

ORIGINAL ARTICLE

Modulation of Functional Connectivity in Auditory–Motor Networks in Musicians Compared with Nonmusicians

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Abstract

Correlation of spontaneous fluctuations at rest between anatomically distinct brain areas are proposed to reflect the profile of individual a priori cognitive biases, coded as synaptic efficacies in cortical networks. Here, we investigate functional connectivity at rest (rs-FC) in musicians and nonmusicians to test for differences in auditory, motor, and audiomotor connectivity. As expected, musicians had stronger rs-FC between the right auditory cortex (AC) and the right ventral premotor cortex than nonmusicians, and this stronger rs-FC was greater in musicians with more years of practice. We also found reduced rs-FC between the motor areas that control both hands in musicians compared with nonmusicians, which was more evident in the musicians whose instrument required bimanual coordination and as a function of hours of practice. Finally, we replicated previous morphometric data to show an increased volume in the right AC in musicians, which was greater in those with earlier musical training, and that this anatomic feature was in turn related to greater rs-FC between auditory and motor systems. These results show that functional coupling within the motor system and between motor and auditory areas is modulated as a function of musical training, suggesting a link between anatomic and functional brain features.

Key words: auditory cortex, brain plasticity, music, resting state, voxel-based morphometry

Introduction

Musical learning is an excellent model to study how auditory–motor networks are related to musical training both structurally and functionally (Zatorre et al. 2007; Herholz and Zatorre 2012). Previous studies have reported evidence that acquiring musical performance skills is associated with functional and structural changes in the brain (Bermudez et al. 2009; Elmer et al. 2012, 2013; Putkinen et al. 2014). Differences in gray matter (GM) volume, surface area, and cortical thickness in different parts of auditory cortices (Heschl's gyrus and planum temporale) have

been reported in whole-brain analyses in cross-sectional (Schneider et al. 2002; Gaser and Schlaug 2003; Bermudez et al. 2009; Elmer et al. 2013) and longitudinal studies (Hyde et al. 2009). Foster and Zatorre (2010) also found that anatomic features of the right auditory cortex (AC) were correlated with improved performance in a musical task, thereby linking structure to behavioral advantage. Besides auditory areas, increases in GM volume have also been identified in several motor and premotor areas in relation to musical training (Sluming et al. 2002; Gaser and Schlaug 2003; Bermudez et al. 2009). More specifically, Bailey

et al. (2014) found differences in GM organization between early-trained and late-trained musicians in the right ventral premotor cortex (vPMC). In the same study, the GM volume from the right vPMC correlated with synchronization accuracy during a rhythm reproduction task. Right vPMC is of interest because it has been related to sensorimotor integration in both neurophysiological and functional imaging studies (Hoshi and Tanji 2007; Zatorre et al. 2007; Chen et al. 2009). Specifically, several authors have proposed that the ventral premotor area plays a critical role in music for which one has an associated motor program (Lahav et al. 2007; Zatorre et al. 2007; Herholz et al. 2015).

In parallel with these GM structural differences, previous diffusion tensor imaging (DTI) studies have also assessed training-related differences in white matter (WM) structures, including the corpus callosum (CC) and the arcuate fasciculus (AF). Inter-hemispheric information transfer, mediated by the CC, has been shown to play an important role in bimanual coordination (Swinnen 2002), which is relevant for musicians because of the bimanual coordination demands that their instruments imply. Research has shown that variation in WM integrity in the CC is related to bimanual coordination (Johansen-Berg et al. 2007). In keeping with this idea, studies have shown that the surface area of the anterior CC is greater in musicians (Schlaug et al. 1995), and more specifically that fractional anisotropy (FA) in the CC regions that interconnect motor cortices is higher in musicians who began training early (Steele et al. 2013). A recent study by Vollmann et al. (2014), which used paired-pulse transcranial magnetic stimulation to the primary motor cortex, compared differences between early-trained musicians and nonmusicians in terms of the amount of interhemispheric inhibition (IHI). They found stronger left-to-right IHI in musicians when compared with nonmusicians, which suggests that IHI is affected by the bimanual demands of musical instruments because the effect was stronger in string players, who move their arms, hands, and fingers more independently than other musicians.

