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Neuroanatomical Correlates of Musicianship as Revealed by Cortical Thickness and Voxel-Based Morphometry

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We used a multimethod approach to investigate the neuroanatomical correlates of musicianship and absolute pitch (AP). Cortical thickness measures, interregional correlations applied to these thicknesses, and voxel-based morphometry (VBM) were applied to the same magnetic resonance imaging data set of 71 musicians (27 with AP) and 64 nonmusicians. Cortical thickness was greater in musicians with peaks in superior temporal and dorsolateral frontal regions. Correlations between 2 seed points, centered on peaks of thickness difference within the right frontal cortex, and all other points across the cortex showed greater specificity of significant correlations among musicians, with fewer and more discrete areas correlating with the frontal seeds, including the superior temporal cortex. VBM of gray matter (GM)--classified voxels yielded a strongly right-lateralized focus of greater GM concentration in musicians centered on the posterolateral aspect of Heschl's gyrus. Together, these results are consistent with functional evidence emphasizing the importance of a frontotemporal network of areas heavily relied upon in the performance of musical tasks. Among musicians, contrasts of AP possessors and nonpossessors showed significantly thinner cortex among possessors in a number of areas, including the posterior dorsal frontal cortices that have been previously implicated in the performance of AP tasks.

Keywords: cortical thickness, voxel-based morphometry, musician, cortex, auditory, frontal

Introduction

The intensive training and practice involved in achieving high levels of musicianship place extraordinary demands on many of the mind's most critical faculties, and scientists have become increasingly aware of the value of musicianship as a model for probing such aspects of cognition as memory (Halpern 1989; Zatorre and Beckett 1989; Tervaniemi et al. 2001; Fujioka et al. 2005), auditory--motor integration (Lahav et al. 2007; Zatorre et al. 2007; Chen et al. 2008), and auditory perception (Pantev et al. 1998, 2003; Tervaniemi et al. 2005). Several studies have investigated aspects of gross cerebral morphology associated with musical training (Münte et al. 2002), mainly with the use of manual segmentation or voxel-based morphometry (VBM) of magnetic resonance images (MRIs). In an instance of the former, Schneider et al. (2002) observed a greater gray matter (GM) volume in the anteromedial portion of Heschl's gyri in musicians as compared to nonmusicians and showed that this volume was positively correlated with a behavioral index of musical proficiency. In a whole-brain VBM investigation, Gaser and Schlaug (2003) detected GM differences between male professional musicians, amateur musicians, and nonmusicians in areas known to be involved in auditory, motor, and visuospatial processing. These included the medial portion of left Heschl's gyrus, widely thought to be primary auditory cortex (Morosan et al. 2001), which differs from the results of Schneider et al. (2002) whose findings were more lateral in Heschl's of both hemispheres, and lateralized to the right hemisphere when considering the whole of Heschl's gyrus. Another VBM study (Sluming et al. 2002) detected a larger GM concentration in Broca's area for a sample of professional male musicians when compared with age- and sex-matched nonmusicians. Several studies have found evidence for changes in motor-related regions. Bangert and Schlaug (2006) were able to distinguish string from keyboard players, in addition to all musicians from nonmusicians, with the use of an index of precentral gyrus morphology, whereas Hutchinson et al. (2003) recorded a greater cerebellar volume in male musicians as compared to nonmusicians. Most of these studies have targeted specific areas of the brain and delineated areas of interest manually with a variety of metrics and definitions. Only 2 studies have performed a whole-brain search (Sluming et al. 2002; Gaser and Schlaug 2003) and, despite the fact that both used highly homogenous subject samples entirely comprised of male professional musicians, they have mutually exclusive sets of results. Clearly, much work remains to be done in the elucidation of the macroscopic cerebral morphology underpinning musicianship.

A small subset of anatomical studies investigating musicianship has probed the correlates of absolute pitch (AP), the ability to identify note names without aid of a reference tone possessed by a minority of musicians (Ward 1999). These few studies have yielded only one partially replicated result: a greater leftward asymmetry in size indices of the planum temporale (PT), a structure most often implicated in auditory and linguistic function (Geschwind and Levitsky 1968; Steinmetz et al. 1989; Westbury et al. 1999; Griffiths and Warren 2002), in AP possessors as compared to control musicians and nonmusicians. Despite this superficial congruence of results, details of the findings as well as the attributed underlying factors and interpretations differ between the studies. Schlaug et al. (1995) found a stronger leftward asymmetry of PT surface area among AP subjects. This result was replicated and extended by Keenan et al. (2001) who showed that a similar asymmetry in an independent sample was mainly driven by a smaller right PT surface rather than a larger left PT surface. In contrast, Zatorre et al. (1998) did not find a difference between AP and non-AP musicians in a similar asymmetry index but rather found that the volume of the left PT in AP musicians was larger than that of control subjects unselected for musical history and positively correlated with a measure of AP proficiency. All these authors have speculated about the relative likelihood of PT anatomy serving as a marker of predisposition to the acquisition of AP versus a reflection of an experiential difference. Despite the fact that the meaning of these collected PT findings remains uncertain, they do suggest that the search for macroscopic anatomical markers associated with AP could aid in its characterization. Few findings have pointed to areas lying outside the temporal lobe. Though it is not the defining feature of the ability, the necessary reliance on conditional associative memory in the performance of a typical AP task has implicated the posterior dorsolateral frontal cortex, known to be critically involved in this type of memory (Petrides et al. 1993; Zatorre et al. 1998; Bermudez and Zatorre 2005). Ohnishi et al. (2001) reported a positive correlation between AP proficiency and blood oxygen level–dependent (BOLD) signal in the left posterior dorsolateral frontal cortex and left PT in response to a sample of classical music to which subjects listened passively. Collectively, these have been the only precisely located brain correlates of AP performance to date.

Functional imaging studies have provided evidence concerning brain areas relevant to the performance of various music-related tasks. Interactions between temporal and frontal areas may be of particular importance (Zatorre et al. 1994, 1996; Griffiths et al. 1999; Halpern and Zatorre 1999; Perry et al. 1999; Gaab et al. 2006). For instance, in a positron emission tomography (PET) experiment by Griffiths et al. (1999), subjects heard pairs of tone sequences, which could differ in either their temporal or pitch composition, and were asked to make a same/different judgment for each pair while attending to either the pitch or temporal dimensions. Results showed a right-lateralized frontotemporal pattern of activation when contrasting the judgment conditions with a resting baseline, which likely reflects, in part, the working memory and pitch analysis demands of the task. Parts of the inferior frontal cortex and frontal operculum have also been implicated in the processing of hierarchical syntax in musical structure (Koelsch et al. 2005; Tillmann et al. 2006). In the work of Tillmann et al. (2006), BOLD signal in the right frontal operculum and left extraprimary auditory areas was stronger when subjects heard sequences of chords that ended with less harmonically related chords than sequences that ended with strongly related chords. Given that the design of stimuli controlled for sensory deviance effects, this finding was thought to reflect the subjects' knowledge (be it implicit or explicit) of the rules governing harmonic sequencing. Together, these findings showing coactivation of frontal and temporal regions suggest an interactive role in various aspects of music cognition.

Another line of functional evidence is converging to reveal the lateral portion of Heschl's gyrus and surrounding extraprimary areas as critically important in the processing of complex pitch. Several studies have shown a sensitivity to pitch processing and/or to spectral composition in the anterolateral aspect of Heschl's gyrus (Zatorre and Belin 2001; Griffiths and Warren 2002; Schönwiesner et al. 2005), whereas responses to patterns of pitches, such as those found in melodies, tend to engage regions anterior and posterior to Heschl's gyrus (Griffiths et al. 1998; Patterson et al. 2002). Using a novel auditory stimulus that permitted independent manipulation of temporal and spectral complexity while maintaining bandwidth and energy constancy, Schönwiesner et al. (2005) demonstrated that areas of the right superior temporal gyrus lying outside Heschl's gyrus were particularly sensitive to spectral manipulation and analogous areas in the left hemisphere to temporal manipulation. Furthermore, there is evidence showing enhanced functional responses specifically to musical tones in musicians. Pantev et al. (1998) used magnetoencephalography to show that the cortical response to piano (but not pure) tones was greater in musicians as compared with nonmusicians and that the amplitude of this response was correlated with the age at which musicians began musical training. Taken together, these findings demonstrate the value of searching for anatomical reflections of the unusual skills developed by musicians in areas known to subserve functions critical to music cognition, such as parts of the frontal and temporal cortices.

Automated methods for *in vivo* extraction of cortical thickness from MRIs, in which deformable models are used to create inner and outer surfaces of the cortex and, subsequently, measure the distance between these surfaces, have been successfully used in experimental and descriptive studies of cerebral anatomy in such diverse populations as Alzheimer's patients (Lerch et al. 2004), attention-deficit/hyperactivity disorder patients (Makris et al. 2007), migraine sufferers (Granziera et al. 2006), and amusic subjects (Hyde et al. 2007). The number of such studies has been increasing rapidly in the last years as the methods have become more sophisticated, reliable, and accessible (Jones et al. 2000; Kabani et al. 2001; Lerch and Evans 2005; Haidar and Soul 2006; Han et al. 2006). The advantages of the data-driven nature of VBM have been well described and exploited. However, as is the case with any approach, it has several notable limitations (Ashburner and Friston 2001; Bookstein 2001). Among them is the fact that typical VBM results communicate information about size, position, and morphology concurrently. Relatively strong nonlinear spatial normalization mitigates this problem to some extent but also risks fitting away variance of interest (i.e., signal). The cortical thickness metric is somewhat more specific and constrained than that provided by VBM and has a biological meaning that is more easily apprehensible than what is referred to as matter density or concentration in VBM. It is also likely less susceptible to positional variance given that the extraction of the cortex will follow the highly corrugated GM surface irrespective of small-scale, local variations in its position. Of course, as the term implies, a cortical thickness analysis is necessarily limited to the cortex and, therefore, cannot be used to examine noncortical GM or white matter. These differences partly motivate a multianalytical approach which endeavors to have each technique inform the other's weaknesses, in an attempt to mutually disambiguate and complement. To our knowledge, *in vivo* cortical thickness measures have yet to be applied to the comparison of musicians and nonmusicians or to the subpopulation of musicians possessing AP. In the work reported here, we have sought to combine a measure of cortical thickness (MacDonald et al. 2000), an interregional correlational analysis technique that reveals how the thickness of a region of interest (ROI) covaries with thicknesses across the entire cortex (Lerch et al. 2006), and VBM (Ashburner and Friston 2000), in a multimethod approach applied to the same data set with the aim of providing the advantage of mutually informing complementarity and, where possible, the strength of convergence.

