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Voxel-Based Morphometry Reveals Increased Gray Matter Density in Broca's Area in Male Symphony Orchestra Musicians

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Broca's area is a major neuroanatomical substrate for spoken language and various musically relevant abilities, including visuospatial and audiospatial localization. Sight reading is a musician-specific visuospatial analysis task, and spatial ability is known to be amenable to training effects. Musicians have been reported to perform significantly better than nonmusicians on spatial ability tests, which is supported by our findings with the Benton judgement of line orientation (JOL) test (P < 0.001). We hypothesised that use-dependent adaptation would lead to increased gray matter density in Broca's area in musicians. Voxel-based morphometry (VBM) and stereological analyses were applied to high-resolution 3D MR images in male orchestral musicians (n = 26) and sex, handedness, and IQ-matched nonmusicians (n = 26). The wide age range (26 to 66 years) of volunteers permitted a secondary analysis of age-related effects. VBM with small volume correction (SVC) revealed a significant (P = 0.002) region of increased gray matter in Broca's area in the left inferior frontal gyrus in musicians. We observed significant age-related volume reductions in cerebral hemispheres, dorsolateral prefrontal cortex subfields bilaterally and gray matter density in the left inferior frontal gyrus in controls but not musicians; a positive correlation between JOL test score and age in musicians but not controls; a positive correlation between years of playing and the volume of gray matter in a significant region identified by VBM in under-50-year-old musicians. We suggest that orchestral musical performance promotes use-dependent retention, and possibly expansion, of gray matter involving Broca's area and that this provides further support for shared neural substrates underpinning expressive output in music and language.

INTRODUCTION

What we do and think changes the patterns of connections within the neural networks of the brain, and on occasions this may lead to alterations in brain structure and function that can be detected by neuroimaging techniques. The effects may be particularly evident in relation to the challenges of disability and disease, but habits and occupation are also likely to have significant effects. With regard to the latter, a previous image analysis study of 3D magnetic resonance (MR) images confirmed the hypothesis that the right hippocampus, known from studies in animals to be involved in spatial memory and navigation, is preferentially enlarged in taxi drivers relative to a control population (Maguire *et al.,* 2000). The results of this study provided support for the suggestion that MRI-derived volume measures of brain structures are, in part, determined by the number and size of neurons and consequently the complexity of their synaptic connections (Mackay *et al.,* 1998; Maguire *et al.,* 2000) and that enhanced performance is associated with larger volumes of associated brain structures. In this study we test the hypothesis that enhanced audiospatial and visuospatial localizational abilities will be reflected in increased gray matter density in left Broca's area.

Previous neuroimaging studies have provided convincing evidence that acquiring musical performance skills is associated with changes in brain structure. Musically trained subjects have been shown to have a left hemisphere advantage in processing musical sounds (Evers *et al.,* 1999), whereas the right hemisphere predominates in musically untrained subjects (Evers *et al.,* 1999; Tervaniemi *et al.,* 1999). Increased leftward asymmetry of the planum temporale was

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identified in musicians who possessed perfect pitch (Schlaug *et al.*, 1995b) and was associated with a reduction in the right hemisphere planum temporal area (Keenam *et al.*, 2001). Increased representation of the left auditory cortex in musicians (Pantev *et al.*, 1998) was timbre-specific for the instrument of training (Pantev *et al.*, 2001). Additionally, increased cortical representation of the fingers of the left hand (i.e., the right motor cortex) has been reported only in string players (Elbert *et al.*, 1995). The age of commencement of musical training has been associated with a larger anterior corpus callosum in musicians (Schlaug *et al.*, 1995a) and an increased length of the posterior wall of the precentral gyrus (Amunts *et al.*, 1997). Authors reporting findings of structural and/or functional differences between the brains of musicians and nonmusicians have considered whether such differences preexist and predispose towards the acquisition of musical skills (Amunts *et al.*, 1997; Elbert *et al.*, 1995; Pantev *et al.*, 1998, 2001; Schlaug *et al.*, 1995a,b). Observation of a significant negative relationship between either cortical response or structure size and the age of commencement of musical training by these authors has been interpreted as evidence of neuroplastic, specifically use-dependent adaptation, which is consistent with animal studies (Bottjer and Johnson, 1997). A significant relationship between brain measure and the age of inception of training has been proposed by Howe (1999) to indicate that the observed differences were outcomes of musical training rather than contributory influences to musicianship.

Various acquired musical performance skills are instrument specific, the most obvious being motor skills, and many studies recruiting musicians have focussed on specialists of a particular instrument, most commonly pianists (Jancke *et al.*, 1997, 2000; Krings *et al.*, 2000; Schlaug *et al.*, 1995a,b). However, there are abilities which are developed by all musicians irrespective of instrument speciality, notably listening and score and sight reading abilities. Specific listening skills, many associated with the analysis of sequential sounds, are required of instrumentalists who regularly perform in ensembles. Ensemble musicians try to synchronize tones meant to be simultaneous, although perfect synchronization is not possible for a variety of reasons, including the restricted accuracy of human motor performance and time perception and the time lag between the production of a player's own tones and the perception of tones produced by others (Rasch, 1988). Additionally, ensemble performers regularly rely on hearing musical cues from other sections of the ensemble, which requires musicians to audiospatially localize each instrumental section. Deutsch (1999) considered that the spatial seating arrangement of many symphony orchestras (Fig. 1) may have evolved from its conduciveness to optimal performance, having found (Deutsch, 1985) that musically trained subjects

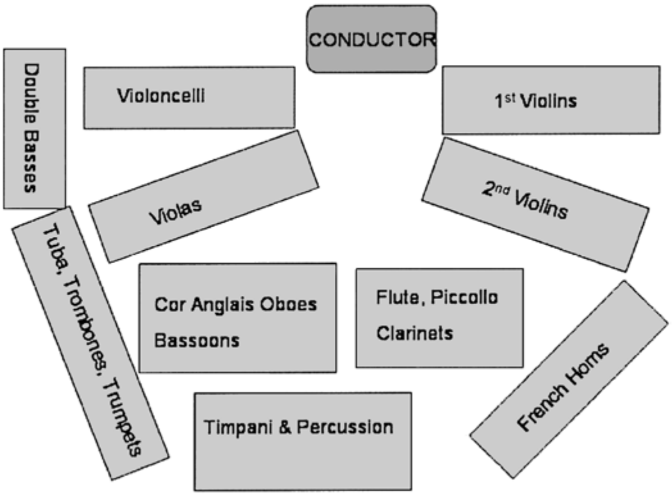

FIG. 1. Typical platform seating arrangement for the different sections of musical instruments of many major symphony orchestras.

identified higher tones more accurately when they were presented to the right ear, while the converse was true for lower tones. Instrument sections are positioned with higher registers to the right and lower registers to the left of each section. Orchestral musicians (and conductors) are used to localizing specific instrumental sounds at particular spatial locations.

