.

Table 5 - 3. **Anatomical location of regions that are differentially engaged in young and older age groups when a visuomotor transformation is required (distorted vs. normal conditions).** BA = Brodmann's Area, YA = young age group, OA = older age group.

Side	Anatomical Location	BA	Talairach Coordinates			*t*(46)	p_{corr}	Cluster Size (voxels)
			x	*y*	*z*			
Contrast: YA>OA								
Right	Angular Gyrus	39	38	-35	24	2.622	0.011	113
	Medial Globus Pallidus	51	20	-8	1	2.694	0.010	98
Left	Superior Temporal Gyrus	41	-58	-11	9	3.015	0.004	49
Contrast: OA>YA								
Right	Inferior Parietal Lobule	40	63	-44	24	2.414	0.020	56
	Postcentral Gyrus	1	53	-20	42	3.864	<0.001	892
	Inferior Frontal Gyrus	6	57	4	24	2.800	0.008	68
	Superior Temporal Gyrus	22	53	5	6	2.612	0.012	50
	Inferior Frontal Gyrus	47	38	31	-3	3.251	0.002	73
	Superior Temporal Gyrus	38	39	19	-30	2.491	0.017	64
	Inferior Frontal Gyrus	47	29	19	-13	3.012	0.004	157
	Caudate Tail		29	-32	12	3.410	0.001	187
	Caudate	48	20	19	24	3.128	0.003	152
	Medial Frontal Gyrus	8	11	25	42	2.803	0.007	57
	Lingual Gyrus	18	8	-77	0	2.429	0.019	66
	Anterior Cingulate Gyrus	24	2	16	24	2.590	0.013	49
Left	Anterior Cerebellum		-7	-35	-30	3.392	0.001	173
	Anterior Cingulate Gyrus	32	-13	34	20	3.185	0.003	193
	Lingual Gyrus	18	-22	-80	0	2.626	0.012	73
	Medial Frontal Gyrus	9	-25	34	24	3.098	0.003	148
	Posterior Parietal Cortex	7	-34	-50	61	2.531	0.015	72
	Hippocampus	54	-35	-20	-9	2.507	0.016	64
	Superior Temporal Gyrus	38	-43	4	-15	2.296	0.026	51
	Middle Frontal Gyrus	8	-46	13	39	2.941	0.005	60
	Postcentral Gyrus	1	-53	-29	48	2.503	0.016	185
	Superior Temporal Gyrus	22	-49	1	-3	2.523	0.015	133
	Postcentral Gyrus	1	-58	-20	24	2.887	0.006	282
	Inferior Temporal Gyrus	21	-58	-32	-15	3.036	0.004	205
	Inferior Parietal Lobule	40	-61	-38	36	2.709	0.010	68
	Precentral Gyrus	6	-51	-2	21	2.777	0.008	78

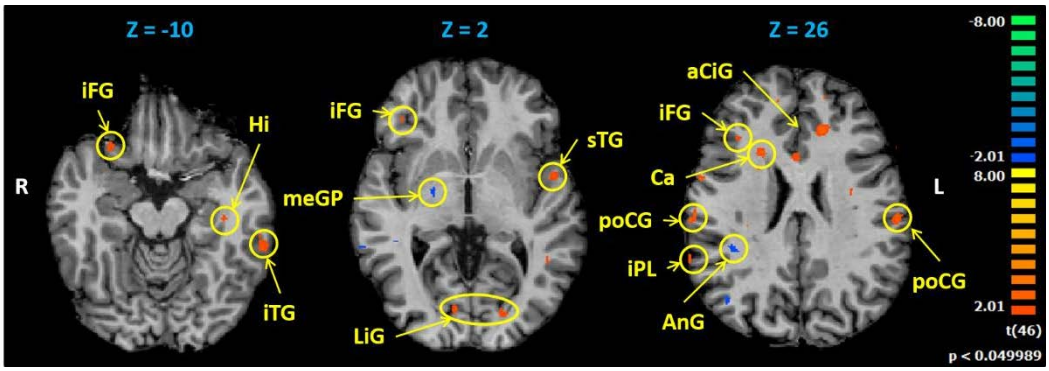

Figure 5 - 8. **Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for young and older age groups** ($p<0.05$, 46 voxel cluster threshold). Axial slices (Talairach coordinate Z = -10, 2, 26) are presented in radiological orientation with the right side of the brain on the left side of the image. Colour scaling indicates confidence, with regions activated for the older age group in orange and the young age group in blue. iFG = inferior frontal gyrus, Hi = hippocampus, iTG = inferior temporal gyrus, meGP = medial globus pallidus, LiG = lingual gyrus, sTG = superior temporal gyrus, aCiG = anterior cingulate gyrus, Ca = caudate, poCG = postcentral gyrus, iPL = inferior parietal lobule, AnG = angular gyrus.

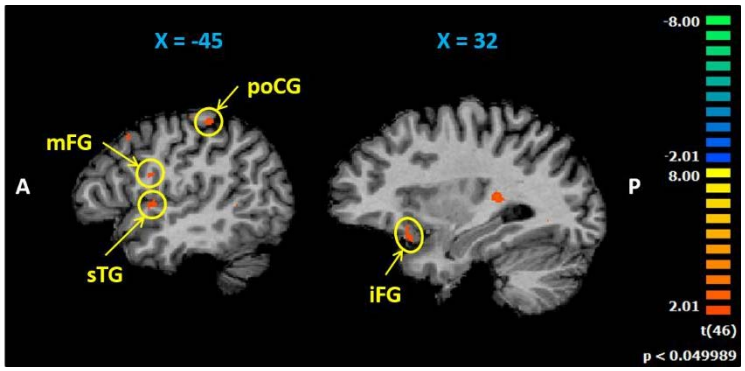

Figure 5 - 9. Group activation maps of observed areas of BOLD signal change for distorted conditions versus normal for young and older age groups ($p<0.05$, 46 voxel cluster threshold). Sagittal slices (Talairach coordinate X = -45, 32) are presented in the left (left image) and right (right image) hemispheres of the brain. The anterior brain is shown on the left side of the image. Colour scaling indicates confidence, with regions activated for the older age group in orange and the young age group in blue. mFG = middle frontal gyrus, sTG = superior temporal gyrus, poCG = postcentral gyrus, iFG = inferior frontal gyrus.

Discussion

The present study examined age-related changes in the neural correlates of visuomotor adaptation of a novel dynamic point-to-point task. The task required sustained attention and integration of sensory information in order to correct hand movements on-line. By studying three age groups, we have been able to perform group analyses to determine that older subjects increasingly activate regions, especially within frontal areas involved in adaptation. These changes likely represent compensatory mechanisms within the motor network in order to maintain performance when age-related decline occurs in the brain.

Activations observed in the young group when compared to the older group were similar to those described previously for visuomotor tasks. The young group had significantly greater ipsilateral angular gyrus and medial globus pallidus activity than the older group during the task. The globus pallidus (Diedrichsen et al., 2005) and angular gyrus (Girgenrath et al., 2008; Gorbet et al., 2004) have previously been found in moving-target visuomotor tasks. Together, this body of research confirm these brain regions are neural correlates of the transformations necessary to re-map movement goals and make successful multidirectional movements. Contrary to previous studies, the superior temporal gyrus was also observed to be a region of greater activity in the young when compared to both the middle and older age groups. This region has been observed to be more activated for older rather than younger adults (Grady et al., 1994; Heuninckx et al., 2008; Lewis, Wing, Pope, Praamstra, & Miall, 2004). So far, no conclusive explanation has been provided for this effect, however previous prism adaptation studies of young, healthy adults have suggested activation of the superior temporal gyrus is implicated in spatial cognition (Luauté et al., 2009; Saj et al., 2013). Additionally, the superior temporal gyrus is preferentially engaged

during a late phase of learning, when adaptation has occurred (Chapman et al., 2010; Clower et al., 1996; Danckert et al., 2008; Luauté et al., 2009), suggesting that young adults may have reached this phase of late learning during the task.

The findings in the present study support that older adults recruit extra frontal brain regions (Heuninckx et al., 2008) and task-specific regions during performance of motor tasks (Van Impe et al., 2011) than younger adults. Frontal regions significantly more activated in the older age group than the young and middle age groups include the inferior frontal gyrus (BA 6, premotor cortex), and medial and middle frontal gyri (BA 8, supplementary motor area). Involvement of these regions reflects an increased need for motor preparation (Heuninckx et al., 2008; Van Impe et al., 2011) and sensitivity to sensory cues (Ward & Frackowiak, 2003) with advancing age, which would be in keeping with the notion that older participants might find the task more demanding. Motor regions involved in the present task include the precentral gyrus (BA 4, primary motor cortex) and the anterior cingulate gyrus. The precentral gyrus is considered to be involved in spatial working memory (Langan & Seidler, 2011) and often becomes increasingly involved with aging (Ward & Frackowiak, 2003). Activation was also observed in the postcentral gyrus (BA 1, primary somatosensory cortex) when comparing the older age group to both the young and middle age groups. It has been suggested previously that this pattern occurs as an increased effort to analyze visual and somatosensory information between the moving target and the movement being produced (Van Impe et al., 2011).

The current study also extends previous work by showing that the often-reported recruitment of more brain regions occurs in aging (Logan, Sanders, Snyder, Morris, & Buckner, 2002; Reuter-Lorenz et al., 1999; Vallesi et al., 2011). It has been found that neural over-recruitment is beneficial for initial task performance in aging as a compensatory method

(Heuninckx et al., 2008). Greater BOLD signal change was observed in the precuneus, ipsilateral anterior cerebellum, and contralateral posterior cerebellum in the older age group compared to the middle age group. In addition, the posterior parietal cortex and contralateral anterior cerebellum were significantly more activated in the older age group compared to the young age group. These regions have previously been shown to be involved in sensorimotor coordination (Van Impe et al., 2011), with parietal regions involved in sensorimotor integration and spatial movement planning (Wenderoth, Debaere, Sunaert, Van Hecke, & Swinnen, 2004), and the cerebellum in timing and coordination (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2004). Moreover, activations seen in the posterior parietal cortex and precuneus together suggest the use of sustained visuospatial attention (Van Impe et al., 2011). The posterior parietal cortex is also involved in hand-eye coordination (Miall et al., 2001), and has been found to be active in performing tasks that require executive functions such as focusing attention and ignoring task-irrelevant information (Stoodley & Schmahmann, 2009).

Several non-sensorimotor regions were recruited by all age groups, such as the superior temporal gyrus, which is involved in auditory processing in motor synchronization to rhythm (Heuninckx et al., 2008; Lewis et al., 2004). This suggests that participants controlled their hand movements by means of a metronome pace, perhaps due to the rhythmic nature of the MRI sounds. This region has also been suggested to be associated with spatial cognition (Luauté et al., 2009; Saj et al., 2013). The inferior frontal gyrus pars orbitalis (BA 47), engaged by the older group, is also involved in integrating external information about motion with internal representations of actions (Heuninckx et al., 2008). Together, activation of these regions appear to reflect integration of external and internal information sources to successfully guide motor coordination.

Possible differences in strategy used by the three age groups should be considered. The fact that older participants use the motor control network brain regions more than young participants may reflect a more deliberative strategic plan with advancing age (Velanova, Lustig, Jacoby, & Buckner, 2007). It is important to question that while the older adults as a group use this network to reach high performance, young and middle aged adults may start to use these regions later in learning. To overcome this potential pitfall, a longer task would be necessary to answer this question. Furthermore, analysis of the phases of motor learning between age groups may reflect use of motor control networks associated with strategic planning later in learning for younger age groups.