There exist strong predictions of differences in auditory and motor regions from existing literature, and we expect greater cortical thickness and GM concentration for musicians in these areas. Given the repeated observation of activity in dorsolateral frontal cortices due to their strong implication in functions heavily taxed during musical performance (such as working memory), we hypothesize a thickness difference between musicians and nonmusicians in these areas as well. Also following from this literature, we predict a degree of right hemisphere lateralization and a privileged correlation of cortical thicknesses between temporal and frontal areas in musicians, areas so often found acting in concert during various musical tasks. In the inspection of AP-related substrates, we might expect to replicate an index of either a larger left or smaller right planum temporale. Finally, given the unusual mnemonic abilities required in the acquisition and establishment of the AP ability, we might also conjecture dimorphisms in memory-related structures, in particular the posterior dorsolateral frontal cortex, which has distinguished AP musicians functionally, and medial–temporal areas such as the parahippocampal cortices and the hippocampus proper.

Materials and Methods

Subjects

Our inclusion criteria for musicians required at least 10 years of formal training and instrumental practice. All subjects were right-handed and free of hearing impairment and neurological disorder. Musicians were primarily recruited through the music faculties of 2 local universities, while most nonmusicians had campus-wide affiliations at these same institutions. All subjects gave informed consent, and behavioral and scanning procedures were approved by the Research Ethics Committee of the Montreal Neurological Institute, McGill University. Sample constitution was as follows: 71 musicians (47 females, 24 males, average age 23.3 years, standard deviation [SD] ±3.2; 16.9 years of musical experience, SD ±3.4, 27 with verified AP, varied instrumental concentration) and 64 nonmusicians (39 females, 25 males, average age 24.4 years, SD ±4.9; less than 3 years musical training). Age, age of commencement of training, total years of playing/training, and hours of current practice were 23.2 (SD ±3.9), 7.6 (SD ±3.2), 15.0 (SD ±4.3), and 13.9 (SD ±9.7), respectively, in non-AP musicians and 23.2 (SD ±3.5), 5.4 (SD ±1.7), 17.0 (SD ±3.9), and 15.4 (SD ±10.5) in AP musicians.

AP Testing of Musicians

We developed and administered a test of AP to 49 of our 71 musicians, among whom were the 27 who reported possessing AP. The remaining musicians who were not tested reported themselves to be nonpossessors of AP. Fundamental frequencies of the test tones corresponded to notes ranging from C_3 to B_5 (3 octaves) and were based on an $A = 440$ Hz equal temperament, with a $2^{1/12}$:1 frequency ratio between adjacent semitones. Each note was presented 3 times, once at each of 3 different intensities (−1, −4, and −7 dB). This summed to 108 trials. The notes were synthetic tones generated by summing a series of sinusoid waveforms including a fundamental frequency and a harmonic series (f, 2f, 3f, etc.), where the difference in amplitude between adjacent harmonics is on the order of 12 dB. Given a 16-bit sampling depth, this yielded approximately 9 harmonics. All notes had a duration of 1 s including 50-ms linear onset and offset ramps. For each note heard, subjects gave an identification response indicating both note name (1 of 12 possible semitones) and octave (1 of 5 choices). Mean absolute deviation from the correct answer (ranging from 0 to 6 semitones) was used as an index of performance.

Image Acquisition

T_1-weighted volumes (time echo = 9.2 ms, time repetition = 22 ms, matrix size: 256 × 256, voxel size: 1 × 1 × 1 mm^3) were acquired on a Siemens Vision 1.5 T MRI scanner.

Cortical Thickness Generation

All MRIs were submitted to the CIVET pipeline (version 1.1.7, http://wiki.bic.mni.mcgill.ca/index.php/CIVET; Ad-Dab'bagh et al. 2006; Zijdenbos et al. 2002). T_1 images were registered to the ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation (Collins, Neelin, et al. 1994; Grabner et al. 2006), RF inhomogeneity corrected (Sled et al. 1998) and tissue classified (Zijdenbos et al. 1998; Tohka et al. 2004). Deformable models were then used to create white and GM surfaces for each hemisphere separately, (MacDonald et al. 2000; Kim et al. 2005), resulting in 4 surfaces of 41 962 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 (Jones et al. 2000; Lerch and Evans 2005; Haidar and Soul 2006). The thickness data were subsequently blurred using a 25-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. 2006). Normalizing for global brain size when it has little pertinence to cortical thickness risks introducing noise and reducing power.

MACACC Analysis

A MACACC analysis (Lerch et al. 2006) is performed by selecting a seed vertex of interest from the cortical surface and testing the correlational strength between this and every other vertex in the cortical thickness surface. This approach is conceptually and computationally similar to some variants of functional connectivity analysis often applied to functional imaging data (Friston et al. 1997; Lee, Harrison, and Mechelli 2003; Worsley et al. 2005). The resulting statistic gives an indication of the degree to which cortical thickness throughout the brain covaries with that of the seed region across subjects. This, in and of itself, does not necessarily indicate anatomical connectivity in the traditional sense of the term, but, along with other lines of anatomical and functional evidence, it can serve as an indication of the possible structural and functional interdependence of different areas.

Voxel-based Morphometry

T_1 images were linearly registered to the ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation (Collins, Neelin, et al. 1994; Grabner et al. 2006), RF inhomogeneity corrected (Sled et al. 1998) and tissue classified (Zijdenbos et al. 1998; Tohka et al. 2004). Each of the GM and white matter tissue classes was then averaged across subjects to create study-specific GM and white matter templates that served as targets for a subsequent nonlinear registration with a 16-mm node spacing between vectors in the deformation grid (Collins, Peters, and Evans 1994). This degree of nonlinear normalization further reduces global variance without distorting local features of anatomy. Resulting GM and white matter images were convolved with a 3-dimensional Gaussian blurring kernel with a 10-mm full-width half-maximum.

Analyses

A series of analyses were performed according to the general linear model: 1) cortical thickness and VBM contrasts of musicians and nonmusicians, 2) MACACC analyses for a pair of seed points for both musicians and nonmusicians, 3) cortical thickness and VBM contrasts of the 12 strongest and 12 weakest performing musicians on the test of AP, and 4) a regression of AP performance onto cortical thickness measures and VBM images of the 49 tested musicians. All statistical thresholds were determined by application of the false discovery rate (FDR) technique (Genovese et al. 2002).

Results

AP Testing of Musicians

Musicians who were tested for AP showed expected differences that largely reflected their self-report as either possessors or nonpossessors of the ability. The group differences in percent correct and mean absolute deviation scores (where lower values indicate better performance) were highly significant. For the identification of note or pitch class, AP possessors showed a greater percentage of correct responses (mean

[M] = 78.8% ± standard error [SE] 3.48 vs. M = 15.1% ± SE 2.09; $t(47) = 14.06$, $P < 0.001$) and smaller mean absolute deviation from the correct note (M = 0.34 semitones ± SE 0.058 vs. M = 2.49 semitones ± SE 0.136; $t(47) = 14.43$, $P < 0.001$). Despite the marked differences in group averages, the distribution of mean absolute deviation scores across all subjects was suitable for regression onto anatomical metrics. Henceforth, we shall refer to AP proficiency rather than absolute mean deviation.

Cortical Thickness—Musicians versus Nonmusicians

In the musicians versus nonmusicians contrast, there was significantly greater thickness for musicians in the superior temporal surfaces, principally posterior to primary auditory areas and corresponding to the PT (Table 1 and Fig. 1*a*,*b*). The effect was bilateral though considerably more extensive in the right hemisphere, extending further along the superior temporal plane, to the medial surface of the temporal lobe, and encompassing primary auditory cortex (Table 1 and Fig. 1*a*,*b*). Broad areas of the lateral frontal lobes were also thicker in musicians, with notable peaks bilaterally in the middle and inferior frontal gyri (areas 9/46 and 47/12; Table 1 and Fig. 1). Other foci included frontal polar regions (Brodmann area [BA] 10), the right pars opercularis and pars triangularis (BA 44/45), the right ventral premotor cortex (BA 6), the left calcarine fissure and lingual gyrus (BA 17), the right anterior cingulate, the right middle temporal gyrus (BA 21), and the medial aspect of the left anterior superior frontal gyrus (BA 32/8). There were no suprathreshold peaks indicating greater thickness in nonmusicians.

Table 1

	Stereotaxic coordinates (MNI space)			t-value
	x	y	z	
Cortical thickness				
Right hemisphere				
Middle frontal gyrus (9/46/10)	42	51	2	3.37
Middle frontal gyrus (9/46)	33	47	23	3.81
Ventrolateral frontal (47)	36	30	−18	3.40
Ventrolateral frontal (47)	40	33	−16	3.32
Middle frontal pole (10)	29	62	−11	2.90
Pars triangularis (44/45)	55	24	10	2.45
Pars triangularis (44/45)	50	23	5	2.57
Pre-central gyrus (6)	54	6	33	2.21
Planum temporale (42)	52	−31	19	3.33
Superior temporal gyrus (22)	48	−9	1	3.65
Middle temporal gyrus (21)	54	2	−34	2.52
Anterior cingulate (32)	4	38	12	3.59
Posterior cinglulate (31)	6	−40	38	3.29
Central sulcus (3,1,2/4)	15	−29	75	2.60
Fusiform gyrus (19)	25	−70	−8	2.92
Left hemisphere				
Middle frontal gyrus (46)	−42	38	26	3.58
Superior frontal gyrus (9)	−14	48	44	3.15
Ventrolateral frontal (area 47)	−40	24	−17	3.39
Ventrolateral frontal (area 47)	−33	23	−22	3.44
Planum temporale (42)	−56	−29	14	2.93
Central sulcus/anterior post-central gyrus (3,1,2)	−36	−26	66	2.92
Anterior cingulate/medial superior frontal (32/8)	−8	33	26	4.31
Calcarine fissure/lingual gyrus (BA 17)	−7	−84	6	2.21
Voxel-based-morphometry				
Right hemisphere				
Posterolateral Heschl's gyrus (41)	58	−18	10	4.61
Posterolateral Heschl's gyrus (41)	49	−19	12	4.61
Posterior cingulate (31)	3	−29	45	4.01
Central sulcus	53	−21	42	3.92
Superior temporal gyrus (22)	58	−1	−7	4.27
Inferior frontal gyrus (45/47)	41	21	−3	3.95
Superior frontal gyrus (6)	3	55	7	4.01
Inferior temporal gyrus (37)	49	−64	−18	4.35
Left hemisphere				
Superior temporal gyrus (20)	−54	−5	2	4.45
Medial frontal gyrus (10)	−4	57	−8	4.39
Central sulcus (3,1,2/4)	−36	−24	61	3.39

Cortical Thickness—Interregional Correlations

Two vertices of interest, corresponding to the main right frontal foci indicating greater cortical thickness in the musicians versus nonmusicians contrast, were selected for a correlational analysis (MACACC, Lerch et al. 2006). For seed 1 (centered at $x = 42$, $y = 51$, $z = 2$), the area of significant correlation in nonmusicians was much more expansive than in musicians, covering the largest part of the cortical surface and with foci in homologous areas of the left hemisphere, posterior PT, and inferior parietal lobules (Fig. 2*a*). In contrast, significant areas in musicians were more constrained and included the superior temporal gyri, inferior parietal lobules, and a contralateral frontal peak lying significantly more posteriorly to the homologue of the seed region (Fig. 2*b*). Correlations with seed 2 (centered at $x = 33$, $y = 47$, $z = 23$) show broadly the same pattern although not as strikingly as with seed 1 (Fig. 2*c*,*d*).