Sight reading is the ability to perform from a score without any preceding practice (Gabrielsson, 1999) and results in the transformation of written musical notation into appropriate motoric sequences. Musical scores are organized in a spatially systematic manner, with different notes being represented at different heights on the musical stave, and require the visual analysis of spatial location and relative height separation (interval analysis) of adjacent notes for extraction of the relevant information (Sergent *et al.*, 1992). In particular, interval analysis of sequential individual notes would appear to be a more important feature of sight reading for orchestral instrumental scores than pattern recognition of chords as found in, for example, piano scores. Visuospatial ability has been shown to be amenable to training effects in adults of both sexes, in both young adults (Stericker and LeVesconte, 1982) and older subjects who have exhibited an age-related decline in this ability (Schaie and Willis, 1986). Stericker and LeVesconte (1982) also reported that following training the sex-related pretest difference favoring males was eliminated. Musicians have been reported to demonstrate consistently enhanced performance on tests of spatial ability and have failed to exhibit the sexual dimorphism reported in nonmusicians (Costa-Giomi *et al.*, 2001; Hassler, 1990, 1991, 1992; Hassler and Birbaumer, 1986; Johnson *et al.*, 1998). We speculate that undertaking score and sight reading on a regular basis may serve as training leading to enhanced performance on other tasks of spatial ability.

Music training has been shown to be associated with left hemisphere dominance in dichotic listening tests using musical stimuli (Bever and Chiarello, 1974; Deutsch, 1985; Gordon, 1980; Johnson, 1977), which compared with right hemisphere dominance in musically naive listeners. Functional neuroimaging studies have identified that listening for the accuracy of musical performance while reading a musical score, a sequence-checking task, activates the left inferior frontal gyrus (Parsons, 2001), as does audiospatial and visuospatial analysis (Bushara *et al.*, 1999; Ng *et al.*, 2000), musical syntax (Maess *et al.*, 2001), processing and organization of sequential sound stimuli (Platel *et al.*, 1997), and sight reading (Sergent *et al.*, 1992). We hypothesized that, since similar requirements exist for sequencing, coordination of behaviour, and the analysis of output for both musical performance and spoken language, Broca's classic speech output region of the inferior frontal gyrus of the left cerebral hemisphere, which is well known to subserve the latter, would show increased gray matter density in musicians.

Many studies that recruited musicians as volunteers state explicitly that the subjects were drawn from the student bodies of music schools or University music departments (Evers *et al.*, 1999; Jancke *et al.*, 1997; Pantev *et al.*, 1998, 2001; Schlaug *et al.*, 1995a,b). The study reported here recruited right-handed male musicians who were full-time playing members of a major British symphony orchestra and consequently differs from previous reported research in two significant aspects. First, all sections of the orchestra were represented in the musician volunteers. We recruited musicians of outstanding performance ability on a variety of instruments rather than specialists of specific instruments which, consequently, precluded the formulation of a specific hypothesis relating to motor cortex. Second, previous studies which have recruited musicians have reported young cohorts, with a mean age somewhere in the third decade of life. The age range of the musicians recruited for this study spanned 26 to 66 years. The potential confound of age was removed by appropriate matching with a control population, although we also performed a secondary analysis in which the effects of age-related changes were examined. Miller *et al.* (1980) proposed that global brain structure volumes remained stable up to age 50 years in both sexes; this has subsequently been supported by the *in vivo* findings of other workers (Bartzokis *et al.*, 2001; Gur *et al.*, 1991; Pfefferbaum *et al.*, 1994; Sullivan *et al.*, 1995). The sensitivity of the frontal lobes, particularly the dorsolateral prefrontal cortex, to age-related volume reduction (particularly in males) has also been reported (Gur *et al.*, 2000; Raz *et al.*, 1997). Consequently, our analysis of age-related effects in brain structure volumes included a separate investigation in the under-50-year-old males in each group.

To investigate structural differences between the brains of male musicians and nonmusicians, we analyzed 3D MR brain images using voxel based morphometry (VBM) (Ashburner and Friston, 2000) and the Cavalieri method of modern design stereology in combination with point-counting (Cruz-Orive, 1993; Roberts *et al.*, 2000). In addition to tests of IQ and executive functions, a battery of neuropsychological tests was administered to investigate spatial ability, memory, and motor functions. Here we report the results of the analysis of tests of general cognitive and spatial ability.

METHODS

Subjects

Participants were 26 right-handed male musicians and 26 age-matched right-handed male nonmusicians (controls). All volunteers gave signed, informed written consent of their willingness to participate in this study and were screened for medical and neurological disorders. The age range was 26–66 years for both musicians and controls, with a mean age of 43.2 (SD 9.3) years for musicians and 42.8 (SD 10.8) years for controls. The difference in mean ages (95% confidence interval) was 0.4 years (−1.2 years to 2.0 years). Handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971).

Musicians' Profiles

The male musicians were all members of a major British symphony orchestra that consists of 82 instrumentalists (52 males, 22 females, 8 vacancies). The musicians' group included 16 string players (9 violin, 2 viola, 2 cello, 3 double bass), 9 wind players (1 flute, 1 clarinet, 1 oboe, 1 bassoon, 4 french horn, 1 trombone) and 1 percussionist. The average age at which musical training commenced was 9.6 years (SD 2.4 years, range 4–13 years), with only 3 musicians commencing training at an age under 7 years and 17 musicians commencing after the age of 10 years. On average, the musicians spent 36 h per week playing their orchestral instrument (SD 5 h range 30–46 h), which included orchestral rehearsal, concert performances, private practice, and playing with other ensembles. The musicians had played in a symphony orchestra for an average of 20.4 years (SD 9.4 years, range 4–44 years), and none reported possessing perfect i.e., absolute, pitch. Insufficient right-handed female musicians volunteered to warrant the inclusion of women in this study.

