EXPERIENCE-DEPENDENT PLASTICITY IN CORTICAL AND CEREBELLAR REGIONS OF EARLY- AND LATE-TRAINED MUSICIANS

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Abstract

Experience-dependent plasticity in cortical and cerebellar regions of early- and late-trained musicians

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A body of current evidence suggests that there is a sensitive period for musical training: people who begin training before the age of seven show better performance on tests of musical skill, and also show differences in brain structure – especially in motor cortical and cerebellar regions – compared with those who start later. In two studies, we investigated distributed patterns of structural differences between early-trained (ET) and late-trained (LT) musicians. First, we examined structural covariation between cerebellar volume and cortical thickness (CT) in sensorimotor regions in ET and LT musicians and non-musicians (NMs). We found that early musical training had a specific effect on structural covariance between the cerebellum and cortex: NMs showed negative correlations between left lobule VI and right pre-supplementary motor area (preSMA) and premotor cortex (PMC), but this relationship was reduced in ET musicians. ETs instead showed a significant negative correlation between vermal IV and right pre-SMA and dPMC. In the second study, we used support vector machine models – a subtype of supervised machine learning – to investigate cortico-cerebellar structural covariation and to better understand the age boundaries of the sensitive period for early musicianship. Our model identified a combination of 17 regions, including 9 cerebellar and 8 sensorimotor regions, that accurately identified ET and LT musicians with high sensitivity and specificity. Critically, this model – which defined ET musicians as those who began their training before the age of 7 – outperformed all other models in which age of start was earlier or later (between ages 5-10). Our model's ability to accurately classify ET and LT musicians provides additional evidence that musical training before age 7 affects cortico-cerebellar structure in adulthood, and is consistent with the hypothesis that connected brain regions interact during development to reciprocally influence brain and behavioural maturation. Together, these results suggest that early musical training has differential impacts on the maturation of cortico-cerebellar networks important for optimizing sensorimotor performance. This work enriches our understanding of how experience-dependent plasticity is affected by early musical training, providing a more nuanced understanding of the interrelated nature of brain development.

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I cannot overstate my gratitude to my incredible supervisor, Dr. Virginia Penhune. Virginia has been a constant source of inspiration, mentorship, and comfort over these past six years. I am one of but a handful of graduate students who can honestly say that my supervisor has been my steadfast supporter and confidante throughout my doctoral work, and I will be forever grateful. I am also grateful to Dr. Robert Zatorre and Dr. Christopher Steele, two experts who have been so generous with their feedback and support over these past few years. Chris' door was often one I knocked on when I needed to borrow a brain or bang my head against some troublesome code. I am also thankful to the support and feedback from my colleagues and friends in the Penhune Lab, as well as members of the Zatorre Lab.

Finally, and most importantly, I am grateful to my family for supporting me through my journey that culminated in this thesis. Ten years ago, I decided I wanted to be a clinical psychologist and took a job as a research assistant. Eight years ago, I started a Master's degree in neuroscience. And six years ago, I finally began the last leg of my journey, this PhD in clinical psychology. Throughout, my partner Dee has been my friend, cheerleader, supporter, and witness to the excitement, stress, joy, and frustration that have accompanied my education. We made two boys, Ian and Jamie, and somehow got through a global pandemic. All of this would also not have been possible without the support of my parents and sisters, where I could always go to share my achievements and hardships and be met with unwavering love.

Contribution of Authors

In collaboration with my supervisor, Dr. Virginia Penhune, I designed the research questions; collected, quality controlled, and processed data; performed analyses; and wrote the manuscripts. Original data collection – approximately 400 individuals spanning 12 studies – was performed by members of the Penhune and Zatorre labs. Dr. Patrick Bermudez and Alex Agapiadis helped with early organization of the data. Additional contributions of authors are as follows:

Article 1

Dr. Christopher J. Steele, Dr. Robert R. Zatorre, and Dr. Virginia B. Penhune contributed to the study conception and design. Data collection, preparation, and analysis were performed by JJS. CJS and Dr. M. Mallar Chakravarty provided analytic tools. JJS and VBP wrote the first draft of the manuscript, and all authors contributed to the final version. All authors read and approved the final manuscript.

Article 2

Dr. Christopher J. Steele, Dr. Robert R. Zatorre, and Dr. Virginia B. Penhune contributed to the study conception and design. Data collection, preparation, and analysis were performed by JJS. JJS and VBP wrote the first draft of the manuscript, and all authors contributed to the final version. All authors read and approved the final manuscript.

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CHAPTER ONE:
INTRODUCTION & BACKGROUND

Introduction

Musical performance represents one of the most complex, multimodal activities in which one can engage. A rich body of research has identified differences in the structure and function of the brains of musicians as compared to non-musician, as well as differences in auditory and motor skills (Amunts et al., 1997; Bermudez et al., 2009; Schlaug et al., 1995; Schneider et al., 2005; Stewart, 2008). Musicians, however, are a heterogeneous group with diverse experience and training. Research into intragroup differences has revealed that a subset of musicians – those who begin their musical training earlier in life – exhibit alterations in brain structure as well as improvements in certain skills: early-trained (ET) musicians show greater cortical surface area and gray matter volume in the ventral premotor cortex (vPMC) and smaller overall and regional cerebellar volumes than their late-trained (LT) counterparts (Baer et al., 2015; Bailey et al., 2014). One proposed mechanism implicated in the differences between early-trained (ET) and late-trained (LT) musicians is the existence of sensitive or critical periods of development in the brain: windows of time in which specific brain regions are more plastic, more sensitive to structural changes as the result of lived experience (Penhune, 2011). The timing and duration of these windows varies across the brain, producing periods in which certain activities may have a stronger and more long-lasting impact on brain development. For example, vPMC appears to have its peak maturational change at or prior to age 8 (Ducharme et al., 2016; Gogtay et al., 2004), while total cerebellar volume peaks during adolescence (Tiemeier et al., 2010). Critically, individual brain regions do not develop in isolation but are instead interconnected in complex functional networks (Ball et al., 2019; Fjell et al., 2019). The cerebellum is indirectly connected to several cortical regions – including premotor, prefrontal, and posterior parietal areas of the cerebral cortex – through the thalamus (Bostan et al., 2013; Daskalakis et al., 2004; Percheron et

al., 1996), forming a number of cortico-cerebellar networks. These networks function in relation to one another rather than in isolation (Kipping et al., 2017; Wang et al., 2016), and interact during development to reciprocally influence maturation – a framework that has been termed *interactive specialization* (Johnson, 2011). Based on this idea, we can hypothesize that interactions between cortex and cerebellum might mutually influence their development. And while previous research into ET/LT differences has focused on individual regions of interest, we know that connected brain regions interact during development. We can therefore further hypothesize that cognitive and behavioural maturation is likely the result of distributed patterns of subtle changes (Bray et al., 2009). Understanding the influence of musical training during early sensitive periods therefore requires a wider lens in which differences can be examined on a whole-brain or network level. This doctoral thesis describes two studies which examine network-level changes in brain structure related to early musical training. The first study examined structural covariation between cerebellar volume and cortical thickness (CT) in sensorimotor regions in ET and LT musicians and non-musicians (NMs). The second study described in this thesis used support vector machine models – a subtype of supervised machine learning – to investigate distributed patterns of structural differences between ET and LT musicians and to better understand the age boundaries of the sensitive period for early musicianship.

Structural and functional brain differences between musicians and non-musicians

The notion that the brains of skilled musicians differ from those of non-musicians can be traced back to the early 20th century: Stewart (2008) describes the experiments undertaken by Auerbach, who dissected the brains of notable contemporary musicians in an effort to locate the source of their superior musical abilities. Auerbach noted differences in temporal and parietal areas and hypothesized that these regions accounted for musical skill. Nearly a century later,

technology such as MRI finally made such research feasible. It turns out that no one structure is responsible for musical ability, but the myriad elements of musicianship – perception, multimodal integration, motor control and execution of musical skills (Zatorre et al., 2007) – engage areas all across the brain: Heschl's gyrus for auditory processing (Schneider et al., 2005), the motor cortex for motor control for instrument manipulation (Amunts et al., 1997), and the corpus callosum for the coordination of sensorimotor processing (Schlaug et al., 1995), among others. In fact, differences in all of these regions have been observed between highly trained musicians and non-musicians with little to no musical training (Gaser & Schlaug, 2003). Studies investigating functional connectivity at rest (rs-FC) – a measure of correlated spontaneous activations in anatomically distinct brain regions – have identified differences in resting state connectivity between musicians and non-musicians. Palomar-García et al. (2016) identified stronger rs-FC between the right auditory cortex and right vPMC in musicians as compared to non-musicians; the authors suggested that this finding was related to changes in the coordination between auditory and motor systems, and noted that this stronger rs-FC was greater in musicians with more years of experience. Functional MRI (fMRI) studies using passive listening tasks – in which musicians and non-musicians are scanned as they are exposed to music – have identified increased activations across the brains of musicians: temporal regions associated with auditory processes, cortical motor regions, regions associated with language processing (such as Broca's area), and parietal regions associated with syntax processing and selective attention to musical stimuli (Olszewska et al., 2021). In addition to these differences in functional activation, structural differences have been identified: musicians tend towards larger primary auditory cortex, motor regions (Bermudez et al 2009), and corpus callosum (Schlaug et al., 1995), as well as greater grey matter density in frontal areas (Abdul-Kareem et al., 2011; James et al., 2014)

and increased cortical thickness in the dorsolateral prefrontal cortex (DLPFC) (Bermudez et al., 2009).

Early- vs. late-trained musicians

Studies investigating musician/non-musician differences typically recruit student or professional musicians with advanced training and compare them with control subjects who have very little to no musical training. However, musicians are not a homogeneous group. Recent evidence suggests that those who begin musical training at an earlier age may have specific behavioural and brain differences compared to those who begin their training later in life. In one of the first studies to examine the effect of the age of start of musical training, the size of the primary motor cortex (M1) was found to be inversely correlated with the age at which musical training commenced: those who began training at an earlier age showed larger M1 than those who began later in life (Amunts et al., 1997). A second early study found that differences observed in corpus callosum size were similarly driven by a group of musicians who began their training before the age of 7, whereas later-trained musicians in this study had corpus callosa comparable with those of the non-musician group (Schlaug et al., 1995). These early studies provided evidence that there is a relationship between age of onset of musical training and structural brain differences. These studies, however, did not control for the effects of years of training, as ET musicians would, by definition, have received more training than their LT counterparts.

Following the early work of Schlaug and Amunts, a number of studies have continued to investigate differences between ET and LT musicians. Bailey & Penhune (2013) confirmed that the age range at which musical training appears to have its strongest effect is between ages 7 and 9, but that the relationship between age of onset of musical training and behavioural and

neuroanatomical enhancements may be non-linear. They examined a single large group of unmatched musicians and, treating age of onset of musical training as a continuous variable, tested their performance on a rhythm synchronization task. The results of this study suggested that age of onset predicts rhythm synchronization performance if musicians began training before age 9, and that the strength of this prediction is strongest when training was initiated before age 7. Subsequent studies have continued to use age 7 as the cutoff point between ET and LT musicians.

Our lab and other researchers have continued to investigate differences in brain structure, function, and behaviour related to sensitive periods for musical training. Further research has uncovered additional anatomical enhancements in ET musicians, which have also been found to be accompanied by performance enhancements on tests of musical ability (even when controlling for practice and training). Using deformation-based morphometry analyses, Bailey et al. (2014) identified greater cortical surface area and gray matter in the right ventral premotor cortex (vPMC) in ET musicians. This region plays a role in sensorimotor integration, and the developmental trajectory of this region – peaking around the age of 8.5 – makes it a prime candidate for plasticity during early musical training (Gogtay et al., 2004). The PMC was additionally shown to be engaged when performing tests of rhythmic synchronization in fMRI, with greater activation in musicians as compared to non-musicians (Chen et al., 2008a). In addition, Steele et al. (2013) compared white matter organization using diffusion tensor imaging (DTI) in ET and LT musicians and found that ET musicians had greater fractional anisotropy – a measure of white matter fiber density – in the posterior midbody/isthmus of the corpus callosum. The authors noted that this region contains fibers which connect the sensorimotor cortices of the left and right hemispheres, and that interhemispheric connections such as this have been shown

to play a critical role in bimanual coordination (Puttemans et al., 2005) – a skill which is honed, in part, by practicing a musical instrument. This region of the corpus callosum also connects the primary motor cortex (M1) and the vPMC.

The cerebellum has also drawn the attention of researchers and has been associated with musical expertise. Although the cerebellum is more classically associated with balance and movement, it has been robustly implicated in musical performance and timing (Keren-Happuch et al., 2014; Zatorre et al., 2007). In particular, the cerebellum is critical for short range (millisecond) timing, whereas processing of longer durations appears to depend on other brain regions (Gibbon et al., 1997): for example, using inhibitory transcranial magnetic stimulation (TMS) over areas of the cerebellum, Koch et al. (2007) were able to impair timing synchronization in the millisecond range, but not longer time intervals. Musicians have previously been found to have larger cerebellar volumes than non-musicians (Hutchinson et al., 2003); however, these studies typically used voxel-based morphometry (VBM) to analyze the cerebellum, which is prone to segmentation errors due to the difficulty in separating densely packed regions of grey and white matter (Whitwell, 2009). Newer methods, such as multi-atlas segmentation, can provide more accurate measures in the cerebellum (Park et al., 2014a). Using this segmentation technique, a recent study in our laboratory found that, compared to LT musicians, ET musicians in fact had smaller volumes in bilateral cerebellar white matter and right lobules IV, V, and VI (Baer et al., 2015). The authors hypothesized that the unexpected direction of these correlations could be related to the cerebellum's role in error-correction and optimization, perhaps representing more efficient motor control processes in ET musicians which require less support from the cerebellum. Alternatively, this finding might be related to the relatively later maturational peak of cerebellar volume (Tiemeier et al., 2010). If this were true,

smaller cerebellar volumes should indeed be related to larger cortical volumes in connected regions. Given the existence of connections between the cerebellum and motor cortices (Bostan et al., 2013; Daskalakis et al., 2004; Penhune & Doyon, 2005; Watson et al., 2014), a relationship between the smaller cerebella and enlarged cortical regions seen in ET musicians is likely.