In summary, this study has shown that visuomotor adaptation in response to dynamic stimuli with continuous visual feedback activates an extensive network of cortical and subcortical regions known to be part of the motor system. The present findings are in partial agreement with several aging studies in which activation levels in frontal regions were shown to increase with advancing age (Grady, 2000; Heuninckx et al., 2008; Madden et al., 2002; Reuter-Lorenz et al., 1999). Visuomotor adaptation in the older age group was associated with activations in motor control and sensorimotor regions, reflecting increased reliance of sensorimotor information processing, as well as frontal regions, reflecting increased performance monitoring. Increased activation and additional recruitment of brain regions in the older age group compared to young and middle aged groups follow the posterior-to-anterior shift in aging theory.

CHAPTER VI: EFFECTS OF AGING ON ANATOMICAL CONNECTIVITY: A DTI STUDY

Abstract

Normal aging is accompanied by progressive white matter degeneration. Several important questions remain about the pattern and nature of these age-related changes. Diffusion tensor imaging (DTI) provides a sensitive measure of decline in white matter integrity, which may potentially identify changes in neural pathways related to visuomotor adaptation. The purpose of the current study was to investigate age-related differences in fractional anisotropy (FA) across the whole brain. Images of 44 healthy participants (age range = 22-80 years, mean = 48.8 ± 17.6) were acquired in this study. With the use of tract-based spatial statistics (TBSS), the effects of age on mean FA in the white matter was examined. Voxel-wise analysis revealed significantly greater FA values in a young age group (range 22-39 years) to a middle age group (range 41-58 years) in the uncinate fasciculus, and from the middle to an older age group (range 65-80 years) in the inferior longitudinal fasciculus. Significantly lesser mean FA values were observed in the older age group compared to the young age group in several white matter regions including the fornix, posterior limb of internal capsule, and cingulum. The results in the present study suggest that age-related differences in white matter integrity may be associated with the structures that are involved in memory, emotion and learning due to the substantial connections with the limbic system. Future investigation of the functional associations of these connections may answer any questions about how the disruption of anatomical connectivity due to decline in white matter integrity is affected by age.

Introduction

Normal aging is known to be associated with neural atrophy, but the mechanisms behind this structural decline are not fully understood. Recently, it has been suggested that white matter degeneration is important in age-related atrophy (Pfefferbaum & Sullivan, 2003), and neuropathological studies have demonstrated that with advancing age, white matter integrity is compromised (Miller, Alston, & Corsellis, 1980). Substantial atrophy in white matter microstructure such as demyelination and axonal loss has been observed (Abe et al., 2002; Moseley, 2002), and such decreases in white matter integrity may precede decline in brain function associated with aging.

Diffusion tensor imaging (DTI) is a non-invasive technique that is sensitive to water proton molecular diffusion to analyze microstructural information (Moseley, 2002). White matter tracts have highly organized microstructural fiber bundles which act as physical barriers that restrict the normally random Brownian motion of water protons, resulting in non-random, or anisotropic, diffusion of water along these fiber bundles. Fractional anisotropy (FA) is a measure that quantifies the variability of diffusion in different directions, which is highest in major white matter tracts and lowest in grey matter when looking at the brain (Smith et al., 2006). Computed FA is a voxel-wise scalar quantity, that is modulated by local factors such as myelin thickness, axon caliber, and packing density, so it is useful to compare across individuals and between groups (Smith et al., 2007).

To date, DTI studies of normal aging have identified a decline of FA in several pre-defined white matter regions (Abe et al., 2002; Salat et al., 2005), including the genu and splenium of the corpus callosum, and the posterior limb of the internal capsule. However, much

variability has been observed, which may be due to the user-defined placement of regions of interest (ROIs), number of ROIs, and differences in size of these regions. Recently, more sophisticated voxelwise techniques have been applied to investigate age-related changes, rather than ROI approaches. These advances in technique are important because in many cases of aging, the spatial location and extent of FA changes are not known a priori. For this reason, researchers have been interested in applying whole-brain voxelwise analyses such as tract-based spatial statistics (TBSS) (Smith et al., 2006). Using TBSS to assess white matter in a voxelised skeleton located within the centres of white matter pathways throughout the brain, it has been demonstrated that FA values decrease with increasing age (Kochunov et al., 2007), which is suggested to be related to white matter atrophy (Vernooij et al., 2008).

Little evidence has been published clarifying the age range that this decline in white matter integrity occurs (Giorgio et al., 2010; Salat et al., 2005). Furthermore, it is unclear whether accelerated degeneration of white matter is localised to particular brain regions, or whether changes are uniform across the brain. The aim of the present study was to investigate age-related differences in the structural microstructure of white matter tracts, which may demonstrate differences in neural pathways underlying visuomotor adaptation. Here, DTI and TBSS were used to characterize structural changes in white matter tract architecture through FA values to determine at what stage of aging the greatest decline occurs, and in which regions. It was hypothesized that older age groups would exhibit a decline in FA when compared to younger age groups.

Methods

Participants

All procedures were reviewed and approved by the Research Ethics Boards at the Thunder Bay Regional Health Sciences Centre (TBRHSC) and Lakehead University. Forty four healthy participants (age range = 22-80 years, mean = 48.8 ± 17.6, 25 males) without history of neurological disorder were recruited from the community and provided written and informed consent prior to participation in this study. Data from seven participants were discarded due to incomplete datasets, and data from three participants were discarded due to excessive motion during a functional MRI data acquisition investigated in a separate paper. Thus analysis was performed on data from 34 participants (50.6 ± 17.7 years; 21 males) in three age groups: young (N = 11, mean = 29.5 ± 5.9, 8 male), middle (N = 11, mean = 50.5 ± 6.5, 7 male), and older (N = 12, mean = 70.1 ± 4.5, 6 male).

Data Acquisition

Magnetic resonance brain images were acquired using a 3 Tesla Achieva scanner (Philips, Maastricht, The Netherlands) and an eight-channel sensory element (SENSE) head coil. Participants lay supine in the magnet bore and the head was supported using memory foam padding to prevent motion artifacts during scanning. Whole-brain diffusion tensor images were acquired using a single-shot spin-echo sequence (TR/TE = 7376/83 ms, FOV = 224 mm, voxel size = 2 x 2 x 2 mm). Diffusion weighting was applied along 32 directions with a b-value of 800 $s \cdot mm^{-2}$, and a single volume with no diffusion weighting (b_o).

Data Preprocessing

Fractional anisotropic images were first created from the diffusion tensor images for each participant. To accomplish this, each DTI raw image was eddy-current corrected, to correct for induced stretches and shears in the diffusion-weighted images from the gradient coils, using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) FDT toolbox (FMRIB, Oxford, England). Binary brain masks were then created to extract the outside-brain data from the non-diffusion weighted images (b=0) for each participant, using FSL's BET toolbox. Finally, DTIFIT (FSL) was used to fit a diffusion tensor model at each voxel. Images were then aligned to the non-diffusion weighted image using affine, multi-scale, two-dimensional registration.

Tract-based spatial statistics in the FSL toolbox was used to compute FA (the dependent variable) across the whole brain of each subject (Smith et al., 2006). FA maps were calculated for each individual using FDT then aligned nonlinearly to FSL's FA standard-space template image (generated from 58 FA maps). This template image was then aligned to the standard coordinate Montreal Neurological Institute (MNI) brain space using affine registration. The aligned images for each individual were averaged to generate a mean FA image that included only the major white-matter pathways. This was achieved through a voxel-wise analysis in the perpendicular direction of a white matter tract to identify the voxel with the highest FA as the center of the tract. The mean FA skeleton image was thresholded at an FA value of 0.2 to exclude nonskeleton voxels.

Statistical Analysis

Data from participants were separated into three age groups: young (N = 11, mean = 29.5 ± 5.9, 8 male), middle (N = 11, mean = 50.5 ± 6.5, 7 male), and older (N = 12, mean = 70.1 ± 4.5, 6 male). First, the mean FA value for each participant was recorded and a Pearson's correlation performed to examine the correlation of FA change with age. An exploratory, voxel-wise group analysis, restricted to only voxels lying in the white-matter pathways of the skeleton mask, was performed using permutation-based nonparametric testing through FSL's Randomise tool. Differences in FA between young vs. middle, middle vs. old, and young vs. old age groups were assessed using an independent t-test. To correct for multiple comparisons and address Type I error, nonparametric permutation tests were conducted, generating cluster-size statistics based on 1000 random permutations. Typical Bonferroni or False Discovery Rate corrections are not recommended for TBSS analysis, as the FA data will contain intrinsic spatial smoothing and these approaches are too conservative (Smith et al., 2007). Only clusters with a corrected p-value < 0.05 are reported.

Results

A plot of the mean global FA of each participant revealed a significant negative correlation (r = -0.68, CI 95%[-0.82,-0.44]) with age (Figure 6 - 1). Voxelwise analysis yielded eight significant clusters in which FA was greater for the younger age group in the contrast ($p<0.05$, threshold $t_{max} = 3$).

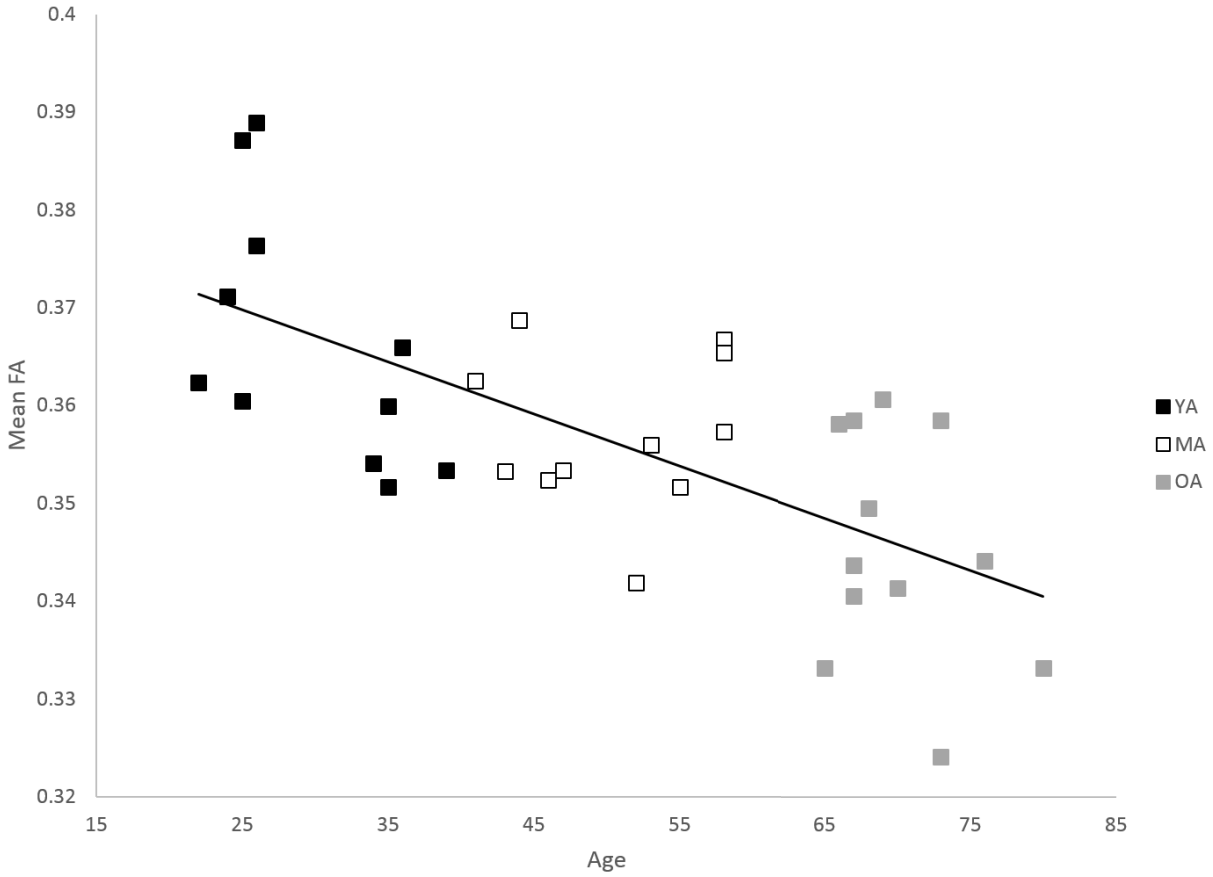

Figure 6 - 1. Scatterplot of global mean FA as a function of age. An overall decrease in FA is correlated with increase in age (r = -0.68, CI 95%[-0.82,-0.44]). A simple linear trend (solid line) is shown.