Image Acquisition

Brain images were acquired with a 1.5 T SIGNA whole body MR imaging system (GE Electric, Milwaukee, WI) using a proprietary quadrature head coil. A series of 124 coronal T_1-weighted images, comprising 1.6-mm-thick tissue slices, were acquired throughout the brain using a 3D spoiled gradient echo sequence. The following parameters were employed: TE, 9 ms; TR, 34 ms; flip angle, 30°. The field of view was 20 cm, which contained a 256 × 256-pixel matrix. A multislice T_2-weighted fast-spin echo sequence was employed (TE, 90 ms; TR, 3000 ms; flip angle, 90°; interslice gap, 10 mm; slice thickness, 3 mm) for the estimation of intracranial volume.

Image Analysis

VBM analysis. Voxel-based morphometry (Ashburner and Friston, 2000) was carried out using Statistical Parametric Mapping software (SPM99) (Wellcome Department of Cognitive Neurology) and MATLAB (Mathworks, Sherborn, MA) on a Sun SPARC 10 workstation. VBM is an objective method of analyzing 3D MR images of the brain to identify regionally specific differences in gray and white matter density between groups of subjects. Three preparatory stages preceded the statistical analysis. First, each image was spatially coregistered with the MNI 305 brain average asymmetric template using a 12 parameter affine transformation into stereotactic space. Second, these normalized images were segmented, using a modified mixture model cluster analysis technique, into gray matter, white matter, and cerebrospinal fluid compartments, with bias correction for image intensity inhomogeneities. Finally, the segmented coregistered images were smoothed by convolving with a 12-mm isotropic Gaussian kernel. Voxel-by-voxel statistical parametric maps of regionally specific differences in gray matter density between musicians and controls were calculated taking total brain gray matter (GM) volume as a confound (ANCOVA). In this context, "density" refers to the amount of tissue, per unit volume, classified as gray matter during the segmentation process. An a priori hypothesis regarding the brain region of interest based on previous findings permitted the use of an uncorrected threshold of $P = 0.01$ taken at the voxel level, and clusters with $P < 0.05$ were considered significant after adjustment for multiple comparisons.

Due to our a priori hypothesis regarding Broca's area, we immediately implemented a small volume correction based on the probability map of Tomaiuolo *et al.* (1999) for the localization of Broca's area, which was centred at a voxel at the midpoint of the 50–75% probability region ($x = -51$, $y = 15$, $z = 9$) and was a box (12 × 8 × 22 mm) to accommodate the 50–75% occurrence volume. Differences in white matter density were assessed statistically for the whole brain, taking total brain white matter volume as a confound (ANCOVA). As no a priori hypothesis existed for white matter or other regions of the GM, an uncorrected threshold of $P = 0.001$ was taken at the voxel level and clusters with $P < 0.05$ were considered significant after adjustment for multiple comparisons.

Regions of interest (ROI) analysis. For each subject, the total volume of gray matter within the small volume previously described was calculated from the corresponding gray matter segmentation image, assuming that the probability of each voxel in the segmentation corresponded to the amount of gray matter present within the particular voxel.

Anatomical localization. The coordinates in Montreal Neurological Institute (MNI) space were transformed to the stereotactic space of Talairach and Tournoux (1988) (URL www.mrc-cbu.cam.ac.uk/imaging/mnispace.html).

Stereology. Volume estimation of eight prefrontal cortex subfields was undertaken using the method described by Gur *et al.* (2000), adapted for stereology using ANALYZE software (Mayo Clinic, Rochester, MN) by a single rater blinded to the identity and grouping of the subjects. Intrarater repeatability was assessed by repeating the point counting procedures on 10 randomly selected brains at least 3 weeks after the first measurement. The method for regional and global volumes estimation involved reorienting the brain volumes in acquired space to a sagittal plane orthogonal to the bicommisural plane (using NRIA software, Brain Behaviour Laboratory, University of Pennsylvania, Philadelphia, PA), parcellating the prefrontal cortex of each hemisphere into four subfields (dorsolateral, dorsomedial, orbitolateral, and orbitomedial), and applying the Cavalieri method in combination with point counting for efficient volume estimation. Cerebral hemisphere volume was estimated using the method described by Mackay *et al.* (1998). In addition, to control for differences in head size, intracranial volume was estimated as described by Howard *et al.* (2000).

Neuropsychological Assessment

Neuropsychological tests were administered to quantify cognitive ability both in general terms and specifically related to spatial ability. Fluid intelligence is considered to be the basic reasoning ability of the brain (Kline, 2000) and was assessed using a standard psychometric test, Cattell's culture fair test of "g," in which the influence of verbal fluency, cultural climate, and educational level is minimized. Duncan *et al.* (2000) have proposed that "g" reflects the function of a specific neural system including the lateral frontal cortex bilaterally. Spatial ability was evaluated using the Benton judgement of line orientation (JOL) test (Benton *et al.*, 1978), which is considered to be a test of spatial ability rather than of spatial perception, being devoid of 3D spatial transformations (Benton *et al.*, 1983; Ng *et al.*, 2000). All 26 musicians and 20 controls completed the JOL test. The raw scores of the JOL test

