Corpus callosum: musician and gender effects

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Previously we found that musicians have significantly larger anterior corpus callosum (CC). In the current study, we intended to replicate and extend our previous results using a new and larger sample of gender-matched subjects (56 right-handed professional musicians and 56 age- and handedness-matched controls). We found a significant gender × musicianship interaction for anterior and posterior CC size; male musicians had a larger anterior CC than non-musicians, while females did not show a significant effect of musicianship. The lack of a significant effect in females may be due to a tendency for a more symmetric brain organization and a disproportionately high representation of absolute pitch (AP) musicians among females. Although a direct causal effect between musicianship and alterations in the midsagittal CC size cannot be established, it is likely that the early commencement and continuous practice of bimanual motor training serves as an external trigger that can influence midsagittal CC size through changes in the actual callosal fiber composition and in the degree of myelinization, which will have implications for interhemispheric connectivity. *NeuroReport* 14:205–209 © 2003 Lippincott Williams & Wilkins.

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INTRODUCTION

The corpus callosum (CC), the main band of interhemispheric axonal fibers in the human brain, performs a key role in the transferal and integration of information between the two hemispheres. Group differences in midsagittal callosal area are generally regarded as neuroanatomic correlates for large-scale differences in interhemispheric connectivity and brain asymmetry [1–3]. It has been shown that midsagittal callosal size correlates with the number of fibers passing through the CC [4], and that the corpus callosum is one of the last main fiber tracts to mature in humans [5]. Increases in CC size have been observed through *in vivo* imaging until at least the third decade of human life, with maximal growth in the first decade [6,7]. As this period of presumed callosal maturation coincides with childhood increases in synaptic density and fine tuning of the neural organization [8,9], it has been proposed that environmental stimuli, especially early in life, might affect callosal development [10]. Animal experiments have provided evidence that differential rearing affects CC size [11].

Extensive musical training, commencing at an early age and continued through life, provides exactly such extraordinary environmental stimuli. Professional musicians, defined as those who are performers, music teachers, or conservatory-level music students, often begin training at an early age, and practice their instruments daily, sometimes up to several hours a day, from childhood throughout their adult lives.

In a previous study, we demonstrated group differences between musicians and non-musicians in the anterior CC, with early-beginning musicians displaying a significantly larger midsagittal anterior CC area [10]. We hypothesized that the increased midsagittal CC size in musicians might be evidence for externally triggered changes in the anatomical composition of the CC. These results were astonishing considering that only a few human studies have found structural brain differences between two groups of subjects as a function of certain skills or intense practice [12]. Animal experiments have provided a wealth of data that structural changes as a function of motor training can be seen [13]. In this study, we intended to replicate our previous results using a new, larger, and gender-balanced sample in order to examine possible differences in the CC size between musicians and non-musicians and to determine whether an interaction exist between musicianship and gender as has been found in other studies.

MATERIALS AND METHODS

Subjects: Our group of subjects consisted of 56 healthy musicians (28 males, 28 females) and 56 healthy non-musician controls matched for age. Due to the possible effect of handedness on midsagittal CC size [2,3], we selected only right-handed subjects. Our subjects were retrospectively selected from a prospective database of high-resolution anatomical MR scans of musicians and non-musicians. Subjects participated in various research protocols, which were approved by the local Institutional Review Board, and all subjects gave informed consent. All musicians selected for this study were classically trained, and either had professional status or were enrolled as full-time students at music conservatories. Of 56 musicians, 18 played keyboard instruments only, 26 played some combination of a keyboard instrument with a string instrument or other instruments, and 12 played string instruments only. We tested the keyboard-only group against the string-only group of musicians in total CC area and found no significant differences ($p > 0.05$). Therefore, for the purpose of this study, we did not further divide our musician group in subgroups depending on instrument played. For our non-musician control group, we selected only those subjects who had received absolutely no musical training and who did not play a musical instrument, most of whom were students or young faculty members at local universities. There was no overlap between our present group of 112 subjects and our previous set of 60 subjects [10].

Subjects' biographical data and musical experience were assessed with a questionnaire that determined age, height, handedness (for details on handedness testing see [10]), instrument(s) learned, age of commencement of musical training, and possession of absolute pitch (Table 1).

