

# Early Musical Training Is Linked to Gray Matter Structure in the Ventral Premotor Cortex and Auditory–Motor Rhythm Synchronization Performance

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## Abstract

■ Evidence in animals and humans indicates that there are sensitive periods during development, times when experience or stimulation has a greater influence on behavior and brain structure. Sensitive periods are the result of an interaction between maturational processes and experience-dependent plasticity mechanisms. Previous work from our laboratory has shown that adult musicians who begin training before the age of 7 show enhancements in behavior and white matter structure compared with those who begin later. Plastic changes in white matter and gray matter are hypothesized to co-occur; therefore, the current study investigated possible differences in gray matter structure between early-trained (ET; <7) and late-trained (LT; >7) musicians, matched for years of experience. Gray matter structure was assessed using voxel-wise analysis techniques (optimized voxel-based morphometry, tra-

ditional voxel-based morphometry, and deformation-based morphometry) and surface-based measures (cortical thickness, surface area and mean curvature). Deformation-based morphometry analyses identified group differences between ET and LT musicians in right ventral premotor cortex (vPMC), which correlated with performance on an auditory motor synchronization task and with age of onset of musical training. In addition, cortical surface area in vPMC was greater for ET musicians. These results are consistent with evidence that premotor cortex shows greatest maturational change between the ages of 6–9 years and that this region is important for integrating auditory and motor information. We propose that the auditory and motor interactions required by musical practice drive plasticity in vPMC and that this plasticity is greatest when maturation is near its peak. ■

## INTRODUCTION

Evidence that early experience differentially influences skill acquisition and brain structure has been observed in several domains. Second language proficiency is enhanced when exposure begins earlier in development (Weber-Fox & Neville, 2001; Flege, Yeni-Komshian, & Liu, 1999) and speech perception is better for those who receive cochlear implants at an earlier age (Nicholas & Geers, 2007; Geers, 2006; Harrison, Gordon, & Mount, 2005). The interaction between brain maturation and experience results in sensitive periods during development where experience has enhanced effects on the brain and behavior (Knudsen, 2004). Sensitive periods have been identified in the visual and auditory systems (for reviews, see de Villers-Sidani & Merzenich, 2011; Hooks & Chen, 2007). Suggestive evidence that early musical training might have similar effects came from studies reporting differences in the corpus callosum, motor cortex, and cortico-spinal tract that were related to the age of start of training or to the hours of practice in childhood (Imfeld, Oechslin, Meyer, Loenneker, & Jäncke, 2009; Bengtsson et al., 2005; Amunts et al., 1997;

Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995). However, none of these studies controlled for the length of musical training and did not show a relationship between differences in brain structure and performance on musically relevant tasks. Work in our laboratory has shown that musicians who begin training before the age of 7 years perform more accurately on an auditory rhythm synchronization task (RST), even after controlling for years of experience (Bailey & Penhune, 2010, 2012). Recently, we have shown that early-trained musicians perform better on a visual–motor synchronization task and have enhanced white matter integrity in the corpus callosum (Steele, Bailey, Zatorre, & Penhune, 2013). Other studies have found that early training enhances music-related neural responses, including auditory brain stem potentials (Wong, Skoe, Russo, Dees, & Kraus, 2007), somatosensory finger representation (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995), and auditory cortical responses (Pantev et al., 1998). Taken together, these results indicate that there may be a sensitive period for musical training where early experience has long-lasting effects on behavior and the brain (see Penhune, 2011; Trainor, 2005, for reviews).

Two neuroanatomical processes may interact to set the stage for sensitive periods: brain maturation and experience-driven plasticity. Given that different brain

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areas have distinct maturational timelines (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Gogtay et al., 2004), sensitive periods may emerge when maturational plasticity in a brain region associated with a specific skill is paired with intensive experience or practice of that skill. Musicians are a good population in which to study the interaction between maturational and experience-dependent plasticity because training begins at different ages, can be quantified, and is known to influence brain structure (for recent reviews, see Penhune, 2011; Wan & Schlaug, 2010; Jäncke, 2009). Furthermore, several components of the anatomical network implicated in musical training undergo their greatest structural change in early childhood (Lebel et al., 2008; Gogtay et al., 2004). Because our previous work showed that early musical training is associated with enhanced white matter connectivity (Steele et al., 2013) and changes in white matter often coincide with changes in gray matter (Scholz, Klein, Behrens, & Johansen-Berg, 2009), the purpose of the current study was to examine effects of early training on gray matter structure within the auditory–motor network. To do this, we compared gray matter structure and performance on an auditory RST in adult musicians who began training before and after the age of 7 years who were matched for years of experience, formal training and hours of current practice. Importantly, we used a series of complementary voxel-wise and surface-based structural MRI data analysis techniques to assess the effect of early training on gray matter structure. We hypothesized that early musical training would be associated with better performance on the RST and differences in gray matter structure in auditory and motor regions.

When investigating the sensitive period hypothesis for musical training, it is important to consider the specific maturational trajectories of gray matter and white matter. Gray matter development appears to follow an inverted U-shaped maturation pattern with increases in volume in early childhood, followed by gradual decreases with age (Gogtay & Thompson, 2010; Gogtay et al., 2004; Sowell, Thompson, Tessner, & Toga, 2001). When examining gray matter maturation rates more locally, it seems that higher-order association areas reach maturity only after the lower-order sensorimotor areas. The primary sensory and motor cortices and the frontal and occipital poles mature first, whereas the rest of the cortex matures more or less in a parietal to frontal fashion, with the exception of the superior temporal cortex, which matures last (Gogtay et al., 2004). White matter maturational trajectories are also nonlinear, with the sensorimotor network coming on-line during early childhood (Paus, 2010; Lebel et al., 2008). Musical training may interact with these brain maturation processes to fine-tune this network most effectively when that training takes place early in development.

