The relationship between brain structure, motor performance, and early musical training

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ABSTRACT

The relationship between brain structure, motor performance, and early musical training

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The current dissertation investigated the relationship between brain structure, motor performance, and musical training. Two structural magnetic resonance imaging (MRI) techniques were used: voxel-based morphometry (VBM) and diffusion tensor imaging (DTI). The first study examined the structural correlates of visuomotor synchronisation performance in normal adults. DTI analyses showed that individual differences in synchronisation performance were negatively correlated with white-matter integrity in a region underlying bilateral sensorimotor cortex. Performance was also positively correlated with radial diffusivity in this region, suggesting the influence of a crossing fibre tract. Fibre tractography identified two fibre populations in this region: the corticospinal tract and superior longitudinal fasciculus (SLF). The SLF links parietal and auditory cortical regions previously shown to be engaged during performance of this task in a functional MRI study with the same sample. VBM analyses showed that grey-matter volume in cerebellar regions important for learning was related to the rate of improvement in synchronisation during learning of the task. The second study explored

how musical training during early childhood may have long-lasting effects on brain structure and sensorimotor synchronisation performance. DTI was used to compare white-matter structure in three groups: (1) early-trained musicians (ET; before age seven), (2) late-trained musicians (LT; after age seven), and (3) nonmusicians. Groups were also tested on a visuomotor synchronisation task. ET and LT were matched for years of musical training and experience to isolate the possible effect of age of onset of musical training. Behaviourally, ET outperformed LT and nonmusicians on the synchronisation task. DTI results showed that ET had greater white-matter integrity than LT in the posterior midbody of the corpus callosum, a region connecting bilateral sensorimotor cortices. Measures of white-matter integrity extracted from this region correlated with both synchronisation performance and age of onset of musical training. These findings provide evidence that musical training during a potential sensitive period in development can differentially influence white-matter structure and behavioural performance. Our results are consistent with literature supporting the links between individual differences in brain structure and performance, and training and structural plasticity. They suggest that brain structure is the result of interactions between pre-existing factors, developmental factors, and training and experience.

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CONTRIBUTIONS OF AUTHORS

This dissertation consists of a general introduction, two studies, and a general discussion. I wrote the general introduction and discussion and adapted them with feedback from Dr. Virginia Penhune. Contributions to the two studies are provided below.

Study 1: Chapter 2

Steele, C. J., Scholz J., Douaud, G., Johansen-Berg, H., Penhune, V.B. Structural Correlates of Skilled Performance on a Motor Sequence Learning Task

I developed the design and goals of this study under the guidance of Dr. Virginia Penhune. I developed the structural imaging analyses with the assistance of Dr. Jan Scholz, under the supervision of Dr. Heidi Johansen-Berg. Dr. Gwenaëlle Douaud provided additional consultation and feedback on the analysis methods and tractography results. I designed and coded all data analysis code/scripts and conducted all behavioural and imaging data processing and analyses. With my co-design and feedback, Avrum Hollinger (Ph.D. Candidate, Music Technology) created the MR-compatible mouse and Alejandro Endo (research technician) coded the stimulus presentation program used in this study. I recruited and tested all participants with the assistance of Jennifer Anne Bailey (research assistant) and Anthony Hopley (undergraduate student). I wrote this manuscript under the guidance of Dr. Virginia Penhune and adapted it with feedback from the co-authors.

Study 2: Chapter 3

Steele, C.J., Bailey, J.A., Zatorre, R.J., Penhune, V.B. Sensitive Periods and the Development of Expertise: Diffusion Tensor Imaging Evidence from Musicians

I developed and implemented all behavioural and image processing and analysis methods with feedback from Jennifer Anne Bailey (Ph.D. Candidate, Psychology) under the supervisory guidance of Dr. Virginia Penhune and Dr. Robert Zatorre. Recruitment and structural imaging data collection was conducted by Jennifer Anne Bailey with the assistance of Amanda Daly, Eva Best (undergraduate student), Michael Spilka (research assistant), and me. Jennifer Anne Bailey and I trained the experimenters and supervised behavioural testing for the TMST. Testing was conducted by Jennifer Anne Bailey, Amanda Daly, Eva Best, and Michael Spilka. I wrote this manuscript with the guidance of Dr. Virginia Penhune and Jennifer Anne Bailey, with feedback from all co-authors.

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Chapter 1: General Introduction

In recording studios and concert halls around the world, groups of highly trained musicians perform intricate series of precise and coordinated movements to create music. Not only is each musician required to order their movements to play the correct notes, but they must also synchronise with their colleagues in order to perform at the correct time. Though this may seem like behaviour that can only be performed by a select group of experts, it is simply a specialised example of how every one of us behaves throughout our daily lives. Virtually all of the actions that we perform throughout the day are sequential in nature, requiring the organisation of multiple movement elements across time (Lashley, 1974). As with playing an instrument, each movement must be accurately executed and precisely timed. Studying how the brain acquires and performs motor sequences helps us to understand how skill is represented within the brain and allows us to ask questions about how specific training is related to brain structure and function. Human brain imaging data and neurophysiological studies in animals have provided us with a relatively good understanding of the functional networks important for motor sequence learning (Hikosaka et al., 1999; Doyon et al., 2009; Penhune and Steele, 2012) (Appendix A). In contrast, we know relatively little about the relationship between brain structure, motor sequence learning, and performance.

The current dissertation combines standard structural magnetic resonance imaging measures of grey-matter volume with diffusion tensor imaging (DTI), a magnetic resonance imaging technique that measures white-matter integrity in the brain. The first study linked individual differences in brain structure to individual differences in motor

sequence performance in normal adults (Chapter 2). It identified the grey-matter and white-matter correlates of skilled performance and related them to the results of a functional magnetic resonance imaging (fMRI) study in the same group (Steele and Penhune, 2010) (Appendix B). The second study explored how musical training during early childhood may have long-lasting effects on brain structure and performance. DTI was used to compare white-matter structure between two groups of adult musicians who began their musical training before and after the age of seven to isolate the possible long-term effects of musical training during an early "sensitive period" in childhood (Chapter 3).

1.1 Motor Learning

Humans are able to learn an incredible variety of motor skills. Motor learning is concerned with how skills are learned through practice and optimised for peak performance (Willingham, 1998). The two most common tasks used to investigate motor learning are motor adaptation and motor sequencing tasks. Motor adaptation tasks measure the ability to adapt movements to respond accurately within an altered environment, such as pointing to a target while holding a robotic arm that influences movement through force feedback (Shadmehr and Mussa-Ivaldi, 1994). With practice, participants learn to adapt their movements within the altered environment to perform accurate reaching movements. In contrast, motor sequence tasks probe our ability to learn, perform, and optimise well-ordered sets of movements such as dialling a phone or playing a piano (Lashley, 1974). The most common sequence learning task is the serial reaction time task (SRTT). The SRTT requires that participants learn to quickly and

accurately reproduce a sequence of visually cued keypresses (Nissen and Bullemer, 1987). Learning is typically assessed by changes in speed and accuracy compared to a random or untrained sequence.

1.1.1 The Temporal Motor Sequence Task

The two studies in this dissertation examined learning on the timed motor sequence task (TMST), a variant of the SRTT that requires participants to reproduce a series of timed keypresses in synchrony with a visual stimulus (Figure 1.1). The TMST has been optimised for the assessment of short and long-term changes as a result of motor sequence learning. It has been used in a number of previous experiments in our laboratory and requires that participants produce a precisely timed sequence of finger taps in synchrony with a complex 10-element sequence of visual cues presented for long or short durations (Penhune and Doyon, 2002, 2005; Savion-Lemieux and Penhune, 2005; Watanabe et al., 2006; Steele and Penhune, 2010). It uses only a single finger on a single button, allowing the assessment of a sequence of movements that does not require multiple effectors or spatial processing (Savion-Lemieux and Penhune, 2005). Learning and performance on the TMST can be separated into two components that are optimised with practice: 1) accuracy – the order of short and long key-presses in the sequence; and 2) synchronization – the precise timing of movements. Accuracy is the more explicit sequence ordering component that improves quickly, while synchronisation is the more motoric sensorimotor integration component that continues to improve across multiple days of practice (Penhune and Doyon, 2002; Steele and Penhune, 2010) and is sensitive to the effects of musical training (Watanabe et al., 2006; Bailey and Penhune, 2010).

Recent functional imaging work from our laboratory has also shown that optimisation of these two components occurs within separable brain networks. Synchronisation improvements were linked to specific increases in primary motor and cerebellar cortex while accuracy was associated with increased activity in more frontal regions (Steele and Penhune, 2010). The studies presented in this dissertation used synchronisation performance on the TMST to probe the relationship between brain structure and skilled motor performance (Study 1) and explore the relationship between skilled performance, training, and white-matter structure in highly trained musicians (Study 2).

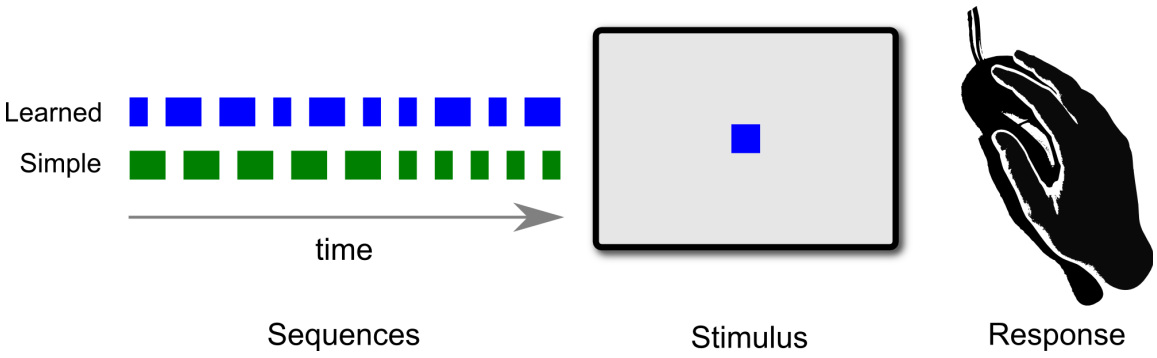


Figure 1.1. TMST Method

The sequence types, visually presented stimuli, and response method are shown.

1.1.2 Motor Sequence Learning

Motor sequence learning is the acquisition and optimisation of a series of interrelated movements through practice (Penhune and Steele, 2012). Take the example of a naïve participant at a piano, it is apparent there is a lot to learn before a melody can be played.

Once the player understands the relationship between pressing the keys and the sounds that they produce, there are two basic components to performing the melody: pressing keys in the correct order (accuracy) and pressing them at the correct time (synchronisation). Initial learning is characterised by acquisition of the sequential order of movements while continued practiced results in the optimisation of motor parameters (such as synchronisation). With practice, accurate and efficient performance will produce the melody as it was meant to be played.

Learning is traditionally broken down into three behaviourally distinct phases: early learning, consolidation, and late learning (Korman et al., 2003; Shadmehr and Krakauer, 2008). Early learning is defined as the learning that occurs during a single session of practice and is characterised by rapid improvements in skill (Karni et al., 1998; Korman et al., 2003). It is thought that this phase of learning creates the initial motor skill representation within the brain: the motor memory. The consolidation phase, initially identified in cognitive learning tasks, is when the motor memory formed during early learning is thought to be fixed in a more permanent state (Brashers-Krug et al., 1996; Doyon and Ungerleider, 2002). The motor memory is resistant to interference from the learning of similar motor skills after this phase. Late learning is characterised by slow incremental improvements in performance over multiple days of practice (Karni et al., 1995).

1.1.3 Models of Motor Sequence Learning

There are two major descriptive models of motor sequence learning. The first is a stage model that describes learning as a progression through fixed stages (Doyon and Benali,

2005) and the second is a component model that describes how two learning parameters are optimised as learning progresses (Hikosaka et al., 2002a). Our recent functional imaging study of motor sequence learning showed that different networks were responsible for the optimisation of different components of learning (Steele and Penhune, 2010). This research precipitated the development of an integrated model of motor sequence learning that combines the stage and components models with ideas from motor control (Penhune and Steele, 2012). Our model proposes that sequence learning is driven by parallel interacting processes such as error correction, stimulus-response association, chunking, and sensorimotor integration that are supported by specific cerebellar, striatal, and motor cortical mechanisms. It provides a framework for motor sequence learning that moves beyond the classification of learning within fixed stages and hypothesises additional mechanisms for the optimisaton of multiple components.

The stage model describes the progression of learning through fixed stages: early learning, consolidation, and late learning (Doyon and Benali, 2005; Doyon et al., 2009). Early learning occurs quickly (i.e., there are rapid behavioural improvements) and involves the cerebellum (CB), rostral striatum, motor cortical, prefrontal, and parietal cortical regions (Figure 1.2A). The early learning stage includes a shift in activity from associative to motor regions of both the CB and the striatum. Late learning is thought to occur more slowly and involves the caudal striatum, motor cortical, and parietal cortical regions. This qualitative change from early to late learning is thought to be mediated through the consolidation stage. Following consolidation, activity in the striatum shifts from rostral to caudal regions and the CB is no longer necessary for the production of

skilled motor responses. Thus, the performance of a well learned motor sequence in the late learning stage is represented within the caudal striatum and motor and parietal cortices.

In contrast, the components model of motor sequence learning focuses on the mechanisms required to learn and optimise two different task components (Hikosaka et al., 2002a). The authors propose that motor sequence skills are handled as two types of sequences when represented within the brain: one spatial and one motor (Figure 1.2B). The spatial sequence, or explicit ordering of the task, requires a high level of attention, is learned quickly, can be identified by rapid improvements in accuracy, and is encoded in the loops between the associative (rostral) basal ganglia (BG), prefrontal and parietal cortices, and the associative (lateral) CB. The motor sequence, or implicit dynamic elements of the task, requires little attention, is learned more slowly, can be identified through improvements in synchronisation, and is encoded between the loops in the motor (caudal) BG, motor cortex, and motor (medial) CB. The two loop circuits communicate from spatial to motor through the supplementary motor area (SMA), preSMA, and premotor cortex (PMC). While learning occurs in both loops simultaneously, the areas involved in representing the spatial sequence and communicating between the two circuits are more important early in learning (when explicit sequence knowledge is used and transformed into the motor sequence via the preSMA/SMA) and less important in later learning (where the areas involved in representing the motor sequence become more dominant). Though originally based on animal studies, this model has found considerable support in human functional imaging and serves as a major theoretical model of motor

sequence learning in humans (Doyon et al., 2002, 2003; Penhune and Doyon, 2002, 2005; Hikosaka et al., 2002b; Maquet et al., 2003; Floyer-Lea and Matthews, 2004, 2005; Lehéricy et al., 2005).

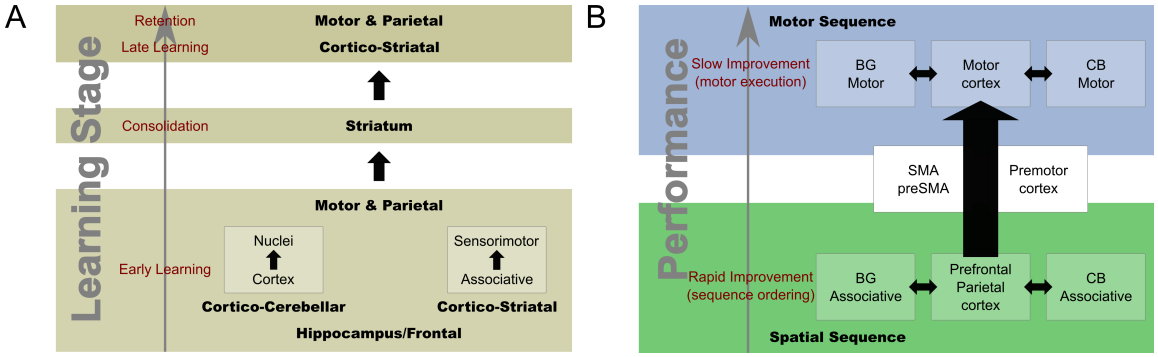


Figure 1.2. Descriptive Models of Motor Sequence Learning

Panel A – Stage model (Doyon and Benali, 2005). Panel B – Components model (Hikosaka et al., 2002a). Both figures have been adapted from the originals to focus on the structures relevant for motor sequence learning.

Based on the existing models and experimental work in our laboratory, an integrated model of motor sequence learning has recently been proposed (Penhune and Steele, 2012). Work from our laboratory established the separability of accuracy and synchronisation components of learning based on the pattern of behavioural changes across practice (Steele and Penhune, 2010), rates of forgetting (Savion-Lemieux and Penhune, 2005), and effects of early musical training (Watanabe et al., 2006). Our recent functional neuroimaging research showed that accuracy and synchronisation were also

optimised by different brain networks (Steele and Penhune, 2010). This study measured learning on the TMST across five days of training, three of which were conducted during functional magnetic resonance imaging sessions. Crucially, we found that a network including primary motor and cerebellar cortex increased in activity as synchronisation performance improved. This network was separable from that linked to improvements in accuracy, which consisted of more frontal regions and the hippocampus. This study was also the first functional imaging study to show that consolidation could be predicted by activity in primary motor cortex during early learning. Study 1 presents the structural imaging results of the sample collected for this study and relates them to the functional imaging results discussed here.

Our model proposes that sequence learning is driven by parallel interacting processes such as error correction, stimulus-response association, and sensorimotor integration that are supported by specific cerebellar, striatal, and motor cortical mechanisms. The regions that are recruited for any particular phase or stage of learning are dependent on the demands of the task that is being performed (Figure 1.3). For example, performance on a sequence where the ordering of elements is already explicitly known will not show differential increases in regions coding the more explicit components of the task, the cortico-striatal system, but will continue to show functional increases in the cortico-cerebellar loop to optimise the more motoric components (e.g., synchronisation, velocity). This differs from the model of Doyon and colleagues (Doyon and Benali, 2005; Doyon et al., 2009) that links phases of learning to processes in particular regions and extends upon that of Hikosaka and colleagues (2002a) by proposing that there are more

than two components of performance that can interact and become optimised across learning. With our model, sequence learning is re-conceptualised as the combined optimisation of multiple components that are supported by distinct and overlapping functional networks in the brain.

