

Cortical structure predicts success in performing musical transformation judgments

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ABSTRACT

Recognizing melodies by their interval structure, or “relative pitch,” is a fundamental aspect of musical perception. By using relative pitch, we are able to recognize tunes regardless of the key in which they are played. We sought to determine the cortical areas important for relative pitch processing using two morphometric techniques. Cortical differences have been reported in musicians within right auditory cortex (AC), a region considered important for pitch-based processing, and we have previously reported a functional correlation between relative pitch processing in the anterior intraparietal sulcus (IPS). We addressed the hypothesis that regional variation of cortical structure within AC and IPS is related to relative pitch ability using two anatomical techniques, cortical thickness (CT) analysis and voxel-based morphometry (VBM) of magnetic resonance imaging data. Persons with variable amounts of formal musical training were tested on a melody transposition task, as well as two musical control tasks and a speech control task. We found that gray matter concentration and cortical thickness in right Heschl's sulcus and bilateral IPS both predicted relative pitch task performance and correlated to a lesser extent with performance on the two musical control tasks. After factoring out variance explained by musical training, only relative pitch performance was predicted by cortical structure in these regions. These results directly demonstrate the functional relevance of previously reported anatomical differences in the auditory cortex of musicians. The findings in the IPS provide further support for the existence of a multimodal network for systematic transformation of stimulus information in this region.

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Introduction

A growing body of research demonstrates that the human cerebral cortex can undergo systematic structural changes as a result of experience and training. Through such study, we are beginning to understand the long-term dynamics of brain anatomy and physiology. Building upon observations of differential brain anatomy in cohorts of trained individuals, such as musicians (Schlaug et al., 1995b), taxi drivers (Maguire et al., 2000), and golfers (Jancke et al., 2009), recent studies have made clear that changes in cortical structure can directly result from intensive training (Driemeyer et al., 2008; Hyde et al., 2009) and also that the degree of behavioral results achieved from training can be predicted in part by preexisting differences in cortical structure (Golestani et al., 2007, 2002; Wong et al., 2008).

Musicians comprise one of the most accessible groups for studying long-term training-induced neural change in part because they often practice in an intensive manner over a period of decades. The consequences of such training include advanced precision of perceptual and motor abilities, as well as differences in functional activation and regional structure in the brain (Munte et al., 2002).

Much of what we know about neural changes after musical training comes from group comparisons of highly trained musicians vs. untrained individuals using regional manual volumetry or voxel-based morphometry (VBM). Schlaug, in several of the first such studies, showed that having advanced musical training is associated with volume differences in the corpus callosum (Schlaug et al., 1995a), auditory cortex (Schlaug et al., 1995b), motor cortex, and cerebellum (Schlaug, 2001). Differences of gray matter anatomy in auditory areas (e.g., Heschl's gyrus and planum temporale) associated with musicianship status have also been reported by Schneider et al. (2002), Gaser and Schlaug (2003), Bermudez et al. (2009), and Bermudez and Zatorre (2005). Neurophysiological, lesion, and functional imaging studies support the idea that the right auditory cortex (AC) has an important role in pitch processing (Bendor and Wang, 2006; Zatorre et al., 2002a). Therefore, it would be reasonable to interpret the anatomical differences found in the right AC as likely being related to pitch processing. However, as yet, there is little direct evidence of such an association.

There are two important limitations to the commonly used group-based approach to morphometric analysis. First, without using information about the duration of training, one can only conclude that there are neuroanatomical differences between highly trained individuals and nonmusicians, but nothing can be said about the rate of change nor even that the differences are a consequence of the

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training. A correlation between an anatomical measure and the duration of training (or the age of training commencement, e.g., Schlaug et al., 1995b) provides stronger implication that the observed differences are consequent to training. Second and perhaps more important, in the absence of behavioral measures, we can only speculate about the behavioral significance of any anatomical differences after training.

Behavioral correlates of neuroanatomical differences in musicians are not frequently studied. Where they are reported, they have thus far been limited to a single performance measure per study, such as a motor sequence task (Schlaug, 2001), absolute pitch perception accuracy (Zatorre et al., 1998) or a combined melody–rhythm discrimination score (Schneider et al., 2005). In these cases, although we may conclude that an anatomical feature is associated with performance on a given task, if there is only one task measure, we have no way to assess the specificity with which the task is linked to anatomy. We have attempted to deal with this issue with the design of this experiment.

Our goal in the present study was to find neuroanatomical features that predict performance on a specific and sophisticated aspect of musical perception—relative pitch processing—that is enhanced by musical training but also plays an important part in everyday musical listening. Identifying melodies by their interval structure, or “relative pitch,” is a fundamental part of musical perception. In fact, it is through transforming a melody into an abstract representation consisting of pitch intervals (rather than absolute pitches) that we are able to recognize familiar tunes regardless of the key in which they are played (Dowling and Harwood, 1986). Relative pitch therefore provides us with a musically relevant perceptual skill, one in which we might expect to see a distribution of performance in untrained individuals as well as considerable training-dependent variation in musicians.

We focus in this study on two cortical areas: auditory cortex (AC) in the right superior temporal gyrus (encompassing lateral Heschl's gyrus and adjacent planum temporale) and multimodal cortex in the intraparietal sulcus (IPS). As the first cortical stage of auditory processing, including the extraction of pitch information, the auditory cortex is often associated with functional and anatomical differences in musicians as described above. In particular, a recent study in our laboratory used both VBM and CT analysis to compare gray matter anatomy in musicians and non-musicians (Bermudez et al., 2009). The greatest gray matter difference common to both analyses was in right AC, corresponding to the lateral portion of Heschl's gyrus. In the present experiment, we therefore wanted to extend this finding to test whether the variation in cortical structure in musicians' auditory cortex is linked to relative pitch ability.

We have recently identified the IPS as playing a role in relative pitch processing. Using fMRI, we demonstrated that brain oxygenation level-dependent (BOLD) signal is greater in bilateral anterior IPS when a melodic pattern discrimination task obliges relative pitch processing (melodic transposition); we further found that performance on this relative pitch task was predicted by BOLD activation in the right IPS (Foster and Zatorre, 2010). The IPS is a multimodal region with a role in performing systematic transformations on sensory representations, such as visuospatial and tactile information (Grefkes and Fink, 2005), as well as more abstract operations like arithmetic (Kong et al., 2005). This prior study was the first demonstration that such transformations also recruit the IPS when applied to musical information. This finding led us to wonder whether differences in cortical anatomy in the IPS, as well as in the right AC, may be linked to relative pitch ability.

Our prediction was that greater cortical thickness and concentration in the AC and IPS would be associated with greater performance on our relative pitch task. Although we felt it likely

that most of this variation, if present, would be explained by musical training, we hypothesized that there might also be a dissociation between ability and training; perhaps there is an intrinsic variation in cortical structure among individuals, and in those who pursue musical instruction, this structure is further modified by their training. We therefore predicted that training would only partially explain the covariation of structure and task performance.

To directly deal with the issue of task specificity, as mentioned earlier, we tested participants on several control tasks: a “simple” melody task that did not require relative pitch, a rhythm discrimination task and a phoneme pattern task. All tasks were matched for duration and number of items to equate the overall working memory load. We compared the degree of anatomical correlation in the relative pitch task with the control tasks, which allowed us to distinguish specific behavioral/anatomical effects related to relative pitch ability vs. more global effects of musical experience. This task performance-based approach to finding behaviorally relevant cortical features is rare in the literature and, in our opinion, provides more direct information about the predictive validity of the findings with respect to relevant behavior than can be found using group contrasts. To test the contribution of training to any anatomy–behavior correlations, we also factored out the effect of training duration and age of commencement from the performance on each task.

Following the example of Bermudez et al. (2009), we have employed two complementary morphometric methods, VBM and CT, in analyzing our anatomical data set. VBM has long been used to detect differences in gray and white matter concentration in the brain. Compared to manual segmentation and volumetry, VBM provides an objective, bias-free method, and as it does not require structure-specific hypotheses, it allows one to test for anatomical effects across the whole brain (Ashburner and Friston, 2000). However, although VBM indicates where there are differences in gray or white matter, it does not provide detailed information on the nature of the changes. For example, systematic differences in gray matter volume may produce a similar result to variation in the shape or position of a cortical feature, even when volume is preserved in the latter case (Ashburner and Friston, 2001).

CT is a more recent technique that directly estimates the thickness of the cortex based on the distance between the white–gray matter interface and the pial surface (MacDonald et al., 2000). In addition to providing a more intuitively concrete measure than VBM, CT has the advantage of sensitivity: the surface-based analysis has many fewer vertices than there are voxels in a 1 mm VBM brain (about 20× fewer) so the problem of multiple comparisons in a whole-brain analysis is diminished, and its surface-based smoothing respects anatomical boundaries much better than the 3D smoothing used in VBM (Lerch and Evans, 2005). By using two different types of anatomical analysis, we stand to benefit from both the convergence and complementarity of these techniques. In addition, since very few studies have performed both VBM and CT analysis on the same data set, we are in a position to compare and cross-validate the two techniques.

