Cerebellar Volume in Musicians

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Total number of words in text: 4004

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Summary

Animal experiments have found microstructural changes in the cerebellum in response to long-term motor skill activity that include an increase in the number of synapses per neuron, glial cell volume, and capillary density. The sum of those microstructural changes were reported to lead to regional volume changes. We investigated whether professional keyboard players, who learn specialized motor skills early in life and practice them intensely throughout life, have larger cerebellar volumes than matched non-musicians. Total brain volumes and cerebellar volumes were measured using high-resolution T1-weighted MR images from a large prospectively acquired database of musicians and non-musicians, selecting all right-handed professional key-board players (n = 56, 28:26 male:female) and age, gender and height matched non-musicians. To correct for intersubject variability, absolute cerebellar volume (aCV) was related to total brain volume (tBV), after demonstration of a strong correlation between these variables ($r=0.686$, $p < 0.001$), as the relative cerebellar volume (rCV where rCV = aCV/tBV %). A highly significant effect of gender was found for all variables: males having significantly greater tBV and aCV but females having significantly greater rCV, therefore the male and female groups were analyzed separately. A significant difference in rCV ($p<0.025$) was found between the musicians (10.38%, SD 0.64) and non-musicians (9.96%, SD 0.71) in the male group. A significant positive correlation ($r^2 = 0.545$, $p = 0.003$, two-tailed) was found between intensity of practice (average hours/day of practice over lifetime of training) and rCV in the male musician group. In the female group, there was no significant difference noted in rCV and aCV between musicians and non-musicians, however there was a strong trend in tBV difference ($p=0.082$) with the female musicians having greater mean tBV than the female non-musicians.

Although self-section for musicianship by individuals with innate brain structural differences cannot be completely ruled out, finding an association between rCV and greater intensity of practice in male musicians might indicate structural adaptation to long-term motor activity in the human cerebellum. The absence of an effect of musicianship on cerebellar volume in the female group may be explained by a possible ceiling effect in the female group as it is demonstrated that females in general have relatively larger cerebellar volumes than males. An effect of musicianship may be present in other brain regions in the female group considering the strong trend for a difference in absolute brain volume between the female musicians and non-musicians.

Keywords: Music, Musicians, Plasticity, Learning, Morphometry

Introduction

Structural differences exist in the human brain, that correlate with gender, handedness, degree of functional lateralization and special skills (Witelson, 1989; Peters, 1991; Steinmetz et al., 1992; Witelson and Kigar, 1992; Schlaug et al., 1995a,b; Amunts et al., 1997; Witelson et al., 1999; Amunts et al., 2000; Maguire et al., 2000). We, as others, have been particularly interested in the brain structure of musicians, whether it differs from that of non-musicians and whether training could account for these differences (Meyer, 1977; Schlaug et al., 1995a,b; Amunts et al., 1997; Zatorre et al., 1998). The study of musicians offers an unrivaled opportunity to investigate the neural correlates of skill acquisition and retainment and those of unique abilities such as absolute pitch or musical sight-reading. Structural brain differences between musicians and non-musicians have been reported to exist so far in the superior temporal lobe (Schlaug et al., 1995a; Zatorre et al., 1998) corpus callosum (Schlaug et al., 1995b) and motor cortex (Amunts et al., 1997). Behavioral correlates are noted in these studies: increased left-ward asymmetry of the planum temporale is seen in musicians with absolute pitch; larger non-dominant motor cortex is seen in key-board players correlating with higher non-dominant index finger tapping rates and earlier commencement of training; larger anterior corpus callosum in musicians who commence musical training before the age of seven. Functional studies have also found differences between musicians and non-musicians that similarly correlate with a measure of musicianship. The magnitude of the increased cortical representation of the fingers of the left hand in string players (Elbert et al., 1995) and the increased auditory cortical representation for tone perception in musicians (Pantev et al., 1998) compared to non-musician using magnetic source imaging correlated with the age at which these musicians began musical training.