All together, these findings paint a complex picture of improved performance and differential brain changes linked to early musical training. However, examining each of these findings in isolation limits our ability to understand the interconnected developmental patterns associated with early musical training, and which are suggested by the interactive specialization framework. In addition, previous research has typically defined early musicianship as those who begin their training before the age of 7. However, we know that the maturational trajectories of brain and behaviour are variable, and that maturation or experience in one domain influences maturation in other domains. It is therefore unlikely that there is an abrupt change in sensitivity to musical experience at age 7, but rather gradual changes in sensitivity to different aspects of training.

Sensitive periods & interactive specialization

While genetics and individual differences play a role in the neural development underlying musical ability (Ullén et al., 2016), musical experience in the form of musical training appears to have a greater impact on brain development and behaviour if initiated during a period of peak maturational change. Developmental trajectories are not the same across the brain, as certain regions are more or less plastic at different stages across the lifespan (Voss et al., 2017). Sensitive or critical periods result from these windows of heightened plasticity, during which certain behavioural experiences may have increased long-term effects on behaviour and the brain (Penhune, 2020). These sensitive periods are not specific to musical ability, and have

been identified across the brain and in many areas: studies in language acquisition, for example, have noted multiple sensitive periods – with windows opening and closing at different ages – for distinct aspects of language: a window for the acquisition of syntax which appears to close around age 7, while that of consonant discrimination of non-native speech sounds begins closing after 10-12 months of age (Werker & Hensch, 2015).

Given that sensitive periods open and close across the brain according to differential developmental trajectories, interconnected regions can therefore be influenced by each other's sensitive periods, creating a cascade of plasticity – a kind of metaplastic scaffold – on which later experience can build. While basic sensory and motor functions linked to individual regions might have smaller and more clearly defined windows, complex abilities spread across interconnected networks likely have broader and less well-defined windows of plasticity. The concept that earlier developing brain regions interact with – and have an impact on – the maturation of later developing regions has been termed *interactive specialization* (Johnson, 2011). Johnson explains that, early in postnatal development, certain cortical regions have broad functionality and the potential to be activated by a wide range of different behaviours, stimuli, and contexts. As an individual engages in new experiences, these regions develop to become more specialized to those experiences. This local specialization has an impact on interconnected regions, as the patterns of activation and maturation are "partly determined by its patterns of connectivity to other regions" (Johnson, 2011, p. 10). As a result, new experiences will be associated with changes across several interconnected regions which comprise networks.

As described above, the wealth of research into ET/LT structural differences has identified a number of individual regions which appear to be influenced by early musical training: ET musicians exhibit structural differences in cortical regions involved in motor control

and auditory-motor integration (Bailey et al., 2014), as well as in the cerebellum (Baer et al., 2015). However, given the insights outlined by Johnson's (2011) *interactive specialization* framework – namely, that anatomically connected and functionally-related regions change together across development – it is critical to investigate not just individual regional differences but how those differences relate to each other. The cerebellum is indirectly connected to cortical motor regions – including the premotor cortex (PMC) – through the thalamus (Bostan et al., 2013; Daskalakis et al., 2004; Percheron et al., 1996), and these connections form cortico-cerebellar networks which mature and function in relation to one another (Kipping et al., 2017; Wang et al., 2016).

How, then, might one examine the relationship between structural differences across different brain regions? Structural covariation is an analysis technique which examines how structural properties of the brain – cortical thickness, surface area, volume – relate to one another (Lerch et al., 2006; Vijayakumar et al., 2021). These properties express variability across brain regions and vary substantially across individuals. Structural covariance is therefore one method of assessing what Mechelli et al. (2005) refer to as "the topographic principles which govern" brain structure. In measuring structural covariance, these properties are measured in multiple regions of interest across a number of individuals, and correlations between each pair of regions are calculated in order to identify so-called structural covariance networks. This technique has been used to examine differences between diseased and healthy individuals as well as among groups of expert populations. For example, Karpati et al. (2018) used structural covariance analysis to examine interregional structural relationships in the brains of dancers, and found a reduced correlation between cortical thickness in the left dorsolateral prefrontal cortex (DLPFC)

and mean whole brain cortical thickness. The authors interpreted this finding to suggest that the DLPFC may be more sensitive to experience-dependent plasticity associated with dancing.

Machine learning

Although structural covariance can be powerful and potentially illuminating, non-inferential multivariate techniques might be more sensitive to the distributed pattern of changes associated with early training. Whereas structural covariance requires hypothesis testing at and across each region of interest, a multivariate pattern analysis (MVPA) technique might be more sensitive to identifying distributed patterns of change (Bray et al., 2009). Rather than treating brain regions independently, MVPA methods are designed to identify patterns in the data and are sensitive to spatially covarying patterns of activity. As Bray et al. (2009) explain, "combining information from multiple spatial locations yields a descriptive power beyond that of single voxels, potentially allowing for greater sensitivity in differentiating between individuals and conditions." For example, Magnin et al. (2009) analyzed whole-brain structural MRI scans using MVPA to differentiate between healthy controls and patients with Alzheimer's disease, identifying a number of highly significant regions of interest (ROIs) that successfully identified the diseased patients.

Recently, advances in computational neuroanatomy, MR statistics, and artificial intelligence (AI) have led to novel efforts in the investigation of complex patterns of neuroanatomical change. Together, these advances have led to a new and rapidly improving technology: machine learning. Put simply, machine learning is the process by which computer algorithms iteratively take in large amounts of data (observations) and produce insights about those data without the need for explicit programming (Lai et al., 2018). Machine learning techniques have in fact become so ubiquitous that they have been applied to uses as diverse as

genomics, finance, astronomy, YouTube rankings and suggestions, handwriting analysis, facial recognition, and autonomous vehicles (Stephens et al., 2015).

The basic process of machine learning is to train a model – typically on a subset of the complete available data set – test the model on the remaining data, and subsequently apply the model to make predictions on new data. This iterative process involves one or more cross-validation phases, in which the model is tested on additional subset(s) of the data and subsequently modified in order to improve generalizability (Lai et al., 2018). Machine learning techniques can be categorized under two large umbrella terms: supervised and unsupervised learning. In unsupervised learning, no ground truths about the data are provided to the model: unsupervised models are tasked with uncovering latent patterns hidden within the data without any additional clues, and clustering techniques are then used to group the data based on the emergent patterns (Lai et al., 2018). Unsupervised learning is most useful when *a priori* classification of groups is not possible, such as when studying a heterogeneous (or unknown) disorder. For example, Zeng et al. (2014) developed an unsupervised machine learning model to identify patients suffering from major depressive disorder based on a single resting state functional MRI (fMRI) in the absence of confirmatory clinical information.

Contrastingly, supervised learning is useful when training datasets are already labeled or categorized, such as with disease vs. healthy control samples, and the goal is to identify patterns unique to each category. In supervised models, the ground truth is provided to the training set – this sample has the disease, this sample does not – and the model is tasked with identifying sets of features unique to each sample which could be used to predict categories in new datasets (Lai et al., 2018). Supervised learning is most commonly used for classification: for example, to uncover the pattern of neuroanatomical differences between healthy and known diseased

individuals, and later that pattern of differences is used to predict individuals who might develop the disorder.

Of the multitude of supervised learning classification methods, support vector machine (SVM) is probably the most common. SVM aims to calculate a linear vector – known as a hyperplane – which separates a cluster of data points into two distinct categories (Amari & Wu, 1999b). Data points which are not easily linearly separable are analyzed in a feature space which allows data to be transformed into infinite higher dimensions until a mathematically optimum hyperplane can be calculated. Lai et al. (2018) describe the optimum hyperplane as one which "minimizes an upper bound on the generalization error through maximizing the margin between [the] hyperplane separating the data classes and the data." Once the optimal hyperplane has been identified – based on the features of the data set – the data can be classified into groups. When considering a method which could identify patterns of structural differences between ET and LT groups based on a set of features – sensorimotor cortical thickness/surface area and cerebellar volume – SVM is well suited to this task.

Summary of thesis studies

The two studies described in this thesis are attempts to investigate the experience-dependent structural changes associated with early musicianship at the network-level. Chapter Two is the first manuscript comprising this thesis, published in *Brain Structure & Function* (2022). This research served both as a replication of previous work from our lab and an investigation into the structural connectivity differences between ET and LT musicians. First, we collected a large sample of ET and LT musicians and examined structural covariation between cerebellar volume and cortical thickness (CT) in sensorimotor regions in ET and LT musicians and non-musicians (NMs). Next, we performed correlation and regression analyses to examine

structural covariation between the cerebellum and cortical motor regions between groups. We hypothesized that 1) ET musicians would show smaller overall and regional cerebellar volumes compared to both LTs and NMs; 2) ET musicians would show greater CT and/or SA in vPMC and possibly other motor regions; and 3) reductions in cerebellar volume in ET musicians would be associated with enlargements in connected cortical motor regions.

In Chapter Three, our focus moved away from localized differences between groups and investigated larger patterns of structural differences between ET and LT musicians. We used support vector machine (SVM) models – a subtype of supervised machine learning (ML) – to investigate distributed patterns of structural differences between early-trained (ET) and late-trained (LT) musicians and to better understand the age boundaries of the sensitive period for early musicianship. The manuscript comprising Chapter Three – recently accepted for publication at the journal *Human Brain Mapping* – employs SVM to identify patterns of cortico-cerebellar structural variation which can differentiate between ET and LT musicians. Cortical thickness (CT) and surface area (SA) of cortical sensorimotor regions as well as the volume of cerebellar regions – a subset of which were previously found to be associated with early musical training – were provided to the SVM classifier for training. Using recursive feature elimination (RFE) with cross-validation, the most salient features were identified, to produce a classifier which could accurately predict ET and LT musicianship (Sanz et al., 2018). The performance of the classifier was evaluated by comparing accuracy, specificity, and sensitivity of the model. To investigate the validity of the age of start (AoS) for early musicianship, we produced and compared several models using different cut-offs from ages 5 through 10. We hypothesized that SVM could be successfully used to predict ET and LT musicians using a sub-selection of regional cerebellar volumes and cortical sensorimotor SA and CT. Additionally, we used SVM to

explore the fit of the classifier at different AoS cut-offs to better understand the age boundaries of the sensitive period for early musicianship.

Broadly, we hypothesized that our analyses would find evidence of differences in the structural covariation of cortico-cerebellar networks between ET and LT musicians. Across both studies, we expected that smaller cerebellar volume would be associated with larger motor regions, and that these differences would be predictive of early musical training.

CHAPTER TWO:
ARTICLE #1

Early musical training shapes cortico-cerebellar structural covariation

Shenker, Joseph (Jake), Christopher J. Steele, M. Mallar Chakravarty, Robert J. Zatorre &

Virginia B. Penhune (2021). Early musical training shapes cortico-cerebellar structural

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Abstract

Adult abilities in complex cognitive domains such as music appear to depend critically on the age at which training or experience begins, and relevant experience has greater long-term effects during periods of peak maturational change. Previous work has shown that early-trained musicians (ET; < age 7) out-perform later-trained musicians (LT; > age 7) on tests of musical skill, and also have larger volumes of the ventral premotor cortex (vPMC) and smaller volumes of the cerebellum. These cortico-cerebellar networks mature and function in relation to one another, suggesting that early training may promote coordinated developmental plasticity. To test this hypothesis, we examined structural covariation between cerebellar volume and cortical thickness (CT) in sensorimotor regions in ET and LT musicians and non-musicians (NMs). Results show that ETs have smaller volumes in cerebellar lobules connected to sensorimotor cortices, while both musician groups had greater cortical thickness in right pre-supplementary motor area (SMA) and right PMC compared to NMs. Importantly, early musical training had a specific effect on structural covariance between the cerebellum and cortex: NMs showed negative correlations between left lobule VI and right pre-SMA and PMC, but this relationship was reduced in ET musicians. ETs instead showed a significant negative correlation between vermal IV and right pre-SMA and dPMC. Together, these results suggest that early musical training has differential impacts on the maturation of cortico-cerebellar networks important for optimizing sensorimotor performance. This conclusion is consistent with the hypothesis that connected brain regions interact during development to reciprocally influence brain and behavioural maturation.

Introduction

Adult abilities in complex cognitive domains such as music appear to depend critically on the age at which training or experience begins, with early age of start associated with long-term effects on behaviour and the brain (Berken et al., 2016; Penhune, 2019; Werker & Hensch, 2015). Across all major neural systems, it has been shown that relevant experience has greater long-term effects during periods of peak maturational change, termed sensitive or critical periods (Knudsen, 2004; Penhune, 2020; Werker & Hensch, 2015). Studies from our laboratory have shown that early-trained musicians (ET; < age 7) out-perform later-trained musicians (LT; > age 7) on tests of musical skill, even when controlling for practice and training (Baer et al., 2015; Bailey & Penhune, 2010, 2013; Ireland et al., 2019; Penhune, 2020; Vaquero et al., 2016). Further, ET musicians exhibit structural differences in brain regions involved in motor control and auditory-motor integration. For example, Bailey et al. (2014) identified greater cortical surface area and gray matter volume in the ventral premotor cortex (vPMC) of ET musicians that was correlated with performance on a rhythm synchronization task. The vPMC plays a role in sensorimotor integration (Binkofski & Buccino, 2006; Zatorre et al., 2007) and appears to have its peak maturational change at or prior to age 8, the period when early training begins (Ducharme et al., 2016; Gogtay et al., 2004). A second study in our laboratory found that ET musicians had smaller volumes in right lobules IV, V, and VI of the cerebellum compared to LT musicians, and that these reductions were correlated with better performance on a timed finger tapping task (Baer et al., 2015). The cerebellum is indirectly connected to cortical motor regions – including the premotor cortex (PMC) – through the thalamus (Bostan et al., 2013; Daskalakis et al., 2004; Percheron et al., 1996) and has been implicated in musical performance, timing, and error-correction (Brown et al., 2015; Keren-Happuch et al., 2014). Critically, these cortico-

cerebellar networks mature and function in relation to one another rather than in isolation (Kipping et al., 2017; Wang et al., 2016).

Thus, smaller cerebellar volumes in parallel with larger volumes in vPMC suggest the possibility that early training promotes coordinated developmental plasticity in these connected regions. Based on this concept, we hypothesized that structural differences as a function of musical training in the cerebellum should show coordinated patterning with functionally connected motor cortical regions, and that this pattern would differ depending on the age of start of such training. This prediction is consistent with the *interactive specialization* framework of neurocognitive maturation, which proposes that anatomically connected and functionally-related regions change together across development (Fjell et al., 2019; Johnson, 2011; Lerch et al., 2006). However, no previous studies have shown a direct relationship between structural differences in the cortex and cerebellum.

