Cortical Thickness Maturation and Duration of Music Training: Health-Promoting Activities Shape Brain Development

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Objective: To assess the extent to which playing a musical instrument is associated with cortical thickness development among healthy youths. **Method:** Participants were part of the National Institutes of Health (NIH) Magnetic Resonance Imaging (MRI) Study of Normal Brain Development. This study followed a longitudinal design such that participants underwent MRI scanning and behavioral testing on up to 3 separate visits, occurring at 2-year intervals. MRI, IQ, and music training data were available for 232 youths (334 scans), ranging from 6 to 18 years of age. Cortical thickness was regressed against the number of years that each youth had played a musical instrument. Next, thickness was regressed against an "Age $\times$ Years of Playing" interaction term. Age, gender, total brain volume, and scanner were controlled for in analyses. Participant ID was entered as a random effect to account for within-person dependence. False discovery rate correction was applied ($p \leq .05$). **Results:** There was no association between thickness and years playing a musical instrument. The "Age $\times$ Years of Playing" interaction was associated with thickness in motor, premotor, and supplementary motor cortices, as well as prefrontal and parietal cortices. Follow-up analysis revealed that music training was associated with an increased rate of thickness maturation. Results were largely unchanged when IQ and handedness were included as covariates. **Conclusion:** Playing a musical instrument was associated with more rapid cortical thickness maturation within areas implicated in motor planning and coordination, visuospatial ability, and emotion and impulse regulation. However, given the quasi-experimental nature of this study, we cannot rule out the influence of confounding variables. J. Am. Acad. Child Adolesc. Psychiatry, 2014; 53(11):1153–1161. **Key Words:** music, MRI, cortical thickness

In our programmatic research on quantitative traits of developmental psychopathology, we have argued that all children exhibit symptoms of inattention, aggression, anxiety and sadness, and emotional dysregulation, and that these symptoms are influenced by genes and environments (both negative and positive). We have hypothesized that purely categorical diagnostic conceptualizations belie the true nature of behavior, as well as its underlying biology. Following from this dimensional conceptualization of psychopathology, children with attention-deficit/hyperactivity disorder (ADHD) are not categorically different from children who do not meet criteria for ADHD; rather, they are quantitatively more severe in that they possess more symptoms than children who do not meet ADHD criteria.[1,2] In support of this dimensional conceptualization of psychopathology, we have published numerous behavioral genetic articles demonstrating that attention problems,[3] aggressive

This article is discussed in an editorial by Dr. Guido K.W. Frank on page 1147.

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behavior,[4] anxiety/depression,[5] and dysregulation[6] are best conceptualized as existing on a continuum, and again are influenced in almost equal parts by genetic and environmental contributions. We have added to our behavioral genetic argument a series of investigations into the brain structural correlates of these same behaviors. Interestingly, we have found that subclinical variance in psychopathological traits (e.g., inattention, anxious/depressed symptoms) largely map to the same neural networks posited to underpin clinically significant psychopathology (e.g., ADHD, major depressive disorder [MDD]). For example, we have reported that subclinical anxious/depressed symptoms in healthy youths are related to cortical thickness maturation within aspects of the medial prefrontal network—a network implicated in the mediation of clinically significant mood and anxiety symptomatology.[7,8] Similarly, we have found that subclinical inattention and hyperactivity among healthy youths are associated with cortical thickness maturation in fronto-parietal areas—regions implicated in the pathophysiology of ADHD, as well as attentional control and behavioral inhibition.[9] We have also revealed associations between normal variance in aggressive behavior among typically developing youths and cortical thickness within the anterior cingulate.[10] Taken together, these findings in typically developing children have added support to the idea that human emotions and behaviors exist on a continuum, rather than in categories, and furthermore, that each type of behavior can be mapped to distinct networks in the human brain. Despite these advances, it remains unclear how environmental factors, including exposure to health promoting activities, may serve to influence both brain development and behavior.