Materials and methods

Subjects

We recruited 68 healthy, right-handed volunteers (aged 17–47 years; mean age 25 years; 39 female) having a wide range of musical experience. Participants reported having no hearing deficits. The age distribution was similar between the sexes (mean age of 26 and 24 years old for males and females, respectively). Handedness was determined by self-report. A detailed self-reported history of musical training was also obtained from each subject, including estimates of practice hours per week for each year or phase of the participant's musical

activities (as applicable). This information was used to calculate a cumulative measure of hours of musical practice, since we were interested in the cumulative anatomical effects of participants' musical experience. The relationship between hours of practice and subjects' performance on our musical tasks was logarithmic; therefore, we used the logarithm of total practice hours for all subsequent analyses involving training duration. Musical experience ranged from 0 to 58,000 practice hours, with a mean of about 5600 hours and a median of 1200 hours. Eight participants reported no musical training whatsoever, and another 16 had musical lessons for a brief period (<6 months) during childhood. These persons were assigned a value of 0 for the log hours measure. Among the musically trained, most practiced mainly classical music. The most common primary instruments were piano and wind instruments, and about 20% also had voice and string instrument training. Level of instruction varied from childhood in-school lessons to private instruction to university musical performance degree programs. For those participants who had received musical training, the age of commencement varied from 3 to 16 years old (mean 9 years old). All participants gave their informed written consent. Ethical approval was granted by the Montreal Neurological Institute's Ethics Review Board.

Tasks

The subjects performed four same–different auditory pattern discrimination tasks: relative pitch, simple melody, rhythm, and phonemes (see example stimuli in Fig. 1). Individual trials consisted of two stimulus pattern presentations; subjects judged whether the two patterns were the same or different, and indicated their response with the left or right button of a computer mouse. Subjects were required to make a response to proceed to the next trial.

Stimulus durations were varied within each task, and the distribution of durations was matched among conditions. Because our study included both musicians and nonmusicians, we desired a broad range of trial difficulties to provide sensitivity across the full range of musical experience. Varying the number of elements (notes or phoneme sounds) among trials was a straightforward means of ensuring a sufficient range of difficulty. It was important that the tasks be sensitive across the range of ability level present

in our sample, as this would permit us to examine covariation between regional cortical structure and task performance.

Simple melody

Stimuli in the simple melody task consisted of unfamiliar melodies in the Western major scale, ranging from 5 to 13 notes in duration. The melodies used pitches between C4 and E6 and were played with harmonic tones low-pass-filtered below 8 kHz. All notes were 320 ms in duration, equivalent to eighth notes at a tempo of 93.75 beats per minute. On half the trials, the pitch of a single note anywhere in the melody was changed by up to ± 5 semitones (median of 2 semitones). The change maintained the key of the melody as well as the melodic contour (the order of upward and downward pitch movement in a melody without regard to magnitude).

Relative pitch

The relative pitch task differed from the simple melody task in two ways: (1) all notes of the second stimulus pattern were transposed 4 semitones higher in pitch (in both “same” and “different” trials); and 2) in “different” trials one note was altered by 1 semitone to a pitch outside the pattern's new key, maintaining the melodic contour. Contour is a particularly salient cue for detecting melodic alterations, and by removing individual pitches and melodic contour as cues, subjects are left only with pitch interval structure as the basis for comparing melodies (Dowling and Harwood, 1986). This task therefore relies upon accurate extraction of intervals from the melodic sequences, as well as using this interval structure to mentally transpose the melody to a different pitch level so the melody pairs can be compared. The transposition distance has an effect on the difficulty of the discrimination. Generally speaking, the more pitches shared between keys, the more difficult it is to identify inexact transpositions that mimic the melodic contour (Dowling and Harwood, 1986). A transposition of 4 semitones results in 3 tones (out of 7) shared between the scales of the two keys. We found this to be a good balance of difficulty for both musicians and nonmusicians.

Rhythm

Stimuli in the rhythm task consisted of rhythmic patterns ranging from 5 to 11 notes in duration, played using a single tone at C5 (523 Hz). The patterns sometimes contained one or more rests (pauses between notes) to generate rhythmic variation. The unaltered rhythmic patterns were often syncopated, but had underlying metric structure and could be notated by conventional musical notation. The average interval between note onsets was 390 ms. In half the trials (“different” trials), the time offset and/or duration of one or more notes was altered in the second pattern. Subjects were instructed to listen for any difference in timing.

Phoneme

The stimuli in the phoneme task were patterns of real speech consonant–vowel syllables (e.g., “ta”) spoken in a monotone. Patterns ranged from 5 to 13 elements in length. The interval between phoneme onsets was 320 ms. The full set of phonemes consisted of 12 permutations of 8 consonants [b, k, f, n, p, r, s, j] and 4 vowel sounds [o, a, u, i]. The phonemes were selected to have minimal semantic association. In half the trials, one of the elements in the second pattern was changed to a different phoneme. The two stimuli in each trial always used different source recordings (of the same speaker), so that acoustical cues unrelated to phoneme identity could not be used as cues in making the same–different judgment.

Figure 1 displays examples of task stimuli and pattern alterations for four conditions: Simple Melody, Rhythm, Relative Pitch, and Phoneme. The stimuli are presented in musical notation, and the phoneme patterns are shown in a table format. Red marks indicate pattern alterations.

Simple Melody – ORIGINAL

Simple Melody – DIFFERENT

Rhythm – ORIGINAL

Rhythm – DIFFERENT

Relative Pitch – ORIGINAL

Relative Pitch – SAME

Relative Pitch – DIFFERENT

PHONEME PATTERN, ORIGINAL

KOH	ROO	RAH	NAH	FOO
-----	-----	-----	-----	-----

PHONEME PATTERN, DIFFERENT

KOH	ROO	RAH	YAH	FOO
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Fig. 1. Examples of task stimuli and pattern alteration in the relative pitch, simple melody, rhythm, and phoneme conditions. The red marks indicate pattern alterations.

Behavioral task procedure

Tasks were administered by a computer running Presentation software (Neurobehavioral Systems, <http://www.neurobs.com/>) during a single session in a sound-treated room. Stimuli were presented binaurally via Sennheiser HD-280Pro headphones driven by a Mackie mixer adjusted to a comfortable sound level. Subjects completed two 30-trial blocks of each task. Task order was counterbalanced, and trials were randomized within each block.

Image acquisition

T₁-weighted images (time echo = 9.2 ms, time repetition = 22 ms, matrix size: 256 × 256, voxel size 1 mm × 1 mm × 1 mm) were acquired on a Siemens Vision 1.5 T MRI scanner. Subjects were scanned within 1 year of their behavioral testing session (mean of 3 months), except for 9 subjects whose scans were acquired 13–34 months before behavioral testing.

Voxel-based morphometry analysis

T₁ images were linearly registered to the ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation (Collins et al., 1994; Grabner et al., 2006), RF inhomogeneity-corrected (Sled et al., 1998) and tissue-classified (Tohka et al., 2004; Zijdenbos et al., 1998). Resulting GM and white matter images were convolved with a 3-dimensional Gaussian blurring kernel with an 8-mm full-width half-maximum.

Covariation of gray matter concentration values with subject performance on the relative pitch task was estimated at each voxel by the general linear model (GLM) with sex modeled in the regression as a covariate, using the software *glim_image* developed at the Montreal Neurological Institute (<http://wiki.bic.mni.mcgill.ca/index.php/GlimImageManPage>). Sex-related differences have been reported in morphometric studies (Amunts et al., 2000; Good et al., 2001; Luders et al., 2009), prompting some investigators to include only male participants (e.g., Gaser and Schlaug, 2003); since our study includes musicians of both genders, we have dealt with this potential issue by explicitly including sex in the linear model.

To find significant gray matter concentration effects across the whole brain, we used random field theory (Worsley et al., 2002) to determine a *T* threshold of 4.41 (corresponding to *P* < 0.05, corrected) for our previously predicted peaks and a *T* threshold of 5.56 for unpredicted peaks.

We wanted to compare the task–anatomy correlations to determine the degree of specificity of the observed effect to the relative pitch task. Peak voxels were found on the basis of the relative pitch–gray matter correlation, but we wanted to reduce any circularity or bias in comparing the values at this one voxel with the other behavioral tasks (Kriegeskorte et al., 2009). We therefore employed a region-of-interest (ROI) approach such that the ROIs were generated based on separate data sources. We defined three ROIs, the first based on the previous VBM result in the AC (Bermudez et al., 2009), and the other two based on fMRI results in the IPS (Foster and Zatorre, 2010); both of these prior studies had guided our hypotheses in the present study. The imaging data were acquired on the same equipment during the same time period as the present study, avoiding any potential concerns about inter-site scanner variability.