To test the hypothesis that early musical training might differentially affect cortico-cerebellar covariation, the present study therefore examined the relationship between cerebellar volume and cortical thickness (CT) and surface area (SA) in sensorimotor regions in ET and LT musicians, matched for years of experience and hours of current practice, as well as non-musician controls (NMs). We selected cortical sensorimotor and connected cerebellar regions, a subset of which were previously found to be associated with early musical training. After first assessing differences in cerebellar volume and CT and SA in sensorimotor regions between ET, LT, and NM groups, we performed correlation and regression analyses to examine structural covariation between the cerebellum and cortical motor regions between groups. We hypothesized that 1) ET musicians would show smaller overall and regional cerebellar volumes compared to both LTs and NMs; 2) ET musicians would show greater CT and/or SA in vPMC and possibly

other motor regions; and 3) reductions in cerebellar volume in ET musicians would be associated with enlargements in connected cortical motor regions.

Materials & Methods

Participants

Participant data was aggregated across a set of studies using the same T1 data acquisition protocol on the same scanner (see below). Participants gave informed consent at the time of the original studies, and only those who had agreed to the re-use of their data were included. Protocols were approved by the Concordia University Human Research Ethics Committee and the Human Research Ethics Board of the Montreal Neurological Institute.

All participants were right-handed, and were administered variants of the Musical Experience Questionnaire (Bailey & Penhune, 2010), from which information on musical training was extracted. The full sample included 76 ET musicians and 54 LT musicians, as well as 45 non-musicians (NM: < 3 years of musical training or experience, not currently practicing). To maintain consistency with previous research, ET musicians were defined as those who began musical training before the age 7 (Amunts et al., 1997; Bailey & Penhune, 2013; Schlaug et al., 1995). A subsample of individuals in both the ET (25%) and LT (37%) musician groups were previously included in the samples used in the Bailey et al. (2014) and Baer et al. (2015) studies. As in previous studies (see, for example, Baer et al., 2015; Bailey & Penhune, 2010, 2013; Bailey et al., 2014; Steele et al., 2013), ET and LT musician groups were matched for years of musical experience, years of formal music training, and current hours of practice. In order to create matched ET and LT groups with an optimal covariate balance, we used the MatchIt and Matching packages in R (Ho et al., 2007; Sekhon, 2011). The resulting ET and LT groups each comprised 54 participants, in addition to the NM group which comprised 45 participants. The

primary instruments reported by participants were: piano (40), strings (27), wind (10), drums (7), and voice (4). Group characteristics and comparison statistics are summarized in Table 2.1.

ET, LT, and NM groups did not significantly differ by age. ET and LT groups did not significantly differ on years of musical training, years of musical experience, or current hours of practice. Groups differed significantly in the distribution of sex, with the LT group weighted towards males and the NM group weighted towards females. To control for this, all analyses included sex as a covariate.

Image acquisition & pre-processing

Structural MRI scans were acquired using a Siemens Trio 3 T MRI scanner with a 32-channel head coil (TR = 2300 ms, TE = 2.98 ms, voxel size = $1 \times 1 \times 1$ mm^3). T1 images were converted to the MINC file format and pre-processed with the CoBrA Laboratory bpipe library (https://github.com/CobraLab/minc-bpipe-library) to perform N4 bias field correction and cropping in order to constrain the field of view to primarily skull and brain tissue. Total brain volume (TBV) was estimated from the whole-brain mask produced by BEaST brain extraction (Eskildsen et al., 2012).

Cerebellar segmentation and volume calculation

The cerebellum was segmented into 33 regions (13 in each hemisphere and seven in the vermis) using MAGeTBrain as described in Park et al. (2014; Chakravarty et al., 2013; Figure 1, Panel A). This tool uses five expert-defined cerebellar atlases to segment a subset of participant scans to generate an expanded set of study-specific atlases, or templates. These study-specific templates are then registered to all study scans to produce a large number of candidate segmentations for each participant. Finally, a process of majority voxel voting produces the final labeled images for computing volume.

The atlases used for cerebellar segmentation in our previous study (Baer et al., 2015, as described in Park et al., 2014) divided the left and right hemispheres of the cerebellum at the midline, thus combining vermal and lateral regions. Hemispheric and vermal regions are known to have differential connectivity (Buckner et al., 2011; Grodd et al., 2001) and are thought to subserve different functions (King et al., 2019; Stoodley & Schmahmann, 2009). Thus a new set of atlases was developed which include seven vermal regions: vermal lobules VI through X were defined based on the protocol from Bogovic et al. (2013), which was informed by the Schmahmann atlas (1999). For vermal lobules III-V, a planar lateral boundary was set for each hemisphere based on the coronal view. As described by Schmamann et al. (1999, see page 16), this boundary was defined by the paramedian sulcus (if present); the lateral edge of buried vermal cortex; and/or the lateral edge of the paramedian white matter. These atlases including the vermis have been used in several subsequent studies (see, for example: Mankiw et al., 2017; Steele & Chakravarty, 2018).

To assess the reliability of the cerebellar segmentation in the current study and to confirm the validity of the NMs as a comparison group, we performed a Pearson correlation to compare mean regional volumes obtained from the NM group to a large, well-defined sample of 327 individuals from the Human Connectome Project in which cerebellar volumes were also estimated using MAGeTBrain (Steele & Chakravarty, 2018).

Fifteen regions of the cerebellum were included in the current study: bilateral lobules IV, V, VI, VIIIA and VIIIB as well as their mid-line vermal components. These regions are associated with motor and timing functions and are the same lobules that were examined in our previous study, with the addition of the vermis (Baer et al., 2015; Stoodley & Schmahmann, 2009). In order to reduce the possibility of type I error, analyses of the sub-regions of the

cerebellum were grouped into three macro regions according to anatomically and functionally relevant hemispherical/vermal boundaries: left and right hemispheres and the mid-line vermis. Differences between groups were assessed for each macro-region using MANCOVA with sex and TBV as covariates in order to control for both the normal variation in brain size across participants as well as the unequal distribution of sex across groups (false discovery rate (FDR)-corrected at 0.05). Lobules within any macro-region which achieved significance between groups were subsequently tested in a series of post-hoc comparisons (FDR-corrected at 0.05).

Segmentation of cortical sensorimotor regions

To examine cortical thickness (CT) and surface area (SA) in sensorimotor regions, anatomical boundaries were identified based on the volumetric Human Motor Area Template (HMAT; see Figure 2.2, Panel B) which includes: bilateral primary motor cortex (M1), ventral and dorsal premotor cortex (vPMC and dPMC), supplementary motor area (SMA), pre-supplementary motor area (pre-SMA), and primary somatosensory cortex (S1) (Mayka et al., 2006). The anatomical boundaries in HMAT were computed by analyzing probability distributions of the normalized stereotaxic coordinates of these regions across 126 previous studies. To extract CT and SA values, T1-weighted MRI images were converted to MINC and pre-processed via the CIVET pipeline, version 2.1.0 (Ad-Dab'bagh, 2006). CIVET is a fully automated image-processing pipeline which performs tissue classification and extraction of grey and white matter surfaces. Following surface extraction by CIVET, cortical surface vertices were labeled according to the HMAT template in MNI space. Average CT and total SA within each cortical sensorimotor region were calculated and extracted. As in the cerebellar volume analysis described above, in the first step differences between groups were assessed across the six cortical regions collapsed within each hemisphere using MANCOVA (FDR-corrected at 0.05). Only sex

was used as a covariate in these analyses, since there is evidence that CT is only marginally related to brain size (Im et al., 2008) and that correcting for TBV is not recommended (Schmansky, 2020). If a significant effect of group was observed for either hemisphere (FDR-corrected at 0.05), post-hoc comparisons for individual regions were carried out (FDR-corrected at 0.05).

Correlation analyses

In order to examine the relationship between cerebellar volumes that differed across groups and those of the cortical sensorimotor regions identified by HMAT, a series of correlations were performed. Cerebellar volumes were first normalized by each participant's TBV, and a series of partial correlations were conducted using sex as a covariate (FDR-corrected at 0.05). A correlation matrix was produced for each group (ET, LT, NM), which related the volumes of cerebellar regions against the average cortical thickness and total surface area of each cortical sensorimotor region. In order to compare the directionality of these relationships across groups, a series of multiple regressions were performed on each pair of regions which were found to be significantly correlated. Each regression compared the relationship between cerebellar volume and CT between all three groups.

Results

Validation of cerebellar volumes in the non-musician control group

Mean cerebellar volumes for all 15 regions of interest were found to be within one standard deviation of the comparison normative sample (see Figure 2.2), and a Pearson correlation revealed these samples to be highly correlated ($r=0.986$, $p<0.001$). In addition to confirming the robustness of the segmentation method, this result confirms that our NM group

represents a normal subsample of the population and is thus an adequate comparison group for the ET and LT musicians, allowing us to accurately assess the directionality of differences.

Comparison of cerebellar volumes across groups

Results revealed a significant main effect of group in all three macro regions of the cerebellum such that ET musicians had overall smaller volumes compared with LTs and NMs (see Table 2.2 and Figure 2.3A). Subsequent FDR-corrected post-hoc comparisons revealed a number of significant group differences in the following regions: vermal IV, right V, left VI, right VIIIA, and vermal VIIIB (see Table 2.2). In all of these comparisons, ET musicians had smaller regional volumes than LT musicians and/or NMs. In right VIIIA, however, although ET musicians had significantly smaller volumes than LT musicians, this was due to LT musicians having significantly larger volumes than NM.

Cortical thickness & surface area in sensorimotor regions

Results of the MANCOVA analysis comparing the six sensorimotor regions from HMAT collapsed across hemisphere for the three groups revealed a significant main effect of group in the right hemisphere for CT (See Table 2.3). Subsequent FDR-corrected post-hoc comparisons revealed group differences in right pre-SMA, dPMC, and vPMC such that both musician groups had greater cortical thickness than NMs in pre-SMA, while ETs had greater cortical thickness in vPMC and LTs had greater cortical thickness in dPMC (see Figure 2.3B). There were no significant group differences for SA.

Cerebellum & cortical sensorimotor correlations

In order to assess the relationship between changes in cerebellar volumes and CT, we performed a series of correlations across the regions found to differ in the group comparisons (Table 2.4). The results of this analysis identified significant negative relationships between

cerebellar left VI and right pre-SMA and PMC for NMs, as well as significant negative relationships between cerebellar vermal IV and right pre-SMA and dPMC for ET musicians. There were no significant correlations for LT musicians. Further, the directionality of these correlations indicated an inverse relationship between cerebellar volume and cortical thickness of the sensorimotor regions. To be able to compare the directionality of these relationships between groups, we performed a multiple regression on each pair of regions which were found to be significantly correlated (Figure 2.4). The results of these regressions paralleled those of the correlation analyses: regressions between left VI and pre-SMA, dPMC, and vPMC were significant for NMs only, while regressions between vermal IV and pre-SMA and dPMC were significant only for ETs. There were no significant regressions for LT musicians.

Discussion

The goal of this study was to investigate whether experience-dependent plasticity effects on cortical and cerebellar regions are related, as well as to test whether early musical training has a differential effect on structural covariation between connected regions of the cerebellum and motor cortex. Our results show that ET musicians have decreased volumes of cerebellar lobules connected to sensorimotor cortices, extending our previous findings in a larger sample (Baer et al., 2015). In parallel, we found that both musician groups had greater cortical thickness in right pre-SMA, dPMC, and vPMC compared to NMs. Most importantly, early musical training had a specific effect on structural covariance between the cerebellum and cortex. While NM controls showed a pattern of negative correlations between left lobule VI and right pre-SMA and PMC, this relationship was reduced in ET musicians. In addition, NMs showed no significant relationship between volumes of vermal lobule IV and motor cortical regions, while ET musicians showed a significant negative correlation between vermal IV and right pre-SMA and

dPMC. These differences in the pattern of structural covariance suggest that early musical training has specific developmental effects on cortico-cerebellar networks important for optimizing sensorimotor performance.

Our findings of greater CT in cortical sensorimotor regions and smaller cerebellar volumes in ET musicians extend those of previous research. Previous work from our lab using deformation-based morphometry showed greater expansion of the deformation field and greater surface area in the right vPMC in ET compared to LT musicians (Bailey et al., 2014). In the current study, both ET and LT musicians show greater CT in premotor regions and SMA compared to non-musicians, but there are no differences between the musician groups. This may be the result of differing measures (CT vs DBM). These findings are consistent with work showing that professional musicians exhibited greater gray matter volume in primary, premotor, and somatosensory areas compared to amateur musicians and non-musicians (Bermudez et al., 2009; Gaser & Schlaug, 2003), as well as work showing that in identical twin pairs the twins who practiced showed enhancements in gray matter volume in premotor regions (de Manzano & Ullen, 2018).

Interestingly, both our result and prior results of differential cortical effects are lateralized to the right hemisphere. While one might expect this effect to be associated with handedness, we believe the laterality of our cortical findings are related to hemispheric specialization in music perception and performance which has been investigated in previous research (see, for example: Bermudez & Zatorre, 2005b; Halwani et al., 2011). In addition, the majority of musical instruments played by our participants require bimanual control, which, for right-handed individuals, entails extensive training of the non-dominant left hand. Additionally, studies of motor control and learning demonstrate greater bilateral engagement of motor regions when

tasks are bimanual and/or more complex (Puttemans et al., 2005). Finally, studies of brain structural differences between musicians and non-musicians typically show changes in right hemisphere auditory and motor regions (Brown et al., 2015; Herholz & Zatorre, 2012). This has been interpreted as relating to both the bimanual training effects described above and to the right hemisphere dominance for the processing of musical stimuli.

Our finding of smaller cerebellar volumes in ET musicians is also supported by recent work showing reductions in volume that are related to training and relevant skill (but see Hutchinson et al. (2003), who found larger total cerebellar volume in male musicians). As described in the Introduction, work from our laboratory has found that, compared to LT musicians, ET musicians had smaller volumes in bilateral cerebellar white matter and right lobules IV, V, and VI, and that smaller volumes were correlated with better performance on a test of timed finger tapping (Baer et al., 2015). Our analyses identified similar volumetric reductions in regions IV, V, and VI, however the reductions in lobules IV and VI were in the vermal area and left hemisphere, respectively. Given that our previous work had shown that ET musicians had GM enhancements in the right ventral premotor cortex, we anticipated that there might be specific effects in structural covariance between the right hemisphere motor regions and the connected left hemisphere cerebellar regions.

