Evidence for a sensitive period for musical training

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Abstract

Evidence for a sensitive period for musical training

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The aim of the current dissertation was to investigate evidence for a sensitive period for musical training. The first study examined behavioural performance on an auditory-motor synchronization task and cognitive abilities in three groups: early-trained musicians, late-trained musicians, and non-musicians. The early-trained musicians were better able to reproduce the auditory rhythms, even after controlling for differences in musical experience using a matching paradigm. Both musician groups outperformed the non-musician group. The second study used these same groups of participants and their performance data to investigate differences in grey matter structure associated with early musical training. Several different structural Magnetic Resonance Imaging analysis techniques were used to examine differences in grey matter between groups and results suggest greater grey matter volume and cortical surface area in the right ventral pre-motor cortex among early-trained musicians. Extracted values from this region of difference correlated with auditory-motor synchronization performance and age of onset in the musician groups. Previous literature supports the role of the pre-motor cortex in the auditory rhythm task, as well as timed motor movements (Chen, Penhune, & Zatorre, 2008). The third study used a larger, un-matched sample of musicians to examine the relationship between age of onset of musical training as a continuous variable and performance on the auditory-motor synchronization task. In addition, individual working memory scores and years of formal training were considered as task correlates. These findings suggest the presence of a non-linear relationship between age of onset of musical training and auditory-motor synchronization performance. Working memory scores seemed to predict task performance, regardless of when musical training began; however, years of formal training was a significant predictor of task performance only among those who began at an earlier age. Taken together, these findings support the hypothesis of a sensitive period for musical training and shed light on the complexity of the relationship between brain maturation processes and training-induced plasticity.

Acknowledgments

The most influential person on this journey for me has been my supervisor, Virginia Penhune. She has been a fantastic supervisor and mentor throughout this process. She has provided me with excellent advice as I have navigated my way through clinical and research avenues. Not only has she been a great supervisory and mentor, but she is an enthusiastic, understanding and caring woman and the university department would not be the same without her. She was a wonderful fit for my development through graduate school and I often thank my lucky stars that I ended up in her lab. Of course, there is always a man behind a woman and, in this case, it is Robert Zatorre. His support and contributions should not go without acknowledgment. These two people make for an excellent and inspiring pair of supervisors, researchers and are all round great people. I hope to continue communication and maybe even collaboration down the road in some way, shape or form. Musical training, ADHD, and the brain? I think it has a nice ring to it.

Being a member of the Penhune lab has been an honour for me and I would like to thank all those who contributed to such a fantastic and stimulating work environment. The early years were strongly influenced by Tal Savion-Lemieux who took me by the hand, supervised me as an honours student and continued to do so as I made my way through the clinical program. Clarisse Longo dos Santos, Sarah Fraser, Kevin Trewartha, Larry Baer and Alejandro Endo were fellow lab members during most of my time at Concordia and they all contributed to the welcoming, motivating and fun lab dynamic. Chris Steele was a strong contributor to this dynamic and has influenced me more than he probably even knows. I have learned an incredible amount from him and he has continued to be a strong source of support from a distance. Without these members, my graduate training experience would not have been the same and I cannot express how grateful I am to have worked alongside such talented and wonderful people. I am certain that the current and newer members of the Penhune lab will continue the tradition!

There are a few people that I have picked up along the way that have helped carry me through to this point and they are definitely worth acknowledging. Jean-Mary Zarate has become a great personal friend, but has also provided me with invaluable support and advice during this process. Rami Nijjar and Ivy Brooker have entertained my endless questions and thoughts throughout our training and deserve many thanks for their patience. The staff members at Springboard Clinic have offered a timely reminder of how powerful optimism and positivity can be and their support has not gone unnoticed. Jonathan Ho has been a tremendous source of support during the last few months of this process. He has been a pillar of strength for me and it would not have been the same without his consistent words of encouragement. I am lucky to have him in my life.

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Contributions of Authors

This dissertation consists of a general introduction, three studies and a general discussion. I wrote the general introduction and general discussion with feedback from my supervisor, Dr. Virginia Penhune, and my internal committee members. The contributions of the three studies are described below.

Study 1: Chapter 2

Bailey, J.A., & Penhune, V.B. (2012). A sensitive period for musical training: Contributions of age of onset and cognitive abilities. *Annals of the New York Academy of Sciences, 1252* (1), 163-70.

The authors of the manuscript designed the experimental method and analyses collaboratively. I modified a previous auditory rhythm task used in the literature and our computer programmer at the time, Alejandro Endo, wrote the scoring program. I recruited and tested participants with the help of Amanda Daly, Michael Spilka, and Eva Best. I scored and analyzed all data and wrote all sections of the manuscript with guidance and feedback from Dr. Virginia Penhune.

Study 2: Chapter 3

Bailey, J.A., Zatorre, R.J., and Penhune, V.B. (*in submission*). *NeuroImage*.

The authors of the manuscript designed the experimental method and analyses collaboratively. The participants were recruited and tested under my supervision, with assistance from Amanda Daly, Michael Spilka, and Eva Best. I performed all image processing and analyses. I wrote all sections of the manuscript with contributions and feedback from Dr. Robert Zatorre and Dr. Virginia Penhune.

Study 3: Chapter 4

Bailey, J.A., and Penhune, V.B. (*in submission*). Investigating a sensitive period for musical training: Is earlier always better? *Frontiers in Psychology (Auditory Cognitive Neuroscience)*.

The authors of the manuscript designed the experimental method and analyses collaboratively. The participants were recruited and tested under my supervision, with assistance from Amanda Daly, Michael Spilka, Eva Best and Dilini Sumanapala. I performed all behavioural and cognitive scoring, with assistance from Dilini Sumanapala. I conducted all data analyses and wrote all sections of the manuscript with guidance and feedback from Dr. Virginia Penhune.

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Chapter 1: General Introduction

Psychologists have long subscribed to the belief that early experiences shape us. Whether it is an individual who experiences trauma or a gymnast who spends hours training, there is no doubt that our early experiences leave a lasting imprint on our behaviours and our brains. Cutting edge research about brain maturation and experience-dependent plasticity offers the tools to investigate the evidence supporting this belief. These two processes – brain maturation and experience-dependent plasticity – may interact to set the stage for sensitive periods in development when the influence of specific experience on the brain and behaviour is strongest and results in long-lasting effects. Sensitive periods have been proposed for the visual and auditory systems, as well as for more complex cognitive skills such as language (Hooks & Chen, 2007; Kral, Hartmann, Tillein, Heid, & Klinke, 2001; Kuhl, 2010; Tomblin, Barker, & Hubbs, 2007; de Villers-Sidani & Merzenich, 2011). The developmental trajectories of the visual, auditory, and language systems are reflected in early childhood behavioural milestones, as well as supported by non-invasive neuroimaging techniques examining changes in brain structure across development (Gogtay et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Musicians are an excellent population to investigate the sensitive period hypothesis because playing a musical instrument is a complex skill, relying largely on the auditory and motor systems (Zatorre, Chen, & Penhune, 2007). It can begin at different ages during development, can be quantified and there is a large amount of evidence that musical training influences brain structure and function at both cortical and subcortical levels (for review see Jäncke, 2009; Strait, Parbery-Clark, Hittner & Kraus, 2012).

The current thesis examines evidence for a sensitive period for musical training by investigating differences between early-trained and late-trained musicians in terms of auditory-motor rhythm synchronization performance, cognitive abilities, and brain structure. The first study examines behavioural differences on an auditory-motor synchronization task between early-trained musicians, late-trained musicians and non-musicians, as well as cognitive differences (Chapter 2; Bailey & Penhune, 2012). In an effort to isolate age of onset of musical training, the two musician groups were matched for years of formal training, years of playing experience and hours of current practice using a matching paradigm (Watanabe, Savion-Lemieux & Penhune, 2007; Bailey & Penhune, 2010). The second study used magnetic resonance imaging (MRI) techniques to examine differences in grey matter features between these groups and relate these differences in brain structure to performance on the auditory-motor synchronization task (Chapter 3; Bailey, Zatorre, & Penhune, *in submission*). The third study took a different approach to investigating the relationship between age of onset of musical training and auditory-motor synchronization task performance. We examined task correlates in a single, large, unmatched sample of musicians to determine if correlates vary as a function of age of onset of musical training (Chapter 4; Bailey & Penhune, *in submission*).

1.1 Definition of a sensitive period

A sensitive period is a window of time during development when the influence of experience or training on behaviour and the brain is stronger than at other points in development. Initial evidence for sensitive periods came from a set of classic studies by Hubel and Wiesel examining visual system development in kittens (1963; 1970). These studies were the first to report that deprivation during certain times in development results in long-lasting effects on system structure and function and initially referred to a critical period. Since then, researchers have learned a significant amount about the visual system, exploring the mechanisms underlying the plasticity of this modality at a systemic, cellular and molecular level (Hensch, 2005; Hooks & Chen, 2007). Along similar lines, a significant amount of work examining the rodent auditory system has revealed periods early in development when sound exposure determines cortical representation of sound frequency and the underlying mechanisms contributing to these developmental periods of sensitivity are also being studied at multiple levels (e.g., Barkat, Polley, & Hensch, 2011; de Villers-Sidani, Simpson, Lu, Lin, & Merzenich, 2008). In humans, the most compelling evidence for sensitive periods comes from research investigating the age at which deaf children receive cochlear implants and recovery of the visual system following removal of cataracts in infants (Harrison, Gordon, & Mount, 2005; Kral, Hartmann, Tillein, Heid, & Klinke, 2001; Lewis & Maurer, 2009; Lewis & Maurer, 2005; Sharma, Gilley, Dorman, & Baldwin, 2007; Svirsky, Teoh, & Neuburger, 2004). Both of these domains of research have identified sensitive periods for the auditory and visual systems in humans. The brain mechanisms underlying language development are still being unraveled; however, researchers have suggested that the capacity for acquiring a second language diminishes over the lifespan and shifts around puberty (Johnson & Newport, 1989; Kuhl, 2011). While learning to play a musical instrument is a complex cognitive skill, similar to language, quantifying musical training in terms of age of onset and experience or practice lends itself more easily to the study of sensitive periods. Moving towards sensitive periods for cross-modal plasticity, evidence has shown that blind individuals recruit occipital cortex for sound localization, pitch and melody discrimination tasks; however, this observed cross-modal recruitment appears to be a function of age of blindness onset (Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008; Voss & Zatorre, 2011). Taken together, it appears that sensitive periods are common across sensory systems and the degree or type of experience-dependent plasticity may depend on an interaction between the timeline of maturation of the specific system and the time at which the experience takes place.

1.2 Development of the auditory-motor system

Playing a musical instrument requires the integration of auditory and motor systems and, therefore, the neurodevelopmental trajectories of these systems are important to consider when investigating the sensitive period hypothesis for musical training. Grey matter development appears to follow an inverted u-shaped pattern with peaks in volume occurring first, followed by a loss of volume (Gogtay et al., 2004; Gogtay & Thompson, 2010; Sowell, Thompson, Tessner & Toga, 2001). When examining grey matter maturation rates more locally, it seems that higher-order association areas reach maturity only after the lower-order sensorimotor areas. The primary sensory and motor cortices mature first, while the rest of the cortex matures more or less in a parietal to frontal fashion, with the exception of the superior temporal cortex, which matures last (Gogtay et al., 2004). In fact, the auditory cortex is thought to have a prolonged development, as compared to the other senses, lasting approximately a decade (Moore & Linthicum, 2007). In comparison with grey matter development, white matter fibre tracts continue to fine-tune themselves well into adulthood. Some studies report a linear growth trajectory of white matter volume across the entire brain and others report quadratic trends in most white matter fibre tracts and linear growth only in the corpus callosum (Giedd, 2004; Lenroot et al., 2007; Paus, 2010). Measures of white matter microstructure suggest that different white matter tracts have distinct maturational timelines (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Paus, 2010). Some connections such as the fornix appear to reach maturity early in childhood (around age 5), but the majority of pathways demonstrate ongoing changes in microstructure until at least pre-adolescence. Of particular importance from these findings is that most fibre tract maturational trajectories are non-linear, with the greatest amount of change occurring in the early childhood years (between ages 5 and 10). Overall, it seems the maturational trajectories of cortical regions and connecting fibre tracts suggest that the sensorimotor network comes online during early childhood. As a result, musical training during these years may fine-tune this network via experience-driven plasticity processes more effectively than musical training later in development.

1.3 Musical Training and the brain

There is ample evidence revealing differences in brain structure in the auditory-motor network between musicians and non-musicians (for review see Wan and Schlaug, 2010 or Jäncke, 2009). The accumulating evidence for experience-based plasticity suggests that these differences are likely a result of the interaction between the effects of musical training and pre-determined factors such as genetics, both contributing to development of brain structure (Chiang et al., 2009; Thompson & Gogtay, 2010; Thompson et al., 2001). Some studies have revealed correlations between measures of brain structure and the amount of musical experience (either training or practice), supporting the idea that reported differences between musicians and non-musicians are partly attributable to experience-dependent plasticity (Foster & Zatorre, 2010; Gaser & Schlaug, 2003; Strait, Parbery-Clark, Hittner, & Kraus, 2012).

Of particular relevance to the sensitive period hypothesis for musical training are the studies that have reported differences between early- and late-trained musicians or neuroanatomical correlates of the age of start of musical training (Amunts, et al., 1997; Bengtsson, et al., 2005; Foster & Zatorre, 2010; Imfeld, Oechslin, Meyer, Loenneker, & Jäncke, 2009; Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995). Schlaug and colleagues observed a larger anterior surface of the corpus callosum, the bundle of white matter fibre tracts connecting the two hemispheres, among musicians compared to non-musicians, and these differences were due to those who began training prior to age seven (1995). Hours of musical practice during childhood and adolescence were reported to predict white matter integrity in the internal capsule, the corpus callosum and the arcuate fasciculus; however, the greatest number of white matter regions correlated with practice hours prior to the age of eleven (Bengtsson, et al., 2005). More recently, Imfeld and colleagues reported differences in white matter measures in the corticospinal tract between those musicians who began prior to age seven and those who began thereafter (2009). These studies have examined white matter fibre tracts of the brain; however, correlates of age of onset of musical training have also been reported in grey matter areas relevant for musical performance. Amunts and colleagues reported that the intrasulcal length of the precentral gyrus in both hemispheres correlated with age of onset of musical training among their musicians (1997). Foster and Zatorre reported a relationship between age of onset of musical training and cortical thickness in the right auditory cortex as well as grey matter concentration in the right intraparietal sulcus (2010). The most methodologically relevant for the second study in the current dissertation (Chapter 3; Bailey, Zatorre, & Penhune, *in submission*), was a longitudinal study examining changes in both grey and white matter regions in six year-old children after 15 months of music lessons and reported increases within the auditory-motor network and the corpus callosum above and beyond the maturational changes observed in the control group (Hyde, et al., 2009).

Overall, this cluster of studies strongly suggests that musical training influences brain structure via experience-dependent plasticity mechanisms and these observed changes may be a function of when musical training began. However, these researchers were not primarily addressing the question of a sensitive period for musical training and therefore, the differences between early- and late-trained musicians have been confounded by differences in years of experience between these groups. It is very likely that musicians who begin training earlier will have accrued more years of training than their late-trained counterparts. Therefore, the reported differences could be the result of experience-dependent plasticity in the adult brain. A series of studies from our laboratory were designed to directly address this issue.

1.4 The sensitive period hypothesis for musical training

In the series of studies described in the current thesis, we wanted to isolate the effects of age of onset of musical training on behavior and the brain. To do this, we tested groups of early- and late-trained adult musicians who were matched in terms of years of playing experience, years of formal training and hours of current practice (Watanabe, Savion-Lemieux, & Penhune, 2007; Bailey & Penhune, 2010). By using this matching paradigm it is possible to control for the potential confound identified in previous studies showing differences between early- and late-trained musicians and directly addresses the sensitive period hypothesis for musical training. In the first experiment from our laboratory, Watanabe and colleagues observed differences between early- and late-trained musicians using a visual-motor synchronization task and found that the early-trained group outperformed the late-trained group, even after several days of training (2007). In a study conducted for my MA thesis, I used the same matching paradigm in a separate sample of early- and late-trained musicians tested on an auditory-rhythm synchronization task and found a similar advantage for ET musicians (Bailey & Penhune, 2010; See Appendix A). There was no evidence to suggest that this performance advantage was associated with enhanced cognitive abilities in the early-trained musicians, as there were no differences on Vocabulary, Digit Span, Letter-Number Sequencing, or Matrix Reasoning scores (Wechsler, 1997; Wechsler, 1999).

The three studies in this dissertation were designed to further investigate the sensitive period hypothesis for musical training. All studies used the same auditory-motor synchronization task developed in Bailey and Penhune (2010; Figure 1.1). In this task participants first listen to and then reproduce a series rhythms that vary in metrical structure (Essens, 1995; Essens & Povel, 1985). Performance on the task is assessed by percent correct, asynchrony (ms) and inter-tap interval deviation. Importantly, a variant of this task has previously been used in functional magnetic resonance imaging (fMRI) studies that identified the underlying functional neural correlates within the auditory-motor network (Chen, Penhune, & Zatorre, 2005; 2008; 2008; 2009).

The first study in the current thesis (Chapter 2) aimed to replicate and extend the behavioural findings from my MA thesis by using the matching paradigm with the addition of a non-musician control group (Bailey & Penhune, 2010). The second study (Chapter 3) used multiple structural MRI analysis techniques to examine differences in grey matter in the same matched samples of early- and late-trained musicians, as well as the control group of non-musicians. In parallel, a second study not reported in this thesis examined white matter differences between early- and late-trained musicians in a subsample of the same groups (Steele, Bailey, Zatorre, & Penhune, 2013; Appendix B). The third study in this thesis (Chapter 4) used a different approach to the sensitive period hypothesis for musical training by investigating the relationship between age of onset, years of formal training, working memory scores and task performance in a single large group of musicians. The purpose of this approach was to investigate whether the predictive value of age of onset of musical training, years of formal training and working memory scores changed across development.

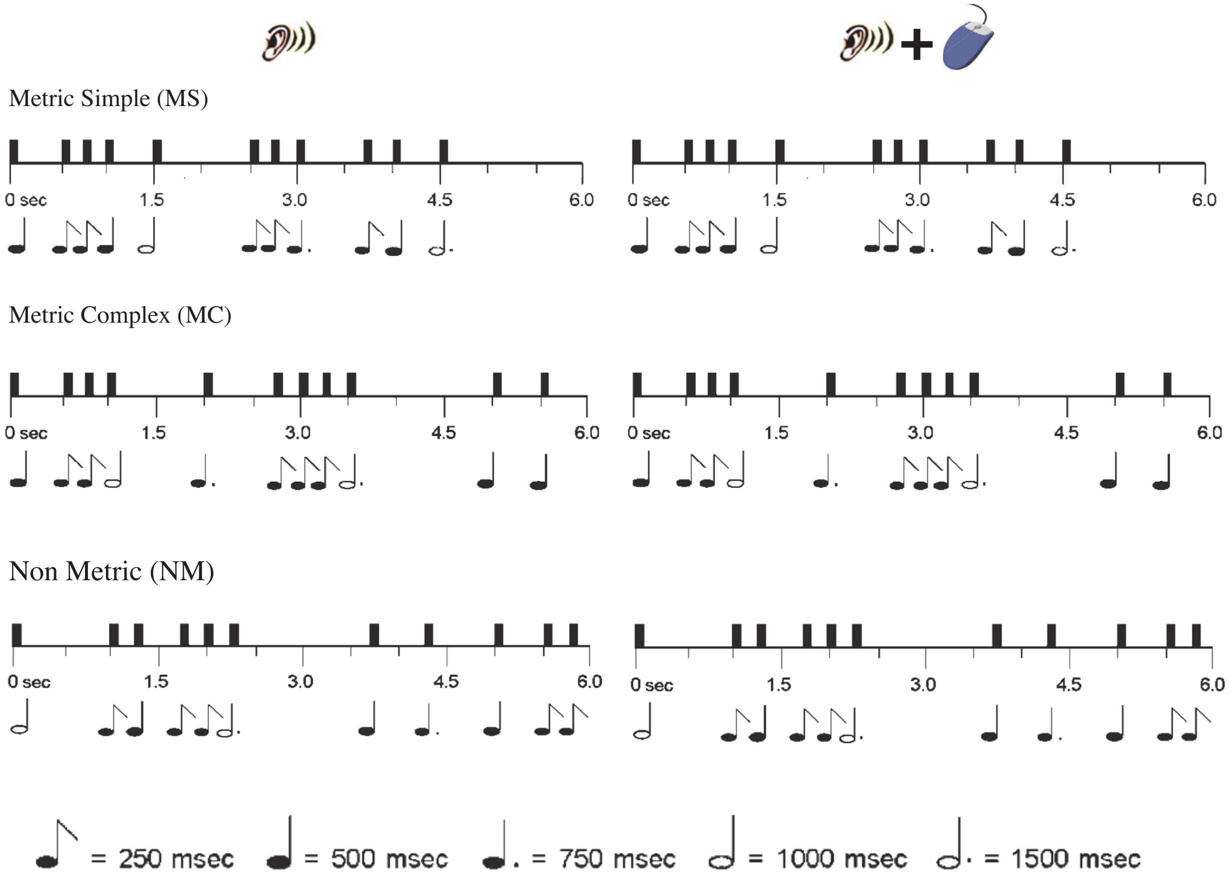


Figure 1.1. Illustration of the auditory-motor synchronization task. Participants were exposed to six rhythms presented in counterbalanced order for approximately two 12-minute blocks. Two different rhythms of each level of rhythmic complexity were used (i.e., 2 MS rhythms, 2 MC rhythms, and 2 NM rhythms). Each trial consisted of a listening component followed by a listening and tapping component.

Chapter 2: A sensitive period for musical training: Contributions of age of onset and cognitive abilities

Bailey, J.A., and Penhune, V.B. (2012). A sensitive period for musical training: Contributions of age of onset and cognitive abilities. *Annals of the New York Academy of Sciences, 1252* (1), 163-70.

2.1 Abstract

The experiences we engage in during childhood can stay with us well into our adult years. The idea of a sensitive period – a window during maturation when our brains are most influenced by behaviour – has been proposed. Work from our laboratory has shown that early-trained musicians (ET) performed better on visual-motor and auditory-motor synchronization tasks than late-trained musicians (LT), even when matched for total musical experience. Although the groups of musicians showed no cognitive differences, working memory scores correlated with task performance. In the current study, we have replicated these findings in a larger sample of musicians and included a group of highly educated non-musicians (NM). Participants performed six woodblock rhythms of varying levels of metrical complexity and completed cognitive subtests measuring verbal abilities, working memory, and pattern recognition. Working memory scores correlated with task performance across all three groups. Interestingly, verbal abilities were stronger among the NM, while non-verbal abilities were stronger among musicians. These findings are discussed in context of the sensitive period hypothesis as well as the debate surrounding cognitive differences between musicians and non-musicians.

2.2 Introduction

The plastic changes that occur in each of our brains as we mature are the result of an interaction between maturational changes and experience. A fascinating example of this interaction is a "sensitive period" – a window of time during development when brain systems are more susceptible to the influence of experience or stimulation. In our lab, we have used trained musicians to study possible sensitive period effects. In these studies, musicians who began training before age seven demonstrated enhanced rhythm synchronization performance compared to musicians who began their training later in development, when matched for total musical experience (Bailey & Penhune, 2010; Watanabe, Savion-Lemieux, & Penhune, 2007). In addition, although these two groups of highly trained musicians did not differ on global cognitive variables, individual working memory scores predicted synchronization performance. In the current study, the sample size has been increased and a non-musician group has been added to further elucidate the association between working memory, musical training and task performance. Including a group of highly educated non-musicians also provides insight into possible cognitive differences between musicians and non-musicians.

As our knowledge about brain plasticity evolves, evidence for sensitive periods related to the acquisition of a variety of skills increases. The idea of a sensitive period may have gained most widespread attention through the results of a number of studies showing that second-language proficiency is greater in individuals who were exposed to the second language before age 11-13 (Johnson & Newport, 1989; Weber-Fox & Neville, 2001). Recent evidence using neuroimaging techniques also supports the idea that the sensory systems have developmental windows of time during which they are most sensitive to stimulation. Differences in occipital recruitment for non-visual functions between early blind individuals and those who acquired blindness later in development suggest that the visual system also has a developmental window during which it is most responsive to stimulation (Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008). Cochlear implantation studies suggest that the auditory system is more responsive the earlier these devices are implanted (Kral, Hartmann, Tillein, Heid, & Klinke, 2001; Sharma, Gilley, Dorman, & Baldwin, 2007). Studies have reported differences in brain structure between early- and late-trained musicians and have associated these differences with the extent of musical experience (Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995; Bengtsson et al., 2005; Imfeld, Oechslin, Meyer, Loenneker, & Jäncke, 2009). However, an important addition to the investigation of a sensitive period is the matching paradigm developed in our laboratory (Watanabe, Savion-Lemieux, & Penhune, 2007). When early- and late-trained musicians are matched for musical experience (years of formal instruction, years of playing, current hours of practice, etc.), the general effects associated with musical experience are controlled for and the age at which they began their musical training is isolated as the variable of interest.

Evidence from previous studies in our lab supports the idea of a sensitive period among musicians, even when cognitive abilities are considered. Early-trained musicians (those who began before age 7) outperformed late-trained musicians (those who began after age 7) on an auditory-motor synchronization task as well as a visual-motor synchronization task, when matched for total musical experience (Bailey & Penhune, 2010; Watanabe, Savion-Lemieux, & Penhune, 2007). The two groups did not differ on cognitive measures such as Vocabulary, Matrix Reasoning, Digit-Span, and Letter-Number Sequencing (Bailey & Penhune, 2010; Wechsler, 1997; Wechsler, 1999). However, working memory scores predicted performance on the rhythm synchronization task across both groups of musicians. A regression analysis revealed that after controlling for working memory, group membership still accounted for variance in task performance. These results suggest that a musician's working memory and age of start of musical training were both contributors to their ability to perform the rhythm synchronization task.

The current study aims to replicate our previous findings in a larger sample of musicians, and shed light on the debate surrounding cognitive differences between musicians and non-musicians. Although cognitive differences between musicians and non-musicians have been reported, there is controversy in the literature over how or why these differences emerge (Schellenberg & Peretz, 2008; Schellenberg, 2011). Studies have used child samples to examine the interaction between music lessons and cognitive and brain development (Hyde et al., 2009; Schellenberg, 2006). Using adults complements studies with children by allowing us to test whether differences associated with musical training persist into adulthood, especially because we are comparing musicians to a group of highly educated non-musicians. In addition, using a group of adult musicians with extensive but variable lengths of musical training allows us to investigate the nature of the association between music lessons and cognitive abilities.

2.3 Method

2.3.1 Participants

Fifty neurologically healthy individuals between the ages of 18 and 36 (M = 25.5 years old, SD = 4.6) participated in this study. Participants were screened for significant head injuries, history of neurological disease or medication that could affect task performance. Of the 50 participants, 30 were highly trained and currently practicing musicians and 20 were non-musicians (< 3 years of musical experience). The musical training and experience of each participant was determined through a Musical Experience Questionnaire (MEQ) that was developed within our laboratory (Bailey & Penhune, 2010). The MEQ quantifies the amount of instrumental, vocal and dance training an individual has received, at what age this training occurred and the amount of time currently dedicated to practicing on a weekly basis. All musicians had extensive musical experience (M = 16.4 yrs; SD = 4.4). Musicians were classified as Early-Trained (ET; $n = 15$) or Late-Trained (LT; $n = 15$) musicians, based on their MEQ data. Those who began their musical experience prior to or at the age of 7 were placed in the ET group and those who began after the age of 7 were classified as LT. The age of seven was chosen based on previous studies (Bailey & Penhune, 2010; Sharma, Gilley, Dorman, & Baldwin, 2007; Watanabe, Savion-Lemieux, & Penhune, 2007). The two groups were matched on years of musical experience, years of formal training and hours of current practice. All participants gave informed consent and the Concordia University Research Ethics Committee had approved the protocol.

2.3.2 Stimuli

The rhythm task used in this study consisted of 6 woodblock rhythms of varying difficulty based on their metrical structure (Essens, 1995; Essens & Povel, 1995). Each test rhythm consisted of 11 woodblock notes and had a total duration of 6 seconds. These rhythms differed in their temporal structure, such that the inter-onset intervals between musical notes varied, but not the duration of the notes themselves. More specifically, each rhythm was made up of five eighth notes (each 250 ms), three quarter notes (each 500 ms), one dotted quarter note (750 ms), one half note (1000 ms) and one dotted half note (1500 ms). Manipulation of the temporal structure of the notes resulted in progressively more complex and less metrically structured rhythms. For a more detailed description of this task and the metrical complexity manipulation, please see Bailey and Penhune (2010).

Participants completed the Digit-Span (DS) and Letter-Number Sequencing (LN) subtests from the Wechsler Adult Intelligence Scale – III (WAIS) and the Vocabulary (VC) and Matrix Reasoning (MR) subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1997; Wechsler, 1999). The DS requires individuals to recall strings of numbers and the LN requires individuals to recall and mentally manipulate strings of letters and numbers. Both of these subtests tap into working memory abilities; however, LN imposes a heavier load on working memory, while DS consists of a rote auditory memory recall section in addition to a mental manipulation section. The VC assesses an individual's ability to orally define words and the MR assesses non-verbal reasoning and visual pattern recognition abilities. Both VC and MR are strongly correlated with global IQ, although they assess different types of intelligence.