These ROIs were created as a conjunction between thresholded voxel *T* maps from the present and previous results. The previous results were thresholded using their published *T* thresholds, and the resulting masks were dilated by 10 mm to allow for a limited degree of spatial variation with the present results. The present results were thresholded at *T* > 2.90, corresponding to *P* < 0.005 (uncorrected), thereby creating a

second mask. The conjunction of these two masks determined the search area for each region of interest: right AC, left IPS, and right IPS. These VBM ROI sizes varied from 420 to 999 voxels (mm³) in volume (Table 2). We then averaged the gray matter concentration values within each ROI for each subject and calculated the Pearson correlation coefficient of these subject mean values vs. individual performance (percent correct) on each task. There were 26 participants out of 135 in the Bermudez et al. data set who also participated in the present study. All 20 subjects in Foster and Zatorre (2010) participated in the present study. Regarding the potential effect of the subject overlap upon the independence of the masks being conjoined, it is important to point out that (1) the masks from Bermudez et al. were based on group contrasts, whereas the masks from the current analysis were based on parametric analyses of task performance; and (2) the mask from Foster and Zatorre (2010) arose from a different imaging modality (task-related BOLD activation in the prior study vs. T₁ anatomical images in the present study). Therefore, the overlapping subjects contributed different data to the masks being conjoined. Significance of task–anatomy correlations within each ROI was assessed using a threshold of 0.201 for Pearson's *r* statistic, corresponding to *P* < 0.05 (1-tailed) with 67 degrees of freedom.

Cortical thickness analysis

All MRIs were submitted to the CIVET pipeline (version 1.1.9, <http://wiki.bic.mni.mcgill.ca/index.php/CIVET>; Ad-Dab'bagh et al., 2005; Zijdenbos et al., 2002). T₁ images were registered to the ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation (Collins et al., 1994; Grabner et al., 2006), RF inhomogeneity-corrected (Sled et al., 1998) and tissue-classified (Tohka et al., 2004; Zijdenbos et al., 1998). Deformable models were then used to create for the white/gray matter and gray matter/cerebrospinal fluid interfaces for each hemisphere separately (Kim et al., 2005; MacDonald et al., 2000), resulting in four surfaces of 40,962 vertices each. From these surfaces, the *t*-Laplace metric was derived by using the Laplacian method for determining the distance between the white and gray surfaces (Haidar and Soul, 2006; Jones et al., 2000; Lerch and Evans, 2005). The thickness data were subsequently blurred using a 20-mm surface-based diffusion blurring kernel in preparation for statistical analyses (Chung and Taylor, 2004). Unnormalized, native-space thickness values were used in all analyses owing to the poor correlation between cortical thickness and brain volume (Ad-Dab'bagh et al., 2005; Sowell et al., 2007). Normalizing for global brain size when it has little pertinence to cortical thickness risks introducing noise and reducing power.

Similar to the VBM analysis described above, we determined the degree of correlation between cortical thickness values and relative pitch task performance across the whole cortical surface, using a vertex-wise GLM analysis. The threshold for the Student's *t* statistic in preselected regions was 1.99, which controlled the false-discovery rate (FDR; Genovese et al., 2002) in each hemisphere to *P* < 0.05; for a whole-brain search, we used a *t* threshold of 2.65, which controlled the FDR to *P* < 0.01.

To compare the task specificity of the cortical thickness effect among the task conditions, we employed the same ROI approach as described above. In the AC, a surface-based mask was generated by thresholding Bermudez et al.'s CT result at the published value. A similar mask based on the present CT results was generated by thresholding the values at the *P* < 0.05 (FDR) level. The ROI was calculated as the conjunction between these two surface masks and comprised 47 vertices. Because both masks originated from data registered to the exact same target (the 6th generation nonlinear ICBM152 template), no dilation of the search area was performed.

In the IPS, voxel-based masks were generated from earlier fMRI results as described for VBM. Surface-based masks for left and right IPS were subsequently generated via the intersection of the voxel-based

masks with the average midcortical surface. Similar masks based on the present CT results were generated by thresholding the values at the $P < 0.05$ (FDR) level. The ROI was calculated as the conjunction between these two surface masks and comprised 21 vertices in the right IPS; however, the conjunction yielded 0 vertices (no overlap) in the left IPS. As with the CT mask in the AC, no dilation of the search area was performed.

Behavioral results

Subjects were scored on each task based on the percentage of correct responses. Performance scores varied among the task conditions (1-way ANOVA, $F = 6.17$, $P < 0.001$); a post-hoc Fisher LSD test showed that whereas the overall task performance was equivalent on the relative pitch, rhythm, and phoneme conditions (Fisher LSD test, $P > 0.05$), average performance was significantly higher on the simple melody task by about 6 percentage points (Fisher LSD test, $P < 0.001$; Fig. 3). Despite the difference in mean performance, there was no ceiling effect on either task; also, the spread of scores was equal between the melody tasks (standard deviation = 0.127), so the potential to detect anatomical correlations relevant to these tasks should be comparable.

As expected, the percent correct performance on each of the musical tasks (relative pitch, simple melody, and rhythm) correlated significantly with the logarithm of lifetime practice hours ($r = 0.52$ – 0.67 , $P < 0.0001$; Table 1 and Fig. 2). Conversely, performance on the phoneme task was not correlated with musical experience ($r < 0.01$), indicating that it was an adequate control task for the variable of musical training.

Since we had included musicians of varying experience level, there was a possibility that musical training and age would be somewhat correlated; older musicians who began training at a similar age may tend to have more training than younger musicians do. However, in our sample, there was no such correlation between age and the training measure ($r = 0.04$) or between age and task performance ($r \leq 0.08$).

Imaging results

Based on results of two recent fMRI and anatomical studies, we were principally interested in three cortical areas: right auditory cortex (encompassing lateral Heschl's gyrus and adjacent planum temporale) and left and right intraparietal sulcus (anterior portion, including ascending and horizontal segments). In the right auditory cortex, Bermudez et al. (2009) found greater gray matter concentration and cortical thickness in musicians. In the anterior IPS, we had previously found that functional activation correlates with relative pitch task performance (Foster and Zatorre, 2010). Therefore, we used these prior studies to generate specific region-of-interest predictions. We also examined the data using whole-brain methods.

Table 1

Summary of mean task performance and the relationship between task performance and musical training parameters (logarithm of total hours of musical training and the age at which musical training was commenced).

Task	% Correct responses	Correlation with training duration (r)	Correlation with age of commencement (r)
Relative pitch	69%	0.63 (***)	−0.29 (*)
Simple melody	76%	0.66 (***)	−0.25 (*)
Rhythm	69%	0.52 (***)	−0.06 (n/s)
Phoneme	69%	0.02 (n/s)	−0.07 (n/s)

n/s: not significant.

* Significant at $P < 0.05$.

*** Significant at $P < 0.001$.

Anatomical differences in auditory cortex

In our whole-brain VBM analysis, the highest correlation between gray matter concentration and performance on any of the tasks was located as predicted in the right Heschl's sulcus, where concentration positively correlated with performance on the relative pitch task ($t = 5.22$; Fig. 3). Although there was no equivalent significant result in left AC, a nonsignificant peak of $t = 3.29$ was located nearby in left planum temporale. A convergent result was found in our analysis of cortical thickness, where there was a corresponding correlation with relative pitch task performance in right Heschl's sulcus ($t = 2.46$; Fig. 3).

To get a better idea of how specifically this anatomical variation was linked with relative pitch processing, we compared it with the other auditory tasks. Although the tasks are sensitive to different aspects of musical perception, performance on each task is also correlated with the duration of musical training (Pearson's $r = 0.52$ – 0.66 ; Table 1), which, as a common source of variance on the behavioral measures, serves as a confound when comparing the specificity of task-anatomy effects. Hence, by factoring out the effect of training from each task performance measure, we may examine the relationship between task performance and local anatomy independently of the contribution of musical training. To mitigate “circular analysis” bias we followed a method similar to the recommendations of Kriegeskorte et al. (2009). Each subject's gray matter concentration values were averaged within a ROI in the AC. This ROI was determined by conjunction of the present thresholded VBM data and a mask generated from a previous VBM contrast of musicians and nonmusicians (Bermudez et al., 2009; see Materials and methods). The same procedure was used for cortical thickness values in the CT analysis. The ROI-averaged anatomical measures were then tested for correlation with subjects' percent correct performance on the behavioral tasks, after factoring out any variance in performance accounted for by training duration.

The ROI in the auditory cortex was found to predict performance significantly on all three musical tasks (relative pitch, simple melody, and rhythm) but not on the phoneme task; however, the proportion of variance accounted for was greatest for the relative pitch task compared to the other two musically relevant tasks. When the effect of training duration is removed, there remains a significant correlation between relative pitch task performance and both gray matter concentration ($r = 0.354$) and cortical thickness ($r = 0.212$; Fig. 4 and Table 2). Conversely, the correlation between anatomy and performance on the other tasks disappears when training duration is factored out ($r = 0.00$ – 0.19). Another potentially determining factor for cortical plasticity is the age at which a musician commences his or her training (Munte et al., 2002). We tested whether the age of commencement accounted for a significant portion of the anatomical variation in this ROI. For gray matter concentration, there was no such correlation ($r = -0.065$; Table 2). Cortical thickness in this ROI was significantly correlated with age of commencement ($r = -0.203$). If both training parameters (duration and commencement age) are factored out of relative pitch task performance, the correlation between performance and cortical thickness falls below the threshold for significance.