Support for our finding that training can produce concurrent reductions in cerebellar volume and increases in cortical volume comes from longitudinal neuroimaging studies of sensorimotor learning in mice. Adolescent mice that spent three weeks training in a re-configurable maze showed decreased volume of lobule VI (Scholz et al., 2015a), and adult mice that had been trained to balance on a rotating rod showed reduced cerebellar volume in lobules III and IX (Scholz et al., 2015b). Importantly, in both of these studies, decreases in cerebellar

volume were accompanied by increases in the volume of connected regions, including M1 and frontal cortex, providing evidence of widespread structural reorganization in cortico-cerebellar networks with intensive training that mirrors the effects we describe.

Our finding of changes in cortico-cerebellar structural covariation with early musical training is also consistent with previous research showing that these regions are anatomically and functionally related. Trans-neuronal tracing studies in macaque monkeys have demonstrated that lobules IV-VI are connected to frontal motor and association regions, including M1 and PMC (Kelly & Strick, 2003), and functional connectivity studies based on resting-state fMRI data in humans have shown that these regions are functionally connected to sensorimotor and prefrontal areas of the cortex (Wang et al., 2016). Further, research has demonstrated that cortico-cerebellar functional connectivity changes with maturation across the lifespan. These fluctuations in connectivity may underlie maturational changes in the development of motor and cognitive function, and thus contribute to sensitive periods for the effects of training.

In an initial study in adults, Wang & Kipping (2016) investigated cortico-cerebellar functional connectivity networks using resting-state fMRI. They found that lobule VI was connected to premotor areas, but also to more widespread cortical regions in the parietal and frontal lobes – a finding consistent with earlier work (Buckner et al., 2011). In contrast, lobule IV was part of the "motor cerebellum," connected primarily to premotor and sensorimotor cortical areas. A subsequent study using the same approach compared functional connectivity in children aged 4-5, 6-7 and 9-10, identifying age-related differences in both the extent and strength of these cortico-cerebellar networks (Kipping et al., 2017). Their results showed that functional connectivity in the majority of these networks peaked at age 6-7, including those involving lobules IV and VI, at which point connectivity within the executive control and default mode

networks began to emerge. These findings support the hypothesis that musical training before age 7 may have a differential effect on structural and functional covariation in sensorimotor networks, changing the relationships between these regions, whereas later musical training – beginning after peak connectivity of this network gives way to more widespread connectivity – does not show similar effects.

While the association between larger cortical volumes and training is well-established, it is less clear why smaller cerebellar volumes might be associated with early training and enhanced performance. The cerebellum is critical for error correction and optimization within the motor system (Koziol et al., 2014; Sokolov et al., 2017), and cerebellar activity decreases as new skills and rules are learned, become automatic, and fewer errors are produced (Balsters & Ramnani, 2011; Penhune & Steele, 2012). It is therefore plausible that musical training during early childhood, the period of strongest connectivity between the motor cerebellum and cortical sensorimotor regions (Kipping et al., 2013; Kipping et al., 2017), might influence error correction circuitry. Rats trained to navigate a series of obstacles had significantly reduced Purkinje cell densities compared to controls (Kleim et al., 1997), and mice exposed to five days of optokinetic response training – a series of slow- and fast-phase eye movements for tracking motion – showed a significant reduction in synapses in the cerebellum (Wang et al., 2014). Cerebellar Purkinje cells drive motor learning and coordination through inhibitory projections (Lee et al., 2015), and are themselves influenced through GABAergic inhibition from their inputs (Steuber et al., 2007). It has therefore been proposed that volume reductions in the cerebellum could be the result of synaptic pruning following training-induced inhibition of Purkinje cells (Scholz et al., 2015a).

Although both structural and functional connections between the cerebellum and cortical motor regions have been established, it remains unclear by what mechanism these regions co-develop. The *interactive specialization* framework proposes that connected brain regions or networks interact during development to reciprocally influence maturation (Johnson, 2011). In the current context, we propose that musical training engages the cortical sensorimotor and cerebellar networks, driving plasticity in both (Penhune, 2020). Critically, maturation of particular regions of the brain happens at different ages, and interactive specialization proposes that earlier-maturing sensorimotor networks interact with later-maturing networks controlling higher-order functions. Earlier developing functions therefore benefit from top-down cognitive input, but at the same time can promote maturation in later-developing regions. In the case of musical training, earlier-developing motor regions may interact with later-developing cerebellar circuits, driving coordinated change. Earlier onset of musical training when sensorimotor regions are rapidly developing (Ducharme et al., 2016; Gogtay et al., 2004) may be particularly effective in stimulating plasticity, both locally and in connected regions. Evidence that functional connectivity between the cerebellum and cortex is greatest at age 6-7 (Kipping et al., 2017) further supports the possibility of correlated change. Although the cerebellum itself is thought to exhibit peak developmental change in adolescence (Tiemeier et al., 2010), early start of music training may still enhance plasticity, both directly and through its network connections. Further, early experience may have a metaplastic effect such that early plasticity may serve as a scaffold on which later experience can build (Steele & Penhune, 2010).

Evidence for metaplastic effects of music training comes from studies showing that musicians have enhanced learning of sensory and motor skills (Herholz et al., 2011; Ragert et al., 2004; Rosenkranz et al., 2007), and greater increases in M1 activity during learning (Hund-

Georgiadis & von Cramon, 1999). Finally, given the diverse sensory, motor and cognitive functions engaged by music training and their widespread loci within the brain (Brown et al., 2015; Zatorre et al., 2007), it is likely that other connected regions – such as prefrontal cortex – may influence experience-dependent network changes in early- and late-trained musicians.

Conclusion

The results of this study show that musical training before age 7 affects cortico-cerebellar structural covariation in adulthood, indicating that early experience has differential impacts on the maturation of these connected regions. Our findings emphasize that early experience promotes plasticity at a network level and are consistent with the hypothesis that reciprocal communication within and between networks is an important ongoing contributor to brain and behavioural maturation. Together with our previous work, this study contributes to building a more complex picture of sensitive period effects, in which long-term plasticity is the product of experience during periods of peak maturational change at both the local circuit and network levels.

Tables & Figures

Table 2.1

Group demographics and comparison statistics.
Values are means (± SD). M = Male, F = Female.

	ET (n=54)	LT (n=54)	NM (n=45)	Statistic	p-value
Age (years)	23.1 ± 3.6	24.7 ± 5.07	24.9 ± 4.7	F=2.654	p=0.074
Sex (m/f)	**29/25**	**38/16**	**17/28**	**X²=10.5**	**p=0.005**
Age of onset musical training	**5.7 ± 1.1**	**10.9 ± 2.7**	**--**	**t(106)=22.5**	**p<.000**
Years of musical training	10.9 ± 3.7	9.2 ± 4.6	--	t(106)=1.754	p=0.18
Years of musical experience	14.4 ± 4.7	13.3 ± 5.2	--	t(106)=0.571	p=0.45
Current hours of practice per week	9.8 ± 9.5	8.5 ± 10.2	--	t(106)=1.330	p=0.25

Table 2.2
Results of cerebellar volume analyses.
Omnibus & post-hoc tests are FDR-corrected at 0.05;
All p-values are Benjamini-Hochberg adjusted

Region	F	p	Post-hoc
Left hemisphere	**1.851**	**0.05**	
Left IV	2.595	0.078	
Left V	2.158	0.119	
Left VI	**3.049**	**0.05**	
Left VIIIA	2.740	0.062	
Left VIIIB	0.675	0.511	
Right hemisphere	**2.567**	**0.01**	
Right IV	2.423	0.092	
Right V	**4.759**	**0.01**	**ET<LT, p=0.016 (d=0.54)** **ET<NM, p=0.018 (d=0.13)**
Right VI	1.565	0.213	
Right VIIIA	**5.539**	**0.005**	**ET<LT, p=0.015 (d=0.58)** **LT>NM, p=0.024** **(d=0.94)**
Right VIIIB	2.747	0.067	
Vermis	**2.499**	**0.01**	
Vermal IV	**4.789**	**0.01**	**ET<NM, p=0.009 (d=0.47)**
Vermal V	2.488	0.087	
Vermal VI	0.53	0.589	
Vermal VIIIA	0.684	0.506	
Vermal VIIIB	**5.574**	**0.005**	**ET<LT, p=0.006 (d=0.73)**

Table 2.3
Results of cortical thickness and surface area analyses.
Omnibus & post-hoc tests are FDR-corrected at 0.05;
All p-values are Benjamini-Hochberg adjusted

Cortical thickness

Region	F	P	Post-hoc
Right hemisphere	**1.987**	**0.05**	
M1	1.665	0.193	
S1	0.642	0.528	
SMA	2.808	0.064	
preSMA	**7.472**	**0.001**	**ET>NM, p=0.018 (d=0.66)**
			LT>NM, p<0.000 (d=0.8)
dPMC	**5.125**	**0.007**	**LT>NM, p=0.009 (d=0.63)**
vPMC	**3.223**	**0.043**	**ET>NM, p=0.04 (d=0.53)**
Left hemisphere	1.387	0.171	

Surface area

Region	F	p	Post-hoc
Right hemisphere	0.981	0.467	
Left hemisphere	1.315	0.209	

Omnibus & post-hoc tests are FDR-corrected at 0.05;
All p-values are Benjamini-Hochberg adjusted

Table 2.4

Correlations between cerebellar volume and sensorimotor cortical thickness.
Highlighted cells are statistically significant at p<.05 after FDR correction at 0.05.
M1=Primary motor cortex; S1=Primary somatosensory cortex; SMA=Supplementary motor area; pre-SMA=Pre-supplementary motor area; dPMC=Dorsal premotor cortex; vPMC=Ventral premotor cortex.

Early-trained musicians (ET)

	Right Pre-SMA	dPMC	vPMC
Left VI	0.1	0.21	0.2
Right V	0.04	0	-0.04
Right VIIIA	0.09	0.07	0.04
Vermal IV	-0.34	-0.27	-0.15
Vermal VIIIB	-0.22	-0.17	-0.09

Late-trained musicians (LT)

	Right Pre-SMA	dPMC	vPMC
Left VI	-0.05	-0.06	-0.07
Right V	-0.07	-0.16	-0.14
Right VIIIA	-0.08	-0.11	-0.14
Vermal IV	0.03	0.01	-0.03
Vermal VIIIB	-0.16	-0.18	-0.21

Non-musicians (NM)

	Right Pre-SMA	dPMC	vPMC
Left VI	-0.39	-0.28	-0.31
Right V	-0.01	0.04	-0.05
Right VIIIA	0.02	-0.09	-0.23
Vermal IV	0	-0.02	-0.01
Vermal VIIIB	0.16	0.12	-0.03

Figure 2.1
Segmentations of cerebellar and cortical regions.
Panel A: Example segmentation and labeling of cerebellar regions on one subject using
MAGeTBrain (Chakravarty et al., 2013). Panel B: Example segmentation and labeling of cortical
sensorimotor regions on one subject using the HMAT parcellation (Mayka et al., 2006) applied to
the surface mesh output of CIVET (Ad-Dab'bagh, 2006).
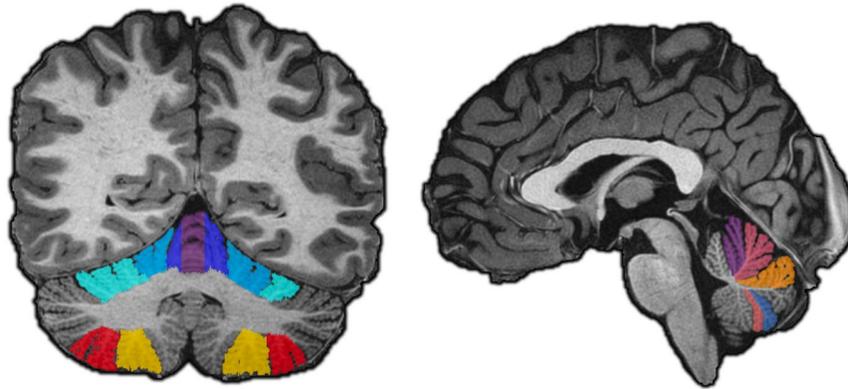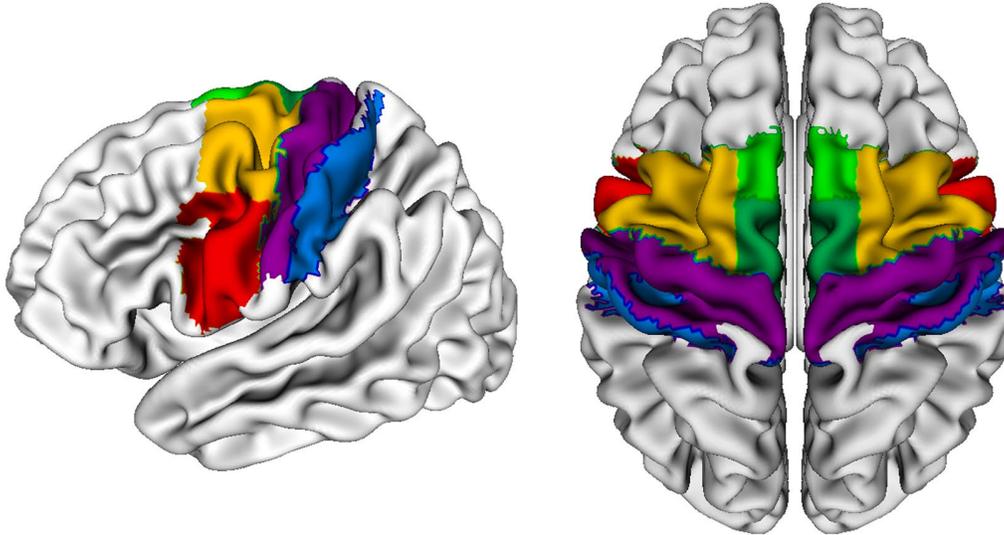
Figure 2.2