It is also important to consider experience-driven plasticity when investigating the sensitive period hypothesis for musical training. Studies using a group comparison method have shown differences between musicians and

nonmusicians in measures of brain structure and function within sensorimotor and prefrontal areas, suggesting training-induced plasticity effects (e.g., Bermudez, Lerch, Evans, & Zatorre, 2008; Chen, Penhune, & Zatorre, 2008a, 2008b; Gaab & Schlaug, 2003; Sluming et al., 2002). Several studies have reported correlations between the amount of musical training and measures of brain structure, strengthening the link between training and plasticity (e.g., Abdul-Kareem, Stancak, Parkes, & Sluming, 2010; Foster & Zatorre, 2010; Gaser & Schlaug, 2003). Although other factors, such as genetic predisposition, may contribute to these findings in adults, a recent structural imaging study in children showed increases in the volume of auditory and premotor cortex as well as the corpus callosum after 15 months of music lessons (Hyde et al., 2009). Overall, the emerging evidence suggests that musical training influences brain structure within the sensorimotor network through the mechanisms of experience-driven plasticity.

The current study investigated possible differences in gray matter structure between early- and late-trained musicians using a multimodal approach. Neuroimaging studies examining gray matter structure are moving beyond using single analysis techniques, and multimodal approaches are becoming more common. Combining multiple techniques can provide more information about the structural characteristics contributing to observed differences. Several whole-brain analyses are available including voxel-based morphometry (VBM), optimized VBM, deformation-based morphometry (DBM), and cortical surface measures such as thickness and curvature (see Good et al., 2001, for a detailed explanation of VBM methodologies). Traditional VBM fits individual brain volumes to a common template and compares gray matter values on a voxel-wise basis. Results of traditional VBM analyses are typically interpreted as revealing differences in gray matter “concentration.” DBM analysis measures the degree of deformation required to fit each participant to a common template (i.e., the Jacobian determinant) on a voxel-wise basis. Results of DBM analyses are typically interpreted as revealing differences in shape or volume. Optimized VBM is a combination of these two techniques, which fits each participant to a common template and then modulates the gray matter concentration value in each voxel by the degree of deformation that was required to fit that participant to the template. Optimized VBM was designed to capture either differences in concentration or differences in shape or volume but can be problematic because it confounds the two factors. In addition to these voxel-wise analysis techniques, surface-based measures such as cortical thickness, surface area, curvature, and gray matter volume are available to identify differences in cortical surface features. In the current experiment, we used both voxel- and surface-based measures and examined the relationships between them to better identify the specific source of observed gray matter differences between our groups of early- and late-trained musicians.