Cortical Thickness—AP versus Non-AP Musicians

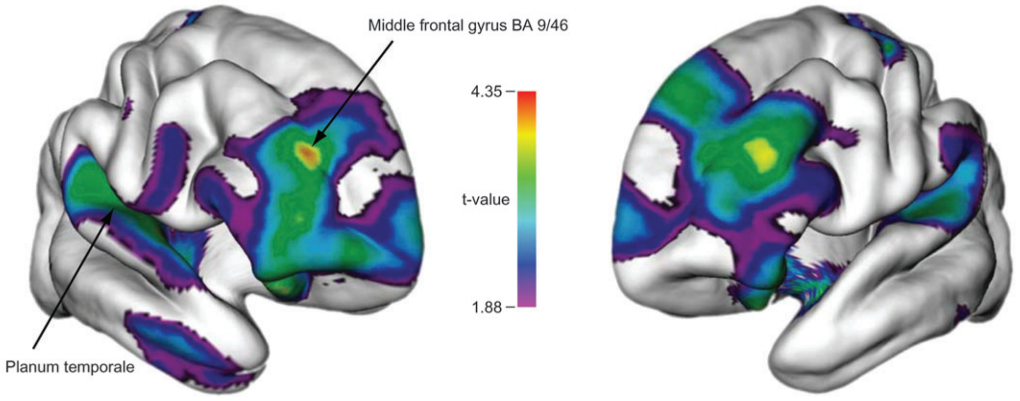
Among the 49 musicians who were tested for AP, a large gamut of ability was observed, with no clear discontinuity between groups. Therefore, from this larger group, AP and non-AP musicians were contrasted by selecting the 12 strongest and 12 weakest performers in the test of AP (the groups were matched for age, sex, and musical experience). All significant findings were in the direction of thinner cortex in the AP group (Table 2 and Fig. 3*a*,*b*) and included the right superior frontal gyrus (BA 9/46), right posterior superior frontal sulcus (rostral BA 6), right ventral premotor cortex (BA 6) and pars opercularis (BA 44), right inferior parietal lobule (BA 40), right anterior medial superior frontal gyrus (BA 46/10), left anterior superior frontal gyrus (BA 10), left posterior superior frontal gyrus (rostral BA 6), left lateral central sulcus (BA 4), left secondary sensory cortex (BA 2/40), left postcentral sulcus and intra-parietal sulcus (IPS) (BA 40), and left precuneus (BA 7/31). Similarly, the regression of AP performance score onto the cortical thickness of the 49 musicians who were tested showed a significant trend for thinner cortex with increasing AP proficiency in right ventral premotor cortex (BA 6) and pars opercularis (BA 44), right inferior parietal lobule (BA 39), left postcentral gyrus (BA 2/40), left middle temporal gyrus (BA 21), and left inferior parietal lobule (BA 40). Only one area, in the left pericalcarine cortex (BA 17), showed increased thickness with increased AP proficiency.

VBM—Musicians versus Nonmusicians

The most prominent difference is a higher GM concentration in musicians as compared to nonmusicians in the right superior temporal area, centered on the posterolateral aspect of Heschl's gyrus (caudal–lateral auditory belt cortex and PT; Table 1 and Fig. 1*c*). A subthreshold negative white matter peak lies immediately posterior and lateral to the positive GM peak, suggesting that at least some portion of the signal is attributable to an expansion of the posterior and lateral extent of Heschl's gyrus. A much weaker and nonsignificant homologous positive GM peak is also evident in the left auditory cortex (approximately centered on $x = -47$, $y = -22$, $z = 13$). There are also

a) Cortical thickness: musicians > non-musicians (RH)

b) Cortical thickness: musicians > non-musicians (LH)



c) Grey matter VBM: musicians > non-musicians

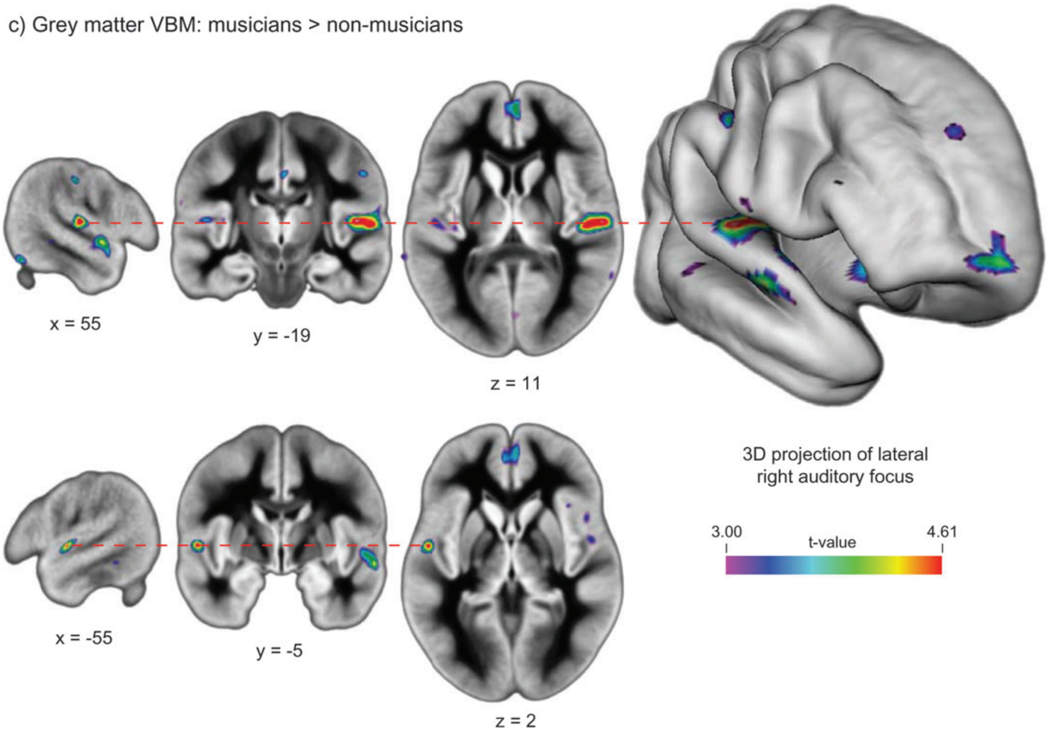


Figure 1. *t*-Statistic maps showing the main findings from the contrast of musicians and nonmusicians both in cortical thickness (*a*, right hemisphere; *b*, left hemisphere) and VBM (*c*). FDR-determined $P = 0.05$ significance thresholds are $t = 1.88$ and $t = 3.7$ for cortical thickness and VBM, respectively. Dorsolateral frontal and superior temporal regions showing greater thickness in musicians have previously been shown important in the performance of many musical tasks. To the right of panel (*c*), the focus of greater GM concentration in the right auditory cortex of musicians is projected to the average cortical surface to facilitate comparison with the cortical thickness findings.

discrete maxima lying anteriorly to Heschl's gyrus in the right superior temporal gyrus (BA 22; Fig. 1*c*), right inferior frontal area (BA 45/47), left superior temporal gyrus (BA 20), and left medial aspect of the frontal polar cortex (BA 10; Table 1). There were no suprathreshold foci for the contrast of white matter.

VBM—AP versus Non-AP Musicians

Within the musician group, AP possessors and nonpossessors were once again contrasted by selecting the 12 strongest and 12 weakest performers in the test of AP. Though a few peaks are listed in Table 2 for the GM contrast, none reached the $P =$ 0.05 significance threshold as determined by FDR. The same is true for the regression of AP proficiency score onto GM and white matter for the 49 musicians who were tested. Some subthreshold peaks in GM included positive correlations in the left pericalcarine area ($x = -9$, $y = -80$, $z = 7$; $t = 3.64$) and right middle temporal gyrus ($x = 63$, $y = -12$, $z = -20$; $t = 4.76$) and negative correlations in the right inferior frontal area ($x = 46$, $y = 12$, $z = 21$; $t = 3.59$) and left orbital frontal cortex ($x = -6$, $y = 60$, $z = -15$; $t = 3.63$). Subthreshold white matter peaks included a positive correlation below the left superior frontal gyrus ($x = -12$, $y = 18$, $z = 55$; $t = -4.20$) and a negative correlation lateral to right cingulate cortex ($x = 16$, $y = 37$, $z = 26$; $t = 4.43$).

Discussion

Using a combination of automated *in vivo* cortical thickness measurement and VBM, we have described a set of anatomical differences between samples of musicians and nonmusicians, as well as anatomical markers related to the ability of AP among musicians. To our knowledge, this is the first application of