Therefore, although a considerable portion of the anatomical variation we see in right auditory cortex can be accounted for by general effects of musical training, when we look at gray matter concentration there remains an equally large part of the variation that is particularly related to relative pitch task performance, independent of musical training duration or the age of commencement. Conversely, when musical training is explicitly factored out from performance on the other musical tasks (simple melody and rhythm), no correlation with anatomical structure remains.

Anatomical differences in IPS

As mentioned above, a previous fMRI experiment in our laboratory showed that BOLD signal in the IPS is related to relative pitch processing

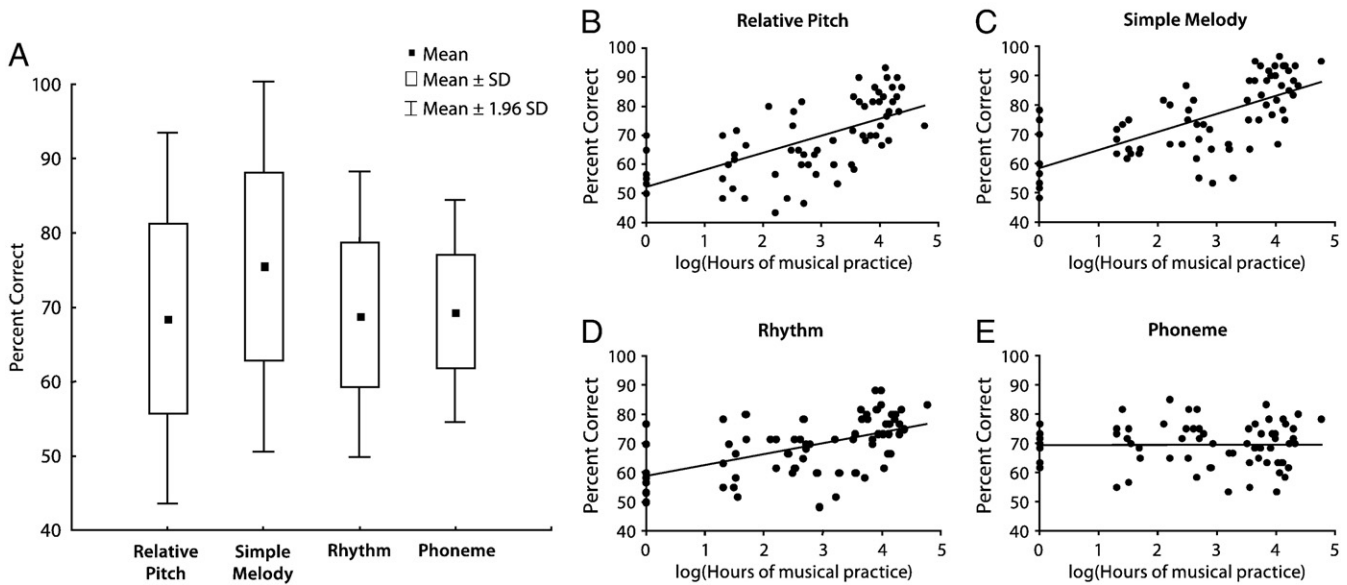


Fig. 2. Behavioral performance on the four tasks (relative pitch, simple melody, rhythm, and phoneme). (A) Box plot showing the distribution across subjects of performance in each task. (B–E) Training duration vs. performance on each task, with one point representing each subject. Subjects reporting no musical training are plotted at zero on the logarithmic abscissa.

(Foster and Zatorre, 2010). In the present experiment, we wanted to see whether there is a corresponding predictive relationship between neural anatomy in the anterior IPS and relative pitch task performance. Using a whole-brain search, we found correlations in bilateral IPS between performance on the relative pitch task and both gray matter concentration (left: $t = 4.07$; right: $t = 3.34$) and cortical thickness (left, $t = 3.32$; right, $t = 3.41$; Fig. 3). Although the VBM peaks in IPS did not reach statistical significance on a whole-brain level, they are very close in location to the significant cortical thickness peaks in IPS, as well as our previous fMRI results in Foster and Zatorre (2010). Following the method described above for the auditory cortex, we defined ROIs in left and right IPS to compare the anatomical correlation of relative pitch task performance with that of the other tasks; we also factored out the variance explained by musical training to see how much anatomical variation is uniquely explained by task performance (Fig. 4 and Table 2). This analysis revealed significant correlations with the simple melody and rhythm tasks, but not with the phoneme task; however, as with the AC, the variance accounted for was greatest for the relative pitch task. When the effect of training duration is removed from each task performance measure, a significant correlation remains between relative pitch task performance and gray matter concentration in left and right IPS, but the correlation with cortical thickness is eliminated.

Unlike the AC, there was a significant correlation between gray matter concentration and the age of musical training commencement in the right IPS ($r = -0.276$). We therefore tested whether factoring out the commencement age affects the task-anatomy correlation at this location. When the effects of both musical training duration and commencement age are factored out of task performance, no correlation between GM concentration and relative pitch task performance remains ($r = 0.146$; Table 2).

Other task-related anatomical differences

Outside the regions of interest in the AC and IPS, there were no whole-brain significant voxels in the VBM analysis for any of the four task conditions. In the CT analysis there were significant whole-brain effects in all tasks (tables are included in the [Supplementary materials](#)); but because they were not matched by VBM findings, their interpretation is uncertain. For the relative pitch task, in addition to the AC and IPS effects already mentioned, performance positively correlated with

cortical thickness in left precuneus, left inferior parietal lobule, bilateral parietooccipital sulcus, left middle frontal gyrus, left precentral sulcus, right precentral gyrus, and left ventrolateral frontal cortex.