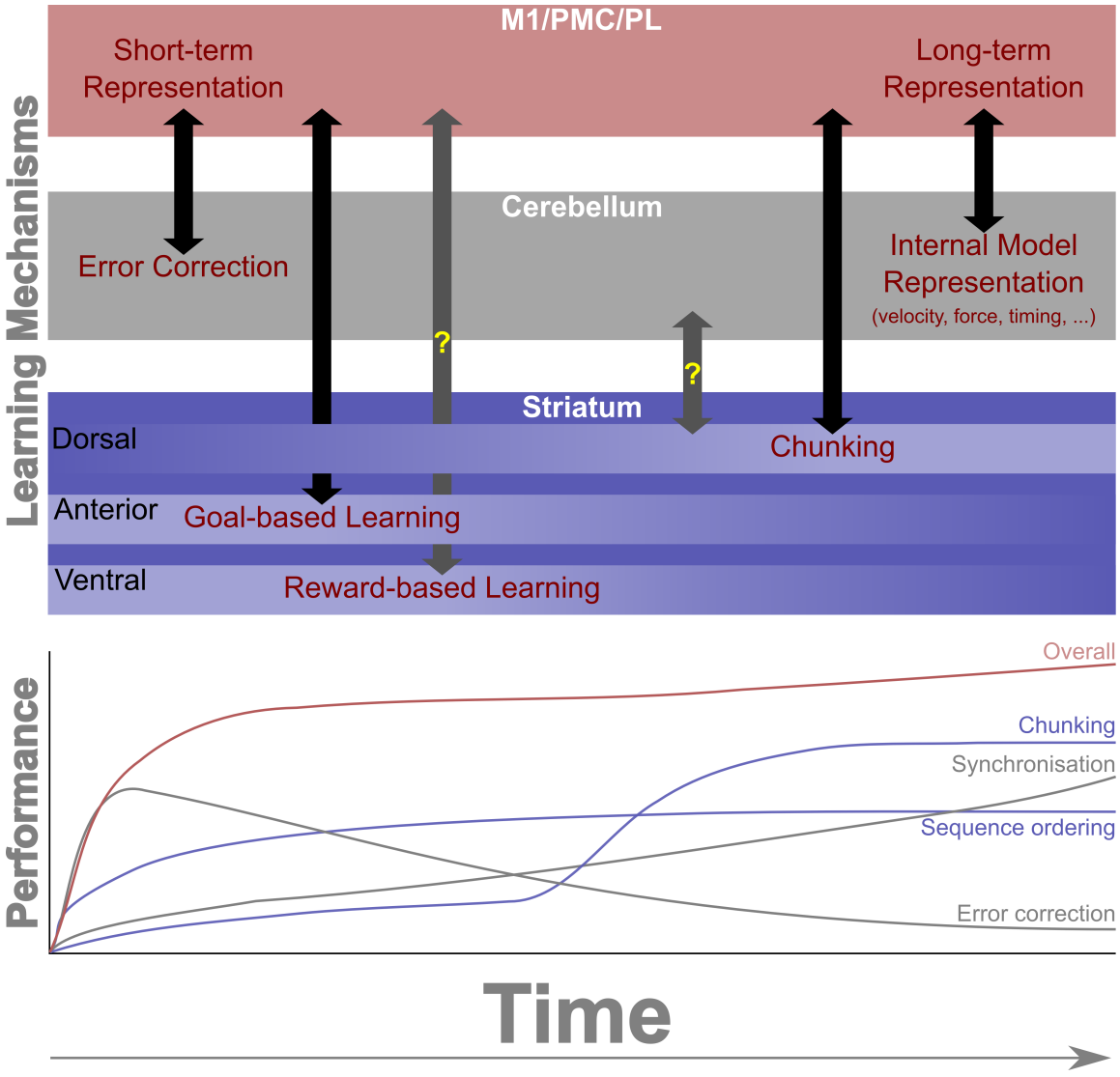


Figure 1.3. Multiple Components Model of Motor Sequence Learning

The top panel illustrates the brain regions and associated mechanisms involved in motor sequence learning and highlights their connectivity. Interactions between regions/mechanisms are depicted by vertical arrows, with lesser known interactions depicted by light arrows. The colour gradient within the striatum represents the relative contribution of each learning mechanism (light = greater contribution; dark = lesser contribution). The bottom panel depicts the idealized learning curve for different components of performance over time. Each component is colour-coded to its associated brain region (Penhune and Steele, 2012)

1.2 Plasticity

Neural plasticity describes the nervous system's ability to change and adapt brain structure and function in response to the environment. It includes plasticity associated with normal development maturation and plasticity resulting from training and experience (Pascual-Leone et al., 2005). Functional brain plasticity has been actively assessed and described in the past two decades of human functional imaging (see section 1.1.3 for an overview of functional neuroplasticity in human motor sequence learning). Structural plasticity has been less well studied, but can be investigated by 1) linking variability in brain structure to variability in performance, 2) assessing differences between experts and controls, and 3) assessing longitudinal change during training. The relationship between brain structure, training, and performance underlying structural plasticity is the topic of the current dissertation.

1.2.1 Brain Structure

Advanced imaging techniques allow us to non-invasively assess brain structural differences between groups, individuals, and over time. The most widely used technique for measuring brain structure is voxel-based morphometry (VBM) (Ashburner and Friston, 2000). VBM provides a measurement of the local grey- and white-matter composition in the brain. Diffusion tensor imaging (DTI) is a recently developed MRI technique that measures the diffusion of water in multiple directions within the brain. The most popular measure derived from DTI is fractional anisotropy (FA), a summary measure of the directionality of diffusion at a given voxel that is interpreted as an index of white-matter integrity (Pierpaoli and Basser, 1996). FA is sensitive to the underlying axon myelination, diameter, and packing density within voxels.

In a pioneering VBM study, Maguire and colleagues found greater grey-matter volume in the hippocampus of licensed London taxi drivers compared to controls (2000). This study was the first to identify grey-matter differences that may be the result of experience dependant structural plasticity. Others have used both VBM and DTI with similar group comparison methods to identify regions where structural plasticity may result from and underlie enhanced skill in such varied groups as bilinguals (Mechelli et al., 2004), ballet dancers (Hänggi et al., 2010), golfers (Jäncke et al., 2009), and musicians (Bermudez et al., 2009; Imfeld et al., 2009). These studies used cross-sectional designs that assume that prior training and/or experience gives rise to the observed structural differences. However, group membership was not randomly selected so it is possible that pre-existing factors, such as genetics, causes both the propensity to train and the observed structural

differences. As such, cross-sectional designs such as these provide indirect evidence for structural plasticity. Study 2 used a group differences approach to identify white-matter regions that may undergo training-related plasticity as a result of early versus late onset musical training.

Though structural imaging studies have traditionally focused on identifying differences between groups, an increasing number of researchers are attempting to link individual variability in the structure of the brain to variability in performance. For example, grey-matter volume from VBM has been linked to second language proficiency in bilinguals (Mechelli et al., 2004), the ability to learn speech sounds (Golestani and Pallier, 2007; Golestani et al., 2007), and musical transformation (Foster and Zatorre, 2010a). With recent advances in DTI and FA processing and analysis techniques, variability in FA has also been linked to measures of bimanual coordination (Johansen-Berg et al., 2007), artificial grammar learning (Flöel et al., 2009), musical training (e.g., Bengtsson et al., 2005) and motor performance (Tuch et al., 2005; Della-Maggiore et al., 2009; Filippi et al., 2010; Taubert et al., 2010; Tomassini et al., 2011). In this dissertation, Study 1 used a purely individual differences approach to link white matter variability measured with DTI to motor sequence performance. Though VBM was used to assess grey-matter volume in Study 1, this dissertation is primarily concerned with the use of DTI to examine the links between white-matter structure, performance, and training. Therefore, we turn now to a detailed discussion of methodology and interpretation of DTI data.

1.2.2 Diffusion Tensor Imaging

DTI is a non-invasive MRI technique for measuring white-matter organisation in-vivo. It

measures the diffusion of water in multiple directions within the brain to construct a three dimensional profile of water diffusion within each voxel (Figure 1.4A). Because water diffusion is more restricted perpendicular to the direction of fibre bundles than along them, the diffusion profile can provide a summary measurement of the integrity of the fibre within the voxel (FA) and estimate its orientation(s) based on the diffusion tensor. The diffusion tensor describes diffusion in the three orthogonal directions, denoted by the eigenvector/eigenvalue parameter pairs $V1/\lambda_1$, $V2/\lambda_2$, $V3/\lambda_3$. The eigenvalues describe the strength of diffusion along the principal diffusion direction (λ_1) and the two orthogonal directions (λ_2 and λ_3) while the eigenvectors describe their orientations (V1, V2, V3). λ_1, λ_2, and λ_3 are used to calculate FA, the most commonly used measure derived from DTI. FA is a single value that describes the shape of the diffusion profile in each voxel; ranging from perfectly isotropic (0, or equal diffusion in all directions) to perfectly anisotropic (1, diffusion in only one direction) (Beaulieu, 2002; Mori and Zhang, 2006) (Figure 1.4B). FA in white-matter is affected by tissue characteristics including axon myelination, diameter, packing density, and orientation (Beaulieu, 2002; Alexander et al., 2007).

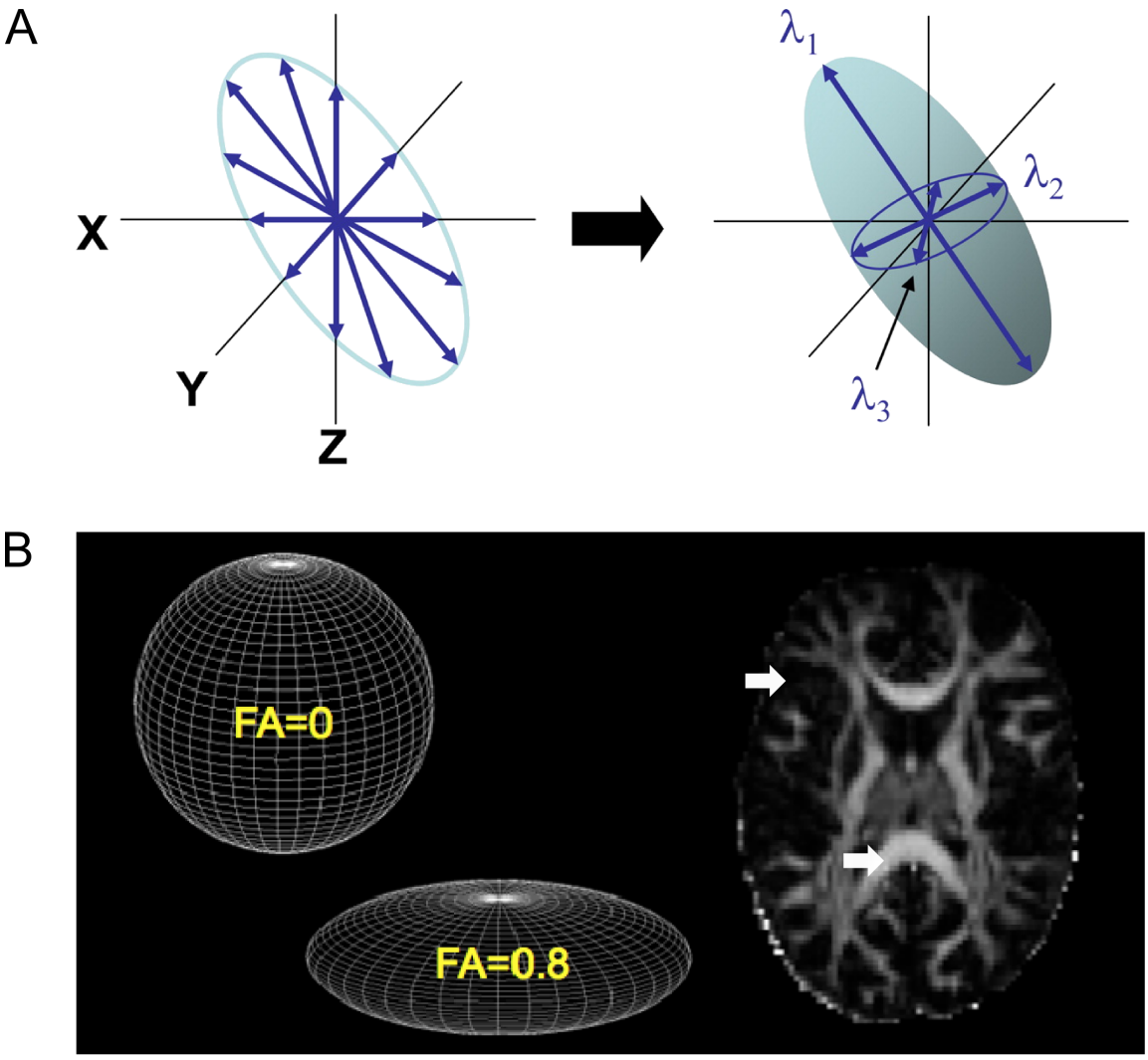


Figure 1.4. The diffusion tensor and FA

Panel A – The diffusion ellipsoid (right) is calculated based on the measured diffusion profile of water within each voxel (left). The diffusion tensor eigenvalues λ_1, λ_2, and λ_3 describe the strength of diffusion along the three perpendicular axes of the diffusion ellipsoid (figure adapted from Mori and Zhang, 2006). Panel B – The tensor eigenvalues are used to calculate FA, which takes on values from 0 (equal diffusivity in all directions; isotropic diffusion) to 1 (diffusivity in only one direction; perfectly anisotropic diffusion).

The top and bottom arrows indicate low and high FA regions in an axial slice of a human brain, respectively.

FA differences between groups or associated with performance normally occur within the fibre tracts connecting regions thought to be responsible for the behaviour of interest (Johansen-Berg, 2010). As greater FA can be linked to structural characteristics of the underlying tissue including myelination, diameter, packing density, or some combination thereof, it is typically thought to relate to enhanced communication between neurons. However, FA may also be influenced by factors such as crossing fibres (Jbabdi et al., 2010). Many regions of white-matter contain multiple fibre populations that cross to connect different regions of cortex. Therefore, within a single voxel, changes in one fibre population may increase or decrease FA depending on the relative strength of the other fibre population, while changes in both may result in no detectable change at all. Current interpretation of FA (and other diffusion-derived measures) is based on animal studies of diffusion and neuroanatomy in fibre tracts where there is a strong single direction (Song et al., 2002; Sun et al., 2008). Therefore, the interpretation of diffusion measures in more complex situations with multiple crossing fibre population is not clear. FA in regions where fibres are less coherent, such as is the case with crossing fibres, may need to be interpreted within the context of the underlying fibre orientations and other diffusion measures such as axial and radial diffusivity (Alexander et al., 2007; Wheeler-Kingshott and Cercignani, 2009).

1.2.3 Individual Differences

Though we can all learn new motor skills, there are marked individual differences in how we learn and improve over time. As such, not every individual can improve performance at the same rate, nor can they attain the same level of expertise. For example, I would be highly unlikely to be able to outperform pre-scandal Tiger Woods on the golf course even if I practiced for the next 20 years. But what is the cause of these differences in ability? As neuroscientists, we expect that behavioural differences are related to individual differences in brain structure and function. The individual differences approach has recently been applied in functional imaging studies of motor learning. Variability in brain function has been linked to performance variability in recent sequence learning studies to identify regions supporting improved performance (Penhune and Doyon, 2005; Steele and Penhune, 2010), error correction (Floyer-Lea and Matthews, 2004; Lehéricy et al., 2005), speed (Orban et al., 2010), and skill transfer (Seidler and Noll, 2008). Though the structural arrangement and connectivity of neurons within the brain is likely the most important factor underlying brain function and behaviour, individual differences in brain structure have received relatively little attention (Van Horn et al., 2008). The relationship between individual differences in brain structure and motor performance is addressed in both Study 1 and 2 of this thesis.

1.2.4 Training-related Plasticity

Evidence for training-related plasticity comes from two sources: 1) relatively short-term longitudinal studies examining changes in brain structure when individuals are trained on a particular task and 2) studies that compare brain structure in people who have

undergone long-term training within a particular domain. Short-term longitudinal studies in humans provide the most direct evidence for structural plasticity as a result of training. The first to identify training-related structural plasticity found increased grey-matter volume in bilateral medial temporal cortex and left intraparietal sulcus after three months of juggling (Draganski et al., 2004). Subsequent work has identified grey-matter plasticity related to three months of preparation for a medical exam (Draganski et al., 2006). More recent longitudinal studies have identified training-related changes in both grey- and white-matter. Scholz and colleagues found co-localised grey-matter volume and FA increases in the intraparietal sulcus after six weeks of juggling practice (2009) and Taubert and collaborators found co-localised prefrontal cortical grey-matter volume and FA increases after six weeks of practice on a balancing task (2010). Together, these longitudinal studies provide good evidence that training can drive structural plasticity in the human brain.

The impact of long-term training on brain structure has been assessed in studies comparing highly skilled individuals who have undergone extensive training in a particular domain to non-expert controls. White-matter structural plasticity has previously been linked to training in domains such as ballet (Hänggi et al., 2010), golf (Jäncke et al., 2009), and music (Imfeld et al., 2009). Musicians are an ideal model for assessing the potential impact of training and experience on brain structure. Musical training and performance is a complex combination of demanding cognitive, sensory, and motor skills (Zatorre et al., 2007) and musicians undergo years of intense training that often begins early in life. Cross-sectional studies such as these provide good evidence for structural

differences between groups; however, it is still possible that the observed structural differences are the result of pre-existing differences rather than training-induced alterations. Though difficult and expensive, a longitudinal design where individuals are randomly assigned to training or control groups at an early age and followed into adulthood would be necessary to test this hypothesis.