Years ago our group decided to pursue research in resilience and wellness. We aimed to determine how health-promoting activities might be associated with better outcomes in children and reported on the behavioral genetic architecture of the health benefits of exercise, music, and reading.[2] Taking this same approach to structural neuroimaging, we aimed to look at a wellness activity reported by others to be health promoting and having an effect on brain structure and function, and to study that activity in the same dataset on which we published our behavioral findings.

One such wellness activity is learning to play a musical instrument. In the context of music training, structural magnetic resonance imaging (MRI) studies display strong evidence for an environmental training effect rather than a genetic predisposition. One study showed increased aptitude after 15 months of training for the experimental group versus the control group on finger motor tasks and melody/rhythmic tasks, but not on nonmusical tasks.[11] Brain deformation changes were observed in motor areas, the corpus callosum, and the right primary auditory region, all areas important for music performance and auditory processing.[11] In addition, unexpected areas increased in volume compared to those of the controls; these included various frontal areas, the left posterior peri-cingulate, and the left middle occipital region. There is evidence that musicians have brain architecture that is altered based on amount of practice and age at which music lessons are initiated.[11,12] In addition, there is evidence that short-term music training in early childhood correlates with musically relevant motor and auditory cortical changes.[11] In their review, Bilhartz *et al.* note a significant association between early musical instruction and spatial–temporal reasoning abilities.[13] One of many studies demonstrating this finding was set in a classroom and consisted of 62 kindergarten children assigned to group keyboard instruction for 20 minutes twice a week in groups of 10.[14] Although visual memory was unchanged compared to that in the control group, spatial–temporal task performance improved in the musical group increasingly over the year, as compared to that in the control group.[14] Childhood practice time correlated with increased fractional anisotropy (FA, a measurement that the investigators used to infer increased microstructural properties of white matter) in bilateral posterior limbs of the internal capsule (the right side showing the only significant difference from that of non-pianists), and 2 corpus callosum tracts (isthmus extending into the upper splenium and the callosal body and fiber tracts in the frontal lobe).[15] These tracts continue to mature at least until age 17 years.[15] Adolescent practice time correlated with increased FA in the splenium (interhemispheric fibers from the superior temporal and occipital cortical areas) and the body of the corpus callosum. Adult practicing time correlated with FA in the left anterior limb of the internal capsule and the fiber bundle in the right temporoparietal junction (the arcuate fasciculus). Bengtsson *et al.*[15] noted that these findings are in line with corticocortical fibers having the most extended myelination cycle (they mature into an individual's 30s).

Given these data as a starting point, we decided to investigate the relationships between music training and cortical structure in a naturalistic sample. Specifically, we examine the extent to which participation in music training is associated with the rate of cortical thickness development among healthy youths. In the National Institutes of Health (NIH) pediatric development data set, we have music training and Wechsler Abbreviated Scale of Intelligence (WASI) IQ data for 232 children aged 6 to 18 years. For 112 of those children, we have images at more than 1 time point, yielding a total of 334 scans in which we test the relationships between cortical thickness and music training. Our aim was to determine whether music training had specific effects on cortical organization in this sample and, if so, whether these brain regions correlate with any of the prior findings that we reported on structural correlates of behavior such as aggression, inattention, anxiety, sadness, or dysregulation. Such data might give us strategies for using health-promoting activities in the prevention or treatment of common quantitative behavioral problems.