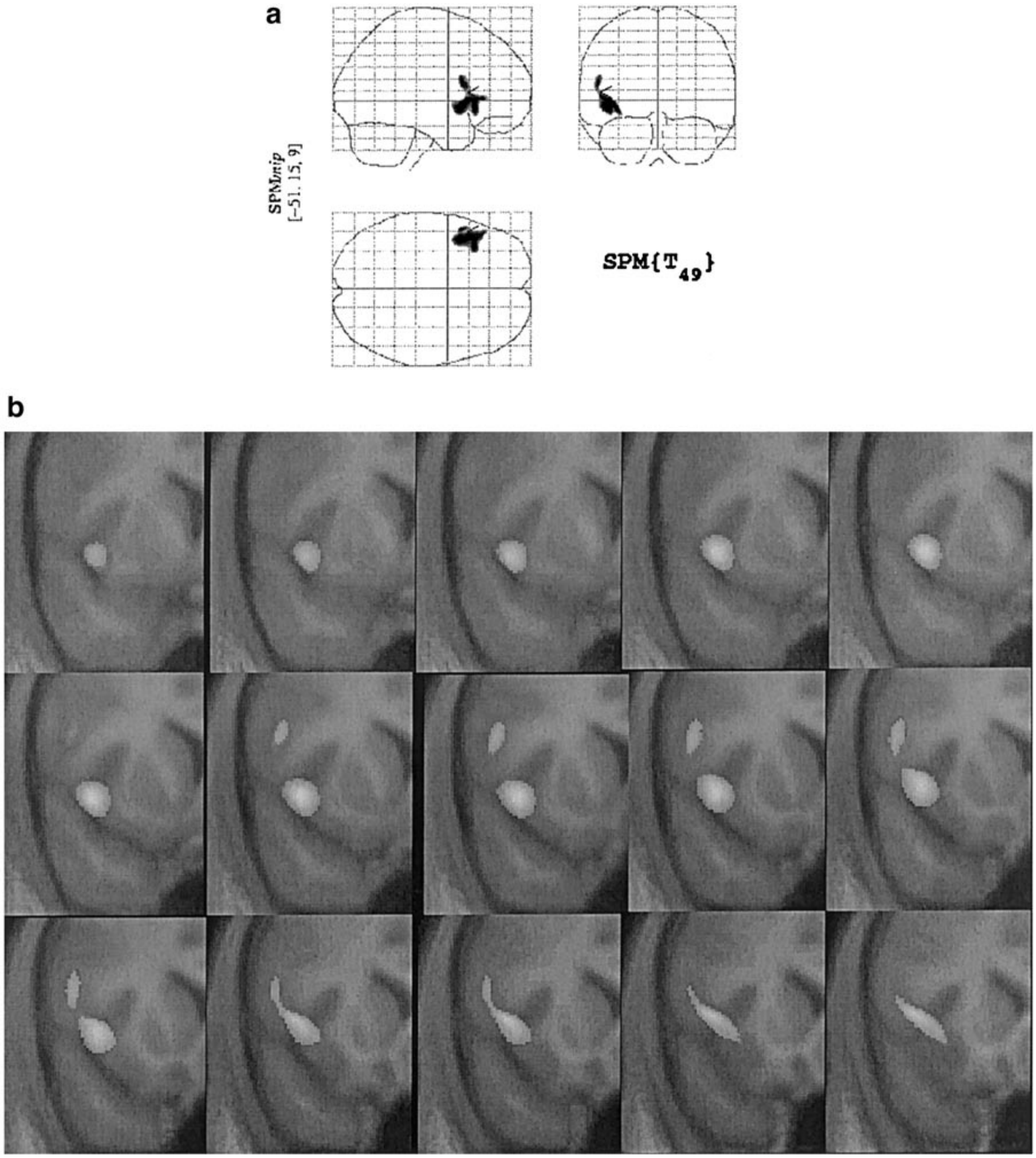

FIG. 2. (a) Statistical parametric maps, in sagittal, coronal and axial projections, showing an increase in gray matter density in musicians compared to controls, with arrows indicating the midpoint of the 50–75% occurrence volume of Tomaiuolo *et al.* (1999). (b) The cluster of increased gray matter density superimposed on coronal slices of a mean brain image of all subjects. The y coordinates in stereotactic space range from +6 (top left-hand image) sequentially through to +20 (bottom right-hand image), accommodating the 50–75% occurrence volume of Tomaiuolo *et al.* (1999). The x coordinates ranged from −46 to −54 and the z coordinates from −7 to 17.

were used in data analysis to allow the investigation of age-related effects in this test. Neuropsychological tests were administered according to the standard requirements prescribed for each test.

RESULTS

VBM. There were no regions of decreased gray matter density within the brains of musicians compared to controls. Figure 2 illustrates the single region of the musicians' brains that showed a significant cluster (volume 699 mm^3, $P = 0.002$) of increased gray matter density within the 50–75% probability regions of Broca's area in the left cerebral hemisphere. The voxel of peak difference ($P = 0.02$, corrected) was $x = -46$, $y = 18$, $z = 3$, with Z score = 3.45. The analysis of white matter revealed no statistically significant differences between musicians and controls.

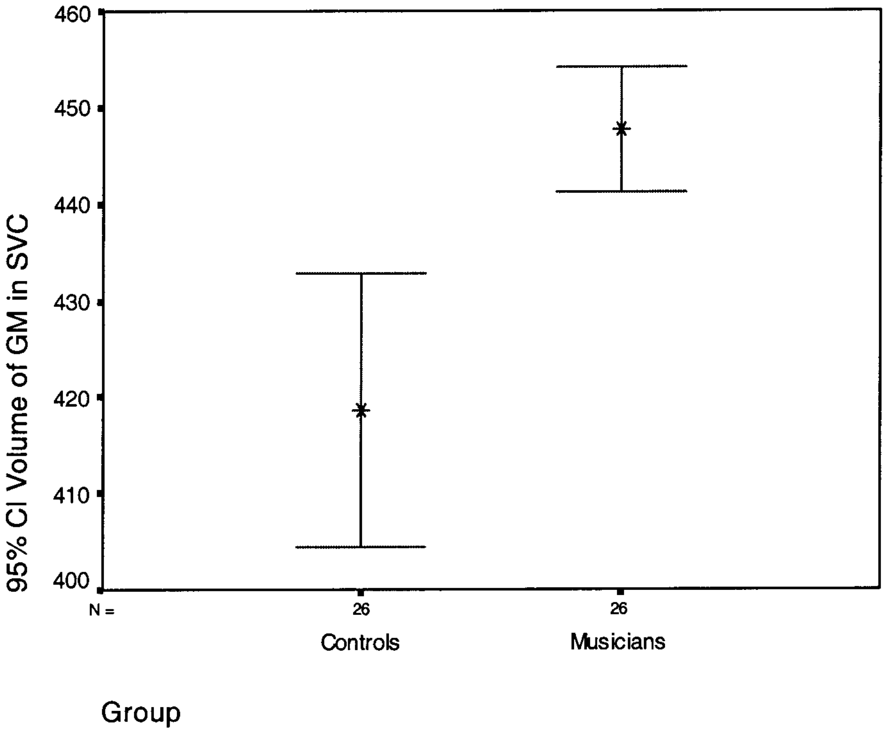

FIG. 3. Mean and 95% CI of volume of gray matter within small volume encompassing the 50–75% occurrence volume of the probability map of Tomaiuolo *et al.* (1999) for musicians and controls.