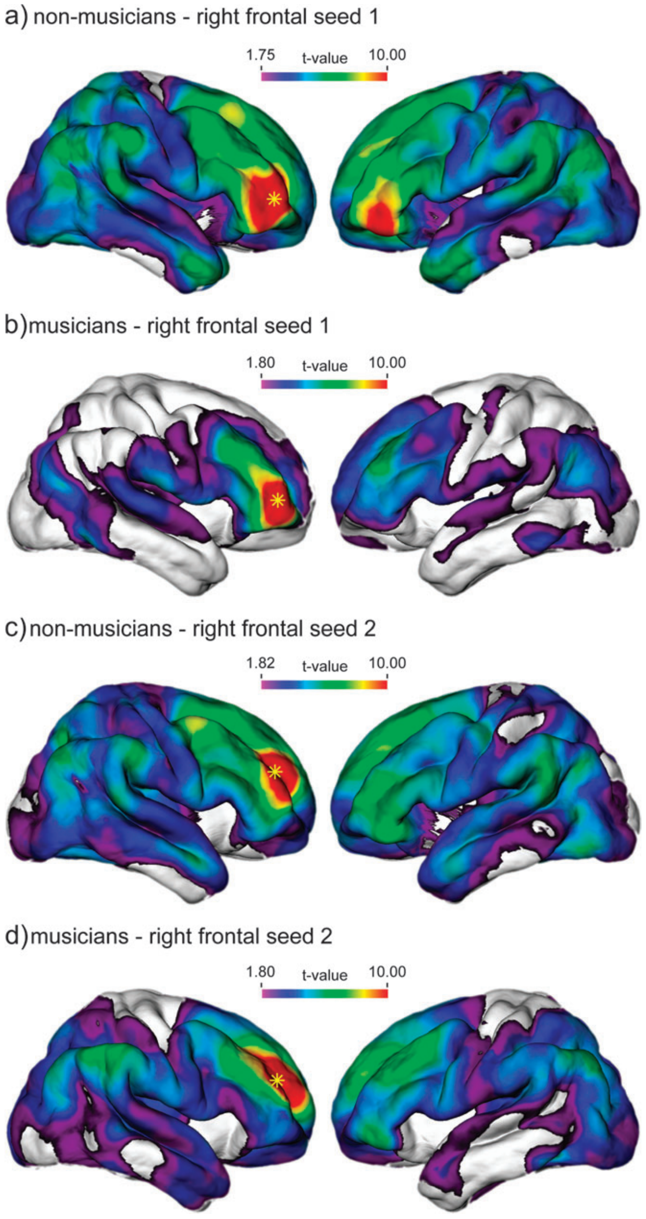


Figure 2. *t*-Statistic maps showing significant interregional correlations using 2 seed vertices in the right frontal cortex (indicated by yellow asterisks) centered on the first 2 peaks reported in Table 1 ($x = 42, y = 51, z = 2$ and $x = 33, y = 47, z = 23$) and shown in Figure 1*a*. All images are FDR thresholded at $P = 0.05$. The pattern of correlation shows greater specificity in musicians (e.g., between frontal and temporal areas) as compared with nonmusicians, especially in the case of seed 1 (panels *a* and *b*), perhaps reflecting the interdependence of these areas in the performance of musical tasks.

Table 2

	Stereotaxic coordinates (MNI space)			t-value
	x	y	z	
Cortical thickness				
Right hemisphere				
Precentral sulcus/pars opercularis (6/44)	54	16	18	−3.99
Inferior parietal lobule/IPS (40)	49	−35	50	−3.55
Inferior parietal lobule (39/19)	40	−74	43	−3.14
Superior frontal sulcus (6)	25	1	56	−3.24
Superior frontal gyrus (9/46)	10	59	34	−2.89
Para-hippocampal (34)	34	−17	−18	−3.93
Medial superior frontal (46/10)	7	54	1	−3.41
Posterior cingulate/post-central sulcus (31)	8	−32	44	−2.68
Left hemisphere				
Superior frontal gyrus (6)	−22	9	64	−2.95
Superior frontal gyrus (10)	−26	62	12	−2.84
Superior frontal gyrus (10)	−15	70	3	−2.85
Central sulcus (4)	−49	−14	40	−2.41
Secondary sensory/supramarginal (2/40)	−60	−24	35	−2.88
Inferior parietal lobule/IPS (7)	−34	−59	48	−3.35
Pre-cuneus (7/31)	−3	−63	37	−3.50
Inferior parietal lobule/IPS (40)	−46	−40	49	−2.87
Voxel-based-morphometry				
Right hemisphere				
Lateral central sulcus (43)	53	−7	9	−3.92
Post-central gyrus (2)	54	−21	37	−3.65
Pre-central gyrus (6)	49	1	41	−3.65
Superior parietal lobule (7)	28	−41	59	−4.49
Left hemisphere				
Superior frontal gyrus (6)	−10	14	55	−5.55

cortical thickness methods and a combined anatomical approach to musicians and AP possessors. As each technique has a somewhat different set of strengths and limitations, a certain complementarity results from the fact that each can partially disambiguate the other. Where they converge, we might have a heightened confidence in the observation.

Musicians versus Nonmusicians—Auditory Cortices

The auditory cortices have previously been shown to be morphologically and functionally distinct in musicians as compared to nonmusicians with the use of several techniques (e.g., Pantev et al. 2001; Schneider et al. 2002; Gaser and Schlaug 2003; Aydin et al. 2005). A number of functional imaging, human lesion, and animal studies have implicated areas lying laterally and posteriorly to primary auditory cortices as being important for the extraction and processing of pitch (Liegeois-Chauvel et al. 1998; Johnsrude et al. 2000; Griffiths and Warren 2002; Bendor and Wang 2005; Schönwiesner et al. 2005; Jamison et al. 2006). For instance, Penagos et al. (2004) used stimuli that were spectrally identical but varied in their strength of pitch salience to show that BOLD response in the anterolateral portion of Heschl's gyrus correlated with the level of pitch salience. In a PET experiment, where subjects were presented with complex stimuli that allowed independent manipulation of either temporal or spectral complexity, Zatorre and Belin (2001) found that the left core auditory cortex (Morosan et al. 2001) responded preferentially to increasing temporal complexity, whereas the right belt and parabelt auditory areas responded preferentially to increasing spectral complexity. Additionally, this area and, to a greater extent, areas lying anteriorly and posteriorly to it along the superior temporal surface are also thought to be sensitive to more complex auditory stimuli such as speech and melody (Zatorre 1988; Zatorre et al. 1994, 2002; Alcock et al. 2000; Binder et al. 2000; Patterson et al. 2002). In a functional magnetic resonance imaging (fMRI) study by Patterson et al. (2002), stimuli that produced a pitch percept elicited activity only in the lateral half of Heschl's gyrus, as compared with the more medial response to noise, and activity in response to melody was located outside the primary auditory cortex in adjacent regions along the superior temporal gyrus. Furthermore, the response to melodic stimuli was more pronounced in the right hemisphere. In a PET experiment by Zatorre et al.

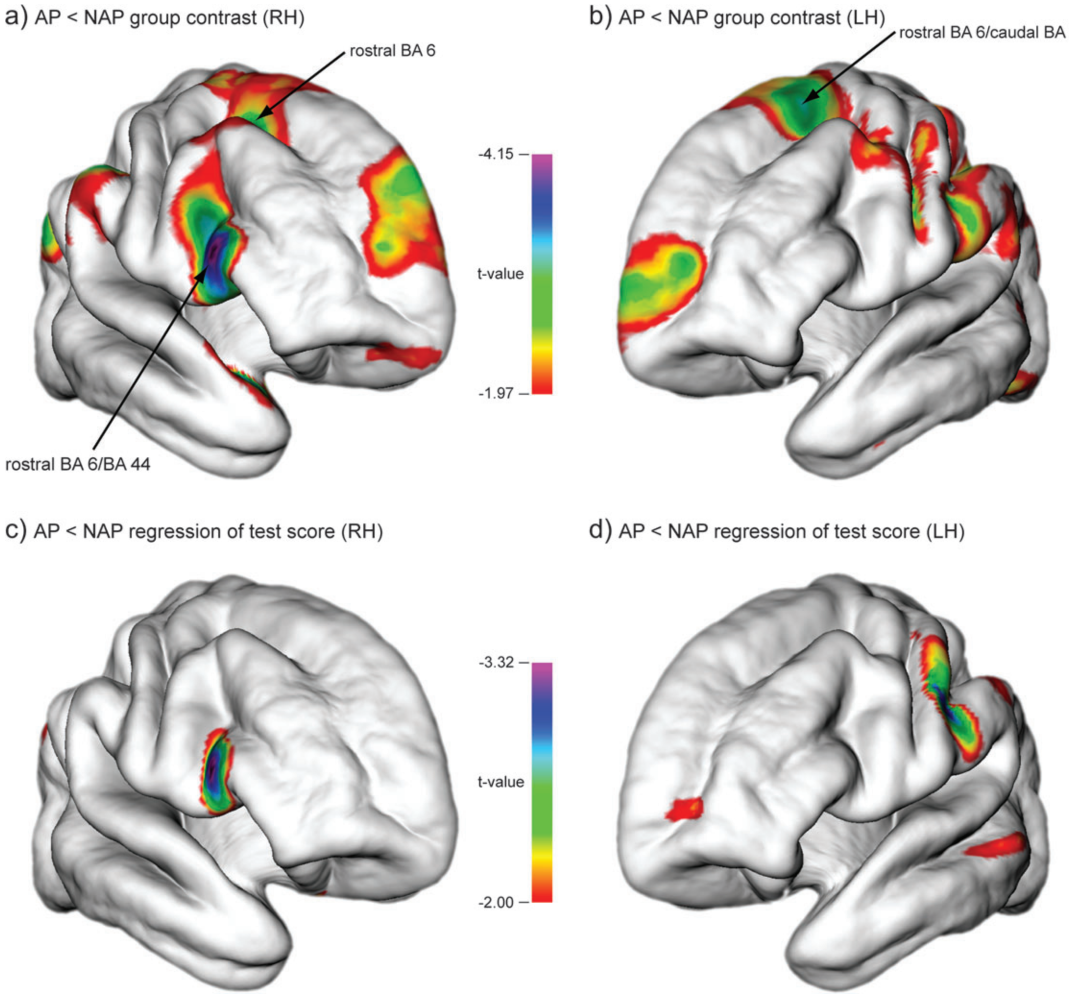


Figure 3. *t*-Statistic maps showing the main cortical thickness findings from the contrast of AP possessors and nonpossessors among musicians (*a*, right hemisphere; *b*, left hemisphere) and the regression of AP proficiency (see Materials and Methods) onto cortical thickness (*c*, right hemisphere; *d*, left hemisphere). All images are FDR thresholded at $P = 0.05$. Peaks of difference in the posterior superior frontal sulcus in the right hemisphere and posterior superior frontal gyrus in the left hemisphere, corresponding to areas rostral BA 6 and rostral BA 6/caudal BA 8, lie in areas previously implicated in the performance of AP tasks.

(1994), blood flow changes were strongly right lateralized to the temporal cortex when the passive perception of a melody was contrasted to a control sequence of white noise. More recently, Hyde et al. (2008) used melody-like sequences to demonstrate a response in the right PT that was proportional to the pitch distance between elements in the melody. Collectively, the location and lateralization of these pitch and melody sensitive areas are consistent with the pattern of anatomical findings we have described in this work. Our main VBM finding in the right auditory cortex lies posterolaterally to primary auditory cortex, and both the cortical thickness and VBM findings in the auditory cortices (illustrated in Fig. 1) show marked rightward asymmetry.