METHOD

Sampling and Recruitment

The NIH MRI Study of Normal Brain Development is a large, multi-site project that establishes a normative database to study the relationship between healthy brain maturation and behavior.[16] Participants were recruited throughout the United States using a population-based sampling method aimed at minimizing selection bias.[17] Using available US Census 2000 data, a representative, typically developing sample was recruited at 6 pediatric study centers. The 6 pediatric centers consisted of the following: Children's Hospital (Boston), Children's Hospital Medical Center (Cincinnati), University of Texas Houston Medical School (Houston), University of California, Los Angeles Neuropsychiatric Institute and Hospital (Los Angeles), Children's Hospital of Philadelphia (Philadelphia), and Washington University (St. Louis). Recruitment was monitored throughout the study, ensuring that enrollment across all pediatric centers was demographically representative with regard to age, gender, ethnicity, and socioeconomic status (full demographic features of participants are provided by Evans[16]). The study was approved by an institutional review board, and informed consent was obtained from parents as well as assent from the children. The Objective 1 database (release 4.0) used in this study included 431 healthy youths, and upon enrollment (i.e., first study visit), ages ranged from 4 years and 6 months to 18 years and 3 months. The study followed a longitudinal design such that participants underwent MRI brain scanning and behavioral testing on 3 separate visits, occurring at roughly 2-year intervals. Given that the aim of the NIH MRI Study of Normal Brain Development was to study healthy, typically developing children, stringent exclusion criteria were used, including the following: meeting criteria for a current or past Axis-I disorder on structured parent or child interview (Diagnostic Interview for Children and Adolescents); exceptions, however, included simple phobia, social phobia, adjustment disorder, oppositional defiant disorder, enuresis, encopresis, nicotine dependency; family history of major Axis-I disorder; family history of inherited neurological disorder or intellectual disability due to non-traumatic events; abnormality on neurological examination; gestational age at birth less than 37 weeks or more than 42 weeks; and intrauterine exposure to substances known or highly suspected to alter brain structure or function (for further information, see Evans[16]). Structural MRI and behavioral data were stored and analyzed within a database at the Data Coordinating Center of the Montreal Neurological Institute (MNI), McGill University, Montreal, Quebec, Canada.

MRI Protocol

To collect data that would permit automated morphometric analysis, as well as accommodate time constraints associated with the participant age range, 30 to 45 minutes of data acquisition were provided. Both General Electric (GE) and Siemens Medical Systems (Siemens) scanners were used in the NIH Normal Brain Development study. Slice thickness of ~1.5 mm was allowed for GE scanners because of the scanners' limit of 124 slices. A 3-dimensional T1-weighted spoiled gradient recalled (SPGR) echo sequence was selected. Intersite reliability was monitored with the American College of Radiology phantom, as well as a living phantom, that were both scanned at regular intervals at each site.[16] All MRI scanners used in the NIH Normal Brain Development study were 1.5-T systems. Further details regarding MRI sequence parameters are provided by Evans.[16]

Automated Image Processing

Quality-controlled native MR images were processed through the CIVET automated pipeline (version 1.1.9, 2006), a fully automated structural image analysis system. Processing steps were implemented using the Canadian Brain Imaging Network protocol (http://www.cbrain.mcgill.ca). To account for gross volumetric differences between participants, native MR images were linearly registered to a standardized MNI-Talairach space based on the ICBM152 dataset.[18-20] Intensity non-uniformity artifacts introduced by the scanner were corrected for using N3.[21] Subsequent classification of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was performed using the Intensity Normalized Stereotaxic Environment for the Classification of Tissue (INSECT) algorithm.[22] The pipeline includes the Constrained Laplacian Automated Segmentation with Proximities (CLASP) algorithm for generating high-resolution hemispheric surfaces with 40,962 vertices per hemisphere.[23-26] Hemispheric surfaces were generated for both the WM/GM interface, as well as the GM/CSF (i.e., pial surface). Both surfaces for each hemisphere were nonlinearly registered to an average surface created from the ICBM152 dataset to establish correspondence of vertices (i.e., cortical points) between participants.[19,24,27] A reverse linear transformation was performed on each participant's images, allowing for cortical thickness estimations to be made at each cortical point in the MR image's native space.[28] At each cortical point, cortical thickness was calculated using the *t*link metric.[29] As has been previously reported by members of our group, blurring along the cortical surface is a critical step in conducting cortical thickness analyses and serves to increase the sensitivity of cortical thickness analysis.[29] To increase the signal-to-noise ratio, each participant's cortical thickness map was blurred using a 20-mm full width at half maximum surface-based diffusion smoothing kernel.[30] This kernel size closely approximates previously recommended values, affording optimal sensitivity for cortical thickness analysis.[29] A visual quality control of the native cortical thickness images of each participant was carried out by members of our group to ensure that there were no significant aberrations in cortical thickness estimates for a given participant (interrater reliability, 0.93).[31]