Motor skill acquisition is an essential facet of musicianship. Although debated (Llinas and Welsh, 1993), a large body of evidence from a variety of disciplines suggests that the cerebellum has an integral role in motor skill acquisition (Marr, 1969; Black et al., 1990; Goodkin et al., 1993; Seitz et al., 1994; Kleim et al., 1997; Kleim et al., 1998a; Mauk et al., 1998; Thach, 1998). The cerebellum appears to be particularly important in the early error-driven adaptation phase of motor skill learning (Fiez, 1999; Ito, 2000) and with increasing skill expertise the cerebellum seems to be less active (Seitz et al., 1994; Toni et al., 1998). Such adaptation to error in motor skill acquisition should be an important part of the life-long, daily, practice of a professional keyboard player. A structural imaging investigation in a group of healthy volunteers found that cerebellar volume significantly correlated with fine motor dexterity (Paradiso et al., 1997). Noting the previously reported correlations between certain brain structures and certain musical skills (Schlaug et al., 1995a,b; Amunts et al., 1997; Zatorre et al., 1998), the importance of the cerebellum to motor skill acquisition, and the observation that the cerebellum seems to be activated in a variety of musical tasks (Parsons, 2001), we investigated whether the cerebellar volume of musicians is greater than that of non-musicians and whether there is a correlation between volume measurements and training intensity parameters.

Subjects and Methods

Subjects

The data was derived from a prospectively acquired database of musicians and non-musicians. In a retrospective analysis we selected all right-handed keyboard players who had complete data sets of their biographical information including lifelong practice times. Fifty-four right-handed keyboard players were identified (28 male and 26 female). They were matched for handedness, gender, approximate height and age to non-musicians from our database. The subjects classified as musicians had to be professional, classically trained keyboard players and the subjects classified as non-musicians had never received formal musical training or played a musical instrument. Twenty-three of the 54 musicians played a string instrument in addition to the piano. Only subjects that were consistently right-handed according to hand preference questionnaires (Annett, 1970; Witelson and Kigar, 1992) and an index finger tapping test (Peters and Durding, 1978) were included in the analysis. Demographic information including a medical history was gathered from each subject. All subjects were considered healthy after a history and examination at the time of imaging. A musical background questionnaire was used to record the age of commencement of musical training, number of years of practice and intensity of lifelong practice (self estimates of the hours of practice per day for each five year interval from the age of commencement, averaged over the number of years of practice to give a lifetime average hours per day). This questionnaire included further questions addressing the acquisition and practice of other motor skills such as sports and typing.

Informed consent was obtained from each subject according to the declaration of Helsinki and the protocol and consent process was approved by the Institutional Review Boards of the Beth Israel Deaconess Medical Center, Boston, and the University of Duesseldorf, Germany.

Methods

All subjects underwent high resolution "anatomical" imaging of the brain using a T1-weighted MR sequence (1 mm^3 voxel size) with sagittal slice orientation (160 slices) on a 1.5 Tesla Siemens Vision MR scanner. Using custom made software implemented in the Advanced Visualization Systems (AVS) software package on Hewlett Packard workstations, MR images were segmented into brain and non-brain tissue (skull and meninges) for whole brain and cerebellar volumetric measurement using a sobel based detection and region growing technique, leading to an image that contained only skull, scalp and meninges. This image was subtracted from the original image, and region growing was applied to this subtraction image to create a new image, representing purely brain without any scalp and skull (Huang et al., 1993; Peters et al., 2000). Regions of interest consisting of at least 30 voxels were drawn in the lateral ventricles and in the 4th ventricle. Regional means and standard deviations were determined from these regions of interest containing CSF. An intensity value consisting of the mean plus two standard deviations of these regions was used as a threshold to separate CSF from brain. The cut-off between the brainstem and spinal cord was the last horizontal slice containing cerebellum. The total segmented brain consisted of the forebrain, cerebellum and brainstem. The cerebellum was segmented manually from the brainstem and cerebellar peduncles using established anatomical landmarks and criteria (Courchesne et al., 1989; Press et al., 1989) similar to those adopted in previous volumetric studies of the cerebellum (Filpek et al., 1994; Luft et al., 1998).

The cerebellar peduncles were removed from the cerebellar white matter in two stages. Initially, on lateral slices on either side, a perpendicular line was drawn from the point where the superior cerebellar peduncle and cerebellar cortex intersect to the anterior tip of the inferior part of the cerebellar hemisphere. Then, on medial slices (those including brainstem), a straight line was drawn from the superior cerebellar peduncle and the cerebellar cortex intersection point to the most dorsal extension of the caudal medulla. The final segmented cerebellum consisted of the cerebellar hemispheres, deep nuclei and vermis (Figure 1).