Regional cerebellar volumes of current NM group and those of the normative sample from Steele & Chakravarty (2018). Error bars are ±1 standard deviation; no direct statistical comparison was made.
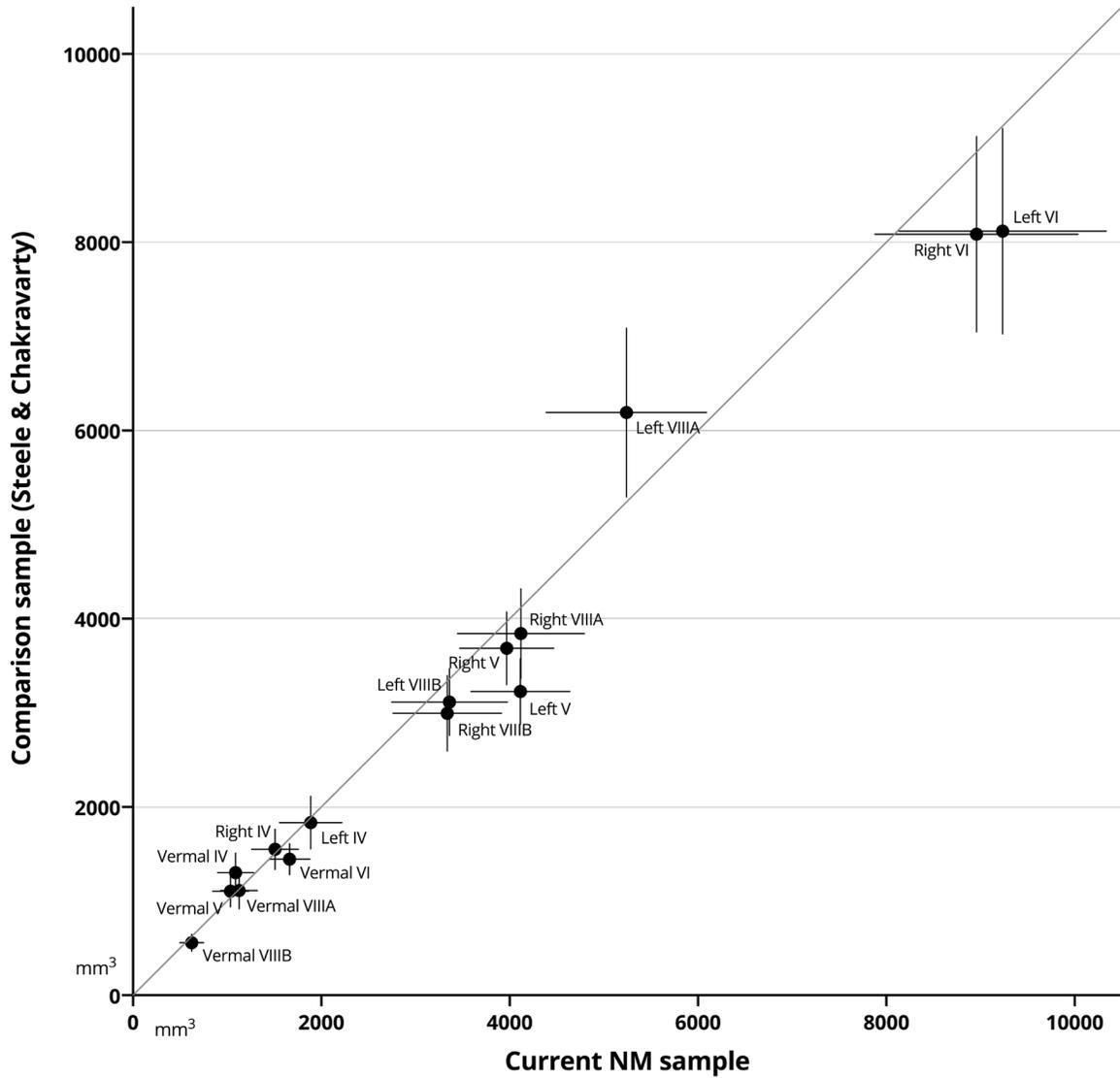
Figure 2.3
Panel A: Regional cerebellar volumes of ET and LT groups relative to NMs.
Panel B: Regional cortical thickness of ET and LT groups relative to NMs.
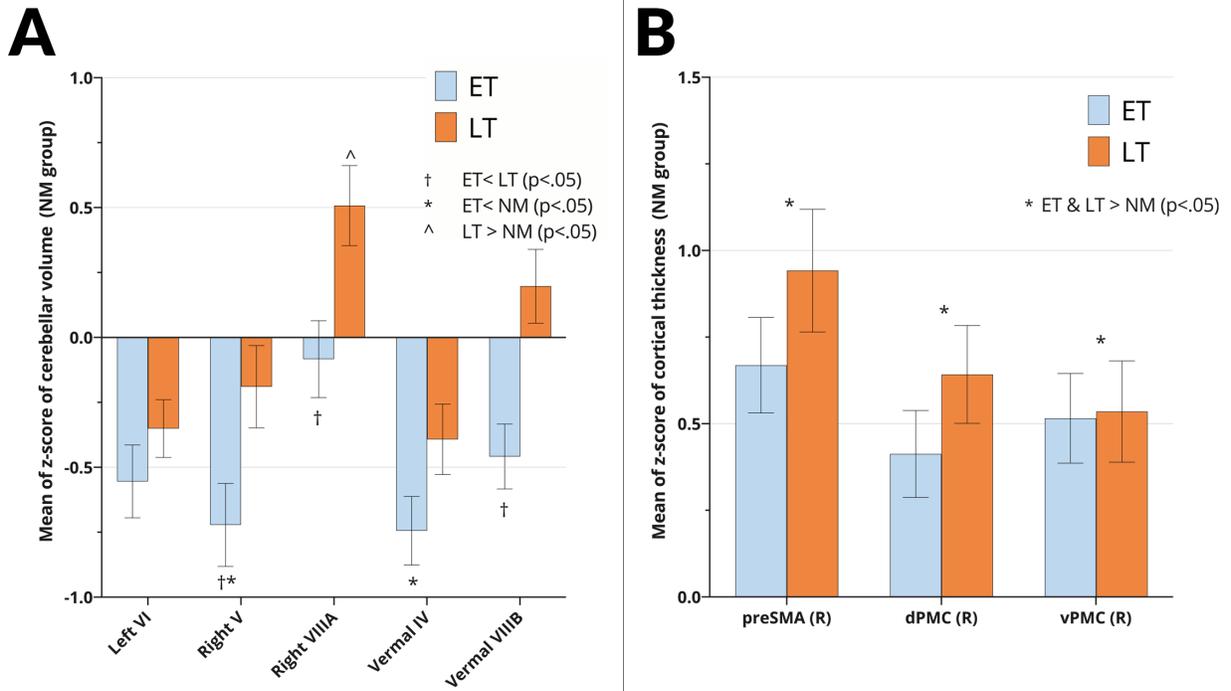
Figure 2.4
Regressions on pairs of regions with statistically significant correlations.
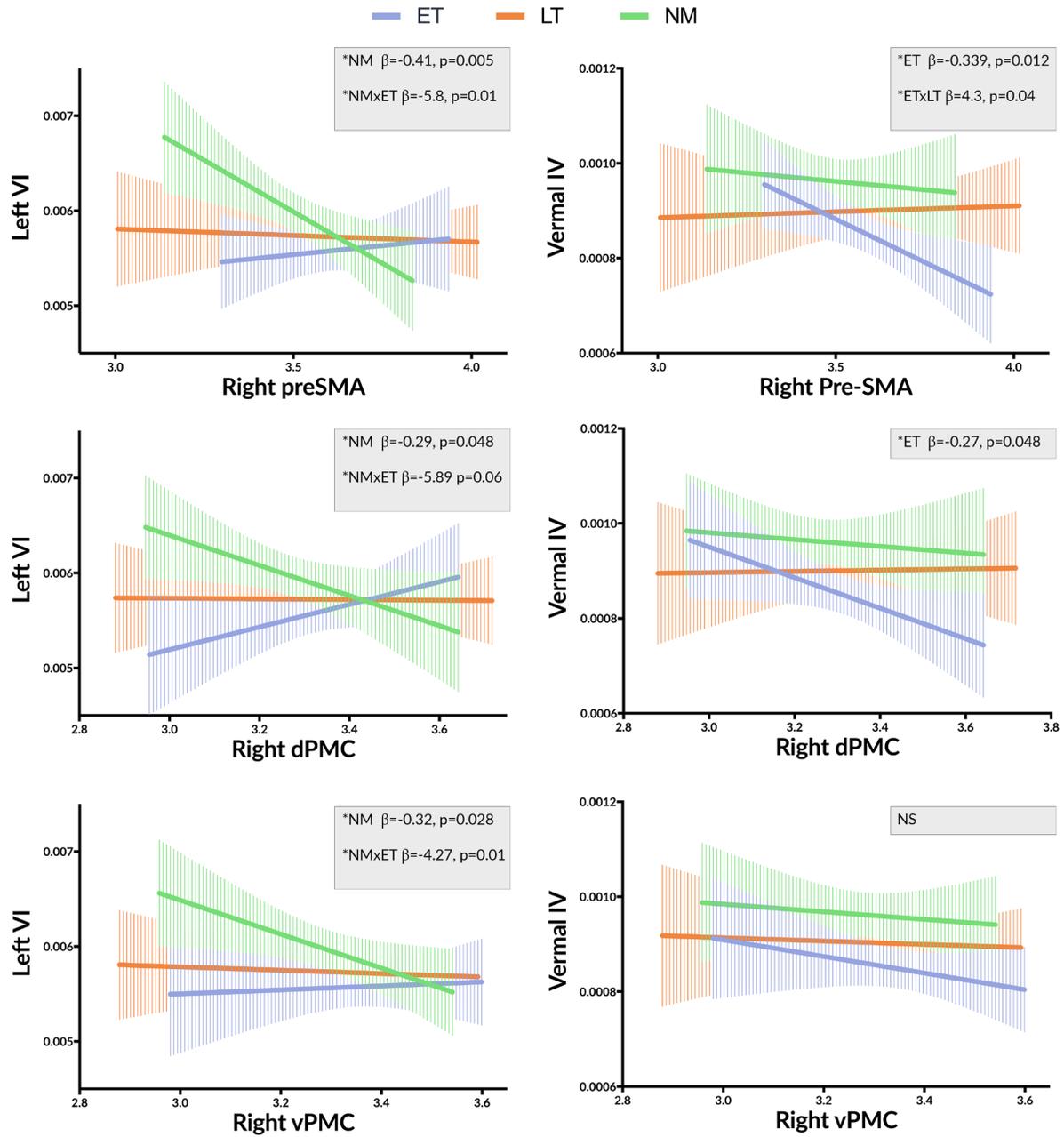
CHAPTER THREE:
ARTICLE #2

Using cortico-cerebellar structural patterns to classify early- and late-trained musicians

Shenker, Joseph (Jake), Christopher J. Steele, Robert J. Zatorre & Virginia B. Penhune (2023).

Using cortico-cerebellar structural patterns to classify early- and late-trained musicians.

Human Brain Mapping.

Introduction

A body of current evidence suggests that there is a sensitive period for musical training: people who begin training before the age of seven show better performance on certain tests of musical skill, and also show differences in brain structure – especially in motor cortical and cerebellar regions – compared with those who start later. In both children and adults, those who begin early (≤7; ET) outperform those who begin later (>7; LT) on tests of melody discrimination and rhythm reproduction (Baer et al., 2015; Bailey & Penhune, 2010; Ireland et al., 2019; Kraus et al., 2009; Penhune, 2020; Vaquero et al., 2016; Watanabe et al., 2007). In addition, ET musicians exhibit greater cortical surface area and gray matter volume in the ventral premotor cortex (vPMC) (Bailey et al., 2014), and smaller volumes in the basal ganglia (Vaquero et al., 2016) and the cerebellum (Baer et al., 2015; Shenker et al., 2022) as compared to late-trained LT musicians.

Previous studies, however, have all relied on univariate methods to assess differences in brain structure across multiple regions independently. However, it seems likely that experience-dependent plasticity for complex skills such as music would engage a more spatially distributed network, and that a multivariate technique would be more sensitive to the distributed pattern of changes associated with early training. The current research therefore uses support vector machine (SVM) models – a subtype of supervised machine learning (ML) – to investigate distributed patterns of structural differences between ET and LT musicians in cortical motor and cerebellar regions known to be structurally and functionally connected.

Brain structural differences between ET and LT musicians were initially observed in a study examining the corpus callosum (Schlaug et al., 1995). Musicians were found to have larger surface area of the anterior corpus callosum, an effect that was greater in those who began their

training at or before the age of 7. A subsequent study of musicians found that the size of the primary motor cortex (M1) was inversely correlated with the age of start (AoS) of musical training: those who began training at an earlier age showed larger M1 than those who began later in life (Amunts et al., 1997). Following these early studies, research from our group and others identified additional neuroanatomical differences associated with early musical training: greater cortical surface area and gray matter in the right ventral premotor cortex (vPMC) (Bailey et al., 2014); greater functional anisotropy – a proxy measure of white matter fiber density – in the posterior midbody/isthmus of the corpus callosum (Steele et al., 2013); smaller gray matter volume in the right putamen (Vaquero et al., 2016); and smaller volumes in hemispheric and vermal cerebellar regions (Baer et al., 2015; Shenker et al., 2022; van Vugt et al., 2021).

In a recent study using a large sample (N=108) we identified a differential pattern of structural differences between ET and LT musicians in the motor cortex and cerebellum (Shenker et al., 2022). Our results identified negative correlations between cerebellar volume and motor cortical thickness and surface area in ET musicians, suggesting that early musical training has differential impacts on the maturation of cortico-cerebellar networks important for optimizing sensorimotor performance (Shenker et al., 2022). This result is consistent with the *interactive specialization* framework, which proposes that connected brain regions or networks interact during development to reciprocally influence maturation (Johnson, 2011). Indeed, widespread structural changes occur as the brain matures, and cognitive and behavioural maturation is likely the result of distributed patterns of subtle changes that are influenced by experience and its timing (Bray et al., 2009). As a multivariate method, SVM is well suited to identify patterns of linked differences in structure characteristic of early musicianship.