Current Sample

In the present study, quality-controlled MR data and music training information were available for 232 youths, ranging from 6.1 to 18.2 years of age, with data available at up to 3 time points for each participant. A total of 334 MRI scans were analyzed for these participants. Of the 232 youths, 150 participants had data available at only 1 time point (64.7%), 62 had data available at 2 time points (26.7%), and 20 participants had data for all 3 time points (8.6%).

Data Analysis

Cortical thickness analyses were carried out using SurfStat, a toolbox created for MATLAB 7 (MathWorks, Inc, Natick, MA) by Dr. Keith Worsley (http://www.math.mcgill.ca/keith/surfstat/). Cortical thickness trajectories across the age range in our total sample have been found to be best described by first-order linear functions in contrast to cubic or quadratic functions, and, as a result, the relation between cortical thickness and age was modeled as a first-order linear function. Cortical thickness analyses were conducted using mixed-effects models. Mixed-effects models provide a way in which to analyze unbalanced longitudinal data while maximizing statistical power (i.e., using all available data).[32-34]

First, each participant's absolute native-space cortical thickness at each point on the cortical surface was linearly regressed against the number of years each participant had played a musical instrument. Age, total brain volume (TBV), gender, and scanner site were statistically controlled for in the model. All terms in the model were mean centered.

$$\textit{Cortical Thickness} = \textit{intercept} + d_1 + \beta_1(\textit{age}) + \beta_2(\textit{TBV}) + \beta_3(\textit{Gender}) + \beta_4(\textit{Scanner Site}) + \beta_5(\textit{Years Playing}) + e$$

In a second model, to test the degree to which music training moderates cortical thickness development, thickness was regressed against an "Age × Years of Playing" interaction term.

$$\textit{Cortical Thickness} = \textit{intercept} + d_1 + \beta_1(\textit{age}) + \beta_2(\textit{TBV}) + \beta_3(\textit{Gender}) + \beta_4(\textit{Scanner Site}) + \beta_5(\textit{Years Playing}) + \beta_6(\textit{age} \times \textit{Years Playing}) + e$$

In each mixed-effects model, participant ID was entered as a random effect to account for within-individual dependence. To control for multiple comparisons, false discovery rate correction was applied to the entire cortical surface ($p \leq 0.05$).

RESULTS

Table 1 shows descriptive statistics for the participants analyzed in the present study. Males and females did not differ with regard to years playing a musical instrument ($t = -0.38$, $p = .70$), or WASI IQ score ($t = 1.91$, $p = .06$). Adjusted household income was available at 305 of the 334 time points that were analyzed. Adjusted household income was not significantly associated with years playing a musical instrument ($r = 0.054$, $p = .35$).

TABLE 1 Demographic Characteristics of Study Sample

Characteristics	N = 232 (334 scans)
Age, y	12.39 (SD = 3.07)
Time playing musical instrument, y	2.15 (SD = 2.50)
Gender	
Female, n (scans; %)	132 (192; 57.5)
Male, n (scans; %)	102 (142; 42.5)
Handedness	
Right, n (%)	303 (90.7)
Left, n (%)	31 (9.3)
IQ	112.97 (SD = 12.30)

Note: Data were available for 132 females (with 192 scans collected on those 132 females; i.e., there were repeated scans on some participants). Similarly, data were available for 102 males (with 142 scans collected on those 102 males; i.e., there were repeated scans on some participants).