Two raters (G.S. and L.H.L.L.), blinded to the identity of the subjects, selected 20 cases randomly from the total 108 cases to define and agree on the above landmarks. Following this process, the inter-rater reliability (Pearson correlation coefficient) for segmented cerebellar volumes on a further 15, previously unselected, brains was found to be 0.92 (two-sided $p < 0.01$). After this only one of these investigators, blinded to subject identity (gender and group), segmented all 108 cases.

Data analysis

Cerebellar volume was normalized to reduce intersubject variability. Correlations (bivariate Pearson correlations with two-tailed tests of significance) were tabulated between a) absolute cerebellar volume (aCV) and total brain volume (tBV) and b) aCV and body height in order to determine whether tBV or height should be selected to correct for inter-subject variability in cerebellar volume due to these factors. There was a high correlation between aCV and tBV ($R2=0.686$, $p < 0.001$) and a lower correlation ($R2=0.335$, $p = 0.001$) between aCV and body height (two-tailed, Pearson Correlation). Therefore we chose to normalize aCV to tBV in order to partial out the inter-subject variability in tBV as a source of variance in aCV measurements, by calculating a relative cerebellar volume (rCV) in each subject as a percent ratio of their total brain volume, where rCV (%) = aCV/tBV x 100. There is precedence in selecting brain volume or weight rather than body height to normalize brain morphometric data (Passingham, 1979; Witelson, 1989; Peters, 1991; Steinmetz et al., 1995).

Three two-by-two (gender x musicianship) factorials were performed. Post-hoc testing employed Bonferroni adjusted comparisons for the planned comparisons, using adjusted Students t-tests. The main effects were significant for gender in terms of tBV and aCV as has been previously described (Nopoulos et al., 2000; Raz et al., 2001). All p values reported are two-tailed. Similarly, Bonferroni adjusted Students t-tests were employed to assess whether the male and female musician groups differed in any of the measures of musicianship recorded from the questionnaire, namely, age of commencement of training, number of years of practice and lifelong intensity of practice. Furthermore we compared the biographic data within each gender group to determine whether there was a difference between musicians and non-musicians in body length and age. This would indicate how well matched the groups were.

Bivariate Pearson correlations with two tailed tests of significance were then performed within the male and female musician groups in order to assess the relationship between tBV, aCV and rCV and age of commencement of training, number of years of practice and intensity of lifelong practice.

Results

Male and female musician group means in tBV, aCV, rCV, height and age between the musicians and non-musicians are noted in Table 1. There was no significant difference within the genders across musicianship for height or age (all p's >0.05). A series of two-way factorials were performed across tBV, aCV, and rCV with musicianship and gender as factors. In terms of tBV, there was no significant interaction ($F(1,104)=0.091$, $p>0.05$), or effect for musicianship ($F=1.75$, $p>0.05$), but there was a significant effect for gender ($F=43.46$, $p<0.0005$) with males having a greater tBV than females. For aCV, there was also no significant interaction ($F=1.05$. $p>0.05$) or main effect for musicianship ($F=3.57$, $p>0.05$). Again a significant effect was found for gender ($F=11.37$, $p<0.001$), with males having a greater aCV than females. An analysis of rCV revealed a significant gender by musicianship interaction ($F=5.27$, $p<0.02$). It is noted that there was also a significant main effect for gender as well ($F=9.02$, $p<0.003$), with females having a greater rCV than males. (Table 1 near here)

Employing planned comparisons, the nature of the interaction was examined within each of the genders. In the female group, it was found that there was no significant difference between the musicians and the non-musicians ($p>0.05$). In the male group there was a significant difference in rCV ($p< 0.025$) between the musicians (10.38%, SD 0.64) and non-musicians (9.96%, SD 0.71) (Figure 1). There was a borderline significant difference ($p=0.055$) between the aCV of the male musicians (146.33 cc, SD 9.58) and non-musicians (139.92 cc, SD 14.37). Male musicians did not differ significantly from male non-musicians in tBV, height or age. (Figure 1 near here)

In the female group, there was no significant difference noted in aCV, rCV, height or age between the musicians and non-musicians. There was a trend for a significant difference ($p = 0.082$) in tBV between the female musicians (1,308.40 cc, SD 92.34) and non-musicians (1,266.61 cc, SD 76.66) despite the fact that female musicians were on average 3cm smaller in height than non-musicians ($p=0.209$).