## METHODS

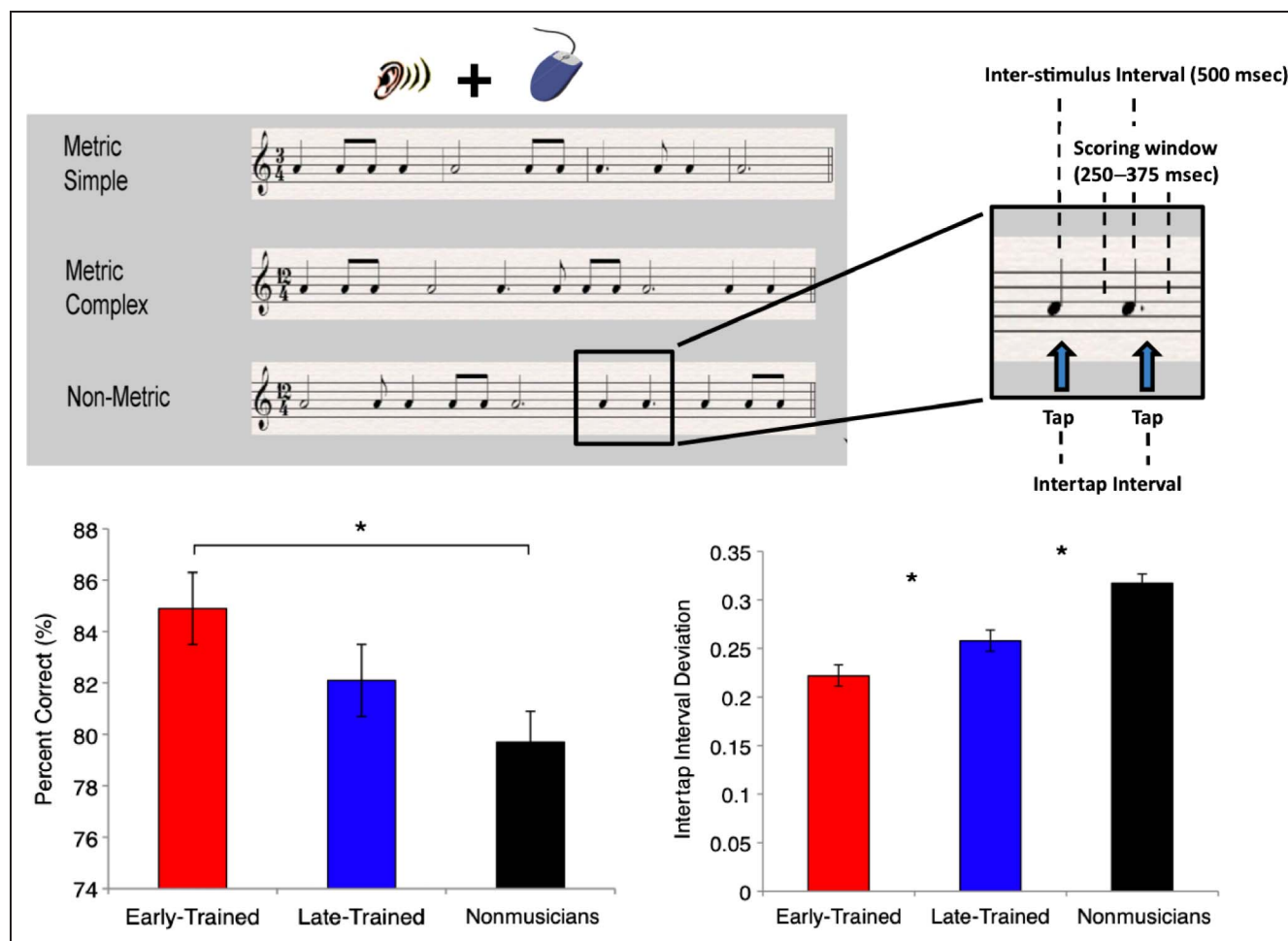
### Participants

Two groups of highly trained and currently practicing musicians participated in this study. These groups were selected based on the age at which they started musical training: those who began at or before the age of 7 years were classified as “ET” ( $n = 15$ ) and those who began after the age of 7 years were classified as “LT” ( $n = 15$ ). The age cutoff of 7 years was based on previous findings (Bailey & Penhune, 2010; Watanabe, Savion-Lemieux, & Penhune, 2007; Schlaug et al., 1995). To ensure that any observed differences in task performance or brain structure were not confounded by differences in experience, the two groups were matched for years of musical experience, years of formal training, and hours of current practice. In addition, a control group of nonmusicians (NM;  $n = 20$ ) also participated in this study. NM had less than 3 years of musical training and were not currently practicing. To assess musical experience, all participants completed the Musical Experience Questionnaire (MEQ) that was developed in our laboratory (Bailey & Penhune, 2010). The

MEQ quantifies the amount of instrumental, vocal, and dance training an individual has received, at what age this training occurred, and the amount of time currently dedicated to practice on a weekly basis. All participants were right-handed, completed a MR safety screening form, and provided written informed consent. The experimental protocol was approved by the McGill University MNH/I Research Ethics Board and the Concordia University Human Research Ethics Committee.

### Behavioral Tasks

The RST requires participants to listen and then tap in synchrony with a series of auditory rhythms varying in metrical complexity (Figure 1). Performance differences on the RST between ET and LT musicians have been observed (Bailey & Penhune, 2010, 2012). It is a modified version of a task used to examine functional correlates of auditory rhythm synchronization among musicians and nonmusicians (Chen et al., 2008a, 2008b). Each rhythm comprises 11 woodblock notes and has a total duration



**Figure 1.** Illustration of the RST and mean performance scores for PC and ITI deviation. ANOVA results indicated a main effect of Group on both performance measures, and post hoc analyses for ITI deviation revealed superior task performance among the early-trained musicians compared with the late-trained musicians. Both musician groups outperformed the nonmusicians on both performance measures. Error bars represent SEM.

of 6 sec. These rhythms differ in their temporal structure, such that the temporal intervals between notes are manipulated, but not the duration of the notes themselves, which were woodblock sounds lasting 200 msec in duration. Essens and Povel (Essens, 1995; Essens & Povel, 1985) developed a model by which musical rhythms can be classified into levels of difficulty based on their metrical structure. Manipulation of the temporal structure of the notes results in three levels of progressively more complex and less metrically structured rhythms. Three levels of metrical complexity were chosen, and participants were exposed to two rhythms at each level: metrically simple, metrically complex, and nonmetrical. Despite these differences in metrical organization, each rhythm is made up of five eighth notes (each 250 msec), three quarter notes (each 500 msec), one dotted quarter note (750 msec), one half note (1000 msec), and one dotted half note (1500 msec). On each trial, one rhythm is presented twice. On the first presentation, participants are instructed to listen carefully, and on the second presentation they are asked to tap in synchrony with the rhythm using the computer mouse. Each rhythm is presented in a counterbalanced fashion six times in each block, and participants perform two blocks. For a more detailed description of the RST, see Bailey and Penhune (2010).

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

To examine any potential differences between groups in cognitive abilities, participants completed the digit span and letter–number sequencing subtests from the Wechsler Adult Intelligence Scale III (Wechsler, 1997) and the vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Digit span and letter–number sequencing are measures of auditory working memory. Vocabulary and matrix reasoning are measures of cognitive abilities that are strongly correlated with global IQ scores. Standard procedure was followed for administering and scoring each subtest.

## Procedure

During an initial behavioral testing session, participants completed the MEQ, the RST, and the four cognitive tests. Structural MRI scans were acquired on a second day using a Siemens Trio 3T MRI scanner with a 32-channel head

coil (repetition time = 2300 msec, echo time = 2.98 msec,  $1 \times 1 \times 1 \text{ mm}^3$ ).

## Behavioral Data Analyses

To compare performance on the RST between the three groups, a repeated-measures ANOVA for both PC and ITI deviation was conducted, with Group as the between-subject factor. Pairwise comparisons for between-group differences were analyzed using a least significant differences correction for multiple comparisons. The result of our matching procedure was evaluated using *t* tests comparing years of musical experience, years of formal training, and hours of current practice between the ET and LT groups. Group differences on the scaled scores of the cognitive tests were assessed using a one-way ANOVA with Group as the between-subject factor, and pairwise comparisons were conducted using a least significant differences correction for multiple comparisons.