There was no first-order association between cerebral cortical thickness and years of playing a musical instrument. The "Age × Years Playing" interaction term was associated with thickness in a number of brain regions, including right premotor and primary motor cortices, left primary and supplementary motor cortices, left angular gyrus, right superior parietal cortex, bilateral dorsolateral prefrontal cortex (DLPFC), left posterior orbitofrontal cortex (OFC), right medial prefrontal cortex (PFC, including part of the medial OFC), bilateral parahippocampal gyri, and left temporal pole ($p \leq 0.05$, false discovery rate corrected) (Figure 1). Of note, these associations remained significant when not controlling for total brain volume (see Figure S1, available online). Similar albeit less significant results were obtained when the analysis was rerun and "years playing an instrument" was dichotomized into "playing an instrument" versus "no history of playing an instrument." There were no significant "Gender × Years Playing" or 3-way "Gender × Age × Year Playing" interactions on cortical thickness, indicating the absence of gender-specific effects on this observed maturational pattern. Results were not meaningfully altered when IQ and handedness were included as covariates in the analyses.

To decompose the "Age × Years Playing" interaction on cortical thickness, thickness values were obtained from peak regions in the right premotor cortex, right motor cortex, and left supplementary motor areas and analyzed within SPSS version 18.0 (SPSS Inc., Chicago, IL). Next, the age-by-thickness relationship was plotted for youths with years of playing a musical instrument partitioned into less than 2 years and greater than or equal to 2 years. This follow-up analysis revealed that music training was associated with an increased rate of age-related thinning (Figure 2). This same pattern was observed in other cortical regions associated with the "Age × Years Playing" interaction term.

In a series of follow-up analyses, we investigated the relationship between years of playing a musical instrument and cortical surface area, as well as the degree to which surface area development was moderated by years of playing a musical instrument. In both analyses, no associations survived false discovery rate correction for multiple comparisons.

DISCUSSION

Music training was associated with the rate of cortical thickness maturation in a number of brain

FIGURE 1 Brain areas where local cortical thickness is associated with the "Age × Years of Playing" interaction (N = 232; 334 time points). Note: Figure is shown at $p \leq .05$ with a false discovery rate correction. Controlled for age, gender, total brain volume, and scanner.