2.3.3 Procedure

During the rhythm task, participants alternated between listening and tapping along while each rhythm played twice (Fig. 2.1). Participants were instructed to tap as accurately as possible with the rhythm as it played during the tapping repetition. Two very basic practice rhythms were administered to familiarize participants with the task. Each rhythm presented in a counterbalanced fashion 6 times over approximately 12 minutes in each block and participants performed two blocks. Once participants had completed the first block of the task, they were asked to perform the DS. Participants then performed the second block of the rhythm synchronization task, followed by VC, LN and finally, MR.

2.3.4 Measures

Musical information was quantified for each participant in terms of years of experience, years of formal training and hours of current weekly practice using the MEQ (Bailey & Penhune, 2010). Individual cognitive abilities were measured using the four chosen cognitive subtests (DS, LN, VC, and MR). Results were scored according to standard procedure. Performance on the rhythm synchronization task was measured using three dependent variables: percent correct (PC), asynchrony (ASYN) and inter-tap-interval (ITI) deviation. A tap was considered correct if it was made within half of the onset-to-onset interval before or after a woodblock note (Fig. 2.2). The ASYN measure was defined as the absolute value of temporal difference between the onset of each woodblock note and the associated mouse key press. The ITI deviation measure indicated the extent of deviation of the participant's tap interval from the actual interval between each pair of woodblock notes. It was calculated by dividing the interval between each pair of the participant's taps by the interval between each corresponding pair of woodblock notes in the rhythms and subtracting this ratio from a value of one. This measure is indicative of how well participants reproduced the temporal structure of the rhythms.

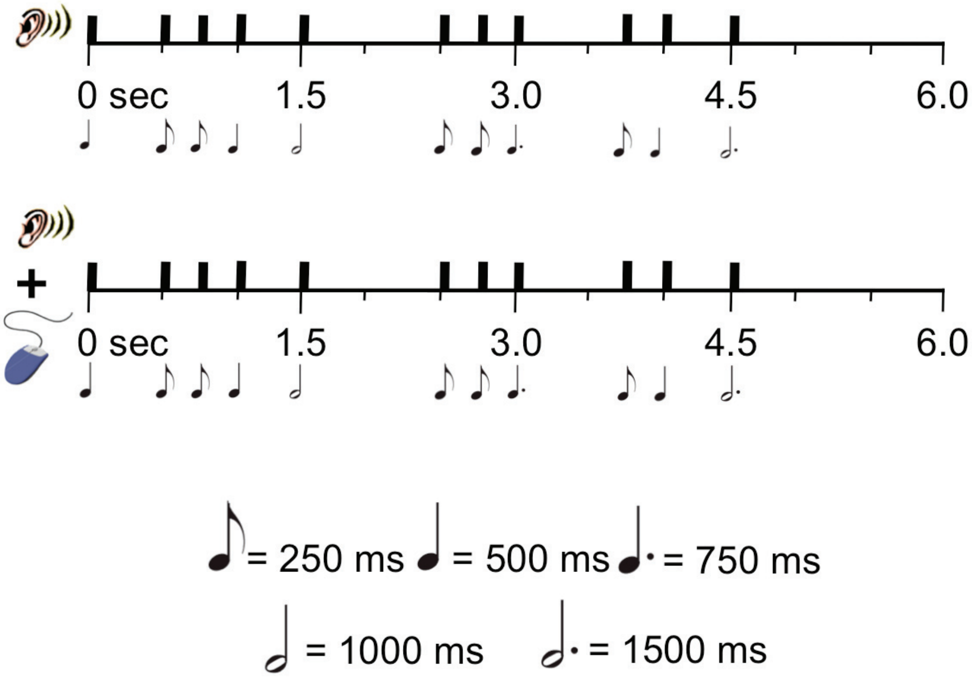


Figure 2.1. Illustration of the auditory-motor synchronization task. Participants were exposed to six rhythms presented in random order for approximately two 12-minute blocks. Two different rhythms of each rhythmic complexity were used. Each trial consisted of a listening component followed by a listening and tapping component.

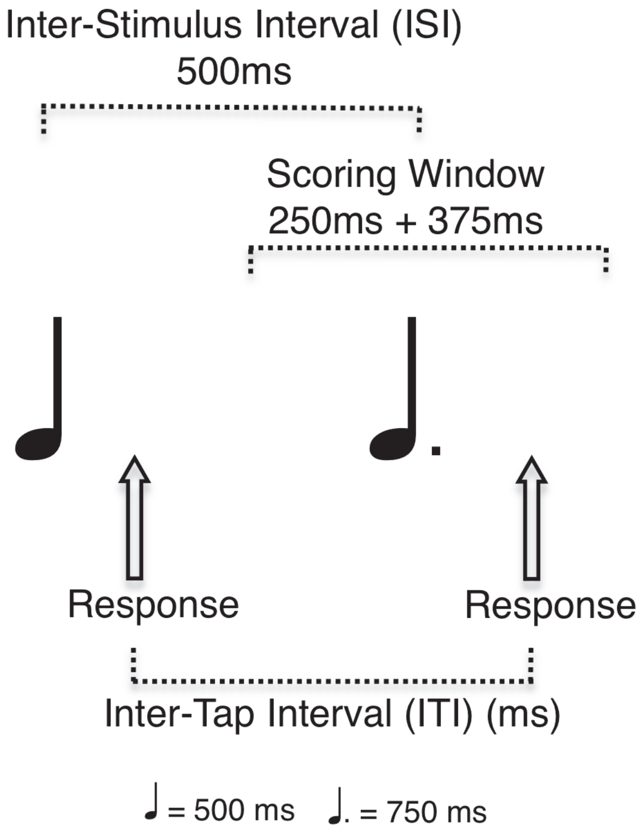


Figure 2.2. Illustration of the scoring method used to evaluate task performance. A response was scored correctly if the mouse tap was made within half of the onset-to-onset interval before and after a woodblock note. Asynchrony was measured as the difference between each woodblock note and the participant's response. ITI deviation was calculated as a ratio of the ITI and the ISI subtracted from 1.

2.3.5 Data Analysis

To compare rhythm synchronization across the three groups, a repeated-measures analysis of variance (ANOVA) for each of the dependent variables was conducted, with group as the between-subjects factor and rhythm type as a within-subjects factor. Pair-wise comparisons for between group differences were analyzed using least significant differences (LSD) correction for multiple comparisons. The result of our matching procedure was evaluated using t-test analyses for years of musical experience, years of formal training, hours of current practice among the musicians. Group differences on the cognitive subtests were assessed using a one-way ANOVA for each cognitive variable with group as the between-subjects factor. Pair-wise comparisons were conducted using an LSD correction for multiple comparisons. The relationships among cognitive measures, musical experience variables and task performance were examined using one-tailed Pearson correlation analyses. Raw scores on the cognitive subtests were used to correlate with performance measures and scaled scores were used when comparing the three groups on the cognitive measures. However, results were consistent whether raw or scaled scores were used in the analyses.

Based on a previously observed relationship between individual working memory abilities and task performance among musicians, a hierarchical regression analysis was conducted with all three groups in order to assess whether the observed group difference persists after individual working memory scores are considered (Bailey & Penhune, 2010). A model was created with total inter-tap interval (ITI) deviation as the dependent measure and both group and working memory as predictors. A composite score for each participant's working memory abilities was created by summing their LN and DS scores and used in the regression analysis.

2.4 Results

2.4.1 Group Comparisons of Musical and Cognitive Measures

Comparison of the ET and LT musicians confirmed that the two groups were well matched in terms of years of musical experience, years of formal training and hours of current practice (Table 2.1). The One-way ANOVA revealed no significant differences in DS or LN scores between groups, although statistical trends towards a main effect of group on MR and VC were observed (Fig. 2.3). Pair-wise comparisons revealed that the non-musician (NM) VC scores were higher than the ET ($p = 0.026$) and the MR scores of the LT were higher than those of the NM ($p = 0.017$). Scaled scores were used for these analyses.

Table 2.1. *Group demographics of musical experience variables*

Group	Age (Yrs)	Age of Onset (Yrs)	Formal Training (Yrs)	Musical Experience (Yrs)	Current Practice (Hrs)
Early-Trained (ET)	23.47 (± 3.85)	5.87 (± 1.19)	11.73 (± 3.97)	16.87 (± 4.10)	15.23 (± 9.97)
Late-Trained (LT)	26.60 (± 5.22)	10.47 (± 2.03)	10.03 (± 4.39)	15.90 (± 4.74)	14.43 (± 7.80)
t-values	-1.87	-7.57**	1.11	0.60	0.25

Note: Standard deviation values are in brackets
** p-value < 0.001

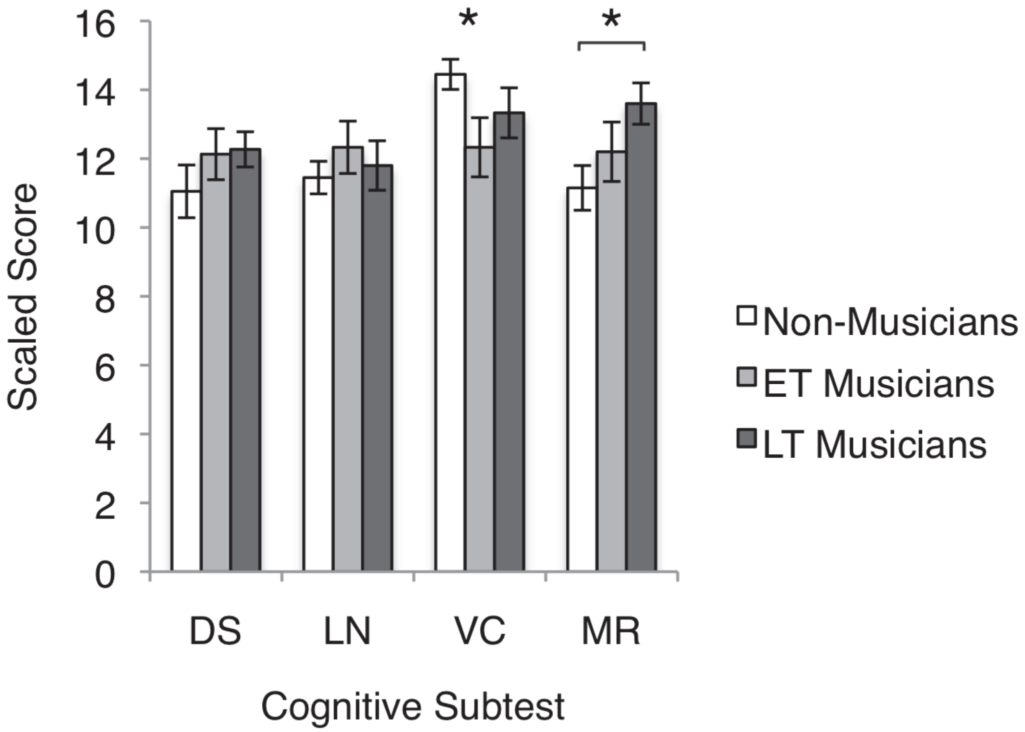


Figure 2.3. Group mean cognitive scaled scores. DS = Digit-Span, LN = Letter-Number Sequencing, VC = Vocabulary, and MR = Matrix Reasoning. No group differences were observed on the two measures of working memory (DS & LN); however statistical trends towards group differences were observed on VC ($p = 0.078$) and MR ($p = 0.055$). Pair-wise comparisons revealed specific group differences (* $p < 0.05$).

2.4.2 Behavioural Measures

The ANOVA comparing accuracy (PC) of the rhythm reproduction task across the three groups showed a significant main effect of group ($F\ (2, 47) = 3.99, p < 0.05$; Fig. 2.4a). Pair-wise comparisons using a LSD correction revealed differences between the ET and NM ($p < 0.01$). These results confirm that all three groups were performing the task correctly overall and the mean performance values were in the expected order (i.e., ET > LT > NM).

The ANOVA comparing performance on the synchronization measure (ASYN) across the three groups revealed a similar pattern of results, such that there was a main effect of group (F (2, 47) = 16.76, $p < 0.001$; Fig. 2.4b). Pair-wise comparisons using a LSD correction revealed lower ASYN scores for the ET and LT when compared to the NM ($p < 0.001$ for both comparisons). In addition, the ET was better able to synchronize their responses than the LT musician group as revealed by lower ASYN scores (p = 0.05). These results suggest that the group differences were heightened on this more sensitive performance measure compared to our more global measure of accuracy (PC).

Consistent with the other performance measures, the ANOVA comparing reproduction of the temporal structure of the rhythms using our Inter-tap Interval measure of deviation (ITI) across the three groups showed a significant main effect of group (F (2, 47) = 20.30, $p < 0.001$; Fig. 2.4c). Pair-wise comparisons using a LSD correction revealed a similar pattern of results as on the ASYN measure such that, the ET had lower deviation scores than the LT ($p < 0.05$) and both musician groups had lower deviation scores than the NM ($p < 0.001$ for both comparisons). These results further illustrate that as the measure of performance increased in sensitivity to temporal aspects of the rhythms, the observed group differences were heightened.

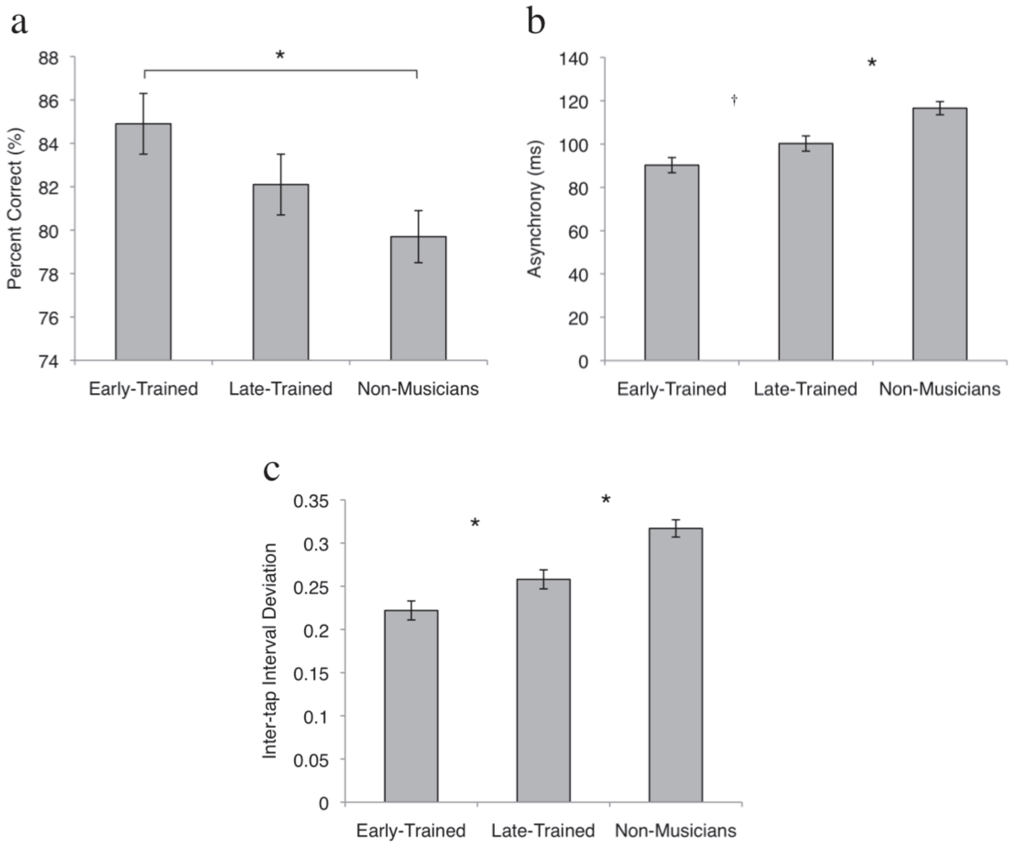


Figure 2.4. Task performance results for all three groups. (a) Percent Correct (PC) (b) Asynchrony (ASYN) (c) Inter-tap Interval Deviation (ITI). Repeated measures ANOVA for each performance measure revealed a significant main effect of group and pair-wise comparisons revealed specific group differences (* $p < 0.05$, † = 0.05). Standard error bars have been used.

2.4.3 *Correlations*

In order to examine the relationship between task performance and cognitive variables across the three groups, raw scores for PC, ASYN and ITI were correlated with raw scores for VC, MR, DS and LN (Table 2.2). Both working memory measures (DS and LN) correlated significantly with the three performance measures (PC, ASYN, ITI) in the expected directions, confirming that the rhythm reproduction task implicates the use of working memory. Surprisingly, VC negatively correlated with the synchronization measure such that higher VC scores were associated with poorer performance of the rhythm task. In addition, MR positively correlated with both synchronization and ITI measures of task performance. These results were likely driven by the group differences observed on these cognitive scores and this will be addressed in the discussion section.

Results from the correlation analyses between the behavioural measures and musical variables in the musicians (Table 2.3) revealed a significant association between years of formal training and ITI deviation ($r = -0.367, p < 0.05$). In addition, age of onset showed a significant relationship with ASYN and ITI, as well as a relationship trending towards significance with PC. In order to examine the association between years of formal training, cognitive scores and task performance, correlations were performed between years of formal training and each cognitive measure. This set of analyses revealed an association trending towards significance between years of formal training and DS ($r = 0.342, p = 0.06$); however, no significant associations with LN, VC or MR.

Table 2.2. *Correlation results between cognitive scores and task performance measures*

Performance Measure	Digit-Span (DS)	Letter-Number Sequencing (LN)	Matrix Reasoning (MR)	Vocabulary (VC)
Percent Correct (PC)	$0.275^{\dagger}$	0.360*	0.147	-0.072
Asynchrony (ASYN)	$-0.258^{\dagger}$	-0.307*	$-0.262^{\dagger}$	$0.269^{\dagger}$
Inter-tap Interval Deviation (ITI)	-0.378**	-0.340*	-0.339*	0.187

Note: Raw scores were used for the cognitive measures
† *p*-values < 0.08 but greater than 0.05
* *p*-values < 0.05
** *p*-values < 0.01

Table 2.3. *Correlation results between musical experience and task performance measures*

Performance Measure	Age of Onset (Yrs)	Formal Training (Yrs)	Musical Experience (Yrs)	Current Practice (Hrs)
Percent Correct (PC)	$-0.352^{\dagger}$	0.010	0.141	-0.052
Asynchrony (ASYN)	0.459*	-0.214	-0.139	-0.079
Inter-tap Interval Deviation (ITI)	0.509**	-0.367*	-0.095	0.046

Note: Raw scores were used for the cognitive measures
† *p*-values < 0.08 but greater than 0.05
* *p*-values < 0.05
** *p*-values < 0.01

2.4.4 Regression Analysis

In order to determine if the amount of variance in ITI deviation during task performance accounted for by group was above and beyond what was explained by individual working memory abilities, a hierarchical regression analysis was conducted using the three groups (Table 2.4). These results confirmed that, while individual working memory abilities were predictive of task performance, group membership accounted for additional portions of the variance in ITI deviation scores.

Table 2.4. *Regression analysis results examining the predictive value of group membership above and beyond working memory to task performance*

	R^2	β	R^2 Change	F
Step 1	0.165		0.165	9.45
Working Memory		-0.406**		
Step 2	0.538			27.336
Working Memory		-0.293**		
Group		0.621**	0.373	

Note: A working memory composite score was used for this analysis comprising of individual raw DS and LN scores
**p-values < 0.01

2.5 Discussion

These findings replicate our previous findings but in a larger sample, and provide further evidence for a sensitive period for musical training that may have a specific impact on sensorimotor synchronization abilities. In this study, the ET musicians were better able to reproduce the rhythms than the LT musicians, even after controlling for years of formal training, playing experience and current hours of practice. In addition, the two musician groups did not differ on the four cognitive measures. In other words, this observed group difference on task performance could not be attributed to differences in musical experience or cognitive ability, but to the developmental window during which musical training began. As expected, non-musician rhythm synchronization abilities were inferior to both musician groups. Although there were no differences in working memory performance across the three groups, individual working memory scores correlated with task performance, suggesting similar reliance on working memory resources for all groups. In further support of the sensitive period hypothesis, the regression results suggest that even after controlling for individual working memory scores, group membership still predicted a significant amount of variance in task performance. This reinforces the idea that musical training, especially early musical training, improves task performance above and beyond the contribution of working memory abilities.

In addition to the differences between ET and LT musicians on the rhythm task, we observed differences in performance on global cognitive variables between musicians and non-musicians. Specifically, the non-musicians obtained higher VC scores, while the musician groups had higher MR scores. These findings are interesting and can shed light on the types of cognitive effects associated with musical training. One hypothesis is that music lessons benefit the underlying cognitive abilities that are measured by MR, and, in contrast, non-musicians are exercising their verbal intelligence via other avenues. If this were the case, one would expect the length of musical training (i.e., years of formal training) to be correlated with MR scores among the musician group, but it is not. Alternatively, one could hypothesize that individuals with strong visual-spatial organization skills are inclined to take up music lessons, and those with strong verbal abilities are likely to take up other non-musical activities. If this were true, then no relationship between length of musical training and MR would be present, yet group differences would persist between musicians and non-musicians. The current data supports this assumption. The more general question of what is driving cognitive differences between musicians and non-musicians is an area of controversy. Recently, Schellenberg and Peretz proposed that the observed association between music lessons and cognition might be mediated by executive function, although a more recent publication by Schellenberg failed to observe convincing evidence that this was the case (Schellenberg & Peretz, 2008; Schellenberg, 2011). In our sample, a weak association between working memory, a component of executive function, and years of formal training was observed among the musicians; however, their scores were not higher than the non-musicians, suggesting that if years of formal training impacts working memory, it does not do so above and beyond other non-musical activities that the non-musicians engaged in. Other factors such as socio-economic status or the family environment may contribute to the differences between the two groups. Both our musicians and non-musicians were either in the process of completing an undergraduate degree or had obtained one, and some were pursuing higher-level education. Thus, in these highly educated samples, any enhanced cognitive abilities observed in musicians over non-musicians are likely to be a combination of innate predisposition and effects associated with exercising the abilities implicated in music lessons during development. Similarly, non-musicians are likely predisposed to engage in other non-musical activities and exercise other abilities during their development.

In summary, this study adds to the building literature in support of a sensitive period for sensorimotor integration abilities among musicians and considers non-musicians as a comparison sample. Any differences in brain structure between early and late-trained musicians associated with these enhanced synchronization abilities have yet to be explored. The results from this study also add to the evidence that musicians and non-musicians possess different cognitive strengths, even in a sample of highly educated adults. However, the exact contributions of innate predisposition and the influence of training remain unknown.

Chapter 3: Early musical training: Effects on auditory-motor rhythm performance and grey matter structure in the ventral pre-motor cortex

Bailey, J.A., Zatorre, R. J., and Penhune, V.B. (*in submission*). Early musical training: Effects on auditory-motor rhythm performance and grey matter structure in the ventral pre-motor cortex. *NeuroImage*.

3.1 Abstract

The idea of a sensitive period, a time during maturation when experience or stimulation has a greater influence on brain development, has been proposed for musical training (Steele, Bailey, Zatorre, & Penhune, 2013). Early-trained musicians (ET) have demonstrated enhanced sensorimotor synchronization abilities compared to late-trained musicians (LT), even when matched for years of musical experience (Watanabe, Savion-Lemieux, & Penhune, 2007; Bailey & Penhune, 2010; 2012). However, the underlying differences in grey matter structure have yet to be explored. The current study investigated performance differences on an auditory-motor synchronization task and differences in grey matter structure between Early-Trained (ET) and Late-Trained (LT) musicians, matched for years of musical experience. Non-Musicians (NM) were included as a control group. Differences in grey matter were analyzed using optimized voxel-based morphometry (VBM), traditional VBM and deformation-based morphometry (DBM). The groups were also compared in terms of surface-based features (cortical thickness, surface area and mean curvature). Group differences between musician groups were identified using DBM and located in the right ventral pre-motor cortex. Surface-based analyses in this region revealed greater cortical surface area among the ET musicians. Extracted values correlated with performance on the Rhythm Synchronization Task

(RST) and age of onset of musical training. Across all participants, extracted traditional VBM values correlated with cortical thickness, while DBM values correlated with cortical surface area, curvature, and grey matter volume. These results highlight the importance of characterizing differences in grey matter observed using VBM-style techniques with additional surface-based measures. In addition, these results add to mounting evidence that early musical training influences brain structure differently than musical training received later in development, supporting the idea of a sensitive period during development for musical training.

3.2 Introduction

Evidence that early experience differentially influences skill acquisition and brain structure has been observed in several domains. For example, second language proficiency is enhanced when exposure begins earlier in development (Weber-Fox & Neville, 2001) and speech perception is better for those who receive cochlear implants at an earlier age (Geers, 2006; Harrison, Gordon, & Mount, 2005). Previous work in our laboratory has investigated the effect of early training among musicians, showing that those who begin before age seven perform more accurately on an auditory rhythm synchronization task that has been shown to engage the auditory and pre-motor cortices (Bailey & Penhune, 2010; 2012; Chen, Zatorre, & Penhune, 2008; Watanabe, Savion-Lemieux, & Penhune, 2007). In addition, we have found that early trained musicians have enhanced white-matter integrity in a region of the corpus callosum which connects the motor cortices of the two hemispheres (Steele, Bailey, Zatorre, & Penhune, 2013). Taken together, these results indicate that early musical training has long-lasting effects on behavior and the brain (Penhune, 2011). Two neuroanatomical processes may interact to set the stage for such a sensitive period: brain maturation and experience-driven plasticity. Given that different brain areas have distinct maturational timelines (Gogtay, et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), sensitive periods may emerge when maturational plasticity in a brain region associated with a specific skill is paired with intensive experience or practice of that skill. Musicians are a good population in which to study sensitive periods because training begins at different ages, can be quantified and is known to influence brain structure (for recent review see Jäncke, 2009 or Wan and Schlaug, 2010). Furthermore, several components of the anatomical network implicated in musical training undergo their greatest structural change in early childhood (Gogtay, et al., 2004; Lebel, et al., 2008). Because our previous work has shown that early musical training is associated with enhanced white matter connectivity, the purpose of the current study is to examine effects of early training on grey matter structure within the auditory-motor network. To do this we compared grey matter structure and performance on an auditory rhythm synchronization task in adult musicians who began training before and after age seven and who were matched for years of experience. Importantly, we used a series of complementary voxel-wise and surface-based structural MRI data analysis techniques to assess the effect of early training on grey matter structure. We hypothesized that early musical training would be associated with better performance on the rhythm synchronization task and differences in grey matter structure in auditory and motor regions.

Previous work from our laboratory has shown that adult musicians who began training before age seven have enhanced sensorimotor synchronization performance in both the auditory and visual domains, even after controlling for potential differences in musical experience using a matching paradigm (Bailey & Penhune, 2010; Watanabe, Savion-Lemieux, & Penhune, 2007). We also showed that these differences were not related to global cognitive abilities and were present even when controlling for the effect of working memory. These findings suggest that early musical training may have specific impacts on auditory-motor integration networks in the brain. This is consistent with the results of previous fMRI studies showing that performance of the auditory rhythm synchronization task recruits auditory association areas and the pre-motor cortex (Chen, Penhune, & Zatorre, 2008). It is also consistent with recent diffusion tensor imaging (DTI) findings in a subgroup of the sample presented here showing differences in the corpus callosum in a region connecting the motor regions of the two hemispheres (Steele, Bailey, Zatorre, & Penhune, 2013). Changes in white matter often coincide with changes in grey matter, although much remains unknown about the exact relationship (Scholz, Klein, Behrens, & Johansen-Berg, 2009). Based on these results, the current study will investigate differences in measures of grey matter between ET and LT musicians matched for total musical experience within the auditory-motor network associated with performance on the auditory rhythm synchronization task.

Grey and white matter maturational trajectories are important to consider when investigating the sensitive period hypothesis for musical training. Grey matter development appears to follow an inverted u-shaped maturation pattern with growth in volume occurring first, followed by a gradual loss of volume (Giedd, et al., 1999; Gogtay, et al., 2004; Gogtay & Thompson, 2010; Sowell, Thompson, Tessner & Toga, 2001). When examining grey matter maturation rates more locally, it seems that higher-order association areas reach maturity only after the lower-order sensorimotor areas. The primary sensory and motor cortices and the frontal and occipital poles mature first, while the rest of the cortex matures more or less in a parietal to frontal fashion, with the exception of the superior temporal cortex, which matures last (Gogtay, et al. 2004). White matter fibre tracts continue to "fine-tune" themselves well into adulthood. Of particular importance from these findings is that most fibre tract maturational trajectories are non-linear, with the greatest amount of change occurring in the early childhood years (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Paus, 2010). Overall, it seems the maturational trajectories of cortical regions and connecting fibre tracts suggest that the sensorimotor network comes online during early childhood. As a result, musical training during these years may fine-tune this network via experience-driven plasticity processes more effectively than musical training later in development.