A significant positive correlation ($r^2 = 0.545$, $p = 0.003$) was found between intensity of practice and rCV in the male musician group (Figure 2). Age of commencement of training and total years of musical training were not significantly associated with rCV in the male musicians. There was no significant correlation found in the female musician group or the whole musician group. In the female musician group there was a small, non-significant, positive trend between intensity of practice ($r^2 = 0.037$. $p = 0.8$) and tBV. Also a small, non-significant, negative trend was found between age of commencement of training ($r^2 = - 0.053$, $p = 0.79$) and tBV in this group (younger age associates with larger tBV). There was no significant differences noted between the male and female musician group in total years of musical training and intensity of practice; age of commencement showed a small significant difference with the female music group starting slightly earlier than the male group (Table 2). (Figure 2 and Table 2 near here)

Discussion

Through morphometric analysis of total brain and cerebellar volume using high resolution MRI, we demonstrated that the male musician group had significantly larger rCV than the non-musician group. The difference in rCV between male musicians and non-musicians is approximately 3.9 % (mean rCV of 10.38 % in male musicians compared to rCV of 9.96% in male non-musicians). There was no difference in total brain volumes and there was a trend in aCV difference between the male musicians and non-musicians supporting the main finding of significantly greater normalized cerebellar volumes, rCV, in the male musicians. For the male musician group, there was a significantly positive correlation between the intensity of practice throughout life and rCV indicating that male musicians who had a greater number of hours per day of musical training had larger rCV. There was a small negative trend between age of commencement of musical training and a small positive trend between the number of years of training and rCV in the male musician group suggesting the younger a musician began training and the longer he trained for then the larger the rCV. Other studies have found correlations between the age of commencement of musical training and the degree of functional or structural difference that was found between musicians and non-musicians (Elbert et al., 1995; Schlaug et al., 1995a; Amunts et al., 1997; Pantev et al., 1998). A longitudinal study is required to definitively establish causal relationships between function and structural change although our study provides regional hypotheses for such investigations.

The finding of significantly greater rCV in male musicians and the positive correlation between rCV and a measure of intensity of training must be viewed in the context of the proposed role that the cerebellum plays in both motor (Thach, 1998) and cognitive (Leiner et al., 1995; Schmahmann and Sherman, 1998) skill learning. Evidence supporting the importance of the cerebellum to motor learning includes physiological experiments characterizing cerebellar long-term depression in conditioned eye-lid responses (Mauk et al., 1998), experiments on motor skill learning in animals (Black et al., 1990; Kleim et al., 1997; Anderson et al., 1994), on motor skill adaptation and performance in patients with cerebellar disease (Goodkin et al., 1993, Pascual-Leone et al., 1993; Martin et al., 1996) and functional imaging studies of complex motor sequence learning (Seitz et al., 1994; Toni et al., 1998). The cerebellar network that was recognized as ideal for motor learning (Marr, 1969) may also support a specific type of cognitive learning where initially effortful tasks are converted to automatic tasks through a repetitive process of trial and error (Fiez, 1999; Ito, 2000). The cerebellar involvement in cognitive skill has been supported by neuroimaging (Kim et al., 1994), anatomical (Middleton and Strick, 1994) and lesion (Fiez, 1992; Schmahmann and Sherman, 1998) data. Furthermore, cerebellar activation has been seen in a variety of musical tasks (Parsons, 2001). Only one morphometric study has correlated cerebellar volume with a marker of learning (Woodruff-Pak et al., 2000). Here, relative cerebellar volume in eight elderly subjects, chosen because age-induced atrophy would introduce variability in cerebellar volume, strongly correlated with the strength of the eyeblink conditioned response.