A second relevant fascicle in musical training is the AF, a prominent WM tract that connects the middle and superior temporal gyrus with premotor regions that has been proposed to participate in audiomotor processing in language and music (Saur et al. 2008; Halwani et al. 2011). Halwani et al. (2011) reported differences in the macrostructure (tract volume) and microstructure (as indexed by FA) of the AF in singers, instrumentalists, and non-musicians. Both groups of musicians had a larger volume and obtained higher FA values in the AF compared with nonmusicians (bilateral effect for singers and lateralized on the right for instrumentalists).

Coordination between auditory and motor systems is necessary for music performance (Pantev et al. 2001; Bangert and Altenmüller 2003; D'Ausilio et al. 2006; Lahav et al. 2007; Zatorre et al. 2007; Jäncke 2012). When learning to play an instrument, the association of motor action with specific sound while receiving auditory feedback is used to guarantee that each note is correctly produced. Previous studies with musicians and people without musical training who learn to play a melody have reported that listening to certain rhythmic patterns activates motor brain regions, and that playing a silent piano keyboard activates auditory regions (Bangert et al. 2006; Baumann et al. 2007; Lahav et al. 2007; Chen et al. 2008, 2009; Herholz et al. 2015). It is noteworthy that Chen et al. (2008, 2009) found activation in the vPMC, but only when sounds were relevant for the motor system, whereas activation of the dorsal premotor cortex was found for all the conditions, but was sensitive to metrical structure. This indicates a relative dissociation between the

dorsal and ventral components of the PMC. Finally, increased auditory-motor coupling during task performance in musicians has also been reported (Chen et al. 2008; Grahn and Rowe 2009).

In short, musical training has been associated with stable changes in the brain: increased audiomotor connectivity and increased IHI. Consequently, it might be expected that training should not only affect those systems separately, but also that it should cause stable, coordinated changes to the brain, which affect the functional connectivity between auditory and motor areas, and also between the motor areas that control the 2 hands.

In the present study, we investigated this question using both anatomic measures and resting-state functional magnetic resonance imaging (rs-fMRI). Rs-fMRI is based on spontaneous low frequency fluctuations (<0.1 Hz) in the blood oxygen level-dependent signal (Biswal et al. 1995) and represents patterns of brain activity in the absence of an external task. These fluctuations are organized in a limited number of brain networks, which are often referred to as resting-state networks (RSNs; Beckmann et al. 2005; Damoiseaux et al. 2006; Shehzad et al. 2009). This approach provides a new tool to examine the coactivation between functional time-series of anatomically separated brain regions independently of any task-related activity. The relevance of these networks lies in the concept that functional communication between brain regions is important to perform cognitive processes that integrate information across different brain regions; therefore, correlations within and between brain areas at rest should be of behavioral significance (Harmelech and Malach 2013; Guerra-Carrillo et al. 2014). In recent years, the investigation of RSNs has gained increasing attention. It is now widely believed that neural activity during rest reflects functionally meaningful activity rather than noise per se (Damoiseaux et al. 2006; Deco and Corbetta 2011; Scheeringa et al. 2012; Sadaghiani and Kleinschmidt 2013). Evidence shows that the activity in the resting state may reflect the repeated history of coactivation within or between brain regions, which may, in turn, be a predictor of efficiency while performing cognitive tasks depending on these areas. For example, perceptual discrimination ability has been related to connectivity within visual networks (Baldassarre et al. 2012), and fluid intelligence and working memory have been related to frontoparietal connectivity (Cole et al. 2012). Changes in rs-fMRI connectivity have also been reported in cross-sectional studies by comparing effects of expertise, such as experienced meditators (Taylor et al. 2013) and expert athletes (Di et al. 2012). Individual differences in rs-fMRI connectivity have also been linked to behavioral abilities, such as learning new sounds of speech (Ventura-Campos et al. 2013). Thus, functional connectivity at rest (rs-FC) can reflect the impact of learning on the brain.