The contrasts and location of these clusters are presented in Table 6 - 1. One of these clusters was found for the young vs. middle age groups in the uncinate fasciculus, one cluster for the middle vs. old age groups in the inferior longitudinal fasciculus, and finally, six clusters were found for the young vs. old age groups in the fornix, cingulum and posterior limb of internal capsule. The mean FA images for each contrast with the FA skeleton are presented in Figure 6 - 2, overlaid onto the mean global FA skeleton for all participants, shown in green. Significantly different clusters, shown in red-yellow, have greater regional mean FA values for the younger age group in the contrast.

Table 6 - 1. **Anatomic location of significantly different FA clusters when comparing age groups.** MNI = Montreal Neurological Institute, YA=young age, MA = middle age, OA = older age, R = right, L = left.

Side	Anatomic Location	Cluster Size (voxels)	MNI Coordinates			p_{corr}
			x	*y*	*z*	
Contrast: YA>MA						
L	Uncinate Fasciculus	18722	-16	39	-7	0.005
Contrast: MA>OA						
R	Inferior Longitudinal Fasciculus	51182	-39	-22	30	0.001
Contrast: YA>OA						
R	Posterior Cingulum	690	18	-17	35	0.019
	Posterior Limb of Internal Capsule	56	23	-41	38	0.050
	Anterior Cingulum	15	20	33	20	0.050
L	Fornix	39	-7	-7	4	0.049
	Posterior Limb of Internal Capsule	31	-17	-19	-11	0.049
	Posterior Cingulum	6576	-16	-22	33	0.019

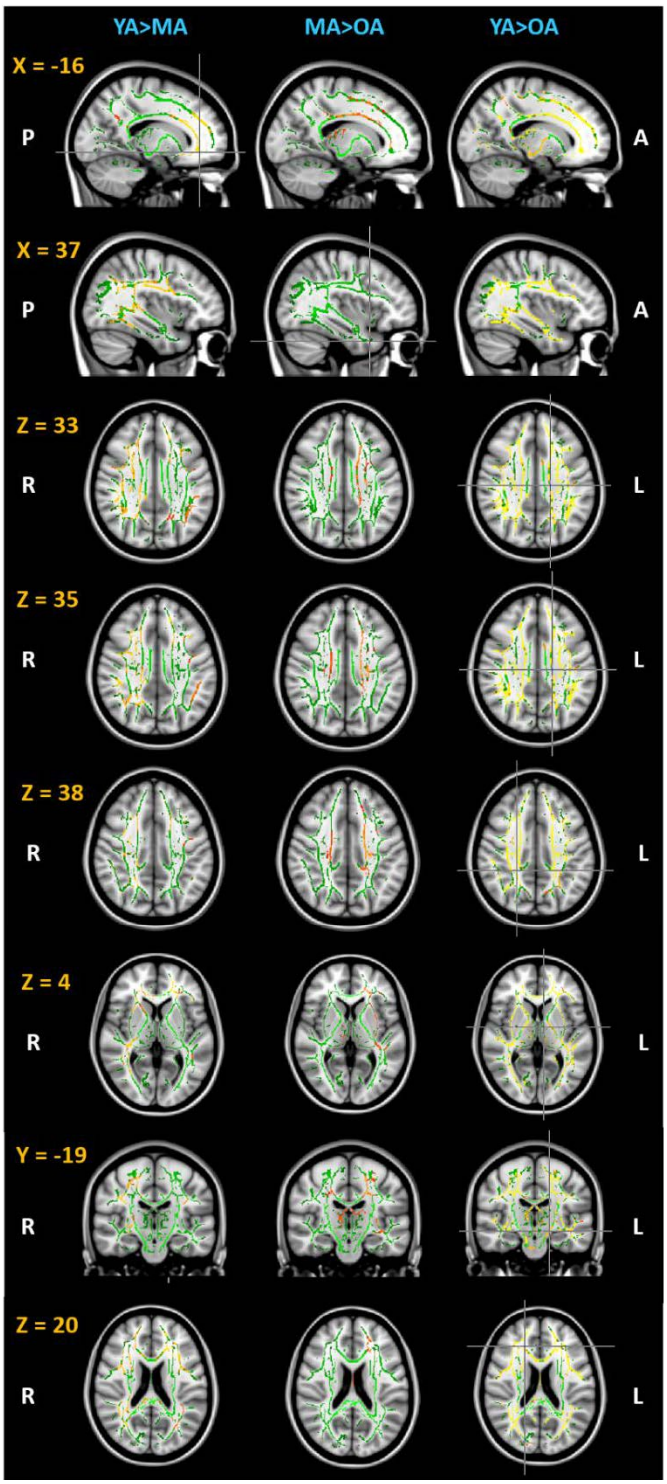

Figure 6 - 2. **Effects of age on FA using TBSS.** White matter tracts in red-yellow show a significant age-related decrease. The crosshair is positioned on the significant cluster of the contrast. Green areas show significant skeleton for group difference. P = posterior, A = anterior, R = right, L = left. MNI coordinates (X,Y,Z) are indicated.

Discussion

In the current study, differences in FA that may in part explain age-related decline in white matter microstructure were explored. The findings revealed evidence in support of this hypothesis in that decline in mean FA was correlated with increased age ($r = -0.68$, CI 95%[-0.82,-0.44]), and significant clusters of higher FA were observed when comparing younger aged groups to older aged groups. When comparing the different age groups, the middle-aged group showed a significant FA decrease compared to young adults in the uncinate fasciculus, which contains connections between the prefrontal cortex and anterior temporal lobe (Burzynska et al., 2010). The older age group showed a decrease in FA compared to the middle age group in the inferior longitudinal fasciculus. This age-related decrease in FA of the inferior longitudinal fasciculus has also been revealed by previous TBSS studies (Inano, Takao, Hayashi, Abe, & Ohtomo, 2011; Vernooij et al., 2008). This small amount of regions with significantly decreased FA between middle and older age groups has been seen previously (Giorgio et al., 2010; Salat et al., 2005). However, in contrast to the current results, these studies both concluded that FA differences were apparent by middle adulthood. It has been suggested that these declines in FA in the transition from young to middle age could be due to reductions in white matter volume (Giorgio et al., 2010).

Significant FA decreases were observed in the posterior limb of internal capsule, anterior and posterior cingulum, and fornix when comparing the young and older age adults groups. In the posterior limb of the internal capsule, a major route for the corticospinal tracts, age-related reduction in FA may suggest that cortico-spinal fibers are involved during aging. Such a result was found by Salat et al. (2005) who reported age-related differences in corticospinal tracts using

voxel-based morphometry (VBM), another voxelwise approach. Similarly, a study using both ROI and TBSS approaches confirmed age-related decrease in this region (Hsu et al., 2008). Other recent studies investigating the internal capsule have also demonstrated decline of white matter integrity with advancing age (Burzynska et al., 2010; Hsu et al., 2008; Sullivan, Rohlfing, & Pfefferbaum, 2010).

These results also demonstrate that two major tracts connecting limbic structures (cingulum and fornix) are both affected by age, which is supported by previous studies (Inano et al., 2011; Pagani, Agosta, Rocca, Caputo, & Filippi, 2008; Sullivan et al., 2010; Vernooij et al., 2008). The limbic system is the anatomical substrate for memory, emotion and learning which has long been related to development of cognitive decline (Vernooij et al., 2008). The cingulum, connecting in the frontal lobe under the cingulate cortex and projecting posteriorly to the parahippocampal gyrus, which is involved in a wide range of motivational and emotional aspects of behaviour and working memory functions, was again found in a previous DTI-based study (Pagani et al., 2008). Pagani et al. (2008) also observed the fornix, which projects from the hippocampus to other limbic regions and the prefrontal cortex and plays a key role in episodic memory.

It is interesting to note that although structural decline is observed throughout white matter (Figure 6 - 1), not all parts of individual tracts are affected (Figure 6 - 2); this can be seen in the TBSS results and differences are apparent in FA measures. Whether age-related changes occur uniformly across the brain, or show a frontal predominance is controversial and previous DTI studies have produced conflicting results. Prominent deterioration in frontal white matter has been reported to be particularly affected in aging (Abe et al., 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) while others have failed to show such differences (Barrick, Charlton,

Clark, & Markus, 2010). The findings of the current study challenge the idea that posterior regions are less susceptible to age-related change than frontal lobe white matter. Although previous DTI studies have provided support for the idea that primarily frontal regions deteriorate with aging, the results of this study are more closely associated with studies where a decrease in FA was found not only in regions of the frontal lobe but also in more posterior regions such as the posterior cingulum and posterior limb of the internal capsule (Salat et al., 2005).

TBSS data demonstrated significant association with age for FA across the brain. FA data revealed a stronger relationship with age in parietal and frontal regions compared to the rest of the brain, suggesting that these regions may suffer greater age-related white matter degeneration. These results show a similar pattern to those reported in recent studies comparing young versus older participants (Davis et al., 2008; Vernooij et al., 2008). The importance of white matter tract atrophy and subsequent disruption of cortical connections has previously been highlighted in mechanisms of age-related cognitive decline (Barrick et al., 2010; Sullivan et al., 2010; Vernooij et al., 2008). These studies support hypotheses of decline in anatomical connectivity by demonstrating a correlation between white matter integrity and various cognitive functions. The importance of characterizing white matter microstructural decline that occur in aging are future understandings of the pathophysiology of degradation in neural systems, and would add to the ability to interpret observable structural changes underlying cognitive decline.

In conclusion, DTI has shown age-related changes in white matter between age groups. Voxelwise analysis revealed a number of regions in which FA decreased with age. TBSS, a relatively new approach for analyzing differences in white matter, was used to circumvent the problem of cross-subject alignment and contamination due to differences in brain morphology (Inano et al., 2011). The pattern of age-related decline of FA mirrors previous investigations,

with frontal and posterior connections being affected. Declining function with normal aging may preferentially arise from weakening of anatomical connections. Future investigations in the functional and effective connectivity associated with these regions would assist in understanding the neural mechanisms of aging.

CHAPTER VII: GENERAL DISCUSSION & CONCLUSIONS

Overview

The goal of this thesis was to determine the effects of age on the neural correlates of visuomotor adaptation using functional magnetic resonance imaging (fMRI) and on white matter integrity using diffusion tensor imaging (DTI). I found evidence that young adults engage more widespread brain regions in the temporal, parietal, frontal, occipital and limbic lobes during the early trials, compared to primarily parietal regions engaged in the late trials of adaptation (Chapter 4). Additionally, I found greater activation in the superior temporal gyrus for a young adult age group, in the inferior parietal lobule for a middle age group, and in a number of motor regions, mostly in the frontal lobe, for an older age group (Chapter 5). Finally, declines in white matter integrity with age were observed in connections between the temporal lobe and frontal, occipital and limbic lobes (Chapter 6). These results support the idea that different brain regions are engaged from an early state of adaptation to late, as movement corrections become more automatic. Moreover, these results support the idea that increases in the number of frontal brain areas activated during a visuomotor task and decreases in white matter integrity are associated with advancing age.