ROI analysis. Musicians possessed larger GM volumes than controls (Fig. 3) [means (95% CI): musicians, 447.62 mm^3 (441.09 to 454.05 mm^3); controls, 418.69 mm^3 (404.49 to 432.90 mm^3)] and there was a statistically significant negative association between gray matter volume and age for the control subjects ($r = -0.62$, $P = 0.00$), but not for the musicians ($r = -0.16$, $P = 0.44$) (illustrated in Fig. 4). No association was

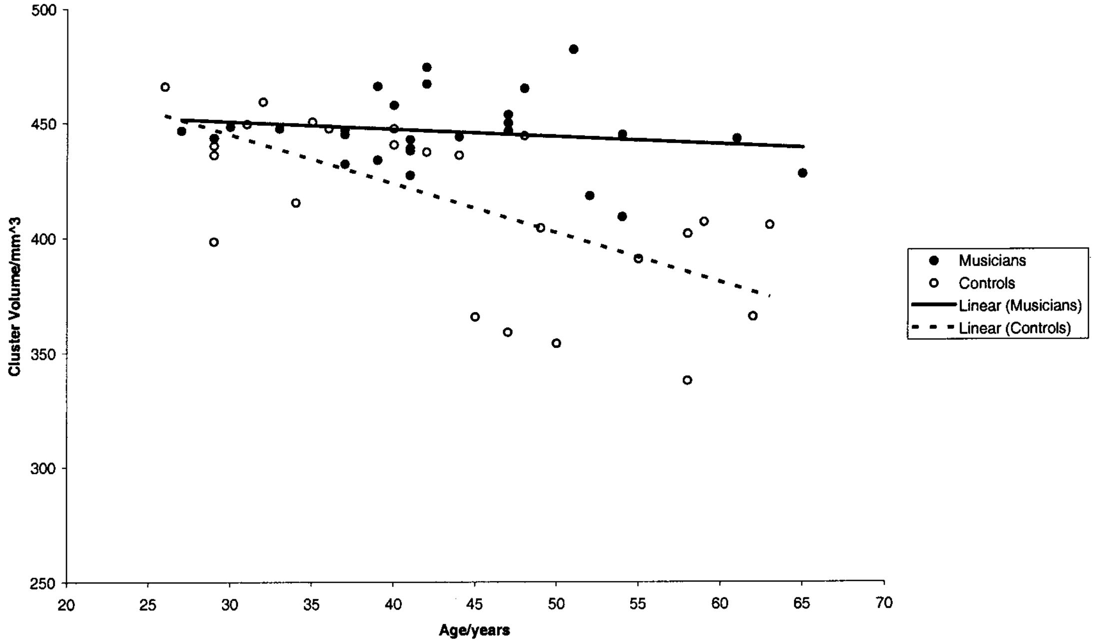

FIG. 4. Gray matter volume from each subject within the small volume plotted against age. There is a statistically significant negative correlation ($R^2 = 0.39$, $r = -0.62$, $P = 0.001$) between the volume of gray matter contributing to the cluster and the age of the control subjects only.

found between years of instrument playing and gray matter volume. However, analysis of the data for under-50-year-old musicians (n = 21) revealed a significant positive correlation between the volume of gray matter within the significant cluster and the number of years of instrument playing when age was partialled out (r = 0.39, P = 0.04). Within the under-50-year-old controls (n = 20), there was a significant negative correlation between the volume of gray matter within the significant cluster and age (r = −0.56, P = 0.01). There was no association between the volume of gray matter within the significant cluster and the age of the commencement of musical training.

Stereology. The intra-class correlation coefficient (ICC) ranged from 0.90 (right medial orbital subfield) to 0.96 (hemispheres, left medial orbital subfield, right medial and lateral dorsal subfields). There were no differences in intracranial volume between musicians and controls (t = −0.36, df = 50, P = 0.72) and no association between intracranial volume and age (r = −0.13, n = 52, P = 0.38), interpreted as the absence of secular effects. Bilaterally, cerebral hemisphere volumes were significantly positively correlated with ICV in both groups ($r > 0.80$, P = 0.00 for both hemispheres for both groups of subjects). Repeated measures ANOVA, covarying for ICV, revealed that hemisphere volumes were significantly larger in musicians than in controls ($F_{1,49}$ = 10.0, P = 0.00). Bilaterally, there was a significant negative correlation between hemisphere volumes and age in controls (left hemisphere, r = −0.48, P = 0.01; right hemisphere, r = −0.43, P = 0.03), but not in musicians (left hemisphere, r = −0.21, P = 0.31; right hemisphere, r = −0.13, P = 0.52), whereas there were no associations between age and hemisphere volumes in under-50-year-old males in either group (controls: right, r = −0.35, P = 0.18; left, r = −0.43, P = 0.10; musicians: right, r = −0.20, P = 0.39; left, r = 0.20, P = 0.39). There were no significant differences between musicians and controls in any of the eight prefrontal cortex (PFC) subfields measured (repeated measures ANOVA, $F_{1,49}$ = 0.04, P = 0.85). Significant negative association between age and volume in the left dorsolateral PFC was identified by step-wise multiple regression in controls (standardized β = −0.52, t = −2.98, P = 0.01), but not in musicians.

Cognitive ability. There was a significant negative correlation between the culture fair score (a measure of fluid intelligence) and age in both groups (controls, r = −0.68, n = 26, P = 0.00; musicians; r = −0.46, n = 26, P = 0.02) and consequently age was entered as a covariate into ANOVA, which revealed no significant difference between musicians and controls ($F_{1,49}$ = 4.0, P = 0.06). The measure of fluid intelligence showed no association with the JOL raw score in either group (musicians; ρ = −0.17, P = 0.40; controls; ρ = 0.23, P = 0.33). Musicians achieved significantly higher JOL raw scores than controls [Mann–Whitney U = 98.5, Z = −3.9, P = 0.00 (mean (SD) : musicians, 29.0 (2.5); controls, 24.8 (4.1))], indicating enhanced performance on this test. JOL raw scores also showed a nonsignificant negative correlation with age in controls (ρ = −0.39, n = 20, P = 0.09), but a significant positive correlation with age in musicians (ρ = 0.37, n = 26, P = 0.05).