## MRI Data Analyses

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

### VBM and DBM Analyses

All VBM and DBM analyses were conducted using FSL tools (Smith et al., 2004). T1 images were brain-extracted using



BET (Smith, 2002), and tissue-type segmentation was carried out using FAST4 (Zhang, Brady, & Smith, 2001). The resulting gray matter partial volume images were aligned to the MNI152 standard template using the affine registration tool FLIRT (Jenkinson & Smith, 2001), followed by a nonlinear registration using FNIRT (Andersson, Jenkinson, & Smith, 2007). The resulting images were averaged to create a study-specific template, to which the native gray matter images were then nonlinearly registered. In the optimized VBM protocol (Good et al., 2001), the registered partial volume images are modulated by the Jacobian determinants of the warp field. In addition, we examined the natural logarithm values of the Jacobian determinants themselves as measures of local expansion or contraction (DBM) as well as gray matter traditional VBM values (Ashburner & Friston, 2000). In all three analyses, final images were smoothed using an isotropic Gaussian kernel with a sigma of 4 mm and voxel-wise GLM was applied using permutation-based nonparametric testing with a cluster-based thresholding approach ( $t = 3.66$ , voxel-wise uncorrected  $p < .001$ ), correcting for multiple comparisons. To assess differences between ET and LT musicians, whole-brain group comparisons were conducted using optimized VBM, DBM, and traditional VBM. For the region of significant difference identified, mean values for all three groups (ET, LT, and NM) were extracted and compared. In addition, these values were correlated with ITI deviation scores on the RST as well as age of onset of musical training.

#### *Cortical Thickness and Surface-based Analyses*

Cortical reconstruction was performed with the FreeSurfer image analysis suite, which is documented and freely available for download on-line ([surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)). The technical details of these procedures have been described in prior publications (Han et al., 2006; Jovicich et al., 2006; Fischl et al., 2002, 2004; Ségonne et al., 2004; Fischl, Liu, & Dale, 2001; Fischl & Dale, 2000; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Dale & Sereno, 1993). In summary, the processing stream includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter (Fischl et al., 2002, 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Ségonne, Pacheco, & Fischl, 2007; Fischl et al., 2001), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Fischl & Dale, 2000; Dale et al., 1999; Dale & Sereno, 1993). Each volume and surface was visually inspected for errors or inaccuracies. Once the cortical models were complete, the creation of surface-based data including maps of cortical thickness, curvature, and surface area was carried out. This

method uses both intensity and continuity information from the entire 3-D MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups. All data maps were smoothed with a 20-mm FWHM Gaussian kernel. A whole-brain group comparison of cortical thickness between the ET and LT musicians was conducted. Additionally, the ROI in the ventral premotor cortex (vPMC) identified in the DBM analysis was imported into FreeSurfer, registered to the average volume, mapped onto the average surface, and finally mapped onto each individual's surface. Group comparisons for mean values of cortical thickness, surface area, curvature, and gray matter volume for this ROI were carried out, as well as correlations with ITI deviation on the RST as well as age of onset of musical training. In addition, a whole-brain search for areas where cortical thickness correlated with musical experience demographics was carried out.

#### *Correlation Analyses between Traditional VBM, DBM, and Surface-based Measures*

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

## RESULTS

### **Behavioral Results**

Statistical comparison of the ET and LT musicians confirmed that there were no significant differences between the two groups in terms of age, years of musical experience, years of formal training, or hours of current practice (Table 1). The NM group had fewer than 3 years of musical training and did not differ in age from either musician group.

Comparisons of cognitive subtest scores revealed no significant between-group differences on digit span or letter-number sequencing (Table 2). A main effect of Group trending toward significance was observed for vocabulary and matrix reasoning ( $p = .078$  and  $p = .055$ , respectively). Post hoc comparisons revealed that vocabulary scores were higher for NM than ET ( $p = .026$ ) and

**Table 1.** Group Demographics of Musical Experience Variables

Group	Age (years)	Age of Onset (years)	Formal Training (years)	Musical Experience (years)	Current Practice (hr)
Early-trained (ET)	23.47 ( $\pm 3.85$ )	5.87 ( $\pm 1.19$ )	11.73 ( $\pm 3.97$ )	16.87 ( $\pm 4.10$ )	15.23 ( $\pm 9.97$ )
Late-trained (LT)	26.60 ( $\pm 5.22$ )	10.47 ( $\pm 2.03$ )	10.03 ( $\pm 4.39$ )	15.90 ( $\pm 4.74$ )	14.43 ( $\pm 7.80$ )
<i>t</i> values	-1.87	-7.57**	1.11	0.60	0.25
Nonmusicians (NM)	26.20 ( $\pm 4.35$ )	-	0.69 ( $\pm 0.79$ )	0.91 ( $\pm 0.75$ )	-

SDs are in parentheses.

\*\* $p < .001$ .

that matrix reasoning scores were higher for LT than NM ( $p = .017$ ). The ET did not outperform the other two groups on any measure.

Comparison of performance on the RST between the three groups revealed a significant main effect of group for both performance measures [PC:  $F(2, 47) = 3.99, p = .03$ ; ITI deviation:  $F(2, 47) = 20.30, p < .001$ ; Figure 1]. Post hoc analyses for PC revealed that ET outperformed NM ( $p = .017$ ), but not LT. Post hoc analyses for ITI deviation revealed that the ET outperformed the LT ( $p < .05$ ) and that both groups outperformed the NM (both  $p < .0001$ ).

## MRI Results

### VBM and DBM Results

When images were analyzed using optimized VBM, where spatially registered voxel-wise gray matter values are modulated by the Jacobian determinants (Good et al., 2001), whole-brain analysis revealed differences between ET and LT musicians in three main areas (ET > LT;  $t_s > 3$ , uncorrected for multiple comparisons): bilateral vPMC (right peak voxel: 50, 8, 24,  $t = 4.31$ ; left peak voxel: -46, 2, 26,  $t = 4.18$ ), left dorsal premotor cortex (peak voxel: -24, 0, 56,  $t = 4.35$ ), and left primary somatosensory cortex (peak voxel: -24, -34, 54,  $t = 3.19$ ). These areas did not surpass the permutation-based nonparametric correction for multiple comparisons. The strongest effect was located in the right vPMC and reached a  $p$  value of .10.