In much previous work, ET musicians have typically been defined as those who began musical training at or before age 7. As described above, Schlaug et al. (1995) observed that differences between musicians and non-musicians were driven by those who began before age 7. Subsequent studies showing behavioural and anatomical differences between ET and LT musicians have used this age cut-off. However, we know that the maturational trajectories of brain and behaviour are variable, and that maturation or experience in one domain influences maturation in other domains (Werker & Hensch, 2015). It is therefore unlikely that there is an abrupt change in sensitivity to musical experience at age 7, but rather gradual changes in sensitivity to different aspects of training.

Evidence for a broader range of sensitivity comes from a study which aggregated behavioural data in a large sample of musicians and examined how different age cut-offs affected the relationship between AoS and performance on a rhythm synchronization task (Bailey & Penhune, 2013). The authors applied different AoS cutoffs to produce varying ET vs. LT group splits, and examined whether AoS was correlated with performance on the task. The results showed that AoS was correlated with rhythm synchronization performance if musicians began their training at or prior to age 9, but not afterwards. This correlation was strongest when age 7 was used to divide the groups.

Further, a recent study of child musicians found that children who began musical training before age 7 performed better on a melody discrimination task, but not the rhythm synchronization task, compared to children who began later (Ireland et al., 2019). This observation suggests that children's rhythmic abilities may take time to mature, and that on-going training after age 7 may be required for adult behavioural differences to appear; indeed, 7-13 year-old children showed continuing improvement on rhythm synchronization tasks with

increasing age (Ireland et al., 2018). Although the ET/LT cut-off at age 7 has persisted in the literature – and has often led to interesting results – there has been little systematic study of whether it is, in fact, the optimal point by which to split these groups. Therefore, an additional goal of the current study was to investigate the age cut-off for defining early musicianship by comparing the predictive power of ML models using different AoS cut-offs.

Using ML to identify patterns of structural differences between ET and LT groups requires a classification method that attempts to predict group membership based on a combination of features (Bray et al., 2009). Of the multitude of classification methods, support vector machine (SVM) is probably the most common. SVM aims to calculate a linear vector – known as a hyperplane – which separates a cluster of data points into two distinct categories (Amari & Wu, 1999a). SVM has been widely used for classifying data across multiple domains, from identifying cancerous tissues (Furey et al., 2000) and brain tumors (Othman et al., 2011) to distinguishing individuals with Alzheimer's disease from healthy individuals (Kloppel et al., 2008; Magnin et al., 2009).

Albouy et al. (2019) combined SVM with both structural and functional magnetic resonance imaging (fMRI) to identify patterns of activations which could distinguish healthy controls from participants with congenital amusia (although the authors noted that the relatively low sensitivity of the model might limit its predictive capacity). Another study used SVM to try to classify musicians and non-musicians based on cortical thickness (Puoliväli et al., 2020). They produced a predictive model that was capable of classifying musicians and non-musicians with a pattern of cortical thickness differences mostly in the frontal, parietal, and occipital lobes of the left hemisphere. However, this model was only accurate in classifying non-musicians, while its ability to correctly identify musicians was near chance, possibly due to the heterogeneity of

musicians comprising the sample. Given that the pattern of differences between expert and non-expert groups is likely to be nuanced, larger, more well-defined samples are crucial for more accurate predictive power.

Overall, the existing research provides significant evidence of the differences between musicians with an AoS before or after age 7, although the application of ML tools within this area of study is minimal. The present study employed SVM to identify patterns of cortico-cerebellar structural variation in regions known to be structurally and functionally connected which can differentiate between ET and LT musicians. Cortical thickness and surface area of cortical sensorimotor regions as well as the volume of cerebellar regions – a subset of which were previously found to be associated with early musical training – were provided to the SVM classifier for training. Using recursive feature elimination (RFE) with cross-validation (Sanz et al., 2018), the most salient features were identified to produce a classifier which could accurately predict ET and LT musicianship. The performance of the classifier was evaluated by comparing accuracy, specificity, and sensitivity of the model. To investigate the optimal AoS to distinguish the effects of early musicianship, we produced and compared several models using different cut-offs from ages 5 through 10. We hypothesized that SVM could be used to successfully predict ET and LT musicians using a sub-selection of regional cerebellar volumes and cortical sensorimotor surface area and cortical thickness. Additionally, we used SVM to explore the fit of the classifier at different AoS cut-offs to better understand the age boundaries of the sensitive period for early musicianship.

Materials & Methods

Participants

A total of 133 participants were included, comprising 79 ET musicians and 54 LT musicians. As per previous research, ET musicians were defined as those who began musical training at or before the age 7 (Amunts et al., 1997; Bailey & Penhune, 2013; Schlaug et al., 1995; Shenker et al., 2022). Participant data were aggregated from studies using the same T1 data acquisition protocol on the same scanner (see below). Participants gave informed consent at the time of the original studies, and only those who had agreed to the re-use of their data were included. Protocols were approved by the Concordia University Human Research Ethics Committee and the Human Research Ethics Board of the Montreal Neurological Institute. All participants were also administered the Musical Experience Questionnaire (Bailey & Penhune, 2010), from which information on musical training was extracted. Participants were the same as those in Shenker et al. (2022). A subsample of individuals in both the ET (25%) and LT (37%) musician groups were previously included in the samples used in the Bailey et al. (2014) and Baer et al. (2015) studies. The primary instruments reported by participants were: piano/keyboard (55), strings (12), wind (10), drums/percussion (7), voice (14), guitar (21), bass (8), and brass (5). 1 musician did not report his/her primary instrument. There were no statistically significant differences between the groups for years of musical experience and current hours of practice. Group characteristics are summarized in Table 1.

Image acquisition & pre-processing

Structural MRI scans were acquired using a Siemens Trio 3 T MRI scanner with a 32-channel head coil (TR = 2300 ms, TE = 2.98 ms, voxel size = $1 \times 1 \times 1$ mm^3). T1 images were converted to the MINC file format and pre-processed with the CoBrA Laboratory bpipe library (https://github.com/CobraLab/minc-bpipe-library) to perform N4 bias field correction and cropping in order to constrain the field of view to primarily skull and brain tissue. Total brain

volume (TBV) was estimated from the whole-brain mask produced by BEaST brain extraction (Eskildsen et al., 2012).

Cerebellar segmentation and volume calculation

The cerebellum was segmented using MAGeTBrain (https://github.com/CoBrALab/MAGeTbrain), an automated method using multiple automatically generated templates of different brains (Chakravarty et al., 2013; Park et al., 2014b). This tool uses five expert-defined cerebellar atlases to segment a subset of participant scans to generate an expanded set of study-specific atlases, or templates. These study-specific templates are then registered to all study scans to produce a large number of candidate segmentations for each participant. Finally, a process of majority voxel voting – where the most frequently occurring label among all the candidate segmentations at each voxel is retained – produces the final labeled images for computing volume. Segmentation parameters and cerebellar atlas were consistent with our previous work (Shenker et al., 2022): the cerebellum was segmented into 33 separate regions across left and right hemispheres and vermal region as described in Park et al. (2014) (Figure 1, Panel A), and volumes were weighted by each participant's total brain volume (TBV). All cerebellar regions were included in the analysis.

Segmentation of cortical sensorimotor regions

To examine cortical thickness and surface area in sensorimotor regions, anatomical boundaries were identified based on the volumetric Human Motor Area Template (HMAT; see Figure 1, Panel B) which includes: bilateral primary motor cortex (M1), ventral and dorsal premotor cortex (vPMC and dPMC), supplementary motor area (SMA), pre-supplementary motor area (pre-SMA), and primary somatosensory cortex (S1) for a total of 24 variables (Mayka et al., 2006). To extract these values, T1-weighted MRI images were converted to MINC and

pre-processed via the CIVET pipeline, version 2.1.0 (Ad-Dab'bagh, 2006), and average cortical thickness and total surface area within each cortical sensorimotor region were calculated and extracted (for additional details, see Shenker et al., 2022).

Machine learning

ML was used in order to more directly investigate structural patterns and salient features which can more accurately delineate ET and LT musicians. Support vector machine (SVM) models were implemented in scikit-learn (version 1.0.2), a Python-based machine learning framework (Pedrosa et al., 2018). 57 features were included in all SVMs: cerebellar volume from MAGeTBrain (33 variables) and cortical thickness (12 variables) and surface area from HMAT (12 variables). The hyperparameters C and gamma were optimized using scikit-optimize, and these optimal values were calculated and used uniquely for each model. Two-fold recursive feature elimination (RFE) was used to identify the optimal number of features for SVM models. The RFE algorithm uses weights generated by the SVM classifier as a ranking criterion, eliminating features one-by-one in order to find an optimal subset of features for classification (Huang et al., 2014; Kuhn & Johnson, 2018). These features were then fed back into the classifier using 10-fold cross validation. A linear kernel was used for each SVM model, as it has been suggested that this is required for RFE to perform most accurately (Guyon et al., 2002; Kuhn & Johnson, 2018). For each model, the following steps were performed: 1) optimize hyperparameters C and gamma; 2) train the model using all predictors; 3) perform feature ranking using RFE; 4) keep the most relevant features as identified by RFE; 5) re-optimize hyperparameters; 6) train the model using only the most relevant features; 7) evaluate model performance. To evaluate the outcome of the models, we used permutation tests to estimate chance performance: using 1000 permutations, chance was estimated at 54% (p=0.316).

Our primary model defined ET musicians as those who began their musical training at or before the age of 7. Additional models using different AoS cut-offs (age of onset ≤ age 5, 6, 8, 9, 10, respectively) were tested in order to better understand the age boundaries of the sensitive period for early musicianship.

Results

Of the 57 features included in the model, RFE identified 17 that were optimal for classifying ET and LT musicians. These included volumes of cerebellar motor lobules III-VI and inferior lobule VIIB, as well as cortical thickness in right primary motor, sensorimotor and vPMC (see Figure 2 for the list of regions). These features are consistent with regions showing differences in our previous study examining cortico-cerebellar covariation in the same groups (Shenker et al., 2022). The average cerebellar volume, surface area, or cortical thickness of each region within each group (ET/LT) is visualized in Figure 2. Although no direct statistical comparisons are made, the overall pattern is consistent with the inverted correlational relationship between cerebellar and motor cortical regions in ET musicians seen in our previous study with overall smaller cerebellar volumes being related to greater cortical thickness (Shenker et al., 2022).

Our primary model, in which ET musicians began their training at or before age 7, achieved an overall accuracy of 74% (sensitivity=78%, specificity=69%) with a Cohen's kappa of 0.47, denoting 'moderate' agreement (Artstein & Poesio, 2008; Landis & Koch, 1977) and an area under the curve (AUC) value of 0.735. Models in which AoS was defined at one year earlier or one year later than the primary model (i.e. AoS≤6, ≤8) performed moderately well, but with greater false positives and/or fewer true positives than the AoS≤7 model. Additional models with ages of start ≤ 5, 9, and 10 all performed more poorly, with a range of Cohen's kappa coefficients

from 0.13 to 0.27 and two which were noncalculable (denoting 'poor' agreement) and AUC

values ranging from 0.5 to 0.541. Metrics of all models are summarized in Table 2 and compared

as a series of receiver operating characteristic (ROC) curves – which were produced by

calculating and plotting the true positive rate against the false positive rate for each AoS model –

in Figure 3.

Discussion

The goal of this study was to identify the most salient motor cortical and cerebellar

structural features which could be used by a ML algorithm to accurately classify ET and LT

musicians. The performance of the classifier was evaluated by comparing accuracy, specificity,

and sensitivity of the model. Our primary model (AoS ≤ age 7) identified a combination of 17

regions which most optimally and accurately classified ET and LT regions, including bilateral

motor-related regions of the cerebellum and motor and premotor regions of the cortex,

predominantly in the right hemisphere. Critically, this model – which defined ET musicians as

those who began their training before the age of 7 – outperformed all other models in which age

of start was earlier or later (between ages 5-10).

These results parallel and expand upon those of our previous study: we examined

differences in cortico-cerebellar covariation in ET and LT groups and found that ET musicians

had decreased overall and regional cerebellar volume, and that this effect was associated with

increased cortical thickness in right premotor regions (Baer et al., 2015; Bailey et al., 2014;

Shenker et al., 2022). As depicted in Figure 2, mean volume, surface area, and cortical thickness

of features used by our SVM model follow these same patterns. The cerebellar regions identified

by our model are largely those which are known to exhibit denser connectivity to sensorimotor

areas: both human and non-human primate studies have identified connections between

sensorimotor areas M1, PMC, and SMA and cerebellar lobules III-VI and VIIA-VIIIB (Kelly &

Strick, 2003; Palesi et al., 2017; Salmi et al., 2010). In addition, the salient cerebellar features

identified by this model are not lateralized – three regions in both the left and right hemisphere

and six vermal regions – which is consistent with previous findings identifying ET/LT

differences across both hemispheres of the cerebellum (Baer et al., 2015; Shenker et al., 2022).

In contrast, the majority of the salient cortical features are lateralized to the right hemisphere –

including the right vPMC, larger in ET musicians, as previously identified by Bailey et al.

(2014). This finding is consistent with previous research suggesting hemispheric specialization in

music perception and performance research (see, for example: Bermudez & Zatorre, 2005a;

Halwani et al., 2011; Palomar-García et al., 2016).

By leveraging a multivariate ML approach, we have been able to identify a distributed

pattern of cerebellar and cortical features predictive of early and late musical training. Previous

research studies have each identified separate features in cortical and subcortical regions related

to early training (Baer et al., 2015; Bailey et al., 2014; Steele et al., 2013; van Vugt et al., 2021).

However, using a multivariate approach has allowed us to examine not just individual structural

differences but more nuanced patterns of coordinated change. Our current findings suggest that

early training in musicianship is, indeed, associated with a broad pattern of differences across a

larger network. This outcome is consistent with the *interactive specialization* model of brain

development, which posits that functionally connected regions develop in tandem, and that

experience that promotes plasticity in one part of the network will promote plasticity in the

others (Johnson, 2011). Indeed, complex abilities such as music perception and performance –

which comprise multiple, overlapping skills – require the contribution of interacting brain

networks (Zatorre et al., 2007).