Some recent studies have been designed to investigate possible stable functional differences in audiomotor connectivity at rest as a result of musical training. Using different seeds in sensory and motor areas of the left hemisphere, Luo et al. (2012) employed rs-fMRI to investigate differences between pianists and controls. Their results in AC showed only that musicians had more connectivity between the left AC and the cerebellum. However, regions of interest (ROIs) were not selected as specifically relevant to music processing. In a more recent study, Fauvel et al. (2014) used a voxel-based morphometry (VBM) analysis and compared musicians and nonmusicians to select relevant ROIs (all in the left hemisphere), which were used to run a seed-based analysis to examine rs-fMRI differences. The results showed that a seed located in the left AC correlated strongly in musicians to several areas, including the left premotor area. Finally, a recent EEG study conducted with string players found increased connectivity at rest between the left and the right AC,

and also between the left AC and the right sensorimotor cortex (Klein et al. 2016). These increased FC values also correlated with musical processing and practice in the musician group.

The present study uses different methodologies to investigate possible FC differences at rest in right and left audiomotor hemispheres as well as within the motor system. Concretely, we used rs-fMRI, along with anatomic MRI (1) to investigate the anatomic correlates of the predicted auditory and motor interactions in musicians compared with nonmusicians; (2) to analyze the functional interactions between auditory and motor regions, and (3) to study the influence of musical training on intrinsic connectivity in the sensory–motor network (SMN) and auditory network. We focused on Heschl's gyrus as a relevant auditory region and on the right vPMC as the relevant motor area because it has been proposed to mediate the direct transformation of sound into movements (Chen et al. 2009). We hypothesized that musicians, as opposed to nonmusicians, will exhibit: (1) greater GM volume in auditory and motor regions; (2) increased FC between the AC and the premotor cortex in resting state; (3) changes in the RSNs implicated in the trained domain, namely auditory network and SMN; and (4) that all these effects will be stronger in musicians with longer and earlier musical training.

Materials and Methods

Participants

Thirty-four healthy participants were recruited for this study. Seventeen participants formed the musician group (7 women, mean age 22.9 years old, standard deviation (SD); ± 2.7) and 17 were included in the nonmusician group (10 women, mean age 21.9 ± 1.8 years old). Musicians were those who currently play or musical students who enrolled in a musical degree program (age of commencement of training 8.3 ± 1.6 years, range = 6–10; mean formal training 10 ± 2.5 years, range = 7–14; mean current practicing time per week was 12.8 ± 9.9 h, range = 4–25). A detailed self-reported history of musical training was also obtained from each subject. It included estimates of practice hours per week for each phase of the participant's musical activities. This information was used to calculate cumulative lifetime practice hours. The most common primary instruments were piano and wind instruments (such as clarinet, saxophone, transverse flute, and trumpet). The nonmusicians had never played a musical instrument and they had received no musical training beyond normal school education. There were no statistically significant between-group differences in gender or age ($P > 0.10$). All the participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). None of them had suffered any neurological or psychiatric disorders and had no history of head injury with loss of consciousness. Written informed consent was obtained from all the participants, following a protocol approved by the Universitat Jaume I, and they received monetary compensation.

Image Acquisition

Images were acquired on a 1.5-T Siemens Avanto (Erlangen, Germany). A 3D structural MRI was acquired for each subject using a T_1 -weighted magnetization-prepared rapid gradient-echo sequence [time repetition/time echo (TR/TE) = 2200/3.8 ms, matrix = $256 \times 256 \times 160$, voxel size = $1 \times 1 \times 1$ mm]. For the rs-fMRI, 270 volumes were recorded over 9 min using a gradient-echo T_2^* -weighted echo-planar imaging sequence (TR/TE = 2000/48 ms, matrix = 64×64 , flip angle = 90° , slice thickness = 4 mm, slice gap = 0.8 mm). Twenty-four interleaved axial slices were acquired, aligned to the

plane that intersected the anterior and posterior commissures (AC–PC) and covered the whole brain.

Voxel-Based Morphometry Analyses

VBM was used, as implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) for the SPM8 package (Wellcome Department of Imaging Neuroscience, London, UK).