Experience-driven plasticity effects among musicians are equally important to consider when investigating the sensitive period hypothesis for musical training. Studies comparing musicians and non-musicians have shown differences in measures of brain structure and functional activation within sensorimotor and prefrontal areas, suggesting training-induced plasticity effects (e.g., Bermudez, Lerch, Evans, & Zatorre, 2009; Chen, Penhune, & Zatorre, 2008; Gaab & Schlaug, 2003; Sluming et al., 2002). Furthermore, several studies have reported correlations between the amount of musical training and measures of brain structure within the sensorimotor network (e.g., Abdul-Kareem, Stancak, Parkes, & Sluming, 2010; Foster & Zatorre, 2010; Gaser & Schlaug, 2003; Halwani, Loui, Rüber, & Schlaug, 2011). While other factors such as genetic predisposition may contribute to these findings, a recent study used a pre-post training design in children looking at the effects of music lessons and found increased volume in the corpus callosum, right primary motor cortex, right primary auditory cortex and other prefrontal areas in the music lesson group after two years of lessons, as compared to the control groups (Hyde, et al., 2009). Overall, the emerging evidence suggests that musical training influences brain structure within the sensorimotor network through the mechanisms of experience-driven plasticity.

The interaction between maturational growth and experience-driven plasticity within the sensorimotor network may result in sensitive periods throughout development. Early sensitive periods in the visual system have been identified when stimulation is required for normal functioning and recent evidence suggests that experience-dependent plasticity is reduced in adulthood but not absent (for review see Hooks and Chen, 2007). Similar to the visual system, studies examining the development of the auditory system have revealed sensitive periods for frequency tuning (for review see de Villers-Sidani and Merzenich, 2011). In humans, studies of hearing and speech proficiency in children who received cochlear implants reveal a clear advantage for children who received their implants in early childhood or infancy (Harrison, Gordon, & Mount, 2005; Geers, 2006; Nicholas & Geers, 2007). Suggestive evidence of a sensitive period among musicians initially came from a study reporting a greater difference in corpus callosum surface area between musicians and non-musicians that was driven by those who began their training prior to age seven (Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995). These findings were corroborated by evidence of greater white matter integrity in the corticospinal tract for early trained musicians (Imfeld, Oechslin, Meyer, Loenneker, & Jäncke, 2009) and a relationship between hours of practice before age 11 and white matter integrity in the corpus callosum and corticospinal tract (Bengstson, et al., 2005). The only previous study examining grey matter differences associated with the age of start of musical training found that the size of the primary motor cortex in musicians was related to the age of start of training (Amunts, et al., 1997). However, none of these studies were designed to address the sensitive period question and therefore, did not control for amount of musical training. An adult musician who began training at age four will likely have more years of practice than an adult musician who began at age 11. As a result, these differences may partly be due to differences in the amount of training between groups and not the age at which training began. Furthermore, previous studies have not directly associated differences in brain structure with auditory-motor task performance, which is important in establishing their relevance. Our recent DTI study showing greater white matter integrity in the corpus callosum for early trained musicians was the first neuroimaging study to control for the length of training between early-trained and late-trained musicians. The current study will use the same approach to examine possible differences in grey matter structure and their relationship to auditory-motor synchronization performance.

Neuroimaging studies examining grey matter are moving beyond using single analysis techniques and multimodal approaches are becoming more common. Combining multiple analysis techniques can provide more information about the structural characteristics contributing to observed differences. Several voxel-wise analyses are available to examine grey matter including traditional voxel-based morphometry (VBM), optimized VBM, and deformation-based morphometry (DBM) (see Good, et al., 2001 for a detailed explanation of VBM methodologies). Traditional VBM analysis removes local differences in volume or shape in order to fit subjects to a common template followed by a voxel-wise comparison of grey matter values. Results of traditional VBM analyses are typically interpreted as revealing differences in grey matter “concentration” and may be influenced by regional differences in both volume and shape. DBM analysis measures the degree of deformation required to fit each subject to a common template (i.e., the Jacobian determinants) on a voxel-wise basis. Results of DBM analyses are typically interpreted as revealing differences in shape or volume. Optimized VBM can be perceived as a combination of these two techniques. Optimized VBM removes local differences in volume to fit each subject to a common template similar to traditional VBM analysis, and then modulates the grey matter value in each voxel by the degree of deformation that was required to fit that subject to the template. Results obtained with optimized VBM analyses are due to a combination of grey matter concentration effects and morphological effects. In addition to these voxel-wise analysis techniques, cortical thickness and surfaced-based measures such as cortical surface area, curvature and grey matter volume are available to identify differences in cortical surface features.

These measures of grey matter structure are differentially correlated with each other, suggesting that they may be associated with unique cortical features. Traditional VBM has been associated with cortical thickness (Bermudez, Lerch, Evans, & Zatorre, 2009; Foster & Zatorre, 2010). Differences observed using optimized VBM have been linked to DBM values, not to traditional VBM values (Eckert, et al., 2006). Furthermore, previous findings suggest that optimized VBM values relate to measures of cortical surface area in some regions and cortical thickness in other regions (Voets, et al., 2008).

Therefore, we can also explore the relationship between these different cortical measures to better understand any observed differences between early- and late-trained musicians.

3.3 Method

3.3.1 Participants

Two groups of highly trained and currently practicing musicians participated in this study. These groups were selected based on the age at which they started musical training: those who began at or prior to the age of 7 were classified as Early-Trained (ET; n = 15) and those who began after the age of 7 were classified as Late-Trained (LT; n = 15). The age cut-off of 7 was based on previous findings (Bailey & Penhune, 2010; Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995; Watanabe, Savion-Lemieux, & Penhune, 2007). To ensure that any observed differences in task performance or brain structure were not confounded by differences in experience, the two groups were matched for years of musical experience, years of formal training and hours of current practice. In addition, a control group of Non-Musicians (NM; n = 20) also participated in this study. NM had less than three years of musical training and were not currently practicing. To assess musical experience, all participants completed the Musical Experience Questionnaire (MEQ) that was developed in our laboratory (Bailey & Penhune, 2010). The MEQ quantifies the amount of instrumental, vocal and dance training an individual has received, at what age this training occurred and the amount of time currently dedicated to practice on a weekly basis. All participants were right-handed, completed a Magnetic Resonance 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 Behavioural Tasks

The Rhythm Synchronization Task (RST) requires participants to listen and then tap in synchrony with a series of auditory rhythms varying in metrical complexity. Performance differences on the RST between ET and LT musicians have been previously observed (Bailey & Penhune, 2010; 2012). It is a modified version of a task used to examine functional correlates of auditory rhythm synchronization among musicians and non-musicians (Chen, Penhune, & Zatorre, 2008). Briefly, it consists of six woodblock rhythms of varying difficulties based on their metrical structure (Essens, 1995; Essens & Povel, 1985). Each rhythm comprises 11 woodblock notes and has a total duration of six seconds. These rhythms differ in their temporal structure, such that the temporal intervals between notes are manipulated, but not the duration of the notes themselves. More specifically, each rhythm is made up of five eighth notes (each 250 ms), three quarter notes (each 500 ms), one dotted quarter note (750 ms), one half note (1000 ms) and one dotted half note (1500 ms). Manipulation of the temporal structure of the notes results in three levels of progressively more complex and less metrically structured rhythm types. On each trial, one rhythm is presented twice. On the first presentation, participants are instructed to listen carefully and on the second presentation they are asked to tap in synchrony with the rhythm using the computer mouse. Each rhythm is presented in a counterbalanced fashion six times in each block and participants perform two blocks. For a more detailed description of the RST, see Bailey and Penhune (2010).

Performance on the RST is measured using two dependent variables: percent correct (PC) and inter-tap-interval (ITI) deviation. A tap is considered correct if it is made within half of the onset-to-onset interval before or after each woodblock note. ITI deviation measures the extent of deviation of the participant's tap intervals from the actual intervals between each pair of woodblock notes. It is calculated by dividing the interval between each pair of the participant's taps by the interval between each corresponding pair of woodblock notes in the rhythms and subtracting this ratio from a value of one. This measure is indicative of how well participants reproduce the overall temporal structure of the rhythms.

To examine any potential differences between groups in cognitive abilities, participants completed the Digit-Span (DS) and Letter-Number Sequencing (LN) subtests from the Wechsler Adult Intelligence Scale – III (WAIS; Wechsler, 1997) and the Vocabulary (VC) and Matrix Reasoning (MR) subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). DS requires individuals to recall strings of numbers and LN requires individuals to recall and mentally manipulate strings of letters and numbers. Both of these tasks are measures of auditory working memory. VC assesses an individual's ability to orally define words and MR assesses non-verbal reasoning and visual pattern recognition abilities. Both VC and MR are strongly correlated with global IQ scores. Standard procedure was followed for administering and scoring each subtest.

3.3.3 Procedure

During an initial behavioural testing session, participants completed the MEQ, the RST and the four cognitive tests. Structural MRI scans were acquired on a second day using a Siemens Trio 3T MRI scanner with a 32-channel head coil (TR = 2300ms, TE = 2.98ms, 1x1x1mm^3).

3.3.4 Behavioural Data Analyses

To compare performance on the RST between the three groups, a repeated-measures analysis of variance (ANOVA) for both PC and ITI deviation was conducted, with group as the between-subjects factor. Pair-wise comparisons for between group differences were analyzed using a least significant differences (LSD) correction for multiple comparisons. The result of our matching procedure was evaluated using t-test comparing years of musical experience, years of formal training, and hours of current practice between the ET and LT groups. Group differences on the cognitive subtests were assessed using a one-way ANOVA for each cognitive variable with group as the between-subjects factor. Scaled scores were used for the cognitive subtest comparisons and pair-wise comparisons were conducted using a LSD correction for multiple comparisons.

3.3.5 MRI Data Analyses

Four types of analyses were conducted to examine group differences in grey matter: optimized VBM, traditional VBM, DBM, and surface-based analyses. In all three VBM-style analyses, there is a processing step that deforms each subject's T1 image in order to register the image to a common template, thus removing significant differences in shape or volume in all subjects. Optimized VBM re-introduces this deformation information by modulating each voxel's grey matter value by the degree of deformation obtained during the image registration process. Traditional VBM compares grey matter values after the subject images have been registered to the template, thus removing any deformation information from the data. Because optimized VBM modulates voxel-wise grey matter values with the deformation value, it is impossible to attribute observed differences to local volume/shape or more fine-grained differences in grey matter such as concentration or density. DBM analysis compares the degree of deformation (expansion or contraction) required to register each individual to the template in a voxel-wise fashion, measuring local differences in volume or shape between groups. In addition to the VBM-style analyses, T1 images were processed using the surface-based stream of FreeSurfer to assess group differences in cortical thickness, surface area, curvature and volume. Using these techniques on the same data set allows for a more comprehensive investigation of grey matter and which cortical surface features are associated with observed differences using the VBM-style techniques.

3.3.5.1 VBM and DBM Analyses

All VBM and DBM analyses were conducted using FSL tools (Smith et al., 2004). T1 images were brain-extracted using BET (Smith, 2002) and tissue-type segmentation was carried out using FAST4 (Zhang, Brady, & Smith, 2001). The resulting grey matter partial volume images were aligned to the MNI152 standard template using the affine registration tool FLIRT (Jenkinson & Smith, 2001), followed by a non-linear registration using FNIRT (Andersson, Jenkinson, & Smith, 2007). The resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly registered. In the optimized VBM protocol (Good, et al., 2001), the registered partial volume images are modulated by the Jacobian determinants of the warp field. In addition, we examined the natural logarithm values of the Jacobian determinants themselves as measures of local expansion or contraction (DBM) as well as grey matter concentration values (traditional VBM; Ashburner & Friston, 2000). In all three analyses, final images were smoothed using an isotropic Gaussian kernel with a sigma of 4mm and voxel-wise GLM was applied using permutation-based non-parametric testing with a cluster-based thresholding approach ($t = 3.66$, voxel-wise uncorrected $p < 0.001$), correcting for multiple comparisons. To assess differences between ET and LT musicians whole-brain group comparisons were conducted using optimized VBM, DBM and traditional VBM. For the region of significant difference identified in the ventral pre-motor cortex (vPMC), mean values for all three groups (ET, LT and NM) were extracted and compared. In addition, these values were correlated with ITI deviation scores on the RST as well as age of onset of musical training. Additional whole-brain analyses were carried out to investigate regions related to musical training across all musicians.

3.3.5.2 Cortical Thickness and Surface-Based Analyses

Cortical reconstruction was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, et al., 2002; Fischl, et al., 2004; Fischl, Sereno, & Dale, 1999a; Fischl, Sereno, Tootell, & Dale, 1999b; Han, et al., 2006;

Jovicich, et al., 2006; Ségonne, et al., 2004). In summary, the processing stream includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne, et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter (Fischl, et al., 2002; Fischl, et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl, et al., 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale, et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Each volume and surface was visually inspected for errors or inaccuracies. Once the cortical models were complete, the creation of surface based data including maps of cortical thickness, curvature and surface area was carried out. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. All data maps were smoothed with a 20-mm full-width/half-maximum Gaussian kernel. A whole-brain group comparison of cortical thickness between the ET and LT musicians was conducted. Additionally, the region of interest (ROI) in the vPMC identified in the DBM analysis was imported into Freesurfer, registered to the average volume, mapped onto the average surface and finally mapped onto each individual's surface. Group comparisons for mean values of cortical thickness, surface area, mean curvature and grey matter volume for this ROI were carried out, as well as correlations with ITI deviation on the RST as well as age of onset of musical training. In addition, a whole-brain search for areas where cortical thickness correlated with musical experience demographics was carried out.

3.3.5.3 Correlation Analyses Between Traditional VBM, DBM, Cortical Thickness and Surface-Based Measures

Finally, correlation analyses were conducted among the extracted structural measures from the ROI in vPMC in order to relate the different VBM-style analyses to cortical surface attributes. More specifically, extracted mean values of deformation, traditional VBM, cortical thickness, curvature, surface area, and total grey matter volume were correlated with each other across all participants. These additional analyses provide a more comprehensive understanding of how these different measures relate to each other.

3.4 Results

3.4.1 Behavioural Results

Statistical comparison of the ET and LT musicians confirmed that there were no significant differences between the two groups in terms of age, years of musical experience, years of formal training and hours of current practice (Table 3.1). The NM group had fewer than three years of musical training and did not differ in age from either musician group.

Comparisons of cognitive subtest scores revealed no significant between-group differences on Digit Span or Letter-Number Sequencing. A marginally significant effect of group was observed for Matrix Reasoning and Vocabulary (Table 3.2). Post-hoc comparisons revealed that Vocabulary scores were higher for NM than ET ($p = 0.03$) and that Matrix Reasoning scores were higher for LT than NM ($p = 0.02$).

Comparison of performance on the Rhythm Synchronization task between the three groups revealed a significant main effect of group for the ITI deviation measure (F $(2, 47) = 20.30$, $p < 0.001$; Fig. 3.1). Post-hoc analyses revealed that task performance of the ET was superior to that of the LT ($p < 0.05$). Both musician groups showed an advantage in task performance compared to the NM group (both $p < 0.0001$).

Table 3.1. *Group demographics of musical experience variables*

Group	Age (Yrs)	Age of Onset (Yrs)	Formal Training (Yrs)	Musical Experience (Yrs)	Current Practice (Hrs)
Early-Trained (ET)	23.47 (± 3.85)	5.87 (± 1.19)	11.73 (± 3.97)	16.87 (± 4.10)	15.23 (± 9.97)
Late-Trained (LT)	26.60 (± 5.22)	10.47 (± 2.03)	10.03 (± 4.39)	15.90 (± 4.74)	14.43 (± 7.80)
t-values	-1.87	-7.57**	1.11	0.60	0.25
Non-Musicians (NM)	26.20 (± 4.35)	-	0.69 (± 0.79)	0.91 (± 0.75)	-

Note: Standard deviation values are in brackets
** *p*-value < 0.001

Table 3.2. *Group cognitive subtest scores*

Group	Digit-Span (DS)	Letter-Number Sequencing (LN)	Vocabulary (VC)	Matrix Reasoning (MR)
Early-Trained (ET)	12.13 (± 2.88)	12.33 (± 2.94)	12.33 (± 3.33)	12.20 (± 3.34)
Late-Trained (LT)	12.27 (± 1.98)	11.80 (± 2.78)	13.33 (± 2.82)	13.60 (± 2.32)
Non-Musicians (NM)	11.05 (± 3.43)	11.45 (± 2.11)	14.45 (± 1.96)	11.15 (± 2.91)
F-values	0.96	0.61	2.69	3.08

Note: Standard deviation values are in brackets
* *p*-value < 0.05

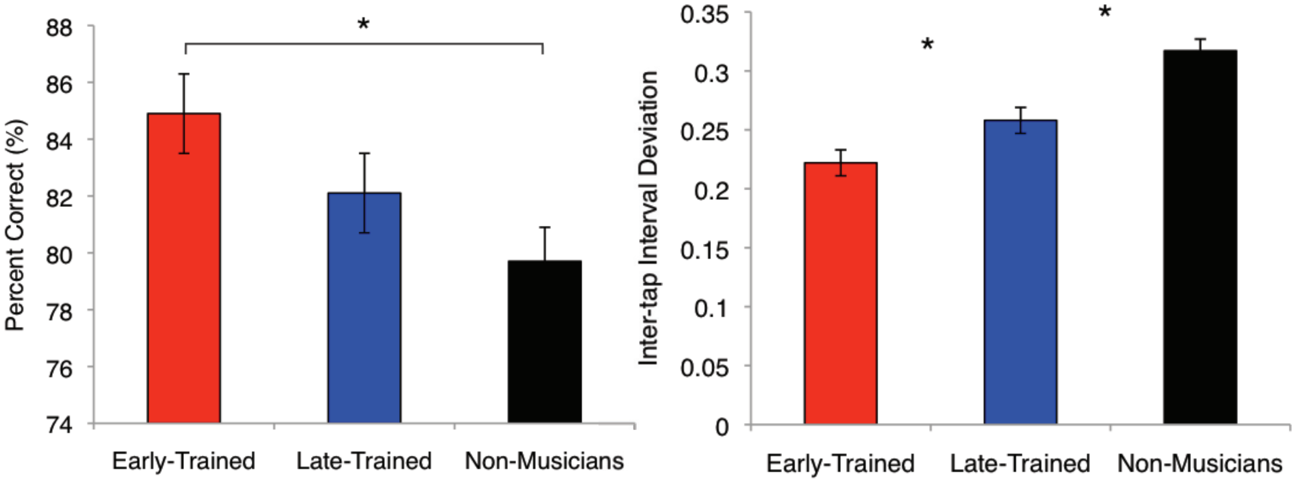


Figure 3.1. Group mean performance scores for the Rhythm Synchronization Task. (a) Percent Correct and (b) Inter-Tap Interval Deviation of all three groups on the Rhythm Synchronization Task. ANOVA results indicated a main effect of group on each performance measure, and post-hoc analyses for Inter-tap Interval Deviation revealed superior task performance among the Early-Trained musicians compared to the Late-Trained musicians. Both musician groups showed an advantage in task performance compared to the Non-Musicians on both performance measures. Error bars represent standard error of the mean.

3.4.2 VBM and DBM Results

When images were analyzed using optimized VBM, where spatially registered voxel-wise grey matter values are modulated by the Jacobian determinants (Good, et al., 2001), the initial whole-brain analysis revealed differences between musician groups in three main areas (ET-LT; t-values > 3, uncorrected for multiple comparisons): bilateral ventral pre-motor cortex (right peak voxel: 50, 8, 24, $t = 4.31$; left peak voxel: -46, 2 26, $t = 4.18$), left dorsal pre-motor cortex (peak voxel: -24, 0, 56, $t = 4.35$), and left primary somatosensory cortex (peak voxel: -24, -34, 54, $t = 3.19$). These areas did not surpass the permutation-based non-parametric correction for multiple comparisons. The strongest effect was located in the right ventral pre-motor cortex and reached a p-value of 0.10.

In order to understand the contribution of traditional VBM grey matter values and local differences in volume or shape contributing to this effect, traditional VBM and DBM analyses were conducted independently. The traditional VBM analysis revealed no significant group differences; however, the DBM analysis revealed a group difference (ET>LT) in the right ventral pre-motor cortex at the same location identified in the optimized VBM analysis (peak voxel: 50, 4, 20, $t = 5.32$; cluster $p < 0.05$, corrected for multiple comparisons; Fig. 3.2a). The ET group required greater contraction in this area than the LT in order to register their volumes to the study-specific template, suggesting that differences in local volume or shape were driving the observed difference in this region in the optimized VBM analysis

Confirming relevance of these findings to auditory-motor synchronization performance, extracted mean deformation values from this ROI were negatively correlated with ITI deviation scores such that better performance was related to higher deformation values (r = -0.354, $p < 0.05$; Fig. 3.2b). Interestingly, the extracted mean grey matter values obtained from the traditional VBM analysis from this ROI showed no effect of group or relation to task performance (t = -0.74 and r = 0.022, $p > 0.05$; Fig. 3.2b). The extracted mean values from the NM group were included for the sake of comparison, as no significant differences were observed using a whole-brain approach in any of the VBM-style analyses. The extracted mean deformation values for the NM in this area of the pre-motor cortex significantly differed from both groups of musicians (ET-NM: t = 2.22, $p < 0.05$; LT<NM: t = -2.79, $p < 0.05$; Fig. 3.2b), although their extracted mean deformation values did not relate to their ITI deviation scores on the rhythm task (r = 0.213, p = 0.19). Furthermore, the mean grey matter extractions from the traditional VBM analysis for the NM did not differ when compared to either musician group (ET-NM: t = 0.17, p = 0.87; LT-NM: t = 1.06, p = 0.30; Fig. 3.2b), nor did they relate to their ITI deviation scores on the rhythm task (r = 0.182, p = 0.23; Fig. 3.2b).

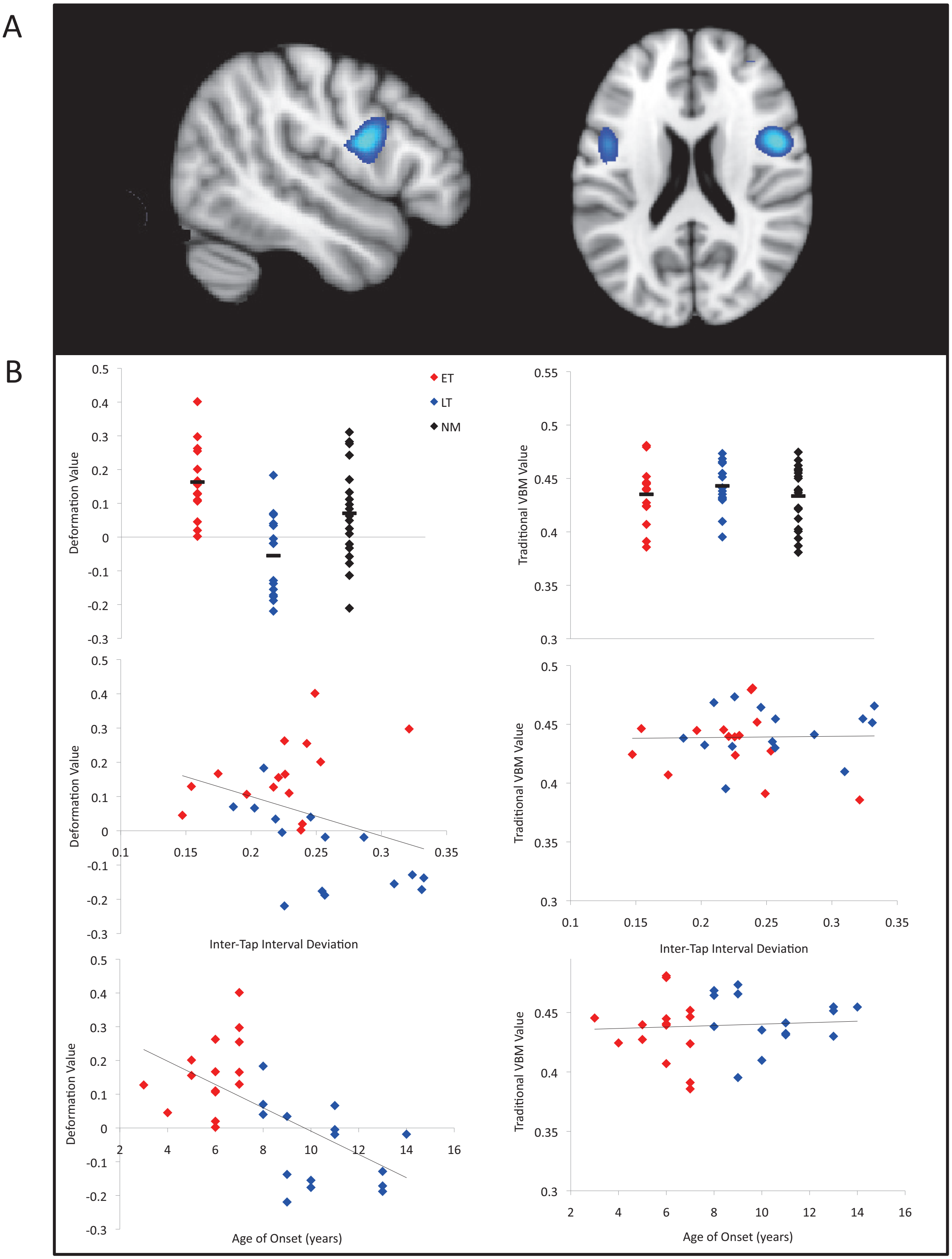

A
B
ET
LT
NM
Deformation Value
Traditional VBM Value
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
0.55
0.45
0.35
0.1
0.15
0.2
0.25
0.3
0.35
Inter-Tap Interval Deviation
2
4
6
8
10
12
14
16
Age of Onset (years)

Figure 3.2. Results from the Deformation-Based Morphometry (DBM) analysis between Early-Trained and Late-Trained musicians. (a) Visual representation of the area of difference observed in the right ventral pre-motor cortex (vPMC), where Early-Trained musicians required significantly greater contraction during the template-fitting process than the Late-Trained musicians (b) Extracted Deformation Values and Traditional VBM Values from the region of interest in the vPMC correlated with task performance and age of onset.

3.4.3 Cortical Thickness and Surface-Based Results

Whole-brain cortical thickness group comparisons revealed no areas of significant difference. However, when an ROI-based approach was carried out using the area of difference in vPMC identified in the DBM analysis, surface-based measures revealed a significant ET>LT group difference for surface area (ET: $M = 216.53$, $SD = 23.23$; LT: $M = 197.00$, $SD = 24.55$; $t = 2.24$, $p < 0.05$; Fig. 3.3b). These findings suggest that differences in surface area are contributing to the observed difference in deformation values in this part of the pre-motor cortex. Interestingly, there were no ET-LT differences in cortical thickness (ET: $M = 2.50$, $SD = 0.23$; LT: $M = 2.50$, $SD = 0.14$; $t = 0.03$, $p = 0.98$), mean curvature (ET: $M = 0.12$, $SD = 0.02$; LT: $M = 0.11$, $SD = 0.02$; $t = 0.50$, $p = 0.62$), or total grey matter volume (ET: $M = 493.73$, $SD = 93.57$; LT: $M = 437.93$, $SD = 112.35$; $t = 1.48$, $p = 0.15$) for this region. The extracted mean values from the NM group were included for the sake of comparison and did not reveal a significant differences in surface area (ET-NM: $t = 1.21$, $p = 0.24$; LT-NM: $t = -0.68$, $p = 0.50$) cortical thickness

(ET-NM: $t = 0.22$, $p = 0.82$; LT-NM: $t = 0.26$, $p = 0.80$), mean curvature (ET-NM: $t = -0.18$, $p = 0.86$; LT-NM: $t = -0.74$, $p = 0.46$), or total grey matter volume (ET-NM: $t = 0.67$, $p = 0.51$; LT-NM: $t = -0.92$, $p = 0.36$) compared to either musician group.