Similar to other structure-to-function correlations (Witelson, 1989; Witelson and Kigar 1992; Schlaug et al., 1995a,b; Amunts et al., 1997; Zatorre et al., 1998; Amunts et al., 2000; Maguire et al., 2000), we are unable to determine whether the structural difference (cerebellar volume) exists as a result of the difference in function (intensity of practice) or whether the structural difference enabled the difference in function to arise. However, there is evidence from animal studies that differences in behavior can lead to structural changes in the cerebellum. Adult rats following 30 days of acrobatic training with low activity demands (motor skill learning animals) had a greater number of synapses per Purkinje cell, greater stellate cell dendritic arborizations, greater volume of molecular layer per Purkinje cell and greater volume of glia per Purkinje cell than those who repetitively performed a simple task with high activity demand (motor exercise animals), in whom there was a greater density of capillaries in the molecular cell layer (Black et al., 1990; Anderson et al.,1994; Kleim et al., 1997; Kleim et al., 1998a). An earlier study of exercising late post-natal mice had similar results and quantified that the molecular layer was 10% larger in area and depth in active compared to inactive infant mice (Pysh and Weiss, 1979). These animal studies demonstrate that motor skill learning is associated with synaptogenesis and an increase in glial volume in the cerebellum. It has been demonstrated that glial cells induce and stabilize CNS synapses, regulate CNS synapse number and may participate in synapse plasticity (Ullian et al., 2001). The sum of such microstructural changes in synapse number and glial volume in these skill-learning animals may amount to the macrostructural volume differences we have documented in the cerebellum of musicians. It is of interest to note that in the same skill learning animals an increased density of synapses per neuron in the primary motor cortex was associated with a reorganization of motor cortical movement representation (Kleim et al., 1996; Kleim et al., 1998b). Similar motor cortical reorganization is seen following motor skill acquisition in humans (Pascual-Leone et al., 1994), although whether this functional change is associated with structural change as seen in these animals is unknown.

The effect of musicianship on the rCV was only significant in the male subgroup and was seen in neither the female subgroup nor, therefore, the whole group. The absence of an effect in the female subgroup may be attributed to two interesting findings from this data, firstly that the female group as a whole had a significantly larger rCV than the male group and secondly that the female musicians, while not having a significant difference in rCV or aCV from the female non-musicians did have a trend for a difference in tBV.

The female group as a whole had a significantly smaller tBV and aCV, a finding that has been reported in many other morphometric studies (Escalona et al., 1991; Filpek et al., 1994; Steinmetz et al., 1995; Luft et al 1998; Nopoulos et al., 2000; Raz et al., 2001). However our results show a significantly larger rCV in the female group compared to the male. It is not apparent why the cerebellum would be relatively larger in females. Functional imaging and behavioral studies have explored the relationship between gender and cognitive skills (Shaywitz et al., 1995) and gender differences in brain morphometry have been associated with differences in function (Witelson, 1989; Witelson and Kigar, 1992; Steinmetz et al., 1992; Amunts et al., 2000). Although some differences in motor skill have been associated with gender (Nicholson and Kimura, 1996), gender effects on cerebellar function have not been examined. Two studies of resting cerebellar metabolism have noted significant gender differences (Volkow et al., 1997; Gur et al., 1995) but have divergent results. Gender could influence skill acquisition and brain morphometry through hormonally mediated mechanisms, estrogen has been noted in animals to increase synaptic density (Woolley and McEwen, 1992) and to facilitate long-term potentiation (Cordoba Montoya and Carrer, 1997) in the hippocampus. Estrogen receptor expression peaks at the initiation of axonal and dendritic growth in rat Purkinje cells during post-natal development (Jakab et al., 2001).

Females, unlike males, reach adult cerebellar volume earlier in childhood (Caviness et al., 1996). If, as our data indicates, the female cerebellum is relatively larger than the male, skill acquisition and long-term motor activity effects on cerebellar volume may reach a ceiling in females that we do not see in males. The effect of skill acquisition in the female musicians therefore may be seen outside the cerebellum in other brain regions. In support of this our data shows a trend for a larger tBV in the female musicians compared to non-musicians and in the female musician group there is a small, non-significant, trend between tBV and intensity of practice and earlier commencement of training.

In conclusion, this study finds a significant difference in relative cerebellar volume between male musicians and non-musicians. Relative cerebellar volume correlates positively with intensity of musical training throughout life in the musician group. There is a strong effect of gender on relative cerebellar volume and therefore the effect of musicianship on cerebellar volume may reach a ceiling in the female group. The female musicians show a trend to larger total brain volumes, indicating that structural differences as a function of musicianship may be found outside the cerebellum in females. This finding adds to others (Elbert et al., 1995; Schlaug et al., 1995a,b; Amunts et al., 1997; Pantev et al., 1998; Zatorre, 1998) which demonstrate structural and functional differences between the brains of musicians and non-musicians that positively correlate with early commencement of musical tuition, although no prior study has found a correlation with training intensity. Based on this correlation and inferences from animal studies, we would propose that the brain structural differences found in musicians are more the result of adaptation to the rigors of musical training, perhaps at a critical period of brain development, rather than the innate properties of a group of individuals who self-select themselves at an early age to become musicians (Zheng and Purves, 1992; Stryker, 1995).