The preprocessing steps were based on the New Segment Toolbox using the Tissue Probability Maps of SPM8. T_1 -weighted images were classified into GM, WM, and cerebrospinal fluid (CSF). They were recorded in a standard template provided by the International Consortium of Brain Mapping (ICBM) using 12-parameter affine transformations. The GM and WM segments were inputted into DARTEL to create a customized DARTEL template of all the subjects. Voxel values were modulated by the non-linear components that derived from normalization (voxel size 1 mm^3); thus, the volume variations that resulted from normalization were corrected on the resulting GM volume maps. Modulation by linear components was not performed to account for the individual global brain size differences in the subsequent analyses (<http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/>). Finally, spatial smoothing was conducted by applying an 8-mm Gaussian Kernel.

Group differences in GM volume were evaluated by a two-sample t-test analysis using an absolute threshold of 0.14 to obtain results only for GM. Following recent recommendations to avoid false positives in MRI analyses (Woo et al. 2014), the statistical criterion was set at $P < 0.05$, family-wise error (FWE) cluster-corrected for multiple comparisons (voxel-level uncorrected threshold of $P < 0.001$, minimum cluster size of 756 voxels).

Finally, we extracted the GM volume (ml) for the structural data at the local maxima between musicians and nonmusicians, which were inputted in the correlation analyses, along with age at which training began, cumulative lifetime practice hours, and years of training to evaluate whether there was a significant relationship between the differences in GM volume and musical training. The IBM SPSS program was employed for this purpose.

Resting-State Analyses

We used the Data Processing Assistant for Resting-State Toolbox (DPARSFA, <http://rfmri.org/DPARSF>; Chao-Gan and Yu-Feng 2010) to carry out resting-state MRI data processing. Preprocessing included the following steps: (1) slice-timing correction for interleaved acquisitions (the 23th slice was used as the reference point); (2) head motion correction where the images are registered to the mean of the images after registering to the first image in the series; (3) T_1 coregister to functional; (4) new segmentation to Dartel; (5) removal of spurious variance through linear regression: 6 parameters from the head motion correction, the global mean signal, the WM signal, and the CSF signal; (6) spatial normalization to the Montreal Neurological Institute (3 mm^3); (7) spatial smoothing with a 4-mm full-width at half-maximum Gaussian Kernel.

Additional steps were carried out in the preprocessing for the seed-based rs-FC analysis: (8) removal of the linear trend in the time-series; (9) band-pass temporal filtering (0.01–0.08 Hz) to reduce the effect of low frequency drift and high frequency noise (Biswal et al. 1995; Lowe et al. 1998).

The resting-state analyses were performed with 2 methods: (1) seed-based resting-state functional connectivity (seed-based rs-FC) and (2) an independent component analysis (ICA).

The ICA analysis was carried out without Step 5 and additional steps.

Seed-Based rs-FC Analysis

We tested the relationship between the auditory and motor areas using the right AC region of interest obtained in the VBM results, and its left-hemispheric homolog, together with the right vPMC ($x = 50, y = 8, z = 24$) area, with coordinates based on Bailey et al. (2014) and the homologous vPMC area in the left hemisphere. The seed regions were created by employing spherical ROI centering on the local maxima peak with a radius of 8 mm.

The mean time course of all the voxels in each seed region was used to calculate pairwise linear correlations (Pearson's correlation). Individuals' r values were normalized to z values using Fisher's z transformation. To analyze the changes in the rs-FC between groups, we performed a two-sample t -test on the z -value with the IBM SPSS Statistics Software. So as to analyze the effect of the 4 rs-FC measures between groups, a multivariate analyses of variance (MANOVA) was conducted. The model assumption was met, including independence of observations and homogeneity of variance and of the covariance matrices as measured by the Levene test and the Box's M test, respectively.

We also performed Pearson's correlation analysis with the z -values obtained for the rs-FC between the seeds regions with: (1) age at which training began; (2) cumulative lifetime practice hours; (3) years of training, and (4) GM volume (ml) of right AC by the IBM SPSS program.

Independent Component Analysis

Group resting-state studies (Beckmann et al. 2005; Damoiseaux et al. 2006; Shehzad et al. 2009) have reported that the spontaneous activity measured by rs-fMRI is organized into a limited number of brain networks, which are often referred to as RSNs. We selected the 2 most relevant ones, according to our hypotheses, for the analysis: The auditory network and the SMN.