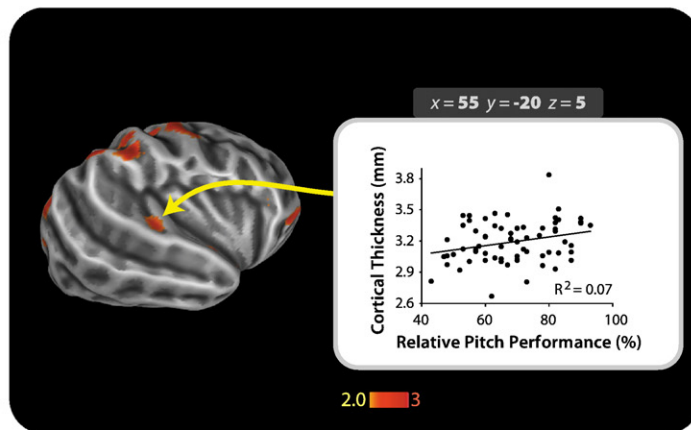
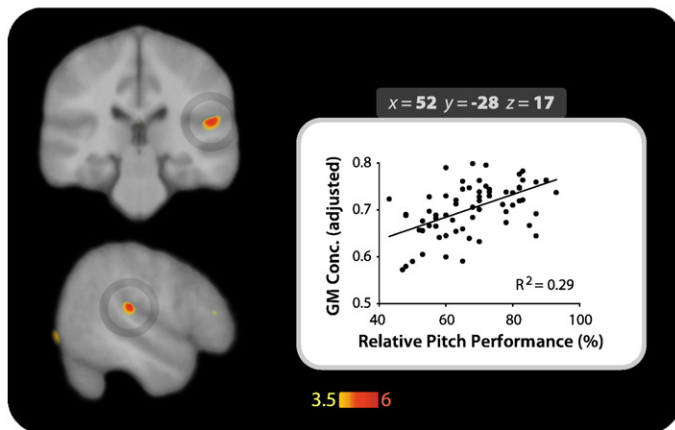
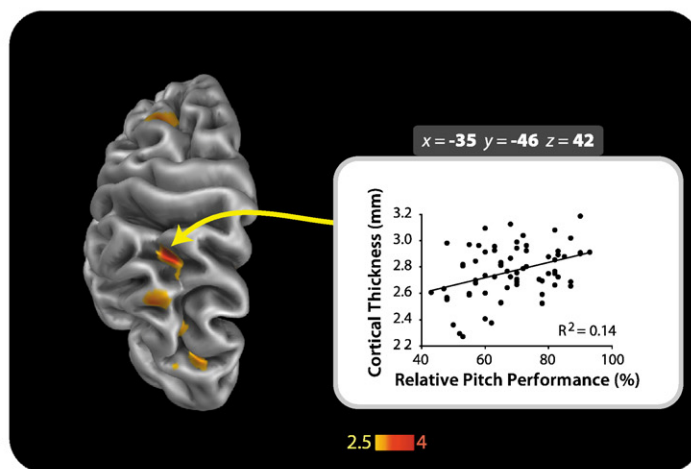
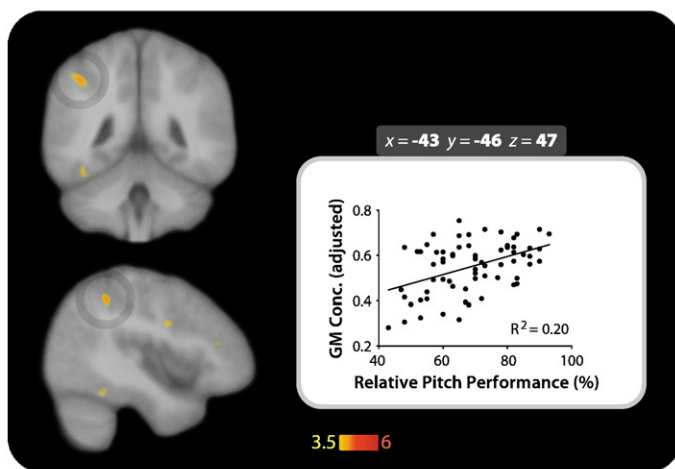
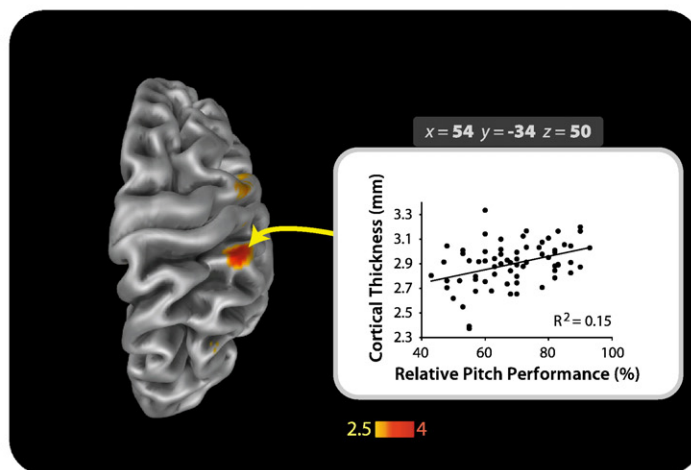
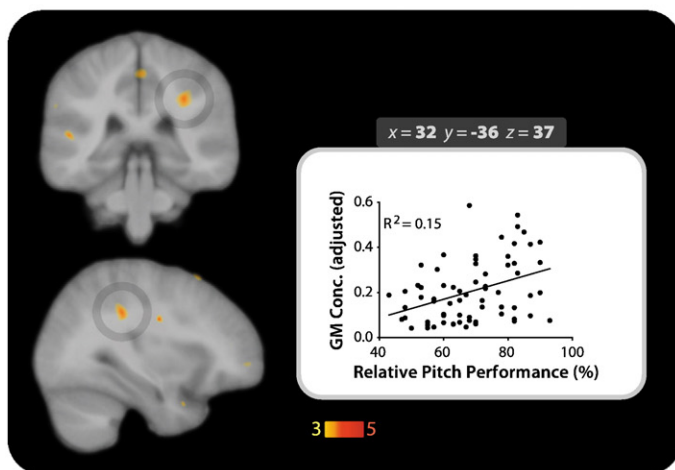
Discussion

Our results show that cortical structure in right auditory (AC) and intraparietal (IPS) cortex predicts performance on a relative pitch task. This variation in gray matter was correlated to a lesser extent with performance on two musical control tasks, but after factoring out variance explained by musical training, only the relative pitch task remained correlated with cortical structure. By using both voxel-based morphometry (VBM) and cortical thickness (CT) to analyze the anatomical data, we are able to show that the anatomical effects identified by VBM are due in part to increases in cortical thickness in the auditory cortex and intraparietal sulcus of higher-performing individuals.

Correspondence of VBM and CT results

Although VBM and CT are both performed upon tissue-segmented T_1 anatomical data, differences in subsequent processing steps result in sensitivity to different anatomical features (Ashburner and Friston, 2000, 2001; MacDonald et al., 2000). We were interested in how the two techniques would compare in identifying behavior-related cortical features. When applied to gray matter tissue maps, VBM is sensitive to systematic differences in gray matter concentration. Typically, image registration during VBM pre-processing includes a 12-parameter linear fit to the registration target; therefore, voxelwise differences in GM concentration may reflect intersubject variation in local gray matter shape, position, or volume (Ashburner and Friston, 2001). In contrast, tight nonlinear registration and surface fitting during CT analysis is intended to exclude variation unrelated to the thickness of the cortical mantle (MacDonald et al., 2000).

Comparing our whole-brain (Fig. 3) and region-of-interest (Fig. 4) results, both techniques reveal a very similar pattern of effects in the predicted regions: right auditory cortex and bilateral intraparietal sulcus. This convergence of results provides good evidence that the relationship between behavior and anatomy is valid. Some degree of spatial variation may be expected between the

AUDITORY CORTEX (right)**INTRAPARIETAL SULCUS (left)****INTRAPARIETAL SULCUS (right)**

Gray Matter Concentration

Cortical Thickness

Fig. 3. Peaks of interest in the imaging analyses of relative pitch task performance vs. gray matter concentration and cortical thickness. VBM images are shown in coronal and sagittal slices passing through each peak; left = left (neurological convention). Data are thresholded at the indicated t values. Accompanying scatter plots show the distribution of subjects' task performance vs. the anatomical value at each peak of interest.

analyses due to different registration targets, however the coordinates of the respective peaks are reasonably close. This correspondence between VBM and CT results suggests that the variation in gray

matter concentration is driven at least in part by cortical thickness differences, rather than other factors (such as positional variation of the cortical mantle).

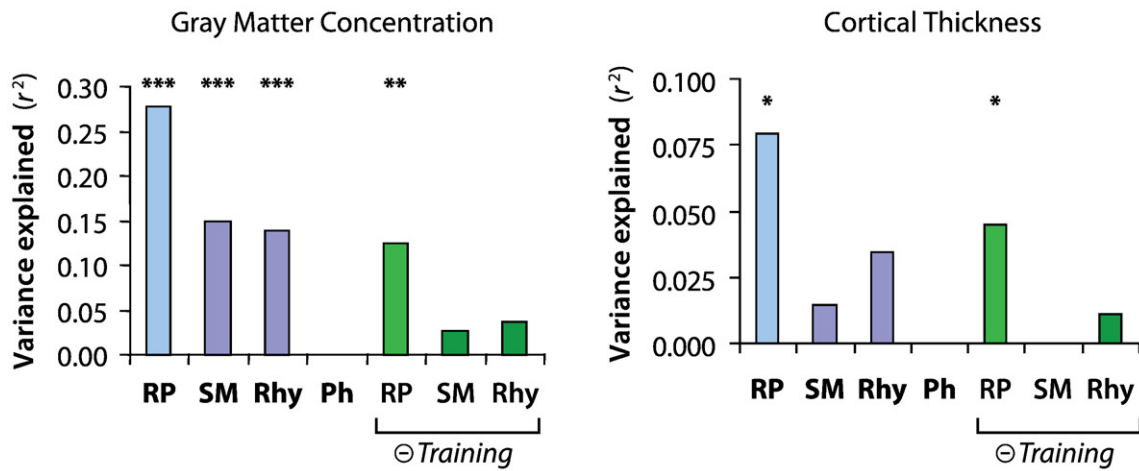
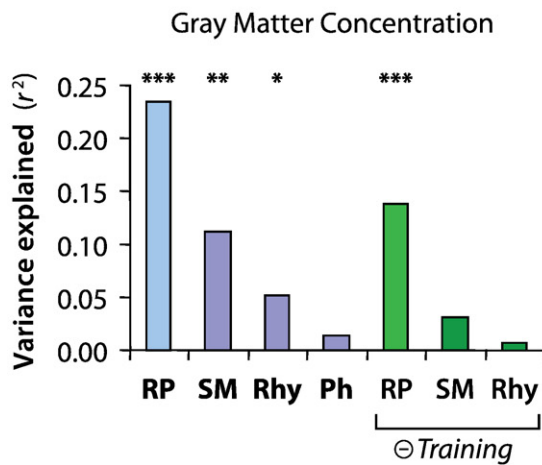
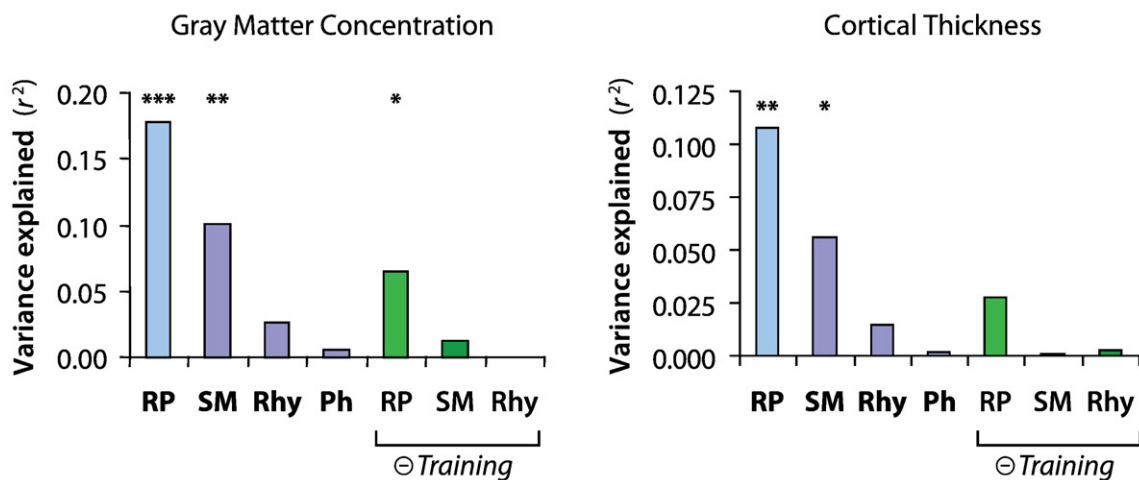
AUDITORY CORTEX (right)**INTRAPARIETAL SULCUS (left)****INTRAPARIETAL SULCUS (right)**