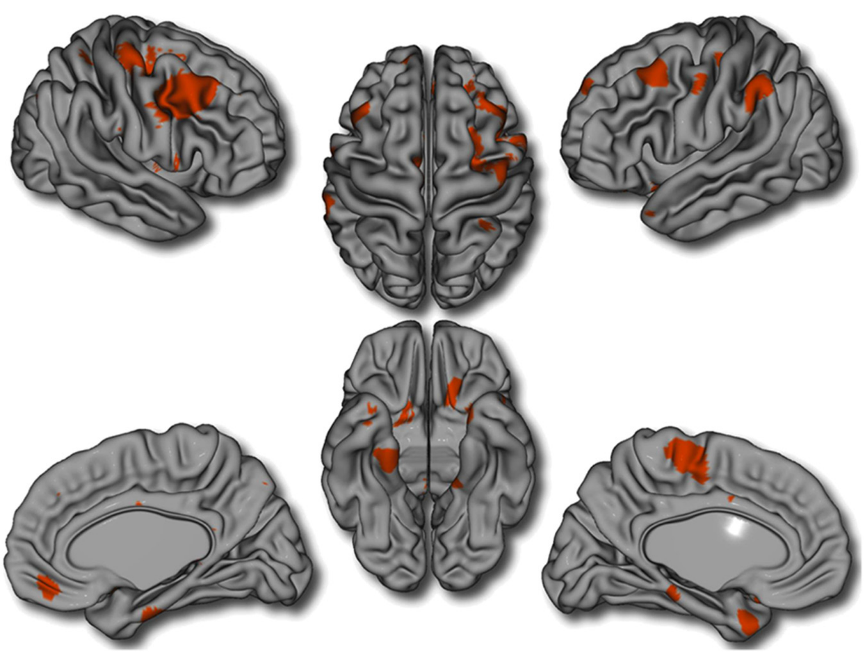
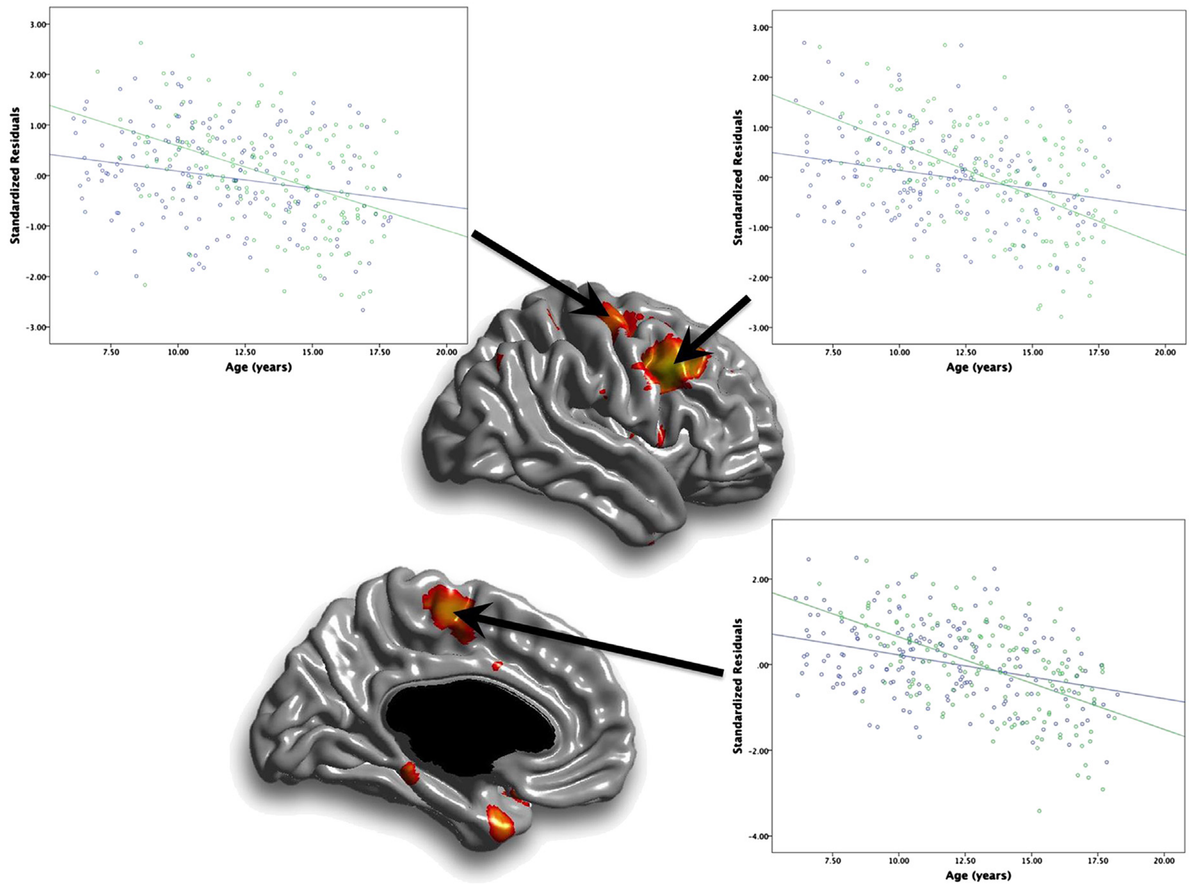


FIGURE 2 Plot of the "Age x Years of Playing" interaction on cortical thickness in the right premotor area, right motor cortex, and left supplementary motor area. Note: For illustrative purposes, the variable "years playing a musical instrument" has been partitioned into less than 2 years (blue data points) and greater than or equal to 2 years (green data points). Values on the *y*-axis are the standardized residuals of the linear regression between local cortical thickness and gender, total brain volume, and scanner site to account for these variables.