An ICA was run using a group ICA from the fMRI toolbox (GIFT) software (<http://icatb.sourceforge.net/groupica.htm>). Previous studies have shown that a high model order ICA produces a refined independent component (IC) associated with known anatomic and functional segmentation (Kiviniemi et al. 2009; Smith et al. 2009; Abou-Elseoud et al. 2010; Ystad et al. 2010; Allen et al. 2011); consequently, 40 ICs were selected to obtain the most networks. We applied the Infomax ICA algorithm (Bell and Sejnowski 1995) to carry out the group-level spatial ICA. To determine the reliability or stability of the ICA algorithm, 50 ICA iterations were

performed using ICASSO, and the best estimate for each IC was utilized. The individual IC maps and time courses were computed by back reconstruction, using both aggregate components and the results from the data reduction step (Calhoun et al. 2001, 2002; Erhardt et al. 2011). The RSNs were classified by visually examining the spatial pattern (by rejecting the ICs related with physiological artifacts) and the frequency spectra (<0.10 Hz; Lowe et al. 1998). We compared the same auditory network and SMN for the 2 groups obtained from the ICA with a two-sample t -test analysis as implemented in SPM [$P < 0.05$ FWE, corrected for multiple comparisons at the cluster level with an auxiliary (uncorrected) voxel threshold of $P < 0.001$, minimum cluster size of 30 voxels].

Finally, we performed a correlation analysis between the differences noted in the intrinsic rs-FC in the SMN (only those for which the two-sample t -test was significant) with: (1) age at which the training began; (2) cumulative lifetime practice hours; and (3) years of training.

Results

Voxel-Based Morphometry

The whole-brain VBM analysis showed a greater GM volume in musicians compared with nonmusicians in one cluster in the right AC (centered on $x = 55, y = -33, z = 21$; $T = 5.76$; $K = 756$). The extension of this cluster goes from the posterior superior temporal gyrus (that encompasses the lateral Heschl's gyrus) to part of the supramarginal gyrus (Fig. 1A). No other between-group differences were found at the predetermined threshold. Using a lower threshold, musicians also showed greater volume in the left AC than nonmusicians (centered on $x = -36, y = 37, z = 15$; $T = 3.37$; $K = 153$; $P = 0.001$).

In the correlation analysis, we observed that the right AC volume negatively correlated with age at which training began, as predicted [$r_{(17)} = -0.4$; $P < 0.05$], one-tailed (Fig. 1B). We also observed that the left AC volume negatively correlated with age at which training began [$r_{(17)} = -0.5$; $P < 0.05$], one-tailed. We found no significant results in the other correlations.

Seed-Based rs-FC

We selected 4 ROIs (right AC, right vPMC, left AC, and left vPMC) and we used them as seeds to perform rs-FC analyses (Fig. 2A). We calculated 2 intrahemispheric and 2 interhemispheric rs-FC measures by combining the 2 AC with the 2 vPMC seed regions (Fig. 2B). Results of MANOVA analysis showed a significant main effect for group ($F_{4,32} = 3.47$; $P = 0.02$). Follow-up post hoc univariate tests revealed that musicians compared with nonmusicians showed higher values in the FC between the right AC and the right vPMC ($F_{1,32} = 9.16$; $P < 0.005$), but not in the other rs-FC measures ($P > 0.10$; Fig. 2B).

We also identified a relationship between the GM volume in the right AC and the rs-FC between the right AC and the right vPMC for all the samples together. We found a significant positive correlation between both variables [$r_{(34)} = 0.60$; $P = 0.001$; Fig. 3A], which indicates that those individuals with greater GM volume in the right AC also showed higher levels of rs-FC between that structure and the right vPMC. When considering each group separately, this correlation was significant for nonmusicians [$r_{(17)} = 0.50$; $P = 0.03$] and came close to significance for musicians [$r_{(17)} = 0.40$; $P = 0.09$].