To understand the contributions of traditional VBM gray matter values and local differences in volume or shape contributing to this effect, traditional VBM and DBM analyses were conducted independently. The traditional VBM analysis revealed no significant group differences; however, the DBM analysis revealed a significant group difference (ET > LT) in the right vPMC at the same location identified in the optimized VBM analysis (peak voxel: 50, 4, 20,  $t = 5.32$ ; cluster  $p < .05$ , corrected for multiple comparisons; Figure 2A). The ET group required greater contraction in this area than the LT to register their volumes to the study-specific template, suggesting that differences in local volume or shape were driving the observed difference in this region in the optimized VBM analysis.

Confirming the relevance of these findings for auditory-motor synchronization performance, extracted mean deformation values from this ROI were negatively correlated with ITI deviation scores such that better performance was related to higher deformation values ( $r = -0.354, p < .05$ ; Figure 2B). Interestingly, the extracted mean gray matter values obtained from the traditional VBM analysis from this ROI showed no effect of group or relation to task performance ( $t = -0.74$  and  $r = 0.022, p = .46$ , respectively; Figure 2B). The extracted mean values from the NM group were included for the sake of comparison, as no significant differences were observed using a whole-brain approach in any of the VBM-style analyses. The extracted mean deformation values for the NM in this area of the premotor cortex significantly differed from both groups of musicians (ET-NM:  $t = 2.22, p < .05$ ;

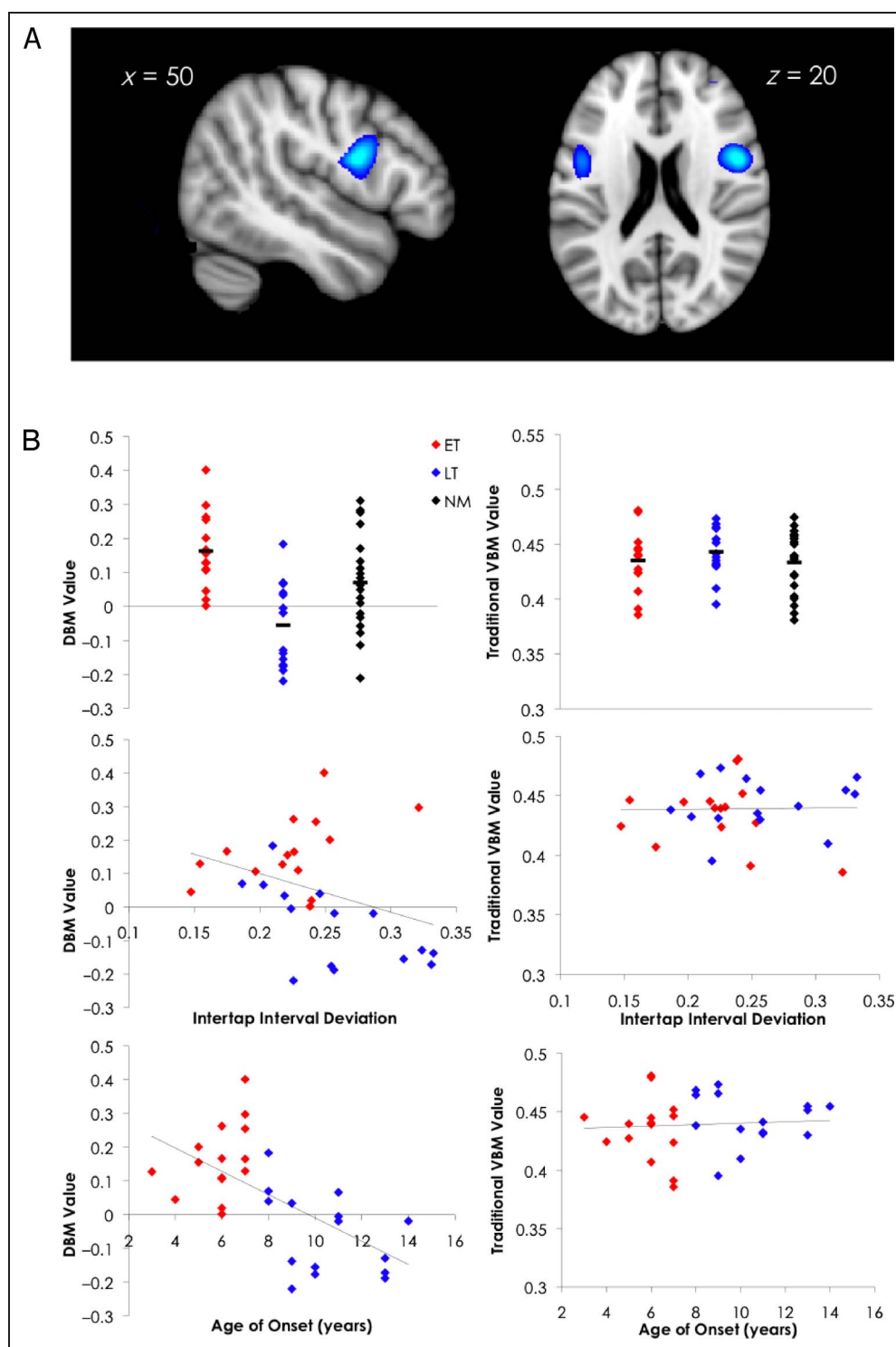
**Table 2.** Group Cognitive Subtest Scores

Group	Digit Span	Letter-Number Sequencing	Vocabulary	Matrix Reasoning
Early-trained (ET)	12.13 ( $\pm 2.88$ )	12.33 ( $\pm 2.94$ )	12.33 ( $\pm 3.33$ )	12.20 ( $\pm 3.34$ )
Late-trained (LT)	12.27 ( $\pm 1.98$ )	11.80 ( $\pm 2.78$ )	13.33 ( $\pm 2.82$ )	13.60 ( $\pm 2.32$ )
Nonmusicians (NM)	11.05 ( $\pm 3.43$ )	11.45 ( $\pm 2.11$ )	14.45 ( $\pm 1.96$ )	11.15 ( $\pm 2.91$ )
<i>F</i>	0.96	0.61	2.69	3.08

SDs are in parentheses.