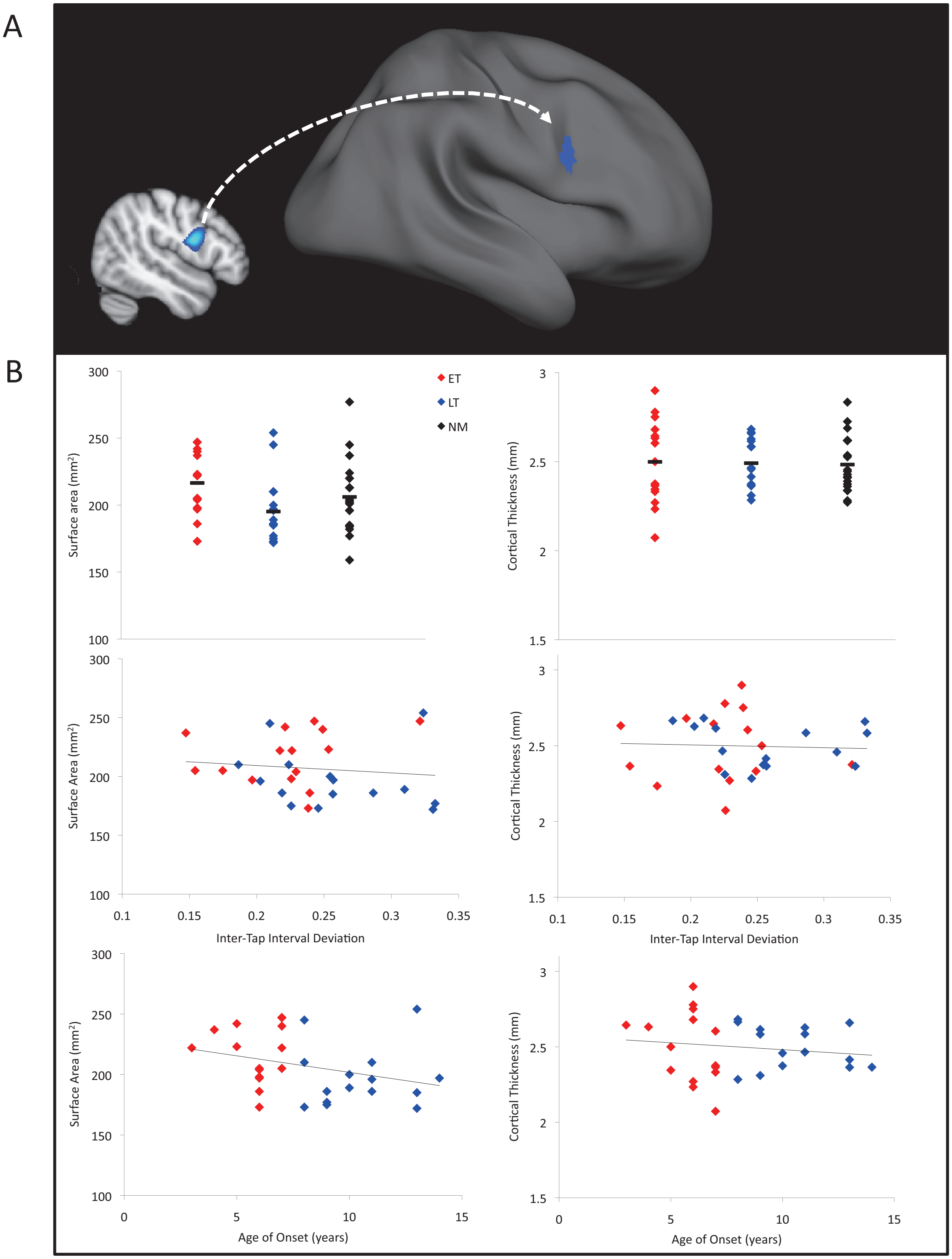

A
B
300
250
200
150
100
Surface area (mm²)
◆ ET
◆ LT
◆ NM
3
2.5
2
1.5
Cortical Thickness (mm)
Surface Area (mm²)
0.1
0.15
0.2
0.25
0.3
0.35
Inter-Tap Interval Deviation
Cortical Thickness (mm)
0.1
0.15
0.2
0.25
0.3
0.35
Inter-Tap Interval Deviation
Surface Area (mm²)
0
5
10
15
Age of Onset (years)
Cortical Thickness (mm)
0
5
10
15
Age of Onset (years)

Figure 3.3. Extracted mean surface-based measures from the right vPMC. (a) Visual representation of the region of interest from the DBM analysis mapped onto the average surface (b) Extracted mean Surface Area and Cortical Thickness values from the right vPMC correlated with task performance and age of onset.

3.4.4 Correlations Between Structural Measures

When correlations between all structural measures extracted from the vPMC ROI were examined across participants, it was observed that cortical thickness correlated with tradition VBM values ($r = 0.284$, $p < 0.05$; Fig. 4) and deformation values correlated with surface area ($r = 0.487$, $p < 0.001$; Fig. 3.4) and curvature ($r = 0.322$, $p < 0.05$). In addition, grey matter volume correlated significantly with all measures of grey matter in this ROI (surface area: $r = 0.732$, $p < 0.001$; cortical thickness: $r = 0.364$, $p <0.01$; curvature: $r = 0.555$, $p < 0.001$; DBM: $r = 0.519$, $p < 0.001$), with the exception of grey matter concentration values ($r = -0.099$, $p = 0.49$). This pattern of results corroborates previous findings in the literature, suggesting that grey matter concentration values using traditional VBM are associated with cortical thickness and DBM measures may be related to other larger, perhaps more variable, cortical features such as surface area, curvature, and grey matter volume (Bermudez, Lerch, Evans, & Zatorre, 2009; Eckert et al., 2006; Foster & Zatorre, 2010; Voets et al., 2008).

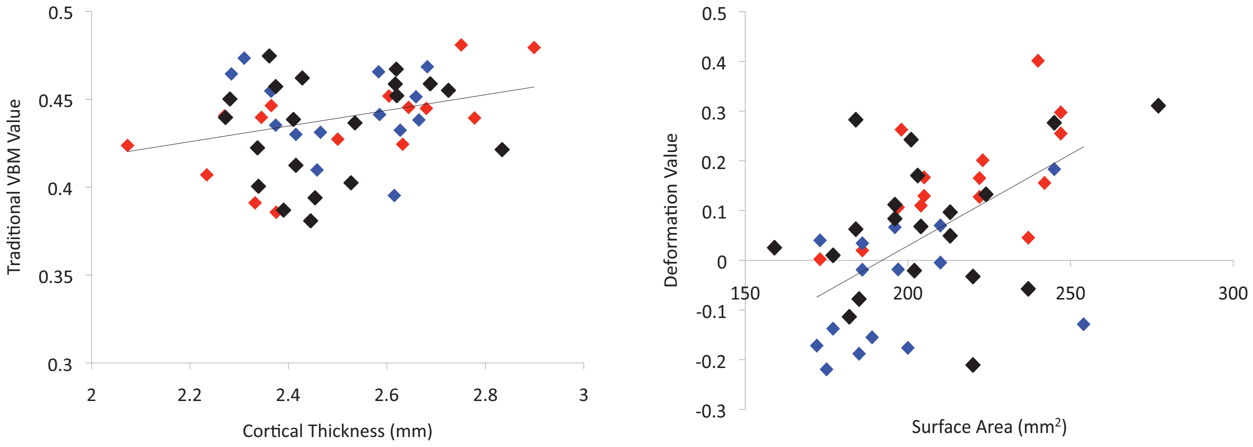


Figure 3.4. Extracted mean structural measures from the right ventral pre-motor cortex. Traditional VBM values correlated with cortical thickness and deformation values correlated with cortical surface area. Early-Trained musicians are presented in red, Late-Trained musicians are in blue and Non-Musicians are in black.

3.4.5 Grey Matter Correlates of Musical Experience

Extracted structural measures from the vPMC ROI data were also correlated with measures of musical experience. As can be seen in Table 3.3, there was a significant negative correlation between years of musical experience and cortical thickness ($r = -0.433$, $p < 0.05$) and a trend-level negative correlation between musical experience and mean curvature ($r = -0.307$, $p = 0.098$). However, none of the whole-brain VBM-style or cortical thickness analyses yielded any significant correlates of age of onset, musical experience or years of formal training.

Table 3.3. *Grey Matter Extractions from the right vPMC ROI and Musical Variables*

Variable	Age of Onset	Years of Experience	Formal Training
Deformation Value	-0.623**	0.175	0.309
Traditional VBM Value	0.071	-0.330	0.121
Surface Area	-0.306	0.190	-0.097
Cortical Thickness	-0.137	-0.433*	0.027
Mean Curvature	0.054	-0.307	-0.241
Grey Matter Volume	-0.294	-0.132	-0.094

* = *p*-value < 0.05
** = *p*-value < 0.01

3.5 Discussion

We investigated the interaction between brain maturation and experience in early- and late-trained musicians by comparing MRI measures of grey matter structure and performance on an auditory rhythm synchronization task. Behavioural analyses revealed enhanced rhythm synchronization performance in the ET musicians, consistent with previous findings (Bailey & Penhune, 2010). Grey matter analyses revealed differences in deformation values in the right vPMC, indicating that ET musicians have greater volume in this region. Very importantly, extracted deformation values from the right vPMC correlated with the age of onset of musical training and with performance on the RST for the musician groups. This finding supports the interpretation that the effect of early training on auditory rhythm synchronization is mediated through plastic changes in the pre-motor cortex. Interestingly, ET musicians also had greater surface area in this region and deformation values were correlated with measures of surface area and curvature. These results further support the interpretation that deformation values may be related to measures of cortical volume or shape. These differences in brain structure and rhythm synchronization performance are unlikely to be accounted for by differences in length of training since the two groups of musicians were matched for musical experience. In addition, correlations of extracted measures of grey matter from this ROI across all three groups revealed that deformation values correlated with measures of surface area and curvature, while traditional VBM grey matter values correlated with cortical thickness. These analyses are in line with previous findings (Bermudez, Lerch, Evans, & Zatorre, 2009; Eckert, et al., 2006; Foster & Zatorre, 2010; Voets, et al., 2008), supporting the idea that traditional VBM and DBM analyses relate to unique aspects of cortical attributes and that optimized VBM may confound these two pieces of information.

The fact that ET musicians have greater grey matter volume in the vPMC is compatible with its role in sensorimotor integration (see Zatorre, Chen and Penhune, 2007 for review) and with the maturational trajectories of grey and white matter in this region. In a previous fMRI using a similar auditory rhythm synchronization task, we found that performance was related to activity in an almost identical location in the right vPMC (peak voxel: 48, 4, 24; Chen, Penhune, & Zatorre, 2008). In that experiment, performance was also related to activity in auditory association areas of the superior temporal gyrus and we hypothesized that this network was important for integrating auditory perception with a motor response. The greatest between-group performance difference in the present study was observed for ITI deviation, indicating that the ET musicians were better at reproducing the overall temporal structure of the rhythms, consistent with greater accuracy in auditory motor integration. This performance difference is not likely to be related to cognitive abilities, given that no significant differences on the cognitive measures between ET and LT musicians persisted. A previous behavioural study using the matching paradigm and the RST on an independent subject sample revealed the same pattern of results (Bailey & Penhune, 2010). The maturational trajectories of grey matter in the vPMC also make it a likely candidate to be differentially impacted by musical training during the early childhood years (Gogtay, et al., 2004). Furthermore, DTI findings in a subsample of the present sample showed that white matter integrity in the region of the corpus callosum connecting motor and pre-motor cortices was correlated with age of onset of musical training (Steele, Bailey, Zatorre, & Penhune, 2013). Overall, the evidence supports the hypothesis that the vPMC is differentially influenced by early musical training, resulting in changes in grey matter volume and enhanced sensorimotor synchronization performance.

The observed group difference in grey matter volume between the ET and LT musicians in the vPMC adds further evidence to support the sensitive period hypothesis for musical training. These results suggest a relationship between the size or shape of the right vPMC and early musical training. Several different processes at the cellular level may be underlying the observed macroscopic changes in the adult brain associated with experience or training (for review see May, 2011 or Zatorre, Fields, and Johansen-Berg, 2012). For example, it has been proposed that changes in white matter structure may be due to axonal remodeling via fibre organization, changes related to myelin, or changes related to astrocytes. Grey matter changes have been attributed to dendritic branching or synaptogenesis, neurogenesis or changes related to glial cells. Axonal sprouting and angiogenesis may underlie both grey and white matter changes. However, during development, cellular competition for resources may be reflected in activity-dependent processes such as synaptic pruning or neuron death in addition to the previously mentioned processes (Stoneham, Sanders, Sanyal, & Dumas, 2010). It has been proposed that the initial surplus of synapses early in postnatal development takes place independent of experience; however, experience-based neural activity is an important factor in determining which synapses are retained and which ones are eliminated, in an effort to develop an efficient and specialized system (Stoneham, et al., 2010). Exciting evidence identifies glial cells and astrocytes as key players in this pruning process (Stephan, Barres, & Stevens, 2012). With respect to the topic of the current dissertation, it might be that the repeated activation of the auditory-motor network, specifically the pre-motor cortex, through daily practice of a musical instrument may alter pruning processes in these regions and result in cortical changes at a macroscopic level if this training begins at a specific time in development.

DBM has been previously used to evaluate differences or changes in grey matter volume and, more specifically, yields voxel-wise estimates of contraction or expansion of grey matter (e.g., Chung, et al., 2001; Hyde, et al., 2009; Leporé, et al., 2010). In the current study, results from the optimized VBM analysis revealed sub-threshold differences between ET and LT in the right vPMC. When separate analyses were performed using traditional VBM and DBM, DBM values showed a significant difference in this region, traditional VBM did not. These results suggest that the group difference observed using optimized VBM was driven by deformation values. These findings are not the first to highlight the importance of considering differences between optimized VBM, traditional VBM and DBM. Eckert and colleagues carried out a similar set of analyses to examine neuroanatomical features associated with Williams Syndrome and reported that DBM data contributed significantly to the optimized VBM results. Taken together, these findings suggest that combining DBM and traditional VBM measures can allow us to identify the contribution of differences in local volume or shape as well as measures of grey matter structure such as concentration or density.

Correlations conducted using the extracted values from the right vPMC ROI across all participants raise the possibility that observed differences using DBM are being driven by differences in surface area, curvature or differences in grey matter volume, whereas observed differences using traditional VBM may be more likely driven by differences in cortical thickness. Previous findings have revealed an association between traditional VBM measures of grey matter and cortical thickness among musicians in the auditory and motor areas (Bermudez, Lerch, Evans, & Zatorre, 2008; Foster & Zatorre, 2010). Similarly, in a study of schizophrenia, decreased grey matter values using optimized VBM were related to cortical thinning in some regions and decreased surface area in others (Voets, et al., 2008) In sum, it is informative to include surface-based measures of morphometry such as cortical thickness, surface area, curvature and local grey matter volume to disambiguate observed differences in DBM or traditional VBM data.

Overall, these findings add support to the proposed sensitive period associated with musical training. Early training was associated with increased deformation values and cortical surface area in the right ventral pre-motor cortex, suggesting a relationship between early musical training and shape or size of musically relevant cortical regions. While much remains unknown about the underlying cellular mechanisms driving these differences; however, the present findings suggest an interaction between experience or training and predetermined developmental processes that influence shape and size of cortical features.

Chapter 4: Investigating a sensitive period for musical training: Is earlier always better?

Bailey, J.A., and Penhune, V.B. (*in submission*). Investigating a sensitive period for musical training: Is earlier always better? *Frontiers in Psychology (Auditory Cognitive Neuroscience).*

4.1 Abstract

A sensitive period associated with musical training has been proposed, such that the influence of musical training on the brain and behaviour is stronger during the early years of childhood. Experiments from our laboratory have directly tested the sensitive period hypothesis for musical training by comparing musicians who began their training prior to age seven with those who began their training after age seven, while matching the two groups in terms of musical experience (Bailey & Penhune, 2010; 2012; Watanabe, Savion-Lemieux, & Penhune, 2007). Using this matching paradigm, the early-trained groups have demonstrated enhanced sensorimotor synchronization skills and associated differences in brain structure (Bailey, Zatorre, & Penhune, *in submission*; Steele, Bailey, Zatorre, & Penhune, 2013). The current study is taking a different approach to investigating the sensitive period hypothesis for musical training by examining a single large group of unmatched musicians (N=77) and exploring the relationship between age of onset of musical training as a continuous variable and performance on an auditory-motor rhythm synchronization task (RST). Replicating previous findings, performance on the RST correlated with individual working memory scores and years of formal training. Age of onset was correlated with task performance for those who began training earlier; however, no such relationship was observed among those who began training in their later childhood years. Interestingly, years of formal training showed a similar

pattern. However, working memory scores were predictive of task performance, regardless of age of onset of musical training. Overall, these results replicate previous findings, support the sensitive period hypothesis for musical training and provide insight into the nature of the relationships between age of onset of musical training, formal training and auditory-motor rhythm synchronization.

4.2 Introduction

A sensitive period suggests an interaction between brain maturation processes and training or experience, such that the effects of that training or experience differ across development (Knudsen, 2004; de Villers-Sidani & Merzenich, 2011). A sensitive period for musical training has been proposed based on evidence that those who begin musical training earlier demonstrate differences in brain structure and enhanced synchronization performance than those who began their training later, even after matching for total amount of training (Bailey & Penhune, 2010; 2012; Steele, Bailey, Zatorre, & Penhune, 2013; Watanabe, Savion-Lemieux, & Penhune, 2008). Specifically, performance on an auditory-motor synchronization task used with early- and late-trained musicians was found to correlate with age of onset of musical training, amount of training, measures of grey matter in the pre-motor cortex, and individual working memory scores (Bailey & Penhune, 2010; 2012; Bailey, Zatorre, & Penhune, *in submission*). These results were observed using a group difference approach comparing early- and late-trained musicians, matched for total amount of musical experience and isolating age of onset of musical training. What remains to be investigated is whether the predictive value of these cognitive and musical training variables for auditory-motor synchronization performance differs for those who begin training earlier. The current study takes a novel approach to investigating the sensitive period for musical training by examining whether the influence of musical training and cognitive abilities on synchronization skills is consistent across development in a single group of adult musicians.

A sensitive period arises when the effects from an experience at a certain time during development are different than the effects of that same experience later on (Knudsen, 2004). Sensitive periods have been proposed for the visual and auditory systems, as well as for language learning (for reviews see Hensch, 2005, Hooks and Chen, 2007, Penhune, 2011, or de Villers-Sidani and Merzenich, 2011). Simplistically, two key variables involved in the sensitive period theory are pre-determined brain maturation trajectories and experience. It is the interaction between these processes that may result in sensitive periods, when the effects associated with a given experience are strongest and exert the greatest influence on brain development. The sensitive period theory has been applied to musical training, predicting that early training has a stronger influence on the brain and behaviour than training later on in development (Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995; Watanabe, Savion-Lemieux, & Penhune, 2007). The anatomical maturational trajectories of grey matter volume and white matter integrity of the auditory-motor system follow non-linear growth curves, with peaks between ages 5 and 10 years old with continued, but more subtle change thereafter (Gogtay, et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Given the accumulating evidence regarding the effects that musical training exerts on brain structure (for review see Jäncke, 2009 or Wan and Schlaug, 2010), it is reasonable to suggest that training of the auditory-motor system via music lessons in childhood may exert a stronger influence on brain structure and, as a result, musical skills.

Previous studies support the sensitive period hypothesis for musical training by finding differences in brain structure or task performance between groups of early-trained and late-trained musicians. One of the first studies to suggest stronger effects associated with early musical training reported enlarged corpus callosum volumes among musicians compared to non-musicians and these differences were greater for those who began their training early (Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995). Imfeld and colleagues reported differences in the corticospinal tract between their early- and late-trained musicians (2009). Bengtsson and colleagues examined the relationship between hours of piano practice during different stages of development and white matter fibre tract organization and reported that fractional anisotropy values correlated with practice hours during development; however, this was seen in a greater number of brain regions correlated with practice hours accrued in early childhood (2005). While these results suggest an association with early training, these studies did not control for the confounding fact that those who began earlier likely had more musical experience at the time of testing. Studies from our laboratory have used a matching paradigm to control for this possibility. This approach involves matching the two groups of musicians in terms of years of total playing experience, years of formal training and hours of weekly practice to isolate the variable of interest – age of onset of musical training. Evidence using this approach has directly supported the sensitive period hypothesis for musical training, such that the early-trained groups of musicians have consistently outperformed the late-trained musicians on a visual-motor synchronization task (Watanabe, Savion-Lemieux, &

Penhune, 2007; Steele, Bailey, Zatorre, & Penhune, 2013), as well as an auditory-motor synchronization task (Bailey & Penhune, 2010; 2012). Interestingly, the matching approach limits the range in years of formal training of musicians because early-trained musicians are adults when tested and, therefore, matched with late-trained musicians with at least 11 years of formal training, if not more. As a result, this matched group approach has shown support for the sensitive period hypothesis in samples of highly trained musicians. What remains to be investigated is the predictive value of musical training variables such as age of onset and amount of formal training on task performance in an unmatched sample of musicians considering age of onset as a continuous variable, as opposed to a grouping variable.

The task we have frequently used to examine differences between early- and late-trained musicians is the Rhythm Synchronization Task (RST; Bailey & Penhune, 2010; 2012; Bailey, Zatorre, & Penhune, *in submission*). This task requires participants to tap in synchrony with a series of auditory rhythms of varying metrical complexity (Chen, Penhune, & Zatorre, 2008). Performance is assessed in terms of inter-tap interval (ITI) deviation, which measures the ability to accurately reproduce the temporal intervals of each rhythm. Previous brain imaging studies have shown that task performance is related to activity in networks important for auditory-motor integration. Previous studies in early and late-trained musicians have revealed that performance on the RST is related to brain structure, musical training and cognitive abilities. In the first study early-trained musicians were better able to reproduce the temporal structure of the rhythms. Although there were no group differences on standard measures of global cognitive function (Vocabulary and Matrix Reasoning), individual working memory scores (Digit Span and

Letter-Number Sequencing) correlated with RST performance (Bailey & Penhune, 2010). A regression analysis confirmed that, even after considering individual working memory scores, early training accounted for additional variance in RST performance. These findings were replicated in a follow-up study (Bailey & Penhune, 2012). Similar to working memory, formal musical training was also related to RST performance, even though the groups did not differ on this variable (Bailey & Penhune, 2010; 2012). Taken together, these results indicate that RST performance is predicted by when musical training begins, the number of years of formal training and individual working memory abilities in highly trained musicians.

According to the sensitive period hypothesis, the effects associated with musical training should differ across development. Using a single, large sample of musicians with a wider distribution of age of onset and years of formal training provides a complementary approach to examining evidence for the sensitive period hypothesis for musical training. Musical training can be quantified in many different ways and this endeavor warrants further attention; however, in the current sample, there are two measures of musical training that have shown a relationship to performance on the RST: age of onset and years of formal lessons. A similar question has been investigated in the domains of second-language acquisition and cochlear implant research. Of these studies, the most relevant to the current data set and question is the work of Johnson and Newport (1989), who investigated the relationship between age of arrival in the United States and English proficiency among second-language learners. They reported that prior to puberty (< age 15), a significant correlation between age of arrival and proficiency measures was observed, but no such relationship was observed for individuals arriving after age 15.

Similarly, Flege and colleagues reported breakpoints in their relationship between age of arrival and language proficiency measures among second-language learners, suggesting that the relationship was not consistent across development (1999). Harrison and colleagues used a binary partitioning method to determine the optimal age to divide their groups of cochlear implant receivers into early and late when examining the relationship between measures of speech proficiency and time passed since the devices had been implanted (2005). Interestingly, the age that best divided their groups varied depending on the performance measure being considered. These studies highlight the complexities involved in investigating evidence for a sensitive period. The current study will evaluate the nature of the relationship between age of onset of musical training and performance on the RST by first considering a linear correlation model, followed by breakpoint analyses comparing correlation values to determine if the relationship between age of onset and task performance changes across development, similar to Johnson and Newport's approach (1989).

While age of onset of musical training is one aspect of training, years of formal training is a second measure that has also shown a relationship with RST performance (Bailey & Penhune, 2010; 2012). These variables are typically strongly correlated with each other in a distribution of unmatched musicians. According to the sensitive period theory, the effect of training or experience should differ across development. Based on this idea, one would expect that years of formal training would predict task performance differently in those who received years of training in their early childhood than those who received their training in later years. In an unmatched sample, we have the opportunity to use a wider distribution of years of formal training and investigate whether its predictive value for performance on the RST changes as a function of age.

Interestingly, one of the strongest predictors of performance on the RST has been individual working memory scores (Bailey & Penhune, 2010; 2012). It has been proposed that musical training is correlated with enhanced IQ scores; however, to date no differences in cognitive abilities between those who begin training early and those who begin training later have been reported (Bailey & Penhune, 2010; 2012; Schellenberg, 2006). There have been arguments made to suggest that executive function is mediating the observed relationship between music lessons and IQ; however, evidence for this is inconsistent (Schellenberg & Peretz, 2008; Schellenberg, 2011). Other studies have suggested that working memory, in particular can be affected by training (Takeuchi et al., 2010), raising the possibility that music lessons improve working memory abilities. If this is true, we would expect to see a correlation between working memory and years of formal training. In a previous study from our lab examining the relationship between working memory and years of formal training among matched early-trained and late-trained musicians, a statistical trend towards significance was observed; however, it remains to be investigated in an unmatched sample of musicians. Furthermore, based on the sensitive period theory, the predictive value of working memory scores for performance on the RST may also change as a function of when this training occurred during development.

4.3 Method

4.3.1 Participants

The current study uses a sample of 77 musicians between the ages of 18 and 37 (M = 24.91, SD = 4.97). This sample includes musicians previously tested in studies comparing early- and late-trained musicians using a matched samples design (Bailey & Penhune, 2010; 2012). For this study we tested additional musicians to cover a broader range of ages of start (3-17). The musical training and experience of each participant was determined through a Musical Experience Questionnaire (MEQ) that was developed within our laboratory (Bailey & Penhune, 2010; 2012). The MEQ quantifies the amount of instrumental and vocal training a musician has received, age of onset of this training, number of years of formal lessons and the amount of time dedicated to practicing on a weekly basis at the time of testing. Musicians had a range of musical experience (Table 4.1). All participants were neurologically healthy and were screened for significant head injuries, history of neurological disease or medication that could affect task performance. All participants gave informed consent and the Concordia University Research Ethics Committee had approved the protocol.

Table 4.1. *Musical demographics*

	Age of Onset (Years)	Formal Training (Years)	Playing experience (Years)	Current Practice (Hours)
Mean	8.43 (±3.57)	10.09 (±4.79)	15.99 (±4.32)	17.28 (±11.12)
Range	3-17	0-20	7-25	0-56

Note: Standard Deviations are in brackets.

4.3.2 Tasks

Participants performed the Rhythm Synchronization Task (RST; Fig. 4.1), which was previously used in Bailey and Penhune (2010; 2012) and which is a variant of the task used in Chen, Penhune and Zatorre (2008). In this task participants are required to listen to and then tap in synchrony with a series of auditory rhythms of varying metrical complexity. The stimuli consists of 6 woodblock rhythms varying in metrical structure and difficulty. Each rhythm lasts 6 seconds and is made up of 11 woodblock notes. Each rhythm contains five eighth notes (250 ms), three quarter notes (500 ms), one dotted quarter note (750 ms), one half note (1000 ms) and one dotted half note (1500 ms). Each trial has two parts: in the first part participants listen to the rhythm without responding, on the second part they listen and tap in synchrony using the computer mouse. Key press responses are recorded by the computer and used to score the data as described below. For a more detailed description of the RST, see Bailey and Penhune (2010; 2012).

Participants completed the Digit Span and Letter-Number Sequencing subtests from the Wechsler Adult Intelligence Scale – III (WAIS) and the Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechlser, 1997; 1999). Digit Span requires individuals to recall strings of numbers and

Letter-Number Sequencing requires individuals to recall and mentally manipulate strings of letters and numbers. Both of these subtests tap into working memory abilities; however, Letter-Number Sequencing imposes a heavier load on working memory, while Digit Span consists of a rote auditory memory recall section in addition to a mental manipulation section. Vocabulary assesses an individual's ability to orally define words and Matrix Reasoning assesses non-verbal reasoning and visual pattern recognition abilities. Both of these subtests are highly correlated with global IQ, but represent different types of intelligence.

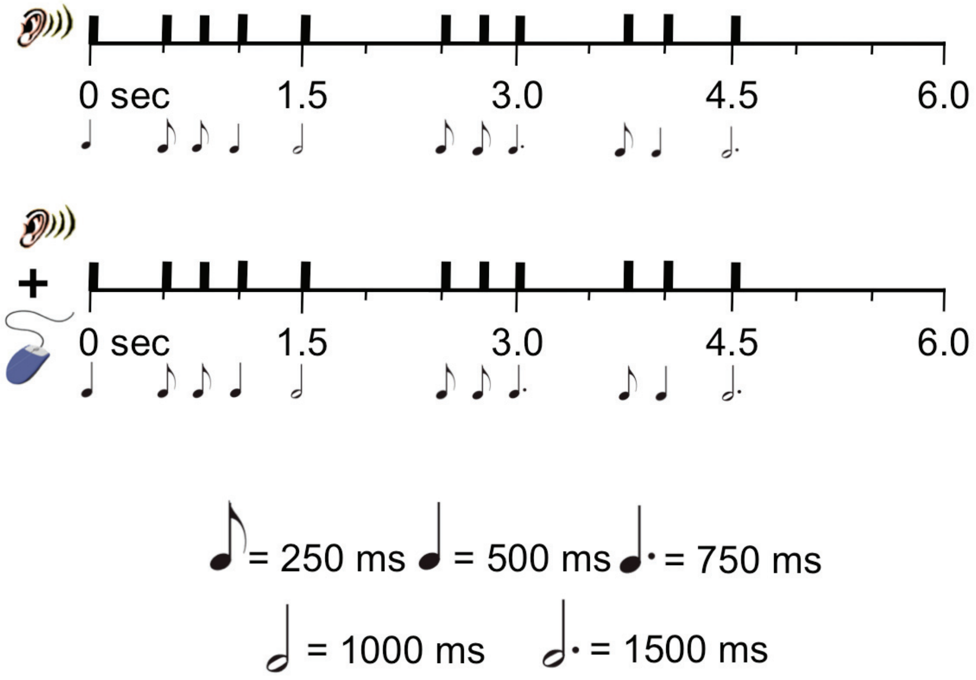


Figure 4.1. Illustration of the Rhythm Synchronization Task (RST). Participants were exposed to six rhythms presented in random order for approximately two 12-minute blocks. Two different rhythms of each rhythmic complexity were used. Each trial consisted of a listening component followed by a listening and tapping component.