Areas of primary and secondary auditory processing along the superior temporal surface have also been implicated as differential morphological markers in volumetric studies using manual segmentation and VBM. The total volume of Heschl's gyrus in the right hemisphere and the GM volume of the anteromedial portion of Heschl's in both hemispheres of professional musicians were reported to be greater than that of nonmusicians in a study by Schneider et al. (2002), whereas the positive correlation between musician status (professional, amateur, and nonmusician) and GM concentration in the auditory cortex found by Gaser and Schlaug (2003) was primarily confined to the medial portion of left Heschl's gyrus. In the results we report here, the cortical thickness contrast revealed greater thickness in musicians bilaterally in secondary auditory areas and more extensively so in the right hemisphere, including parts of Heschl's gyrus, portions lying anteriorly to Heschl's, and the medial aspect of the superior temporal lobe (Fig. 1*a*,*b* and Table 1). In contrast to the results of Gaser and Schlaug (2003), the dimorphism we observe in the auditory cortex with the use of VBM is at the lateral and posterior aspect of Heschl's gyrus and strongly lateralized to the right hemisphere (a similar but much weaker and nonsignificant pattern is evident in the left hemisphere). Although there are some methodological differences in the details of our VBM method, we suspect that sample constitution is much more pertinent to the disparity between our results and those of Gaser and Schlaug (2003). These authors established a highly homogenous subject sample (only professional keyboard players among musicians and only male subjects throughout the study), whereas our sample was intended to be more broadly representative, with a variety of instrumental concentration,

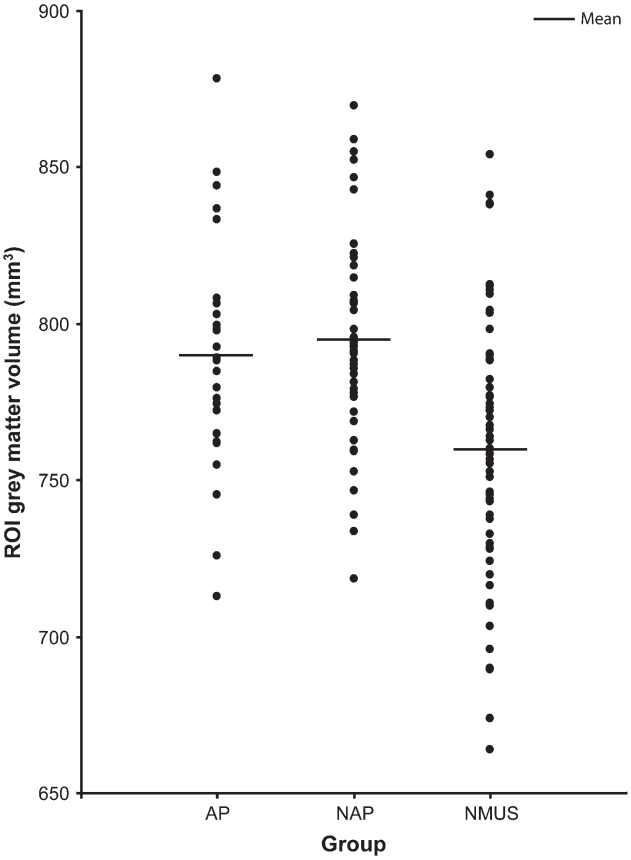


Figure 4. Plot showing the sum of GM concentration inside an ROI defined by thresholding at a $P = 0.05$ level of significance the peak of difference in right auditory cortex resulting from the VBM contrast illustrated in Figure 1*c*. The difference in mean volume between nonmusicians and both musician groups (AP possessors and nonpossessors) is mainly attributable to the lower third of nonmusician values, and the maximum values attained by all groups are in a similar range.

AP ability, degree of current practice, and with no constraint on sex. Given documented effects of sex and instrument of practice on brain morphology (Amunts et al. 2000; Good et al. 2001; Luders, Gaser, et al. 2004; Bangert and Schlaug 2006; Sowell et al. 2006), this is likely a factor in the divergence between some of our respective findings. For instance, several studies have shown stronger indices of GM in the right temporal area of females as compared with males (Witelson et al. 1995; Good et al. 2001; Sowell et al. 2006). That said, the rightward asymmetry of our findings in auditory cortices might reasonably be interpreted as an anatomical correlate of the functional asymmetries observed in the studies cited above. As described in the preceding paragraph, these and other studies have not only pointed to the lateral portion of Heschl's and areas lying posteriorly and anteriorly to it as sites for the extraction and processing of pitch and other complex sounds but have also discerned a rightward hemispheric asymmetry in the relative importance of these cortices in such processing. If we are to conjecture that increased indices such as cortical thickness and GM concentration are plausible reflections of such functional specialization and lateralization, then our findings are strongly congruent with the preponderance of functional evidence accrued to date.

Our cortical thickness findings in auditory cortices partially converge with and encompass our main VBM finding. The morphology of the PT is highly variable (Steinmetz et al. 1989; Westbury et al. 1999) and, given that the cortical thickness measure is somewhat less susceptible to certain dimensions of positional variance than is VBM, this likely accounts to some extent for the relative lack of convergence between the techniques in the posterior PT. Nonetheless, the cortical thickness asymmetry in and immediately surrounding Heschl's is concordant with the VBM findings, and both results are well supported by the functional literature discussed above. Hemispheric asymmetry in degree of morphological variability is one of many factors that might contribute to detected asymmetries such as those we have found in auditory regions. We note, however, that the right auditory cortex has been described as having greater morphological variability than its left hemisphere homologue (Penhune et al. 1996; Westbury et al. 1999), which makes the detection of strong rightward asymmetry in our findings more convincing still.

Musicians versus Nonmusicians—Frontal Cortices

The dorsolateral frontal cortex is thought critical to several aspects of complex cognitive function, including many of those subsumed under the rubric of executive function or cognitive control (Petrides 1994, 2005; Koechlin et al. 2003; Aron 2007). The mid-dorsolateral frontal cortex is thought to be of particular importance in subserving working memory function and, more specifically, modality-independent monitoring of information in working memory (Owen et al. 1998; D'Esposito et al. 2000; Petrides 2000), a ubiquitous aspect of cognition that is necessarily and heavily relied upon in music perception and production. In an fMRI experiment (Postle et al. 1999), where subjects had to either retain or alphabetize a letter string during a delay period before identifying the position of a probe letter, activity in dorsolateral frontal areas was associated with the monitoring and manipulation required by the alphabetization condition as compared with the retention condition. In a PET study by Owen et al. (1999), a "2-back" task, which required the subject to constantly monitor information in working memory, elicited activity bilaterally in both mid-dorsolateral and mid-ventrolateral cortices, whereas a task that used the same stimuli but required the retention of spatial information evoked a response only from the right mid-ventrolateral cortex. Functional imaging studies that have investigated the performance of musically relevant tasks have frequently observed the coactivation of temporal and frontal cortices (Zatorre et al. 1994, 1996; Griffiths et al. 1999; Halpern and Zatorre 1999; Perry et al. 1999). For instance, in a PET study by Zatorre et al. (1994), when subjects heard melodies comprised of 8 tones and had to judge whether the second or last tone was higher or lower than the first, regional cerebral blood flow maxima were observed predominantly in right frontal and temporal regions when compared with a control condition in which subjects passively listened to melodies. This activity, above and beyond that associated with passive listening to melodies, was likely related in part to the maintenance and monitoring of tonal information in working memory for the purpose of making the response demanded by the task. The bilateral peaks we report in areas 9, 46, and 47 (Petrides and Pandya 1999) showing greater cortical thickness among musicians could possibly reflect the extraordinary demands placed on a network of regions involved in mnemonic retention, monitoring, and retrieval (Owen et al. 1998; Petrides and Pandya 2002; Kostopoulos and Petrides 2003) during many years of musical training and practice.

Other lines of evidence also implicate frontal cortices in music cognition (Patel et al. 1998; Koelsch et al. 2005). Recently, Tillmann et al. (2006) conducted an fMRI study investigating the involvement of lateral frontal areas in the processing of musical syntax. They did so by presenting chord progressions, constructed either of pitched phonemes or instrumental timbres, and having subjects perform a phoneme or timbre discrimination task on the last chord of the progression, which was either harmonically strongly related or less related. Crucially, the stimuli were carefully controlled to reduce the likelihood of response to priming or sensory deviance, which have often served as alternative explanations for effects observed in similar protocols (Patel 2003; Tillmann et al. 2003; Koelsch 2005). Results showed that the relative lack of harmonic congruence caused by the less related as compared with the strongly related final chord evoked a stronger BOLD response in the right frontal operculum. This activity is thought to be analogous to the electrophysiological frontal negativity observed in similar experimental designs where expected regularities defined by musical progressions are violated (Koelsch et al. 2000, 2001; Maess et al. 2001). Closely corresponding areas in our results (BA 44/55; Table 1 and Fig. 1*a*) show greater cortical thickness in musicians and thus, perhaps, reflect a long-term adaptation to the intense exercise of abilities subserved by the right hemisphere analogue to Broca's area in the practice of music. At the other extreme of musical ability, differences in cortical thickness in right frontal and temporal areas have been implicated as potential contributors to amusic disorders. All areas found by Hyde et al. (2007) to correlate with the global score of the Montreal Battery of Evaluation of Amusia (Peretz et al. 2003), including right BA 44/45 and 47, are among those which distinguish musicians from nonmusicians in the present results (Fig. 1*a*,*b*). In contrast to our findings, Hyde et al. (2007) posit that the thicker cortex in amusic subjects reflects a malformation of tissue which underlies the observed dysfunction.

With the exception of greater cortical thickness for musicians in the right ventral premotor cortex (BA 6) and superior central sulcus of the left hemisphere, we saw few clear effects in the motor/sensory cortices or the cerebellum with either cortical thickness or VBM, contrarily to what we might have expected from previous reports (Gaser and Schlaug 2003; Hutchinson et al. 2003). Hutchinson et al. (2003) manually delineated a total cerebellar volume and, therefore, our respective results cannot be directly compared, but Gaser and Schlaug (2003) performed VBM with a broadly equivalent approach and at a voxel resolution nominally equal to ours. Once again, we believe that sample constitution is the most pertinent factor in the relative disparity of observations. A larger cerebellar volume was observed in male but not female musicians in the work of Hutchinson et al. (2003) and, as previously mentioned, Gaser and Schlaug (2003), whose findings included greater GM concentration in primary motor and cerebellar areas, used a male-only sample, citing known sex effects on cerebral morphology and lateralization (Amunts et al. 2000; Good et al. 2001; Luders, Gaser, et al. 2004; Luders, Narr, et al. 2004; Sowell et al. 2006). Similarly, Lee et al. (2003) found a larger area of the anterior corpus callosum, comprised in part of fibers interconnecting motor areas, in male but not female musicians. It would seem, therefore, that cerebellar and motor cortex findings may not generalize across musician populations of both sexes. Musical instrument of concentration is another likely variable (Elbert et al. 1995; Bangert and Schlaug 2006). To the extent that specialization of motor cortex is related to the unique interface of a given instrument, we can expect concomitant variability in morphological correlates to a variety of instruments. As a possible illustration of such an effect, the studies of Gaser and Schlaug (2003) and Hutchinson et al. (2003) maximized the likelihood of detecting motor area differences by using keyboard players exclusively, whereas the subjects of Sluming et al. (2002) had diverse instrumental concentrations and did not show differences in any traditional motor areas.