Fig. 4. Proportion of anatomical variance (gray matter concentration, cortical thickness) accounted for by task performance in each region of interest. For the bars designated by “(-) Training,” the logarithmic effect of training duration has been partialled out from task performance scores. RP, relative pitch task; SM, simple melody task; Rhy, rhythm task; Ph, phoneme task. ***Significant at $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

Table 2

Region of interest (ROI) analyses of voxel-based morphometry (VBM) and cortical thickness (CT) data in each of three regions. ROIs were defined by conjunction between the present results and data from the study indicated in "ROI source," as further described in the [Materials and methods](#). Subjects' gray matter concentration (VBM) and thickness (CT) values were averaged within each ROI; the correlations between relative pitch task performance, training duration, and age of training commencement vs. these average anatomical values (across subjects) are indicated.

Location	Analysis	ROI source	ROI conjunction size	RP corr. (r)	RP – TrDur (r)	RP – TrDur – TrAge (r)	Training duration corr. (r)	Training age corr. (r)
R. AC	VBM	Bermudez et al. (2009) (VBM)	999 voxels	0.528 (***)	0.354 (**)	N/A	0.398 (***)	–0.065 (n/s)
	CT	Bermudez et al. (2009) (CT)	47 vertices	0.282 (*)	0.212 (*)	0.189 (n/s)	0.183 (n/s)	–0.203 (*)
L. IPS	VBM	Foster and Zatorre (2010) (fMRI)	594 voxels	0.485 (***)	0.372 (***)	N/A	0.307 (*)	–0.140 (n/s)
	CT	Foster and Zatorre (2010) (fMRI)	0 vertices	N/A	N/A	N/A	N/A	N/A
R. IPS	VBM	Foster and Zatorre (2010) (fMRI)	435 voxels	0.427 (***)	0.260 (*)	0.146 (n/s)	0.349 (**)	–0.276 (*)
	CT	Foster and Zatorre (2010) (fMRI)	21 vertices	0.329 (**)	0.165 (n/s)	N/A	0.313 (*)	–0.115 (n/s)

AC, auditory cortex; IPS, intraparietal sulcus; n/s, not significant; RP, relative pitch task performance; – TrDur, log(hours of training) factored out from task performance; – TrAge, linear effect of age of commencement factored out from task performance.

* Significant at $P < 0.05$.

** Significant at $P < 0.01$.

*** Significant at $P < 0.001$.

Our hypotheses were guided by two previous studies about melody- and musicianship-related effects. In [Bermudez et al. \(2009\)](#), differences in both gray matter concentration and cortical thickness were observed between musicians and nonmusicians, but the behavioral significance of these effects was unknown. In [Foster and Zatorre \(2010\)](#), relative pitch task performance was predicted by functional activation in IPS, but it was unknown whether differences in task performance might be related to cortical anatomy in this region. The ROI analyses in the present study directly tested for spatial correspondence with these prior results ([Fig. 4](#) and [Table 2](#)). In all but one analysis, a conjunction was found. In left IPS, although there was no conjunction for the CT analysis, there are corresponding peaks in the CT and prior fMRI analyses that are separated by about 19 mm, both situated in the intraparietal sulcus. We discuss the implications of these results for pitch processing in the AC and IPS in a following section.

In the broader scope of music-related morphometric differences, a number of earlier studies have reported increases of gray matter volume or concentration in auditory cortex (e.g., [Gaser and Schlaug, 2003](#); [Hyde et al., 2009](#); [Schlaug et al., 1995b](#); [Schneider et al., 2002](#)). The present results suggest that one specific outcome of these differences in the right hemisphere is improved pitch interval processing, and that other auditory parameters, like temporal processing (i.e. rhythm), are not affected to an equivalent degree. At the same time, in identifying a particular relationship between anatomy and behavior our results do not exclude other roles for this region.

There are few previous reports of musically relevant structure-function relationships in parietal association cortex. In a VBM study, [Gaser and Schlaug \(2003\)](#) found gray matter concentration in right superior parietal lobule to correlate with musician status. [Bermudez and Zatorre \(2009\)](#) used a deformation-based analysis to search for effects associated with musical training, and they found a region of cortical expansion in right intraparietal sulcus. This locus of expansion lies directly between our VBM and CT peaks in right IPS.

Training-correlated and training-independent anatomical variation

The present results augment previous studies by showing that musical training is correlated both with perceptual task performance and regional cortical structure ([Tables 1 and 2](#)). Our primary goal in this study was to establish a specific link between cortical anatomy and relative pitch perceptual performance. As an important part of this question, we were interested to measure how much of this performance-anatomy correlation was independent of musical training. In auditory cortex, the VBM results show that a significant portion of the relative pitch task performance is explained by gray matter anatomical variation independently of musical training ([Table 2](#)). In the IPS, the results are less clear. After factoring out significant training-related parameters, no significant correlation between relative pitch and

cortical structure remains in the right IPS. In the left IPS, relative pitch task performance does seem to have a specific relationship with gray matter concentration independent of training in the VBM analysis, but we could not evaluate this in the CT analysis as there was no conjunction upon which to define a ROI.

Some earlier studies have shown that age of commencement plays a role in musical performance ([Bailey and Penhune, 2010](#); [Watanabe et al., 2007](#)) and has morphometric correlates in musicians ([Schlaug et al., 1995a](#)). Associations between commencement age and functional activation strength during musical auditory and motor paradigms have also been reported ([Elbert et al., 1995](#); [Pantev et al., 1998](#)). In two of our ROI analyses, cortical structure was predicted by the age of commencement (cortical thickness in right AC and gray matter concentration in right IPS). The present findings hence support the idea that age of training commencement plays a role in terms of brain morphology. However, in general, duration of training appeared to be a more prominent factor in cortical structure than the age of commencement in our sample. It seems likely that both factors interact with one another, and the nature of this potential interaction will be an important topic for future research.

What does it mean for there to be a link between task performance and regional cortical anatomy independent of training? With the present data, we cannot say whether the training-independent cortical variation stems from genetic or other innate factors, or to experiential factors not measured by our estimate of training. However, the dissociation between performance-related and training-related anatomical variation gives us confidence that gray matter structure in the AC, and most probably the IPS as well, is specifically linked with relative pitch processing during musical perception. Given that training and task performance each explain only part of the measured anatomical variation, it is a reasonable conclusion that experiential and preexisting factors both drive cortical structure in the AC and IPS. On the one hand, carefully controlled longitudinal studies have demonstrated cortical changes resulting from regular training in adults and children ([Driemeyer et al., 2008](#); [Hyde et al., 2009](#)). However, preexisting anatomical variation in auditory cortex has also been shown to predict differences in perceptual learning performance ([Golestani et al., 2007](#), 2002; [Wong et al., 2008](#)). Taken together, these findings suggest that brain structure affects task-relevant skill per se and is in turn modified by subsequent training; whether these factors are additive, or as seems likely, interactive, is a topic for future research.

Implications for our understanding of relative pitch processing

Taking the present results together with our previous functional imaging findings ([Foster and Zatorre, 2010](#)), it is evident that the AC and IPS both play important roles in relative pitch processing. A number of studies support the specialization of auditory cortex, especially in the

right hemisphere, for pitch and spectral processing (Griffiths et al., 1999; Schonwiesner et al., 2005; Zatorre and Belin, 2001). In particular, there is evidence for a pitch sensitive region in the lateral aspect of Heschl's gyrus (Bendor and Wang, 2006; Gutschalk et al., 2004; Johnsrude et al., 2000; Penagos et al., 2004; Schonwiesner and Zatorre, 2008), and in the corresponding region of the Marmoset brain (Bendor and Wang, 2005). However, in our previous fMRI study using the same relative pitch task (Foster and Zatorre, 2010), auditory cortex was recruited during task performance, but the magnitude of functional recruitment was not performance-dependent, in contrast with the IPS. This suggests that although the AC is part of the cortical network involved in relative pitch perception, the more specific operations relevant to this task are performed elsewhere.