The Effects of Age on the Early Phase of Adaptation

In the first study of this thesis, the underlying neural correlates of visuomotor adaptation were assessed between two states of learning: early adaptation trials and late adaptation trials.

Through this, it was determined that frontal and motor regions (inferior parietal lobule, posterior parietal cortex, putamen) and sensory regions (middle occipital gyrus, postcentral gyrus) were engaged in early visuomotor adaptation trials, when compared to late trials which recruited primarily parietal regions. The observed activation in the parietal and temporal regions during early adaptation agrees with previous imaging studies of visuomotor adaptation (Anguera et al., 2007; Clower et al., 1996; Krakauer et al., 2004; Seidler et al., 2006). In the second study, the same task and fMRI paradigm were used, and since only the first scan was used for analysis of BOLD signal change, it is safe to assume that the regions activated during the task for each age group was during the early stages of adaptation. This assumption is in line with theories of motor learning regarding the engagement of distinct neural correlates at different stages of learning (Doyon & Benali, 2005; Willingham, 1998).

Consistent with known correlates of early adaptation, the inferior parietal lobule had greater BOLD signal change for the middle age group than both the young and older age groups, suggesting that this region is more engaged in middle-aged adults than young or older. In addition, temporal and cerebellar regions were observed to have increased activity compared to the young group. In line with the results from Chapter 4, the middle age group also engaged the supplementary motor area (BA 8) and putamen to a greater extent than the young group. The primary motor cortex (precentral gyrus, BA 4), premotor cortex (BA 6), supplementary motor area, and primary somatosensory cortex (postcentral gyrus, BA 1) were engaged to a greater extent for older participants than both the young and middle age groups, which are regions previously shown during early adaptation studies (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2010; Anguera et al., 2007). The postcentral gyrus was also observed in the early phase of the first study in this thesis. The observed results suggest that motor association areas are

implicated to a greater extent with advancing age, while core motor regions are recruited later in life to perform necessary transformations. These findings are consistent with several imaging studies showing that older adults exhibit stronger and more widespread activation patterns in the early phase of adaptation during motor tasks (Heuninckx et al., 2008; Ward & Frackowiak, 2003).

The Effects of Age on Neural Structure and Function

The functional neuroimaging study of aging found in Chapter 5 reports an extensive pattern of age-related change in visuomotor neural correlates. The results suggest that age-related decline occurs in the task-related activation of frontoparietal networks as well as the lingual gyrus and temporal regions, which has been interpreted previously as a compensatory recruitment of regions outside task-relevant pathways (Cabeza et al., 2004; Grady, 2000). Functional MRI studies of aging have been primarily concerned with the localization of age-related change in cortical function. The networks mediating cortical function establish connectivity through white matter pathways, and changes in function may results from white matter changes at various points within cortical networks. DTI provides information about the properties of white matter, and one measure of white matter integrity is fractional anisotropy (FA). FA tends to decrease with advancing age, suggesting that a corresponding decline in structural integrity could compromise information transfer among functional networks (Moseley, 2002). The DTI study of aging found in chapter 6 reports age-related decline in the integrity of the uncinate fasciculus, inferior longitudinal fasciculus, cingulum, fornix, and the posterior limb of internal capsule. This decline in white matter integrity may be related to the observed

increases in functional activation as a function of compensation due to age. However, the use of fMRI and DTI measures combined in the assessment of age-related change has not been well-reported in the literature (Madden et al., 2007).

Overall, the results support the hypothesis that increased activation in functional networks is related to declines in white matter integrity with advancing age. As anticipated, regions thought to be structurally disconnected were not highly activated in the older age groups compared to younger. The uncinate fasciculus, a tract with decreased FA in the middle compared to young group, is a frontotemporal tract that connects the inferior frontal gyrus to the hippocampus, amygdala, and anterior temporal lobe (Burzynska et al., 2010). As anticipated, the inferior frontal gyrus and hippocampus were determined to have greater BOLD signal change for the young group when compared to the middle group. The inferior longitudinal fasciculus, a tract with decreased FA in the older compared to middle group, is an association fiber that connects temporal and occipital lobes medially (Vernooij et al., 2008). As expected, the medial inferior temporal gyrus was preferentially engaged for the middle age group compared to the older age group, but contrary to expectations, the lingual gyrus was preferentially engaged for the older age group compared to the middle. The latter finding may suggest that information was propagated through a compensatory tract.

Similar results were observed for the young and older age group comparisons, where compensatory pathways of information transfer can be expected (Takeuchi, Oouchida, & Izumi, 2012). The fornix, a limbic tract that connects the hippocampus and anterior thalamus, and projects to the cingulate cortex (Inano et al., 2011; Pagani et al., 2008), had a decreased FA for the older age group, however the hippocampus and anterior cingulate gyrus had greater activity for the older age group. The cingulum, which also connects the anterior cingulate gyrus to the

medial temporal lobe at the parahippocampal gyrus (Vernooij et al., 2008) was structurally compromised with age as well. Finally, the posterior limb of internal capsule which contains corticospinal tract fibers, which arise in the motor cortex, and sensory fibers, which arise in the thalamus (Hsu et al., 2008; Salat et al., 2005; Sullivan et al., 2010). This tract also connects to the lenticular nucleus (composed of the globus pallidus and putamen), the lower visual cortex and superior temporal gyrus. The lingual gyrus was preferentially engaged for the older group compared to the young group, while the globus pallidus and superior temporal gyrus had greater activation in the young group than the older group.

It is important to note that the comparisons of functional and structural changes with advancing age discussed here are not statistically correlated. In order to properly analyze the relationship between white matter decline and increase in functional activation, one of two methods can be followed: (1) a voxelwise analysis of DTI data, for example TBSS, followed by a region-of-interest (ROI) analysis of functional images to determine the BOLD signal change of structurally disconnected regions; or (2) a voxelwise analysis of fMRI data, followed by an ROI analysis of DTI images, such as tractography, to determine anatomical connectivity of task-related regions. After analyzing the data in such a manner, a regression model can then be defined with FA and BOLD signal change as predictors. Due to the time constraints associated with completing a Master's thesis, I was unable to perform these analyses at the time being. However, with the appropriate amount of time, they are possible to perform.

Strengths

This study analyzed data from three age groups, allowing more detailed investigation of aging through more narrow age ranges than those that exist in the literature to date. The task used incorporated aspects of previous studies to induce multidirectional movements. It is anticipated that these types of movements are more natural than movements in a single direction to a stationary target, so may be better suited for future rehabilitation strategies after neural injury such as stroke. Moreover, interruptions in visual feedback and use of perceptual components seen in previous studies have been removed to narrow the task into a closed-loop motor control study.

FMRI is a non-invasive technique that has many advantages over other functional neuroimaging techniques such as positron emission tomography (PET) and electroencephalography (EEG). A major strength of fMRI in comparison to PET is that it has a high spatial resolution, and does not use radiation. PET of the brain uses radioactively-labelled isotopes of glucose injected into the body to produce a three-dimensional image of sugar uptake by the brain to analyze metabolism. During EEG, a cap composed of several electrodes is placed on the head to record electrical impulses of the brain and determine areas of neural activity through these patterns in electrical processes. The benefit of fMRI is that it is a whole-brain technique, whereas EEG can only measure function of cortical structures near the surface of the skull. In addition to these comparisons, MRI can provide high resolution structural images in the same scan for coregistration of functional images (Glover, 2012).

Strengths in the DTI analysis include the automated and validated techniques for quantification of white matter integrity. The voxelwise analysis technique used, tract-based spatial statistics (TBSS; Smith et al., 2006), is an automated method which has been shown to be more robust and accurate than other voxelwise analysis techniques (such as voxel-based

morphometry, VBM) which are prone to residual misalignment and in which the amount of spatial smoothing greatly affects the results (Smith et al., 2007). Moreover, TBSS brings together the strengths of whole-brain VBM methods and localized region-of-interest (ROI) analyses by sampling center-of-tract voxel values in individual space. It therefore enables reliable detection of localized differences in diffusivity parameters in all major white matter tracts, and of group differences of these parameters.

Limitations

There are a couple of potential limitations to the task used in this study. First, in the absence of specific instructions (i.e., participants were blind to the manipulation in cursor feedback), participants may have varied in how they used visual representation of the task. For example, some participants may not have recognized that there was a distortion in cursor movement, some may have overcome the distortion by using movement strategies to reach the target, and some may have reached the path of the target and waited for the target to reach the cursor. The first example raises questions about limitations associated with the MRI-compatible trackball. The trackball creates an additional transformation because it is more sensitive than an ordinary computer mouse, and participants may not attribute the cursor distortions to an experimenter-controlled manipulation but to this sensitivity. One concern is whether there was a potential bias between young, middle and older adults in their computer use, and how this would translate to trackball use for the task. To address this caveat, participants were asked to rate their computer usage on a scale from one to five (five being usage of a computer every day). Three participants rated their usage at 3, all of which were recruited into the middle age group. Eight

participants rated their usage at 4, and the remainder at 5. Because the majority of the participants rated their usage as high, it is unlikely that much bias was introduced based on computer familiarity since there was no difference between groups. To minimize any bias, practices were given outside and then inside the MRI to familiarize participants with the equipment. Moreover, it is anticipated that this would influence all conditions including normal control of the cursor, and since behaviour during distortion trials to normal are being related, it should not be an overly concerning factor in analysis.

Second, motor performance might improve with strategic control of the task, rather than learning of adaptation to movements. For example, a participant may move the trackball laterally to test for an x-flip distortion, and then move the trackball vertically to intercept the cursor with the target, rather than making an accurate trajectory. Additionally, limitations of the experimental setup did not allow for eye-tracking during imaging. Analysis of eye movements may have answered questions about individual-specific target locations. For example, a participant may find a spot within the circle of target movement in order to move the cursor to and wait for the target to intercept the cursor, rather than moving the cursor directly to the target. Eye-tracking would provide information of where participants' eyes are directed during movement of the cursor, and would answer any questions of between-groups differences in movement plans. While we see a trend in the improvement of cursor behaviour from the early phase to the late phase in behavioural analyses, not all results are statistically significant. It is likely that this is due to the low number of trials in the task, as participants may not reach a late phase of learning by the second scan.

Although sample size calculations were performed prior to data collection, these calculations pose a potential limitation as there were no fMRI pilot studies from which to create

base estimations. Initial studies of fMRI paradigms are essential in estimating the sample size required to achieve a specific power because of the two sources of variability introduced in fMRI results: intra- and inter-subject variability (Desmond & Glover, 2002). Intra-subject variability is introduced as noise within the time series, and inter-subject variability is introduced through activation differences between subjects, and both types of variability affect power. A way to overcome this potential limitation is to collect the data only until the specific power wanted is achieved. Any sample size estimations for future studies with the same paradigm can then be accurate.