MR data acquisition and morphometric analysis: All subjects were scanned using a whole-body Siemens 1.5 T MRI machine, acquiring T1-weighted brain images using an MPRAGE sequence, with a typical voxel resolution of 1 mm^3. Non-normalized anatomical images were analyzed using custom-made software tools running under Matlab (Mathworks Inc., Natick, MA, USA; http://www.mathworks.com/products/matlab) with an SPM99 interface tool (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) to delineate the contour of the CC in midsagittal images. In addition, this software allowed us to correct for misalignment of the midsagittal slice, by aligning brains to the horizontal plane of the anterior commissure and posterior commissure, and to the interhemispheric fissure. This ensured that a true midsagittal image was used for delineating the CC. Delineation was performed with an interactive procedure using manually determined control points and cubic spline interpolation. The total midsagittal CC area (A0) and seven sub-areas (A-1-A7) were calculated, using the subdivision procedure as reported previously [10] and equivalent to that originally developed by Witelson [2] for postmortem analysis. All analysis was performed by one investigator who was blinded to subjects' identity and group; intra-observer reliability for measuring total CC area for a random subset of subjects ($n = 30$) taken from our present sample was $r = 0.98$ (Pearson correlation). For the present study, only the anterior half of the CC (the sum of A1–A4) and the posterior half of the CC (sum of A5–A7) were analyzed. This division roughly divides the CC in an anterior part that contains interhemispheric fibers of homotopic primary sensorimotor, premotor, supplementary motor, and other prefrontal regions, and a posterior part that contains interhemispheric fibers of homotopic posterior parietal, temporal, and occipital brain regions [14].

In addition to the midsagittal CC area, we also measured the absolute brain volume of all subjects to correct for the effects of brain volume on absolute CC size and possible group differences in brain volume. All brains were normalized using a linear affine transformation to the SPM99 anatomical template. Normalized images were then segmented into gray matter, white matter, and cerebrospinal fluid, using the SPM99 probability maps. We then reversed the linear affine transformations to return images to their original dimensions, and counted gray and white matter voxels to determine absolute brain volume (all brains had a voxel resolution of 1 mm^3). It has been suggested that midsagittal CC area relates more closely to brain volume raised to the two/thirds power rather than to full brain volume [15], due to a geometric rule: the cross-sectional area of a three-dimensional object increases as the two/thirds power of the volume of the object. Therefore, we used the two-thirds power of brain volume (henceforth referred to as adjusted brain volume) to correct for the influence of brain volume on CC size in all our statistical analyses.

Statistical analysis: All statistical analyses were performed using SPSS 11.0 for Windows. We first calculated a 2×2 MANOVA on our entire dataset, using musicianship and gender as independent variables, adjusted brain volume as covariate, and anterior and posterior CC areas as dependent variables. We then performed one-way ANOVAs within each gender group, using musician status as fixed factor, adjusted brain volume as co-variate, and anterior and posterior CC areas as dependent variables.

Previous studies have shown differences in hemispheric lateralization between musicians with and without absolute pitch (AP) [16], and other studies have demonstrated possible lateralization effects on callosal size [17]. We performed an ANOVA with AP/non-AP as independent variable, brain volume as covariate and anterior and

Table 1. Group biographical data.

Group	Age range (years)	Age (mean ± s.d.; years)	Height (mean ± s.d.; cm)	Age at commencement of musical training (mean ± s.d.; years)
All males ($n = 56$)	18–35	25.7 ± 4.9	180.2 ± 6.2	n/a
Male musicians ($n = 28$)	18–35	25.8 ± 5.0	180.6 ± 7.7	6.1 ± 2.0
Male non-musicians ($n = 28$)	18–33	25.5 ± 4.8	179.6 ± 9.0	n/a
All females ($n = 56$)	18–34	24.4 ± 4.7	165.2 ± 7.0	n/a
Female musicians ($n = 28$)	18–34	24.1 ± 4.7	164.1 ± 5.9	4.1 ± 1.4
Female non-musicians ($n = 28$)	18–32	24.6 ± 4.7	166.6 ± 8.1	n/a

No significant differences were found between musicians and non-musicians for age or height within the genders (all $p > 0.10$).

posterior CC as dependent variables within each gender group to determine whether a difference in callosal size exist between AP and non-AP musicians.

We also tested whether CC sizes obtained with the current morphometric method differed from those obtained with the morphometric method used in our previous study.

RESULTS

We found a significant correlation between brain volume and midsagittal CC size in our data sample ($R = 0.238$; $F = 6.577$; $p = 0.012$); therefore, we used adjusted brain volume as a co-variate for statistical tests of CC size.

The MANOVA with gender and musicianship as main effects and anterior and posterior CC as dependent variables found no significant overall difference for the main effects of gender ($F(1,107) = 1.128$, $p = 0.291$) and musicianship ($F(1,107) = 0.272$, $p = 0.603$), but a significant gender × musicianship interaction ($F(1,107) = 8.245$, $p = 0.005$).

To further explore the gender × musicianship interaction, we performed a series of one-factorial ANOVAs within each gender with musicianship as a factor. We found significant differences in anterior corpus callosum size ($F(2,53) = 3.559$; $p = 0.035$) and a trend for a difference in the posterior CC size in the male group comparing musicians with non-musicians ($F(2,53) = 2.916$; $p = 0.063$; Fig. 1). Subregion A3 showed the largest group difference of individual callosal regions. No significant differences between musicians and non-musicians were found in the female group for either anterior or posterior CC (Table 2).