DISCUSSION

Voxel-based morphometry has confirmed our hypothesis of increased gray matter density and volume in Broca's area of the left inferior frontal gyrus (LIFG) in symphony orchestra musicians. Although this finding was not reflected in the analysis of the stereological volume estimates, it should be borne in mind that the parcellation method was not focused specifically on Broca's area or even the LIFG as the dorsolateral subfield also included the middle frontal gyrus, lateral superior frontal gyrus, and frontal pole. Given the macroscopic level of the analyses, the results do not shed light on the microscopic mechanisms, such as neurogenesis (Gould *et al.*, 1999), that might underlie the structural changes that we report. Evidence from functional studies has identified the LIFG as subserving a variety of musically relevant activities: music discrimination (Platel *et al.*, 1997), visuospatial and audiospatial localization (Haxby *et al.*, 1991; Martinkauppi *et al.*, 2000), processing and organization of sequential sound stimuli (Platel *et al.*, 1997), musical syntax processing (Maess *et al.*, 2001), sight reading (Sergent *et al.*, 1992), and score reading while listening to the accuracy of a performance (Parsons, 2001). All of these activities are essential contributors to musical performance by ensemble instrumentalists and thus the region of significantly increased gray matter density identified in VBM analysis has particular functional relevance for symphony orchestra musicians. With possible interaction between brain development and skill acquisition, musical performance could thus be an environmentally enriching activity which could promote generation and/or retention of functionally relevant cortical tissue.

Previous studies (Elbert *et al.*, 1995; Pantev *et al.*, 1998) have emphasized the early age of the commencement of musical training in interpreting their findings. Our cohort of musicians had a mean age of the commencement of musical training of 9.6 years (SD = 2.4, range 4–13 years) and mean duration of instrument playing of 33.8 years (SD = 9.0, range 19–54 years). There was no association between the volume of gray matter within the significant cluster and the age of the commencement of musical training, but there was a significant positive correlation between the volume of gray matter within the significant cluster and the number of years of instrument playing in under-50-year-old musicians, which we interpret as evidence of use-dependent adaptation. In under-50-year-old controls, we found a negative correlation between the volume of gray matter within the significant cluster and age. However, within this age grouping there were no associations between age and cerebral hemisphere volumes of either controls or musicians. The statistically significant negative correlation of gray matter density with age in the left IFG in controls but not male symphony orchestra musicians is consistent with the finding that dorsolateral PFC volumes (and also hemisphere volumes) bilaterally exhibited a significant negative association with age in controls but not musicians. The particular susceptibility of dorsolateral PFC to age-related effects, in males specifically, has been reported previously (Cowell *et al.*, 1994; Gur *et al.*, 2000; Raz, *et al.*, 1997). We interpret increased gray matter density in male musicians in the left IFG as reflecting use-dependent adaptation associated with musical performance which commenced in childhood and which has continued throughout adulthood. Neuroplastic development throughout adolescence and adulthood in musicians may promote the retention of cortical tissue as observed in male musicians. This finding may be equivalent to that reported by Maguire *et al.* (2000) of increased gray matter density found in the right posterior hippocampus of taxi drivers and which was associated with the length of time as a taxi driver. In this latter study, none of the taxi-driving subjects could have commenced their occupation prior to the age of 18 years and consequently the proposed use-dependent adaptation would have been acquired during adulthood.

Our study adds to previous findings of enhanced performance in tests of spatial ability in musicians (Costa-Giomi *et al.*, 2001; Hassler, 1990, 1991, 1992; Hassler and Birbaumer, 1986; Johnson *et al.*, 1998). Orchestral musicians are renowned for their sight reading ability, which constitutes a significant component of their daily work activity, in addition to the audiospatial localization of sounds. Spatial ability has been shown to be amenable to training effects in young and old alike (Schaie, 1994; Stericker and LeVesconte, 1982), while performance of the Benton JOL test has been reported to recruit the IFG bilaterally (Ng *et al.*, 2001). It must be noted that in our subjects this test did suffer from a ceiling effect, as 3 controls and 17 musicians achieved the maximum raw score of 30 correct trials. Equally noteworthy is the fact that there was a significant positive correlation between age and raw score for musicians. Enhanced performance by musicians on this test of spatial ability may relate to the development and use of the visuospatial analysis skill of sight reading in musicians which has served as a training effect for other spatial tasks.

Music is considered to be one of the most ancient and universal forms of human communication, and its vocalized form may have preceded spoken language (Darwin, 1871; Miller, 2000). Verbal and musical languages share many features, including written form, grammar, and expressive output, and speech has musical features in prosody. Lashley (1951) proposed that sequencing and coordination of behaviour may be regarded as a form of grammar, having both syntactic and linguistic features, expressed through the movement of limbs, an essential requirement in musical performance. We have reported that orchestral musicians possess a region of significantly increased gray matter density within the left IFG including Broca's area, a region known to be critically important for language (Zatorre *et al.*, 1992). Music and language share many common features in expressive output, and those aspects of musical performance that are established in symphony orchestra musicians may be especially relevant for understanding the neural bases of language.

From an evolutionary viewpoint, it has been suggested, originally by Darwin (1871), that musical performance is a sexually selected trait with no associated survival benefit at the level of the individual in that music performance appears to have no adaptive value in surviving predation or infection or in obtaining food (Miller, 2000; Sluming and Manning, 2000). We acknowledge that the findings that we report in musicians do not identity the causative mechanisms. However, we interpret our findings to reflect use-dependent development and/or the retention of gray matter density within a brain region that has particular functional relevance in orchestral musicians and which may constitute a survival benefit to the individual musical performer. In particular, we propose that musical performance is an environmentally enriching activity which, at least in part, mitigates age-related brain atrophy.

REFERENCES

Amunts, K., Schlaug, G., Jancke, L., Steinmetz, H., Schleicher, A., Dabringhaus, A., and Zilles, K. 1997. Motor cortex and hand motor skills: Structural compliance in the human brain. *Hum. Brain Mapping* **5:** 206–215.

Ashburner, J., and Friston, K. 2000. Voxel based morphometry—The methods. *NeuroImage* **11:** 805–821.

Bartzokis, G., Beckson, M., Lu, P., Nuechterlein, K., Edwards, N., and Mintz, J. 2001. Age related changes in frontal and temporal lobe volumes in men. *Arch. Gen. Psychiatry* **58:** 461–465.