Acknowledgements

This work was in part supported by an IFMR grant and by a Doris Duke Clinical Scientist Development Award to Dr. Schlaug. Dr. Hutchinson is supported by a Clinical Investigator Training Program (CITP) fellowship from Beth Israel Deaconess Medical Center – Harvard/MIT Health Sciences and Technology, in collaboration with Pfizer Inc. We thank Julian Keenan PhD for help with the statistical analysis.

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	Height	Age	tBV	aCV	rCV
Males (56)	181.03* (6.43)	25.96 (4.45)	1,408.57* (102.38)	143.12* (12.52)	10.17+ (0.69)
Females (52)	166.01* (6.69)	23.80 (5.07)	1,287.50* (86.63)	135.70* (10.45)	10.55+ (0.65)
Male Non-Musicians (28)	180.89 (6.37)	25.43 (4.62)	1,405.17 (120.03)	139.92# (14.37)	9.96+ (0.71)
Male Musicians (28)	181.18 (6.41)	27.10 (6.34)	1,411.97 (84.54)	146.33# (9.27)	10.38+ (0.63)
Female Non-Musicians (26)	167.19 (6.05)	24.07 (4.97)	1,266.61# (76.66)	134.75 (11.36)	10.64 (0.66)
Female Musicians (26)	164.85 (7.20)	23.54 (5.26)	1,308.40# (92.34)	136.66 (9.58)	10.47 (0.64)

Table 1: Means (+/-SD) for the following variables: Height (cm), Age at MRI scan (years), tBV (in cc), aCV (in cc), rCV (% of absolute brain volume) in the groups studied (n =). Significant differences: * $p<0.001$, + $p<0.05$. # comparisons where a trend was found for differences between musicians and non-musicians: aCV between male musicians and non-musicians ($p = 0.055$) and tBV between female musicians and non-musicians ($p = 0.082$).

	Age of commencement	Intensity of practice	Years of practice
Male musicians (28)	6.48 (2.02)+	2.52 (1.00)	19.67 (5.98)
Female musicians (26)	4.67 (1.83)+	2.27 (1.13)	19.44 (4.87)

Table 2: Mean (+/- SD) for the following variables for the musician subgroups (n =): Age of commencement of musical training (years of age); Intensity of practice (average hours per day over lifetime of practice); Years of practice (years of practice since commencement of musical training). + Significant difference $p < 0.005$.