4.3.3 Procedure

All participants followed the same procedure for data collection. Participants first completed one block of the RST followed by the Digit Span test. They then performed the second block of the RST, followed by Vocabulary, Letter-Number Sequencing and finally, Matrix Reasoning.

4.3.4 Measures

Information about musical training and experience from the MEQ was quantified for each participant to produce measures of years of experience, years of formal training and hours of weekly. Cognitive subtest results were scored according to standard procedure. A composite score for each participant's working memory abilities was created using their Letter-Number Sequencing and Digit Span scores and was used as the Working Memory variable. Performance on the RST was measured using three dependent variables: percent correct (PC), asynchrony (ASYN) and inter-tap-interval (ITI) deviation. A tap was considered correct if it was made within half of the onset-to-onset interval before or after a woodblock note (Fig. 4.2). ASYN was defined as the absolute value of temporal difference between the onset of each woodblock note and the associated mouse key press. ITI deviation was calculated by dividing the interval between each pair of the participant's taps by the interval between each corresponding pair of woodblock notes in the rhythms and subtracting this ratio from a value of one. This measure evaluates the extent of deviation of the participant's tap interval from the actual interval between each pair of woodblock notes and is indicative of how well participants reproduce the temporal structure of the rhythms.

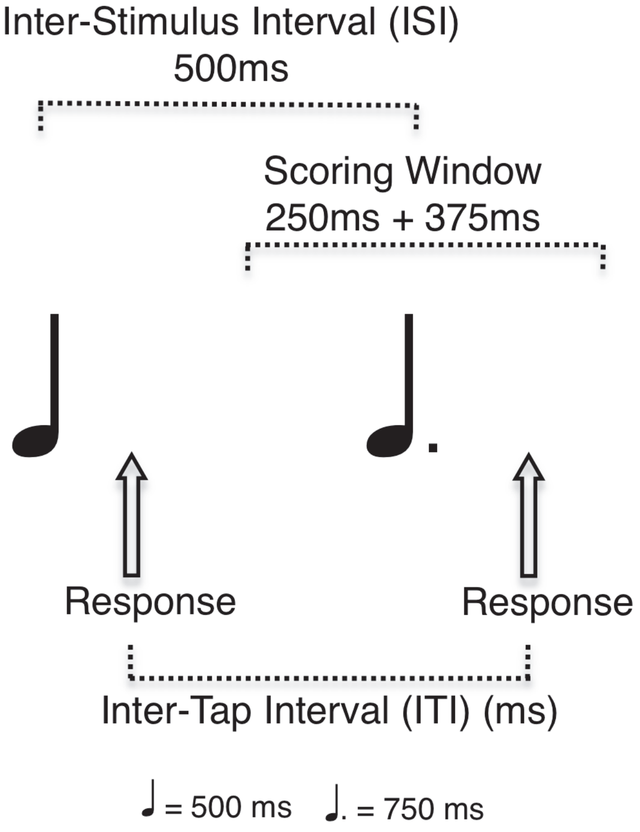


Figure 4.2. Illustration of the scoring method used to evaluate task performance. A response was scored correctly if the mouse tap was made within half of the onset-to-onset interval before and after a woodblock note. Asynchrony was measured as the difference between each woodblock note and the participant's response. ITI deviation was calculated as a ratio of the ITI and the ISI subtracted from 1. This figure was taken from Bailey and Penhune (2012).

4.3.5 Data Analysis

In order to replicate findings from Bailey and Penhune (2010; 2012) that age of onset of musical training, individual working memory scores and amount of formal training contribute to RST performance in this larger and unmatched sample, one-tailed Pearson correlation analyses were conducted between the variables: ASYN, ITI Deviation, Age of Onset, Working Memory and Formal Training.

To test for evidence of an age break point in the data the musicians were split using four different age of onset cut-off values. Early- and late-trained groups were defined as before or after ages 6, 7, 8 and 9 (ET ≤ 6, $n = 30$, LT > 6, $n = 47$; ET ≤ 7, $n = 38$, LT > 7, $n = 39$; ET ≤ 8, $n = 45$, LT > 8, $n = 32$; ET ≤ 9, $n = 50$, LT > 9, $n = 27$). Correlation analyses were conducted between Age of Onset and RST performance for each of the ET and LT groups. Correlation coefficients were compared in each condition by calculating a z-test statistic according to the method designed by Fisher and slopes were calculated using regression models and compared using t-test analyses. Subsequently, the Formal Training and Working Memory measures were correlated with task performance in the ET and LT group providing the strongest evidence for a sensitive period (before and after age 9). These analyses were conducted to investigate differences in task correlates as a function of age of onset of musical training.

4.4 Results

Correlation analyses revealed a significant relationship between ITI Deviation and both Working Memory and Formal Training (Table 4.2). Performance measures on the RST did not demonstrate a significant linear correlation with Age of Onset across all musicians (Table 4.2); however, Age of Onset and Formal Training were significantly correlated with each other ($r = -0.534$, $p < 0.001$).

Using four different break points in Age of Onset to split the musicians into ET and LT groups yielded results suggesting the presence of a non-linear relationship between Age of Onset of musical training and RST performance. All four break point conditions resulted in differential correlations between groups, with the ET group showing a positive correlation between age of onset and task performance (ASYN and ITI Deviation) and the LT group showing no correlation between Age of Onset and task performance. Of the four different conditions, when age 9 was used to divide the groups, the correlations between Age of Onset and task performance reached trend-level in the ET group (Fig. 4.3d) and provide the strongest evidence for a non-linear relationship between Age of Onset and task performance. However, the results from the Fisher transformation tests and slope comparison analyses suggest that the relationship between Age of Onset and task performance is most different when age 7 was used to divide the groups. The correlation results in each of the break point conditions are illustrated in Figure 4.3 and the results from the Fisher transformation tests and slope comparisons can be found in Tables 4.3 and 4.4.

To further investigate evidence for non-linear relationships in the data, task correlates were examined in each musician group, using age 9 ($ET \leq 9$, $LT > 9$) as the break point in the age of onset variable. A significant correlation between Formal Training and task performance (ITI Deviation) was observed for musicians who began training at age 9 or younger (Fig. 4.4 – $r = -0.345$, $p < 0.01$); however, this relationship was not significant among musicians who began training later (Fig. 4.4 – $r = -0.161$, $p > 0.05$). Working Memory correlated with task performance in both groups (Fig. 4.5). This change in task correlates between groups provides additional support for the presence of a sensitive period during development associated with musical training. Finally, Figure 4.6 illustrates the relationship between Formal Training and Working Memory as a function of age of onset of musical training.

Table 4.2. *Pearson correlation analyses of musical demographics, working memory scores and RST Performance*

RST Performance Measures	Age of Onset (Years)	Formal Training (Years)	Working Memory
Asynchrony (ASYN)	-0.001	-0.118	-0.396**
Inter-Tap Interval (ITI) Deviation	0.032	-0.224*	-0.464**

Note: A composite score for Working Memory was created from raw scores on the Digit Span and Letter-Number Sequencing cognitive subtests.
* p-values < 0.05
** p-values < 0.001

Table 4.3. *Comparison of Pearson correlation coefficients of task performance and age of onset between Early- and Late-Trained musicians in each age of onset break point condition*

Age of Onset Cut-off (Years)	Early-Trained (ET) Correlation Coefficient (ASYN / ITI)	Late-Trained (LT) Correlation Coefficient (ASYN / ITI)	Fisher's transformation z-value (ASYN / ITI)
ET ≤ 6 > LT	0.185 / 0.210	-0.106 / -0.060	1.2 / 1.12
ET ≤ 7 > LT	0.230 / 0.191	-0.063 / -0.060	1.25† / 1.07
ET ≤ 8 > LT	0.182 / 0.143	-0.052 / 0.091	0.98 / 0.22
ET ≤ 9 > LT	0.220 / 0.204	0.052 / -0.012	0.68 / 0.87

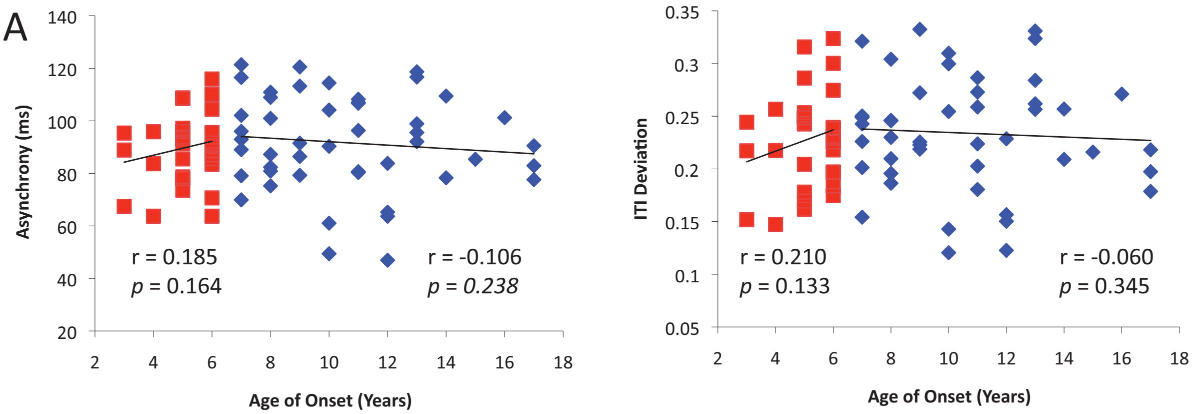
† p-values $= 0.1$

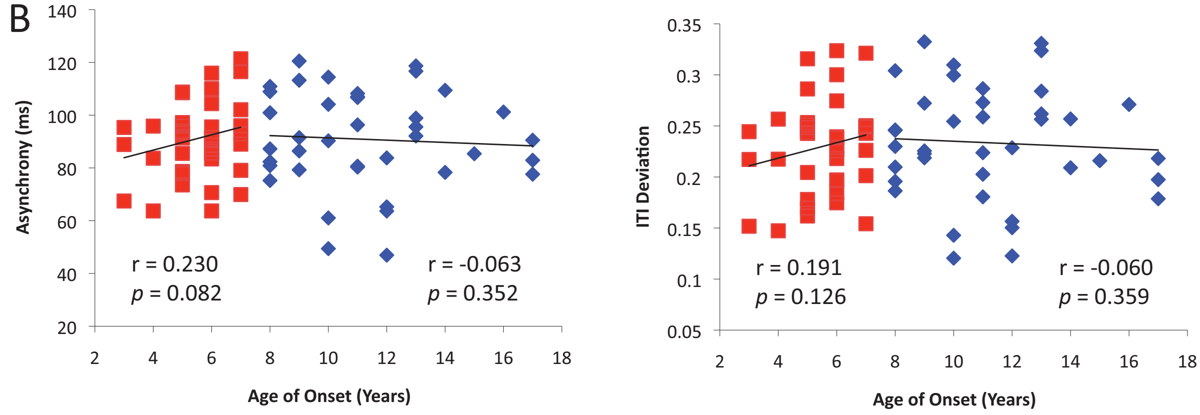
Table 4.4. *Comparison of slope values between Early- and Late-Trained musicians in each age of onset break point condition*

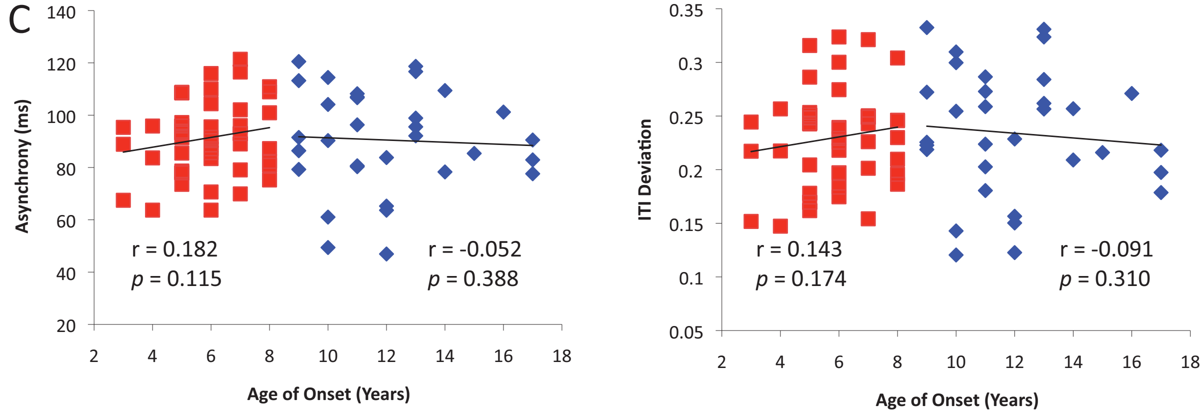
Age of Onset Cut-off (Years)	Early-Trained (ET) Slope (ASYN / ITI)	Late-Trained (LT) Slope (ASYN / ITI)	t-value (ASYN / ITI)
ET ≤ 6 > LT	2.653 (2.659) / 0.01 (0.009)	-0.659 (0.918) / -0.001 (0.003)	1.177 / 1.159
ET ≤ 7 > LT	2.893 (2.040) / 0.008 (0.006)	-0.432 (1.125) / -0.001 (0.003)	1.427* / 1.342*
ET ≤ 8 > LT	1.869 (1.537) / 0.005 (0.005)	-0.418 (1.454) / -0.002 (0.004)	1.089 / 1.093
ET ≤ 9 > LT	1.984 (1.269) / 0.006 (0.004)	0.455 (1.755) / 0.000 (0.005)	0.706 / 0.937

Note: Standard error values of unstandardized b coefficients (i.e., slope values) are in brackets

* p-values < 0.1


A
Asynchrony (ms)
140
120
100
80
60
40
20
2
4
6
8
10
12
14
16
18
Age of Onset (Years)
r = 0.185
p = 0.164
r = -0.106
p = *0.238*
ITI Deviation
0.35
0.3
0.25
0.2
0.15
0.1
0.05
Age of Onset (Years)
r = 0.210
p = 0.133
r = -0.060
p = 0.345


B
Asynchrony (ms)
140
120
100
80
60
40
20
2
4
6
8
10
12
14
16
18
Age of Onset (Years)
r = 0.230
p = 0.082
r = -0.063
p = 0.352
ITI Deviation
0.35
0.3
0.25
0.2
0.15
0.1
0.05
Age of Onset (Years)
r = 0.191
p = 0.126
r = -0.060
p = 0.359


C
Asynchrony (ms)
140
120
100
80
60
40
20
2
4
6
8
10
12
14
16
18
Age of Onset (Years)
r = 0.182
p = 0.115
r = -0.052
p = 0.388
ITI Deviation
0.35
0.3
0.25
0.2
0.15
0.1
0.05
Age of Onset (Years)
r = 0.143
p = 0.174
r = -0.091
p = 0.310

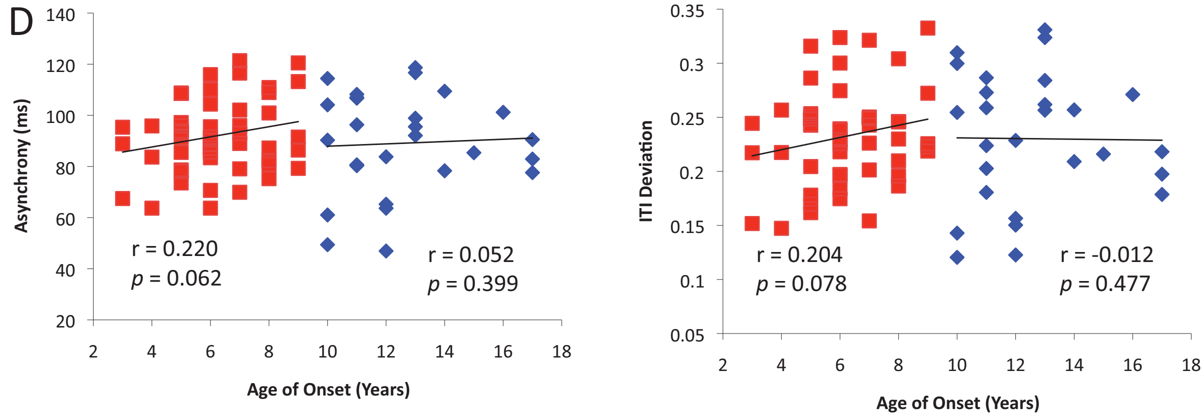

D
Asynchrony (ms)
140
120
100
80
60
40
20
2
4
6
8
10
12
14
16
18
Age of Onset (Years)
r = 0.220
p = 0.062
r = 0.052
p = 0.399
ITI Deviation
0.35
0.3
0.25
0.2
0.15
0.1
0.05
Age of Onset (Years)
r = 0.204
p = 0.078
r = -0.012
p = 0.477

Figure 4.3. Results from break point analyses using ages 6, 7, 8, and 9 as cut-off values. Within each group, correlations were calculated between age of onset and RST performance variables Asynchrony (ms) and Inter-tap Interval Deviation (ITI).

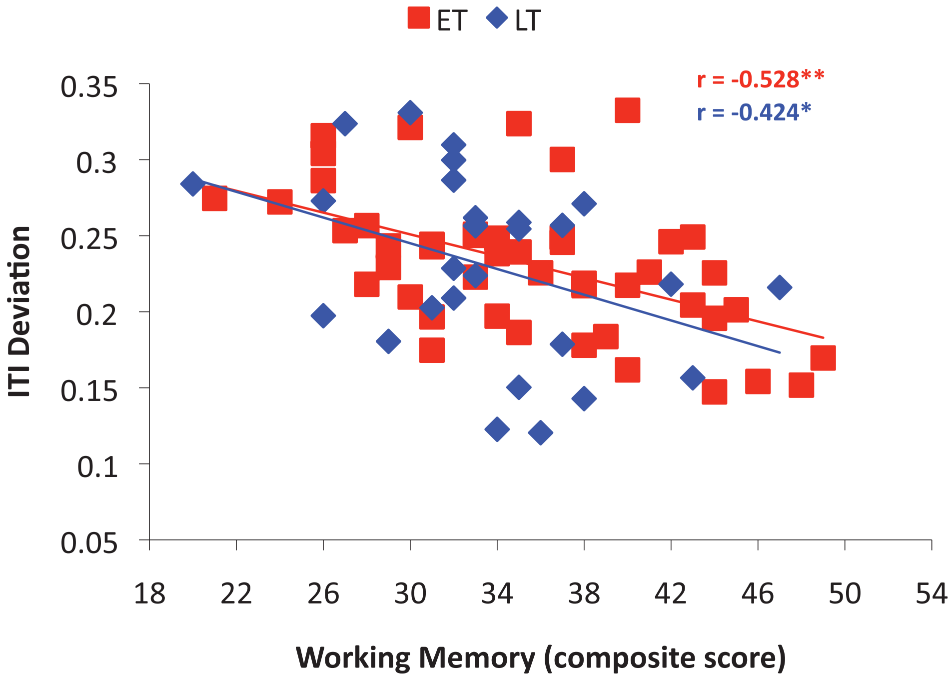


Figure 4.4. Correlations between RST performance (Inter-tap Interval Deviation) and Working Memory in Early-Trained (ET) and Late-Trained (LT) musicians using 9 years old as the age of onset cut-off value.

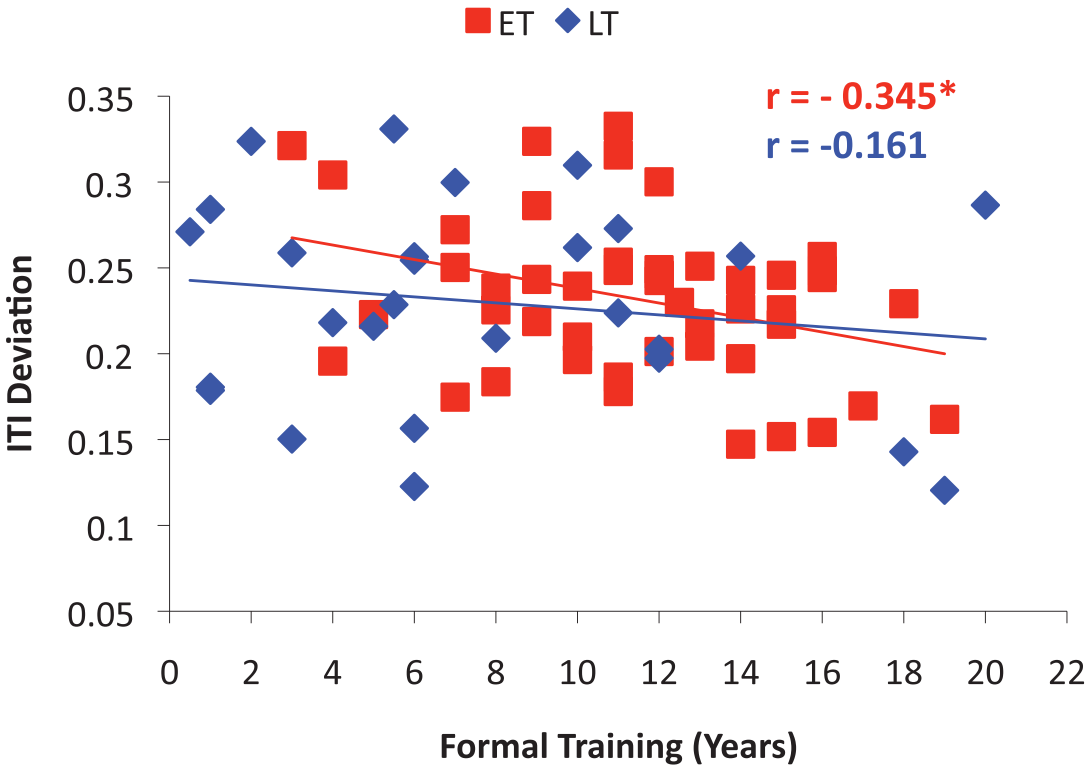


Figure 4.5. Correlations between RST performance (Inter-tap Interval Deviation) and Formal Training in Early-Trained (ET) and Late-Trained (LT) musicians using 9 years old as the age of onset cut-off value.

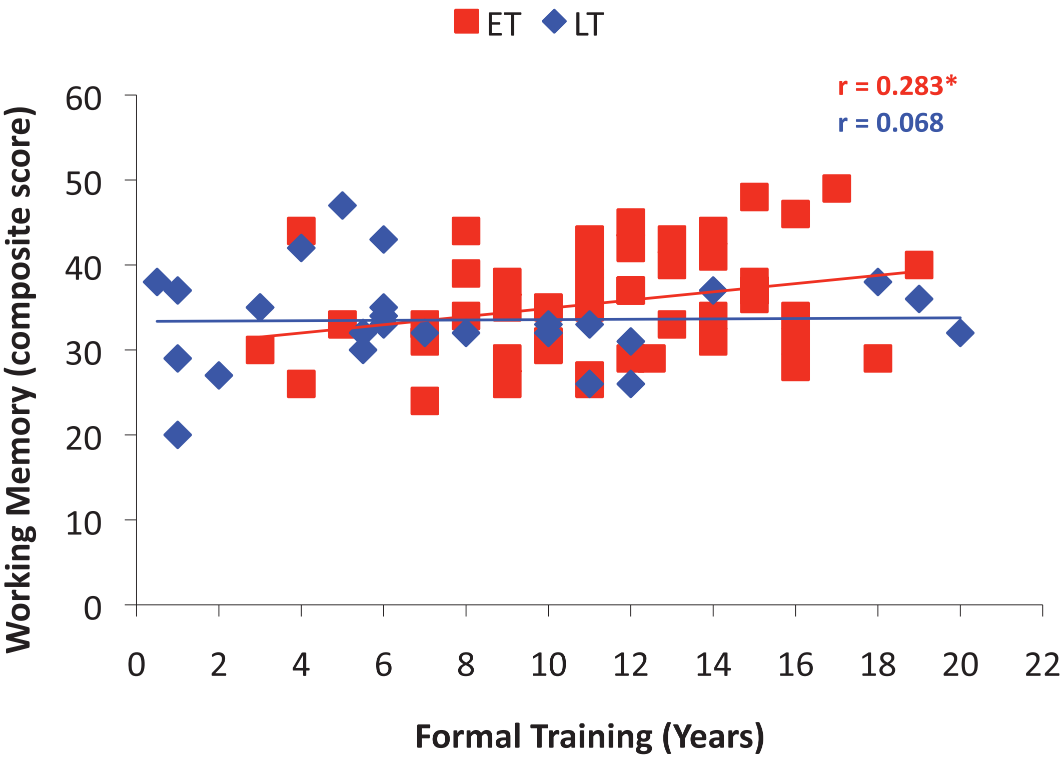


Figure 4.6. Correlations between Working Memory and Formal Training in Early-Trained (ET) and Late-Trained (LT) musicians using 9 years old as the age of onset cut-off value.

4.5 Discussion

The results from this study add to the growing body of evidence supporting a sensitive period for musical training. However, these findings highlight the complexity of the interactions between age of onset of musical training and other factors, such as type of training and individual differences in working memory. The simple correlation breakpoint analyses suggest that age of onset predicts rhythm synchronization performance if musicians begin training at or prior to age 9, but not afterward. In addition, examining task correlates using this age to split musicians into Early-Trained and Late-Trained groups revealed that performance on the RST, as assessed by ITI Deviation, correlated with years of formal training only in the Early-Trained group. Working memory scores correlated with ITI Deviation in both groups; however, this correlation was stronger among those who began their training prior to or at age 9. Overall, these results suggest that effects associated with age of onset or amount of formal training may vary across development and may plateau after a certain age. While these results are consistent with previous literature, they also introduce a new level of complexity into our understanding of sensitive period effects for musical training.

Previous studies from our laboratory have investigated a sensitive period for musical training by comparing groups of early and late-trained musicians (before and after age seven) who were matched for years of experience in an effort to isolate the effects of age of onset (Bailey & Penhune 2010; 2012; Steele, Bailey, Zatorre, & Penhune, 2013; Watanabe, Savion-Lemieux, & Penhune, 2007). In contrast, the current study was designed to determine the nature of the relationship between age of onset of training and auditory-motor rhythm synchronization abilities in large sample of musicians who began their training at a broad range of ages. The results from the simple correlations analyses support the hypothesis that the relationship between age of onset and task performance is not linear across development. These results are supported by previous research examining sensitive periods in the language and auditory domains (Flege, Yeni-Konshian, & Liu, 1999; Johnson & Newport, 1989; Harrison, Gordon, & Mount, 2005; Svirsky, Teoh, & Neuburger, 2004). Furthermore, a non-linear relationship between age of onset and auditory-motor synchronization mirrors the maturational trajectories of the brain regions that comprise the auditory-motor neural network (Gogtay, et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). These results are not contradictory to previous findings observed using the matching paradigm, but shed light on the nature of the relationship between age of onset of musical training and auditory-motor synchronization abilities across a group of musicians with a wider range of musical experience and training. The present findings suggest that age of onset of musical training affects auditory-motor synchronization abilities, if that training happens prior to a certain age but this effect stabilizes later in development.

The age at which this effect changes likely varies, depending on the task being considered. For example, a study examining performance on several speech perception measures among children who had received cochlear implants used binary partitioning analyses to examine the age of implantation that best divided performance on several tasks (Harrison, Gordon, & Mount, 2005). Importantly, the optimal age to split their groups varied between 4.4 and 8.4 years old, depending on the different measures of speech perception. The current study suggests that age 9 best splits musicians into early and late groups when considering performance on the RST; however, it would be likely that this age would vary depending on the task used and abilities under consideration. The optimal split age likely depends on environmental influences and maturational growth trajectories of the neural networks implicated in performing the chosen task.

A secondary, but related, finding from the current study is that Formal Training relates to RST performance only in early starters. This observation is compatible with previous findings using the matching paradigm. Although groups were matched in terms of the number of years of formal training, it may be that music lessons during the earlier years have a stronger influence on training auditory-motor synchronization skills implicated in the RST than music lessons during the later years. Given the strong correlation with age of onset of musical training ($r = -0.534$), it is not surprising that the Formal Training variable in the current sample is showing similar evidence for a non-linear effect on RST performance. Alternately, there are potential differences in the type of formal instruction received in early childhood compared to during the later years and this question warrants further exploration. Musical training programs beginning before children are able to read focus on learning by listening and reproducing music from a model. These skills may be particularly relevant for the auditory-motor synchronization task used here. Superior performance on the RST requires an ability to apply a metrical structure onto an auditory rhythm and then reproduce this rhythm. The question remains as to whether the observed difference in correlation between Formal Training and RST performance is due to differences in type of training paradigms, the cognitive ability to apply a metrical structure to a rhythm, the motor ability to reproduce it or a combination of these and other possibilities. Future studies are required to determine if this effect is due to the type of training received or the age at which this training was received.