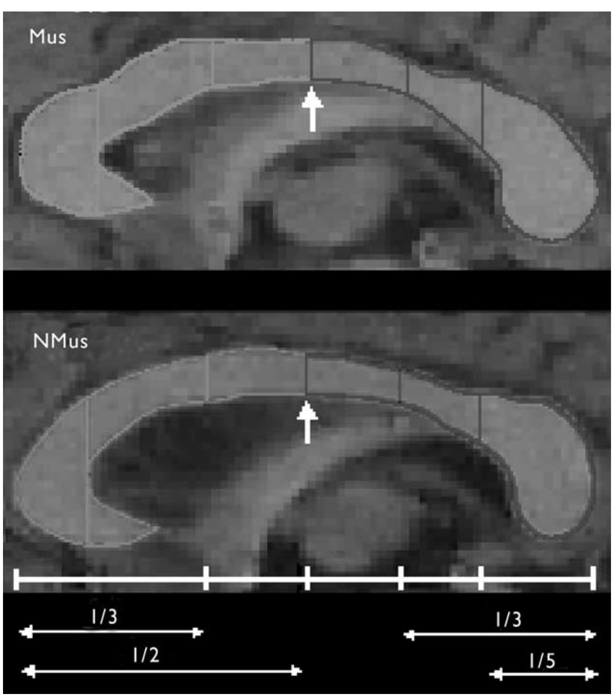

Fig. 1. Midsagittal images of a male musician and male non-musician. The delineation of the CC and the division into seven subareas was done according to Witelson [2]. Half of the transcallosal distance marks the border between the anterior (pink) and posterior CC subregions (blue).

Table 2. Group morphometric data.

Group	Absolute CC area (mm^2)		
	Total	Anterior	Posterior
Male musicians ($n = 28$)	665 ± 91	342 ± 44[a]	323 ± 50[b]
Male non-musicians ($n = 28$)	619 ± 70	323 ± 40[a]	296 ± 37[b]
Female musicians ($n = 28$)	591 ± 55	304 ± 30	286 ± 31
Female non-musicians ($n = 28$)	624 ± 75	322 ± 42	302 ± 39

[a]Significant difference between male musicians and male non-musicians, $p < 0.05$.
[b]Trend for difference between male musicians and male non-musicians, $0.05 < p < 0.10$.

An ANOVA was perfomed to explore the relationship between absolute pitch and midsagittal CC size, since we had an unequal number of AP musicians within each gender group. Although there were slight differences in the group mean anterior and posterior CC size, mainly in the female musician group (non-AP-female/AP-female: 305.2 *vs* 303.8 mm^2 for anterior CC and 292.0 *vs* 283.0 mm^2 for posterior CC), with almost identical values in the male group, there was no statistically significant effect of AP for either anterior or posterior CC size within the male or the female musician group.

A final analysis was performed to compare the current morphometric method with those previously used by Schlaug *et al.* [10], which involved automatic segmentation of the CC from surrounding tissue with manual oversight. A subset of the brains from our previous study ($n = 24$) were measured using the morphometric method employed in this study. Previous and current measurements of the same brains showed that the previous measurements were significantly larger (mean difference = 22 mm^2), suggesting some discrepancy between the measurement methods. However, we found a Pearson correlation of 0.96 ($p < 0.0005$) between the two sets of measurements, suggesting that results of both measurement techniques are highly correlated with each other.

DISCUSSION

The primary finding of this study is that male musicians have larger anterior midsagittal CC areas than non-musician controls. This replicates our previous finding in a new and independent sample. However, our results also indicate an interaction between gender and musicianship, considering the large anterior CC effect in males but not females.

In comparing our present method to our previous method of CC measurements, we found that our previous methods tended to find slightly larger callosal areas. Of the few MRI studies that have been published reporting group callosal size, the variability of sizes is quite large [18], suggesting that all *in vivo* measurements of CC area are prone to bias of some degree. Our present method using splines to define the outer contour of the CC and measuring the number of voxels within that contour allowed more user control over CC delineation than our previous method, and our results in non-musician control subjects can be externally verified with measurements in other studies (for review see [18]).