1.2.5 Musicians

VBM studies comparing musicians and nonmusicians provide indirect evidence for structural plasticity as a result of musical training and/or performance. Musicians have been shown to have greater grey-matter volume in premotor, sensorimotor, and cerebellar cortex (Gaser and Schlaug, 2003), as well as right auditory cortex (Bermudez and Zatorre, 2005). Differences in white-matter have also been observed in the anterior corpus callosum (Schlaug et al., 1995; Schmithorst and Wilke, 2002) and cortico-spinal tract (Imfeld et al., 2009). As in the previous juggling and balance examples, a more direct link between musical training and structural plasticity can be demonstrated with longitudinal training designs. Hyde and colleagues (2009), collected structural brain images of six year-olds before and after fifteen months of musical training and compared them to controls. While brain structure did not differ between the two randomly assigned groups prior to training, primary motor, midbody of the corpus callosum, and right primary auditory regions showed greater change between scans in the group that underwent training (Hyde et al., 2009). These findings support the interpretation that the differences between the brains of musicians and controls are likely due to intense musical training.

Within the studies comparing musicians to nonmusicians, some results suggest that early training has a differential effect on brain structure. Differences between musicians and nonmusicians in the anterior corpus callosum were found to be greater for early-trained musicians (Schlaug et al., 1995), as was the estimated size of motor cortex (Amunts et al., 1997), and the cortical representation of the auditory cortex (Pantev et al., 1998). More recently, training during early childhood has been shown to be related to white-matter in the corpus callosum of adult musicians (Bengtsson et al., 2005). Together, this research suggests that there may be particular periods during early development where intensive training can have a differential impact on brain structure. However, these studies did not control for differences between early- and late-trained musicians in the number of years of training and experience. Recent studies in our laboratory showed behavioral differences between early and late-trained musicians matched for years of training and experience (Watanabe et al., 2006; Bailey and Penhune, 2010). Study 2 in the current dissertation used DTI to assess the possible effects of early musical training on the structure of the brain in a new matched sample of early- and late-trained musicians.

1.2.6 Sensitive Periods

Musicians are an ideal model for investigating the possible effects of early musical training because they allow us to probe the interaction between typical developmental plasticity and training-related plasticity on adult brain structure and performance (Penhune, 2011).

A sensitive period is a developmental time window when experience has strong and long-lasting effects on behaviour and the brain (Knudsen, 2004). Experience during this period

has a greater impact on behaviour and the brain than that experienced outside the sensitive period window but is not required for normal development. A critical period is a special case of a sensitive period where experience is *essential* for normal development. The first evidence for critical periods came from studies where cats were monocularly deprived during early development. Depriving the eye of input between the ages of 4-8 weeks resulted in abnormal behavioural and brain structural development that could not be corrected (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970). Similar work with rats has defined a critical period between days 11-13 where exposure to normal auditory stimuli is required for normal development of primary auditory cortex (de Villers-Sidani et al., 2007). Most evidence for sensitive periods in humans comes from studies with children who have received cochlear implants for profound deafness (Sharma et al., 2007; for reviews, see Kral and Sharma, 2012). In general, those who receive implants between 3.5-4 years show greater speech perception performance than those who receive implants after the age of 6/7, suggesting a sensitive period that may begin closing at 4 years of age.

The first study to assess brain structural differences between musicians and nonmusicians found greater cross-sectional area in the anterior region of the corpus callosum – a finding driven by the subgroup of musicians who began training before the age of seven (Schlaug et al., 1995). This finding provided the initial suggestion that musical training experienced before a particular age, perhaps within a sensitive period, could have a differential impact on brain structure and performance. Age of onset of musical training has subsequently been related to motor cortical size (Amunts et al., 1997) and auditory cortical representation (Pantev et al., 2001). Correlational evidence for the role of early

training on brain structure found that retrospective reports of hours of musical practice prior to the age of eleven was positively correlated with FA in more regions of the brain than hours of training during adolescence or adulthood (Bengtsson et al., 2005). Though suggestive of a sensitive period, these studies did not control for the fact that musicians who begin training earlier will have a greater number of years of training and/or experience than those who began later and are the same age. Behavioural studies in our laboratory comparing training- and experience-matched groups of early-trained (ET) and late-trained musicians (LT) have recently addressed this issue. These studies used highly skilled musicians who were classified as either ET – musicians who began training prior to the age of seven – or LT – musicians who began training after the age of seven and who were matched for years of musical experience, years of formal training, and hours of current practice. Even with these strict controls, ET had significantly greater visuomotor synchronisation performance on the TMST (Watanabe et al., 2006), and auditory-motor synchronisation than LT (Bailey and Penhune, 2010). Based on this work, Study 2 used DTI to assess the possible structural effects of early training.

1.3 Current Studies

This dissertation includes two research studies that have been submitted for publication. The first study (Chapter 2) reports the grey-matter and white-matter correlates of synchronisation performance on the TMST after five days of training in normal adults. This study used synchronisation performance on the TMST as an index of innate final ability and learning (rate of acquisition of skill). It used an individual differences design to identify the structural regions of the brain that support synchronisation. The second

study (Chapter 3) investigates the white-matter structural and behavioural consequences of musical training during a possible sensitive period in development. This study compares white-matter structure and synchronisation performance of early-trained and late-trained musicians. Groups differed on the age of onset of musical training but were matched for years of training and experience.

Chapter 2: Structural correlates of skilled performance on a motor sequence learning task

Steele, C. J., Scholz J., Douaud, G., Johansen-Berg, H., Penhune, V.B. Structural Correlates of Skilled Performance on a Motor Sequence Learning Task

2.1 Abstract

The brain regions functionally engaged in motor sequence learning and performance are well established, but the structural characteristics of these regions and the fibre pathways involved have been less well studied. Therefore, the current study used diffusion tensor imaging, probabilistic tractography, and voxel-based morphometry to determine the structural correlates of skilled motor performance. Further, we compared these findings with fMRI results in the same sample. We correlated final performance and rate of improvement measures on a temporal motor sequence task with skeletonised fractional anisotropy (FA) and whole brain grey matter (GM) volume. Final synchronisation performance was negatively correlated with FA in white-matter underlying bilateral sensorimotor cortex – an effect that was mediated by a positive correlation with radial diffusivity. Multi-fibre tractography indicated that this region contained crossing fibres from the corticospinal tract and superior longitudinal fasciculus (SLF). The traced SLF linked parietal and auditory cortical regions that have been shown to be functionally engaged in this task. Thus, we hypothesise that enhanced synchronisation performance on this task may be related to greater fibre integrity of the SLF. Rate of improvement on synchronisation was positively correlated with GM volume in cerebellar lobules HVI and

V – regions that showed training-related decreases in activity in the same sample. Taken together, our results link individual differences in brain structure and function to motor sequence learning and performance on the same task. Further, it shows the utility of using multiple MR measures and analysis techniques to specify the interpretation of structural findings.

2.2 Introduction

As anyone who has ever learned to type or play a video game knows, no two individuals are able to reach the same level of performance on a motor skill, nor do they follow the same trajectory of improvement as they learn. As neuroscientists, we assume that such individual differences are related to brain structure and function, but relatively few studies have linked performance variability in learning to variability in the brain. Over the last twenty years, work with animals and functional neuroimaging studies in humans have identified the major brain regions involved in learning motor skills (Hikosaka et al., 2002a; Doyon and Benali, 2005; Ashe et al., 2006; Doyon et al., 2009; Penhune and Steele, 2012). Work from our lab and those of others has examined the relationship between individual differences in motor performance and brain function (Seidler et al., 2002; Penhune and Doyon, 2005; Grafton et al., 2008; Seidler and Noll, 2008; Orban et al., 2010; Steele and Penhune, 2010), but individual differences in structure have rarely been explored (Van Horn et al., 2008). However, several recent studies have shown that individual differences in both white matter (WM) and grey matter (GM) structures can be related to motor learning and performance (Tuch et al., 2005; Johansen-Berg et al., 2007; Della-Maggiore et al., 2009; Tomassini et al., 2011). Only one of those studies combined

data from both structural and functional MRI (Tomassini et al., 2011). Crucially, the authors found that premotor and cerebellar regions showed co-localised structural and functional correlations with behaviour (Tomassini et al., 2011). These results underscore the importance of combining data from multiple methodologies to provide a more nuanced view of how brain structure and function are related to behaviour.

Following this model, the current study combines fMRI data from a study of motor sequence learning (Steele and Penhune, 2010) with diffusion tensor imaging (DTI – to assess white matter integrity and tractography) and voxel-based morphometry (VBM – to assess GM volume). The goal is to examine the relationship between individual differences in performance, brain function, and underlying structure at the end of training. Results from the fMRI experiment revealed learning- and performance-related functional changes in specific regions of motor, cerebellar, and parietal cortex. Based on this, we hypothesised that individual differences in WM and GM structure in these regions would be related to individual differences in learning and performance.

The majority of structural studies of individual differences find that better performance is associated with higher FA or greater GM volume (Golestani and Pallier, 2007; Golestani et al., 2007; Bermudez et al., 2009; Della-Maggiore et al., 2009; Jäncke et al., 2009; Scholz et al., 2009; Foster and Zatorre, 2010b; Tomassini et al., 2011). Individual differences in structural measures reflect differences in the microsctructural organisation of tissue related to task performance. Greater FA, an index of fibre integrity, may represent a greater ability for neurons in connected regions to communicate (Fields, 2005, 2008); greater GM volume may indicate greater cell density and synaptic connections

that could support enhanced information processing. However, some studies have found that better performance is associated with lower FA values (Tuch et al., 2005; Taubert et al., 2010). These somewhat counter-intuitive findings have been interpreted as potentially resulting from fibres that cross the identified tract. Analyses that could assess the contribution of crossing fibres to FA values have typically not been conducted. FA values in WM are affected by factors such as axon myelination, diameter, and packing density (Beaulieu, 2002; Alexander et al., 2007), but may also be influenced by the presence of crossing fibres (Douaud et al., 2009, 2011; Jbabdi et al., 2010). FA values in one fibre population can be affected by the relative strength of a second crossing fibre population in the same region. One way to assess the contribution of crossing fibres to FA is by assessing the differential contributions axial and radial diffusivity. However, because axial and radial diffusivity are defined relative to the axis of greatest diffusivity, rather than to particular tracts, their interpretation is non-trivial in a complex human brain with multiple fibre crossings (Jbabdi et al., 2010; Douaud et al., 2011). Therefore, fibre tractography should also be used to determine the underlying tract orientation in addition to clarifying FA correlations/differences by analysing axial and radial diffusivity.

While most neuroimaging studies of motor learning examine task performance on a single day, the current study examined how much an individual can learn across five days of practice. By combining this behavioural data with cross-sectional DTI and T1 structural images obtained on the final day, we can identify the structural correlates of learning ability and compare them with the brain regions functionally responsible for learning on the same task. The results of our previous fMRI experiment showed that

though most motor-related regions decreased in activity with learning, there were performance-related increases in specific regions including the motor cortex, cerebellum, and superior parietal lobule (PLs) (Steele and Penhune, 2010). Therefore, in the current study we hypothesised that behavioural measures of learning ability would be positively correlated with FA and GM volume in the regions functionally implicated in this task: motor cortex, cerebellum, and PLs. The secondary goal of this study was to more fully describe the contributions of axial and radial diffusivity to our FA findings and discuss them within the context of underlying tract organisation defined by DTI tractography.

2.3 Materials & Method

2.3.1 Participants

The participants in this study were those tested in a previously published fMRI study (Steele and Penhune, 2010). The sample consisted of thirteen participants (5 female) between the ages of 18 and 27 (M=22.4; SD=2.9 years) who gave written informed consent. All were right handed (assessed using a handedness questionnaire adapted from Crovitz and Zener (1962), neurologically normal, and had less than three years of musical experience (assessed using the Index of Musical Training and Experience; (Penhune et al., 1999)). The experimental protocol was approved by the McGill University MNH/I Research Ethics Board and the Concordia University Human Research Ethics Committee.

2.3.2 Task, Stimuli, & Procedure

The temporal motor sequence task (TMST) used in this experiment requires participants to reproduced a temporally complex sequence of finger taps in synchrony with a visual stimulus. This task is sensitive to long and short term changes in performance and brain

activity (Penhune and Doyon, 2005; Savion-Lemieux and Penhune, 2005; Steele and Penhune, 2010). Learning and performance on this task can be separated into two components: 1) accuracy – learning of the order of short and long key-presses in the sequence; and 2) synchronization – the precise timing of movements. A detailed description of the task, stimuli, and procedure is presented in a previously published functional imaging study (Steele and Penhune, 2010). In brief, participants learned to press and release a mouse button in synchrony with the onset and offset of a visually-presented sequence of 10 elements (5 [S]hort – 300ms; 5 [L]ong – 600ms; interstimulus interval – 300ms). Each element was presented on screen for the specified duration as a large coloured block – participants were instructed to press the mouse button when the block appeared and release when it disappeared. Five long and five short elements were arranged to create a sequence corresponding to a non-standard musical rhythm that is difficult to learn (the learning sequence – LRN: S L L S L S S L S L), a simple control sequence of five long followed by five short (L L L L L S S S S S), and a control sequence that was only observed. Four sequences of each condition were combined to create 40s blocks. Four blocks of each condition were pseudorandomly presented about three 40s blocks of rest to create a single training run. Participants were trained on the stimuli and taught LRN on the beginning of the first day and practised it for 3 runs of 4 blocks (16 trials) per day over 5 consecutive days, for a total of 240 trials. The current study focused on the relationship between the slope of improvement and final performance on LRN and cross-sectional structural imaging data acquired on the final day of training. T1 and diffusion-weighted images (DWI) were acquired with an 8-

channel head coil in a Siemens Trio 3T MRI scanner on the final day of practice (T1 – TR=23ms, TE=7.4ms, FOV=256mm, flip angle=30°, 1x1x2mm^3; DWI – 3 runs of 32 directions, b=1000 s/mm^2, 1.7x1.7x5mm^3, five b=0 images per run).

2.3.3 Data Analysis

2.3.3.1 Behavioural

Learning was assessed for each run of practice for changes on two measures of performance: percent correct (PCOR) – the percentage of correctly produced long and short key-presses within the sequence, a measure of the accurate production of elements within the sequence and percent synchronisation (PSYN) – a measure of the synchronization of key-press response with visual stimuli. PCOR was defined as the percentage of key-press responses that were initiated between 300ms before the stimulus and the end of the stimulus and had key-press duration of less than M + 2SD (for short elements) or greater than M - 2SD (for long elements). PSYN was defined as the absolute lag between the onset and offset of the stimulus and the onset and offset of the response, divided by the actual stimulus element duration (Steele and Penhune, 2010). As this calculation results in values that are smaller for better performance, scores were subtracted from 100 obtain a score that increased with performance. A score of 100% on PCOR represents perfect knowledge of the ordering of long/short elements within the sequence. A score of 100% on PSYN indicates that the key-press and release response exactly matched the onset and offset of the visual stimuli.

For the purposes of this study two measures were used: final performance – PCOR and PSYN for the last run of training on Day 5; and learning slope – r-value of the best fit

linear regression line passing through participants' PCOR and PSYN run averages for the 15 runs of the experiment (PCORslp, PSYNslp). Both measures index learning potential (how proficient you can become and how quickly that level can be attained) that we reasoned may be represented within the structure of the brain (Tomassini et al., 2011). Final PCOR/PSYN and PCORslp/PSYNslp were then correlated with imaging measures as described below.

2.3.3.2 Diffusion Imaging

All imaging data were analysed using the FMRIB Software Library (FSL 4.1.5) (Smith et al., 2004). Diffusion images from three diffusion runs were concatenated, corrected for eddy current, and averaged. The FMRIB diffusion toolbox (FDT) was used to create voxelwise maps of diffusion parameters including FA and the eigenvalues of the diffusion tensor. Images were then analysed using FSL's tract-based spatial statistics (TBSS) (Smith et al., 2006) which first requires images to be nonlinearly aligned to the FMRIB58_FA standard space template. The mean FA image was calculated and thinned to produce the study-specific FA skeleton – which represents the centres of all tracts common to all participants. Each participant's aligned FA data was then projected onto individual FA skeletons that were subsequently used in group permutation-based nonparametric statistical analyses. The mean FA skeleton was thresholded at FA > 0.25 to limit analyses to regions where major tracts existed in all individuals.

To determine the fibre regions that are important for skilled performance on this task, FA was correlated with final performance and slope measures for each participant with age as a covariate of no interest. Regions where FA was found to correlate significantly with

performance were further investigated by assessing axial and radial diffusivity values. Whole-brain axial and radial diffusivity images were registered to the standard space using each individual's nonlinear warp field (obtained from the FA image registration) and projected onto the mean FA skeleton. Regions identified in the FA correlational analysis were used to extract axial and radial diffusivity values from the same skeleton regions in all individuals. Partial correlation analyses, with age as a covariate of no interest, were then used to identify relationships between variables.

Probabilistic tractography was used to better characterise the directionality of fibre tracts in regions of interest. This allows the interpretation of diffusion measures within the context of the underlying fibre tract organisation. Significant voxels from the FA analysis were converted into a binary mask in each individual's 1mm isotropic transformed diffusion space and then used to seed probabilistic tractography. Two different tractography analyses were conducted: one with target masks placed superiorly/inferiorly along the putative corticospinal tract (probable CST; inclusion planar regions at z=54, 6, -11; exclusion at x=±42 y=43), the other with target masks placed laterally, anteriorly, and posteriorly to capture the association fibres/probable superior longitudinal fasciculus (probable SLF; inclusion planar regions at x=±35, ±47 y=42, -50; exclusion regions identical to CST inclusion). An additional exclusion plane was placed at x=0 for both fibre populations. Both fibre directions were randomly sampled 10,000 times for each voxel in the seed mask. Each fibre population was averaged across participants and thresholded at 10% of the maximum particle number to obtain anatomically plausible tracts. This analysis produces delineations of the fibre tracts passing through the mask

region, and can be used to visually differentiate the different fibre populations.