areas distributed throughout the right premotor and primary cortices, the left primary and supplementary motor cortices, bilateral parietal cortices, bilateral orbitofrontal cortices, as well as bilateral parahippocampal gyri. Our finding that music training was associated with cortical thickness development in the premotor and primary motor cortices is not surprising, given that both regions contribute to the control and execution of movement. It is posited that the premotor region plays a particularly important role in the preparation and sensory guidance of movement, both of which are key characteristics of music training. In the same way, the supplementary motor area is thought to play a role in the planning and coordination of movement, again key skills in music production. With regard to bilateral parietal associations, the posterior parietal cortex serves to integrate multisensory information that may be related to motoric activity. Taken together, it is reasonable that we found evidence of accelerated cortical development in these regions, given the motoric and multimodal sensory integration associated with music training. Although speculative, increased cortical thickness maturation might reflect pruning processes associated with the prolonged playing of a musical instrument. Alternatively, the expedited thinning observed in this study may stem from the myelination of lower cortical layers associated with music-related fiber pathways—the "thinning" may reflect an altered boundary between cortical gray matter and white matter, and thus the "thinning" is merely an artifact of MRI. Our findings further suggest that music training is associated with cortical thickness development but not cortical surface area development. This latter finding is not surprising, given the evidence indicating that cortical thickness and surface area represent independent properties of the primate cortex, each underpinned by largely unique genetic factors.[35]

Music training was also found to influence cortical thickness maturation within aspects of the DLPFC. Myriad imaging and neuropsychological studies have implicated the DLPFC in aspects of executive functioning, including working memory, attentional control, as well as organization and planning for the future. Interestingly, developmental structural neuroimaging studies have shown that participants with quantitatively higher scores on attention problems exhibit delayed cortical thickness maturation in portions of the DLPFC as well as other cortical regions (see Figure S2, available online, taken from Ducharme *et al.*[9]). Future research may benefit from examining the extent to which music training affects cortical development among youths with clinically significant attention problems. Although entirely speculative, it is possible that music training's influence on cortical maturation, particularly in prefrontal regions, may serve to mitigate aspects of ADHD symptomatology. Music training was also associated with the rate of cortical thickness development in both orbitofrontal and ventromedial prefrontal cortices, brain areas that play a critical role in inhibitory control, as well as aspects of emotion processing. Indeed, portions of the OFC have been implicated in emotion regulatory processes via top-down modulation of the amygdalae. Future research would benefit from looking at the degree to which music training affects brain development as well as measures of behavioral and affective regulation.

Decomposition of the "Age × Years Playing a Musical Instrument" interaction on cortical thickness revealed evidence of music training being associated with more rapid cortical thickness development in a number of cortical regions. It is noteworthy that, when looking at youths less than 10 years of age, time playing a musical instrument was positively associated with cortical thickness in regions such as the right DLPFC. Thus, it is possible that early exposure to music training may be associated with long-term effects on cortical development. However, given that youths in the present study were not randomly selected to take part in music training, we cannot rule out possible confounding factors.

Sadly, the National Educational Longitudinal Survey (managed by the National Center for Education Statistics at the Office for Educational Research and Improvement, United States Department of Education) has reported that 74.2% of 10th graders "rarely or never" participate in out-of-school music, art, or dance lessons. This same study also found that 85.9% of 12th graders "rarely or never" participate in out-of-school music, art, or dance lessons. Such statistics, when taken in the context of our present neuroimaging results, underscore the vital importance of finding new and innovative ways to make music training more widely available to youths, beginning in childhood.