\* $p < .05$ .

**Figure 2.** Results from the DBM analysis between early-trained and late-trained musicians. (A) Visual representation of the area of difference observed in the right vPMC. (B) Extracted DBM values and traditional VBM values from the ROI in the vPMC for each group, correlated with task performance, and age of onset.



LT < NM:  $t = -2.79, p < .05$ ; Figure 2B), although their extracted mean deformation values did not relate to their ITI deviation scores on the RST ( $r = 0.213, p = .19$ ). Furthermore, the mean gray matter extractions from the traditional VBM analysis for the NM did not differ when compared with either musician group (ET-NM:  $t = 0.17, p = .87$ ; LT-NM:  $t = 1.06, p = .30$ ; Figure 2B), nor did they

relate to their ITI deviation scores on the RST ( $r = 0.182, p = .23$ ; Figure 2B).

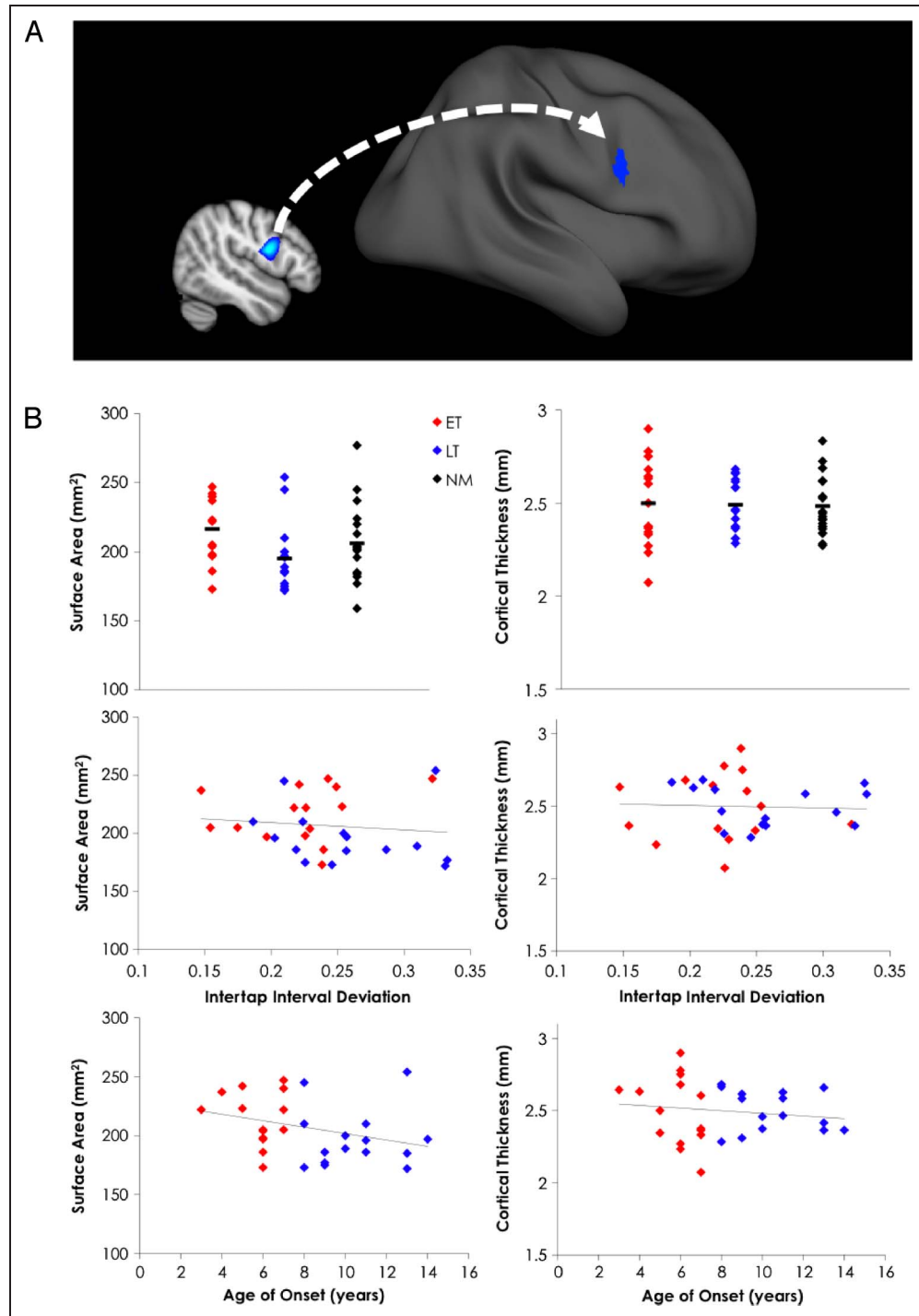
#### Cortical Thickness and Surface-based Results

We conducted a whole-brain analysis examining differences in cortical thickness but found no significant group

differences. As a follow-up step to examine the relationship between DBM values and cortical surface measures, the ROI in the right vPMC identified with DBM was imported into FreeSurfer, and values for cortical thickness, surface area curvature, and volume were extracted. This ROI approach revealed a significant group difference between ET and LT for surface area (ET:  $M = 216.53$ ,  $SD = 23.23$ ; LT:  $M = 197.00$ ,  $SD = 24.55$ ;  $t = 2.24$ ,  $p < .05$ ; Figure 3B), such that ET musicians had greater