A regression correlation may have better captured exactly when age-related differences occur, rather than a between-groups analysis. Moreover, a longitudinal study assessing the effects of aging within individuals would give a better idea of BOLD signal changes and aging. There was also an asymmetry in sex representation within the three age groups. Though in my dataset there were no apparent sex differences, previous research has suggested that male and female and performance in visuomotor tasks may not be equal, and differences may continue into later years of life (Gorbet & Sergio, 2007). Further analysis of sex-related differences in both behaviour and underlying neural correlates of visuomotor adaptation would need to be performed. In order to achieve this with the current task design, each age group would need an equal representation of sexes, and twice the number of participants must be recruited to fulfill the requirement of having 12 participants per group analyzed. Then, differences in activation patterns between sexes within each age group can be determined.

In this study, multiple-participant data were used to evaluate the effect of aging on DTI changes characterized by fractional anisotropy. My results only reflect differences among participants in different age groups rather than changes associated with aging in each individual.

Furthermore, because the study contains different cohort of participants in different age groups, it may be less sensitive to brain changes across the lifespan. Therefore, a longitudinal study of these changes would be a better way to demonstrate the relationship between FA changes and aging. A diffusion tensor model was used to investigate the effects of age on white matter integrity. Although this mathematical model is widely applied to represent diffusion, it cannot accurately represent voxels containing multiple fiber bundles with different orientations (Jbabdi, Behrens, & Smith, 2010).

Future Directions

Future directions will involve investigating the influence of the target velocity and target path on task difficulty and adaptation behaviour. Because the path of target movement is predictable and uniform in a single trial, it may be too easy for already high performers. Randomized comparison of groups with predictable target movement and velocity versus unpredictable target movement and velocity may answer questions about novelty on visuomotor adaptation. Likewise, differences in neural correlates between high performers and low performers will be investigated. By separating participants by their performance levels on the task used in this thesis, analysis of the brain regions used during the task for each may reveal succinct differences in areas used for learning and when adaptation occurs.

To answer any questions regarding whether adaptations to errors due to visual perturbations or change in target location, measure of coordination between eye and hand movements using an eye tracker will be used in future studies. The eye tracker will be used simultaneously with fMRI acquisition to reveal the functional anatomy of eye movements used

in the task, to develop a better understanding of the interaction between cognitive and sensorimotor brain systems, and how these change with aging. To analyze this, the BOLD signal would be parametrically compared to the coordination of eye and hand movements on each condition. For example, the distorted conditions in this task require an increased degree of hand-eye coordination to successfully interact with the target than normal cursor control. One question to be answered is whether the increase in hand-eye coordination is associated with a greater BOLD signal in well-known motor coordination regions such as the cerebellum.

In this thesis, DTI and fMRI have been acquired in the same subjects. This may be beneficial to analyze together in the future. To accomplish this, regions of interest will be determined from the fMRI results and used as seed regions for DTI analysis. Tractography will be used on the DTI data to map anatomical connections only between these regions, which can then be compared between age groups. Moreover, functional connectivity can be analyzed using the same regions of interest, to determine how functional connections involved in visuomotor adaptation can decline with aging. These analyses together will map the changes in functional anatomy underlying visuomotor adaptation with aging.

In addition to aging, the demonstration that the human motor system can adapt to distorted visual feedback while interacting with moving targets may have important implications when the ability to adjust our movements declines due to neurodegenerative disease or neural injury, such as stroke. Analysis of stroke patients in comparison to age-matched controls in the current study may answer questions about how stroke patients adapt to errors in movement differently than participants who age normally. Additionally, it may reveal how the brain compensates for weakened or atrophied connections associated with injury by showing which brain regions are associated with visuomotor adaptation in stroke patients. Furthermore,

knowledge of how stroke patients use visuomotor adaptation behaviourally and neurally can aid in the development of rehabilitation tools for clinical use.

Conclusions

This thesis aimed to provide evidence of the effects of aging on visuomotor adaptation behaviour as well as on structural and functional neural changes. While differences in behavioural performance of the dynamic point-to-point task were not statistically significant between fMRI scans, differences in BOLD signal change were observed. Consistent with previous literature, young adults engaged the putamen and parietal regions in the early adaptation trials, and temporal regions in the late adaptation trials. Importantly, the older age group engaged similar regions during the early phase of the visuomotor task as the young adults in Chapter 4, as well as regions seen previously in the literature. In addition, more widespread regions with greater activation were observed with advancing age. Age-related differences also occurred in the integrity of the white matter regions related to networks involved in visuomotor adaptation. Frontotemporal and occipitotemporal fibers exhibit relatively greater age-related decline in white matter integrity, which is associated with greater fMRI activation for older adults when compared to young. Additional research combining behavioural performance, fMRI, and DTI will be valuable in determining the neural mechanisms of age-related differences in visuomotor adaptation.

In conclusion, the current research confirms that changes in performance and neural activity do occur as manual actions are learned, and that functional and anatomical changes occur with advancing age. This study advances previous research by investigating several more-

refined age groups over the adult lifespan rather than one young group compared to one older group that is typically studied. This approach may allow study of the non-linear nature of aging. In the future, further studies of smaller age ranges may determine when in aging neural changes have an impact on the decline in visuomotor ability. The use of a novel moving-target task bridges multiple areas of existing research. This study offers analysis of more natural movement patterns than conventional static-target tasks and moving-target tasks without continuous visual feedback. Findings may contribute to the development of rehabilitation interventions for individuals who have suffered motor loss with age, due to injury such as stroke, or due to disease such as neurodegeneration. Future analysis of the functional and effective connectivity between these regions will further our understanding of the mechanisms of neural aging.

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APPENDIX A: RESEARCH ETHICS BOARD APPROVED DOCUMENTS

i: Participant Information Package and Consent Form

TITLE: Investigation of the neural mechanisms underlying changes in healthy aging
PI: LAWRENCE-DEWAR, Jane TBRHSC P#: 2012107 VERSION DATE: Oct 21, 2014
Appendix 3 – MRI Study Information Package
Date

Dear Prospective Participant:

You are receiving this information package because you have contacted our lab at the Thunder Bay Regional Research Institute and are invited to participate in our study called **Investigation of the neural mechanisms underlying changes in motor learning in healthy aging**. This study will be performed at the Thunder Bay Regional Health Sciences Centre using the research dedicated MRI system.

Please find the following documents enclosed:

- Study Information Sheet
- MRI Information Sheet
- Prescreening Form
- Consent Form
- Map with directions to the study location

Please:

1. Read the enclosed material. It contains information that we hope will answer any questions you may have about this study. Please ask me to explain anything that you do not clearly understand. If you have further questions, please feel free to contact me.

2. Carefully review the list of medical conditions that might exclude you from this study. This is for your safety. If you have any of the exclusion criteria, you should not enter the study. If you have any questions or concerns, please contact me.

3. Please allow yourself at least 24 hours after reading the information in this package before scheduling an appointment. When you wish to participate in this study, **please call me to arrange a date and time**. At that time I will review a pre screening form to confirm you are eligible for the study.

Thank you for your interest in our research study.

Sincerely,

Jane Lawrence Dewar, PhD
Scientist, Thunder Bay Regional Research Institute

Phone: 684-7289
Email: dewarja@tbh.net
Website: lawrencedewarlab.com

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Appendix 3 – MRI Study Information Package

RESEARCH SUMMARY AND INFORMED CONSENT

Title of Research Project:
Investigation of the neural mechanisms underlying changes in motor learning in healthy aging

Researcher involved:

Jane Lawrence-Dewar, Principal Investigator (807) 684-7289

This document, reviewed and approved by the Thunder Bay Regional Health Sciences Centre Research Ethics Board, contains information regarding the purpose of the study, the methods involved, and the risks and benefits of participating. If you find any of the provided information unclear or have further questions, or after taking time to review this information you wish to make an appointment, please contact Jane Lawrence-Dewar at (807) 684-7289. If you have any concerns regarding your rights as a research participant, or wish to speak to someone other than a research team member about this research project, you are welcome to contact the:

Chair, Research Ethics Board
Thunder Bay Regional Health Sciences Centre
980 Oliver Road, Thunder Bay, Ontario P7B 6V4
phone: 807-684-6422 fax: 807- 684-5904
email: ResearchEthics_Chair@tbh.net

This study will also serve as the graduate research of Lakehead University students who are part of the research team. Therefore, this study has also been reviewed and approved by the Lakehead University Research Ethics Board. If you would like to speak to someone outside of the research team at Lakehead University, please contact:

Sue Wright, Research Ethics Board
Lakehead University
Phone: 807-343-8283
Email: research@lakeheadu.ca

WHAT IS THE RESEARCH ABOUT?

If we are learning how to do a new skill, we may learn by observation or watching someone else do it. We may also learn by changing or adapting our movements until we are successful. Our lab is interested in the areas of the brain that are needed for this type of learning and how brain activity in these areas change in natural aging. To observe brain activity we use a type of Magnetic Resonance Imaging (MRI) called functional MRI (fMRI). Enclosed in the package you received is a sheet with more information about this technique.

In the future, we hope that the results of this study will help us understand how injury to these brain regions affect the abilities of stoke patients to learn how to regain hand function and use this knowledge to improve rehabilitative care.

AM I ELIGIBLE TO PARTICIPATE?

All participants who participate in this research study must be right-handed, healthy individuals, between 20 and 85 years of age and must pass a prescreening check to be completed by the investigator prior to scheduling the study appointment as well as by the MR technologist at the study appointment. This study involves entering a high magnetic field which may not be safe for all individuals. An MRI information sheet is included in your participant package to help answer any questions you may have.

You may not participate in the study if you:

1. Have a history of neurological injury or disease
2. Have a physical impairment or affliction that limits use of your right hand
3. Have metal implants inside your body
4. Have a medical condition that could be made worse by stress
5. Are claustrophobic
6. Are or may be pregnant
7. Weigh more than 350 pounds

This study is purely voluntary. You may decide not to participate in this study or you withdraw from the study at any time.

WHAT WILL I HAVE TO DO?

When you call to make an appointment, you will be asked a series of questions to confirm you are eligible. These will include several questions to make sure that there are no metal objects in your body so that it is safe for you to have an MRI done. A copy the detailed prescreening form with the questions that Jane Lawrence-Dewar will ask you when you make an appointment is enclosed for you to review.

You will make one visit to the Thunder Bay Regional Health Sciences Centre where you will have a MRI of your brain using the research dedicated MRI system. The scan itself will take about 60 minutes, but allow a total of 2 hours for the visit.

At your appointment for the Research MRI, an MR technologist will go through the MR Safety Screening Form with you. You will be offered the option of a pregnancy test if you think there is a chance you could be pregnant. The investigator will explain all of the details of the experiment and review this consent form with you as well as answer any questions you may have. You should make sure that all your questions are answered and you agree to participate in the study before signing the consent form.

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Appendix 3 – MRI Study Information Package

Before entering the magnet room, you will be asked to change into clothing which does not contain metal. You have a choice of wearing your own clothing, if it is metal-free (e.g., jogging suit) or the hospital gowns that we can provide. Before you enter the magnet room, we will ask you to remove all metal objects, such as keys, coins, since they could be attracted to the MRI scanner with great force.

For the MRI scan, you will be positioned comfortably on your back and provided with soft earplugs to reduce the noise from the MRI scanner (the sound it produces is a loud knocking noise). A special receiver will be placed around your head. You will then be slid into the large, tunnel-shaped scanner until your head is at the centre of the magnet. The tunnel approximately 2 feet wide and is open at both ends.

We may monitor your pulse rate using a small sensor on your finger, or your breathing using a strap placed over your abdomen. These monitors are used to improve the quality of images for the study.

During the scan, the MR operator will talk with you regularly through a two-way intercom to let you know what to do. During the study, you will be asked to make a series of arm movements to target objects placed in the magnet. For example, on some trials, you will be asked to reach out and pick up a target object. On others, you will be asked to look at target objects or visual images. You may also be given a trackball to control a cursor during a computer based task.