Benton, A., Hamsher, K., Varney, N., and Spreen, O. 1983. *Contributions to Neuropsychological Assessment: A Clinical Manual*. Oxford Univ. Press, Oxford.

Benton, A., Varney, N., and Hamsher, K. 1978. Visuospatial judgement: A clinical test. *Arch. Neurol.* **35:** 364–367.

Bever, T., and Chiarello, R. 1974. Cerebral dominance in musicians and non-musicians. *Science* **185:** 537–539.

Bottjer, S., and Johnson, F. 1997. Circuits, hormones and learning: Vocal behaviour in songbirds. *J. Neurobiol.* **33:** 602–618.

Bushara, K., Weeks, R., Ishii, K., Catalan, M.-J., Tian, B., Rauschecker, J., and Hallet, M. 1999. Modality specific frontal and parietal areas for auditory and visual spatial localisation in humans. *Nat. Neurosci.* **2:** 759–766.

Costa-Giomi, E., Gilmour, R., Siddell, J., and Lefebyre, E. 2001. Absolute pitch, early musical instruction, and spatial abilities. In *Biological Foundations of Music* (R. Zatorre and I. Peretz, Eds.), Vol. 930, pp. 394–396. N. Y. Acad. Sci., New York.

Cowell, P., Turetsky, B., Gur, R., Grossman, R., Shtasel, D., and Gur, R. 1994. Sex differences in aging of the human frontal and temporal lobes. *J. Neurosci.* **14:** 4748–4755.

Cruz-Orive, L. 1998. Systematic sampling in stereology. *Bull. Int. Statist. Inst.* **55:** 451–468.

Darwin, C. 1871. *The Descent of Man, and Selection in Relation to Sex*. Murray, London.

Deutsch, D. 1985. Dichotic listening to melodic patterns and its relationship to hemispheric specialisation of function. *Music Percept.* **3:** 1–28.

Deutsch, D. 1999. Grouping mechanisms in music. In *The Psychology of Music* (D. Deutsch, Ed.), pp. 299–348. Academic Press, San Diego, CA.

Duncan, J., Seitz, R., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F., and Emslie, H. 2000. A neural basis for general intelligence. *Science* **289:** 457–460.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., and Taub, E. 1995. Increased cortical representation of the fingers of the left hand in string players. *Science* **270:** 305–308.

Evers, S., Dannert, J., Rodding, D., Rotter, G., and Ringelstein, B. 1999. The cerebral haemodynamics of music perception. *Brain* **122:** 75–85.

Gabrielsson, A. 1999. The performance of music. In *The Psychology of Music* (D. Deutsch, Ed.), pp. 501–602. Academic Press, San Diego, CA.

Good, C., Johnsrude, I., Ashburner, J., Henson, R., Friston, K., and Frackowiak, R. 2001. A voxel based morphometric study of aging in 465 normal adult human brains. *NeuroImage* **14:** 21–36.

Gordon, H. 1980. Degree of ear asymmetries for perception of dichotic chords and for illusory chord localisation in musicians of different levels of competence. *J. Exp. Psychol. Hum. Percep. Performance* **6:** 516–527.

Gould, E., Reeves, A. J., Graziano, M. S. N. A., and Gross, C. G. 1999. Neurogenesis in the neocortex of adult primates. *Science* **286:** 548–552.

Gur, R., Mozley, P., Resnick, S., Gottlieb, G., Kohn, M., Zimmerman, R., Herman, G., Atlas, S., Grossman, R., Berretta, D., Erwin, R., and Gur, R. 1991. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **88:** 2845–2849.

Gur, R. E., Cowell, P. E., Latshaw, A., Turetsky, B. I., Grossman, R. I., Arnold, S. E., Bilker, W. B., and Gur, R. C. 2000. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Arch. Gen. Psychiatry* **57:** 761–768.

Hassler, M. 1990. Functional cerebral asymmetries and cognitive abilities in musicians, painters and controls. *Brain Cognit.* **13:** 1–17.

Hassler, M. 1991. Maturation rate and spatial, verbal and musical abilities—A seven year longitudinal study. *Int. J. Neurosci.* **58:** 183–198.

Hassler, M. 1992. Creative musical behaviour and sex hormones: Musical talent and spatial ability in the two sexes. *Psychoneuroendocrinology* **17:** 55–70.

Hassler, M., and Birbaumer, N. 1986. Witelson's dichaptic stimulation test and children with different levels of musical talent. *Neuropsychologia* **24:** 435–440.

Haxby, J., Grady, C., Horwitz, B., Ungerlieder, L., Mishkin, M., Carson, R., Herscovitch, P., Schapiro, M., and Rapoport, S. 1991. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc. Natl. Acad. Sci. USA* **88:** 1621–1625.

Howard, M., Cowell, P., Boucher, J., Broks, P., Mayes, A., Farrant, A., and Roberts, N. 2000. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *NeuroReport* **11:** 2931–2935.

Howe, M. 1999. *Genius Explained*. Cambridge Univ. Press, Cambridge, UK.

Jancke, L., Schlaug, G., and Steinmetz, H. 1997. Hand skill asymmetry in professional musicians. *Brain Cognit.* **34:** 424–432.

Jancke, L., Shah, N., and Peters, M. 2000. Cortical activitions in primary and secondary motor areas for complex bimanual movements in professional pianists. *Cognit. Brain Res.* **10:** 177–183.

Johnson, J. K., Cotman, C. W., Tasaki, C. S., and Shaw, G. L. 1998. Enhancement of spatial–temporal reasoning after a Mozart listening condition in Alzheimer's disease: A case study. *Neurol. Res.* **20:** 666–672.

Johnson, P. 1977. Dichotically stimulated ear differences in musicians and nonmusicians. *Cortex* **13:** 385–389.

Jordan, K., Heinze, H. J., Lutz, K., Kanowski, M., and Jancke, L. 2001. Cortical activations during the mental rotation of different visual objects. *NeuroImage* **13:** 143–152.

Keenan, J., Thangaraj, V., Halpern, A. R., and Schlaug, G. 2001. Absolute pitch and planum temporale. *NeuroImage* **14:** 1402–1408.

Kline, P. 2000. *A Psychometric Primer*. Free Assoc. Books, London.