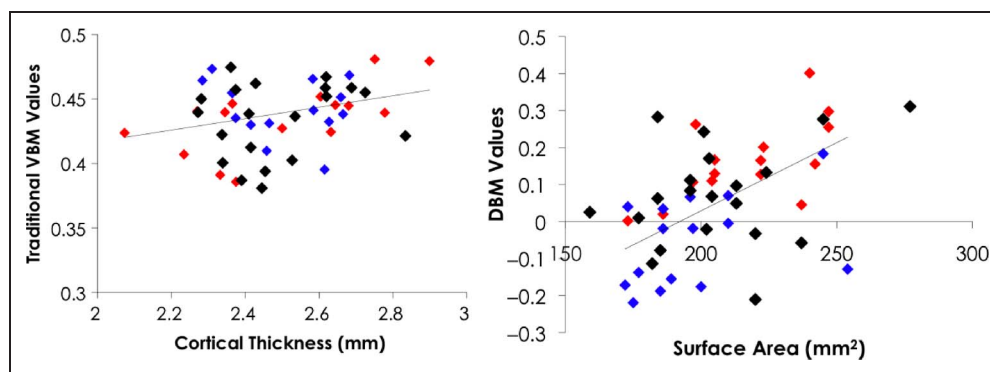
surface area in this region. These findings suggest that differences in surface area are contributing to the observed difference in deformation values in this part of the premotor cortex. Interestingly, there were no ET–LT differences in cortical thickness (ET:  $M = 2.50$ ,  $SD = 0.23$ ; LT:  $M = 2.50$ ,  $SD = 0.14$ ;  $t = 0.03$ ,  $p = .98$ ), mean curvature (ET:  $M = 0.12$ ,  $SD = 0.02$ ; LT:  $M = 0.11$ ,  $SD = 0.02$ ;  $t = 0.50$ ,  $p = .62$ ), or total gray matter volume (ET:  $M = 493.73$ ,  $SD = 93.57$ ; LT:  $M = 437.93$ ,  $SD = 112.35$ ;

**Figure 3.** Extracted mean surface-based measures from the right vPMC. (A) Visual representation of the ROI from the DBM analysis mapped onto the average surface. (B) Extracted mean surface area and cortical thickness values from the right vPMC for each group, correlated with task performance and age of onset.





**Figure 4.** Extracted mean traditional VBM values correlated with cortical thickness and DBM values correlated with surface area for all groups from the ROI in the right vPMC.



$t = 1.48, p = .15$ ) for this region. The extracted mean values from the NM group were included for the sake of comparison and did not reveal any significant differences in surface area (ET-NM:  $t = 1.21, p = .24$ ; LT-NM:  $t = -0.68, p = .50$ ) cortical thickness (ET-NM:  $t = 0.22, p = .82$ ; LT-NM:  $t = 0.26, p = .80$ ), mean curvature (ET-NM:  $t = -0.18, p = .86$ ; LT-NM:  $t = -0.74, p = .46$ ), or total gray matter volume (ET-NM:  $t = 0.67, p = .51$ ; LT-NM:  $t = -0.92, p = .36$ ) compared with either musician group.

#### Correlations between Structural Measures

When correlations between all structural measures extracted from the right vPMC ROI were examined across participants, it was observed that cortical thickness correlated with traditional VBM values ( $r = 0.284, p < .05$ ; Figure 4) and DBM values correlated with surface area ( $r = 0.487, p < .001$ ; Figure 4) and mean curvature ( $r = 0.322, p < .05$ ). In addition, gray matter volume correlated significantly with all measures of gray matter in this ROI (surface area:  $r = 0.732, p < .001$ ; cortical thickness:  $r = 0.364, p < .01$ ; curvature:  $r = 0.555, p < .001$ ; DBM:  $r = 0.519, p < .001$ ), with the exception of the traditional VBM values ( $r = -0.099, p = .49$ ). This pattern of results corroborates previous findings, suggesting that gray matter values using traditional VBM are associated with cortical thickness and DBM values may relate to other larger, perhaps more variable, cortical features such as surface area, curvature, or gray matter volume (Foster & Zatorre, 2010; Bermudez et al., 2008; Voets et al., 2008; Eckert et al., 2006).

## DISCUSSION

### Summary of Main Findings

We investigated the interaction between brain maturation and experience in ET and LT musicians by comparing MRI measures of gray matter structure and performance on an auditory-motor RST. Behavioral analyses revealed enhanced synchronization performance in the ET musicians, consistent with previous findings (Bailey & Penhune, 2010). Gray matter analyses revealed significant differences

in deformation values in the right vPMC, indicating that ET musicians have greater gray matter in this region. Importantly, extracted deformation values from the right vPMC correlated with the age of onset of musical training and with performance on the RST for the musician groups. Interestingly, ET musicians also had greater surface area in this region, and deformation values were correlated with measures of surface area and curvature. These results further support the interpretation that deformation values may be related to measures of cortical volume or shape. These differences in brain structure and auditory rhythm synchronization performance are unlikely to be accounted for by differences in length of training because the two groups of musicians were matched for musical experience. These findings support the interpretation that the effect of early training on auditory rhythm synchronization performance is mediated through plastic changes in the premotor cortex.

### Why the vPMC?

The fact that ET musicians have greater gray matter volume in the right vPMC is compatible with its role in sensorimotor integration (see Chen, Penhune, & Zatorre, 2009; Hoshi & Tanji, 2007; Zatorre, Chen, & Penhune, 2007, for reviews) and with the maturational trajectories of gray matter and white matter in this region. In a previous fMRI study using the same task, synchronization performance was found to be related to activity in an almost identical location in the right vPMC (peak voxel: 48, 4, 24; Chen et al., 2008a, 2008b). In that experiment, performance was also related to the interaction between premotor cortex and auditory association areas of the superior temporal gyrus, and it was hypothesized that this network was important for integrating auditory perception with a motor response. This study adds to these findings by indicating that this cortical network can be anatomically modified in an age-sensitive manner. The performance difference we observed is not likely to be related to cognitive abilities, given that there were no significant differences between ET and LT musicians on any cognitive measure, consistent with previous results (Bailey & Penhune, 2010).