After the scan has been completed and you have left the magnet room, we will ask you to fill out a questionnaire about how the study went for you. We will also ask you if you would like remain on our potential participant list for future studies you may be ligible for of if you would like us to erase your contact information from our database. You can ask to have your name and information removed from our list at any time.

IS THE STUDY CONFIDENTIAL?

Normally, only people directly involved with the research procedure are allowed in the area while a study is being conducted.

Information gathered in this research may be published or presented in public forums; however your name will not be used or revealed. Records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act. All data obtained during your scan will be stored with an alpha-numerical code instead of your name. Only your file, which is kept securely in the Principal Investigator's office, will have information which relates your name to the code. Identifying information will be kept for 7 years. Anonymous data may be kept indefinitely.

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Appendix 3 – MRI Study Information Package

It is possible that our records will be audited by the Research Ethics Board. We have formatted our forms to seal personal information to facilitate inspection of our forms without revealing personal information.

WHAT ARE THE POSSIBLE HARMS OR BENEFITS?

Metal objects can be attracted to the scanner with great force. If a metal object hit anyone in the way, it could cause serious injury. It is for this reason that we are cautious in our procedures and ask that you change into metal free clothing and remove jewelry and items from your pockets.

Metal can also be located inside your body if you have had a surgery or implant. Some metal objects may move or heat up. We will screen you to make sure that it is safe for you to participate. You must tell us if you have had surgery, as metal may be left in your body after certain types of surgery. Please consider if you have any of the following:

- Previous Surgery involving metal, such as: clips, rods, screws, pins, wires.
- Heart pacemaker
- Implanted electrodes, pumps or electrical devices
- Cochlear (inner ear) implants
- Intraocular lens (eye) implants
- Any metallic foreign body, shrapnel or bullet (Have you have ever been a grinder, metal worker, welder, wounded during military service, etc.?)
- Intrauterine contraceptive device (IUD) or contraceptive diaphragm
- Dental work held in place by magnets
- Non-removable dental braces and retainers
- Metal dental work, unless it is composed predominantly of precious or semiprecious alloy or amalgam (Please discuss with the researcher)
- Tattooed eyeliner
- Some tattoos (if you have tattoos, please discuss with the researcher)
- Non-removable metal jewellery (body piercing)

MRI is completely painless, but some people have felt minor, transient discomforts during MRI scans (e.g. dizziness, lightheadedness or a feeling of continued motion after being moved into the magnetic field) which usually subside within a few minutes. In rare cases, the dizziness progressed to the point of nausea, but subsided quickly outside the magnetic field. Some people may have a feeling of claustrophobia while they are in the scanner. Please let us know immediately if you experience claustrophobia or any other discomforts, and we will stop the study. Participation in the study is voluntary and you are free to withdraw at any time without penalty.

No long-term adverse effects of MRI have been reported. We would contact you if any new risks are discovered. Please contact us or ask your physician to contact us if you experience any effects that you feel may be a result of your participation in the study.

This is a research study so you will not personally benefit by participating in this study. Eventually, the results of this study may benefit future stroke patients.

WHAT ELSE SHOULD I KNOW?

You have the right to withdraw from the research study at any time and for any reason. The investigators reserve the right to end your participation for any reason. If the study is ended before completion, any information you have already provided will be retained.

This is not a diagnostic scan and the investigator is not clinically trained. We cannot provide you with any medical information regarding your scan. The images obtained are for research purposes only and the methods used for are different than those used in the clinic. That being said, it is possible that your scan could reveal something unexpected.,If the investigator notices an irregularity in a scan, the scan will be forwarded to a radiologist. In addition, scans from one in every ten participants will be randomly selected and forwarded to the radiologist. If the radiologist identifies something that should be followed up further they will contact the physician you identify with a report. If you have a general practitioner or family physician, you are invited to provide their contact information. If you do not have a physician, a report will be sent to neurologist Dr. Ayman Hassan.

We will give you $25 to cover any expenses you incur to participate in this research study. You may also request a copy of some of the images.

The goal of this study is to better understand what brain areas become active during a motor learning task. We do not anticipate that the results of this study will directly lead to commercialization.

Please contact us if you would like any more information about the study. Please let us know if you would like copies of any published scientific reports about the research project.

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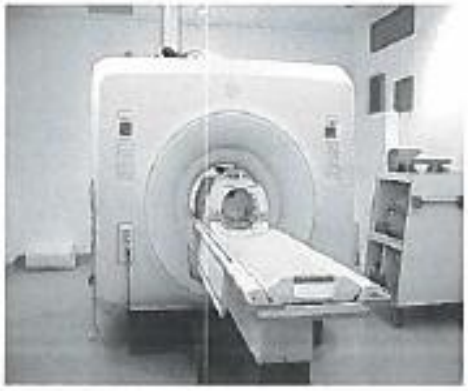
ADDITIONAL INFORMATION SHEET:
Magnetic Resonance Imaging

What is magnetic resonance imaging (MRI)?



Magnetic resonance imaging (MRI) is an imaging method based on a large magnetic field. By entering the hole or "bore" of the MRI, you are entering a magnetic field much larger than that experienced by the earth's magnetic field. In hospitals or research centres, the most common strength of magnetic field is 1.5 or 3 Tesla (T). The research dedicated MRI scanner housed on the first floor of the thunder Bay Regional Health Sciences Centre is a 3 T system.

MRI uses the water in your body as a source of signal. By applying a radiofrequency (RF) pulse, we are able to disturb the "spins" away from aligning with the magnetic field. When we remove the RF pulse, the spins realign themselves with the field but how quickly this occurs depends on the type of imaging being performed and the type of tissue that the spins are in. This is how we are able to obtain contrast between bone, fat, muscle, fluid and tissues such as the brain.

What is Functional magnetic resonance imaging (fMRI)?
Functional magnetic resonance imaging (fMRI) is a method of detecting areas of activity in the brain and spinal cord. When an area of the brain or spinal cord becomes "active" it needs more oxygen. To compensate for this, there is a much greater increase in blood flow and therefore oxygen to the area. Oxygenated and deoxygenated blood have different magnetic susceptibilities therefore, there is a localized change in signal that can be detected in an area of neuronal activity.

During a fMRI scan there will be periods where we will ask you to do nothing or "rest". During other times you may be asked to do a task such as move your hand or look at pictures. By comparing the signal in your brain during the times that you are "resting" and those when you are doing the task, we can identify what areas of the brain or spinal cord are active.

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STUDY PRESCREENING FORM

You do not need to complete this form. If you choose to participate in this study, prior to booking an appointment, Dr. Lawrence-Dewar will review over the following criteria to confirm your eligibility for the study. Some of these criteria are important for the design of our experiment but most are because of safety concerns related to entering a MRI. It is important that you answer them to the best of your knowledge.

Handedness

Which hand do you use for the following tasks:

	Right	Left		Right	Left
Comb your hair	☐	☐	Brush teeth	☐	☐
Hammer a nail	☐	☐	Eat soup	☐	☐
Swing a hockey stick	☐	☐	Throw ball	☐	☐
Swing a tennis racket	☐	☐	Write name	☐	☐

Medical History

Do you have a history of:	Yes	No
Neurological disease (Parkinson's, Alzheimer's, etc)	☐	☐
Brain injury (Stroke, Traumatic Brain injury)	☐	☐
Diagnosed brain tumor	☐	☐
Seizures/Epilepsy	☐	☐
Arthritis (primarily affecting your right arm/hand)	☐	☐
Headache/Migraine	☐	☐

What medications are you currently taking?

_____

_____

Demographic information:

Sex (circle): Male Female Age: _____ years

Computer usage(circle): 1 2 3 4 5
Low High

Participant number: _____

STUDY PRESCREENING FORM (CONTINUED)

MR Safety

Do you have the following:	Yes	No
Stents, wire mesh, or metal implants	☐	☐
Cardiac pacemaker	☐	☐
Aneurysm clips in head	☐	☐
Neuro/bio stimulator device	☐	☐
Implanted insuluin pump	☐	☐
Hearing aid	☐	☐
Cochlear/ear implant	☐	☐
Shrapnel	☐	☐
Piercings	☐	☐
Dental implants (non-removable dentures, bridges, crowns)	☐	☐
Artificial limb or joint	☐	☐
Metal rods, screws, plates, nails	☐	☐
IUD	☐	☐
Tattoos	☐	☐
Have you ever been a metal worker (welder)?	☐	☐
Are you or could you be pregnant?	☐	☐
Have you previously had surgery? If yes what and when?	☐	☐

To the best of your knowledge is any metal left behind? ☐ ☐

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Appendix 3 – MRI Study Information Package

CONSENT FORM FOR MRI STUDY

By signing this consent form you acknowledge and agree that:

- I have received a copy of and I have read the Research Summary and accompanying information sheets.
- I understand the nature of the study, including the potential risks and benefits.
- I have had adequate time to consider the information.
- I have talked to Dr. Jane Lawrence Dewar. All my questions about the study have been answered.
- If I have any more questions, I may call Dr Jane Lawrence Dewar at the Thunder Bay Regional Research Institute at 684-7289.
- I realize that by signing this document I am not waiving any legal rights.
- I understand that information regarding my personal identity will be kept confidential with the following exceptions:
- I give permission to disclose information to a radiologist, and if further follow up is needed, the identified physician below (check one):

□ I have named Dr. _____ at _____ as the physician to be contacted for follow-up purposes.

□ I agree to have neurologist, Dr. Ayman Hassan, as the physician to be contacted for follow-up purposes. Dr. Hassan can contact me with the information I provide below.

I hereby agree to participate in the research protocol, "Investigation of the neural mechanisms underlying changes in motor learning in healthy aging" and I understand that I can end my participation at any time and for any reason. My consent has been given freely.

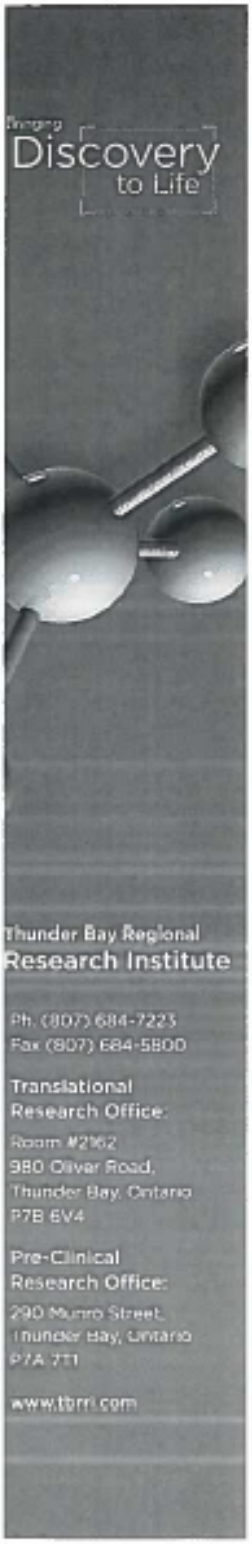
Seal line (all information below this line is confidential and will be sealed)

Participant information:
Name (Print): Contact information (for follow up)

Signature:

Investigator information:
Name (Print):

Signature: Date:



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DIRECTIONS TO THE RESEARCH STUDY

** PLEASE BRING THIS PAPER WITH YOU TO THE STUDY**

After you have reviewed all of the provided information, if you have any questions or wish to volunteer for this study, please contact Dr. Jane Lawrence-Dewar at (807)684-7289. She will book an appointment for the study if you wish to do so. Participation is completely voluntary and you can withdraw from the study at any time.