Unlike the Formal Training variable in the current sample, working memory abilities are related to RST performance consistently across all musicians. This result has been previously observed (Bailey & Penhune, 2010; 2012) and is not significantly related to age of onset of musical training overall ($r = -0.116$, $p > 0.1$). It is clear that individual working memory abilities are implicated in task performance; however, the correlation between Working Memory and RST performance appears consistent across development, as evidenced by similar correlation values, regardless of when training began.

Overall, the current study provides additional evidence for the sensitive period hypothesis for musical training and offers a more complex view of the relationship between age of onset of musical training and auditory-motor synchronization abilities. These results suggest the presence of a non-linear relationship between age of onset of musical training and auditory-motor synchronization, such that age at which training begins is related to auditory-motor synchronization abilities in adults, if that training began prior to a certain age. This idea of a non-linear relationship is mirrored by growth trajectories of brains regions in the auditory-motor neural network and suggests that brain plasticity may plateau across development.

Chapter 5: General Discussion

The primary aim of the current thesis was to investigate evidence for a possible sensitive period for musical training. The first study compared early-trained and late-trained musicians in terms of their auditory-motor synchronization skills, as well as a group of non-musician controls. The two musician groups were matched in terms of years of formal training, years of playing experience and hours of current practice. The second study compared the same groups in terms of brain structure using structural neuroimaging grey matter analysis techniques to investigate regions of particular sensitivity to training during early childhood. The third study took a different approach to investigating evidence for a sensitive period by examining the predictive value of working memory and formal training for auditory-motor synchronization performance as a function of age of onset of musical training.

5.1 Review of Main Findings

The first study in this dissertation aimed to replicate previous behavioural and cognitive findings among early-trained and late-trained musicians from my MA thesis (Bailey & Penhune, 2010). Consistent with these previous findings, early-trained musicians were better able to reproduce the temporal structure of rhythms compared to the late-trained musicians, despite being matched for total years of musical experience. Both musician groups outperformed the non-musician control group. While no significant differences in cognitive measures between the early- and late-trained musicians were observed, there were differences observed between the late-trained musician and non-musician groups. The non-musician group demonstrated superior vocabulary skills, while the late-trained musicians demonstrated superior non-verbal reasoning skills although neither of these cognitive measures related to performance. In addition to age of onset of musical training, individual working memory scores and years of formal training were found to be significant predictors of performance on the auditory rhythm synchronization task. These findings support the hypothesis of a sensitive period for musical training and the role of working memory and formal training in task performance.

The second study compared the groups in terms of grey matter features by using three different VBM-style whole-brain analysis techniques as well as cortical surface-based morphometry measures. These analyses revealed a difference in local volume or shape in the early-trained musician group compared to the late-trained musician group in the right ventral pre-motor cortex, supported by greater cortical surface area among the early-trained musicians. Musicians performance on the rhythm synchronization task was correlated with extracted grey matter deformation values from pre-motor cortex, a region that has been previously been shown to be correlated with performance in fMRI studies using the same task (Chen, Penhune, & Zatorre, 2008). These findings suggest that musical training during early childhood may influence grey matter structure in the pre-motor cortex more so than training during later childhood and these changes are related to auditory-motor synchronization, adding additional support to the hypothesis of a sensitive period for musical training.

In previous studies we used a matching paradigm has been used to isolate age of onset of musical training as a variable of interest. In contrast, the third study examined a single large sample of musicians with a wider distribution of training. In this sample of musicians, age of onset appears to be a stronger predictor of auditory-motor synchronization skills the earlier musical training begins. In other words, age of onset may have a non-linear relationship with auditory-motor synchronization skills, such that after a certain age, the effect diminishes. Interestingly, individual working memory scores were equally predictive of task performance, regardless of when musical training began. However, formal training was only predictive of performance for those who began their lessons early in childhood. Overall, these results also support a sensitive period for musical training, such that the predictors of auditory-motor synchronization skills vary as a function of when musical training began. This final set of analyses suggests that the relationship between age of onset of musical training and adult auditory-motor synchronization skills may be more complex than previously thought.

5.2 Potential Mechanisms Underlying a Sensitive Period for Musical Training

Several different processes at the cellular level may be underlying the observed macroscopic changes in the adult brain associated with experience or training (for review see May, 2011 or Zatorre, Fields, & Johansen-Berg, 2012). For example, it has been proposed that changes in white matter structure may be due to axonal remodeling via fibre organization, changes related to myelin, or changes related to astrocytes. Grey matter changes have been attributed to dendritic branching or synaptogenesis, neurogenesis or changes related to glial cells. Axonal sprouting and angiogenesis may underlie both grey and white matter changes. In addition, activity-dependent processes such as synaptic pruning or neuron death may contribute to structural changes, reflecting cellular competition for resources (Stoneham, Sanders, Sanyal, & Dumas, 2010). It has been proposed that the initial proliferation of synapses early in postnatal development takes place independent of experience, but that experience-dependent neural activity is an important factor in determining which synapses are retained and which ones are eliminated in the development of an efficient and specialized system (Stoneham, et al., 2010). Exciting new evidence identifies glial cells and astrocytes as key players in this pruning process (Stephan, Barres, & Stevens, 2012). In the context of musical training, it might be that the repeated activation of the auditory-motor network, specifically the pre-motor cortex, through daily practice of a musical instrument may alter pruning processes in this region and result in cortical changes at a macroscopic level if this training begins at a specific time in development.

5.3 Integrating evidence from white matter and grey matter

In a companion experiment to the second study of this dissertation, we observed differences between early-trained and late-trained musicians in the posterior mid-body of the corpus callosum (Steele, Bailey, Zatorre & Penhune, 2013). Further analyses using tractography revealed that these voxels of difference contained fibres connecting the motor cortices of the two hemispheres. These results were interpreted to be related to bimanual coordination and the impact that early musical training may have on development of this ability. Based on these, one might expect to observe differences in grey matter in the primary motor cortex, yet results from the second study in the current thesis (Chapter 3) revealed differences located in the pre-motor cortex. The primary motor cortices are among the first cortical regions to mature (peak at or prior to age 5) and therefore may be less likely to be directly influenced by musical training (Gogtay et al., 2004), given that most early-trained musicians used in these studies began at age five or six. The present findings indicate that early musical training beginning at age five or six has more of an impact on pre-motor cortex than on primary motor cortex, likely due to its more protracted development (peak at approximately age 8.5; Gogtay, et al., 2004). The corpus callosum and the fibres connecting the primary motor cortices, on the other hand, are undergoing a significant amount of maturational change around age five or six, making it a strong candidate to demonstrate training-induced effects associated with playing a musical instrument (Thompson, et al., 2000; Westerhausen, et al., 2011). Furthermore, the group difference was observed using DBM, which is sensitive to changes in shape or volume. Given the maturational timeline of the primary motor cortical areas, it seems unlikely that musical training at age five or six alters any of the maturational processes that determine shape or volume; however, this may be more likely for pre-motor cortical areas. The observed finding that early musical training impacts structural development in the pre-motor cortex may be related to the integral role of this region in auditory-motor integration and execution of timed motor movements. Perhaps, to invoke maximum training-induced effects in grey matter structure, training must begin prior to or in conjunction with pruning processes in any cortical area. If this is the case, then observing training-induced changes in shape or volume associated with training that began at ages five or six in the pre-motor cortex and not the primary motor cortex makes sense.

5.4 Additional Contributing Factors

It is important to consider potential pre-existing differences between early- and late-trained musicians that may be contribute to the observed findings in addition to the age at which they began their musical training. For example, genetic factors are important determinants of cortical development (Chiang, et al., 2009; Gogtay & Thompson, 2010; Thompson, et al., 2001) and these may influence when a child has the requisite skills to start musical lessons such as fine-motor coordination, attention span, visual tracking abilities, auditory perception as well as other executive functions or cognitive abilities. The observed findings are likely driven by an interaction between pre-determined differences (e.g., genetics) and environmental influences (e.g., age of start of musical training). Interestingly, the domain of epigenetics is a growing area of research investigating environmental influences on gene regulation or expression, reiterating the idea that the debate of nature versus nurture has shifted to investigating the mechanisms underlying their interaction (Meaney, 2010; Szyf, 2009).

5.5 Future Directions

The findings from the current dissertation support the idea of a sensitive period for musical training; however, there are several outstanding questions that could be addressed with a longitudinal study in children, including a former early-trained adult musician group that are no longer practicing musicians and more stringent quantification of musical experience within the field of music research. A longitudinal study comparing groups of age-matched controls and children beginning music lessons at age six and older would provide the opportunity to monitor any training effects on brain structure during that potential sensitive period. Using adults provides essential information about long-lasting changes in brain structure associated with musical training and using children would provide the opportunity to observe training-induced changes as the groundwork for these changes is laid out. Hyde and colleagues observed training-induced differences in the auditory-motor network among children taking music lessons after 15 months (2009). A longitudinal study designed to compare training-induced changes in children who begin earlier with those who begin later is an important next step. The combination of DBM, traditional VBM, surface-based measures and FA is a comprehensive package of analyses likely to capture and characterize longitudinal changes in brain structure. Having age-matched control groups (i.e., non-musicians) for each age group would provide group differences in brain structure volume or shape at different ages associated with musical training. To examine the sensitive period directly, one could compare changes in DBM measures associated with musical training between those who begin earlier with those who begin later. For example, perhaps a larger increase in the right ventral pre-motor cortex volume will be observed in the group who begins at age five compared to the increase observed in the group that begins training at age ten. Based on the theory of a sensitive period, one would expect greater deviations from the age-matched controls during a certain window of development and this would illustrate a sensitive period for musical training. In addition, the finding from study three that formal training predicted auditory-motor synchronization skills more so for those who began training at a young age warrants further investigation. Is this additional evidence that formal lessons leave a stronger imprint during early years and therefore applying rules of metrical structure becomes more efficiently executed? Or is it due to differences in the quality of formal training that these two age groups received? This could be controlled for by testing groups of children of different ages following the same musical training program such as the Suziki program or the Royal Conservatory program. Lastly, cognitive scores could be monitored to determine whether music lessons have training effects on working memory, given our findings from the third study (Chapter 4) that music lessons in early childhood correlate with individual adult working memory scores and that previous studies have suggested training-induced effects on working memory abilities and associated brain structure (Takeuchi, et al., 2010). Previous studies have also observed a correlational relationship between amount of musical training and working memory (Schellenberg, 2006). In addition, adult and child musicians have shown enhanced working memory scores compared to their non-musician counterparts (Schellenberg, 2011; Parbery-Clark, Skoe, Lam, & Kraus, 2009). Whether music lessons train working memory and, if so, whether the sensitive period hypothesis is relevant to the development of working memory are important questions to address in future studies.

A simple study with adults could assess the contributions of continued practice to the observed differences between early-trained and late-trained musicians by including a group of adult musicians who began their training at an early age, continued through their childhood years but then stopped and are no longer practicing at the time of testing. Comparing them to our currently practicing musician groups would provide valuable information about the permanency of the influence training during a putative sensitive period has on behaviour and the brain. If the current findings are due to the timing of the experience, then perhaps one may expect to find that the former early-trained musicians fall between the practicing early-trained and late-trained musicians. However, if continued practice is required for these differences to manifest or be maintained, then perhaps one may expect the former early-trained musicians to fall between the late-trained musicians and the non-musicians.

Finally, like any area of research, the tools used to measure musical experience are evolving and warrant more standardization within the literature. Even over the course of my graduate work, the Musical Experience Questionnaire (MEQ), originally designed by Watanabe and colleagues, has been modified, is being used by other laboratories working with musicians in Montreal and is now available online. Certain details such as measuring musical experience in years or practice hours warrant standardization within the literature, as they have both been used to quantify musical experience or training. An individual who accrues most of their practice hours in their adulthood is different from an individual who accrued most of their practice time during early childhood, yet their hours of practice could be similar. Using years to quantify experience is not particularly accurate either, given that children will often take some summer months off from music lessons or may take lessons for only one part of the school year. Ideally, a combination of practice hours and years is recommended or practice hours on a weekly or monthly basis. Furthermore, differentiating between musical experience and training is also an important area within the field of music research as musicians who are self-taught may have a significant amount of playing experience but little formal training. This is especially important when comparing early-trained and late-trained musicians, as those that are early-trained likely all began with lessons and formal training; however, those who began in their adolescent years may have initially taught themselves and then began formal musical training. These two types of music profiles not only differ in type of musical background but also likely differ in terms of their motivation when they first began their training. Motivation is an area that remains largely unexplored within the music neuroscience literature, yet likely also has a significant role in training-induced brain plasticity for musicians, as it is a driving force for behaviour change and related brain plasticity. One could imagine that motivational sources for early-trained musicians are factors such as parental approval or teacher praise, whereas late-trained musicians may be motivated by factors such as peer approval or increased self-esteem. Whether a child is practicing on a daily basis because they are told to or because it is their choice likely alters any training-induced effects on behaviours, cognitive abilities, or brain structure that music lessons offer. Recent research has demonstrated that music can be rewarding on a neurological level (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011); however, it has yet to be tested whether children and adults alike find this to be true. More research on motivating factors for children pursuing music lessons is required to understand how that may impact the sensitive period hypothesis.

5.6 Conclusion

The current dissertation investigated evidence for a sensitive period for musical training using early-trained and late-trained adult musicians. This hypothesis was supported by enhanced performance on an auditory-motor synchronization task among early-trained musicians, even after controlling for years of musical experience, years of formal training, and hours of practice. Importantly, there were no group differences in cognitive abilities. Neuroimaging analyses revealed differences in grey matter morphometry in the right ventral pre-motor cortex between early- and late-trained adult musicians, in a region that has been associated with auditory-motor synchronization task performance. Lastly, correlates of auditory-motor synchronization task performance vary as a function of age of onset of musical training in a sample of unmatched musicians, adding further support to the idea of a sensitive period for musical training. These findings likely emerge due to the interactive nature of brain maturation processes and experience-dependent plasticity. This series of studies adds complexity to the idea of a sensitive period for musical training by taking into consideration individual working memory abilities and years of formal training. In addition, the final study in the current dissertation presents the idea that the relationship between age of onset and auditory-motor synchronization abilities may mimic the non-linear curve of brain maturation trajectories across development (Gogtay et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008).

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Appendix A

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RESEARCH ARTICLE

Rhythm synchronization performance and auditory working memory in early- and late-trained musicians

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Abstract Behavioural and neuroimaging studies provide evidence for a possible "sensitive" period in childhood development during which musical training results in long-lasting changes in brain structure and auditory and motor performance. Previous work from our laboratory has shown that adult musicians who begin training before the age of 7 (early-trained; ET) perform better on a visuomotor task than those who begin after the age of 7 (late-trained; LT), even when matched on total years of musical training and experience. Two questions were raised regarding the findings from this experiment. First, would this group performance difference be observed using a more familiar, musically relevant task such as auditory rhythms? Second, would cognitive abilities mediate this difference in task performance? To address these questions, ET and LT musicians, matched on years of musical training, hours of current practice and experience, were tested on an auditory rhythm synchronization task. The task consisted of six woodblock rhythms of varying levels of metrical complexity. In addition, participants were tested on cognitive subtests measuring vocabulary, working memory and pattern recognition. The two groups of musicians differed in their performance of the rhythm task, such that the ET musicians were better at reproducing the temporal structure of the rhythms. There were no group differences on the cognitive measures. Interestingly, across both groups, individual task performance correlated with auditory working memory abilities and years of formal training. These results support the idea of a sensitive period during the early years of childhood for developing sensorimotor synchronization abilities via musical training.

Keywords Sensitive period · Early-trained · Late-trained · Sensorimotor · Musicians · Rhythm synchronization · Working memory · Cognitive abilities

Introduction

Many professional musicians have been training since a very young age. As a result, there is a common assumption that superior musical performance is associated with early training. However, is this because starting at a young age allows for more years of training? Or, is there something specific about being exposed to this type of experience during an early, sensitive period of development? Behavioural evidence in support of a sensitive period for musical training comes from a phenomenon known as "absolute" or "perfect pitch". Individuals with "perfect pitch" are able to identify a note in the absence of a standard, and the development of this ability is strongly associated with experience during early childhood (Takeuchi and Hulse 1993; Trainor 2005; Zatorre 2003). Neuroanatomical differences between early- and late-trained musicians have also been observed, supporting the idea of a sensitive period (Amunts et al. 1997; Pantev et al. 1998; Schlaug et al. 1995). However, these studies did not control for differences between early- and late-trained groups in terms of years of musical experience, which may have contributed to the observed differences in neuroanatomical structure. In a recent study from our laboratory, Watanabe et al. (2007) observed increased sensorimotor synchronization abilities in early-trained musicians compared to late-trained

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musicians, even after matching the two groups on years of musical experience. The present study further investigates the idea of a sensitive period for sensorimotor abilities.

The concept of a sensitive period must be defined in relation to the narrower concept of a “critical” period. A critical period differs from a sensitive period in that during this restricted window of time, sensory input is required for normal functioning to develop. The effects that follow deprivation of sensory input during a critical period cannot be reversed by sensory exposure at a later time (Innocenti 2007). For example, there are critical periods very early during development of the visual system when stimulation or experience is necessary to develop normal binocular vision (Hooks and Chen 2007; Wiesel and Hubel 1965). What is being proposed in this paper in terms of the development of musical abilities is not a critical period, but a sensitive period. A sensitive period is a window of time during which experience is particularly influential on development of functioning (Knudsen 2004). Evidence suggests that the mechanisms involved in sensitive periods are highly influenced by experience in addition to biological determinants (Hooks and Chen 2007; Tomblin et al. 2007).

A large portion of the evidence for sensitive periods in human development comes from the study of speech and language development, as well as second-language acquisition. The idea of a sensitive period for language development was initially inspired by two main observations. Case studies showed that children who had been deprived of exposure to language in early childhood failed to fully develop language abilities even after being exposed later in life (Curtiss 1977) and evidence showed that children who underwent surgical removal of the left hemisphere were able to develop normal language abilities as long as surgery occurred early in childhood. Lenneberg (1967) suggested that the effects associated with deprivation of speech can be overcome if stimulation is restored early enough during development. As a result, he proposed the idea of a “sensitive” period for language development. This idea has been applied to second-language acquisition, and evidence suggests that exposure to a second language in early childhood is associated with greater levels of adult proficiency than exposure later in life (Weber-Fox and Neville 2001). Further support for the existence of sensitive periods in development has come from work with congenitally deaf children who receive cochlear implants. Several large-scale studies have shown that children who receive implants before the age of 3–4 show better auditory and speech perception than later recipients (Kral et al. 2001; Sharma et al. 2007; Svirsky et al. 2004). This is consistent with the developmental changes in the anatomy of the auditory system that have been linked to different stages of speech and language development (Moore and Linthicum 2007).

Additional support for the existence of sensitive periods in development comes from studies of trained musicians. While studies have examined the influence of musical training on brain development during childhood (Hyde et al. 2009; Shahin et al. 2004), some of the strongest evidence for a sensitive period comes from the study of “absolute” or “perfect” pitch in adults. This ability has been strongly associated with musical training during the early years of childhood (Takeuchi and Hulse 1993; Trainor 2005; Zatorre 2003). Further evidence comes from studies showing a relationship between musical training and changes in brain structure (e.g. Bangert and Schlaug 2006; Bermudez and Zatorre 2005; Gaab and Schlaug 2003; Gaser and Schlaug 2003; Hutchinson et al. 2003; Schlaug et al. 1995, 2005). Among the literature demonstrating this relationship, three studies in particular support the idea of a sensitive period. Schlaug et al. (1995) observed volumetric differences in the anterior corpus callosum between early- and late-trained musicians. Pantev et al. (1998) observed increased auditory and motor cortical representations among musicians compared to non-musicians and reported that these increases were correlated with age at which musical training began. Finally, Amunts et al. (1997) reported changes in the morphology of the motor cortex in musicians related to training of the non-dominant hand. More importantly, they showed that these changes were related to the age of commencement of training. Overall, the evidence suggesting that musical experience influences structural development of the auditory and motor systems is convincing. Given that there is a maturational timeline for neuroanatomical development of both auditory and motor systems and that musical experience is associated with structural differences, there may be a window of time in early childhood development during which the influence of musical training on aspects of structural development of sensorimotor networks is strongest.

Taken together, these findings suggest that there may be a sensitive period for musical training, similar to that observed for language acquisition. However, none of these studies were designed to directly address the impact of early versus late training, and thus did not control for differences between early- and late-trained musicians in the total number of years of musical training and experience. By definition, a musician who begins training early has more years of experience than one who begins later when both are the same age. Therefore, it is possible that the observed differences in performance and brain structure could simply be accounted for by the group difference in duration of musical training. A previous experiment in our laboratory examined possible behavioural differences in early- and late-trained musicians who were matched for years of musical training and experience. Watanabe et al. (2007) observed sensorimotor performance differences between the two groups of adult musicians using a visually presented sequence. Participants were asked to synchronize their mouse button presses with a temporally complex sequence presented on a computer monitor. The early-trained group performed significantly better than the late-trained group in terms of response synchronization, supporting the idea that musical training during a sensitive period in early childhood results in superior sensorimotor synchronization abilities. The observed group difference persisted across 5 days, suggesting that this superior synchronization ability remains even after individual performances plateau. While this experiment provides evidence that early training can affect adult motor performance, the visuomotor sequencing task used is unlike the integration abilities required in a typical musical performance. Therefore, it is possible that early-trained musicians might only outperform late-trained musicians on this relatively unusual and difficult task. To address this question, the present experiment aimed to replicate these findings using a more musically relevant auditory rhythm synchronization task.

A second question that could be raised about our previous findings (Watanabe et al. 2007) is whether the performance difference observed between groups was mediated by enhanced overall cognitive functioning in the early-trained group. Correlational studies have demonstrated positive associations between music lessons in school-aged children and cognitive abilities such as verbal memory, non-verbal reasoning, spatial–temporal reasoning, reading, spelling, speech recognition and mathematics (e.g. Anvari et al. 2002; Forgeard et al. 2008; Jentschke and Koelsch 2009; Moreno et al. 2009; Saffran 2003; Schellenberg 2001, 2004, 2006; Schlaug et al. 2005). More specifically, Schellenberg (2004, 2006) showed a positive association between duration of music lessons in school-aged children and Intelligence Quotient (IQ) scores, while controlling for socio-economic status and effects associated with participation in a non-musical activity. Although the musicians in our previous study had been matched for years of musical training and other practice variables, it is possible that they also differed in cognitive function. Therefore, a secondary goal of the present study was to investigate whether early- and late-trained musicians differ in terms of specific cognitive abilities. Within a group of undergraduate students, above and beyond the relationship with overall IQ scores, the specific cognitive measures that were most commonly associated with musical training were working memory and non-verbal reasoning (Schellenberg 2006). Based on these findings, musicians in the current study were asked to complete a non-verbal reasoning task and two auditory working memory tasks. In addition, a vocabulary test was included as a measure of crystallized knowledge.

The main goal of this experiment was to replicate and extend the findings observed by Watanabe et al. (2007) that support the idea of a sensitive period for sensorimotor integration abilities to the more familiar and more musically relevant auditory domain. A secondary goal was to investigate whether these two groups of equally trained musicians would differ in terms of their overall cognitive abilities, given that their musical training took place during different developmental windows.

Method

Participants

Twenty-four currently practicing, neurologically healthy musicians between the ages of 18 and 34 ($M = 26.4$ years old, SD = 4.4) participated in this study. Participants were screened for significant head injuries, history of neurological disease or medication that could affect task performance by completing a Medical Screening Information form. The musical training and experience of each participant was determined through a Musical Experience Questionnaire (MEQ) that was developed within our laboratory. The MEQ quantifies the amount of instrumental, vocal or dance training an individual has received in their lifetime, at what age this training occurred and the amount of time currently dedicated to practicing music on a weekly basis. All musicians had extensive musical experience ($M = 17.5$ years; SD = 4.4), as evaluated by the MEQ. The sample was selected to form two groups of musicians: early-trained (ET; $n = 12$) and late-trained (LT; $n = 12$). Those who began their musical experience prior to or at the age of 7 were placed in the ET group, and those who began after the age of 7 were considered LT. The age of seven was chosen based on the previous study conducted by Schlaug et al. (1995). The two groups were individually matched on years of musical experience, years of formal training and hours of current practice, as determined by the MEQ. All participants gave informed consent, and the Concordia University Research Ethics Committee had approved the protocol.

Stimuli

Due to the high degree of musical training obtained by our participants, the 6 woodblock test rhythms were selected to cover a range of complexity. Essens and Povel (1985) and Essens (1995) developed a model by which musical rhythms can be classified into levels of difficulty based on their metrical structure. Each test rhythm consisted of 11 woodblock notes and had a total duration of 6 s. These rhythms differed in their temporal structure, such that the intervals between musical notes varied, but not the length of notes themselves. In musical terminology, each rhythm consisted of five-eighth notes (each 250 ms), three quarter notes (each 500 ms), one dotted quarter note (750 ms), one half note (1,000 ms) and one dotted half note (1,500 ms). Manipulation of the temporal structure of the notes resulted in progressively more complex and less metrically structured rhythms. Three levels of metrical complexity were chosen, and participants were exposed to two rhythms at each level: metrically simple (MS), metrically complex (MC) and non-metrical (NM). An auditory stimulus delivery program was used to counterbalance the rhythms. These rhythms were played through a pair of earphones, and participants used a computer mouse to tap out the rhythms. A similar auditory rhythm paradigm was previously used for an fMRI study conducted by Chen et al. (2008) examining the network of activation during auditory–motor synchronization.

In addition to the rhythmic stimuli, the experimental protocol included two subtests from the Wechsler Adult Intelligence Scale—III (WAIS; Wechsler 1997), Digit-Span (DS) and Letter-Number Sequencing (LN), as well as two subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999), Vocabulary (VC) and Matrix Reasoning (MR). The DS requires individuals to recall strings of numbers, and the LN requires individuals to recall and mentally manipulate strings of letters and numbers. Both of these subtests tap into working memory abilities. The VC assesses an individual's ability to orally define words, and the MR assesses non-verbal reasoning and visual pattern recognition abilities. Both VC and MR are strongly correlated with global IQ and can also be considered as measures of crystallized and fluid intelligence, respectively.

Procedure

Participants alternated between listening and tapping along while each rhythm played twice in row (Fig. 1). Participants were instructed to use their right index finger and the

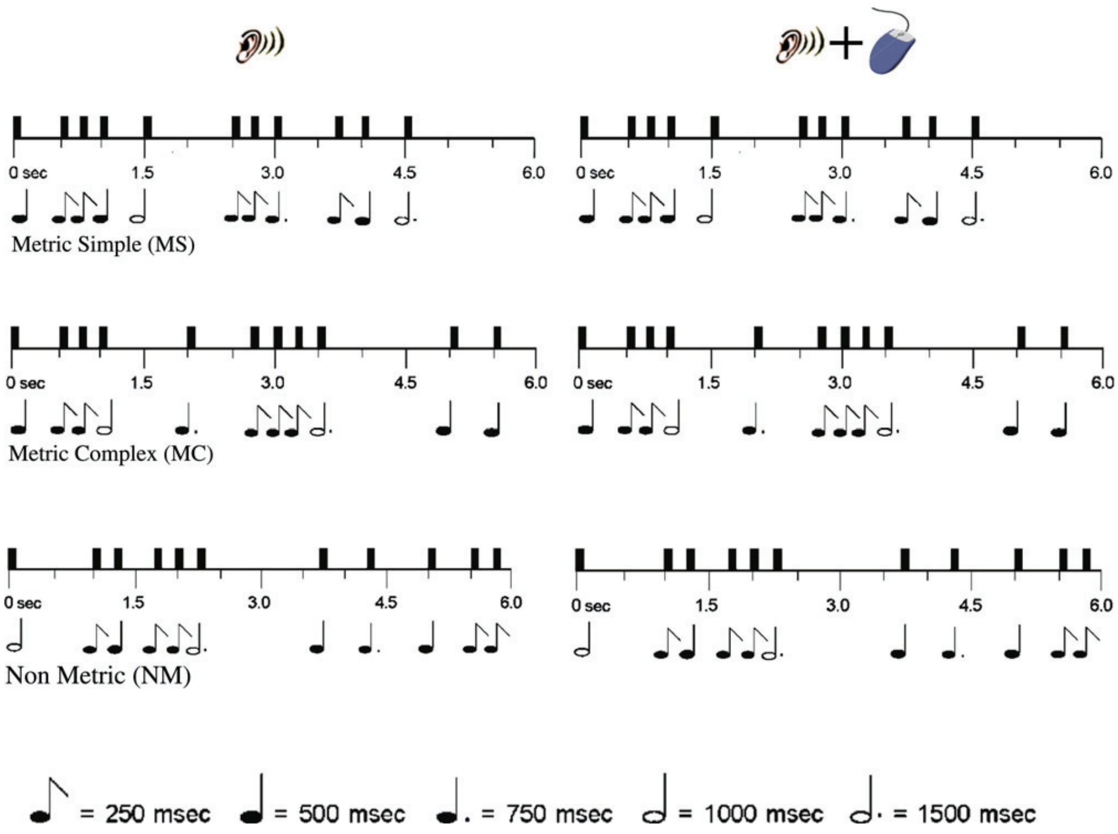

Fig. 1 Illustration of the rhythm task. Participants were exposed to six rhythms presented in random order for approximately two 12-min blocks. Two different rhythms of each rhythmic complexity were used (i.e., 2 MS rhythms, 2 MC rhythms, and 2 NM rhythms). Each trial consisted of a listening component followed by a listening and tapping component

left button of the computer mouse to tap along with the rhythm as it played during the tapping repetition. Two very basic practice rhythms were administered to familiarize participants with the task. A block consisted of the six rhythms repeatedly presented in a counterbalanced fashion for 12 min. Each rhythm was performed 6 times in each block. Once participants had completed the first block of the task, they were asked to perform the DS. Participants then performed a second block of the rhythm synchronization task, followed by the VC, the LN and finally, the MR.