Figure 1

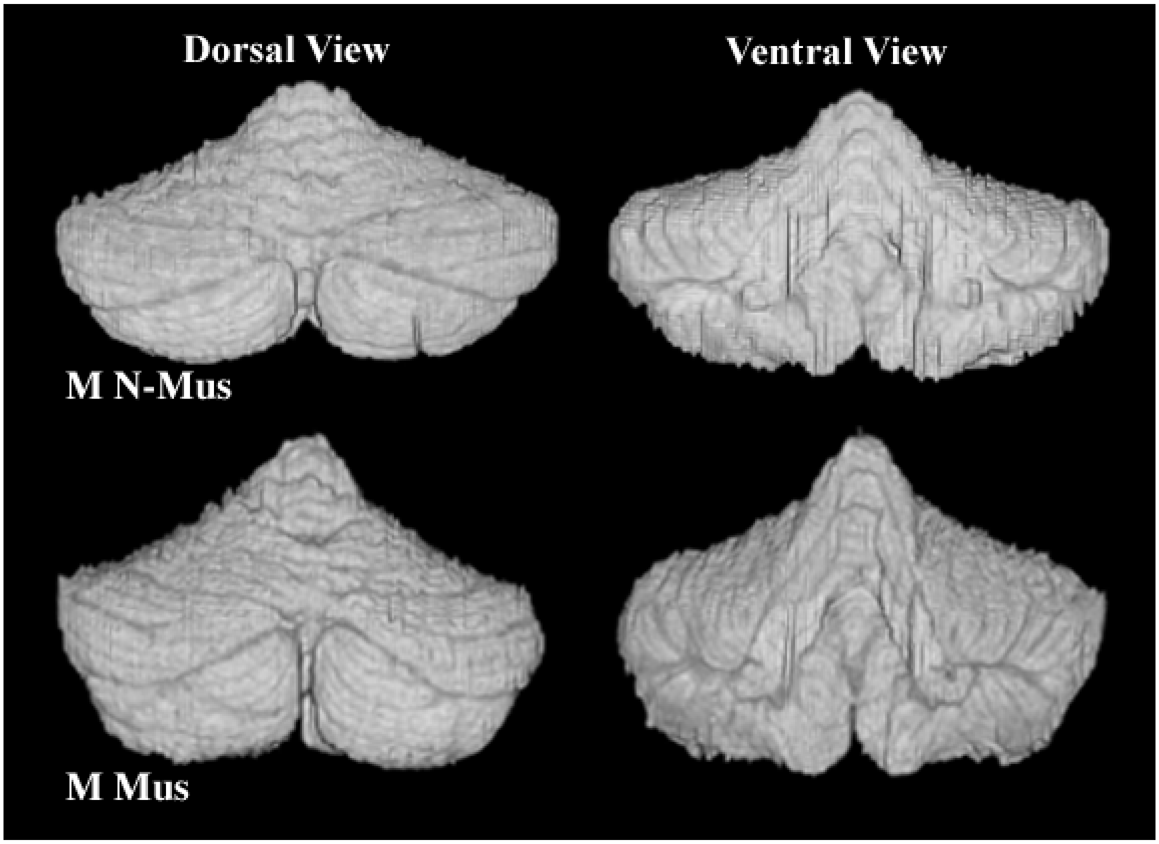

Figure 1: Cerebellar volume differences were found between the male musicians (MMus) and male non-musicians (MN-Mus). Figure 1 shows a typical example for each group.

Figure 2

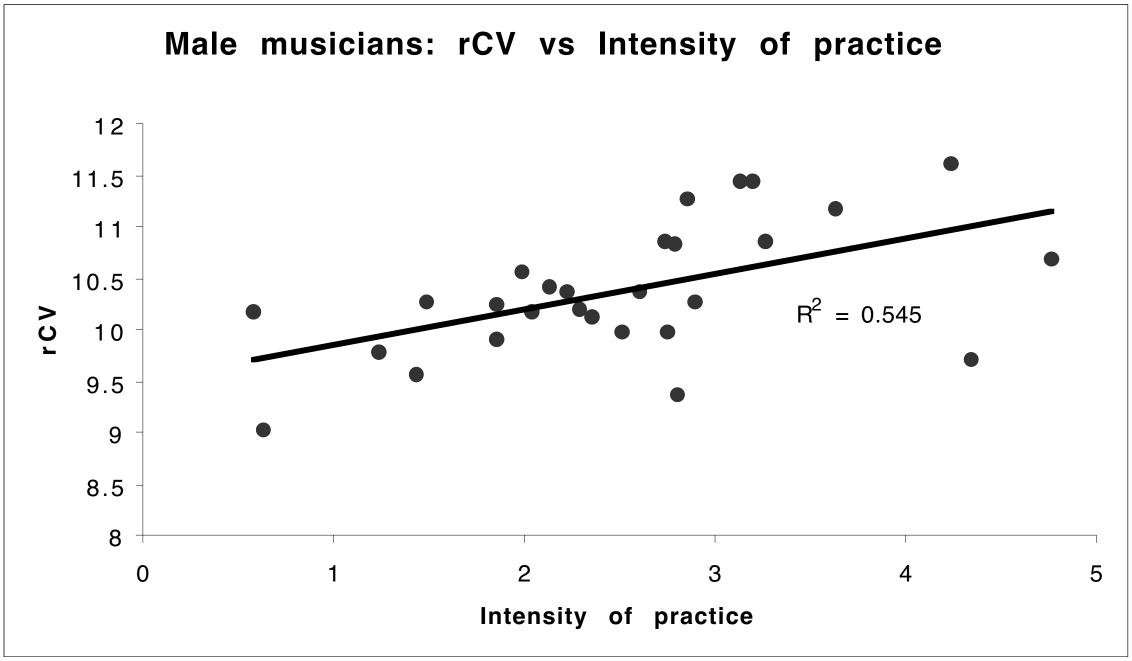

Figure 2: Plot of rCV (%) vs Intensity of Practice (hours/day averaged over lifetime) for the male subgroup. The correlation is significant ($r^2 = 0.545$, p=0.003).