Generally noteworthy is the complementarity of results in frontal regions between cortical thickness and VBM in the findings we present. Frontal cortices are considered among the most morphologically variable in the human brain (Tomaiuolo et al. 1999; Chiavaras et al. 2001), and it is likely that the cortical thickness extraction, in following the corrugation of the cortical mantle, is better able to overcome part of the positional variance with which all anatomical methods must contend. This serves as a clear illustration of the benefits of complementarity in a multimethod approach, particularly in an exploratory context. For instance, in the group contrast of musicians and nonmusicians, we report peaks in the left superior central sulcus in both cortical thickness and VBM GM results (see Results and Table 1). In this and other examples (see Tables 1 and 2), though the VBM peak is below the significance threshold and extremely focal, we can lend it somewhat more credence than we otherwise might due to its convergence with significant cortical thickness findings.

In sum, the collected functional findings described above regarding frontal lobe involvement in a variety of musical tasks are in line with the anatomical differences we observe between musicians and nonmusicians in those same regions of cortex.

Musicians versus Nonmusicians—Interregional Thickness Correlation

Two vertices corresponding to the main frontal foci indicating greater cortical thickness in the musicians versus nonmusicians contrast (first 2 coordinates reported in Table 1; Fig. 1*a*) were selected for a correlational analysis. This method computes the strength of correlation between the cortical thickness of the selected seed and that of all other points throughout the cortex across a group of subjects (Lerch et al. 2006). The result allows one to inspect the degree to which areas covary in thickness across subjects and, thereby, serves as an indication of possible structural and functional interdependence. With our data set, this analysis was undertaken to support and extend the findings of the musician versus nonmusician cortical thickness contrast and further the argument that links the finding to literature demonstrating an important functional relationship between frontal and auditory cortices in the performance of musical tasks. Although not conforming precisely to the prediction of a stronger correlation between these areas in musicians, the results can nonetheless be interpreted in support of the underlying proposition. Figure 2 shows areas throughout the cortex that are significantly correlated with each seed point for musicians and nonmusicians separately. One can observe a marked difference in pattern between the 2 populations, particularly for seed 1. Specifically, a much broader area throughout the surface of the nonmusician brains is correlated with the seed area as compared with the correlations in the musicians (Fig. 2*a*,*b*). The pattern evident in musicians can be construed as a selective and partial departure from the typical profile of thickness covariation seen in the nonmusician population, one that reflects the plastic effects of music-related activities. We interpret the more constrained area of significant correlation in musicians as an indication of greater specificity in the relationship between thicknesses of frontal and auditory regions. Neuroanatomical (Petrides and Pandya 1988; Romanski et al. 1999) and diffusion tensor imaging (Duffau et al. 2008; Rilling et al. 2008) work has clearly established connectivity between these 2 areas and, as discussed earlier, there is a literature showing frequent coactivation of auditory and lateral frontal areas during the performance of musically relevant tasks. We therefore suggest that, rather than representing independent phenomena, the frontal and temporal cortical thickness findings in the group contrast of musicians and nonmusicians are meaningfully related to each other in a way similar to that suggested by the functional imaging work reviewed above.

AP versus Non-AP Musicians

When directly contrasting the 12 best and 12 poorest performing musicians on our test of AP, a number of regions showed thinner cortex in the strongest performers (AP possessors), most notably in the posterior dorsal frontal region bilaterally (rostral area 6, caudal 8). These areas are similar to those implicated in a pair of related studies investigating the functional neurocorrelates of AP performance. In the first (Zatorre et al. 1998), both AP and non-AP musicians listened passively to single notes and, in a separate condition, identified ascending or descending major or minor thirds. It was noted that the left posterior dorsolateral frontal cortex was active when AP possessors identified single notes, as it was when both group identified intervals. In the light of data from a number of monkey, human lesion, and imaging studies which have shown that the posterior dorsolateral frontal cortex (BA 8 and rostral BA 6) is critically involved in aspects of conditional associative memory (Halsband and Passingham 1985; Petrides 1985; Crowne et al. 1989; Halsband and Freund 1990; Petrides et al. 1993; Lepage et al. 2003), this result was interpreted as a reflection of the ability to retrieve an arbitrary conditional association between a stimulus attribute (pitch or interval value) and a verbal label (note or interval name). A follow-up experiment (Bermudez and Zatorre 2005) sought to verify this interpretation by teaching musically naive subjects to discriminate between 4 types of musical sounds and associate each to an arbitrary label. BOLD activity in posterior dorsolateral areas 8 and rostral 6 was observed when subjects identified the learned stimuli. In our cortical thickness results, we have a difference in thickness in similar areas (rostral BA 6 and caudal BA 8; Fig. 3*a*,*b*) that differentiates the strongest from the poorest performers in a test of AP. This area's implication in the performance of typical AP tasks, by subserving conditional associations between mnemonic representations for a series pitches and their names, reflects the unique application of a universal ability. Nonetheless, this conditional association is a constituent behavior of AP identification, and the dorsal frontal cortex underlying it has functionally (Zatorre et al. 1998) and, now, structurally distinguished AP possessors from nonpossessors. These are the first anatomical data consistent with this functional finding and the first to point to regions outside the PT as potential sites of interest in the anatomical characterization of AP.

In the regression of AP performance onto cortical thickness across all musicians tested on our AP task, stronger performance was once again associated with thinner cortex in right ventral premotor cortex (BA 6) and right pars opercularis (BA 44), right inferior parietal lobule (BA 39), and left postcentral gyrus (BA 2/40; Fig. 3*c*,*d*), all of which largely overlapped with the group contrast. Only one area, in the left pericalcarine cortex, showed a positive correlation between thickness and AP proficiency. A subset of foci from the regression analysis and group comparison with VBM was consistent with the cortical thickness findings but fell below significance thresholds (see Results and Table 2). Neither the group contrast nor the regression in either cortical thickness or VBM revealed any effects in the PT. As noted in the Introduction, findings in the PT have been inconsistent and their significance is still largely unknown. All but one of the relevant studies have used manual segmentations of the PT (Schlaug et al. 1995; Zatorre et al. 1998; Keenan et al. 2001; Luders, Gaser, et al. 2004), which can circumvent some types of morphological variability that encumber automated methods such as VBM and cortical thickness but are also subject to somewhat arbitrary delineation definitions and human error. In the only other VBM inspection of AP-related anatomy to date, Luders, Gaser, et al. (2004) only detected a leftward PT asymmetry in male musicians, and therefore, a majority of female subjects in our sample may have attenuated effects similar to those previously observed. The data of Ohnishi et al. (2001) showing a positive correlation between BOLD signal in the left PT and AP proficiency (though BOLD was also correlated with age of inception of musical training), along with the correlation between AP proficiency and PT volume provided by Zatorre et al. (1998), are the only 2 behavioral relationships to the PT which we possess. Our data suggest that AP may be associated with a number of functional and anatomical differences with multiple loci. In addition to areas in the posterior dorsal frontal cortex discussed above, we should perhaps dedicate further attention to the right ventral premotor and pars opercularis areas that showed thinner cortex among AP subjects in both the group contrast and regression analyses.

As stated above, nearly all significant differences in our analyses of anatomy related to AP yielded thinner cortex and lower GM concentration for AP possessors. The interpretation of relative increases or decreases in thickness is not yet clear, and the microstructural and functional significance of cortical thickness remains somewhat uncertain. Many factors influence this measure, including cell size, number, packing density, and number of connections and extent of their myelination (Gittins and Harrison 2004; Eickhoff et al. 2005), all of which interact with MRI acquisition, the resultant signal, and subsequent processing. A better understanding of these contributions and their relationship to the gross, macroscopic metrics available through analysis of cortical thickness and VBM, will serve more confident interpretations of results (Jones et al. 2000; Kabani et al. 2001; Lerch and Evans 2005; Haidar and Soul 2006; Han et al. 2006). None of the AP-related differences overlap with those found in the contrast of musicians and nonmusicians. In other words, AP musicians seem to exhibit an anatomical profile that is different from either that of nonmusicians or the rest of their musician cohort. This may be an indication that possessors of AP incur somewhat different training effects as compared with nonpossessors. As has been suggested elsewhere (Chin 2003; Bermudez 2008), AP may be a musical domain manifestation of a number of interacting factors (developmental stage during acquisition/musical training, cognitive/perceptual style, etc.; Costa-Giomi et al. 2001; Saffran 2003; Moreno Sala MT, Costa-Giomi E, in preparation), in which case the anatomical differences observed may also reflect, in part, factors that extend beyond musical training.

Plasticity and Innate Disposition

The perennial debate over the relative contribution of experience-dependent anatomical plasticity versus preexisting and predisposing anatomy to the macroscopic dimorphisms we observe between 2 adult populations of interest is well illustrated in the case of musicians and nonmusicians, as well as the special case of AP. Understanding that most realistic scenarios should posit an interaction between predisposing biology and experience, and believing our results to be such a case, we wish to draw attention to the distribution of GM densities among musicians with AP, musicians without AP, and nonmusicians (Fig. 4). We created an ROI volume by thresholding (at $P = 0.05$, $t = 3.7$; Fig. 1*c*) the peak of significance in the right posterolateral portion of Heschl's gyrus resulting from the VBM GM contrast of musicians and nonmusicians. We then extracted the volume of GM concentration encompassed by this ROI for each subject and plotted the values by group membership. One can see the contribution to the observed effect illustrated in Figure 1*c*; the musician subgroups do not differ from each other, but each differs significantly from the nonmusicians and, therefore, also as a single musician group. Especially noteworthy is the fact that the maximum GM values among nonmusicians extend to the same range as musicians (only 3 musicians surpass the maximum attained by nonmusicians). The difference in central tendency is attributable principally to the largely nonoverlapping lower end of the nonmusician distribution. In other words, as far as this limited index of anatomy is concerned, a large proportion of the nonmusician sample is indistinguishable from the musician sample. The vast majority of anatomical studies of musicians and other populations (understandably) focus on the experiential plastic effects of a given variable of interest on brain anatomy, as indeed we have throughout much of this text. The distributions we have just described allow us to speculate about predisposing anatomy and highlight the scientific value of searching for anatomical markers that may act as predictors of outcome (e.g., Golestani et al. 2002; Wong et al. 2008). Is it the case, for instance, that the top third of nonmusicians in this sample would excel as compared with the bottom third in the training of a novel task subserved by cortex in our ROI? Could they, with reasonable efforts, achieve performance levels comparable to those of musicians with similar anatomy in tasks requiring pitch analysis? Such questions must be addressed in order to inform the speculation on the interacting balance of predisposing biology and experience as they relate to effects such as those presented in this paper.