Measures

Musical information was quantified for each participant in terms of years of experience, years of formal training and hours of current weekly practice. Individual cognitive abilities were measured using the four chosen cognitive subtests (DS, LN, VC and MR). Results were scored according to standard procedure; however, raw scores were used for each cognitive measure in order to provide a measure of ability regardless of participant age and because of increased variance. Performance on the rhythm synchronization task was measured using three dependent variables: percent correct (PC), asynchrony (ASYN) and inter-tap interval (ITI) deviation. A tap was considered correct if it was made within half of the onset-to-onset interval before or after a woodblock note (Fig. 2). The ASYN measure was defined as the absolute value of temporal difference between the onset of each woodblock note and the associated mouse key press. The ITI deviation measure indicated the extent of deviation from the actual interval between each pair of woodblock notes. It was calculated by dividing the interval between each pair of the participant's taps by the interval between each corresponding pair of woodblock notes in the rhythms. This measure is indicative of how well participants are reproducing the temporal structure of the rhythms.

Data analysis

To compare rhythm synchronization across groups, a repeated-measures analysis of variance (ANOVA) for each of the dependent variables was conducted, with group as the between-subjects factor and rhythm type as the within-subjects factor. Significant differences across rhythm types for the two groups were analysed using simple Bonferroni correction for multiple comparisons. Group differences in musical experience, years of formal training, hours of current practice and cognitive measures were assessed using *t*-test analyses. The relationships among musical demographics, cognitive measures, age and task performance were examined using Pearson and partial correlation analyses. Raw scores on the cognitive subtests were used in order to examine cognitive abilities, regardless of age.

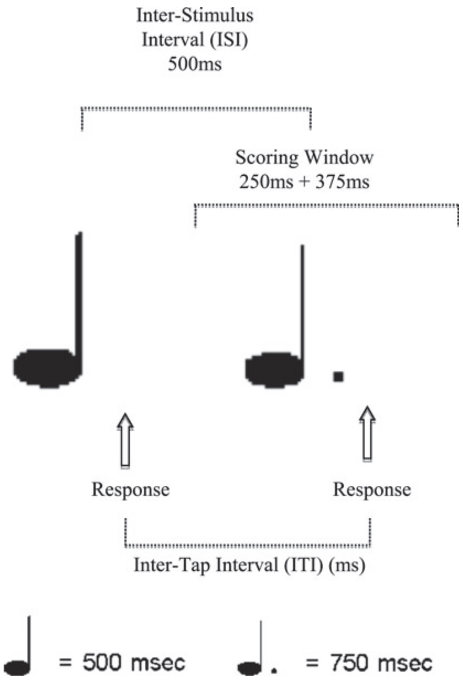

Fig. 2 Illustration of the scoring method used to evaluate rhythm task performance. A response was scored correctly if the mouse tap was made within half of the onset-to-onset interval before and after a woodblock note. Asynchrony was measured as the difference between each woodblock note and the participant's response. ITI deviation was calculated as a ratio of the ITI and the ISI

Follow-up analysis

A hierarchical regression analysis was conducted in order to assess whether group explains a significant amount of variance in task performance, above and beyond that explained by working memory abilities. A model was created with total inter-tap interval (ITI) deviation across rhythms as the dependent measure and both group and working memory as predictors. A composite score for each participant's working memory abilities was created using their Letter-Number Sequencing (LN) and Digit-Span (DS) scores and was used as the working memory predictor variable in the regression model. In step 1 of the model, the working memory composite score was entered as the sole predictor of task performance. In step 2, group was added as a second predictor to determine whether any additional variance was explained by the age of training onset, above and beyond the variance accounted for by working memory abilities.

Results

Group comparisons of matching variables

Comparison of the ET and LT musicians confirmed that the two groups were well matched in terms of years of musical experience, formal training and hours of current practice (Table 1). Another set of analyses comparing the two groups on their cognitive subtest performance scores demonstrated that the two groups did not differ in their cognitive abilities, as assessed by the VC, MR, DS and LN (Table 2). Raw scores are reported; however, it should be made explicit that no group differences were found when using scaled scores either (VC: $t = 0.377$, $P = 0.710$; MR: $t = -0.643$, $P = 0.527$; DS: $t = 0.725$, $P = 0.476$; LN: $t = 1.522$, $P = 0.142$). As expected, the two groups differed in terms of age of onset ($P < 0.01$).

Behavioural measures

Analysis comparing accuracy (PC) of the rhythm reproduction between the two groups showed a significant main effect of rhythm type (F (2, 21) = 19.5, $P < 0.001$), with no main effect of group (Fig. 3). Pair-wise comparisons revealed that performance decreased as metrical complexity increased (simple > complex > non-metrical), such that accuracy on the MS rhythms was higher than the MC and NM rhythms ($P = 0.026$ and $P < 0.01$, respectively), and accuracy on the MC rhythms was higher than the NM rhythms ($P < 0.01$). These results confirm our manipulation of metricality, such that regardless of group, accuracy decreased as the metrical complexity of the rhythms increased.

Analysis comparing the reproduction of the temporal structure of the rhythms measured by inter-tap interval (ITI) deviation between the two groups showed a significant main effect of group (F (1, 22) = 6.0, $P < 0.05$) such that the ET group was better able to reproduce the temporal intervals of the rhythms than the LT group (Fig. 3). A main effect of rhythm type was observed as well (F (2, 21) = 43.6, $P < 0.001$), indicating that, regardless of group, the ITI deviation on the MS rhythms was lower than the MC and NM rhythms ($P < 0.01$ for both), and ITI deviation on the MC rhythms was lower than the NM rhythms ($P < 0.01$).

A similar pattern of results was revealed on the synchronization measure (ASYN). There was no main effect of group, but a significant main effect of rhythm type (F (2, 21) = 71.6, $P < 0.001$). Pair-wise comparisons revealed that ASYN on the MS rhythms was lower than ASYN on the MC and NM rhythms (both comparisons $P < 0.01$), and ASYN on the MC rhythms was lower than on the NM rhythms ($P < 0.01$) (Fig. 3).

Correlations

In order to examine the relationship between task performance and cognitive variables, raw scores for PC, ASYN and ITI were correlated with raw scores for VC, MR, DS and LN (Table 3). No significant correlations were found between the behavioural measures and VC or MR scores. However, LN scores were found to be significantly correlated with PC,

Table 1 Group demographics of musical variables

Group	Age	Age of onset	Years of musical experience	Years of formal training	Hours of current weekly practice
Early-trained	25.0 (±3.8)	5.92 (±1.0)	18.67 (±4.5)	10.00 (±4.2)	19.50 (±10.9)
Late-trained	27.8 (±4.7)	10.67 (±3.0)	16.42 (±4.3)	7.33 (±4.2)	23.75 (±16.3)
t-values	−1.62	−5.17**	1.26	1.54	−0.75

Standard deviation values are in brackets

** $P < 0.01$

Table 2 Group cognitive subtest raw scores

Group	Vocabulary (VC)	Matrix reasoning (MR)	Digit span (DS)	Letter-number sequencing (LN)
Early-trained	63.6 (±5.7)	29.8 (±4.3)	22.3 (±4.8)	13.3 (±2.4)
Late-trained	63.3 (±7.0)	29.8 (±2.6)	19.8 (±4.2)	11.6 (±2.7)
t-values	0.128	−0.057	1.36	1.61

Standard deviation values are in brackets

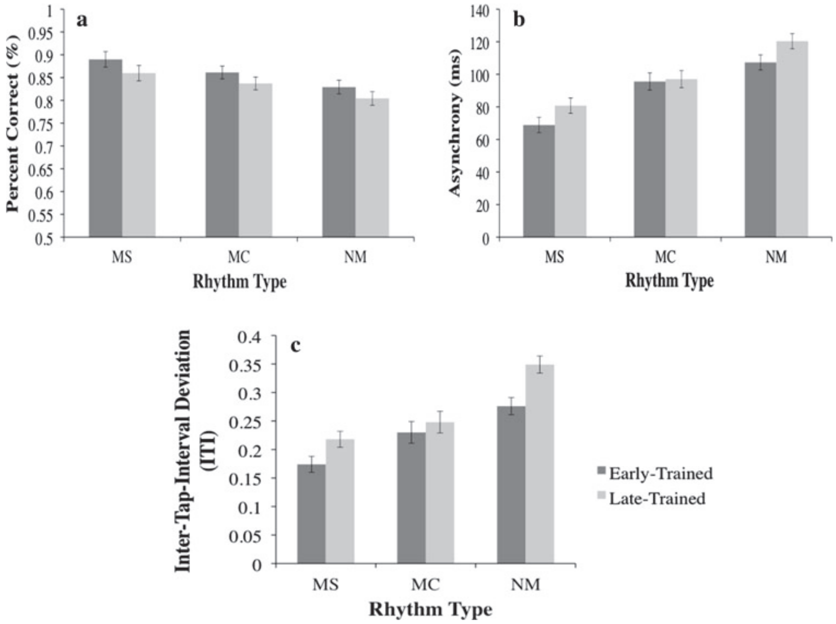

Fig. 3 Performance results of the rhythm task as measured by **a** percent correct (PC), **b** asynchrony (ASYN) and **c** inter-tap interval deviation (ITI). Repeated-measures ANOVA analyses on each performance measure revealed a significant main effect of rhythm type and a significant main effect of group for ITI deviation

Table 3 Pearson correlations of cognitive subtest raw scores and behavioural measures

Behavioural measure	Vocabulary (VC)	Matrix reasoning (MR)	Digit span (DS)	Letter-number sequencing (LN)
Percent correct (PC)	−0.218	0.173	0.256	0.423*
Asynchrony (ASYN)	0.088	−0.297	−0.499*	−0.557**
Inter-tap interval (ITI) deviation	−0.022	−0.348	−0.549**	−0.563**

* $P < 0.05$, ** $P < 0.01$

Table 4 Pearson correlations of musical demographics and behavioural measures

Behavioural measure	Age	Age of onset	Years of musical experience	Years of formal training	Hours of current weekly practice
Percent correct (PC)	−0.130	−0.204	0.114	0.490**	−0.074
Asynchrony (ASYN)	0.147	0.060	0.003	−0.486**	0.025
Inter-tap interval (ITI) deviation	0.190	0.190	−0.035	−0.627**	0.134

** $P < 0.01$

ASYN and ITI deviation, and DS scores were significantly correlated with ASYN and ITI deviation.

Results of the correlational analyses between the behavioural measures and musical variables (Table 4), as well as behavioural measures and age variables indicated a significant correlation between formal training and PC, ASYN and ITI deviation ($r = 0.49$, $P < 0.05$; $r = -0.49$, $P < 0.05$; $r = 0.63$, $P < 0.01$). Neither age variable (age of onset and age) showed a significant relationship with task performance. In order to examine the association between years of formal training, cognitive scores and task performance, correlations were performed between years of formal training and each cognitive measure (Table 5). This set of analyses revealed a significant correlation between years of formal training and both DS and LN, but no significant correlation with VC or MR. In addition, partial correlation analyses between ITI deviation, years of formal training and LN raw scores were conducted in order to examine the partial contributions of formal training and working memory to task performance (Table 6). These results indicated that working memory abilities and years of formal training each accounted for unique portions of the variance in task performance.

Table 5 Pearson correlations of cognitive subtest raw scores and years of formal training

	Vocabulary (raw)	Matrix reasoning (raw)	Digit span (raw)	Letter-number sequencing (raw)
Years of formal training	0.152	0.375	0.510*	0.429*

* $P < 0.05$

Table 6 Partial correlation analyses between task performance, years of formal training and working memory

Control variable		Correlation
Letter-number sequencing (raw)	Total ITI deviation (%) Years of formal training	−0.516*
Years of formal training	Total ITI deviation (%) Letter-number sequencing (raw)	−0.419*

* $P < 0.05$

Table 7 Hierarchical regression analysis predicting ITI deviation scores from working memory composite scores and group

	R^2	β	R^2 change	F
Step 1	0.352		0.352	11.927
Working memory composite score		−0.593**		
Step 2	0.436			8.124
Working memory composite score		−0.496**		
Group		0.307*	0.085	

* $P < 0.05$, ** $P < 0.01$

Regression analysis

In order to determine whether the amount of variance in ITI deviation during task performance accounted for by group was above and beyond what was explained by working memory abilities, a hierarchical regression analysis was conducted. As the values indicate in Table 7, group accounted for a significant amount of variance unexplained by the individual working memory composite scores. These results confirm that, while individual working memory abilities were associated with ITI deviation scores, the grouping variable determined by age at which training onset began accounted for additional portions of the variance in ITI deviation scores.

Discussion

The results from this study show that ET musicians have enhanced auditory rhythm synchronization abilities compared to LT musicians, even when matched for years of experience, formal training and hours of current practice. The greatest difference between the two groups was seen on the measure of ITI deviation, indicating that the ET musicians were better able to reproduce the temporal structure of the rhythms. These group differences cannot be attributed to differences in verbal abilities, non-verbal reasoning or working memory, as there were no differences on these measures. These results support the existence of a possible sensitive period during development associated with long-lasting enhancement of sensorimotor integration and timing. While differences in task performance between the two groups were not mediated by cognitive ability, across all musicians, both working memory and years of formal training were associated with task performance.

Given that the two groups of musicians were matched in terms of musical experience, the enhanced performance on the rhythm synchronization task observed in the ET group cannot be attributed to greater years of training, but instead to the developmental window during which training began. The performance difference between the ET and LT groups observed in the present study, taken together with previous results from our laboratory (Watanabe et al. 2007), supports the presence of a sensitive period in development during which musical training results in long-lasting improvements in sensorimotor integration and movement timing. This is consistent with the idea that experience during a sensitive period contributes differentially to later learning and performance (Knudsen 2004; Trainor 2005). This could be related to the interaction between developmental changes occurring in the brain during the sensitive period and specific training that stimulates this development, resulting in greater potential for future maturation or more efficient integration. This is consistent with developmental changes in motor performance, and structural maturation of fibre pathways supporting sensorimotor functions (Barnea-Goraly et al. 2005; Garvey et al. 2003; Savion-Lemieux et al. 2009; Thomas and Nelson 2001; Paus et al. 1999). For example, the anterior portion of the corpus callosum was reported to be larger in musicians who began training before age 7 compared to those who began later in childhood (Schlaug et al. 1995). A model predicting the growth trajectory of the corpus callosum from structural MRI scans demonstrated that development of the anterior portion of the corpus callosum precedes the posterior portion and that growth in the anterior region continues until approximately age 7 (Thompson et al. 2000). A study examining white matter differences among adult piano players showed that a larger number of brain regions correlated with practice in the group that began training earlier (≤11 years old) compared to those who began later (Bengtsson et al. 2005). Among the brain regions demonstrating this correlation in those who began training earlier were the isthmus and the body of the corpus callosum. The isthmus contains fibres connecting auditory regions, and the body of the corpus callosum connects frontal and premotor regions important for movement sequences and bimanual coordination. Support for the fact that musical training can result in rapid changes in the brain during childhood comes from a recent study showing that structural changes were observed in children after 15 months of music lessons and that these changes were associated with increases in performance on auditory and motor tasks (Hyde et al. 2009). All of these findings illustrate the potential for a sensitive period in childhood, when motor and sensory regions are still undergoing maturation during which musical training has an optimal effect on structural development.

The results of the current experiment are an extension of the findings from a previous study showing that ET musicians performed better than LT musicians on a visuomotor synchronization task (Watanabe et al. 2007). As described in the Introduction, one goal of the present experiment was to assess whether this difference would be observed using a more musically relevant task. These results clearly show that ET musicians have enhanced performance on the more familiar auditory rhythm reproduction task, indicating that training during the putative sensitive period is associated with improved sensorimotor integration in both the auditory and visual modalities. It should be noted that group differences on a measure of asynchrony were observed on the second day in our previous study (Watanabe et al. 2007). Group differences were observed on the ITI deviation measure of synchronization in the current study, which only examined task performance on a single day. One could predict that, given a second day of the auditory–motor task, the two groups would deviate in performance on the ASYN variable as well based on our previous findings.

Given that the two groups did not differ in their performance on measures of verbal ability, non-verbal reasoning and working memory, the enhanced performance of the ET group cannot be attributed to differences in the abilities measured. However, correlational analyses showed that across both groups of musicians, working memory abilities were a significant contributor to task performance. To assess whether group accounted for variance in task performance (ITI deviation) above and beyond individual working memory abilities, a hierarchical regression analysis was performed. These results showed that group was a significant predictor of task performance (ITI deviation), even when individual working memory abilities were considered. Previous findings have demonstrated an association between basic timing tasks and intelligence (Helmbold et al. 2007; Rammsayer and Brandler 2007). These studies have concluded that the relationship is not due to top-down processes such as working memory, but rather is associated with basic neural efficiency (Madison et al. 2009; Ullén et al. 2008). However, these studies do not consider musical training, and the tasks used are very basic and purposefully designed to require little involvement of working memory abilities (Helmbold et al. 2007; Rammsayer and Brandler 2007).

Previous findings indicated that musical training during childhood is associated with verbal abilities and non-verbal reasoning (e.g. MR) (Forgeard et al. 2008; Jentschke and Koelsch 2009; Schellenberg 2004, 2006). The current study does not support an association between musical training and verbal or non-verbal reasoning abilities within a group of highly trained adult musicians. It is important to distinguish between effects of musical training that may have short-term impact in childhood and those that last well into adulthood. It may be that music lessons trigger premature development of cognitive abilities, but some of these differences wash out as other children's cognitive abilities develop through other avenues of experience.

While the cognitive abilities of the two groups did not differ at the time of testing, an important question is whether this was true at the time of start of musical training. The cognitive tasks used in this study are subtests from the WAIS-III or the WASI. Overall, IQ scores are thought to be more or less stable across development and, in the absence of significant neurological disruption, demonstrate limited change from childhood to adulthood. If, however, the ET group had higher IQ scores as children, the LT group would have had to demonstrate a differential increase in IQ scores during their development, as the two groups do not differ currently. In light of the stability associated with IQ levels across the age span, the difference in task performance observed in these adult musicians is unlikely to be associated with potential group differences in IQ scores at an earlier time during childhood.

Although years of formal training and working memory scores were correlated with each other, they also accounted for unique portions of the variance in task performance. In other words, it was not the case that all individuals who performed well on the task had high working memory scores and many years of formal training. There were individuals with high working memory scores and few years of formal training that performed well and vice versa. This pattern of results suggests that components of formal music lessons, not general musical experience, are associated with better rhythm performance and enhanced auditory working memory abilities. Formal training may contribute to task performance in several ways. First, formal lessons emphasize explicit learning of a wide variety of complex rhythmic structures; potentially giving musicians with more formal training a better ability to parse the rhythms they were required to imitate (Chen et al. 2008). Second, formal lessons emphasize intensive and precise practice of rhythms, facilitating the development of motor skills required for precise timing and execution. Finally, formal lessons may emphasize tasks requiring, and thus enhancing working memory. An important distinction should be made in the literature between effects of formal music lessons and effects of playing music, as suggested by Schellenberg and Peretz (2008). Many aspects of music lessons are similar to scholastic requirements (e.g. attention, practice, self-discipline, memorization, reading, counting). Perhaps, formal lessons provide a scaffolding instructional approach for all skills involved in playing a musical instrument, including executive functions such as working memory (Schellenberg and Peretz 2008).

The present study shows convincing evidence for a possible sensitive period for musical training. However, it is possible that the musicians who began training at an early age differed in terms of pre-existing abilities, motivation and environment. Individual differences with respect to motor development, cognitive development or other genetic factors may play an important role in the group difference observed in this study. More specifically, children with innate enhanced sensorimotor skills might be those who begin earlier, and because of their better skills, get more out of their training. In addition, perhaps those who begin training at a younger age are inclined do so because of family influences, higher motivation levels, or other factors that were not evaluated in this study. Future studies should aim to evaluate these important areas to determine exactly which factors are underlying this observed performance difference.

In conclusion, these results provide evidence for a possible sensitive period for musical training before the age of seven as demonstrated by performance differences between ET and LT musicians on a rhythm synchronization task. These findings are consistent with neuroimaging findings that show differential effects of early training on brain structure. Group performance differences observed within this sample cannot be attributed to cognitive ability, as the two groups did not differ on measures of verbal and non-verbal reasoning or working memory abilities. Very interestingly, across both groups, working memory scores were associated with task performance, as were years of formal training. This suggests that formal training may be an important mediator of the effects of musical experience.

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Appendix B

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Behavioral/Cognitive

Early Musical Training and White-Matter Plasticity in the Corpus Callosum: Evidence for a Sensitive Period

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Training during a sensitive period in development may have greater effects on brain structure and behavior than training later in life. Musicians are an excellent model for investigating sensitive periods because training starts early and can be quantified. Previous studies suggested that early training might be related to greater amounts of white matter in the corpus callosum, but did not control for length of training or identify behavioral correlates of structural change. The current study compared white-matter organization using diffusion tensor imaging in early- and late-trained musicians matched for years of training and experience. We found that early-trained musicians had greater connectivity in the posterior midbody/isthmus of the corpus callosum and that fractional anisotropy in this region was related to age of onset of training and sensorimotor synchronization performance. We propose that training before the age of 7 years results in changes in white-matter connectivity that may serve as a scaffold upon which ongoing experience can build.

Introduction

Highly skilled musicians such as Yo-Yo Ma, Oscar Peterson, and Pablo Casals began training in early childhood, all before the age of 7 years. Such observations suggest that there may be a sensitive period when early musical training has greater effects on the brain and behavior than training later in life. Such periods of heightened sensitivity would likely interact with preexisting individual differences in ability, along with environmental factors, to result in the expertise observed in such outstanding musicians.

A sensitive period is defined as a developmental window where experience has long-lasting effects on the brain and behavior (Knudsen, 2004). Neurophysiological studies in animals show that exposure or training during specific periods in development can produce enhanced structural and functional plasticity in visual, auditory, and somatosensory regions of the brain (Hensch, 2005). Evidence for sensitive periods in humans comes from studies of second language learning showing that early exposure results in greater proficiency (Johnson and Newport, 1989; Kuhl, 2010), studies of deaf children showing that receiving cochlear implants earlier results in better language development (Sharma et al., 2007), and studies of blind persons showing greater neuronal reorganization following early blindness (Sadato et al., 2002; Frasnelli et al., 2011).

Musicians are an excellent model for investigating possible sensitive period effects on brain and behavior, as training often begins early and is quantifiable (Bengtsson et al., 2005; Wan and Schlaug, 2010; Penhune, 2011). Evidence for a possible sensitive period for musical training came from a study showing that the anterior corpus callosum (CC) was larger in musicians than nonmusicians, and that the difference was greater for those who began training before the age of 7 years (Schlaug et al., 1995). Further, the extent of the representation of the left hand (Elbert et al., 1995) and motor cortex size (Amunts et al., 1997) have also been shown to be related to early onset of training.

However, none of these studies controlled for the fact that musicians who begin earlier typically have more training than those who begin later. Music and other forms of training induce gray and white matter changes (Hyde et al., 2009; Imfeld et al., 2009; Scholz et al., 2009), and brain structural measures have been shown to be related to the amount of training (Gaser and Schlaug, 2003; Bengtsson et al., 2005; Imfeld et al., 2009; Foster and Zatorre, 2010). Therefore, previously observed differences thought to be related to age of onset may be influenced by, or even artifacts of, differences in the duration of training. Further, previous studies did not demonstrate any relationship between differences in brain structure and performance, which is critical in establishing their relevance. Work from our laboratory has shown that early-trained musicians (ET; training begun before the age of 7 years) outperform late-trained musicians (LT; training begun after the age of 7 years) on auditory and visual sensorimotor synchronization tasks—even when matched for years of training and experience (Watanabe et al., 2007; Bailey and Penhune, 2012). Based on these studies, we hypothesized that early musical training might have a differential impact on plasticity in

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Table 1. Group demographic variables

	ET	LT	NM
n	18	18	17
Male/female	10/8	14/4	10/7
Age of onset of musical training (years)			
Mean (SD)	5.72 (±1.13)	10.78 (±2.46)	—
Range	3–7	8–18	—
Age (years)*			
Mean (SD)	22.72 (±4.14)	27.61 (±5.34)	26.41 (±4.71)
Range	18–32	19–35	21–36
Years of formal training			
Mean (SD)	11.5 (±3.22)	9.42 (±5.13)	0.35 (±0.53)
Range	3–16	1–20	0–1.58
Years of experience			
Mean (SD)	16.72 (±3.89)	16.58 (±4.88)	0.68 (±0.61)
Range	12–25	9.5–24	0–2
Hours of current practice (hours per week)			
Mean (SD)	15 (±10.20)	13.25 (±7.52)	—
Range	3–35.5	4–34	—

*Significant difference in age between ET and LT; $t_{(34)} = 3.07$, $p < 0.05$.

white-matter fibers connecting sensory and motor regions, resulting in better sensorimotor integration. To test this hypothesis, the current study used diffusion tensor imaging (DTI) to compare white-matter structure in ET and LT musicians matched for years of training and experience. We also specifically examined the relationship between brain structure and sensorimotor synchronization performance to test the hypothesis that structural changes induced by early learning would be directly related to behavioral enhancements.

Materials and Methods

Participants

We tested 36 highly trained musicians who were divided into two groups: ET, who began their training before age 7 ($n = 18$, 8 females); and LT, who began their training after age 7 ($n = 18$, 4 females). Groups were matched for years of musical experience (total years of training and practicing music), years of formal training (total years enrolled in music lessons), and hours of current practice as assessed by the Musical Experience Questionnaire developed in our laboratory (Bailey and Penhune, 2012) (Table 1). The age cutoff for ET and LT was based on previous studies (Schlaug et al., 1995; Watanabe et al., 2007). All musicians had at least 7 years of musical experience, were currently practicing, and were enrolled in a university music program or performing professionally. We also tested a group of nonmusician controls (NM; $n = 17$, 7 females) who had less than 3 years of musical experience and were not currently practicing an instrument or undergoing musical training. All participants were right-handed, neurologically normal, and were not taking any medication that could affect task performance. All participants completed an MR safety screening form and provided written informed consent. The experimental protocol was approved by the McGill University Montreal Neurological Hospital and Institute Research Ethics Board and the Concordia University Human Research Ethics Committee.

Behavioral task

The temporal motor sequencing task (TMST) was used to assess motor timing and synchronization (Steele and Penhune, 2010; Penhune and Steele, 2012). The TMST (Fig. 1*A*) requires participants to tap in synchrony with a 10-element sequence of short and long visual cues that form a temporal sequence or rhythm. Previous work in our lab has shown that ET show better synchronization performance than LT on this task, even after 5 d of practice (Watanabe et al., 2006). In the present study, TMST performance was assessed on 2 consecutive days consisting of three blocks of 16 trials. Before testing, participants completed a block of training sequences to establish the mean and standard deviation of their short and long responses for scoring (described below) and practiced the sequence until they were able to reach 80% accuracy across three consecutive trials.

Scoring. Learning was assessed with two measures of performance: percentage correct (PCOR) and percentage synchronization (PSYN). PCOR is the percentage of long and short key-presses that fell within a 300 ms window around the visual stimulus and had a duration within 2 SD of each participant's mean for the short or long elements in the sequence (for additional scoring details, see Steele and Penhune, 2010). A score of 100% on PCOR represents perfect knowledge of the ordering of long/short 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. 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 stimulus duration. PSYN scores were subtracted from 100 to obtain a score that increased with performance. A score of 100% on PSYN indicates that the key press and release response exactly matched the onset and offset of the visual stimuli.

Analyses. Omnibus *F* tests were used to assess learning on PCOR and PSYN and planned comparisons were conducted for all blocks (one-tailed *t* tests, $\alpha = 0.05$, ET > LT and LT > NM compared separately for all blocks). Measures of final performance for PSYN, operationalized as performance on the last block of the second day of training, were calculated for use in behavioral and brain-behavior correlations (PSYN Final).

MRI data acquisition and analysis

We collected both standard high-resolution T1 (MPRAGE T1: TR = 2300 ms, TE = 2.98 ms, $1 \times 1 \times 1$ mm) and diffusion-weighted images (99 directions, TR = 9340 ms, TE = 88 ms, b = 1000 s/mm^2, $2 \times 2 \times 2$ mm) on a Siemens Trio 3T MRI using a 32-channel head coil.