Studies will take place at the Thunder Bay Regional Health Sciences Centre. If you require parking, the closest lots to the main entrance are A1 and B.

When you enter the main entrance of the hospital you will see an information booth. Turn right and proceed towards the main staircase. At the bottom of the staircase is a hall on the right. Proceed down the hall watching for the sign for Diagnostic Imaging. Once you find the Diagnostic Imaging reception let them know you are here for a research study on the research MRI and provide them with this piece of paper.

TO DIAGNOSTIC IMAGING RECEPTION:

PLEASE CALL THE RESEARCH 3T CONSOLE ROOM (x 6569) TO NOTIFY DR. JANE LAWRENCE-DEWAR THAT HER RESEARCH PARTICIPANT HAS ARRIVED. SHE WILL COME GET THEM. PLEASE DO NOT ENTER THEIR INFORMATION INTO THE CLINICAL COMPUTER SYSTEM.

ii: Exit Questionnaire

TITLE: Investigation of the neural mechanisms underlying changes in healthy aging
PI: LAWRENCE-DEWAR, Jane TBRHSC P#: 2012107 VERSION DATE: June 4, 2014

Research Study Exit Questionnaire

Your responses are confidential and voluntary. This questionnaire is meant to provide us with feedback about your experience only.

All studies:
What did you notice during the study?

Did you notice anything change during the study?

Did you find anything particularly challenging?

Please circle the correct response:

Based on your experience, would you participate in a study like this again? Yes No

Based on your experience, Would you recommend this study to a friend? Yes No

Participant number: _____

MRI Studies ONLY:

Did you experience any of the following while in the MRI:

	Yes	No
Nausea	☐	☐
Headache	☐	☐
Dizziness	☐	☐
Sleepiness	☐	☐
Claustrophobia	☐	☐
Anxiety	☐	☐
Heat	☐	☐
Cold	☐	☐
Tingling	☐	☐
Discomfort	☐	☐

Other:

_____

_____

_____

Participant number: _____

All Participants:

Do you participate in any activities that require you to observe and repeat behaviours of others (e.g. fitness classes, or skill-specific training)? If so, please describe below.

Exit Questionnaire – Permission for further contact

When you first contacted the lab, your contact information was collected in a secure, password protected database. This information is not shared with anyone. With your permission we will keep this information indefinitely, to contact you if you become eligible for another study of Dr. Jane Lawrence-Dewar's in the future. Your information will otherwise be erased. You make ask to be removed from the list at any time.

☐ I give Dr. Jane Lawrence Dewar permission to retain my contact information with the purpose of contacting me if I become eligible for another research study in her lab. I understand that this information will not be shared with anyone.

I would prefer to be contacted by (please circle) : e-mail Phone

☐ I do not wish to be contacted. Please erase my contact information.

As this page contains your signature, it will be attached to your consent form and kept separate from all data.

Seal Line (Identifying information below this line will be sealed).

I understand that I can request that Dr. Jane Lawrence-Dewar remove my name and contact information from this list at any time and if I do so it will be deleted immediately.

Signature:

Date:

iii: Recruitment Poster

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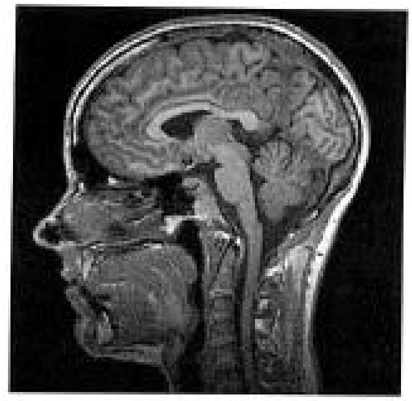
VOLUNTEERS NEEDED FOR RESEARCH STUDY

Researchers as the Thunder Bay Regional Research Institute (TBRRI) are conducting brain imaging studies to investigate changes in motor learning in natural aging.



During the study we use a type of Magnetic Resonance Imaging (MRI) to take images of the brain. During some scans you will be asked to do a task such as look at images or reach for objects.

To be eligible for this study you must:

- Be between the ages of 20 and 85 years old
- Be right handed
- Have normal or corrected to normal vision (wear corrective lenses)
- Have no history of brain injury or disease
- Have no physical or psychological condition that would prevent you from entering a magnet field (for example but not limited to: pace maker, metal implants, anxiety, claustrophia)

The study takes place at the Thunder Bay Regional Health Sciences Centre. The whole study will take 2 hours but you will only be in the MRI for 1 hour. You will be compensated $25 for your time and costs incurred for participating. You may also request an image of your brain.

To request more information about this study please contact:

Investigator: Dr. Jane Lawrence-Dewar (807) 684-7289.

For more information about your rights as a research participant, contact the Thunder Bay Regional Health Sciences Centre Research Ethics Office at 684-6422.

Brain Imaging Study Contact:
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iv: Lakehead University REB Approval

Lakehead UNIVERSITY

Research Ethics Board
t: (807) 343-8283
research@lakeheadu.ca

October 21, 2014

Principal Investigator: Dr. Jane Lawrence-Dewar
Student Investigators: Shayna Parker, Andrea Hantjis, Andrea Pepe
Health Sciences
Lakehead University
Thunder Bay Regional Research Institute
Room 3115, 980 Oliver Road
Thunder Bay, ON P7B 6V4

Dear Dr. Jane Lawrence-Dewar:

Re: REB Project #: 072 14-15 / Romeo File No: 1464121
Granting Agency: Thunder Bay Regional Research Institute
Granting Agency Project #: 1463991

On behalf of the Research Ethics Board, I am pleased to grant ethical approval to your research project titled, "Investigation of the neural mechanisms underlying changes in healthy aging".

Ethics approval is valid until October 21st, 2015. Please submit a Request for Renewal form to the Office of Research Services by September 21st, 2015 if your research involving human subjects will continue for longer than one year. A Final Report must be submitted promptly upon completion of the project. Research Ethics Board forms are available at:https://www.lakeheadu.ca/research-and-innovation/forms. During the course of the study, any modifications to the protocol or forms must not be initiated without prior written approval from the REB. You must promptly notify the REB of any adverse events that may occur.

Completed reports and correspondence may be directed to:

Research Ethics Board
c/o Office of Research Services
Lakehead University
955 Oliver Road
Thunder Bay, ON P7B 5E1
Fax: (807) 346-7749

Best wishes for continued success with your research project.

Sincerely,

Dr. Lori Chambers
Chair, Research Ethics Board

v: Thunder Bay Regional Health Sciences Centre REB Approval

RESEARCH ETHICS BOARD
Re-Approval Application

Please complete, sign and submit this form to the Research Ethics Office
If you require any assistance, please contact: REO@tbh.net

TBRHSC Research Ethics Office Use Only

Re-approval Granted on: June 18, 2014

Starting on: June 18, 2014 Expiring on: June 18, 2015

~~REB meeting date:~~ to be ratified Sept 22, 2014

Signature of Chair: [signature]

Date: 18 June 2014

Thunder Bay Regional Health Sciences Centre
MAY 09 2014
Research Ethics Board

TBRHSC REB # 2012107 Current expiry date: May 28, 2014

Principal Investigator: Dr. Jane Lawrence Dewar

Full Study Title: Investigation of the neural mechanisms underlying changes in motor learning in healthy aging

1.	Study Status	Yes	No
	Enrollment Closed/Completed	☐	☒
	All Assessments/Intervention Completed	☐	☒
	Follow-up Completed	☐	☒
	Data verification/Data analyses Completed	☐	☒

FOR STUDIES INVOLVING CHART REVIEWS		
Study Status	Yes	No
Review of all charts completed	☐	☒

2.	**Number of local study participants** (since study initiation)		
	Enrolled in Study	A	11
	In active intervention phase of study	B	0
	In follow-up phase of study	C	0
	Completed study	D	11
	Withdrew from study	E	0

NOTE:

All participants need to be accounted for

A = B + C + D + E + F

Comments, if needed:

REB Re-Approval Application version September 2011.1 ...page 1 of 2

	Deceased, lost-to-follow up, transferred	F	0	

3.	Reports/Updates of Research Study	Yes	No	Check if attachment
a.	Has an interim data analysis been done? → If Yes, attach a summary.	☐	☒	☐
b.	Have articles been published or presentations given using results of the study? → If Yes, submit a copy of the abstract(s) or a list of references	☐	☒	☐
c.	Have all serious adverse events been reported? [✓] not applicable → If No, include with this report.	☐	☐	☐
d.	Has new literature changed your assessment of risk/benefits for participants?	☐	☒	☐
	→ If Yes, have participants been informed? → If No, attach an explanation of how & when participants will be informed	☐	☐	☐
e.	Have there been any changes in investigators since the last approval?	☒	☐	☐
	→ If Yes, has the REB been notified? → If No, submit an amendment with this application	☐	☒	☐
f.	Is there new evidence from other studies that impact your study? → If Yes, attached summary	☐	☒	☐
g.	Have there been any changes to the local study protocol or consent form? → If Yes, submit an amendment form with this application.	☒	☐	☐
h.	Are study results available? → If Yes, attach a brief summary of study results to date.	☐	☒	☐

Principal Investigator's Signature:
(sign final hard copy after printing) Jane Lawrence Dewar

Print Name: Jane Lawrence Dewar

Date: [month day, year] May 8 2014

vi: TBRHSC REB Amendment Approval

Regional Health

RESEARCH ETHICS BOARD
Amendment Application

Please complete, sign and submit this form to the Research Ethics Office
If you require any assistance, please contact REO@tbh.net

TBRHSC REB #:	2012107	Current REB Expiry Date:	May 28,2014
Principal Investigator:	Dr. Lawrence-Dewar		
Full Study Title:	Investigation of the neural mechanisms underlying changes in motor learning in healthy aging		
Person Completing Form:	J. Lawrence-Dewar	Submission Date:	June 4, 2014

Attach a copy of all related documentation: a summary of changes, rationale for changes, one copy clearly indicating all changes proposed, and one final revised copy (clean copy).

PROPOSED CHANGES TO: (check all that apply)	Revised Version Date	Support Documentation attached
NOTE: Significant changes to the originally approved research study may constitute a new research study application. Please consult the Research Ethics Office at REO@tbh.net if there is a change in the research question, recruitment strategy and/or level of risk.		
Research Question		☐
Study objectives, design or methodology	June 4, 2014	☒
Data Management/Statistical analysis		☐
Study instruments, questionnaires, etc.		☐
Eligibility Criteria (inclusion/exclusion criteria)		☐
Recruitment methods		☐
Number of participants globally		☐
Number of participants locally		☐
Level of Risk		☐
Information Sheet or Letter		☐
Consent Form		☐
Study end date		☐
Change in Principal Investigator/Co-Investigator	June 4, 2014	☒
Medication Dosage or Medical Procedure		☐
Product Monograph (REB approval required)		☐
Investigator Brochure (REB approval required)		☐
No Objection Letter/Investigational Testing Authorization		☐
Other (specify):	June 4, 2014	☒
Incidental findings (addition of Appendix 6)		☐

Actions Required when implemented:	Yes	No	Documentation attached
Will the changes impact the implementation of the project locally? Consult the Research Ethics Office regarding the need to submit a revised organizational impact review through the RDC?	☐	☒	
Will the changes impact recruitment of future participants (potential harms/benefits, increased risk, discomfort or inconvenience)?	☐	☒	
Will the changes impact current participants (potential harms/benefits, increased risk, discomfort or inconvenience)?	☐	☒	
What follow-up do you propose for participants who are already enrolled in the study?			
Inform study participants	☐	☒	When?
Re-consent all participants with revised consent/assent forms	☐	☒	When?
Re-consent active participants with the revised consent/assent forms	☐	☒	When?
No action required	☒	☐	
Other: attach explanation	☐	☒	

Principal Investigator's Signature:
(sign final hard copy after printing) Jane Lawrence Dewar

Print Name: Jane Lawrence Dewar

Date: [month day, year] June 4/14

For Research Ethics Office Use Only

	FULL BOARD REVIEW & APPROVAL	X	DELEGATED APPROVAL
The following amendment(s) have been reviewed and approved by the full board of the TBRHSC Research Ethics Board at the REB meeting dated _____. The quorum for approval was free from conflict and did not involve any member that is associated with this project.		The following amendment(s) have been reviewed and approved by the Chair of the Thunder Bay Regional Health Sciences Centre (TBRHSC) Research Ethics Board. This approval will be reported at the next full REB meeting.	