2.3.3.3 Voxel-based Morphometry

To assess individual differences in GM volume that were related to task performance, T1 images were analysed with the voxel-based morphometry tools in FSL (Douaud et al., 2007). Images were brain extracted (Smith, 2002), then segmented by tissue type to produce 3D grey matter partial volume images (Zhang et al., 2001). Each image was first aligned to the MNI152 template brain with an affine transform (Jenkinson et al., 2002). A study-specific grey matter template was generated by averaging all linearly aligned GM images. The group mean GM image was used as the target for nonlinear registration of the original native space GM images using a b-spline representation of the registration warp field (Rueckert et al., 1999). The resulting nonlinearly aligned GM images were smoothed with a Gaussian kernel of σ=4 (~9.4mm) prior to statistical analyses. Whole-brain GM volume values were correlated with behavioural measures to identify cortical regions responsible for skilled performance and rate of improvement on this task.

Statistical analyses of FA and VBM data were conducted using FSL's randomise with 5000 permutations and threshold-free cluster enhancement (Smith and Nichols, 2009). All analyses were controlled for the effects of age (entered as a covariate of no interest) and results were considered significant at $p < .05$, fully corrected for multiple comparisons. Analyses resulting in significant correlations were rerun while controlling for both age and gender to confirm that the unequal number of males and females in this sample did not bias the results.

2.4 Results

2.4.1 Behavioural

Subjects were trained to produce accurate and synchronised button presses in response to a 10 element visually presented motor sequence across five days of practice. Within-subjects ANOVAs revealed that performance on PCOR, the more explicit sequence ordering measure, improved significantly over the course of the experiment (PCOR: $F(4,48) = 9.80$, $p < .01$, $\eta 2 = .45$) while PSYN, the more procedural sensorimotor integration measure, showed a statistical trend toward improvement on LRN ($p = .10$) (see Steele and Penhune, 2010 for further details). Final performance scores indicated that participants were able to perform well by the end of the experiment (PCOR: M = 93.13, SD = 7.06; PSYN: M = 70.16, SD = 10.84). Figure 2.1 illustrates the distribution of final performance scores on PCOR and PSYN. PCORslp (M = .80, SD = .82) and PSYNslp (M = .5, SD = .96) measures indicated that participants, on average, improved over the course of the experiment.

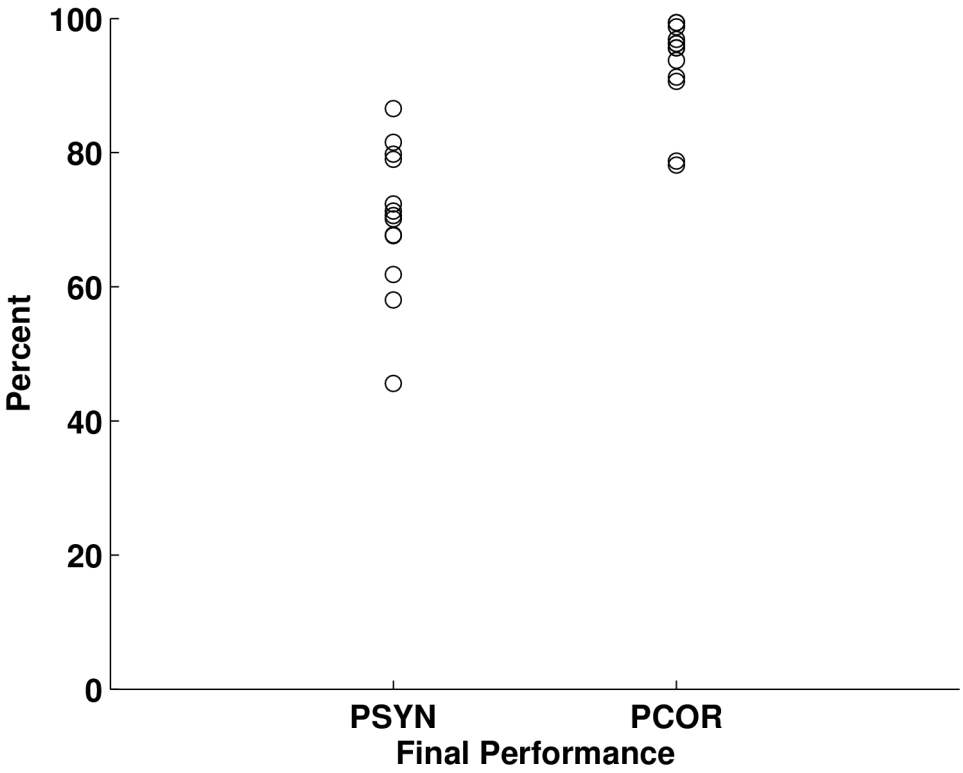


Figure 2.1. Plot of individuals' final performance on PCOR and PSYN

Points represent individual mean scores for the final run of Day 5.

2.4.2 Diffusion Measures

2.4.2.1 FA – Behaviour Correlation

FA was correlated with behaviour to identify individual differences in white matter integrity related to performance. Final PSYN was found to correlate negatively with FA within bilateral corticospinal tract (CST), such that participants with greater final synchronisation performance had lower FA in these clusters. In the left hemisphere, one

cluster was located directly below the hand area of the primary motor cortex (M1) (Yousry et al., 1997) and the other was located more inferiorly in the CST and extended into the temporal/parietal junction. The significant clusters in the right hemisphere were located in approximately the same regions as those in the left, though had reduced spatial extent. Figure 2.2 shows the regions of the FA skeleton negatively correlated with final PSYN performance overlaid with the regions where functional activity was positively correlated with PSYN performance (see Table 2.1 for a list of peak voxels and their locations). Final PCOR showed a similar relationship with FA in the same region of the left hemisphere as final PSYN, though this relationship was not significant after correcting for multiple comparisons. This finding indicates that the relationship between FA in this region and the task is a general one, rather than specific to a particular component of performance. A subsequent analysis including gender as an additional covariate of no interest found the same pattern of results as reported above: the cluster with peak voxel at -27, -30, 16 remained significantly correlated with Final PSYN and the remaining clusters dropped below significance to p=.07, fully corrected for multiple comparisons. There were no statistically significant correlations between PCORslp/PSYNslp and FA.

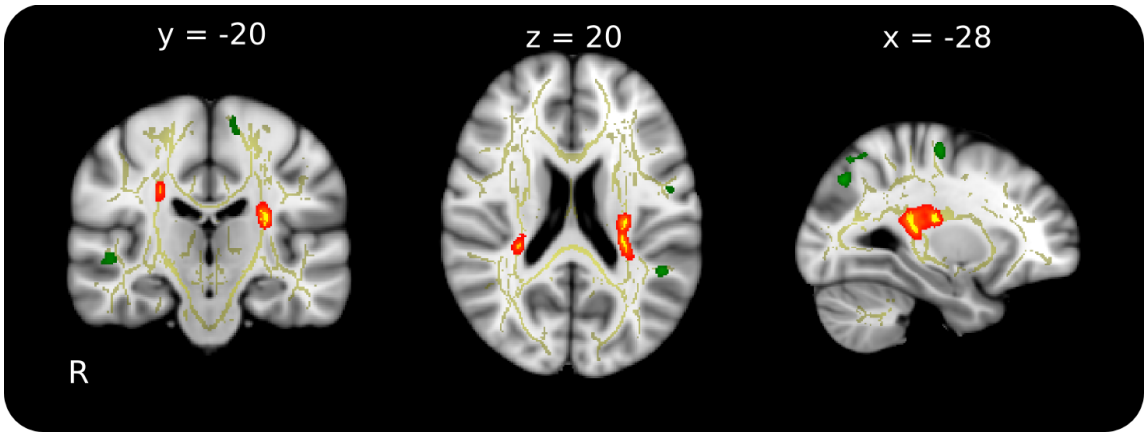


Figure 2.2. Relationship between final synchronisation performance and FA in WM underlying motor cortex in the context of regions functionally involved in this task

This negative correlation suggests that those with greater performance have lower FA in these regions that correspond well to areas functionally implicated in the task. Red-Yellow: correlation between FA and final synchronisation ($p < .05$, corrected for multiple comparisons); Green: functional correlation between synchronisation performance and BOLD across the five days of the experiment ($p < .001$, cluster corrected); Yellow: mean FA skeleton ($FA > .25$). Significant voxels in the FA skeleton were thickened and overlaid on the ICBM 152 T1 for display.

	Location	Peak t-stat	x	y	z
FA – PSYN final	**L CST/SLF**	-6.46	-27	-30	16
		-4.36	-28	-20	19
	R CST/SLF	-6.34	31	-34	16
		-5.70	25	-22	31
		-3.99	20	-26	48
VBM – PSYN slope	**Lobule V**	12.38	-4	-58	-16
	R Lobule HVI	8.7	32	-48	-30

Table 2.1. Coordinates and peak t-statistics for significant correlations.

2.4.2.2 Axial and Radial Diffusivity

Axial and radial diffusivity values were extracted from the identified region to investigate their contributions to the negative correlation between FA and final PSYN. Axial diffusivity is the diffusivity along the axis of greatest diffusion and radial diffusivity is the mean of diffusivity in the two perpendicular directions. Radial diffusivity was found to positively correlate with final PSYN ($r = 0.79$, $p < 0.005$) while axial diffusivity did not ($p = 0.18$). In addition, FA and radial diffusivity were negatively correlated ($r = -0.91$, $p < 0.001$). Figure 2.3 shows the partial correlation between radial diffusivity and final PSYN performance. The positive correlation between radial diffusivity and performance combined with the strong negative correlation between FA and radial diffusivity indicates that the observed negative relationship between FA and performance is driven by the positive relationship between radial diffusivity and performance.

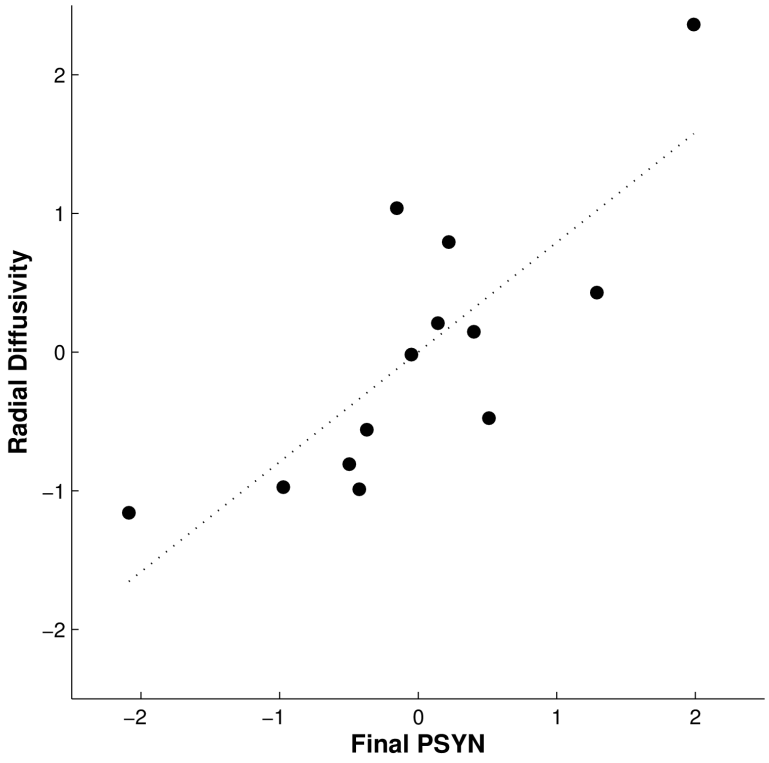


Figure 2.3. Relationship between radial diffusivity and final performance on PSYN

This plot depicts the partial correlation between radial diffusivity and final PSYN after the effects of age have been removed. Each value is a residual converted to a z-score, and represents individual scores. The dotted line represents the best fit linear regression line through the data ($r = .79$, $p < .005$).

2.4.2.3 Tractography

Probabilistic tractography was used to identify the tracts crossing the region identified in the FA-behavioural analysis to more precisely interpret the results of the FA, axial, and radial diffusivity analyses. Based on location, we expected that the clusters identified in

the behavioural regression analyses could contain fibres not only from the CST but also from the SLF. To test this possibility, we performed probabilistic tractography on two combinations of target and exclusion masks designed to delineate ascending/descending (probable CST) from association fibres (probable SLF). Using the region where FA was found to significantly correlate with final PSYN as the seed (inclusion planar regions at z=54, 6, -11; exclusion at x=±42 y=43), the ascending/descending tract extends superiorly to the sensorimotor cortex and inferiorly to the brainstem; this tract location is consistent with the CST (coloured Red-Yellow in Figure 2.4) (Wakana et al., 2004) and the cortical target of its trajectory corresponds well with the motor cortical regions found to increase with improvements in PSYN (green in Figure 2.4) (Steele and Penhune, 2010). The tract identified with same seed and lateral/anterior/posterior target masks (inclusion planar regions at x=±35, ±47 y=42, -50; exclusion regions identical to CST inclusion) is consistent with the course of the SLF: extending anteriorly to the frontal lobe along the external capsule, posteriorly across the superior part of the CST to the parietal lobe, and laterally to the auditory cortical regions of the temporal lobes (coloured Blue-Lightblue in Figure 2.4) (Mori et al., 2002; Wakana et al., 2004; Makris et al., 2005). The tract termination points show remarkable agreement with the parietal and auditory cortical regions previously found to be involved in optimising this component of the task (green in Figure 2.4) (Steele and Penhune, 2010). The excellent correspondence between the functionally-defined motor, parietal, and auditory cortical regions important for PSYN optimisation and the tracts identified in this analysis underscore the importance of these regions and their connections in the optimisation and performance of this task.

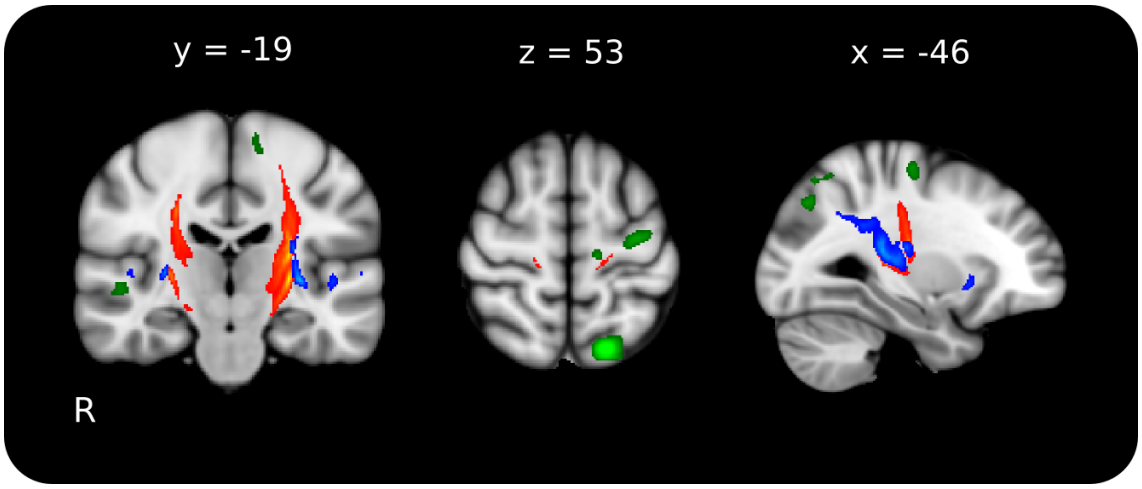


Figure 2.4. Mean probabilistic tractography results for each target region, originating from the performance-FA seed mask

Red-Yellow: tract resulting from the ascending/descending waypoint masks; Blue-Lightblue: tracts resulting from the lateral waypoint masks; Green: functional correlation between synchronisation performance and BOLD across the five days of the experiment ($p < .001$, cluster corrected). The delineation between the ascending/descending fibres of the CST and the laterally projecting fibres can be clearly seen. Tractography was conducted on each individual, averaged, and thresholded at 10% of maximum for display. Lighter colours indicate higher particle count. The tractography seed mask contained all voxels in the skeleton that showed a significant negative correlation between FA and final PSYN performance in both hemispheres. Tracts have been overlaid on the ICBM 152 T1 average for display.

2.4.3 Voxel-based Morphometry and Performance

To complement the WM findings, we used VBM to examine regions of the grey matter that may contribute to the acquisition and performance of the TMST. PSYNslp was positively correlated with grey matter volume in right cerebellar lobules HVI and V (Schmahmann et al., 2000), two regions known to be specifically connected to the motor cortex (Figure 2.5, depicted in red to yellow) (Kelly and Strick, 2003; O'Reilly et al., 2009; Stoodley and Schmahmann, 2009). Refer to Table 2.1for a list of peak voxels and their locations. Importantly, these regions showed significant learning-related decreases in BOLD signal between Day 2 and Day 5 in the functional study with the same participants (Figure 2.5, depicted in green) (Steele and Penhune, 2010, supplementary materials). An additional analysis including age and gender as covariates of no interest found the same two regions to be significantly correlated with PSYNslp, though at a reduced spatial extent. There were no significant correlations with any of the other measures.

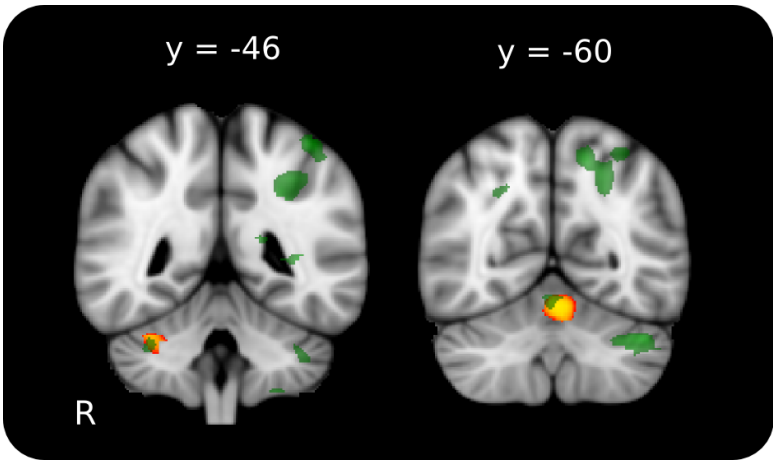


Figure 2.5. Positive relationship between rate of improvement on synchronisation and GM volume in cerebellar lobules HVI and V

The cerebellar structures identified here correspond well with two regions where BOLD activity decreased across learning on this task. Red-Yellow: significant correlation between GM volume and rate of improvement ($p < .05$, corrected for multiple comparisons); Semi-Transparent Green: task-specific decrease in BOLD activity between Day 2 and Day 5 ($p < .001$, cluster corrected). Significant regions are overlaid on the ICBM 152 T1 average for display.