Finally, Pearson's correlation analyses, done with the 3 musical experience variables, showed a significant relationship

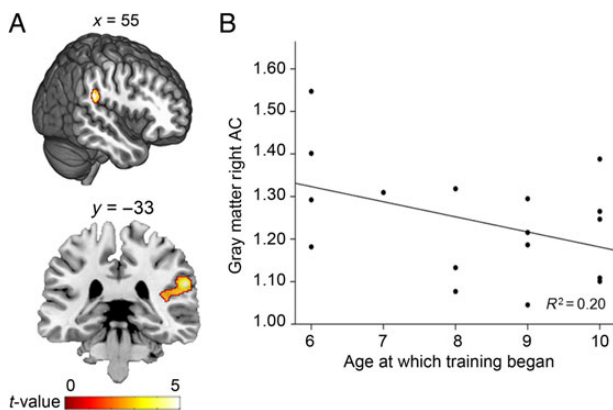


Figure 1. (A) Brain regions with GM differences between musicians and nonmusicians (FWE cluster-corrected at $P < 0.05$, voxel-wise threshold of $P < 0.001$ with a cluster size criterion of 756 voxels). The right side of the image is the right side of the brain. (B) The scatter plot shows the correlation between the regional GM volume at the local maxima of the right auditory cortex ($x = 55, y = -33, z = 21$) and age at which training began.

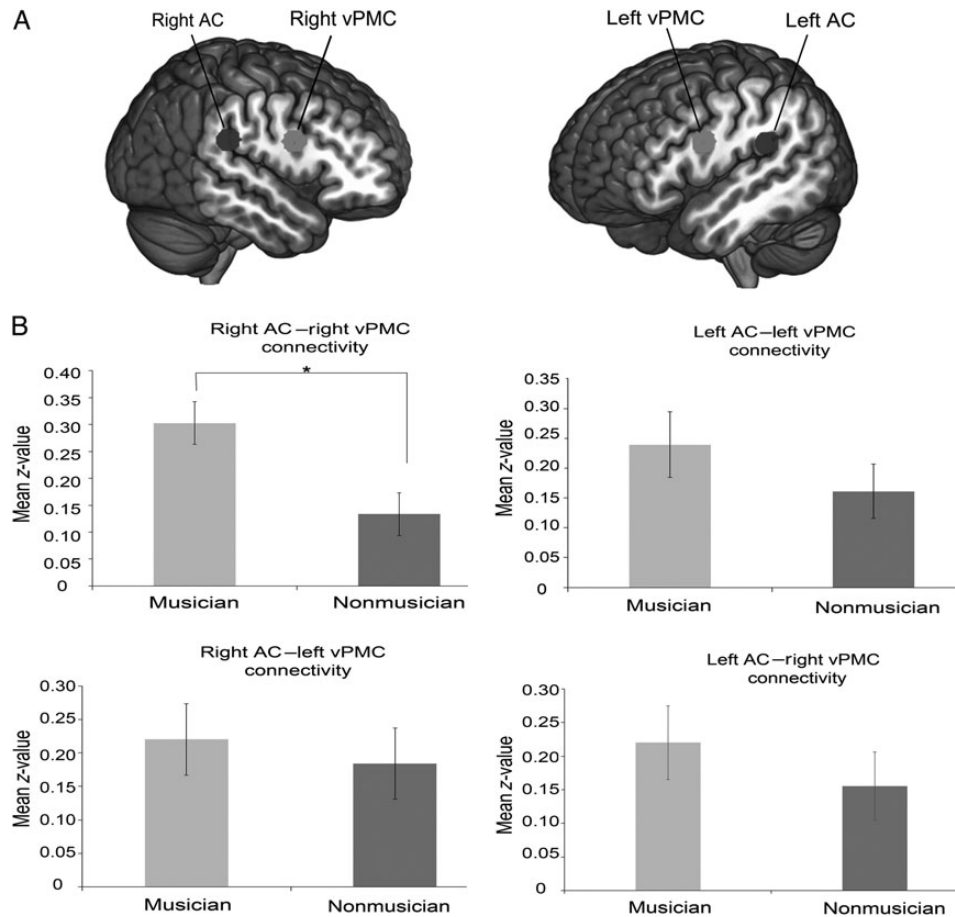


Figure 2. (A) Illustration of the location of the 4 seed ROIs in the right hemisphere (right AC and the right vPMC) and the left hemisphere (left AC and the left vPMC). (B) The graph shows the comparison of functional connectivity at rest (mean z-value) between the 2 intrahemispheric and the 2 interhemispheric rs-FC measures. The only significant difference was between the right AC and the right vPMC in musicians compared with nonmusicians. * $P = 0.001$.

between years of training and the rs-FC between the right AC and the right vPMC [$r_{(17)} = 0.50$; $P < 0.05$], one-tailed (Fig. 3B). We found no significant results in the other correlations.