Conclusion

We believe that our data, in conjunction with studies described throughout this text, support the notion that years of intense musical training and practice, likely combining with a gamut of biological dispositions, create a variety of specialized abilities that are reflected in the macroscopic function and structure of the brain (Münte et al. 2002). More specifically, by virtue of the special training effects incurred by musicians, we provide additional evidence for the role of the lateral portion of Heschl's gyrus and other areas lying outside the primary auditory cortex along the superior temporal gyrus in the extraction and processing of pitch and other complex sounds such as melodies. Our results are also consistent with lines of evidence showing a right hemisphere specialization in these processes. Similarly, the differences evinced in frontal cortices between musicians and nonmusicians are broadly supported by a functional literature demonstrating the frequent and extensive implication of these areas in the performance of various musical tasks by dint of their involvement in a variety of executive functions such as the maintenance, monitoring and retrieval of tonal information, and hierarchical processing of musical structure. Finally, we have searched for anatomical indices associated with the ability of AP and have primarily detected decreases in cortical thickness as compared with nonpossessing musicians in a number of regions, among them the posterior dorsal frontal cortices which have been independently shown to be critically important in conditional associative memory and, therefore, the labeling of notes in a typical AP task. Though a universal ability, conditional associative memory is applied in a unique way by musicians with AP in the establishment of a long-term representation for the pitch of a musical note and its pairing with a conventional name. AP, as a readily operationalized yet complex ability, continues to serve as an interesting alternative model for a number of cognitive systems.

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References

Ad-Dab'bagh Y, Singh V, Robbins S, Lerch J, Lyttelton O, Fombonne E, Evans A. 2005. Native-space cortical thickness measurement and the absence of correlation to cerebral volume. 11th Annual Meeting of the Organization for Human Brain Mapping (OHBM). Toronto.

Ad-Dab'bagh Y, Lyttelton O, Muehlboeck JS, Lepage C, Einarson D, Mok K, Ivanov O, Vincent RD, Lerch J, Fombonne E, et al. 2006. The CIVET Image-Processing Environment: A Fully Automated Comprehensive Pipeline for Anatomical Neuroimaging Research. 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, ed. (Florence, Italy, NeuroImage).

Alcock KJ, Wade D, Anslow P, Passingham RE. 2000. Pitch and timing abilities in adult left-hemisphere-dysphasic and right-hemisphere-damaged subjects. Brain Lang. 75:47–65.

Amunts K, Jancke L, Mohlberg H, Steinmetz H, Zilles K. 2000. Interhemispheric asymmetry of the human motor cortex related to handedness and gender. Neuropsychologia. 38:304–312.

Aron AR. 2007. The neural basis of inhibition in cognitive control. Neuroscientist. 13:214–228.

Ashburner J, Friston K. 2000. Voxel-based morphometry—the methods. Neuroimage. 11:805–821.

Ashburner J, Friston KJ. 2001. Why voxel-based morphometry should be used. Neuroimage. 14:1238–1243.

Aydin K, Ciftci K, Terzibasioglu E, Ozkan M, Demirtas A, Sencer S, Minareci O. 2005. Quantitative proton MR spectroscopic findings of cortical reorganization in the auditory cortex of musicians. AJNR Am J Neuroradiol. 26:128–136.

Bangert M, Schlaug G. 2006. Specialization of the specialized in features of external human brain morphology. Eur J Neurosci. 24:1832–1834.

Bendor D, Wang X. 2005. The neuronal representation of pitch in primate auditory cortex. Nature. 436:1161–1165.

Bermudez P. 2008. The neural correlates of absolute pitch [Doctoral dissertation]. Montreal (Canada): McGill University.

Bermudez P, Zatorre RJ. 2005. Conditional associative memory for musical stimuli in nonmusicians: implications for absolute pitch. J Neurosci. 25:7718–7723.

Binder J, Frost J, Hammeke T, Bellgowan P, Springer J, Kaufman J, Possing J. 2000. Human temporal lobe activation by speech and nonspeech sounds. Cereb Cortex. 10:512–528.

Bookstein FL. 2001. "Voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage. 14:1454–1462.

Chen JL, Penhune VB, Zatorre RJ. 2008. Moving on time: brain network for auditory-motor synchronization is modulated by rhythm complexity and musical training. J Cogn Neurosci. 20:226–239.

Chiavaras MM, LeGoualher G, Evans A, Petrides M. 2001. Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. Neuroimage. 13:479–496.

Chin CS. 2003. The development of absolute pitch: a theory concerning the roles of music training at an early developmental age and individual cognitive style. Psychol Music. 31:155–171.

Chung MK, Taylor J. 2004. Diffusion smoothing on brain surface via finite element method. In: Biomedical imaging: nano to macro, 2004. IEEE International Symposium on. 1:432–435.

Collins D, Peters T, Evans A. 1994. An automated 3D non-linear deformation procedure for determination of gross morphometric variability in the human brain. In: Visualization in biomedical computing: Proc SPIE 2359:180–194.

Collins DL, Neelin P, Peters TM, Evans AC. 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr. 18:192–205.

Costa-Giomi E, Gilmour R, Siddell J, Lefebvre E. 2001. Absolute pitch, early musical instruction, and spatial abilities. Ann N YAcad Sci. 930:394–396.

Crowne DP, Dawson KA, Richardson CM. 1989. Unilateral periarcuate and posterior parietal lesions impair conditional position discrimination learning in the monkey. Neuropsychologia. 27:1119–1127.

D'Esposito M, Postle BR, Rypma B. 2000. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res. 133:3–11.

Duffau H, Thiebaut de Schotten M, Mandonnet E. 2008. White matter functional connectivity as an additional landmark for dominant temporal lobectomy. J Neurol Neurosurg Psychiatry. 79:492–495.

Eickhoff S, Walters NB, Schleicher A, Kril J, Egan GF, Zilles K, Watson JD, Amunts K. 2005. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum Brain Mapp. 24:206–215.

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.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 6:218–229.

Fujioka T, Trainor LJ, Ross B, Kakigi R, Pantev C. 2005. Automatic encoding of polyphonic melodies in musicians and nonmusicians. J Cogn Neurosci. 17:1578–1592.

Gaab N, Schulze K, Ozdemir E, Schlaug G. 2006. Neural correlates of absolute pitch differ between blind and sighted musicians. Neuroreport. 17:1853–1857.

Gaser C, Schlaug G. 2003. Brain structures differ between musicians and non-musicians. J Neurosci. 23:9240–9245.

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 15:870–878.

Geschwind N, Levitsky W. 1968. Human brain: left-right asymmetries in the temporal speech region. Science. 161:186–187.

Gittins R, Harrison PJ. 2004. A quantitative morphometric study of the human anterior cingulate cortex. Brain Res. 1013:212–222.

Golestani N, Paus T, Zatorre RJ. 2002. Anatomical correlates of learning novel speech sounds. Neuron. 35:997–1010.

Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. 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 AL, Budge MM, Smith D, Pruessner J, Collins DL. 2006. Symmetric atlasing and model based segmentation: an application to the hippocampus in older adults. Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv. 9:58–66.

Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. 2006. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med. 3:e402.

Griffiths TD, Buchel C, Frackowiak RS, Patterson RD. 1998. Analysis of temporal structure in sound by the human brain. Nat Neurosci. 1:422–427.

Griffiths TD, Johnsrude IS, Dean JL, Green GGR. 1999. A common neural substrate for the analysis of pitch and duration pattern in segmented sound? Neuroreport. 10:3825–3830.

Griffiths TD, Warren JD. 2002. The planum temporale as a computational hub. Trends Neurosci. 25:348–353.

Haidar H, Soul JS. 2006. Measurement of cortical thickness in 3D brain MRI data: validation of the Laplacian method. J Neuroimaging. 16:146–153.

Halpern AR. 1989. Memory for the absolute pitch of familiar songs. Mem Cognit. 17:572–581.

Halpern AR, Zatorre RJ. 1999. When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cereb Cortex. 9:697–704.

Halsband U, Freund HJ. 1990. Premotor cortex and conditional motor learning in man. Brain. 113(Pt 1):207–222.

Halsband U, Passingham RE. 1985. Premotor cortex and the conditions for movement in monkeys (Macaca fascicularis). Behav Brain Res. 18:269–277.

Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R, et al. 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage. 32:180–194.

Hutchinson S, Lee LH, Gaab N, Schlaug G. 2003. Cerebellar volume of musicians. Cereb Cortex. 13:943–949.

Hyde KL, Lerch JP, Zatorre RJ, Griffiths TD, Evans AC, Peretz I. 2007. Cortical thickness in congenital amusia: when less is better than more. J Neurosci. 27:13028–13032.

Hyde KL, Peretz I, Zatorre RJ. 2008. Evidence for the role of the right auditory cortex in fine pitch resolution. Neuropsychologia. 46:632–639.

Jamison HL, Watkins KE, Bishop DV, Matthews PM. 2006. Hemispheric specialization for processing auditory nonspeech stimuli. Cereb Cortex. 16:1266–1275.

Johnsrude IS, Penhune VB, Zatorre RJ. 2000. Functional specificity in the right human auditory cortex for perceiving pitch direction. Brain. 123(Pt 1):155–163.

Jones SE, Buchbinder BR, Aharon I. 2000. Three-dimensional mapping of cortical thickness using Laplace's equation. Hum Brain Mapp. 11:12–32.

Kabani N, Le Goualher G, MacDonald D, Evans AC. 2001. Measurement of cortical thickness using an automated 3-D algorithm: a validation study. NeuroImage. 13:375–380.

Keenan JP, Thangaraj V, Halpern AR, Schlaug G. 2001. Absolute pitch and planum temporale. Neuroimage. 14:1402–1408.

Kim JS, Singh V, Lee JK, Lerch J, Ad-Dab'bagh Y, MacDonald D, Lee JM, Kim SI, Evans AC. 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.

Koechlin E, Ody C, Kouneiher F. 2003. The architecture of cognitive control in the human prefrontal cortex. Science. 302:1181–1185.

Koelsch S. 2005. Neural substrates of processing syntax and semantics in music. Curr Opin Neurobiol. 15:207–212.

Koelsch S, Fritz T, Schulze K, Alsop D, Schlaug G. 2005. Adults and children processing music: an fMRI study. Neuroimage. 25:1068–1076.

Koelsch S, Gunter T, Friederici AD, Schroger E. 2000. Brain indices of music processing: "nonmusicians" are musical. J Cogn Neurosci. 12:520–541.

Koelsch S, Gunter TC, Schroger E, Tervaniemi M, Sammler D, Friederici AD. 2001. Differentiating ERAN and MMN: an ERP study. Neuroreport. 12:1385–1389.

Kostopoulos P, Petrides M. 2003. The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval. Eur J Neurosci. 17:1489–1497.