2.5 Discussion

The current study examined the relationship between individual differences in the ability to learn a motor task and structural brain measures collected on the final day of practice. Importantly, we compared these findings with the results of a previous functional brain imaging study in the same sample. Behavioural regression analyses found that better final synchronisation performance was negatively correlated with FA bilaterally in fibre tracts

underlying sensorimotor cortex, such that participants with lower FA showed better final performance. The direction of this relationship may appear counter-intuitive. However, radial diffusivity in this region was positively correlated with performance and multi-fibre tractography revealed that this region is an area of CST/SLF crossing fibres – meaning that the interpretation of FA in which bigger is better does not always apply. Functional imaging results with the same sample found positive relationships with synchronisation performance in motor, parietal, and auditory cortical regions that corresponds well with both identified tracts (Steele and Penhune, 2010). These findings raise the possibility that skilled performance on this task is associated with enhanced fibre integrity in the SLF. Enhanced fibre integrity in the SLF could result in reduced FA in regions where it crosses the CST. Additional VBM analyses revealed a positive relationship between learning rate and GM volume in right cerebellum that were co-localised with functional decreases observed in the fMRI data (Steele and Penhune, 2010), thus providing further evidence for the cerebellum's role in skilled motor performance.

Better final performance on the TMST was related to lower FA in the CST/SLF inferior to bilateral sensorimotor cortex, and this effect was mediated by a positive correlation with radial diffusivity (Figures 2.2, 2.3). Our tractography results confirmed that this region contained fibres from both the CST and SLF (Makris et al., 2005) (Figure 2.4). Although we were unable to detect tract-specific relationships – likely as a result of the non-isotropic voxel sizes used in the current study – we speculate that greater diffusivity along the course of the SLF in this region may be responsible for the observed positive

correlation of performance with radial, rather than axial, diffusivity. Though increases/greater radial diffusivity has been linked to dysmyelination in uniformly oriented fibre populations (Pierpaoli et al., 2001; Sun et al., 2008), the presence of crossing fibres in this region makes interpretation more difficult (Jbabdi et al., 2010; Douaud et al., 2011). Therefore, we have hypothesised that radial diffusivity in part reflects the fibre integrity of the SLF, where the principal diffusion direction is typically oriented anterior-posterior. The possibility that the negative correlation between FA and skill learning could be driven by variation in the SLF is an attractive one. The SLF connects parietal and auditory cortical regions functionally implicated in performance of this task and in an fMRI study with the same participants (Penhune and Doyon, 2002, 2005; Steele and Penhune, 2010). In support of our hypothesis, a previous study found a *positive* relationship between FA in the SLF and motor sequence learning (Tomassini et al., 2011). This finding is in a more anterior region of the SLF (y = -10) that would be unlikely to be influenced by crossing fibres from the CST. Also possibly consistent with our findings, a recent study showed that *nonmusicians* had *greater* FA than musicians in bilateral CST regions similar to those observed in our results (Imfeld et al., 2009). The authors speculate that their counter-intuitive findings are due to increased axonal permeability due to long-term sensorimotor training in musicians, but do not consider the potential effect of crossing fibres. The overlap between the regions functionally implicated in improvement on the TMST and the tractography results presented here provides further evidence for the importance of the SLF in motor sequence learning.

The results of behavioural regression analyses with VBM grey matter values showed that

individual differences in cerebellar lobules HVI and V were related to the rate of improvement of synchronisation on the TMST. These regions overlap with those that showed learning-related decreases in activity in the fMRI data from the same subjects (Figure 2.5). Co-localisation of behaviourally-relevant structural differences and functional changes identified with independent analyses provides further evidence for the role of the cerebellum in motor tasks – a finding that is compatible with a proposed role for the cerebellum in processing error-related feedback (Ohyama et al., 2003). Crucially, lobules HVI and V are structurally and functionally connected to motor cortex (Kelly and Strick, 2003; O'Reilly et al., 2009; Stoodley and Schmahmann, 2009), show performance-related changes in functional activity during motor tasks (Penhune and Steele, 2012), and form part of a network of regions responsible for the optimisation of motor behaviour (Ramnani, 2006).

Studies identifying relationships between cerebellar GM volume and performance are rare, with only two that use non-expert populations (Tomassini et al., 2011; Kühn et al., 2012). Our results are in agreement with those of Kühn and collaborators (2012), who found that GM volume in lobule VI was related to fine motor control, and directly support those of Tomassini and colleagues (2011) who also identified a relationship between motor sequence performance and GM volume in lobule VI. Though the design of the current study did not allow us to address learning-related changes in GM volume, previous work has identified increases in cerebellar synapse number and glial cell volume as a result of practice and learning (Kleim et al., 2002, 2007). We hypothesise that the observed performance-related individual differences in GM are in part due to differences

arising from previous training and experience. Thus, greater cell or synaptic density in the cerebellum may support enhanced information processing ability (and thus a faster rate of behavioural improvement) that is related to decreasing functional activity as performance improves.

The causes of inter-individual variability in brain structure are not fully understood, but likely include pre-existing genetic contributions and contributions from learning and the environment. The design of our study was not able to disentangle these effects. FA is affected by WM properties including axon myelination, diameter, and packing density. Differences in these properties could lead to the individual differences in performance observed in our study through pre-existing differences or training-induced changes in axon conduction velocity and synaptic synchronisation (Fields, 2005, 2008), or density of innervation. Greater fibre integrity along the SLF would be consistent with the idea, proposed by Fields, that increased/greater myelination observed in relation to learning or performance may underlie enhancements in synchronised activity between task-relevant regions (Fields, 2005, 2011). Similar to WM measures, individual differences in GM volume could be influenced by multiple factors such as neuronal and glial cell density, synaptic density, vascular architecture, and cortical thickness. Though the physiological basis for GM volume differences in humans has not been fully explained, previous work has established the feasibility of identifying individual differences in brain structure that are related to: learning of foreign language sounds (Golestani and Pallier, 2007; Golestani et al., 2007), performance on musical tasks (Foster and Zatorre, 2010a), bimanual coordination (Johansen-Berg et al., 2007), and timed finger tapping (Ullén et al., 2008).

This study identified regions where performance is related to brain structure but its design does not allow us to conclude whether the observed effects are due to previous experience, training, or a combination of the two. Our study comprised a brief training regime (five days) followed by structural data acquisition on the final day. A number of studies have identified structural changes after multiple weeks of training (Draganski et al., 2004; Boyke et al., 2008; Scholz et al., 2009; Taubert et al., 2010), but others have also reported changes with short-term training (Landi et al., 2011), TMS (May et al., 2007), and drug intervention (Tost et al., 2010). This study provides a link between skilled performance and brain structure in regions known to be functionally involved with task performance. With only a single timepoint we cannot comment on how the regions that we have identified may change as a result of practice; however, given the overlap with previous fMRI results, structural changes in the SLF and cerebellar lobules HVI and V may occur with training on similar motor sequence tasks. Future studies employing longitudinal methods and longer periods of training could be used to address these questions.

We have identified individual differences in performance that are related to brain structures important for motor sequence learning and performance. There was a negative relationship between FA and performance in a region of the CST-SLF fibre crossing that may reflect greater fibre integrity in the SLF of skilled performers – and is consistent with the idea of enhanced communication/synchronisation between regions functionally important for this task. Two regions of the cerebellum (lobules HVI and V) where GM volume is important for the speed at which sequence skill is acquired during learning

were also identified. Our multimodal cross-sectional individual differences design also illustrates the importance of considering multiple structural measures (GM volume, FA, diffusivities, tractography) within the context of functional results to help provide a more global interpretation of the processes involved in motor sequence learning and performance.

Chapter 3: Sensitive periods and the development of expertise: Diffusion tensor imaging evidence from musicians

Steele, C.J., Bailey, J.A., Zatorre, R.J., Penhune, V.B. Sensitive Periods and the Development of Expertise: Diffusion Tensor Imaging Evidence from Musicians

3.1 Abstract

Training accrued during a "sensitive period" in development may have stronger effects on the brain and behaviour than training accrued later in life. Musicians undergo extensive training that can begin at virtually any age, thus providing an excellent human model for sensitive periods. Previous neuroimaging research suggests that the corpus callosum and auditory regions may differ depending on when musicians begin training, yet this work did not account for the effects of duration of training/experience on brain structure. This study explores the impact of training on white-matter and synchronisation performance during a potential sensitive period by comparing early-trained (ET) and late-trained musicians (LT) matched on training and experience. Replicating previous findings, ET demonstrated superior synchronisation performance versus LT and nonmusicians controls. ET had greater white-matter integrity than LT in the posterior midbody of the corpus callosum transcallosally connecting bilateral sensorimotor cortex. Fractional anisotropy in this region correlated with both age of onset (musicians) and synchronisation across groups. In addition, a large region of white-matter in the left temporal lobe (extending to the internal/external capsules) correlated with

synchronisation across groups. Crucially, mean fractional anisotropy extracted from this region was also correlated with age of onset in musicians. Our results fit well with other research highlighting the role of the corpus callosum and auditory regions in musical training and performance, and support the idea that training during a sensitive period in development has a greater influence on brain structure and performance than training later in life.

3.2 Introduction

Highly skilled individuals such as chess masters, professional athletes, and musicians often follow rigorous practice regimes that begin in early childhood: Garry Kasparov, Tiger Woods, and Yo-Yo Ma were all practising and performing by the age of five. Such observations suggest that early training may have stronger effects on the brain and behaviour than training accrued later in life (Knudsen, 2004). Musicians are an excellent model for investigating sensitive periods as training can be initiated at almost any age and follows well established training regimes (Wan and Schlaug, 2010; Penhune, 2011). Previous neuroimaging studies provide suggestive evidence that brain structure is related to the age of onset of musical training (Schlaug et al., 1995; Amunts et al., 1997; Pantev et al., 1998). However, none of these studies assessed behavioural differences between groups or controlled for the fact that musicians who began training early have more training and experience than those who began later. The current study used musician groups matched on years of training and experience to investigate a possible sensitive period in human development.

A sensitive period can be defined as a developmental time window where experience has

strong and long-lasting effects on the brain and behaviour (Knudsen, 2004). Evidence for sensitive periods comes from animal studies (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970) and children with cochlear implants showing better speech perception due to earlier implantation (Kral and Sharma, 2012). The first suggestive evidence for a sensitive period for musical training comes from a study reporting larger corporal collosa in musicians who began training prior to the age of seven (Schlaug et al., 1995). Musical training during childhood also correlates with white-matter integrity in the corpus callosum of adult musicians (Bengtsson et al., 2005). Further, a longitudinal study found increased corpus callosal volume after musical training conducted between the ages of six and eight (Hyde et al., 2009). Musicians who begin training earlier have also been shown to have longer precentral gyri (Amunts et al., 1997) and larger auditory cortex representation (Pantev et al., 1998). However, since training can induce grey- and white-matter structural changes in the human brain (Draganski and May, 2008; Scholz et al., 2009), and previous studies were not designed to control for the duration of musical training and experience, previous results may not be interpretable as evidence for a sensitive period. Recent work from our laboratory addressed these issues to show that early-trained musicians (ET) have superior sensorimotor synchronisation performance to late-trained musicians (LT) even when matched for years of training and experience (Watanabe et al., 2006; Bailey and Penhune, 2010). Though white-matter is clearly linked to musical training (e.g., Hyde et al., 2009) and performance to training onset (e.g., Watanabe et al., 2006), no neuroimaging study has yet controlled for training and experience to explore how white-matter and behaviour is influenced by training during a

potential sensitive period in development. Here we use diffusion tensor imaging in ET and LT matched for training and experience to address this question.

3.3 Method

3.3.1 Participants

Eighteen early-trained (8 females) and eighteen late-trained musicians (4 females) were recruited for this study. Groups were matched on the number of years of musical training and total amount of musical experience. All musicians had at least seven years of musical experience, were currently practising, and enrolled in a university music program or performing professionally. Based on the criterion established by previous studies reporting group differences, ET began training prior to the age of seven and LT began training after the age of seven (Schlaug et al., 1995; Watanabe et al., 2006; Bailey and Penhune, 2010). An additional group of seventeen nonmusician controls were recruited for this study (7 females). Controls were not currently practising an instrument or undergoing musical training and had less than three years of musical experience. All participants were screened to exclude those with head injury, history of neurological damage or disease, or were on medication that could affect task performance. All participants were right-handed, completed an MR safety screening form, and provided written informed consent. The experimental protocol was approved by the McGill University MNH/I Research Ethics Board and the Concordia University Human Research Ethics Committee.

3.3.2 Stimuli & Task

The temporal motor sequencing task (TMST) requires that participants produce a

sequence of single- finger taps that are precisely synchronised to the onset and offset of a visually presented stimulus (Figure 3.1). This task measures response accuracy (knowledge of the explicit order of elements within the sequence) and synchronisation (the precise timing of movements in response to visual stimuli), and has previously been used in behavioural and neuroimaging experiments within our laboratory (Penhune and Doyon, 2002, 2005; Savion-Lemieux and Penhune, 2005; Watanabe et al., 2006; Steele and Penhune, 2010; Penhune and Steele, 2012). Briefly, stimuli were 100x100 pixel coloured squares that appeared for either 300ms (short) or 600ms (long) and were grouped into 10- or 12-element sequences with 300ms interstimulus intervals. Participants were instructed to "synchronise the onset and offset of your mouse-click response to the onset and offset of the block that appears on the screen." Four simple practice sequences were used to familiarise participants with the task and to calculate each individual's mean and standard deviation for short and long at the beginning of each day. Five short and five long stimuli were arranged to create the learning sequence that resembles a non-standard musical rhythm and is difficult to learn. A simple sequence made up of the same elements was used as a baseline task (Figure 3.1). Learning and simple sequences were arranged into 4-trial units repeated 4 times per block for three blocks; there were a total of 16 trials of each sequence per block. Stimuli were delivered and responses recorded by an in-house program developed in C#. An attached LCD screen was used to display the stimuli at a resolution of 1024x768 and behavioural responses were collected via a standard PC mouse connected to a USB port. All behavioural data was processed and scored with Mathworks MatLab.

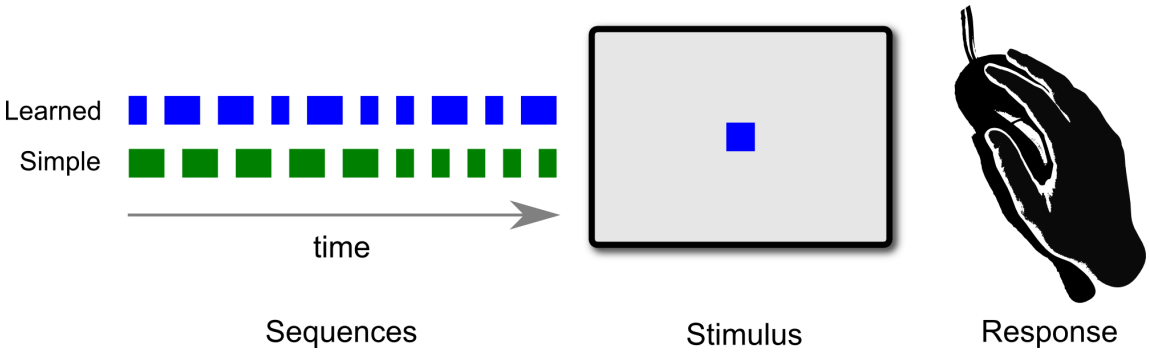


Figure 3.1. TMST method

The sequence types, visually presented stimuli, and response method are shown.

3.3.3 Procedure

Participants performed the TMST across two consecutive days and underwent structural MRI scanning in a separate session. Behavioural testing was identical for both days. Participants were familiarised with the TMST and completed a block of training sequences to establish the mean and standard deviation of their short and long responses for scoring (described below). The learning sequence was practiced until 80% of the long and short intervals were correctly performed within ±2SD across three consecutive trials. Three blocks (48 trials) of the TMST were then administered. Measures of age of onset of musical training, years of formal training, and years of musical experience were collected through administration of the Musical Experience Questionnaire (MEQ) prior to the first day of testing (Bailey and Penhune, 2010). Structural MRI scans were acquired with a 32-channel head coil in a Siemens Trio 3T MRI scanner (MPRAGE T1 – TR=2300ms,

TE=9.8ms, 1x1x1mm^3; DWI – 99 directions, TR=9340ms, TE=88ms, b=1000 s/mm^2, 2x2x2mm^3).

3.3.4 Data Analysis

3.3.4.1 Behavioural

Learning was assessed with two measures of performance: percent correct (PCOR) and percent synchronisation (PSYN). PCOR is the percentage of correctly produced long and short key-presses within the sequence and represents a measure of the accurate production of elements within the sequence. PSYN is a measure of the synchronization of key-press response with visual stimuli, and represents a measure of sensorimotor integration. PCOR is the percentage of key-press responses that were initiated between 300ms before the stimulus and the end of the stimulus and had key-press duration of less than M + 2SD (for short elements) or greater than M - 2SD (for long elements). PSYN was calculated based only on correct responses and is the absolute lag between the onset and offset of the stimulus and the onset and offset of the response, divided by the actual stimulus element duration. PSYN scores were subtracted from 100 to obtain a score that increased with performance. A score of 100% on PCOR represents perfect knowledge of the ordering of long/short elements within the sequence while a score of 100% on PSYN indicates that the key press and release response exactly matched the onset and offset of the visual stimuli. We operationalised PCOR as the more explicit component of the ordering of elements within the sequence and PSYN as the component more closely tied to sensorimotor integration and control (Watanabe et al., 2006; Steele and Penhune, 2010; Penhune, 2011).