Resting-State Networks

We identified 2 RSNs, based on those reported in previous studies (Beckmann et al. 2005; Damoiseaux et al. 2006; Shehzad et al. 2009). The auditory network was formed by bilateral middle and superior temporal gyri, the posterior insular cortex, the superior temporal sulcus, and Heschl's gyrus, whereas the SMN was formed by the bilateral supplementary motor area (SMA) and bilateral precentral/postcentral gyri (see Supplementary Fig. 1). The results showed no significant differences between groups in the auditory network. However, when comparing the SMN, we found significant differences between the nonmusician and musician groups in 2 different areas of the precentral/postcentral gyri (BA 3/4; right precentral/postcentral $x = 18$, $y = -30$, $z = 60$; $T = 6.76$; $K = 68$ and left precentral/postcentral $x = -30$, $y = -30$, $z = 57$; $T = 5.59$; $K = 30$; Fig. 4A) in the direction of lower magnitude in the musicians. As these areas correspond mainly to hand control (Grafton et al. 1992; Yousry et al. 1997; Indovina and Sanes 2001), we calculated the correlation between both areas by employing spherical ROIs centering on the local maxima peak with a radius of 8 mm. Results confirmed a lower magnitude, that is, a lower rs-FC for musicians (mean = 0.51 ± 0.26)

than nonmusicians (mean = 0.74 ± 0.22 ; see the individual values in Fig. 4B). It is important to stress at this point that the 3 musicians with highest values for the rs-FC measures played the trumpet, an instrument played only with one hand.

Finally, the Pearson's correlations with musical experience revealed that the rs-FC between the brain areas that controlled both hands correlated negatively with cumulative lifetime practice hours [$r_{(17)} = -0.4$, $P < 0.05$], one-tailed (Fig. 4C), such that those who had practiced most had the lowest levels of connectivity between the hand motor areas.

Discussion

In the present study, we investigated the impact of musical training on rs-FC within and between auditory and motor regions using rs-fMRI and anatomic MRI. We provide data to demonstrate that musical training affects not only auditory and motor systems separately, but also their interactions, particularly in the right hemisphere, even in the absence of any specific task. In addition to replicating the effect of musical training on GM concentration in AC, we also found that musical training was associated with increased rs-FC between the right AC and the ventral premotor region, and importantly, that this rs-FC enhancement correlated with the AC anatomy thus linking brain structure and brain function. Conversely, we observed for the first time reduced rs-FC between the motor cortical regions

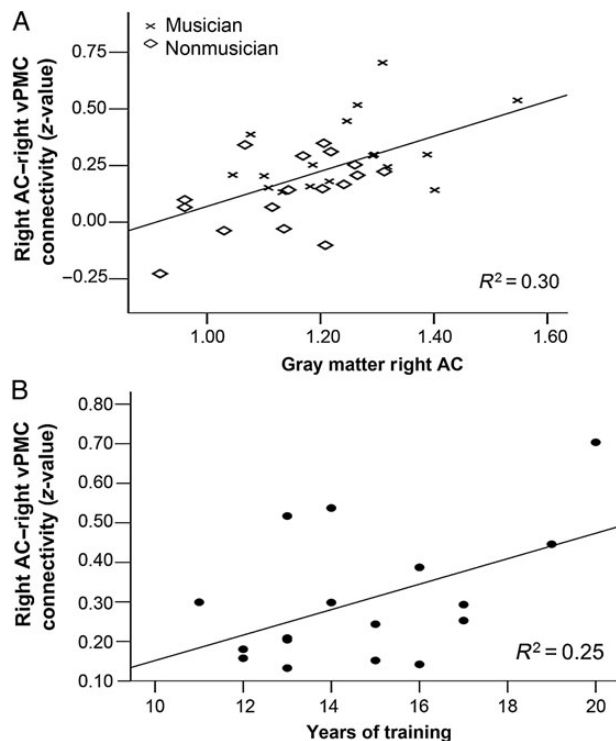


Figure 3. (A) The scatter plot shows the correlation between the regional GM volume at the local maxima of the right AC with the rs-FC between the right AC and the right vPMC (z-value), with a positive correlation in both groups. (B) The scatter plot shows how the rs-FC between the right AC and the right vPMC (z-value) correlated significantly with years of training.

that control both hands of musicians. All these effects were stronger in musicians with earlier or longer training.