In addition, our primary model – based on AoS≤7 – outperformed models with other AoS cutoffs (≤6, ≤8, ≤9, and ≤10). The AoS≤7 model demonstrated high accuracy and sensitivity (true positives, i.e. correct classification of ET musicians when they really were ET musicians) without sacrificing specificity (true negatives, i.e. correct classification of LT musicians when they really were LT musicians). Models testing classification at other age cut-offs were less accurate: models in which AoS was defined at one year earlier or one year later than the primary model (i.e. AoS≤6, ≤8) performed moderately well, but AoS≤6 produced more false positives and AoS≤8 produced fewer true positives than the AoS≤7 model. Models using AoS≤5, AoS≤9, and AoS≤10 showed little to no predictive power. In other words, the unique pattern of cortico-cerebellar structural variation identified by the classifier could most accurately predict groups based on the AoS≤7 cut-off, and other models were capable of classifying one group but not the other or were prone to classification errors. Together, these results indicate that musical training at or before age 7 has a joint effect on cortical and cerebellar structure in adulthood and supports the hypothesis that the sensitive period for coordinated developmental plasticity in cortico-cerebellar regions – promoted by early musical training – may end at or around age 7. However, sensitive periods for complex skills such as music or language are unlikely to exhibit abrupt cut-offs. Instead, such skills are likely to depend on a cascade of developmental and experience-dependent plasticity effects with basic sensory processes being affected earlier and more complex processes affected later (Penhune, 2022; Werker & Hensch, 2015).

Previous research has demonstrated that the cortico-cerebellar connectivity underlying the motor and cognitive functions associated with musicianship changes across the lifespan and may therefore contribute to sensitive periods for the effects of training (Fjell et al., 2019; Kipping et al., 2017; Tiemeier et al., 2010). Earlier onset of musical training when sensorimotor regions

are rapidly developing (Ducharme et al., 2016; Gogtay et al., 2004) may be particularly effective in stimulating plasticity, both locally and in connected regions. Grey matter volume of anterior motor regions – including M1 and PMC – have a peak rate of change between the ages of 6 and 8 (Giedd et al., 1999). Evidence that functional connectivity between the cerebellum and cortex is greatest at age 6-7 further supports the possibility of correlated change. Kipping et al. (2017) investigated cortico-cerebellar functional connectivity networks using resting-state fMRI in children aged 4-5, 6-7 and 9-10. They identified age-related differences in both the extent and strength of these cortico-cerebellar networks and found that functional connectivity in the majority of these networks peaked at age 6-7. These observations suggest that plasticity is heightened during these developmental windows, and that long-term plasticity may be the product of experience during periods of peak maturational change at both the local circuit and network levels.

It is unlikely, however, that all musician-associated skills fall into one distinct sensitive period. There is evidence of multiple sensitive periods across the cortex associated with diverse behaviours, and these cascading sensitive periods occur at different temporal windows and are sensitive to different types of behaviour (Penhune, 2021). Studies in language acquisition, for example, have noted multiple sensitive periods – with windows opening and closing at different ages – for distinct aspects of language: a window for the acquisition of syntax which appears to close around age 7, while that of consonant discrimination of non-native speech sounds begins closing after 10-12 months of age (Werker & Hensch, 2015). While the sensitive period described in the current research appears to close around age 7, this window – possibly one of many – may be unique to the complex pattern of cortico-cerebellar plasticity and may not represent the totality of differences between ET and LT musicians. Research in children supports

this hypothesis: while children who began musical training before age 7 outperformed same-aged LT peers on simple melody discrimination, there was no difference in children's performance on rhythm synchronization or transposed melody discrimination tasks (Ireland et al., 2019). Adult ET musicians, however, do outperform adult LT musicians on rhythm synchronization tasks (Baer et al., 2015). Early start of music training may enhance plasticity, both directly and through network connections, and early experience may have a metaplastic effect such that early plasticity may serve as a scaffold on which later experience can build (Steele & Penhune, 2010). Finally, it is important to note that the current research focused only on cortical sensorimotor regions and the cerebellum due to previous evidence of their implication in early musical training. Future studies with a larger number of participants – and enough statistical power – would benefit from replicating these analyses across the whole brain in order to uncover potential contributions from – and interactions between – other brain regions. More specifically, future research in this domain might consider investigating the basal ganglia. Previous work examining structural and functional differences between ET and LT musicians has shown a reduced volume of the putamen (Vaquero et al., 2016) and a pattern of cortico-striatal functional connectivity that was unique to ET musicians (van Vugt et al., 2021). These findings suggest that the cortico-cerebellar network-level differences observed in this study may be part of a larger series of network-level changes associated with early training. Similarly, it would be interesting to examine interactions between the auditory and motor systems given the importance of sensorimotor integration to musical performance (Zatorre et al., 2007). Finally, a larger sample size would additionally allow us to better control for the potential impacts of biological sex, which could be the source of some variance in the current analyses.

Conclusion

This study used a multivariate classification approach to identify patterns of cortico-cerebellar structural variation which can differentiate ET and LT musicians, emphasizing that early experience promotes plasticity at a network level. In addition, these patterns were most robust when classifying musicians who began their training at or before age 7, providing new evidence for a sensitive period for music experience in middle childhood. Together with previous work, this study helps build a more nuanced understanding of how early musical experience interacts with sensitive periods to effect network-level changes in the brain.

Table 3.1
Group demographics. Values are means (± SD). M = Male, F = Female.

	ET (n=79)	LT (n=54)
Age (years)	22.8 ± 3.5	24.7 ± 5.2
Sex (m/f)	40/39	38/16
Age of onset musical training	5.4 ± 1.1	10.4 ± 2.7
Years of musical training	12.2 ± 4	9.2 ± 4.6
Years of musical experience	15.2 ± 4.4	13.3 ± 5.1
Current hours of practice per week	11.8 ± 11.3	8.5 ± 10.2

Table 3.2
Confusion matrices and performance metrics of SVM models. True positives and true negatives (ET and LT musicians, respectively) are found in the top left and bottom right cell of each matrix. Our primary model (AoS≤7) is highlighted.

ET≤5

	ET	LT
ET	4	35
LT	2	92

Accuracy: 72%
Sensitivity: 66%
Specificity: 72%
Cohen's kappa: 0.13

ET≤6

	ET	LT
ET	36	25
LT	19	53

Accuracy: 67%
Sensitivity: 65%
Specificity: 68%
Cohen's kappa: 0.33

ET≤7

	ET	LT
ET	62	17
LT	17	37

Accuracy: 74%
Sensitivity: 78%
Specificity: 69%
Cohen's kappa: 0.47

ET≤8

	ET	LT
ET	72	22
LT	19	20

Accuracy: 69%
Sensitivity: 79%
Specificity: 47%
Cohen's kappa: 0.27

ET≤9

	ET	LT
ET	105	0
LT	28	0

Accuracy: 79%
Sensitivity: 78%
Specificity: noncalculable
Cohen's kappa: noncalculable

ET≤10

	ET	LT
ET	114	0
LT	19	0

Accuracy: 85%
Sensitivity: 14%
Specificity: noncalculable
Cohen's kappa: noncalculable

Figure 3.1

Segmentations of cerebellar and cortical regions.

Panel A: Example segmentation and labeling of cerebellar regions on one subject using MAGeTBrain (Chakravarty et al., 2013). Panel B: Example segmentation and labeling of cortical sensorimotor regions on one subject using the HMAT parcellation (Mayka et al., 2006) applied to the surface mesh output of CIVET (Ad-Dab'bagh, 2006).
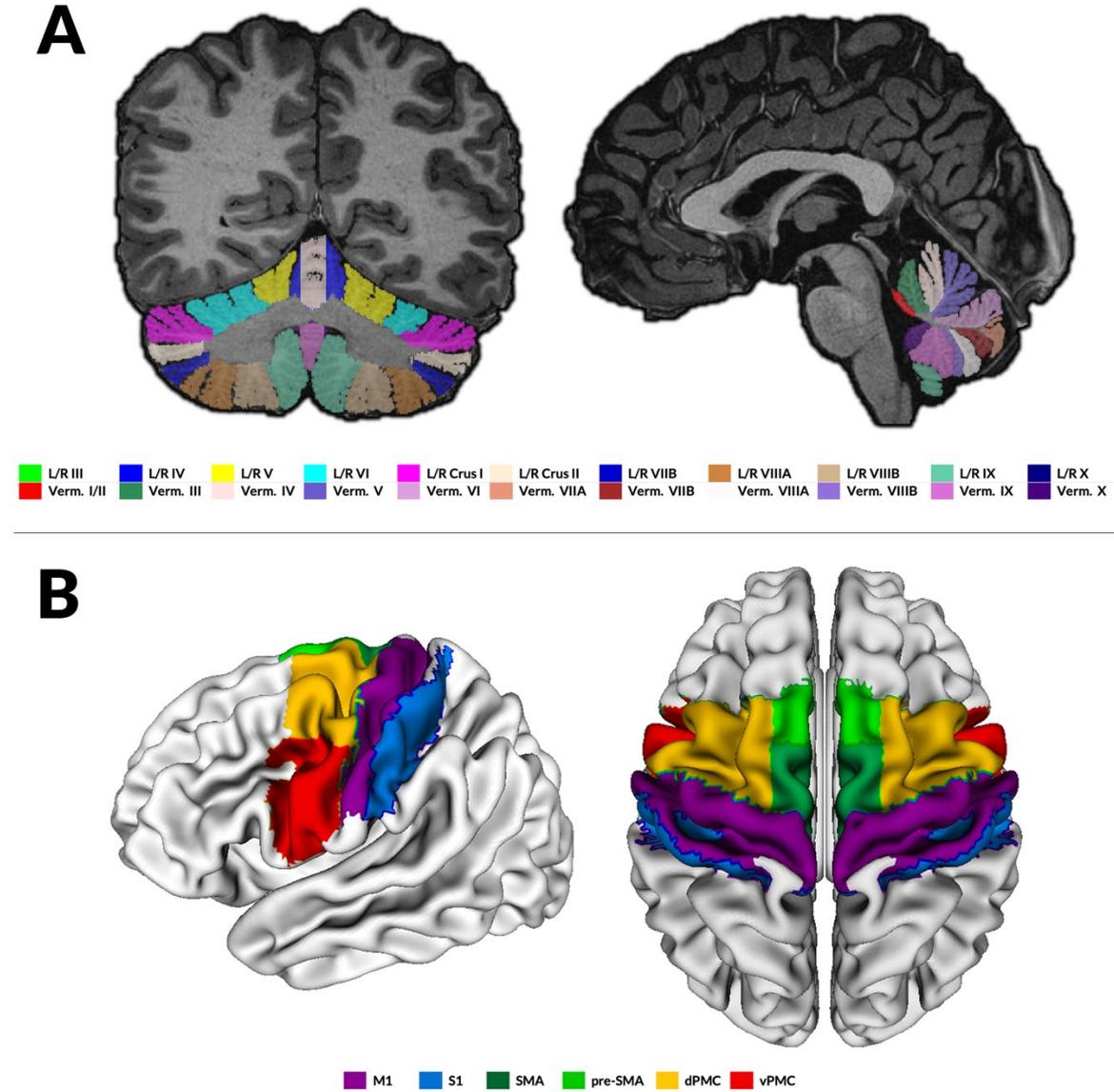
Figure 3.2