The maturational trajectory of gray matter in the vPMC makes it a likely candidate to be differentially affected by musical training in early childhood (Gogtay et al., 2004). The primary motor cortices are among the first to mature (approximate peak at or before the age of 5; Gogtay et al., 2004); but the premotor cortex has a more protracted development (approximate peak at the age of 8.5; Gogtay et al., 2004). Given that the ET musicians typically began at the age of 5 or 6, their first few years of training would coincide with time of maximum plasticity in the premotor cortex. Our previous findings in a subset of the same population showed that white matter integrity in the region of the corpus callosum connecting premotor and motor cortices correlated with age of onset of training (Steele et al., 2013). This suggests that gray matter plasticity in premotor cortex may be in part related to changes in the fibers connecting this region in the two hemispheres. A large number of studies have indicated that auditory and premotor regions interact when playing, listening to, or imagining musical sequences (Brown et al., 2013; Chen, Rae, & Watkins, 2011; Chen et al., 2008a, 2008b; Lahav, Saltzman, & Schlaug, 2007). Thus, the interaction between auditory and premotor regions required for musical practice is likely a key contributor to driving plasticity. Several prior studies have shown that auditory areas are subject to plastic changes as a function of musical training (Foster & Zatorre, 2010; Bermudez et al., 2008; Gaser & Schlaug, 2003; Schneider et al., 2002). Auditory regions have a longer maturational trajectory than motor regions, with changes on-going into young adulthood, perhaps explaining why we did not observe differences between ET and LT musicians in these areas. Taken together, these results suggest that there may be a cascade of sensitive periods depending on the maturational timelines of particular brain regions and their interactions with specific experience (de Villiers-Sidani & Merzenich, 2011; Kuhl, 2010).

### Proposed Mechanism

There are a number of different microstructural processes that may underlie the observed macroscopic changes in the adult brain associated with experience or training (for reviews, see Zatorre, Fields, & Johansen-Berg, 2012; May, 2011). For example, it has been proposed that macroscopic changes in gray matter may be attributed to changes in dendritic spine morphology (Kolb, Cioe, & Comeau, 2008) or synaptogenesis (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996). Glial cells are also thought to be involved in learning and may contribute to training-induced changes in gray matter (Dong & Greenough, 2004). Of particular relevance to the idea of a sensitive period, cellular competition for resources during development may be reflected in activity-dependent processes such as synaptic pruning or neuron death (Zatorre et al., 2012; Stoneham, Sanders, Sanyal, & Dumas, 2010). It has been proposed that the initial proliferation of synapses early in postnatal

development takes place independent of experience, but that experience-based neural activity is an important factor in determining which synapses are retained to develop an efficient and specialized system (Stoneham et al., 2010). Evidence identifies glial cells and astrocytes as key players in this pruning process (Stephan, Barres, & Stevens, 2012). In the context of the current study, it may be that repeated activation of the auditory–motor network through daily practice of a musical instrument may alter pruning processes when that practice begins early in development, resulting in the macroscopic cortical changes we observed in vPMC. Alternately, early training could lead to increased gray matter via the mechanisms previously stated (e.g., changes in dendritic morphology, synaptogenesis, or glial cells) before the pruning process or early training may lay the foundation upon which increases in gray matter can occur with continued practice. The exact mechanisms accounting for the observed differences require more investigation.

### Differences between DBM and VBM and Their Relation to Cortical Measures

DBM has been used to evaluate differences or changes in gray matter volume and, more specifically, yields voxel-wise estimates of contraction or expansion of gray matter (e.g., Leporé et al., 2010; Hyde et al., 2009; Chung et al., 2001). In the current study, results from the optimized VBM analysis revealed subthreshold differences between ET and LT in the right vPMC. When separate analyses were performed using traditional VBM and DBM, DBM values showed a significant difference in this region, whereas traditional VBM did not. These results suggest that the group difference observed is driven by local differences in shape or volume. These findings are not the first to highlight the importance of considering differences between optimized VBM, traditional VBM, and DBM. Eckert and colleagues (2006) examined neuroanatomical features associated with Williams Syndrome and reported that DBM data contributed significantly to their optimized VBM results, similar to the current findings. In addition, correlations of extracted measures of gray matter from this ROI across all three groups revealed that deformation values correlated with measures of surface area and curvature, whereas traditional VBM gray matter values correlated with cortical thickness. Previous findings have revealed an association between traditional VBM measures of gray matter and cortical thickness among musicians in the auditory and motor areas (Foster & Zatorre, 2010; Bermudez et al., 2008). In a study of schizophrenia, decreased gray matter values using optimized VBM were related to cortical thinning in some regions and decreased surface area in others (Voets et al., 2008). In summary, it is informative to include surface-based measures of morphometry such as cortical thickness, surface area, curvature, and local gray matter volume to disambiguate observed differences in VBM and DBM data.

## Other Contributing Factors

In addition to the age of start of training, other factors may contribute to the observed differences in gray matter structure between early and late-trained musicians. Genetic factors underlying individual differences in auditory, motor, or cognitive abilities (e.g., executive functions) may make it more or less likely that a child will begin training early and/or persist in training. Furthermore, family history of musical training, family support for training, and child motivation may also be relevant. Importantly, we know that genetic and environmental factors interact, making isolating their contributions extremely challenging. In the future, longitudinal studies in children who begin lessons at different ages may at least allow us to assess the influences of these different factors. Lastly, we evaluated years of experience, formal training, and hours of current weekly practice; in the future, it would be interesting to investigate the contribution of cumulative hours of practice or practice intensity.

## Conclusion

Our findings revealed that musicians who began training before the age of seven showed enlargement of the vPMC that was related to enhanced auditory–motor synchronization performance. Premotor cortex is known to interact with auditory association areas during perception and production of musical sequences. This suggests that musical training in early childhood stimulates cellular processes that either promote growth or reduce pruning in this region. Although much remains unknown about the precise mechanisms that underlie these changes, we propose that an interaction between maturation and specific experience results in a sensitive period where musical training has a differential impact on the brain and behavior.

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