Omnibus F-tests were used to assess learning on PCOR and PSYN and planned comparisons for the sensorimotor integration component, PSYN, were conducted for all blocks (one-tailed t-tests, α=.05, ET>LT and LT>NM compared separately for all blocks). Measures of final performance for PSYN, operationalised as performance on the last block of the second day of training, were calculated for use in behavioural and brain-behaviour correlations (PSYN Final). To assess the relationship between performance and training, PSYN Final was correlated with age of onset and years of formal training in musicians overall and for ET and LT separately. All correlations were were assessed for significance at α=.05.

3.3.4.2 Diffusion Imaging

All imaging data were analysed using the FMRIB Software Library (FSL 4.1.7) (Smith et al., 2004). Diffusion images were corrected for eddy current distortions prior to creating voxel-wise maps of diffusion parameters. Images were then prepared using FSL's tract-based spatial statistics, which first nonlinearly aligns images to the FMIRB58_FA standard space template, calculates a mean FA image, and then thins it to produce the study-specific FA skeleton representing the centres of the tracts common to all participants (Smith et al., 2006). The aligned FA data was then projected onto individual FA skeletons that were subsequently used in permutation-based nonparametric statistical analyses. Skeletonised FA values were thresholded at FA>.20 prior to analyses. Volumetric (non-skeletonised) FA images were minimally smoothed (sigma=1mm) prior to analyses. The same nonlinear warp and skeletonisation parameters were used with the tbss non-FA pipeline to create skeletonised and volumetric images of mean diffusivity

(MD), axial diffusivity (AD), and radial diffusivity (RD). Non-parametric permutation-based analyses were conducted with 5000 permutations for all analyses, with age and sex entered as covariates of no interest. Results were assessed for significance after multiple comparisons (α=.05) using threshold-free cluster enhancement (Smith and Nichols, 2009).

Group Difference Contrasts and Brain-Behaviour Correlations. Whole-brain skeletonised between-group subtraction analyses were used to identify white-matter regions that may differ between musician groups. To determine the WM regions directly related to skilled performance on the TMST, final performance measures across all participants (ET, LT, NM) were correlated with skeletonised FA. Regions identified in these analyses were used as masks to extract FA, AD, and RD values for plotting, partial correlations, or 1-tailed t-tests to specify findings.

Probabilistic Tractography. Probabilistic tractography was used to better characterise the location and connectivity of findings. Significant voxels were first converted to binary masks in each individual's 1mm isotropic transformed diffusion space and then used to seed a two fibre model of probabilistic tractography (Behrens et al., 2007). Both fibre directions were randomly sampled 10,000 times for each voxel in the seed mask, averaged across groups, and thresholded for display. Thresholded tracts were converted into binary masks that were used to extract diffusion measures from each individual's nonlinearly registered voxelwise maps.

3.4 Results

3.4.1 Behavioural

ET and LT differed on the age of onset of musical training and current age such that ET began training at a younger age and were younger overall (age of onset $t(34)=7.92$, $p<.001$**: ET – 5.72 ±1.13, range 3-7yrs; LT – 10.78 ±2.46, range 8-18yrs) (age $t(34)=3.07$, $p<.05$*: ET – 22.74 ±4.14, range 18-32yrs; LT – 27.61 ±5.34, range 19-35yrs). Years of formal training and experience did not differ between musician groups (formal training $p=.15$: ET – 11.5 ±3.22, range 3-16yrs; LT – 9.42 ±5.13, range 1-20yrs) (experience $p=.93$: ET – 16.72 ±3.89, range 12-25yrs; LT – 16.58 ±4.88, range 9.5-24yrs). NM controls were older than ET ($t(33)=2.47$, $p<.05$*: NM 26.41 ±4.71, range 21-36yrs) and no different from LT ($p=.49$). Because of the significant age difference between groups and the unequal number of males and females, age and sex were used as covariates of no interest in the structural analyses.

Performance differences across groups and blocks of training were assessed with F-tests and planned t-tests. Accuracy, as measured by the percentage of correct responses on the learning sequence (PCOR), differed by group and block (group: $F(2,50)=6.18$, $p<.05$*, $\eta2=.20$; block: $F(5,250)=8.89$ $p<.001$**, $\eta2=.15$), with no interaction (group*block: $F(10,250)=.85$, $p=.59$). Because musicians' PCOR did not differ on the final block of practice, PCOR was not included in any other analyses ($t(34)=.11$, $p=.92$). Performance on the measure of sensorimotor synchronisation (PSYN) also showed significant differences between groups and over blocks (group: $F(2,50)=21.26$, $p<.001$*, $\eta2=.46$; block: $F(5,250)=25.87$ $p<.001$**, $\eta2=.34$), with no interaction (group*block:

F(10,250)=.28, p=.99). Overall, performance differed between groups and improved across training blocks. Planned directional t-tests revealed that ET had greater performance than LT (ET > LT: blocks 1-6, p<.05*) and LT had greater performance than NM (LT > NM: blocks 1-2, p<.05* & blocks 3-6, p<.001**). Our results indicate that musicians have an advantage in sensorimotor synchronisation, that the advantage is greater in ET than in LT, and that it is maintained over the course of training (Figure 3.2). They are in agreement with the findings of a behavioural experiment showing differences between ET, LT, and NM across five days of training on the TMST (Watanabe et al., 2006).

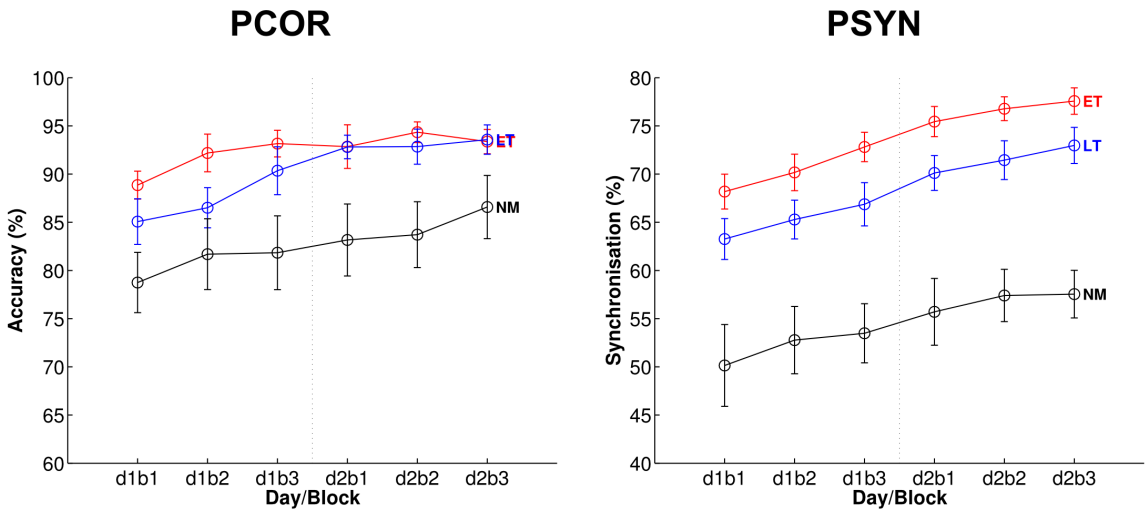


Figure 3.2. Percent Correct (PCOR) and Percent Synchrony (PSYN) across blocks

Group means for each measure are plotted for each day and block. Early-trained (ET) in Red; Late-trained (LT) in Blue; Nonmusicians (NM) in Black. Error bars depict ±SEM. The vertical dotted line between d1b3 and d2b1 denotes the boundary between days of

training.

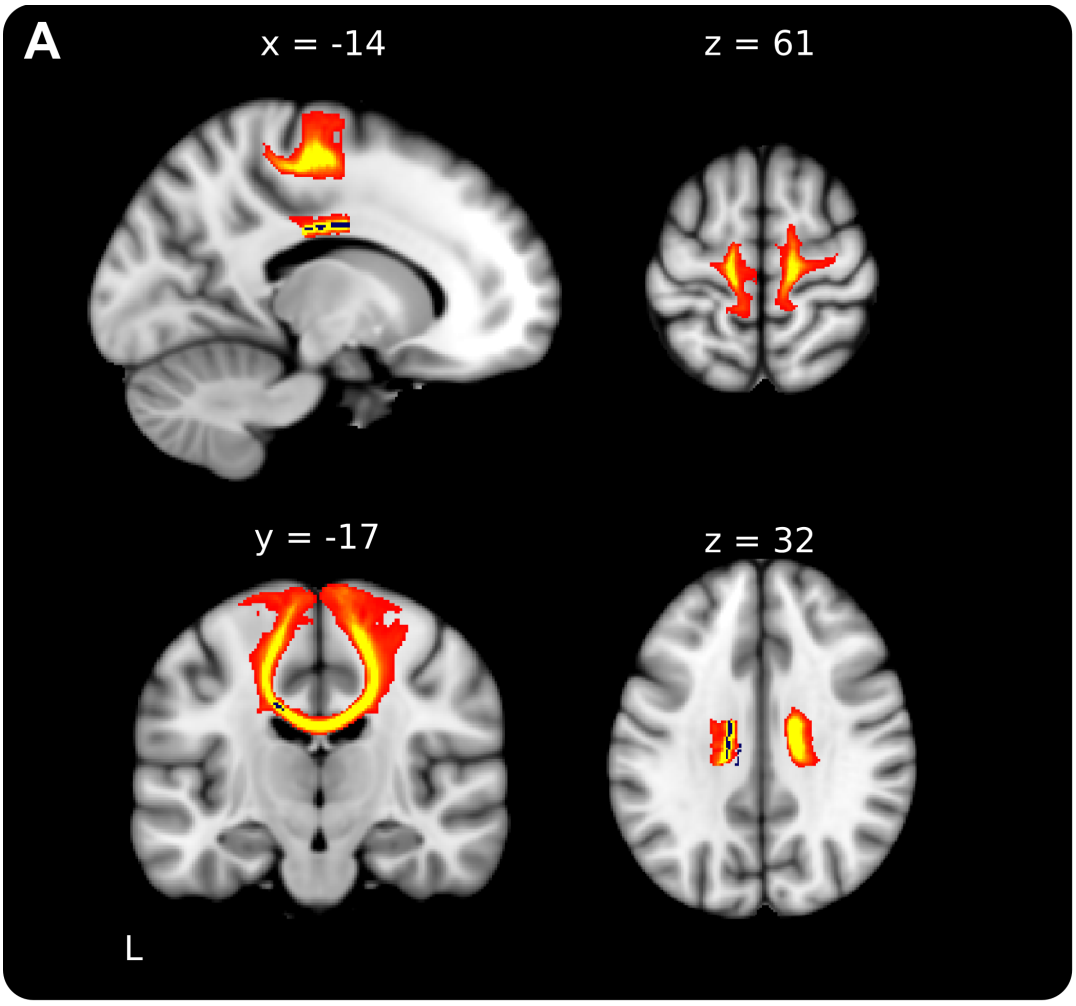
To determine if performance on the TMST was related to particular aspects of musicians' training, PSYN Final was tested for its relationship with age of onset, years of formal training, and years of experience. PSYN Final was significantly correlated with age of onset ($r=-.33$, $p=.05$*) and years of formal training ($r=.37$, $p<.05$*) but not years of experience ($p=.41$) across all musicians. Additionally, though groups were matched for years of formal training and experience there was still the possibility that these measures could be related to age of onset across the full sample of musicians. Age of onset was significantly correlated with years of formal training ($r=-.41$, $p<.05$*) but not years of experience ($p=.99$), indicating that those who began musical training later had fewer years of formal training than those who began earlier. To ensure that the relationship between age of onset and extracted brain structural measures was not due to differences in the amount of formal training, analyses where years of formal training could potentially impact our results were conducted with years of formal training as a variable of no interest to control for its potential effect.

3.4.2 Imaging

3.4.2.1 Group Differences

Skeletonised FA values were compared to determine between-group differences in white-matter structure. ET had significantly greater FA than LT in a region of the corpus callosum including the posterior midbody and anterior portion of the isthmus (peak voxel: -14, -11, 32, $t=4.55$, Figure 3.3A). The significant region was deprojected into

each musician's registered space to confirm that voxels making up the skeleton were retrieved from the location represented by the group analysis. An additional analysis comparing smoothed whole-brain FA between ET and LT was used to confirm these findings in non-skeletonised space. In the voxelwise analysis, the more posterior region of the skeletonised group difference, corresponding to anterior isthmus bordering the posterior midbody, was the only region where ET had greater FA than LT (peak voxel: -12, -22, 32, $t=5.42$, $p<.05$* fully corrected). To investigate whether the anterior corpus callosum showed differences between groups as reported by others (Schlaug et al., 1995; Schmithorst and Wilke, 2002), the threshold was reduced to $p<.10$ (fully corrected). Consistent with these studies, a large portion of bilateral anterior corpus callosum had greater FA in ET than LT at this reduced significance level.


A
x = -14
z = 61
y = -17
z = 32
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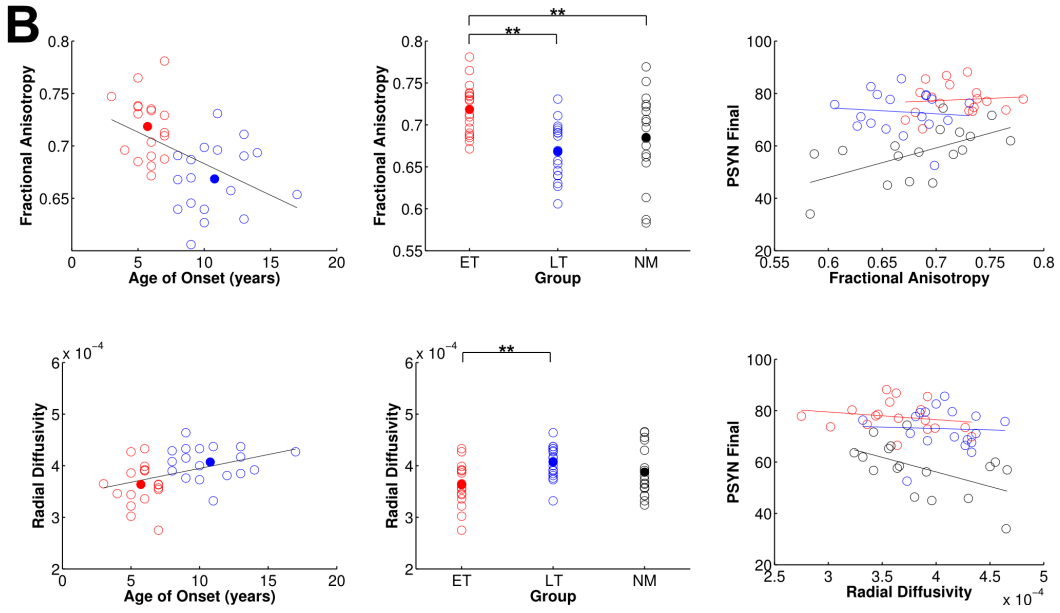
B
Fractional Anisotropy
Age of Onset (years)
Fractional Anisotropy
Group
ET
LT
NM
**
**
PSYN Final
Fractional Anisotropy
Radial Diffusivity
x 10^-4
Age of Onset (years)
Radial Diffusivity
x 10^-4
Group
**
PSYN Final
Radial Diffusivity
x 10^-4

Figure 3.3. ET vs LT group difference and extractions

Panel A – ET > LT group difference in skeletonised FA (blue) in posterior midbody of the corpus callosum. The tract based on this seed connects the right and left sensorimotor cortices through the posterior midbody of the corpus callosum – represented as the red-yellow underlay (where red-yellow represents a threshold of 1-10% of maximum particle count and bright yellow depicts 10% and greater). Panel B – Extracted values from peak corpus callosal posterior midbody voxel plotted against age of onset, group, and PSYN Final. FA and RD plots are shown on the top and bottom rows respectively. In all plots, ET is depicted in red, LT in blue, and NM in black. Group means are depicted with filled circles. * $p<.05$; ** $p<.001$

To determine whether white-matter in the corpus callosum is specifically affected by the age at which musical training begins, age of onset was correlated with extracted diffusion measures. FA, AD, and RD were extracted from the peak posterior midbody voxel identified in the ET vs. LT skeletonised whole-brain analysis. Crucially for the identification of a sensitive period, both FA and RD were significantly correlated with the age of onset of musical training when controlling for age, sex, and years of formal training (FA: $r=-.40$, $p<.05$*; RD: $r=.36$, $p<.05$*) (Figure 3.3B, left column). These findings strongly suggest that white-matter in the posterior midbody of the corpus callosum is differentially affected by the age at which musical training commences. Extracted diffusion measures were also compared between groups. In addition to the ET > LT group difference identified in the skeletonised whole-brain analysis, ET had

significantly greater FA than NM (ET > NM: t(33)=4.70, p<.001**; LT > NM: p=.86). There was also a significant difference between musicians such that RD was lower in ET (ET < LT: t(34)=3.59, p<.001**; ET < NM: p=.06; LT < NM: p=.92; Figure 3.3B, middle column). There were no AD differences between groups (ET > LT: p=.07; ET > NM: p=.13; LT > NM: p=.60). Overall, the extractions show that white-matter this region of the posterior midbody of the corpus callosum is sensitive to the age of onset of musical training and the observed group difference in FA is primarily driven by differences in RD.

To determine if this region of the corpus callosum is also important for task performance, FA extracted from the peak voxel was correlated with PSYN Final (Figure 3.3B, right column). There was a significant positive correlation across all participants (All: r=.30, p<.05*) that was predominantly driven by the correlation within NM (ET: p=.67; LT: p=.80; NM: r=.57, p<.05*). The FA PSYN Final correlation in NM was, in turn, primarily influenced by RD (All: p=.06; ET: p=.71; LT: p=.79; NM: r=-.59, p<.05*).