Diffusion imaging. All imaging data were analyzed using the FMRIB Software Library (FSL 4.1.7) (Smith et al., 2004). Diffusion images were corrected for eddy current distortions before creating voxelwise 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 fractional anisotropy (FA) image, and then thins it to produce the study-specific FA skeleton representing the centers of the tracts common to all participants (Smith et al., 2006). The aligned FA data were then projected onto individual FA skeletons that were subsequently used in permutation-based nonparametric statistical analyses. Skeletonized FA values were thresholded at FA > 0.20 before analyses. Volumetric (non-skeletonized) FA images were minimally smoothed ($\sigma = 1$ mm) before analyses. The same nonlinear warp and skeletonization parameters were used with the Tract-Based Spatial Statistics non-FA pipeline to create skeletonised and volumetric images of axial diffusivity (AD) and radial diffusivity (RD). Nonparametric 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 ($\alpha = 0.05$) using threshold-free cluster enhancement (Smith and Nichols, 2009). Additional *post hoc* analyses were conducted at $p < 0.10$ to investigate the degree of overlap with previous findings. Presented *p* values are fully corrected for multiple comparisons.

Group differences and correlations. We addressed the question of whether age of onset of training is related to white-matter organization in two complementary ways. First, we performed a whole-brain skeletonized between-group subtraction analysis to identify white-matter regions that may differ between musician groups matched on years of formal training and experience. This categorical contrast picks up group differences. We also performed a correlational analysis to examine white-matter differences that may be a function of age of onset of training. To this end, the age at which musicians began training was correlated with whole-brain skeletonized FA. Finally, to determine the global relationship between white-matter structure and performance on the TMST regardless of training-related variables, PSYN Final across all participants (ET, LT, NM) was correlated with skeletonized FA. Regions identified in these analyses were subsequently used as masks to extract FA, AD, and RD values for plotting, partial correlations, or one-tailed *t* tests to specify findings as required.

Probabilistic tractography. Probabilistic tractography was used to better characterize the location and connectivity of findings. Significant voxels were first converted to binary masks in each individual's 1-mm-isotropic-transformed diffusion space and then used to seed a two-fiber model of probabilistic tractography (Behrens et al., 2007). Both fiber 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.

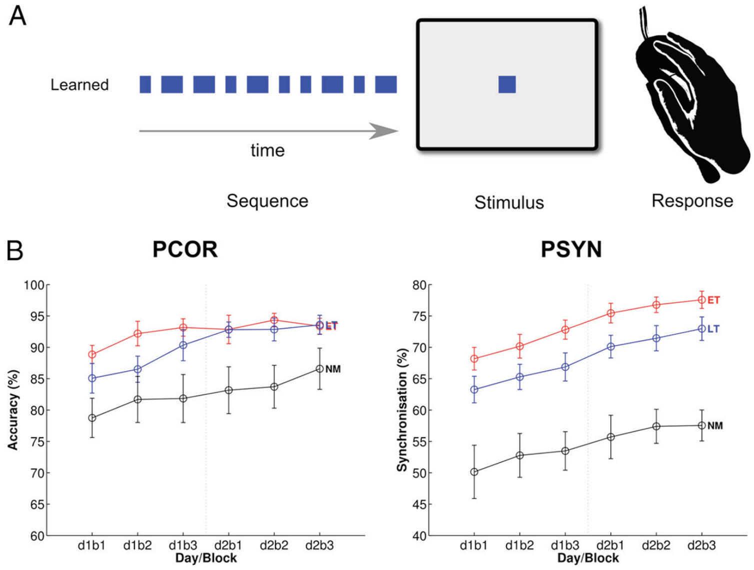

Figure 1. Behavioral task and group performance data. ***A***, Temporal motor sequence task. The learned sequence, visually presented stimuli, and response method are shown. ***B***, Performance data from the TMST. PCOR and PSYN are shown across blocks. Group means for each measure are plotted for each day (d) and block (b): ET are shown in red, LT in blue, and NM in black. Error bars depict ±SEM. The vertical dotted line between d1b3 and d2b1 denotes the boundary between days of training.

Results

Behavioral

Musician groups were well matched for musical training variables, with no significant differences in years of formal training, years of experience, or current hours of practice (Table 1). All musicians were currently playing one or more instruments that required the coordinated use of both hands and were highly trained, with a mean of 16.65 and range of 9.5–25 total years of experience. Nonmusicians had very little experience (mean, 0.68 years; range, 0–2 years). As expected, ET and LT differed on current age (ET: mean, 22.72 years; LT: mean, 27.61 years). There was no difference in age between musicians and nonmusicians (musicians: mean, 25.17 years; NM: mean, 26.41 years). The significant age difference and unequal number of males and females between groups led us to include both age and sex as covariates of no interest in the subsequent structural analyses. In addition, the relationship between our grouping variable, age of onset, and the other demographic measures was also assessed. Age of onset was significantly correlated with years of formal training ($r = -0.41, p < 0.05$) but not years of experience ($p = 0.99$) or hours of current practice ($p = 0.83$). Thus, to more precisely isolate the effects of age of onset across musician groups, we also used years of formal training as a covariate of no interest in correlational analyses described below.

Performance on the TMST across groups and blocks of training were assessed with 3 × 6 (group × block) repeated-measures ANOVA *F* tests and planned *t* tests. Accuracy, as measured by the percentage of correct responses on the learned sequence (PCOR), differed by group and block (group: $F_{(2,50)} = 6.18, p < 0.05, \eta^2 = 0.20$; block: $F_{(5,250)} = 8.89, p < 0.001, \eta^2 = 0.15$), with no interaction (group × block: $F_{(10,250)} = 0.85, p = 0.59$). All groups improved across blocks, with musicians exhibiting better performance than non-musicians (Fig. 1*B*, left). Planned directional *t* tests revealed that ET had better performance than LT on block 2 (ET > LT: $p < 0.05$) and LT showed better performance than NM on blocks 3–6 (LT > NM: blocks 3–6, $p < 0.05$). Performance on the measure of sensorimotor synchronization (PSYN) also showed significant differences between groups (group: $F_{(2,50)} = 21.26, p < 0.001, \eta^2 = 0.46$; block: $F_{(5,250)} = 25.87, p < 0.001, \eta^2 = 0.34$), with no interaction (group × block: $F_{(10,250)} = 0.28, p = 0.99$). Overall, synchronization performance differed between groups, was sustained across 2 d of training, and improved across blocks (Fig. 1*B*, right). Planned directional *t* tests revealed that ET had better synchronization performance than LT across all blocks (ET > LT: blocks 1–6, $p < 0.05$) and LT had better performance than NM (LT > NM: blocks 1–2, $p < 0.05$; blocks 3–6, $p < 0.001$). These results show that musicians have an initial advantage in sensorimotor synchronization that is sustained even after 2 consecutive days of training, and is in agreement with findings of a previous experiment using the same task (Watanabe et al., 2007). Because PSYN was more sensitive to between-group differences, PSYN Final was used as a regressor for investigating subsequent brain–behavior correlations.

Diffusion imaging

Group differences

To determine the white matter structural differences related to early training, skeletonized FA values were compared between musician groups. 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, $t = 4.55$; Fig. 2*A*). To confirm that voxels making up the skeleton were retrieved from the location identified in the group analysis, the significant region was deprojected onto each musician's normalized scan and reviewed. This review confirmed that the region of interest was in the same location in all individuals. To investigate whether we might also find group differences in a more anterior region of the CC as reported by others (Schlaug et al., 1995), the threshold for the skeletonized FA contrast was reduced to $p < 0.10$ (fully corrected). Consistent with previous studies, this analysis showed that ET had greater FA in a large portion of bilateral rostral body and midbody of the CC.

To compare FA in the anterior midbody/isthmus between groups, we extracted FA, RD, and AD from the peak voxel identified in the skeletonized contrast. To visualize the group difference results, Figure 2*B* includes a plot of the extracted FA values by group (top left). There was a significant group difference in RD such that ET had lower values than LT and NM (ET < LT: $t_{(34)} = 3.59, p < 0.001$; ET < NM: $p = 0.06$; LT < NM: $p = 0.92$; Fig. 2*B*, left). There were no

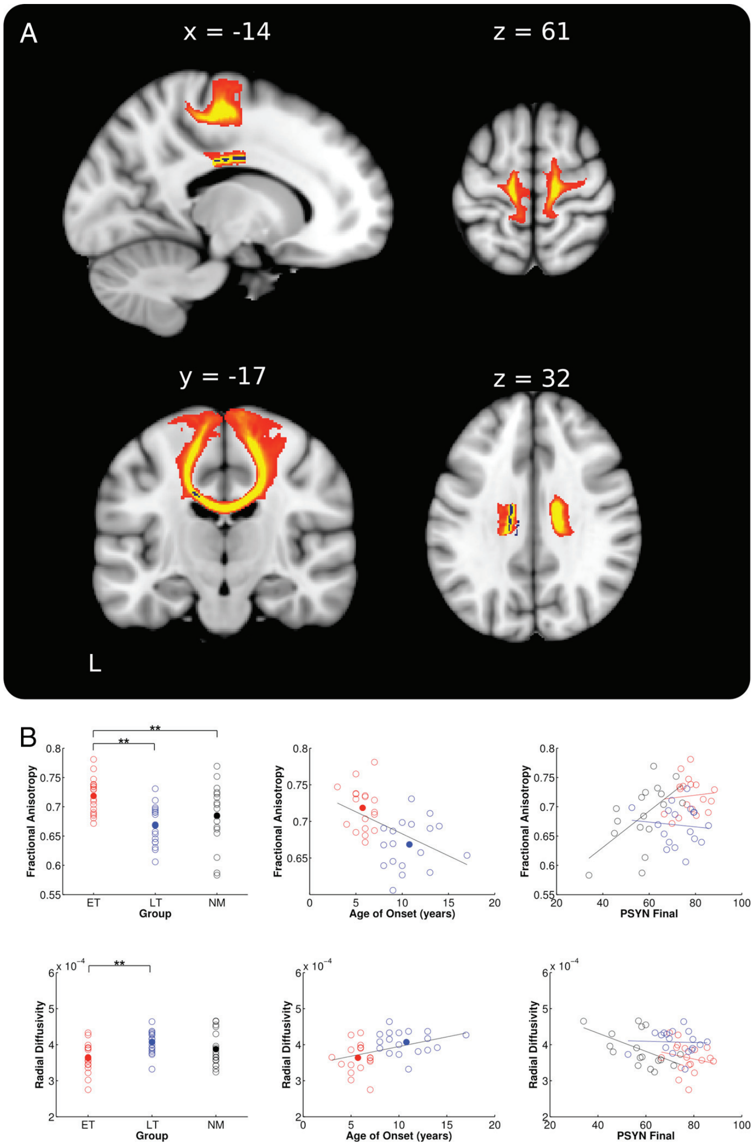

Figure 2. ET versus LT group FA differences and extractions. ***A***, ET > LT group difference in skeletonized FA (blue) in posterior midbody of the corpus callosum. The tract based on this seed connects the right and left sensorimotor cortices and is represented as the red-yellow underlay (where red represents a threshold of 1–10% of maximum particle count and bright yellow depicts 10% and greater). ***B***, FA (top) and RD (bottom) values from the peak CC voxel plotted against group, age of onset, and PSYN Final. Values for ET are depicted in red, LT in blue, and NM in black. Group means are depicted with filled circles. Raw values were used for all plots while statistics were based on the corrected values as stated in the text. $^{**}p < 0.001$.

significant group differences in AD (ET > LT: $p = 0.07$; ET > NM: $p = 0.13$; LT > NM: $p = 0.60$).

As an additional confirmation that the skeletonized group contrast accurately represented the location of group difference, we performed a smoothed whole-brain FA comparison between ET and LT. The results showed that the only location where ET had greater FA than LT was in a very similar region of the posterior midbody/isthmus of the CC (peak voxel: −12, −22, 32, $t = 5.42$, $p < 0.05$ fully corrected). This region overlaps with the skeletonized group difference.

Correlations with region of interest extractions

To further assess the relationship between age of onset of musical training and white matter in the CC, we correlated age of onset with extracted diffusion measures with age and sex, and years of formal training as covariates of no interest. Age of onset of musical training was significantly correlated with both FA and RD (FA: $r = -0.40$, $p < 0.05$; RD: $r = 0.36$, $p < 0.05$; Fig. 2*B*, middle). Together, these results demonstrate that white matter plasticity in the posterior midbody of the CC is differentially affected by the age at which musical training begins.

We also explored the possibility that the synchronization performance advantage of ET may be linked to enhanced FA in the midbody/isthmus of the CC. FA extracted from the peak voxel identified in the skeletonized group contrast was correlated with PSYN Final (Fig. 2*B*, right). There was a significant positive correlation across all participants (All: $r = 0.30$, $p < 0.05$); however, this effect was predominantly driven by the correlation within NM (ET: $p = 0.67$; LT: $p = 0.80$; NM: $r = 0.57$, $p < 0.05$). Consistent with a link between RD, greater myelination, and greater performance, the significant correlation between PSYN Final and FA in NM was driven by a significant correlation with RD (NM: $r = -0.59$, $p < 0.05$) while there was no relationship with AD (NM: $p = 0.46$). These findings indicate that while there is an overall relationship between variability in white matter integrity in the CC and synchronization performance, this effect is not significant for musicians who may be at ceiling for both diffusion measures and performance.

Correlations with age of onset

As an independent analysis to further establish the relationship between age of onset of musical training and FA, age of onset was regressed against whole-brain skeletonized FA. Age of onset was significantly correlated with FA in bilateral rostral body and midbody of the corpus callosum (Fig. 3), overlapping with the regions identified in the group-difference contrast. When years of formal training was included as an additional covariate of no interest, nearly identical results were obtained slightly below threshold ($p < 0.08$, fully corrected).

Probabilistic tractography

In a next step, fiber tractography was used to assess the structural connectivity of the posterior midbody/isthmus region. A seed mask was created from the significant CC cluster from the skeletonized ET–LT contrast, and the results were thresholded for display. The mean tract passed through the posterior midbody/isthmus of the CC to connect the right and left sensorimotor cortices (Fig. 2*A*). The tract identified here is consistent with CC 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 (Fig. 2*A*). FA was greater in ET than LT (ET > LT: $t_{(34)} = 2.11$, $p < 0.05$; ET > NM: $p = 0.07$; LT > NM: $p = 0.72$); there were no differences between groups on RD (ET < LT: $p = 0.09$; ET < NM: $p = 0.16$; LT < NM: $p = 0.36$) or AD (ET > LT: $p = 0.21$; ET > NM: $p = 0.38$; LT > NM: $p = 0.71$). There was no evidence for correlation between diffusion measures and age of onset (FA: $p = 0.37$; RD: $p = 0.31$). These results indicate that the group difference identified within the CC is also true for the tract that connects right and left sensorimotor cortex through this region.

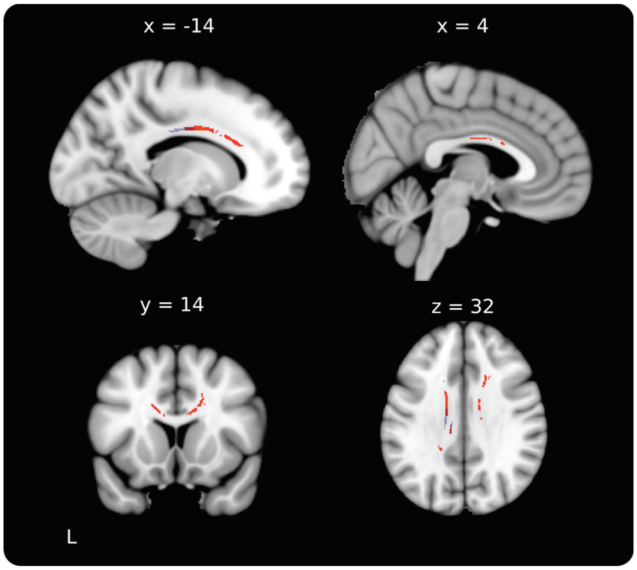

Figure 3. Correlation between FA and age of onset of musical training. FA was significantly correlated with age of onset of musical training across musicians in bilateral rostral body and midbody of the corpus callosum (red). This region overlaps with the more posterior midbody location identified in the group contrast between ET and LT (overlayed in semitransparent blue visible in the top left and bottom right slices).

Correlations with sensorimotor synchronization performance

To directly test the global relationship between FA and performance on the TMST, PSYN Final was regressed against whole-brain skeletonized FA. Across all groups, PSYN Final was correlated with FA in an extensive region of the left temporal lobe (Fig. 4*A*), extending into the posterior limbs of the internal and external capsules. This same region was not present, even below threshold, in the right hemisphere. Mean diffusion values from the entire significant ROI were extracted to better represent the extensive area of interest. Mean FA did not differ between musician subgroups but differed between musicians and nonmusicians (ET > LT: $p = 0.10$; ET > NM: $t_{(33)} = 3.98$, $p < 0.001$; LT > NM: $t_{(33)} = 2.56$, $p < 0.05$; Fig. 4*B*, left). Again, differences in RD appear to be driving the FA differences (RD: ET < LT: $p = 0.18$; ET < NM: $t_{(33)} = 2.98$, $p < 0.05$; LT < NM: $t_{(33)} = 2.07$, $p < 0.05$). There were no AD differences between groups (AD: ET > LT: $p = 0.24$; ET > NM: $p = 27$; LT > NM: $p = 52$).

We next correlated age of onset with extracted FA and RD values in this region to determine whether they showed a similar relationship to that found in the CC. Our results showed a significant negative correlation between age of onset and FA and a significant positive correlation between age of onset and RD when controlling for age, sex, and years of formal training (FA: $r = -0.41$, $p < 0.05$; RD: $r = 0.38$, $p < 0.05$; Fig. 4*B*, middle). In addition, the groupwise correlations with PSYN Final revealed that the overall significant correlation with FA was driven by correlations within LT and NM (ET: $p = 0.74$; LT: $r = 0.59$, $p < 0.05$; NM: $r = 0.63$, $p < 0.05$). Again, this finding appears to have been primarily driven by RD (ET: $p = 0.77$; LT: $r = -0.62$, $p < 0.05$; NM: $r = -0.61$, $p < 0.05$) and not AD (ET: $p = 0.99$; LT: $p = 0.67$; NM: $p = 0.13$).

Discussion

Our results show that early musical training has a differential impact on white matter structure and sensorimotor synchronization performance, providing evidence for a sensitive period where experience produces long-lasting changes in the brain and behavior. Consistent with previous findings, ET outperformed LT on a sensorimotor synchronization task across 2 d of practice (Watanabe et al., 2007). Group comparisons of diffusion imaging data showed that ET had greater FA and lower radial diffusivity in the posterior midbody/isthmus of the CC even when matched for years of formal training, years of experience, and hours of current practice. Fiber tractography showed that this region includes tracts that connect to the sensorimotor cortices in the two hemispheres. Extracted FA and radial diffusivity values in the CC correlated with age of onset of musical training. These correlations were confirmed by a whole-brain regression analysis showing that age of onset was negatively correlated with FA in the same region. Behavioral regression analysis showed that across all groups, synchronization performance was significantly correlated with FA in temporal lobe pathways. Crucially, FA in both the CC and temporal lobe was significantly correlated with the age of onset of musical training despite controlling for years of formal training.

Corpus callosum and bimanual coordination

DTI analyses showed that ET had greater FA and reduced radial diffusivity in the posterior midbody/isthmus of the CC and that those who began earlier had higher FA. The posterior midbody contains the fibers that connect the sensorimotor cortices of the two hemispheres (Hofer and Frahm, 2006; Chao et al., 2009). This region undergoes significant developmental changes between the ages of 6 and 8 years (Westerhausen et al., 2011), when our ET would have begun their training. Individual differences in FA in this subregion of the CC have been shown to be less strongly influenced by genetics (Chiang et al., 2009), and are thus more likely to be influenced by environmental factors such as musical training. Consistent with this, 6-year-olds who received 15 months of musical training showed increased volume in a similar region of the CC (Hyde et al., 2009), and FA in this region in adult musicians has been linked to hours of practice before the age of 11

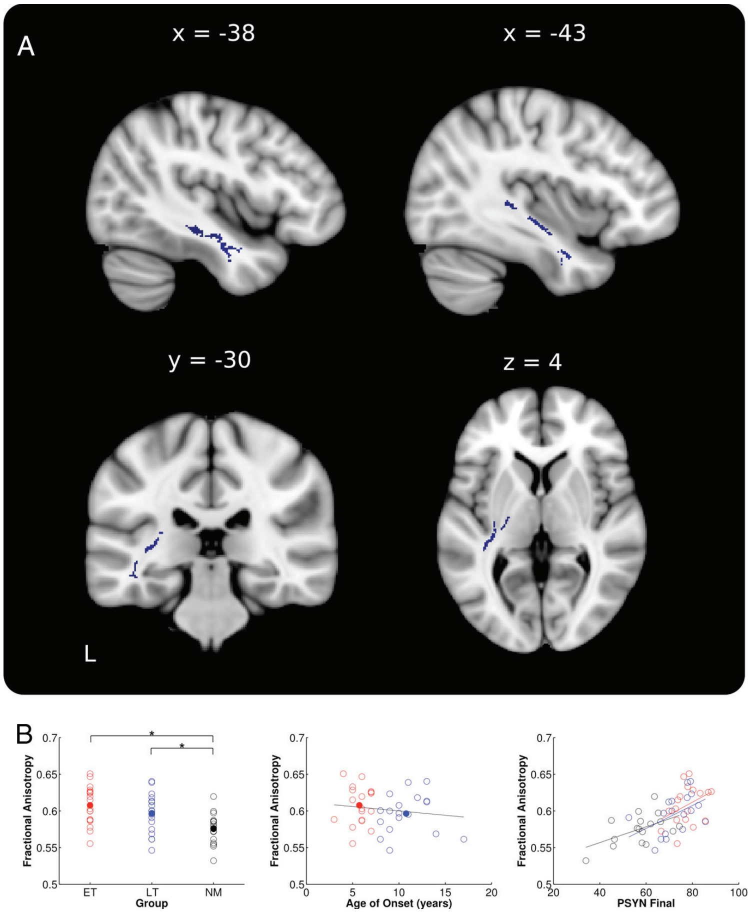

Figure 4. Whole-brain FA correlations with PSYN Final. ***A***, Skeleton voxels significantly correlated with PSYN Final in left temporal lobe and posterior limb of the internal and external capsules (blue). ***B***, Mean values extracted from the region of significant correlation plotted against group, age of onset, and PSYN Final. ET are shown in red, LT in blue, and NM in black. Group means are depicted with filled circles. Note that raw values were used for all plots while statistics were based on the corrected values as stated in the text. $^*p < 0.05$.

years (Bengtsson et al., 2005). Playing a musical instrument requires the coordinated action of the two hands and interhemispheric interactions mediated by the CC have been shown to play a prominent role in bimanual coordination (Swinnen, 2002). The size of the CC and FA have been shown to be related to bimanual task performance in children (Kurth et al., 2012) and adults (Johansen-Berg et al., 2007; Muetzel et al., 2008; Gooijers et al., 2013). Further, the size of the primary motor cortex connected through this region has been shown to be related to the age of onset of musical training (Amunts et al., 1997). Early musical training, by requiring practice of bimanual skills, may place greater demands on interhemispheric interactions between sensorimotor regions, thus promoting the development of enhanced connections that are indexed by increased FA. Contrary to expectations, we found no evidence that LT differed from non-musicians, even though ET and LT had the same amount of musical training while non-musicians had almost none. This lends further strength to the argument that the onset of training, rather than the amount of experience or practice, is the driving factor behind the observed FA differences. Finally, whereas musicians were specifically selected for extensive musical training, the control group was merely selected to have little or no experience; hence, the wide range of FA values in this group could reflect a diversity of adaptations that obscure possible differences with the LT group.

In addition to differences in the CC, we found that FA in the left temporal lobe was significantly correlated with synchronization performance and with age of onset across musician groups. This region includes fibers from auditory cortex that connect to the motor and parietal cortices through the arcuate fasciculus (Petrides and Pandya, 1988; Glasser and Rilling, 2008). Importantly, synchronization performance on our task has previously been shown to recruit both auditory and motor regions in non-musicians (Steele and Penhune, 2010) and structural differences in the arcuate fasciculus have been hypothesized to support the stronger auditory–motor associations found in musicians (Wan and Schlaug, 2010; Halwani et al., 2011). Finally, white matter in the temporal lobes and arcuate fasciculus continues to develop into adulthood (Lenroot and Giedd, 2006; Hasan et al., 2010), making it susceptible to the effects of childhood training.

Together, our findings indicate that early musical training enhances the development of white matter pathways in the CC and temporal lobe that support interhemispheric interaction and sensorimotor integration. Enhanced white matter plasticity in ET in these regions may be the result of an interaction between training during an early sensitive period and ongoing practice. Thus, early training may induce initial changes in white-matter connectivity that serve as a scaffold on which later training continues to build.

Evidence for sensitive periods

Evidence for the effects of experience on brain structure and function during specific periods of early development has been found in the auditory (Chang and Merzenich, 2003; de Villers-Sidani et al., 2007), somatosensory (Fox, 1992), and visual (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970) domains (Knudsen, 2004; for review, see Hensch, 2004). Rat pups exposed to specific frequencies between days 9–13 of life show expanded functional representation for these frequencies as adults (de Villers-Sidani et al., 2007). Studies with congenitally deaf cats have shown microstructural changes in the dendrites of auditory cortex (Wurth et al., 2001) and changes in cortical excitability that can be ameliorated by early cochlear implantation (Klinke et al., 1999; Kral et al., 2000). Human studies show that deaf children who receive implants before 3–4 years of age show better auditory/speech perception than those who receive implants later (Svirsky et al., 2004;

Sharma et al., 2007). Kral and Eggermont (2007) have hypothesized that such plasticity is a result of the interaction between bottom-up sensory information and top-down feedback from higher-order areas involved in functions such as language, attention, and motivation or reward. It has also been proposed that there may be a sequence of overlapping sensitive periods that occur as progressively more complex functions come online (de Villers-Sidani and Merzenich, 2011). Thus, early experience may produce changes in lower-level processes on which later experience can build.

White matter plasticity as measured by FA is hypothesized to be based on experience-dependent neuronal firing (Fields, 2005; Zatorre et al., 2012); thus, interaction between different functional regions may be particularly important for neuronal change. Musical training is a rich source of bottom-up stimulation to the sensory and motor systems, and places demands on cognitive systems involved in auditory–motor integration, attention, and memory (Zatorre et al., 2007; Wan and Schlaug, 2010). Further, cortical plasticity has also been shown to be influenced by the reward value of stimuli (Beitel et al., 2003; Fritz et al., 2007) and music has been shown to engage the reward system (Blood and Zatorre, 2001; Salimpoor et al., 2011). Thus, musical training may be particularly effective in driving structural changes.

Mechanisms of experience-dependent plasticity

Differences in FA may reflect variation in white matter features, such as axon myelination, diameter, packing density, and geometry (Beaulieu, 2002; Alexander et al., 2007). When we decomposed FA into axial and radial diffusivity, our findings were shown to be primarily driven by lower radial diffusivity in ET. Increases in radial diffusivity have been linked to decreased myelin protein content (Song et al., 2002), dysmyelination (Sun et al., 2008; Klawiter et al., 2011), and axon degeneration (Pierpaoli et al., 2001). By inference, lower radial diffusivity values have thus been interpreted as indexing greater myelin integrity. In keeping with this interpretation, greater radial diffusivity in the CC of ET is a possible indicator of greater myelination. Increased FA in the CC of mice following training has also been related to increased expression of a myelin marker (Blumenfeld-Katzir et al., 2011). As described above, changes in white matter may arise from experience-dependent, temporally synchronized neuronal firing in connected regions (Fields, 2005; Zatorre et al., 2012). Neuroimaging studies have shown greater functional connectivity in musicians between auditory and motor regions (Zatorre et al., 2007; Chen et al., 2008), as well as between premotor cortex and thalamus (Krause et al., 2010). By stimulating interactions between sensory and motor regions—and between these regions and systems important for attention, learning, and memory—musical training may drive synchronized firing and thus neural change.

Effects of training or preexisting differences?

Preexisting factors, whether genetic or environmental, may also influence both the propensity to begin training early and the observed differences in brain structure and behavior. Genetic factors have been linked to the ability to acquire absolute pitch (Zatorre, 2003) and to measures of musical aptitude (Ukkola et al., 2009). However, other evidence strongly suggests that preexisting differences are not the only cause of the observed enhanced callosal connectivity in ET. As described above, white matter in this region of the CC may be under less strong genetic control than other regions (Chiang et al., 2009), undergoes normative developmental plasticity between the ages of 6 and 8 years (Westerhausen et al., 2011), and changes as a result of training (Hyde et al., 2009). Nevertheless, the only possible direct tests for a sensitive period would come from studies using randomized designs (musical vs nonmusical training, with age as a parameter) or from longitudinal studies assessing changes in brain structure and performance across development. The present findings can serve to motivate such studies, providing specific hypotheses concerning neural and behavioral correlates of early training.

In conclusion, our findings provide compelling evidence that early musical training can produce long-lasting changes in behavior and the brain. We propose that early training interacts with preexisiting individual differences in brain organization and ongoing maturational processes to produce differential changes in white matter structure. Early musical experience may promote plasticity in motor and auditory connectivity that serves as a scaffold upon which ongoing training can build.

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