Krings, T., Topper, R., Foltys, H., Erberich, S., Sparing, R., Willmes, K., and Thron, A. 2000. Cortical activation patterns during complex motor tasks in piano players and control subjects: A functional magnetic resonance imaging study. *Neurosci. Lett.* **278:** 189–193.

Lashley, K. 1951. The problem of serial order in behaviour. In *Cerebral Mechanisms in Behaviour* (L. Jeffress, Ed.). Wiley, New York.

Mackay, C., Roberts, N., Mayes, A., Downes, J., Foster, J., and Mann, D. 1998. An exploratory study of the relationship between face recognition memory and the volume of medial temporal lobe structures in healthy young males. *Behav. Neurol.* **11:** 3–20.

Maess, B., Koelsch, S., Gunter, T., and Friederici, A. 2001. Musical syntax is processed in Broca's area: An MEG study. *Nat. Neurosci.* **4:** 540–545.

Maguire, E., Gadian, D., Johnsrude, I., Good, C., Ashburner, J., Frackowiac, R., and Frith, C. 2000. Navigational related structural change in the hippocampi of taxi drivers. *Proc. Nat. Acad. Sci. USA.* **97:** 4398–4403.

Martinkauppi, S., Rama, P., Aronen, H., Korvenjola, A., and Carlson, S. 2000. Working memory of auditory localisation. *Cereb. Cortex* **10:** 889–898.

Miller, A., Alston, R., and Corsellis, J. 1980. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: Measurements with an image analyser. *Neuropathol. Appl. Neurobiol.* **6:** 119–132.

Miller, G. 2000. Evolution of human music through sexual selection. In *The Origins of Music* (N. Wallin, B. Merker, and S. Brown, Eds.) pp. 329–360. MIT Press, Cambridge, MA

Munte, T., Kohlmetz, C., Nager, W., and Altenmuller, E. 2001. Neuroperception: Enhanced audiospatial tuning in conductors. *Nature* **409:** 580.

Ng, V. W., Bullmore, E. T., de Zubicaray, G. I., Cooper, A., Suckling, J., and Williams, S. C. 2001. Identifying rate-limiting nodes in large-scale cortical networks for visuospatial processing: An illustration using fMRI. *J. Cognit. Neurosci.* **13:** 537–45.

Ng, V. W., Eslinger, P. J., Williams, S. C., Brammer, M. J., Bullmore, E. T., Andrew, C. M., Suckling, J., Morris, R. G., and Benton, A. L. 2000. Hemispheric preference in visuospatial processing: A complementary approach with fMRI and lesion studies. *Hum. Brain Mapping* **10:** 80–86.

Oldfield, R. 1971. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* **9:** 97–113.

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

Pantev, C., Roberts, L. E., Schulz, M., Engelien, A., and Ross, B. 2001. Timbre-specific enhancement of auditory cortical representations in musicians. *NeuroReport* **12:** 169–174.

Parsons, L. M. 2001. Exploring the functional neuroanatomy of music performance, perception and comprehension. In *The Biological Foundations of Music* (R. Zatorre and I. Peretz, Eds.), Vol. 930, pp. 211–231. N. Y. Acad. of Sci., New York.

Pfefferbaum, A., Mathalon, D., Sullivan, E., Rawles, J., Zipursky, R., and Lim, K. 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch. Neurol.* **51:** 874–887.

Platel, H., Price, C., Baron, J.-C., Wise, R., Lambert, J., Frackowiak, R., Lechevalier, B., and Eustache, F. 1997. The structural components of music perception. *Brain* **120:** 229–243.

Rasch, R. 1988. Timing and synchronisation in ensemble performance. In *Generative Processes in Music: the Psychology of Performance, Improvisation and Composition* (J. Sloboda, Ed.), pp. 70–90. Oxford Univ. Press, Oxford.

Raz, N., Gunning, F., Head, D., Dupuis, J., McQuain, J., Briggs, S., Loken, W., Thornton, A., and Acker, J. 1997. Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal grey matter. *Cereb. Cortex* **7:** 268–282.

Roberts, N., Puddephat, M., and McNulty, V. 2000. The benefit of stereology for quantitative radiology. *Br. J. Radiol.* **73:** 679–697.

Schaie, K. 1994. The course of adult intellectual development. *Am. Psychol.* **49:** 304–313.

Schaie, K., and Willis, S. 1986. Can decline in adult intellectual functioning be reversed? *Dev. Psychol.* **22:** 223–232.

Schlaug, G. 2001. The brain of musicians: A model for functional and structural adaptation. In *Annals of the New York Academy of Sciences* (R. Zatorre and I. Peretz, Eds.), Vol. 930, pp. 281–299. New York, USA: NY Acad. Sci., New York.

Schlaug, G., Jancke, L., Huang, Y., Staiger, J. F., and Steinmetz, H. 1995a. Increased corpus callosum size in musicians. *Neuropsychologia* **33:** 1047–55.

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

Sergent, J., Zuck, E., Terriah, S., and MacDonald, B. 1992. Distributed neural network underlying musical sight-reading and keyboard performance. *Science* **257:** 106–109.

Sluming, V., and Manning, J. 2000. Second to fourth digit ratio in elite musicians: Evidence for musical ability as an honest signal of male fitness. *Evol. Hum. Behav.* **21:** 1–9.

Stericker, A., and Le Vesconte, S. 1982. Effect of brief training on sex-related differences in visual–spatial skill. *J. Pers. Social Psychol.* **43:** 1018–1029.

Sullivan, E., Marsh, L., Mathalon, D., Lim, K., and Pfefferbaum, A. 1995. Age-related decline in MRI volumes of the temporal lobe grey matter but not hippocampus. *Neurobiol. Aging* **16:** 591–606.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotaxic Atlas of the Human Brain* (M. Rayport, Translator), Thieme, Stuttgart.

Tervaniemi, M., Kujala, A., Alho, K., Virtanen, J., Ilmoniemi, R., and Naatanen, R. 1999. Functional specialization of the human auditory cortex in processing phonetic and musical sounds: A magnetoencephalographic study. *NeuroImage* **9:** 330–336.

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

Zatorre, R., Evans, A., Meyer, E., and Gjedde, A. 1992. A lateralisation of phonetic and pitch discrimination in speech processing. *Science* **256:** 846–849.