Comparison of standardized mean regional volume (cerebellum), surface area, or cortical thickness for optimal 17 regions included in SVM models.
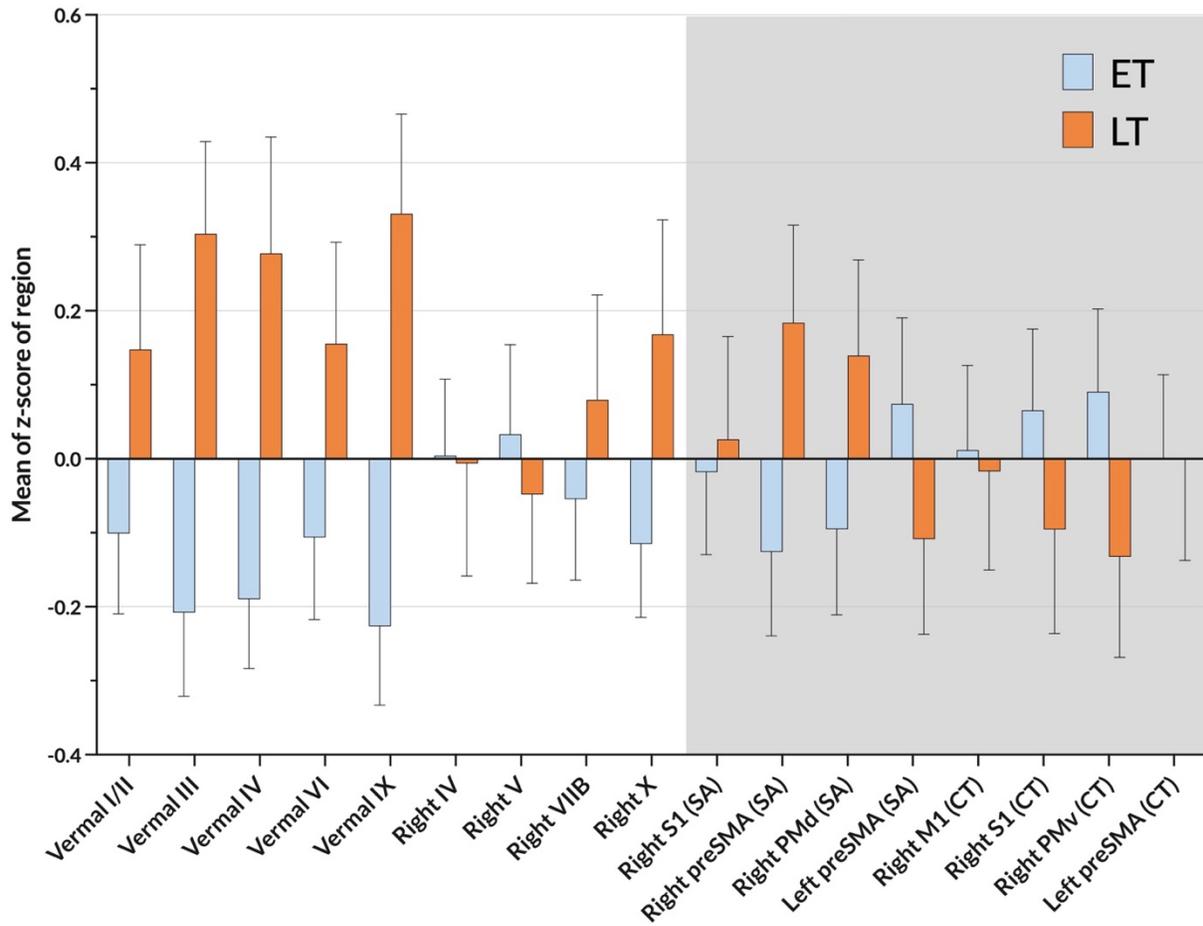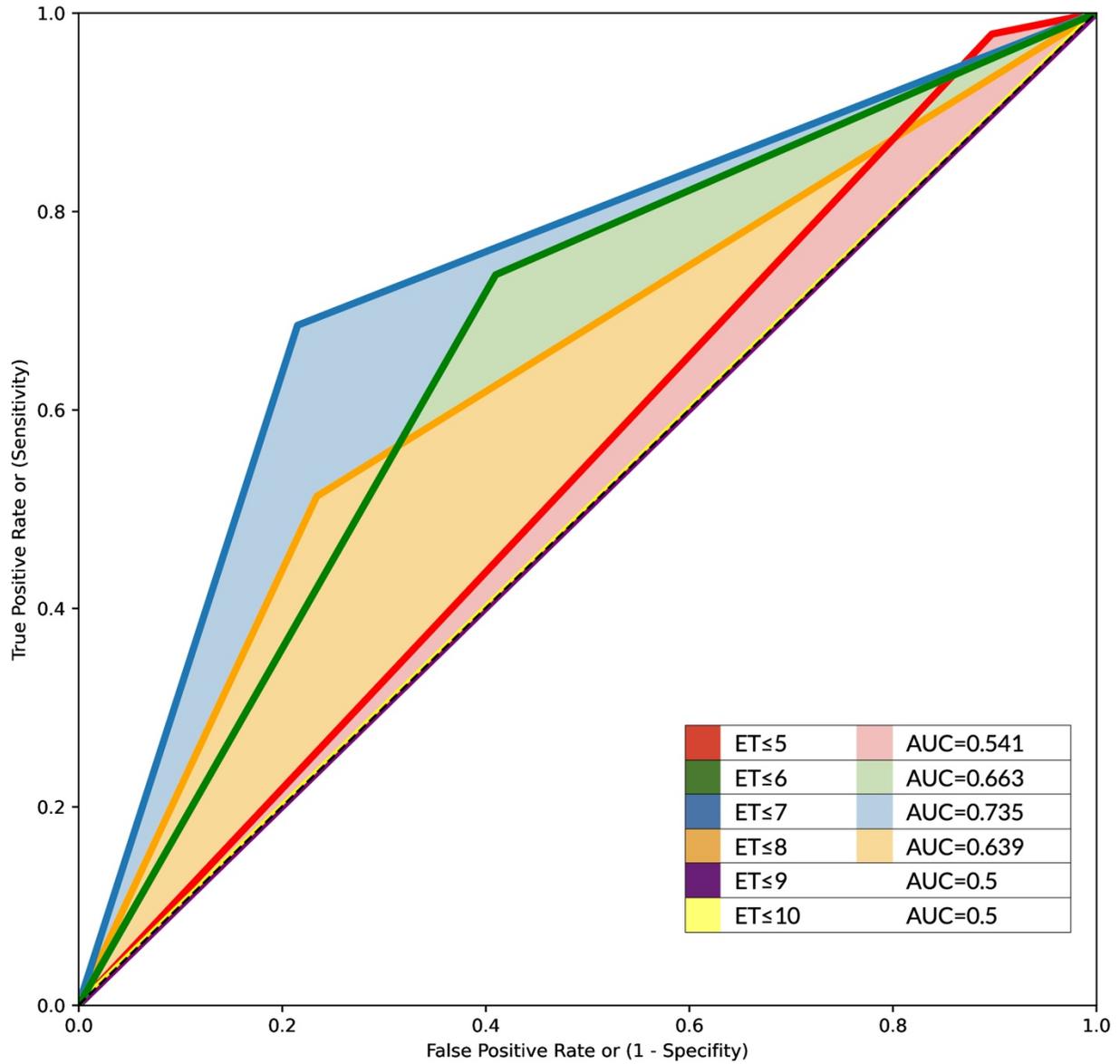
Figure 3.3

ROC curves and AUC values of models varying the age of onset of musical training criterion. The blue line represents the model based on AoS≤7, the classifier that could most accurately predict group membership.

CHAPTER FOUR:
GENERAL DISCUSSION

In both studies described above, we examined how structural features of the cerebellum and sensorimotor cortical areas might be interrelated, and how those relationships might differ in ET and LT musicians. Although we used different methodology in each study – structural covariation in study one and machine learning models in study two – our results consistently showed a negative relationship between cerebellar volume and the size of cortical sensorimotor regions, and that this relationship is altered in ET musicians. These findings add considerable evidence that early musical training is associated with a broad pattern of differences across a larger network. In addition, our results confirm that the sensitive period for coordinated structural change in the cortico-cerebellar network is centered around age 7, as musical training initiated before or after this age shows less pronounced effects. As posited by the *interactive specialization* framework, our findings suggest that these functionally connected regions – the cerebellum and cortical sensorimotor areas – develop in synchrony, and that behaviours and/or experiences which promote plasticity in one part of the network impact development in connected regions (Johnson, 2011). While we might intuitively expect that specialization through training would consistently lead to increases in brain structures – much like how muscles enlarge with physical training – the reality appears to be more complex: although the enlargement of some structures – such as sensorimotor cortical regions – is associated with early musicianship, other structures – such as the cerebellum – appear to reduce in size. The findings detailed in this thesis provide evidence not just of the existence of these bidirectional changes but contextualizes how these changes are interrelated.

Taken together, the results of the studies in this thesis support the existence of a sensitive period for music training that is centered around age seven. Although learning a musical instrument can be done at any time in life, engaging in this complex skill when associated brain

regions are more plastic appears to lead to enhancements in adult musical skill (Baer et al., 2015; Bailey & Penhune, 2010; Ireland et al., 2019; Kraus et al., 2009; Penhune, 2020; Vaquero et al., 2016; Watanabe et al., 2007) and alterations in brain structure (Amunts et al., 1997; Baer et al., 2015; Bailey et al., 2014; Schlaug et al., 1995; Steele et al., 2013; van Vugt et al., 2021). The division between early- and late-trained musicians at age 7 coincides with the peak rate of change for gray matter volume of the cortical sensorimotor regions – including premotor cortex – which are known to be involved in auditory-motor integration (Giedd et al., 1999; Zatorre et al., 2007). Although peak maturation of the cerebellum occurs later in adolescence (Tiemeier et al., 2010), cortico-cerebellar connectivity peaks at age 6-7, coinciding with peak maturation in motor regions (Kipping et al., 2017). As described above, sensitive periods for complex skills such as music or language are unlikely to exhibit abrupt cut-offs. Instead, such skills are likely to depend on a cascade of developmental and experience-dependent plasticity effects with basic sensory processes being affected earlier and more complex processes affected later (Penhune, 2022; Werker & Hensch, 2015). This suggests that plasticity is heightened during these developmental windows, and that long-term plasticity may be the product of experience during periods of peak maturational change at both the local circuit and network levels. This is consistent with the findings from our second study showing that classification before and after age seven was sometimes above chance but was overall less accurate.

Studies in child musicians provide additional insights into the interaction between early music training and sensitive periods in brain maturation. One study of 8-10-year-old children engaging in music lessons identified larger volume of the auditory cortex in children who practiced more (Seither-Preisler et al., 2014). This increase was associated with measures of both musical and cognitive aptitude, as well as measures of auditory processing. Further, Ireland et al.

(2019) found that children who began musical training before age 7 performed better on a melody discrimination task, but not a rhythm synchronization task, compared to children who began later. While this finding is not consistent with studies on adult musicians in which ET musicians outperformed their LT counterparts on rhythm tasks (Bailey & Penhune, 2010, 2012; Vaquero et al., 2016; Watanabe et al., 2007), it is consistent with our understanding of the development of rhythmic abilities: infants have the ability to perceive beat (Hannon et al., 2018; Winkler et al., 2009), but auditory-motor integration does not fully develop until mid- to late adolescence (Drewing et al., 2006; Gogtay et al., 2004). This suggests that children's rhythmic abilities may take time to mature, and that on-going training after age 7 may be required for adult behavioural differences to appear; indeed, 7-13 year-old children showed continuing improvement on rhythm synchronization tasks with increasing age (Ireland et al., 2018). In the case of rhythmic abilities, early musical training may provide a scaffold onto which later rhythmic training may build (Johnson, 2011; Steele & Penhune, 2010). This, again, is consistent with the *interactive specialization* framework: early musical training may induce specialized changes onto which later training – in this case, more complex rhythmic abilities – can build (Johnson, 2011).

Although the second study in this thesis examined only ET and LT musicians, our first study included a sample of non-musicians. Our results suggested a normative negative correlation between cerebellar volume and the size of cortical sensorimotor areas which – although altered and perhaps enhanced in ET musicians – was nonetheless present in non-musicians. A recent study from our group investigated this normative pattern in a large sample using MRI scans from the Human Connectome Project (HCP). The authors used regression analyses to investigate structural covariation between the cerebellum and the entire cortex in a

large sample of healthy adults (Alasmar et al., 2023). Their analyses revealed a similar negative relationship: cerebellar volume was predominantly negatively related to cortical thickness (CT), particularly in sensorimotor, parietal, and frontal regions of the left hemisphere. The authors also identified a positive relationship between cerebellar volume and cortical surface area (SA); they suggest that these divergent relationships may be due to the more plastic nature of CT, which is thought to be more malleable by experience (Amlien et al., 2016; Yoon et al., 2012), as opposed to the more genetically determined SA (Sanabria-Diaz et al., 2010). This mirrors our finding that larger cerebellar volumes are related to reduced CT in sensorimotor regions, possibly because this feature is more susceptible to plastic changes induced by music training.

Future research into sensitive period effects on brain structure would benefit from investigating network-level relationships in additional regions of interest or across the whole brain. Whereas the current research focuses on cortico-cerebellar relationships, musical ability represents a complex collection of auditory and motor skills which have been associated with regions across the entire brain (Zatorre et al., 2007). Future research in this domain might consider investigating the basal ganglia, which have been implicated in beat perception and production perception (Grahn, 2009; Kung et al., 2013) and which have functional connections between the cerebellum and cortex. There is additional evidence that the representations of well-learned skilled movements are dependent on a striatal-cortical circuit (recruiting the striatum and supplementary motor area) rather than a cerebellar-cortical circuit (Doyon & Ungerleider, 2002). The motor sequences mastered during early musical training may therefore be more dependent on the striatum than the cerebellum. Previous research has, in fact, found differences in parts of the basal ganglia between ET and LT musicians: using voxel-based morphometry (VBM) analyses, Vaquero et al. (2016) found that early-trained pianists had smaller gray-matter volume

in the putamen (part of the striatum). Among other functions, the putamen acts as a relay station between the cerebellum and cortical regions (Bostan & Strick, 2010); critically, greater putamen–cerebellar functional connectivity has been associated with better motor performance, whereas greater putamen–M1 functional connectivity can be predictive of poorer motor performance (Simioni et al., 2016). Further, van Vugt et al. (2021) investigated functional connectivity in expert pianists who started their musical training before or after age 7. ET musicians showed higher connectivity in a strial-cortical-sensorimotor network, which was associated with better performance on a test of motor timing expertise. These findings suggest that early musical training may have an impact on functional connectivity between the striatum and sensorimotor cortical regions, and that the cortico-cerebellar network-level differences observed in this thesis may be part of a larger series of network-level changes associated with early musicianship.

Moving away from a region-of-interest approach and towards whole-brain analyses could uncover new information about how brain connectivity is changed by music training. However, modeling structural networks across the entire brain would require a large sample, ideally including other structural and functional measures not collected here. A number of studies have employed more complex analyses to model structural networks, and offer additional methodological possibilities: Lerch et al. (2006) used cortical thickness from T1 MRIs to produce a method termed MACACC (Mapping Anatomical Correlations Across Cerebral Cortex), which applies cross-correlations of cortical thickness values across the tens of thousands of vertices spanning the cortex in order to identify cortical changes with and across cortical networks. This technique allows for the investigation of whether the cortical thickness in one area changes in tandem with other regions. Chen et al. (2008b) identified what they termed "topological modules" using a cortical thickness-based measure which has been refered to as

structure-based modular architechture. Modularity, in this context, refers to the myriad modules which comprise a brain network; this technique examines cortical morphological features, such as local area and volume, in order to identify underlying connectivity patterns. Further, the addition of resting state fMRI and/or diffusion tensor imaging (DTI) might allow future researchers to employ graph theoretical analysis of structural and functional connectivity (Guye et al., 2010). Graph theory groups together data structures from multiple sources – including structural morphology from MRI and connectivity from DTI – to form representations of networks which can be quantified at a number of levels. Future studies might also leverage a larger, purpose-built sample to verify and hone the machine learning models built in our second study. Whereas our modest sample size constrained the validation methods available to us, a larger sample might combine cross-validation with a more traditional train/test split which might produce a more accurate and generalizable model (Kuhn & Johnson, 2018).

Finally, future studies would benefit from including behavioural measures upon which to ground the interpretation of structural and functional differences between ET and LT musicians. Tests of musical aptitude – pitch and melody discrimination, rhythmic synchronization and production – have been used successfully in a number of the studies cited throughout this work. These tasks allow us to quantify differences in musical skills, providing context for differences in structural and functional connectivity between ET and LT musicians. In addition, cognitive and perhaps even personality measures might illuminate differences in ET/LT musicians stemming from variables outside of musical experience. Previous research has linked personality variables such as "openness to experience" with hours of lifetime practice (Butkovic et al., 2015), and cognitive measures – such as tests of working memory – have been associated with heightened musical ability (Swaminathan et al., 2021).

General conclusion

Previous work has provided evidence for a sensitive period for music training and identified brain and behavioural differences between musicians who begin their training before or after age 7. The goal of this thesis was to investigate interrelated differences in sensorimotor cortical and cerebellar regions in early- and late-trained musicians. Across two studies, we found evidence of a negative correlation pattern between sensorimotor cortical and cerebellar regions which is altered in ET musicians. Using support vector machine models, we were able to use structural properties of these regions to predict early musicianship and to validate that the window of heightened sensitivity for musical training appears to peak at around age 7. Together, these findings enrich our understanding of how experience-dependent plasticity is affected by early musical training, providing a more nuanced understanding of the interrelated nature of brain development.

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