Fibre tractography was used to assess the structural connectivity of the posterior midbody/isthmus region. A seed mask was created from the significant cluster of the skeletonised ET vs. LT FA analysis, and the results were thresholded for display (Figure 3.3A). The mean tract passed through the posterior midbody/isthmus of the corpus callosum to connect the right and left sensorimotor cortices (Figure 3.3A). While this finding is not in line with cortical connectivity predictions based primarily on animal studies (Witelson, 1989), the tract identified here is consistent with corpus callosal connectivity reported in recent DTI-based human tractography studies (Hofer and Frahm, 2006; Chao et al., 2009). Mean diffusion parameters extracted from the tract-defined

volume showed strikingly similar results to those found in the prior skeleton-based extractions (the tract was thresholded at 10% and is depicted in bright yellow in Figure 3.3A). FA was greater in ET than LT and marginally greater than NM (ET > LT: $t(34)=2.11$, $p<.05$*; ET > NM: $p=.07$; LT > NM: $p=.72$); there was a marginal RD difference between ET and LT (ET < LT: $p=.09$; ET < NM: $p=.16$; LT < NM: $p=.36$); and no differences in AD (ET > LT: $p=.21$; ET > NM: $p=.38$; LT > NM: $p=.71$). There was no evidence for correlation between diffusion measures and age of onset (FA: $p=.37$; RD: $p=.31$). These results indicate that that the group difference identified within the corpus callosum is also true for the tract that connects right and left sensorimotor cortex through this region.

3.4.2.2 White-matter Correlates of Sensorimotor Synchronisation

To directly test the relationship between white-matter integrity and task performance, whole-brain skeletonised FA was correlated with PSYN Final. Across all groups, FA in an extensive region of the left temporal lobe (TL) was significantly positively correlated with PSYN Final (Figure 3.4A). This ROI extended along the length of the left TL and into the posterior limbs of the internal and external capsules. Note that this same region was not present below threshold in the right hemisphere. Mean diffusion values from the entire significant ROI were extracted to better represent the extensive area of interest. To determine if white-matter in this region shows a similar relationship to that found in the posterior midbody of the corpus callosum, extracted FA and RD values were correlated with age of onset. Partial correlations (with age, sex, and years of formal training as covariates of no interest) identified a significant negative correlation between age of

onset and FA and a significant positive correlation between age of onset and RD (FA: r=-.41, p<.05*; RD: r=.38, p<.05*) (Figure 3.4B, left). Again, this finding strongly indicates that white-matter in this region is differentially affected by the age at which musical training begins – providing further evidence for an interaction between age of onset of training and brain structure. Mean FA extracted from this region did not differ between musician groups but differed between ET/LT and NM (ET > LT: p=.10; ET > NM: t(33)=3.98, p<.001**; LT > NM: t(33)=2.56, p<.05*) (Figure 3.4B, middle). Again, differences in RD appear to be driving the FA differences (ET < LT: p=.18; ET < NM: t(33)=2.98, p<.05*; LT < NM: t(33)=2.07, p<.05*). There were no AD differences between groups (ET > LT: p=.24; ET > NM: p=27; LT > NM: p=52). In addition, the group-wise correlations with PSYN Final revealed that the overall significant correlation with FA was driven by correlations within LT and NM (ET: p=.74; LT: r=.59, p<.05*; NM: r=.63, p<.05*). Again, this finding appears to have been primarily driven by RD (ET: p=.77; LT: r=-.62, p<.05*; NM: r=-.61, p<.05*) and not AD (ET: p=.99; LT: p=.67; NM: p=.13). These findings provide further evidence for a possible sensitive period where the effect of musical training on the development of white-matter structure differs depending on the age at which training begins.

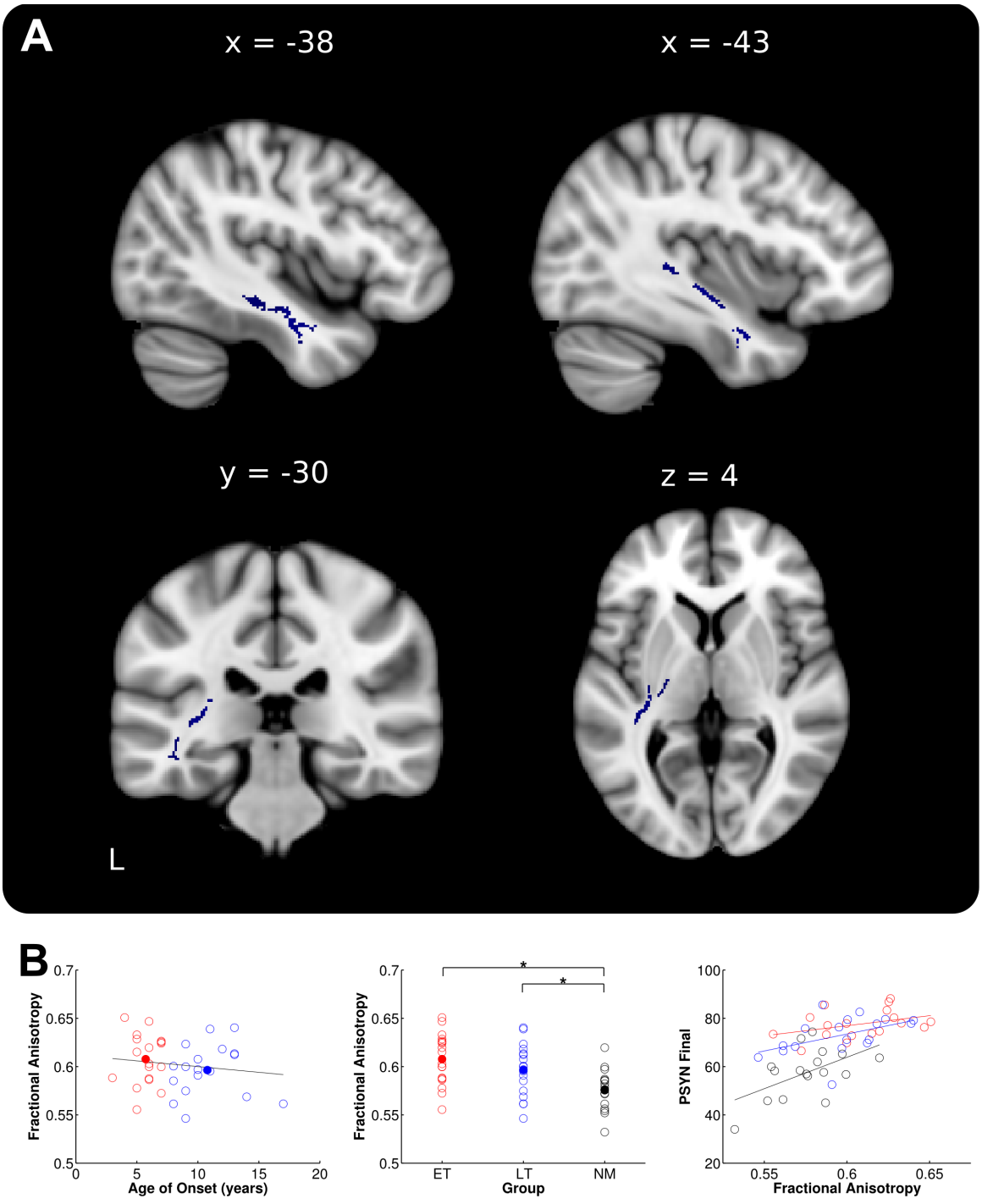

Figure 3.4. Whole-brain FA correlations with PSYN Final

Panel A – Skeleton voxels significantly correlated with PSYN Final in left TL and

posterior limb of the internal and external capsules (blue). Panel B – Extracted mean values from significant finding plotted against age of onset, group, and PSYN Final. In all plots, ET is depicted in red, LT in blue, and NM in black. Group means are depicted with filled circles. * $p<.05$

3.5 Discussion

Our results show that early musical training has a differential impact on white-matter structure and behaviour. Further, we provide evidence for a possible sensitive period where enhanced sensorimotor experience produces long-lasting changes in the brain and behaviour. ET had greater synchronisation performance than LT across all blocks of training, as has previously been shown (Watanabe et al., 2006). ET also had greater FA than LT in the posterior midbody/isthmus of the corpus callosum connecting right and left sensorimotor cortex. This difference exists even though musician groups were matched for years of formal training and experience. Synchronisation performance across groups was significantly correlated with FA in the TL and internal and external capsules. Extractions from the overall ROI showed that musician groups had greater FA than nonmusicians. Crucially, FA from both the posterior midbody/isthmus and TL region was significantly correlated with the age of onset of musical training despite controlling for years of formal training. Together, these results provide strong evidence that early musical training has a differential impact on WM structure and behaviour, and indicate a possible sensitive period where musical training can affect adult brain structure and performance.

3.5.1 Connectivity and Interactions

Our results strongly suggest that white-matter integrity in the corpus callosum and TL is differentially affected by musical training during a sensitive period in development. ET had greater FA in the posterior midbody/isthmus than LT and FA from this region correlated with age of onset across musicians even after controlling for years of formal training (Figure 3.3). FA in the body and isthmus/splenium of the corpus callosum has previously been linked to self-reported hours of practice before the age of eleven in musicians who began training early (age of onset 5.8 ±1.4) (Bengtsson et al., 2005). A similar posterior region of the body of the corpus callosum was found to undergo structural changes after fifteen months of musical training commenced at six years of age (Hyde et al., 2009). The posterior midbody/isthmus region found in our study, and overlapping with the findings described above, transcallosally connects sensorimotor cortices (Hofer and Frahm, 2006; Chao et al., 2009). Though all musicians in our study were right handed, performing most musical instruments requires auditory and visual perception to be synchronised with the action and somatosensation of both hands/limbs. The central portion of this tract connects bilateral motor cortex (M1), where sulcal length has been shown to be related to the age of onset of musical training (Amunts et al., 1997). In addition to the findings described above, FA underlying auditory cortical regions in the left TL was significantly correlated with synchronisation performance and age of onset (Figure 3.4). Our finding includes a region of the arcuate fasciculus, the main fibre tract connecting auditory and motor cortex (Glasser and Rilling, 2008), and is consistent with its proposed role in the strong auditory-motor associations found in musicians (Wan and

Schlaug, 2010) and the functional recruitment of auditory and motor regions during performance of the TMST in nonmusicians (Steele and Penhune, 2010). These findings are consistent with evidence for enhanced auditory cortical representation in the left hemisphere of musicians who began training earlier (not controlled for training or experience) (Pantev et al., 1998). In summary, our principal findings show increased white-matter integrity in ET within tracts supporting the precise sensorimotor and auditory-motor integration demands of musical training and performance (Zatorre et al., 2007). Our findings suggest that both sensorimotor hemispherical and auditory-motor connectivity can be altered by musical training during a sensitive period in development, and that this may be linked to motor/auditory cortical differences between musicians and controls. Further, they suggest that the complex and integrated nature of musical training makes it an excellent driver for white-matter plasticity during a sensitive period.

3.5.2 Possible Mechanisms

We hypothesise that engaging in musical training during a sensitive period in human development drives the white-matter plasticity underlying behavioural differences in adult musicians. The individual and group differences in FA that we observed could be driven by factors such as axon myelination, diameter, and packing density (Beaulieu, 2002; Alexander et al., 2007). These factors may be the result of changes in myelination through experience-related firing (Fields, 2005) and/or alterations in packing density due to axon proliferation or pruning during the sensitive period. But how do these differences arise? Because neural circuits are more labile during sensitive periods, the presentation of behaviourally-relevant experience during this period has a larger effect on circuits'

configuration than similar experience obtained at other times (Knudsen, 2004). The interaction between bottom-up (incoming sensory information) and top-down factors (such as motivation/reward and attention) during sensitive periods is thought to be of critical importance (Kral and Eggermont, 2007). Pioneering animal work identified critical periods in development where bottom-up sensory information is essential for cortical development and normal functioning. Monocularly-deprived cats fail to develop normally functioning visual cortex if deprivation occurs during a critical period of 4-8 weeks (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970). Similar work with rats has defined a critical period between days 11-13 where exposure to normal auditory stimuli is required for normal development of primary auditory cortex (de Villers-Sidani et al., 2007). Musical training is a rich source of bottom-up stimulation to the tactile, visual, and auditory systems and involves a high degree of sensorimotor integration (Zatorre et al., 2007). Higher-level cognitive factors such as motivation and reward may help orient attention to behaviourally-relevant sensory information and drive plasticity (Kilgard et al., 2002). Music provides intense pleasure and reward (Blood and Zatorre, 2001; Salimpoor et al., 2011) and musical training/performance may create a positive feedback loop that reinforces the neural circuits involved. When the process of learning to produce a piece of music begins, the reward of producing and perceiving the correct sounds may act as motivation to the musician. With practice, the association between correct playing positions and the correct (pleasurable) sounds are formed and reinforced. Thus, musical training provides both the bottom-up and top-down factors necessary to drive structural plasticity during a sensitive period in development.

3.5.3 Other Factors

The current work provides evidence for the presence of a possible sensitive period for the effects of musical training on brain structure and behaviour. However, it is possible that pre-existing individual differences lead some children to begin training early while others begin later (and some not at all). IQ is unlikely to be the cause (Hyde et al., 2009; Bailey and Penhune, 2010), but genetic differences linked to auditory and motor development, motivation, and social skills are more difficult to rule out. Other factors such as socioeconomic status and home environment may also play a role. A randomised longitudinal experiment that follows participants into adulthood may be the only way to test for these effects.

This study provides three pieces of evidence for the existence of a sensitive period during which musical training produces long-lasting effects on adult brain structure and performance. First, we provide behavioural evidence for a sensorimotor synchronisation advantage for musicians who began training before the age of seven. Second, those who began training early had greater FA in the sensorimotor region of the corpus callosum, a region that was also significantly correlated with age of onset over and above the effect of training. Third, FA extracted from the TL region where synchronisation was positively correlated with FA was significantly correlated with age of onset in musicians over and above the effect of length of training. Together, our results suggest that extensive training conducted early in life has a differential impact on plasticity that results in long-lasting effects upon both the structure of the brain and behaviour.

Chapter 4: General Discussion

The purpose of the current dissertation was to investigate the relationship between brain structure, performance, and training. Study 1 used individual differences in performance to identify white-matter and grey-matter differences that were related to skilled visuomotor synchronisation performance. Study 2 explored how musical training during early childhood may affect white-matter structure and motor performance. Importantly, the second study matched musicians on years of training and experience to isolate the effects of training during a putative sensitive period. Overall, our results show that individual differences in performance are linked to brain structural differences in regions that are functionally implicated in learning and performance of the visuomotor sequencing task. We also provide evidence that intensive training during a sensitive period in development may have a long lasting effect on brain structure and behavioural performance that is greater than training accrued at other times.

4.1 Review of Findings

Study 1 used an individual differences approach to examine the structural correlates of visuomotor synchronisation performance in normal adults. Our results show that the integrity of white-matter located inferior to bilateral motor cortex is related to peak synchronisation performance. Synchronisation and fractional anisotropy (FA) in this region were negatively correlated; however, this relationship was driven by a positive correlation with radial diffusivity (RD). Fibre tractography showed that the cortical spinal tract (CST) and superior longitudinal fasciculus (SLF) cross in this region. The identified tracts anatomically connect motor, parietal, and auditory cortical regions found to be

functionally correlated with synchronisation performance in an fMRI study using the same task in the same sample (Steele and Penhune, 2010) (Appendix B). In addition, a VBM analysis in the same group showed that a more rapid rate of improvement in synchronisation was linked to greater grey-matter volume in cerebellar lobules HVI and V, regions that are important for motor learning. Together, these findings suggest that skilled synchronisation performance is associated with enhanced fibre integrity in the SLF and that the rate of learning is related to grey-matter volume in the cerebellum.

Study 2 investigated how white-matter structure and synchronisation performance may be influenced by early childhood musical training. Early-trained musicians (ET – before the age of seven) had greater FA in the posterior midbody of the corpus callosum than late-trained musicians (LT – after the age of seven) and nonmusicians that connects bilateral somatosensory cortices. Tractography results confirmed that this region connects sensorimotor cortices, and that mean FA extracted from this tract is also greater in ET than LT and nonmusicians. Since ET and LT were matched for years of musical training and experience, these findings may be the result of greater plasticity induced by commencing musical training earlier during a potential sensitive period in development. This interpretation was supported by a negative correlation between age of onset of musical training and FA extracted from this region of interest (across musicians and controlled for age, sex, and years of formal training). Behavioural regression analysis showed that synchronisation performance was positively correlated with FA across all groups in a large region of the left temporal lobe (TL) and the posterior limbs of the internal and external capsules. Mean FA in this region was also greater in ET and LT than

nonmusicians and related to age of onset in musicians. Overall, these findings link early musical training during a potential sensitive period in development to white-matter structural and synchronisation performance differences in adults.

4.2 The Negative Relationship Between FA and Performance

The principal finding of Study 1 was a negative correlation between FA and performance that was driven by a positive correlation between performance and radial diffusivity. Fibre tractography revealed that the negative correlation was present in a region where the corticospinal tract (CST) and superior longitudinal fasciculus (SLF) cross. The combination of these results led to the hypothesis that fibre integrity in the SLF is positively linked with skilled synchronisation performance, and illustrates the importance of considering multiple diffusion measures and underlying tract organisation when assessing FA.

4.2.1 Fractional Anisotropy and Performance

When investigating the relationship between FA and performance, we have the intuitive expectation that higher FA is good, and that it will be related to enhanced performance. Higher FA values have been linked to larger calibre axons with greater myelination, and because conduction velocity is linked with axon diameter (Gillespie and Stein, 1983), we expect that larger axons result in faster conduction/enhanced communication that should, in turn, lead to enhanced performance. Another interpretation of higher FA values is the presence of more densely packed fibres, meaning that greater FA could also reflect enhanced connectivity between regions, again leading to enhanced performance. While the majority of studies investigating FA and performance report findings consistent with

this understanding, a number of researchers including ourselves have found counterintuitive results (Tuch et al., 2005; Imfeld et al., 2009; Hänggi et al., 2010; Taubert et al., 2010). One of the first studies to establish a relationship between FA and performance found that longer reaction times (i.e., poorer performance) on a randomised motor sequence task were positively correlated with FA (Tuch et al., 2005). Similarly, the work of Taubert and colleagues identified regions where FA decreased as learning progressed (2010). In addition, there are two recent studies where lower FA is associated with the more experienced/specialised group (Imfeld et al., 2009; Hänggi et al., 2010). The authors speculate that other properties of local white-matter, such as crossing fibres, may be the cause of these findings but do not fully investigate these hypotheses.