Developing a strategy to bring music training to more children may well result in improved brain-behavior health. However, like many health-promoting activities, it appears that music training in childhood is an activity of those with sufficient wealth. Although the most potent changes in neuroarchitecture correlate with number of hours of practice, the work of Bilhartz *et al.*[13] showed that, despite being assigned to experimental groups receiving different levels of intervention, household income influenced the actual training that the children received; children in higher-income households ultimately received greater exposure to music training, despite random group assignment.[13]

Others outside of the United States have been more aggressive about the possibility of delivering music training to the disadvantaged. In Caracas, Venezuela, Masetro Abreu developed "El Sistema" (http://elsistemausa.org/), a music education program implemented throughout the country that currently serves more than 500,000 Venezuelan children and has served more than 2 million of America's most at-risk children. In addition to demonstrating that music training can be delivered in a school setting nationwide to at-risk children, the program has resulted in a 20% reduction in school drop-out, a 22% increase in participation in community activities, and a 28% increase in employment for those children who participate in the program.[36] There are champions of the El Sistema approach in many cities around the United States, and perhaps someday more children in this country will have access to the benefits of the health-promoting, brain-building activity of music training.

The present study has several limitations that must be considered. First, participants were not randomly assigned to study conditions. Given the quasi-experimental nature of this study, we cannot rule out the possibility that confounding factors might have influenced our results. As reported above, in this sample, adjusted household income was not associated with years spent playing a musical instrument. However, children who are afforded the opportunity to play musical instruments are undoubtedly exposed to other health- and wellness–promoting activities that may affect brain development. Randomized controlled studies may help to more definitively identify brain maturational patterns associated with music training. Second, only structural neuroimaging data were acquired as apart of the NIH Normal Brain Development study, so we cannot speak to the functional implications of more rapid cortical thickness maturation in fronto-parietal regions. Future studies incorporating multimodal neuroimaging techniques may help to link structural and functional findings. Despite these limitations, this study represents the largest investigation of the association between playing a musical instrument and brain development. &

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FIGURE S1 Brain areas where local cortical thickness is associated with the "Age × Years of Playing" interaction (N = 232; 334 time points). Note: Figure is shown at $p \leq .05$ with a false discovery rate correction. Controlled for age, gender, and scanner.

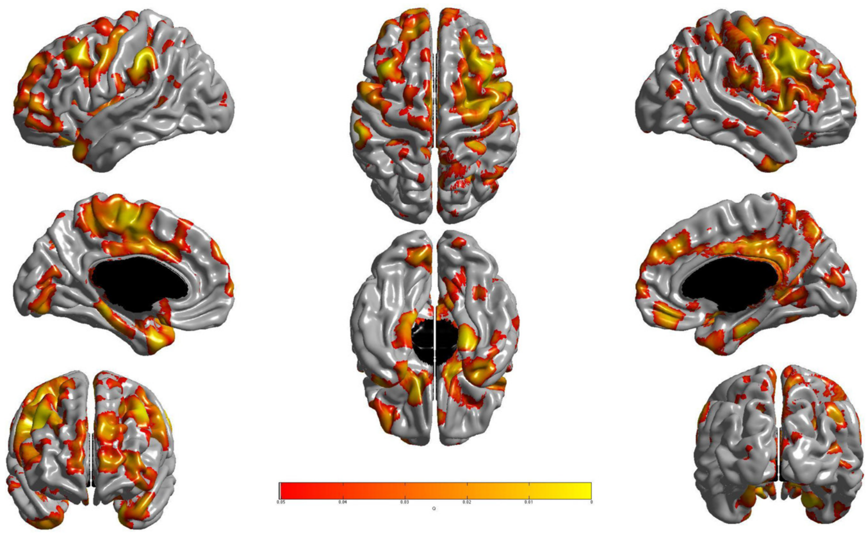

FIGURE S2 Brain areas where local cortical thickness is associated with the "Child Behavior Checklist Attention Problems by Age" interaction in the cross-sectional analysis (n = 257). Note: Figure is shown at $p \leq .05$ with a false discovery rate correction. Controlled for age, gender, total brain volume, and scanner. (Reprinted from Ducharme *et al.*, J Am Acad Child Adolesc Psychiatry 2012;51:18-27.e12. © 2012 with permission from Elsevier.)