The relative pitch task relies upon accurate extraction of intervals from a melodic sequence, as well as using this interval structure to transpose the melody to a different pitch level. We have previously proposed (Foster and Zatorre, 2010) that the IPS, a key region for visuospatial and abstract transformations (Jordan et al., 2001; Zacks, 2008), provides an ideal cognitive apparatus for performing this latter step of transforming melodic information. The IPS receives converging anatomical inputs from visual, auditory, and tactile sensory cortices (Frey et al., 2008; Schroeder and Foxe, 2002). Subregions within the sulcus, such as the macaque anterior intraparietal area (AIP) and its proposed human homologue hIP2, are specialized for representing the perceived world in various frames of reference (e.g., body, head, or retina-centered space), as well as systematically transforming sensory information among these frames of reference in order for perception to guide action (Culham and Kanwisher, 2001; Grefkes and Fink, 2005). In humans, the anterior IPS also has important roles in more abstract operations such as arithmetic (Kong et al., 2005). IPS activation is often reported in auditory paradigms, both for spatial operations (Alain et al., 2001; Maeder et al., 2001; Weeks et al., 2000; Zatorre et al., 2002b) and for nonspatial tasks (Cusack, 2005; Gaab et al., 2003; Zarate and Zatorre, 2008). The IPS is therefore in a prime position to systematically manipulate auditory representations, as is required in our relative pitch task.

There is evidence suggesting that spatial and musical transformations share common processing in parietal cortex. Mental rotation is a commonly used visuospatial paradigm that requires precise mental transformation of sensory information (Gogos et al., 2010; Jordan et al., 2001). Functional activation in anterior parietal cortex in this task is clearly linked with the transformation operation because the local BOLD signal is parametrically related to the angle of mental rotation (Gogos et al., 2010). There is a close correspondence between the activation patterns reported in these visuospatial rotation paradigms (Gogos et al., 2010; Jordan et al., 2001) and the performance-dependent functional activation we observe during the relative pitch task (Foster and Zatorre, 2010), as well as our present anatomical findings in the IPS. A recent study in our laboratory provides more evidence that the IPS is important for musical transformations. Zatorre et al. (2010) found that bilateral anterior IPS was recruited while subjects discriminated exact from inexact temporal reversals of melodies. This reversal task involves a manipulation of musical information in the temporal dimension, whereas in our relative pitch task the transformation is in the pitch dimension. The mental melodic reversal produced BOLD activation in anterior portions of the IPS, which overlaps with the IPS anatomical ROIs in the present study.

Given these similarities of brain loci and cognitive demands, it seems likely that a common cognitive mechanism residing in the IPS subserves transformations of both spatial information and musical information. In each case, internal relationships must be preserved, while global properties like spatial position, pitch level, or temporal note order are transformed. In the context of our relative pitch task, pitch interval relationships are probably

calculated in auditory cortex, with the subsequent manipulation of the interval sequence in “pitch space” being performed in parietal cortex.

Since this study included participants with a wide range of musical experience, it is possible that multiple strategies were used. Our analyses are only able to resolve behavior–anatomy effects that are sufficiently consistent within the sample as to exhibit a significant correlation. While we cannot exclude other cortical networks from being involved in relative pitch processing, our results show that within a wide-ranging sample of musicians and nonmusicians, right AC and bilateral IPS are the regions most reliably implicated in relative pitch processing.

Conclusions

Using voxel-based morphometry and cortical thickness analysis, we observed a specific correlation between accurate relative pitch processing and cortical structure in right auditory cortex (AC) and bilateral anterior intraparietal sulcus (IPS). The results are consistent with the idea that right-lateralized pitch processing in auditory cortex supports more complex manipulations of musical pitch sequences that engage parietal areas. The correspondence between previously reported functional activation in both regions and the current anatomical effects suggests that there is a coupling between the phenomena. Our results in AC reinforce earlier reports of musician-associated gray matter increases and extend these findings by providing a strong behavioral interpretation in terms of pitch processing. The results in IPS correspond closely with prior functional imaging studies of relative pitch, as well as mental melody reversal and visuospatial rotation, supporting the possibility of a common, multimodal network for systematic transformation of stimulus information in this region.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.06.042.

References

- Ad-Dab'bagh, Y., Singh, V., Robbins, S., Lerch, J., Lyttelton, O., Fombonne, E., Evans, A.C., 2005. Native space cortical thickness measurement and the absence of correlation to cerebral volume. In: Zilles, K. (Ed.), *Proceedings of the 11th Annual Meeting of the Organization for Human Brain Mapping*. NeuroImage, Toronto.
- Alain, C., Arnott, S.R., Hevenor, S., Graham, S., Grady, C.L., 2001. “What” and “where” in the human auditory system. *Proc. Natl. Acad. Sci. USA* 98, 12301–12306.
- Amunts, K., Malikovic, A., Mohlberg, H., Schormann, T., Zilles, K., 2000. Brodmann's areas 17 and 18 brought into stereotaxic space—where and how variable? *NeuroImage* 11, 66–84.
- Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. *NeuroImage* 11, 805–821.
- Ashburner, J., Friston, K.J., 2001. Why voxel-based morphometry should be used. *NeuroImage* 14, 1238–1243.
- Bailey, J.A., Penhune, V.B., 2010. Rhythm synchronization performance and auditory working memory in early- and late-trained musicians. *Exp. Brain Res.* 204 (1), 91–101.
- Bendor, D., Wang, X., 2005. The neuronal representation of pitch in primate auditory cortex. *Nature* 436, 1161–1165.
- Bendor, D., Wang, X., 2006. Cortical representations of pitch in monkeys and humans. *Curr. Opin. Neurobiol.* 16, 391–399.
- Bermudez, P., Zatorre, R.J., 2005. Differences in gray matter between musicians and nonmusicians. *Ann. NY Acad. Sci.* 1060, 395–399.