Lahav A, Saltzman E, Schlaug G. 2007. Action representation of sound: audiomotor recognition network while listening to newly acquired actions. J Neurosci. 27:308–314.

Lee DJ, Chen Y, Schlaug G. 2003. Corpus callosum: musician and gender effects. Neuroreport. 14:205–209.

Lee L, Harrison LM, Mechelli A. 2003. A report of the functional connectivity workshop, Dusseldorf 2002. Neuroimage. 19:457–465.

Lepage M, Brodeur M, Bourgouin P. 2003. Prefrontal cortex contribution to associative recognition memory in humans: an event-related functional magnetic resonance imaging study. Neurosci Lett. 346: 73–76.

Lerch JP, Evans AC. 2005. Cortical thickness analysis examined through power analysis and a population simulation. Neuroimage. 24: 163–173.

Lerch JP, Pruessner JC, Zijdenbos A, Hampel H, Teipel SJ, Evans AC. 2005. Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. Cereb Cortex. 15:995–1001.

Lerch JP, Worsley K, Shaw WP, Greenstein DK, Lenroot RK, Giedd J, Evans AC. 2006. Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. Neuroimage. 31:993–1003.

Liegeois-Chauvel C, Peretz I, Babai M, Laguitton V, Chauvel P. 1998. Contribution of different cortical areas in the temporal lobes to music processing. Brain. 121(Pt 10):1853–1867.

Luders E, Gaser C, Jancke L, Schlaug G. 2004. A voxel-based approach to gray matter asymmetries. Neuroimage. 22:656–664.

Luders E, Narr KL, Thompson PM, Rex DE, Jancke L, Steinmetz H, Toga AW. 2004. Gender differences in cortical complexity. Nat Neurosci. 7:799–800.

MacDonald D, Kabani N, Avis D, Evans AC. 2000. Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. Neuroimage. 12:340–356.

Maess B, Koelsch S, Gunter TC, Friederici AD. 2001. Musical syntax is processed in Broca's area: an MEG study. Nat Neurosci. 4:540–545.

Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, Caviness VS, Faraone SV, Seidman LJ. 2007. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex. 17:1364–1375.

Morosan P, Rademacher J, Schleicher A, Amunts K, Schormann T, Zilles K. 2001. Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. Neuroimage. 13:684–701.

Münte TF, Altenmuller E, Jancke L. 2002. The musician's brain as a model of neuroplasticity. Nat Rev Neurosci. 3:473–478.

Ohnishi T, Matsuda H, Asada T, Aruga M, Hirakata M, Nishikawa M, Katoh A, Imabayashi E. 2001. Functional anatomy of musical perception in musicians. Cereb Cortex. 11:754–760.

Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Carpenter TA, Minhas PS, Turkheimer FE, Williams EJ, Robbins TW, et al. 1999. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur J Neurosci. 11:567–574.

Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. 1998. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc Natl Acad Sci USA. 95:7721–7726.

Pantev C, Engelien A, Candia V, Elbert T. 2001. Representational cortex in musicians. Plastic alterations in response to musical practice. Ann N Y Acad Sci. 930:300–314.

Pantev C, Oostenveld R, Engelien A, Ross B, Roberts LE, Hoke M. 1998. Increased auditory cortical representation in musicians. Nature. 392:811–814.

Pantev C, Ross B, Fujioka T, Trainor LJ, Schulte M, Schulz M. 2003. Music and learning-induced cortical plasticity. Ann N Y Acad Sci. 999:438–450.

Patel AD. 2003. Language, music, syntax and the brain. Nat Neurosci. 6:674–681.

Patel AD, Gibson E, Ratner J, Besson M, Holcomb PJ. 1998. Processing syntactic relations in language and music: an event-related potential study. J Cogn Neurosci. 10:717–733.

Patterson RD, Uppenkamp S, Johnsrude IS, Griffiths TD. 2002. The processing of temporal pitch and melody information in auditory cortex. Neuron. 36:767–776.

Penagos H, Melcher JR, Oxenham AJ. 2004. A neural representation of pitch salience in nonprimary human auditory cortex revealed with functional magnetic resonance imaging. J Neurosci. 24:6810–6815.

Penhune VB, Zatorre RJ, MacDonald JD, Evans AC. 1996. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb Cortex. 6:661–672.

Peretz I, Champod AS, Hyde K. 2003. Varieties of musical disorders. The Montreal battery of evaluation of amusia. Ann N Y Acad Sci. 999:58–75.

Perry DW, Zatorre RJ, Petrides M, Alivisatos B, Meyer E, Evans AC. 1999. Localization of cerebral activity during simple singing. Neuroreport. 10:3979–3984.

Petrides M. 1985. Deficits in non-spatial conditional associative learning after periarcuate lesions in the monkey. Behav Brain Res. 16:95–101.

Petrides M. 1994. Frontal lobes and behaviour. Curr Opin Neurobiol. 4:207–211.

Petrides M. 2000. The role of the mid-dorsolateral prefrontal cortex in working memory. Exp Brain Res. 133:44–54.

Petrides M. 2005. Lateral prefrontal cortex: architectonic and functional organization. Philos Trans R Soc Lond B Biol Sci. 360:781–795.

Petrides M, Alivisatos B, Evans AC, Meyer E. 1993. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA. 90:873–877.

Petrides M, Pandya DN. 1988. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. J Comp Neurol. 273:52–66.

Petrides M, Pandya DN. 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci. 11:1011–1036.

Petrides M, Pandya DN. 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci. 16:291–310.

Postle BR, Berger JS, D'Esposito M. 1999. Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. Proc Natl Acad Sci USA. 96:12959–12964.

Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, Behrens TE. 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nat Neurosci. 11:426–428.

Romanski L, Tian B, Fritz J, Mishkin M, Goldman-Rakic P, Rauschecker J. 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat Neurosci. 2:1131–1136.

Saffran JR. 2003. Absolute pitch in infancy and adulthood: the role of tonal structure. Dev Sci. 6:35-43.

Schlaug G, Jancke L, Huang Y, Steinmetz H. 1995. In vivo evidence of structural brain asymmetry in musicians. Science. 267:699-701.

Schneider P, Scherg M, Dosch HG, Specht HJ, Gutschalk A, Rupp A. 2002. Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. Nat Neurosci. 5:688-694.

Schönwiesner M, Rubsamen R, von Cramon DY. 2005. Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. Eur J Neurosci. 22:1521-1528.

Sled JG, Zijdenbos AP, Evans AC. 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging. 17:87-97.

Sluming V, Barrick T, Howard M, Cezayirli E, Mayes A, Roberts N. 2002. Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians. Neuroimage. 17:1613-1622.

Sowell ER, Peterson BS, Kan E, Woods RP, Yoshii J, Bansal R, Xu D, Zhu H, Thompson PM, Toga AW. 2006. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex. 17:1550-1560.

Steinmetz H, Rademacher J, Huang Y, Hefter H, Zilles K, Thron A, Freund H-J. 1989. Cerebral asymmetry: MR planimetry of the human planum temporale. J Comput Assist Tomogr. 13:996-1005.

Tervaniemi M, Just V, Koelsch S, Widmann A, Schroger E. 2005. Pitch discrimination accuracy in musicians vs nonmusicians: an event-related potential and behavioral study. Exp Brain Res. 161:1-10.

Tervaniemi M, Rytkonen M, Schroger E, Ilmoniemi RJ, Naatanen R. 2001. Superior formation of cortical memory traces for melodic patterns in musicians. Learn Mem. 8:295-300.

Tillmann B, Janata P, Bharucha JJ. 2003. Activation of the inferior frontal cortex in musical priming. Brain Res Cogn Brain Res. 16:145-161.

Tillmann B, Koelsch S, Escoffier N, Bigand E, Lalitte P, Friederici AD, von Cramon DY. 2006. Cognitive priming in sung and instrumental music: activation of inferior frontal cortex. Neuroimage. 31: 1771-1782.

Tohka J, Zijdenbos A, Evans A. 2004. Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage. 23:84-97.

Tomaiuolo F, MacDonald JD, Caramanos Z, Posner G, Chiavaras M, Evans AC, Petrides M. 1999. Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis. Eur J Neurosci. 11:3033-3046.

Ward WD. 1999. Absolute pitch. In: Deutsch D, editor. The psychology of music. San Diego (CA): Academic Press. p. 265-298.

Westbury CF, Zatorre RJ, Evans AC. 1999. Quantifying variability in the planum temporale: a probability map. Cereb Cortex. 9:392-405.

Witelson SF, Glezer II, Kigar DL. 1995. Women have a greater density of neurons in the posterior temporal cortex. J Neurosci. 15: 3418-3428.

Wong PC, Warrier CM, Penhune VB, Roy AK, Sadehh A, Parrish TB, Zatorre RJ. 2008. Volume of left Heschl's gyrus and linguistic pitch learning. Cereb Cortex. 18:828-836.

Worsley KJ, Chen JI, Lerch J, Evans AC. 2005. Comparing functional connectivity via thresholding correlations and singular value decomposition. Philos Trans R Soc Lond B Biol Sci. 360:913-920.

Zatorre RJ. 1988. Pitch perception of complex tones and human temporal-lobe function. J Acoust Soc Am. 84:566-572.

Zatorre RJ, Beckett C. 1989. Multiple coding strategies in the retention of musical tones by possessors of absolute pitch. Mem Cognit. 17:582-589.

Zatorre RJ, Belin P. 2001. Spectral and temporal processing in human auditory cortex. Cereb Cortex. 11:946-953.

Zatorre RJ, Belin P, Penhune VB. 2002. Structure and function of auditory cortex: music and speech. Trends Cogn Sci. 6:37-46.

Zatorre RJ, Chen JL, Penhune VB. 2007. When the brain plays music: auditory-motor interactions in music perception and production. Nat Rev Neurosci. 8:547-558.

Zatorre RJ, Evans AC, Meyer E. 1994. Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci. 14:1908-1919.

Zatorre RJ, Halpern AR, Perry DW, Meyer E, Evans AC. 1996. Hearing in the mind's ear: A PET investigation of musical imagery and perception. J Cogn Neurosci. 8:29-46.

Zatorre RJ, Perry DW, Beckett CA, Westbury CF, Evans AC. 1998. Functional anatomy of musical processing in listeners with absolute pitch and relative pitch. Proc Natl Acad Sci USA. 95:3172-3177.

Zijdenbos AP, Forghani R, Evans AC. 1998. Automatic quantification of MS lesions in 3D MRI brain data sets: validation of INSECT. In: Proceedings of the First International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer-Verlag. p. 439-448.

Zijdenbos AP, Forghani R, Evans AC. 2002. Automatic Pipeline Analysis of 3-D MRI Data for Clinical Trials: Application to Multiple Sclerosis. IEEE Transactions on Medical Imaging. p. 1280-1291.