Previous studies of the microscopic fiber organization of the corpus callosum provide a context for our findings. It was shown by Aboitiz and colleagues [4] that greater midsagittal CC area correlates with increased density of mid-diameter myelinated axons ($< 2\,\mu m$ diameter); La Mantia and Rakic [19] found that such axons connect higher order cortical processing areas in monkeys. In mapping interhemispheric connections in the rhesus monkey, Pandya and Seltzer [14] found that, in simplified terms, connections between homotopic primary sensorimotor, premotor, supplementary motor, and prefrontal brain regions coursed through the anterior half of the CC, while connections between homotopic parietal, temporal, and occipital brain regions were located in the posterior half of the CC. Lesion research in humans has shown similar topographical organization as the above findings for the rhesus monkey [20]. In light of these studies, our findings of group differences in the anterior CC point to a difference in the interhemispheric connectivity between right and left motor regions in male musicians. The precise underlying microstructural differences in the CC are not known, although it is possible that these differences could be due to more myelinated transcallosal fibers, thicker myelinated fibers, or more axon collaterals in male musicians.

Recently Ridding and colleagues [21] described a neurophysiological correlate of the morphological differences seen in our studies. They found a decreased transcallosal inhibitory effect in musicians compared to non-musician controls [21]. An increase in the interhemispheric facilitatory connections or a change in the net balance of facilitatory and inhibitory connections could be a consequence of our anatomical findings.

Several studies support the proposal that environmental factors during development and maturation of the CC could change the callosal microstructure. It has been shown that the CC is one of the last fiber tracts in humans to become myelinated [5]. *In vivo* imaging has demonstrated increases in callosal size until the middle of the third decade, with the most dramatic growth observed in the first decade [6], a period concurrent with increases in synaptic density and motor coordination, according to studies of children [8,9]. Frost and Innocenti [22] have demonstrated in animal studies that sensory deprivation in the visual domain results in a lower number of callosal connections, but conclude that there are many other factors affecting callosal development; we infer that intense and extended sensorimotor experience can have a similar effect as visual experience, and correspondingly that increased sensorimotor experience can have a positive effect on callosal growth. Similar observations were made in animals [11,23].

An alternative explanation of our results could be that musicians are genetically predisposed to have a larger CC size (and presumably other functional and structural adaptations of the brain) that would make them more likely to acquire musical skills and succeed as a musician. However, noting the vast amount of evidence compiled in animal experiments supporting the idea of structural neuroplasticity [13], we believe that this self-determinate view of group differences is a less likely explanation of the differences observed.

There was a mild, non-significant, trend for female musicians to have smaller anterior and posterior halves of the CC than female non-musicians. This is an interesting and new observation and needs to be explored further in future studies. At this point we can offer two possible explanations for this observed trend. The first explanation might be a confounding due to absolute pitch (AP), for which we did not control; the incidence of absolute pitch among our female musician group was much higher than for the male musician group (18 of 28 *vs* 8 of 28). AP musicians have been shown to have a higher degree of hemispheric lateralization than non-AP musicians and non-musicians [16], and several studies have suggested that CC size varies inversely with degree of lateralization or hemispheric asymmetry; i.e. more symmetrically organized brains tend to have a larger CC [1,2,17,24]. We observed a slight difference in posterior CC size between female non-AP and AP musicians, however, this was not statistically significant.

Another explanation for our sexually dimorphic results in the CC involves the possibility of a more general dimorphism between males and females. There are reports of right-handed females showing increased symmetry or decreased functional lateralization [25] compared with right-handed males; Amunts [25] showed that such symmetry was consistent across right-handed, left-handed, and mix-handed females with regard to a marker of primary motor cortex size. If such increased tendency for a more symmetric brain organization indeed exists in females, we could speculate that female musicians, through intense bimanual training of both the dominant right hand and the non-dominant left hand, might not cause a significant change in lateralization as compared to female non-musicians, thus causing no lateralization-related effect on CC size and therefore no significant difference between musicians and non-musicians. Alternatively, female musicians, through intense bimanual training, might develop their non-dominant left hands enough to deviate from the greater trend towards symmetry presumed normal for females and acquire a trend towards rightward asymmetry, thus developing a smaller CC due to a more asymmetric brain. In right-handed males, on the other hand, with a general tendency towards more leftward lateralization, intense bimanual training would perhaps decrease lateralization by increasing the functional importance of right hemisphere motor systems, thus leading to greater CC size in professional musicians. All of these proposed theories could consistently explain our dimorphic results, and should merit further research.

CONCLUSION

We found a gender $\times$ musicianship interaction in the midsagittal size of the anterior CC; male musicians had larger anterior CC than male non-musicians. This finding replicates the result of our previous study, and based upon anatomical and developmental research, suggests that male musicians might develop greater interhemispheric connectivity and increased hemispheric symmetry between motor areas and other frontal brain regions. The early commencement of intensive instrumental training during critical time periods of callosal development might trigger these differences. Details of the gender-by-musicianship interaction and the possibility of a sexual dimorphism in midsagittal callosal size alterations needs to be explored further in future studies.

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