- Bermudez, P., Zatorre, R.J., 2009. Anatomical markers of musicianship and absolute pitch as revealed by deformation-based morphometry. *NeuroImage* 47, S88–???
- Bermudez, P., Lerch, J.P., Evans, A.C., Zatorre, R.J., 2009. Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. *Cereb. Cortex* 19, 1583–1596.
- Chung, M.K., Taylor, J., 2004. Diffusion smoothing on brain surface via finite element method. 2004 IEEE International Symposium on Biomedical Imaging: Macro to Nano, pp. 432–435.
- Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18, 192–205.
- Culham, J.C., Kanwisher, N.G., 2001. Neuroimaging of cognitive functions in human parietal cortex. *Curr. Opin. Neurobiol.* 11, 157–163.
- Cusack, R., 2005. The intraparietal sulcus and perceptual organization. *J. Cogn. Neurosci.* 17, 641–651.
- Dowling, W.J., Harwood, D.L., 1986. *Melody: Attention and Memory*. Music Cognition. Academic Press, San Diego, pp. 124–152.
- Driemeyer, J., Boyke, J., Gaser, C., Buchel, C., May, A., 2008. Changes in gray matter induced by learning—revisited. *PLoS ONE* 3, e2669.
- Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., Taub, E., 1995. Increased cortical representation of the fingers of the left hand in string players. *Science* 270, 305–307.
- Foster, N.E., Zatorre, R.J., 2010. A role for the intraparietal sulcus in transforming musical pitch information. *Cereb. Cortex* 20 (6), 1350–1359.
- Frey, S., Campbell, J.S., Pike, G.B., Petrides, M., 2008. Dissociating the human language pathways with high angular resolution diffusion fiber tractography. *J. Neurosci.* 28, 11435–11444.
- Gaab, N., Gaser, C., Zaehle, T., Jancke, L., Schlaug, G., 2003. Functional anatomy of pitch memory—an fMRI study with sparse temporal sampling. *NeuroImage* 19, 1417–1426.
- Gaser, C., Schlaug, G., 2003. Brain structures differ between musicians and non-musicians. *J. Neurosci.* 23, 9240–9245.
- Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage* 15, 870–878.
- Gogos, A., Gavrilescu, M., Davison, S., Searle, K., Adams, J., Rossell, S.L., Bell, R., Davis, S.R., Egan, G.F., 2010. Greater superior than inferior parietal lobule activation with increasing rotation angle during mental rotation: an fMRI study. *Neuropsychologia* 48, 529–535.
- Golestani, N., Paus, T., Zatorre, R.J., 2002. Anatomical correlates of learning novel speech sounds. *Neuron* 35, 997–1010.
- Golestani, N., Molko, N., Dehaene, S., LeBihan, D., Pallier, C., 2007. Brain structure predicts the learning of foreign speech sounds. *Cereb. Cortex* 17, 575–582.
- Good, C.D., Johnsrude, I., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage* 14, 685–700.
- Grabner, G., Janke, A.L., Budge, M.M., Smith, D., Pruessner, J., Collins, D.L., 2006. Symmetric atlas and model based segmentation: an application to the hippocampus in older adults. *Med. Image Comput. Assist. Interv.* 9, 58–66.
- Grefkes, C., Fink, G.R., 2005. The functional organization of the intraparietal sulcus in humans and monkeys. *J. Anat.* 207, 3–17.
- Griffiths, T.D., Johnsrude, I., Dean, J.L., Green, G.G., 1999. A common neural substrate for the analysis of pitch and duration pattern in segmented sound? *NeuroReport* 10, 3825–3830.
- Gutschalk, A., Patterson, R.D., Scherg, M., Uppenkamp, S., Rupp, A., 2004. Temporal dynamics of pitch in human auditory cortex. *NeuroImage* 22, 755–766.
- Haidar, H., Soul, J.S., 2006. Measurement of cortical thickness in 3D brain MRI data: validation of the Laplacian method. *J. Neuroimaging* 16, 146–153.
- Hyde, K.L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A.C., Schlaug, G., 2009. Musical training shapes structural brain development. *J. Neurosci.* 29, 3019–3025.
- Jancke, L., Koeneke, S., Hoppe, A., Rominger, C., Hanggi, J., 2009. The architecture of the golfer's brain. *PLoS ONE* 4, e4785.
- Johnsrude, I.S., Penhune, V.B., Zatorre, R.J., 2000. Functional specificity in the right human auditory cortex for perceiving pitch direction. *Brain* 123 (Pt 1), 155–163.
- Jones, S.E., Buchbinder, B.R., Aharon, I., 2000. Three-dimensional mapping of cortical thickness using Laplace's equation. *Hum. Brain Mapp.* 11, 12–32.
- Jordan, K., Heinze, H.J., Lutz, K., Kanowski, M., Jancke, L., 2001. Cortical activations during the mental rotation of different visual objects. *NeuroImage* 13, 143–152.
- Kim, J.S., Singh, V., Lee, J.K., Lerch, J., Ad-Dab'bagh, Y., MacDonald, D., Lee, J.M., Kim, S.I., Evans, A.C., 2005. Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *NeuroImage* 27, 210–221.
- Kong, J., Wang, C., Kwong, K., Vangel, M., Chua, E., Gollub, R., 2005. The neural substrate of arithmetic operations and procedure complexity. *Brain Res. Cogn. Brain Res.* 22, 397–405.
- Kriegeskorte, N., Simmons, W.K., Bellgowan, P.S., Baker, C.I., 2009. Circular analysis in systems neuroscience: the dangers of double dipping. *Nat. Neurosci.* 12, 535–540.
- Lerch, J.P., Evans, A.C., 2005. Cortical thickness examined through power analysis and a population simulation. *NeuroImage* 24, 163–173.
- Luders, E., Gaser, C., Narr, K.L., Toga, A.W., 2009. Why sex matters: brain size independent differences in gray matter distributions between men and women. *J. Neurosci.* 29, 14265–14270.
- MacDonald, D., Kabani, N., Avis, D., Evans, A.C., 2000. Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. *NeuroImage* 12, 340–356.
- Maeder, P.P., Meuli, R.A., Adriani, M., Bellmann, A., Fornari, E., Thiran, J.P., Pittet, A., Clarke, S., 2001. Distinct pathways involved in sound recognition and localization: a human fMRI study. *NeuroImage* 14, 802–816.
- Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, C.D., 2000. Navigation-related structural change in the hippocampi of taxi drivers. *Proc. Natl Acad. Sci. USA* 97, 4398–4403.
- Munte, T.F., Altenmüller, E., Jancke, L., 2002. The musician's brain as a model of neuroplasticity. *Nat. Rev. Neurosci.* 3, 473–478.
- Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L.E., Hoke, M., 1998. Increased auditory cortical representation in musicians. *Nature* 392, 811–814.
- Penagos, H., Melcher, J.R., Oxenham, A.J., 2004. A neural representation of pitch salience in nonprimary human auditory cortex revealed with functional magnetic resonance imaging. *J. Neurosci.* 24, 6810–6815.
- Schlaug, G., 2001. The brain of musicians. A model for functional and structural adaptation. *Ann. NY Acad. Sci.* 930, 281–299.
- Schlaug, G., Jancke, L., Huang, Y., Staiger, J.F., Steinmetz, H., 1995a. Increased corpus callosum size in musicians. *Neuropsychologia* 33, 1047–1055.
- Schlaug, G., Jancke, L., Huang, Y., Steinmetz, H., 1995b. In vivo evidence of structural brain asymmetry in musicians. *Science* 267, 699–701.
- Schneider, P., Scherg, M., Dosch, H.G., Specht, H.J., Gutschalk, A., Rupp, A., 2002. Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nat. Neurosci.* 5, 688–694.
- Schneider, P., Sluming, V., Roberts, N., Scherg, M., Goebel, R., Specht, H.J., Dosch, H.G., Bleeck, S., Stippich, C., Rupp, A., 2005. Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference. *Nat. Neurosci.* 8, 1241–1247.
- Schonwiesner, M., Zatorre, R.J., 2008. Depth electrode recordings show double dissociation between pitch processing in lateral Heschl's gyrus and sound onset processing in medial Heschl's gyrus. *Exp. Brain Res.* 187, 97–105.
- Schonwiesner, M., Rubsamen, R., von Cramon, D.Y., 2005. Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. *Eur. J. Neurosci.* 22, 1521–1528.
- Schroeder, C.E., Foxe, J.J., 2002. The timing and laminar profile of converging inputs to multisensory areas of the macaque neocortex. *Brain Res. Cogn. Brain Res.* 14, 187–198.
- Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans. Med. Imaging* 17, 87–97.
- Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cereb. Cortex* 17, 1550–1560.
- Tohka, J., Zijdenbos, A., Evans, A., 2004. Fast and robust parameter estimation for statistical partial volume models in brain MRI. *NeuroImage* 23, 84–97.
- Watanabe, D., Savion-Lemieux, T., Penhune, V.B., 2007. The effect of early musical training on adult motor performance: evidence for a sensitive period in motor learning. *Exp. Brain Res.* 176, 332–340.
- Weeks, R., Horwitz, B., Aziz-Sultan, A., Tian, B., Wessinger, C.M., Cohen, L.G., Hallett, M., Rauschecker, J.P., 2000. A positron emission tomographic study of auditory localization in the congenitally blind. *J. Neurosci.* 20, 2664–2672.
- Wong, P.C., Warrier, C.M., Penhune, V.B., Roy, A.K., Sadeh, A., Parrish, T.B., Zatorre, R.J., 2008. Volume of left Heschl's gyrus and linguistic pitch learning. *Cereb. Cortex* 18, 828–836.
- Worsley, K.J., Liao, C.H., Aston, J., Petre, V., Duncan, G.H., Morales, F., Evans, A.C., 2002. A general statistical analysis for fMRI data. *NeuroImage* 15, 1–15.
- Zacks, J.M., 2008. Neuroimaging studies of mental rotation: a meta-analysis and review. *J. Cogn. Neurosci.* 20, 1–19.
- Zarate, J.M., Zatorre, R.J., 2008. Experience-dependent neural substrates involved in vocal pitch regulation during singing. *NeuroImage* 40, 1871–1887.
- Zatorre, R.J., Belin, P., 2001. Spectral and temporal processing in human auditory cortex. *Cereb. Cortex* 11, 946–953.
- Zatorre, R.J., Perry, D.W., Beckett, C.A., Westbury, C.F., Evans, A.C., 1998. Functional anatomy of musical processing in listeners with absolute pitch and relative pitch. *Proc. Natl Acad. Sci. USA* 95, 3172–3177.
- Zatorre, R.J., Belin, P., Penhune, V.B., 2002a. Structure and function of auditory cortex: music and speech. *Trends Cogn. Sci.* 6, 37–46.
- Zatorre, R.J., Bouffard, M., Ahad, P., Belin, P., 2002b. Where is 'where' in the human auditory cortex? *Nat. Neurosci.* 5, 905–909.
- Zatorre, R.J., Halpern, A.R., Bouffard, M., 2010. Mental reversal of imagined melodies: a role for the posterior parietal cortex. *J. Cogn. Neurosci.* 22, 775–789.
- Zijdenbos, A.P., Forghani, R., Evans, A.C., 1998. Automatic quantification of MS lesions in 3D MRI brain data sets: validation of INSECT. Proceedings of the First International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer-Verlag, pp. 439–448.
- Zijdenbos, A.P., Forghani, R., Evans, A.C., 2002. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *IEEE Trans. Med. Imaging* 21, 1280–1291.