Because FA is a relative measure that summarises diffusivity in the three directions of the diffusion tensor, the measures that make up the FA value can be used to clarify the relationship between FA and performance. FA is calculated based on axial (λ_1, measured along the axis of greatest diffusivity) and radial (the average of λ_2 and λ_3, diffusivity perpendicular to the axis of greatest diffusivity) diffusivity (Figure 1.4). The two diffusivity measures can be analysed separately to gain more specific information about the source of FA differences or correlations. To the best of our knowledge, only two studies have investigated the nature of counterintuitive FA differences/correlations by assessing the contribution of axial and radial diffusivity (Imfeld et al., 2009; Taubert et al., 2010). Taubert and colleagues (2010) found that the negative correlation between FA and performance was influenced by negative correlations with both axial and radial diffusivity. Imfeld and colleagues (2009) reported lower FA in the corticospinal tract of

musicians compared to nonmusicians that was driven by a combination of lower axial and greater radial diffusivity. A negative relationship between FA and performance (or decreases in one group relative to another) could be due to either a negative relationship with axial diffusivity or, positive relationship with radial diffusivity, or some mix of the two. Since axial and radial diffusivity are defined relative to the axis of greatest diffusivity, it is rarely a trivial task to determine how these measures relate to underlying tract structure (Jbabdi et al., 2010). Therefore, in addition to clarifying FA correlations/differences by analysing axial and radial diffusivity, an understanding of the orientation of underlying fibre tracts is necessary to describe the observed relationship. As we have shown in Study 1, diffusion tractography can be used to assess the major fibre tracts passing through a given region to help accomplish this task (Johansen-Berg and Rushworth, 2009).

We have interpreted our radial diffusivity findings as due to the presence of crossing fibres of the SLF. Alternatively, animal research has linked radial diffusivity to the integrity of axon myelination. Mice with a mutated gene that reduces myelin protein expression show increased radial diffusivity (Song et al., 2002). Further, the process of Wallerian degeneration, characterised by dysmyelination, results in increases in radial diffusivity (Sun et al., 2008). Similar work compared affected and non-affected hemispheres of human stroke patients to assess the effects of axon degeneration on measures of diffusion (Pierpaoli et al., 2001). The authors found that degeneration was linked with increased radial diffusivity, but caution that this is only the case when the region is made up of a single fibre tract (Pierpaoli et al., 2001). Thus, the link between

myelination and radial diffusivity is limited to studies of myelin depletion, and to major tracts where axons are uniformly oriented. Animal models present a best-case scenario for the interpretation of radial diffusivity, but do not necessarily reflect reality within the more complicated structure of the human brain. The presence of multiple fibre orientations and non-uniformly oriented axons complicates the interpretation of diffusion measures because these scenarios are not well characterised (Alexander et al., 2007; Wheeler-Kingshott and Cercignani, 2009). Therefore, the link between radial diffusivity and myelination may not be valid when crossing and/or fanning fibres are present, as is the case in our finding and in many other regions of the human brain (Pierpaoli et al., 2001; Sun et al., 2008). As with FA, differences in radial diffusivity should be interpreted with caution and in combination with additional information from other diffusion measures and the tract(s) of interest. Future work could combine DTI with magnetization transfer methods for assessing myelin content to help with the interpretation of white-matter findings.

4.2.2 Future Directions

A longitudinal motor sequence training study has been designed to expand upon the findings in Study 1. This study trains participants across six days on a complex 4-finger visuomotor synchronisation task. Participants in this combined functional and structural MRI study will undergo T1, DTI, and magnetization transfer imaging (to assess myelination) on the first and final days of training. This study has been designed to utilise individual differences in brain structure, function, and behaviour in a single cohort to characterise optimisation of multiple components of skill (such as synchronisation,

accuracy, chunking, and velocity) over a six day training period, identify the functional and structural correlates of these components, and determine how their relationships may change with learning. It will also allow us to more closely investigate the nature of the negative correlation identified in Study 1 and help to clarify whether it is the result of pre-existing differences or related to training. This study represents a next step in our understanding of the processes involved in motor sequence learning and provides evidence for how learning is represented and affects change in the brain.

4.3 Training During a Putative Sensitive Period in Development

The second study in this dissertation presented evidence that the corpus callosum may be particularly susceptible to training-related plasticity during early childhood. We found that ET had greater FA in the posterior midbody of the corpus callosum than LT. Since groups were matched for years of training and experience, we hypothesised that our findings were due to plasticity induced by commencing training earlier during a potential sensitive period in development and not simply a result of training or experience. The results of this study provide compelling evidence for the presence of a human sensitive period.

4.3.1 Plasticity in the Corpus Callosum

The corpus callosum is the primary pathway connecting homologous regions of the right and left hemispheres. It is important for interhemispheric communication (van der Knaap and van der Ham, 2011) and the coordinated use of the right and left hands. Cross-sectional area of the corpus callosum linearly increases through adolescence (Lenroot and Giedd, 2006) – indicating that it may continue to undergo plastic changes into adulthood.

This finding is difficult to interpret because it is based on the entire cross-sectional area of the corpus callosum. Two other studies illustrate changes in the corpus callosum across development. Fibres extending from the genu and splenium show FA increases until 11 years of age, followed by maintenance (Lebel et al., 2008). While this study did not assess FA within the posterior midbody location identified in Study 2, a more recent longitudinal experiment by Westerhausen and colleagues (2011) identified specific increases in thickness of the genu, anterior and posterior portions of the body, and splenium of the corpus callosum between the ages of six and eight. These findings establish that the corpus callosum continues to show normative changes during development and that the posterior midbody region identified in Study 2 shows normative developmental changes during early childhood (6-8 years).

The posterior midbody/isthmus of the corpus callosum connects the sensorimotor cortices (Hofer and Frahm, 2006; Chao et al., 2009) and thus plays a vital role in supporting performance on bimanual tasks. Though all participants in Study 2 were right handed, performing most musical instruments requires synchronisation of auditory and visual information with motor and somatosensory information from both the right and left hands/arms. Greater FA in the posterior midbody/isthmus of ET identified in Study 2 may be the substrate supporting the enhanced bimanual sensorimotor communication necessary for professional musical performance, and may also be the result of training-induced plasticity during a sensitive period in development. In short, bimanual sensorimotor integration training and experience during a period when brain structure is undergoing normative developmental change may cause specific plastic changes in task-

relevant regions. The structural effects of these changes can then be observed in the same task-relevant brain regions in adults, along with their behavioural consequences.

4.3.2 Sensitive Period Mechanisms

The combination of typical developmental and training-related plasticity during a particular period in development produces long-lasting effects on brain structure and behaviour. During a sensitive period, structural changes are driven by the interaction between bottom-up (incoming sensory information) and top-down factors (such as reward and attention) (Kral and Eggermont, 2007). Pioneering studies on monocularly-deprived cats illustrated the importance of sensory stimulation on cortical development during critical periods (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970). Similar results have also been obtained in the auditory domain (Chang and Merzenich, 2003; de Villers-Sidani et al., 2008). Top-down factors such as attention can also play a role during sensitive periods. For example, attention can modulate selectivity of the auditory cortex (Fritz et al., 2007) and may influence its development (Polley et al., 2006).

We hypothesise that the unique properties of musical training experienced during a sensitive period in early childhood are strong drivers of the structural plasticity underlying behavioural differences in adult musicians. Musical training provides bottom-up stimulation to the tactile, visual, and auditory systems, involves a high degree of sensorimotor integration, and requires precise timing and execution of motor responses (Zatorre et al., 2007). The intense pleasure and reward associated with music (Blood and Zatorre, 2001; Salimpoor et al., 2011) may serve to orient attention and modulate plasticity from the top-down. Early musical training would both affect brain structure and

behaviour at an early age and could pre-set the circuits for plasticity later in life. A previous longitudinal study found increased grey-matter in the body of the corpus callosum in children who underwent fifteen months of musical training compared to controls (Hyde et al., 2009). This region corresponds well with that identified in the current study and is suggestive evidence that structural plasticity during childhood may underlie the differences that we have identified here. Consistent with previous results from our laboratory (Watanabe et al., 2006; Bailey and Penhune, 2010), the behavioural results of Study 2 showed that ET performed better than LT when matched for years of training and experience. Additional analyses showed that FA in a large region of white-matter in and around the temporal lobe was significantly correlated with age of onset of musical training. The adjacent cortical regions of the temporal lobe and white-matter of the internal/external capsule have been linked to musicianship/music performance (Bengtsson et al., 2005; Zatorre et al., 2007; Bermudez et al., 2009) and our results indicate that they are affected by musical training during early development. Individual differences in FA that are correlated with age of onset could be driven by factors such as axon myelination, diameter, and packing density (Beaulieu, 2002; Alexander et al., 2007). Training-related changes in axon myelination could be caused by increased use (Fields, 2005) and changes in packing density could be the result of axon proliferation or decreased pruning during the sensitive period (Knudsen, 2004). Consistent with this interpretation, other work has shown that earlier trained musicians have decreased left > right asymmetry in the motor cortex (Amunts et al., 1997) that is presumably due to increased synaptic density (Kleim et al., 1996). A training-related increase in the number

(and density) of fibres passing through this region of the corpus callosum connecting right and left sensorimotor cortex may underlie the findings that we have observed.

4.3.3 Alternative Hypotheses

While we have hypothesised that the observed differences between ET and LT are a result of training-dependent plasticity during early childhood, we cannot rule out the possibility that these differences are due to other factors. Because we did not randomly assign participants to groups, there are two main factors that could contribute to our results: 1) pre-existing factors influencing both brain structure and the propensity for musical training, and 2) individual differences in environment. Pre-existing genetic factors may influence the propensity to train at an early age, the motivation to continue training and performing, and the observed structural differences. In line with this idea, genetic factors have been linked to the ability to acquire perfect pitch (Zatorre, 2003) and measures of musical aptitude (Ukkola et al., 2009). However, there are two lines of evidence that make this interpretation of our results unlikely. First, training-dependent changes in corpus callosal white-matter structure have previously been observed. Hyde and colleagues (2009) identified greater grey-matter change in the body of the corpus callosum in children who underwent fifteen months of musical training compared to controls. The experimenters randomly assigned six year old children to the groups and, crucially, showed that there were no structural differences prior to training. The corpus callosal region found to increase after practice corresponds well with that identified in Study 2, suggesting that training-dependent structural plasticity during childhood may underlie the differences that we have identified. Second, genetics may exert little

influence on the variability of white-matter integrity in the body of the corpus callosum. Structural equation modelling from identical and fraternal twins was used to determine the influence that genetic and environmental factors have on FA in the brain (Chiang et al., 2009). The authors showed that approximately 70-90% of individual variability in FA of regions of the genu, splenium, and part of the isthmus is attributable to genetic factors. Interestingly, their evidence also shows that environmental factors may be particularly important for explaining FA variability in the body of the corpus callosum, though this was not the focus of the experiment and is not discussed in detail. Again, this region of the corpus callosum corresponds with that identified in Study 2 and the findings of Hyde and colleagues (2009). Similar to the pre-existing differences discussed above, home environment may also have influenced our results. Factors such as family support, exposure to music in the home, and access to music lessons may also play important roles.

4.3.4 Future Directions

The only way to fully address the issues raised in the previous section would be to conduct a long-term longitudinal study with random assignment. Children would need to be assigned to musical training at an early age and multiple measures of brain structure and performance assessed at multiple time points. A study with children entering highly structured and intensive musical lessons for one year is currently being planned in our laboratory. However, multiple cohorts of children randomly assigned to begin training at different ages would need to be assessed to actually test for the presence of a sensitive period for musical training. It is also possible that the full impact of musical training

during early childhood may not be observable until adulthood. Sensitive periods may serve to create the initial "scaffolds" for plasticity in later life, establishing the connectivity and interactions between neurons and regions responsible for task performance (Knudsen, 2004). Task-relevant training during a sensitive period may expand the plasticity scaffold to allow a greater range of structural (and behavioural) changes as an adult.

4.4 Visuomotor Synchronisation Performance

Both studies in this dissertation used the temporal motor sequence task (TMST) to assess visuomotor synchronisation performance. Visuomotor synchronisation performance improvement across days of practice was consistent with that reported in previous experiments – exhibiting less rapid optimisation and lower final performance than that observed for the more explicit sequence accuracy component (Penhune and Doyon, 2002; Savion-Lemieux and Penhune, 2005; Steele and Penhune, 2010). The group differences identified in Study 2 closely match those found in a previous behavioural study comparing ET, LT, and nonmusician performance on the TMST over five days of practice (Watanabe et al., 2006). Both studies show a sustained visuomotor synchronisation advantage for musicians such that ET>LT>nonmusicians and an initial advantage for accuracy that diminished with practice. Consistent with these findings, musicians have been shown to have superior performance on other tasks including auditory rhythm synchronisation (Chen et al., 2008; Bailey and Penhune, 2010), melody discrimination (Foster and Zatorre, 2010b), and sensorimotor integration during finger tapping (Repp, 2010). These findings also parallel those of other research that has separated learning into

multiple components that are optimised over different timecourses and may undergo different developmental trajectories. Sequence learning on different tasks has also been separated into components related to explicit and implicit processes (Ghilardi et al., 2009), feedforward and feedback control (Grafton et al., 2008), and accuracy and sensorimotor integration (Savion-Lemieux et al., 2009). These findings, along with ours, are in line with the idea that learning and performance can be broken down into individual components that are optimised over different time periods and may be linked to different structural/functional networks in the brain (Penhune and Steele, 2012).

4.4.1 White-matter Correlates

Visuomotor synchronisation performance was linked to different regions of white-matter in the two studies presented in this dissertation. The first study used nonmusicians and linked peak synchronisation performance after five days of practice to fibre integrity in bilateral SLF. The second study used musicians and nonmusicians and linked synchronisation performance after two days of practice to a large region of the left TL and the posterior limbs of the internal and external capsules. White-matter in the posterior region of the internal capsule identified in Study 2 is primarily made up of fibres from the CST (Kretschmann, 1988; Lee et al., 2011). In addition, the only other structural imaging study of motor sequence learning also found a positive correlation between FA in the SLF and performance improvement (Tomassini et al., 2011). The results of these studies suggest that sequence learning and visuomotor synchronisation performance is related to white-matter integrity in both the SLF and CST. These tracts connect primary motor, temporal, and parietal regions whose activity was found to be positively correlated with

synchronisation performance in a functional imaging study with the same sample as in Study 1 (Steele and Penhune, 2010). We propose that these regions work together to support motor sequence performance, and that the integrity of the pathways that connect these regions and descend to the spinal cord contribute to skilled synchronisation performance.

There are two methodological factors that may contribute to differences in the findings of the two studies. First, participants in the Study 1 practiced the TMST over five sessions while those in Study 2 practiced for only two days. Performance at the end of two days of practice may not necessarily map directly on to maximum ability after five days of practice. In addition, two thirds of the population in Study 2 were musicians who may not necessarily show the same relationship between white-matter structure and behaviour. However, the correlation between mean FA extracted from this region and synchronisation is still significant within the nonmusician group (Figure 3.4). Second, differences in DTI resolution between the two studies may have contributed to the identification of different regions across the two studies. Diffusion-weighted images were acquired at 2.5x2.5x5mm for Study 1 and 2x2x2mm for Study 2. Larger voxel sizes have greater signal to noise ratio that should result in a more accurate measure of FA within the voxel (Laganà et al., 2010). However, larger voxels may also be more susceptible to partial volume effects. Larger voxels have a greater chance of straddling tissue or population boundaries. Including different tissue types (white/grey/cerebrospinal fluid) and different fibre populations in a single voxel (such as in regions of crossing fibres) will undoubtedly bias results (Assaf and Pasternak, 2007). Tissue-based partial volume

effects are less of an issue because the two studies presented in this dissertation used a skeletonisation procedure during data processing. A mean FA volume is first calculated, and then thinned to produce a two-dimensional skeleton representing the major fibre tracts. The voxel with the largest FA that is close to the skeleton in each individual is then projected onto the skeleton (Smith et al., 2006). Maximum FA is normally within the centre of the tract; therefore, the voxels in each participant's FA skeleton represent the maximum FA in the given region of the tract. Since skeletonised FA comparisons essentially compare tract centres, they are less likely to suffer from partial volume effects (or alignment errors). However, the interpretation of FA in voxels that include multiple fibre orientations, such as regions of crossing fibres, needs to be nuanced by considering the underlying fibre architecture and additional diffusion measures (Alexander et al., 2007). When combined with statistical clustering techniques, studies with larger voxels are more sensitive to the effects of crossing fibres and may therefore detect effects that could not be found with smaller voxels. Consistent with the recruitment of auditory regions in performance of the TMST, The correlation between FA in the left TL and synchronisation performance in Study 2 is consistent with the recruitment of superior temporal gyrus during learning and performance of the TMST (Penhune and Doyon, 2005; Steele and Penhune, 2010). In summary, our combined results indicate that visuomotor synchronisation is supported by white-matter in the SLF, CST, and underlying temporal cortex.

4.5 Conclusions

The current dissertation investigated the relationship between brain structure, motor

performance, and musical training. Specifically, our results showed that visuomotor synchronisation performance is related to individual differences in white-matter integrity in fibre tracts connecting cortical regions functionally involved in synchronisation performance. The combination of diffusion- and tractography-based measures used in these studies provided the additional context necessary for interpretation of our results. We also demonstrated that musical training during a sensitive period in early childhood may lead to enhanced structural plasticity in a region of the corpus callosum connecting bilateral sensorimotor cortices. Crucially, this finding was linked to the age at which musical training began rather than the amount of training or experience – suggesting the presence of a sensitive period for musical training. Our results are consistent with a growing body of literature supporting the links between individual differences in brain structure and performance, and training and structural plasticity. They suggest that brain structure is the result of interactions between pre-existing factors, developmental factors, and training and experience.

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Appendix A

Penhune VB, Steele CJ (2012) Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning. Behavioural Brain Research 226:579–591.

Appendix B

Steele CJ, Penhune VB (2010) Specific Increases within Global Decreases: A Functional Magnetic Resonance Imaging Investigation of Five Days of Motor Sequence Learning. J Neurosci 30:8332–8341.