The Thunder Bay Regional Health Sciences Centre Research Ethics Board is guided by the policies and ethical standards put forth by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Subjects as well as the ICH Good Clinical Practice (GCP) guidelines.

Signature: _____
Chair, TBRHSC Research Ethics Board

Date: 5 June 2014
month day, year

Comments from REB:

APPENDIX B: SUPPLEMENTARY MATERIALS

i: Inclusion/Exclusion Criteria

Inclusion criteria for this study consisted of right-handed individuals aged 18 to 80 years. Handedness was tested using an eight-question shortened version of the Edinburgh handedness task because hand dominance is believed to play a role in the neural basis of motor function. In order to maintain homogeneity of the sample, only right-handed individuals were recruited for this research program. Exclusion criteria consisted of individuals with neurological impairment from injury, disease, or otherwise that could affect the coordination of the right hand, such as tremor or arthritis, or vision. Visual acuity was determined prior to the study by the participant. It was necessary that participants could see clearly either with normal or corrected-to-normal vision (i.e., through corrective lenses). Because participants were in a magnetic field bore during the imaging studies, additional exclusion criteria will apply. Individuals with metal inside their body, as the metal could be magnetic, individuals who have anxiety from small spaces or claustrophobia since the bore is enclosed, women who are or may be pregnant because the implications of high magnetic fields on fetuses is yet unknown, and individuals weighing more than 350 pounds, which is the maximum weight the magnet bore can hold, were not permitted to enter the magnetic field for safety reasons.

ii: Sample Size Calculation

Based on a previous literature, a mean difference in BOLD signal change, or effect size, of 0.5% between groups with a variability of 0.7% (Desmond & Glover, 2002) was anticipated. In order to establish an 80% power with a confidence level of $\alpha<0.05$, the calculated sample size from power analysis was 12 participants per group (Poldrack, Mumford, & Nichols, 2011). This value was determined by rearranging the following power calculation:

$$n = [\sigma(z_{1-\beta} + z_{1-\alpha/2})^2] / \Delta$$

$$n = [0.7(0.845 + 1.96)^2] / 0.5$$

$$n = 11.01 \approx 12 \text{ participants}$$

With a 20% attrition rate, the number of participants collected per group is 15. This attrition rate is necessary to compensate for discarded datasets – i.e., datasets with head motion, withdrawn participants, and complications with stimulus delivery. A total of 45 participants were assigned to three groups with 15 participants per group based on the participants' age. Group 1 consisted of individuals aged 22 to 39, group 2 aged 41 to 59, and group 3 aged 65 to 80. These age ranges were determined based on published and accepted methods found in the literature.

iii: Participant Demographics

*italicized information indicates voluntarily withdrawn participants

Group	Participant Number	Sex	Age	Computer Use (/5)	Handedness (/8)	Medical History	Medication	Glasses
1	01	M	29	5	8	None	diabetes mellitus, hypertension	
	02	F	23	4	8			
	03	M	26	5	8			
	04	M	29	5	7			
	05	M	26	5	7			
	06	F	24	5	8			
	07	M	25	4	8			Y
	08	M	26	5	7			
	09	M	36	5	7			
	11	M	35	5	8			
	12	M	25	4	8			
	14	F	22	5	8			
	18	F	34	5	8			
	27	M	39	5	7			
	46	M	35	5	7			
2	10	M	47	5	8	Headache/ Migraine (not during study)	insomnia, antidepressants	Y
	13	F	44	5	4			
	15	*F*	*55*	*5*	*8*			*Y*
	16	F	46	5	8			Y
	17	F	46	5	8			
	19	M	41	5	8			
	20	F	53	5	8			

	21	F	46	3	8			
	22	F	41	4	8			
	24	F	55	5	7			
	26	F	58	5	8			
	28	M	43	5	8			
	29	M	58	3	8			
	30	M	53	5	7			Y
	31	M	52	3	7			
	42	M	58	4	7			
3	23	M	69	5	8	Peripheral neuropathy Headache/ Migraine	blood pressure, blood thinners, cholesterol, diuretic, aspirin, insulin, Glaucoma drops, Parkinson's medication, anti-restless leg syndrome	
	25	F	65	5	8			Y
	32	F	64	5	8			
	33	F	66	5	8			
	34	F	67	5	8			
	35	M	73	5	7			
	36	M	70	5	8			
	37	F	68	4	8			
	38	F	67	5	8			
	39	M	73	5	7			
	40	F	71	4	8			
	41	*M*	*66*	*5*	*8*			
	43	F	76	4	8			
	44	F	67	5	8			
	45	M	80	5	8			

iv. Participants' Exit Questionnaire Responses

*italicized information indicates voluntarily withdrawn participants

Group	Participant Number	Anything Noticed	Changes Noticed	Challenges	Experiences After
1	01	Noises, trackball.	Orientation of trackball and sounds of MRI.	No.	Headache, sleepiness
	02	Trackball stuck sometimes.	Even when the target was not gotten, the next round came up.	Speed seemed too quick for moving target at times.	Dizziness, sleepiness
	03	Tested psycho motor skills.	No.	The ball moving.	None
	04	Ability to control cursor changed in terms of speed and axis.	Significantly improved control after inverted challenges.	Trackball was difficult.	Tingling- Mild muscle twitching bilaterally along back/sides during DTI pulses. Have been experienced before, but seemed to be synced with the MRI.
	05	No.	Something pushing on head after about 35-45 minutes.	Staying still after about 45 minutes.	Heat, discomfort
	06	Ball tracker changes directions.	Ball tracker changes directions.	Not particularly.	Sleepiness, claustrophobia, anxiety, discomfort

	07	Well organized, loud, difficult to control mouse.	Orientation or responsiveness of trackball changed.	Trackball seemed unpredictable, tight fit with the coil.	Mild sleepiness, heat, and discomfort
	08	No.	No.	When the axis were reversed.	Sleepiness, anxiety, discomfort- Had muscles spasms in back during last scan. Was uncomfortable due to position assumed at the start of the scan.
	09	Trackball often got stuck and there were distortions in trackball movement.	Switch in trackball movement.	Trackball was finicky.	Sleepiness
	11	Started to anticipate the position of target towards the second part of tests.	Speed or target and direction of trackball changed.	Using the trackball was difficult.	Sleepiness
	12	Could improve based on mistakes.	Pattern of movement and speed changed.	Difficult to control cursor.	None
	18	Trackball was not moving in correct direction at certain times.	Trackball responsiveness.	No.	None
	27	Had to adapt to the orientation of the trackball. Title gave clues as to what to	Trackball orientation. “Watch”, “Imagine”, and “Do” functions changed.	Became boring and difficult towards end. Trackball was not totally responsive.	Sleepiness

		expect.			
	46	Target had tendency to move counter clockwise. Trackball went through periods of moving in unpredictable directions.	"Imagine" and "Do" actions began to blend together. Hitting the target box became easier when the cursor moved in the direction it was supposed to.	Separating "Watch" and "Imagine" actions.	Sleepiness, discomfort
2	10	To make it easier moved one axis at a time during distortions.	The axis of trackball changes.	Trackball sometimes jumped.	None
	3	Direction of tracker changed.	Trackball direction and speed changed.	Recognizing the distortion within time given. Staying focused.	Headache, sleepiness, cold, discomfort
	14	Trackball was switched.	Trackball movements.	Trying to stay focused while starting to get sleepy.	Nausea, dizziness, sleepiness
	15	*N/A*	*N/A*	*N/A*	*N/A*
	16	Trackball did not respond in the same direction as indicated.	Trackball movement changed.	None.	Sleepiness, cold
	17	Trackball cursor motion changed direction.	Trackball cursor motion changed direction.	Using the trackball provided difficulty.	Nausea- at the very beginning.
	19	Cursor moved in different directions.	Cursor moved in different directions.	No.	Sleepiness
	20	Delayed reaction with cursor.	Cursor would move in opposite direction.	Paying attention and staying focused.	Discomfort- minor discomfort in neck and right arm.

	21	The cursor was going in the opposite direction to where it was being directed.	Cursor seemed to be moving faster towards the end.	No.	Sleepiness, cold.
	22	Blank screen during task.	The direction of the trackball changed.	Focusing on the task after a few minutes.	Sleepiness, heat.
	24	The direction went opposite sometimes.	The direction went opposite.	Moving the trackball. Staying focused.	Sleepiness, tingling, discomfort
	26	Anticipating the cursor's movement was not always correct. Should have waited to watch the video before doing action.	Got better as the testing progressed.	The trackball.	None
	28	Strategized more as task went on. Cursor moved in opposite direction.	Task became easier when paying attention to time between trials. Became bored.	Trackball was not very sensitive and got stuck at the edge of the screen sometimes.	None
	29	Hard to hear when being given instructions.	Cursor direction was distorted. Target would speed up and slow down.	Staying focused.	Sleepiness
	30	Got very tired.	No.	No.	Sleepiness
	31	The cursor was going in different directions.	The noise from the MRI.	No.	Sleepiness
	42	Had to focus after about4-5 minutes into the tasks.	Cursor became reversed.	Blurred image on the screen during the second test.	None
3	23	Consistent.	Moving the trackball.	Staying awake.	Sleepiness, anxiety
	25	Trackball was hard to	Got bored.	Lying on back for a long	Discomfort

	control.		time.	
32	Directions were confusing.	The easier it was to touch, the better results (in terms of getting the target).	Catching target and using the trackball.	None
33	When the trackball was moved faster, it appeared not to work.	Cursor was doing the opposite of what was expected.	Trackball and cursor would sometimes go in different directions. The difference between "Watch" and "Imagine" and "Imagine" and "Do".	Sleepiness, discomfort from staying in the same position.
34	Changes in noise.	The noise.	Never played video games, so the trackball task was difficult.	Discomfort-goggles were too tight towards the end.
35	Orientation of cursor. Foot twitched when target was captured.	Stopped worrying about being successful, and just tried to get target.	Glasses caused strain. Not moving was challenging.	Headache
36	No problems. Lying down and staying still was not a problem.	Sensitivity of head from resting on the bed.	Hitting the target.	Sleepiness
37	The cursor was very frustrating.	No.	No.	None
38	Trackball was difficult to control.	Sound seemed to vary.	Using track ball. Keeping still.	Sleepiness, discomfort.
39	Trackball was frustrating to use.	No.	No, fairly straightforward.	None
40	No.	No.	No.	Nausea, dizziness, sleepiness

41	*N/A*	*N/A*	*N/A*	*N/A*
43	Having the task explained made it enjoyable.	No.	Was like a game.	Sleepiness
44	Trackball response changed.	Trackball did not always give the same response.	No.	Sleepiness
45	Started to think about the movement of the cursor before actually moving.	The time allowed seemed to increase	No.	Sleepiness, discomfort