GM—Musicians and Nonmusicians

In a whole-brain analysis (Fig. 1A), we found a significantly greater GM volume in the right AC in the musician group. With a more liberal threshold, we also found differences in the left AC. Morphological differences in the auditory regions are consistent with previous studies which measured different features of anatomic organization, such as cortical volume, thickness, and surface area (Schneider et al. 2002; Gaser and Schlaug 2003; Bermudez et al. 2009; Foster and Zatorre 2010; Elmer et al. 2013), although the lateralization and precise location of effects varied. Our results also revealed that the right AC volume was greater for those musicians who reported an earlier training age. Previous studies have observed that age of commencement is related to various anatomic changes [for review see Penhune (2011)], but not typically in the AC. However, previous cross-sectional studies have related structural differences in the right AC with behavioral ability. Schneider et al. (2002) related the volume of Heschl's gyrus to an earlier neural response to sinusoidal tones and to better music aptitude; Foster and Zatorre (2010) also found that cortical thickness in auditory regions predicted performance in a melody transposition task. Longitudinal studies in children have also demonstrated changes in the right AC, which resulted from regular training, and correlated with improvements in musically relevant motor and auditory skills (Hyde et al. 2009). Our results are thus in agreement with the suggestion that musical training may influence brain structures (AC) that control relevant primary functions for perceiving musical sounds and playing a

musical instrument, especially when training commences early. However, such analyses do not allow one to determine the relationship between changes in local anatomic features and their consequences for network-level functions, which is why we then examined auditory-motor interactions.

Relationship Between Auditory and Motor Regions

One of our principal findings is that musical training was associated with an increase in the audiomotor interactions in the right hemisphere when there was no specific task involved, thus extending conclusions from previous task-based studies (Chen et al. 2008; Grahn and Rowe 2009). We found a stronger rs-FC between the right AC and the right vPMC in musicians compared with nonmusicians. As we found between-group differences in a resting state, we conclude that the functional interactions between auditory and premotor regions reflect intrinsic and stable changes, which relate to musical training. Recent interpretations of rs-FC have suggested that spontaneous activity patterns in the rs-fMRI reflect a priori biases and an individual's propensities as a result of experience (Harmelech and Malach 2013). This means such activity will reflect individual differences in training in various activities, including music performance. This possibility was reinforced by the fact that the rs-FC between the right audiomotor regions was stronger in musicians with more years of training. Future studies will need to study whether the degree of audiomotor interactions could also be associated with specific behavioral indicators of musicians' performance or of general cognitive functioning, such as attention or working memory.

Auditory information can be utilized to guide the learning of motor behaviors in both music (Finney and Palmer 2003; Zatorre et al. 2007) and speech (Hickok and Poeppel 2007). The auditory system is critical for music, and previous studies have reported that it is altered by musical training (Zatorre et al. 2007; Pantev and Herholz 2011; Herholz and Zatorre 2012). Instrumental training could influence reorganization in the AC via sensory-motor interactions. Several previous studies have separated the effects of auditory exposure alone from active instrumental training with an auditory-sensorimotor and an auditory-only protocol (Lappe et al. 2008, 2011). These studies showed that sensorimotor system involvement leads to more robust plastic changes in the AC than when sounds are attended to only with no motor production. Conversely, premotor cortex activity with auditory stimulation is enhanced specifically for tonal patterns that a listener already knows how to play (Lahav et al. 2007; Herholz et al. 2015). Direct auditory-motor transformations are also highly relevant during music performance and have been shown to involve the vPMC (Chen et al. 2008, 2009). The right vPMC has been specifically proposed to mediate the direct transformation of sounds into movements, and this area is recruited only when sounds are relevant for the motor system, and neither by the sound-alone condition nor by the motor alone condition (Chen et al. 2008, 2009). Thus, the pattern observed here of increased FC between right auditory and ventral premotor regions during rs-fMRI complements previous data showing FC correlates of the left AC (Luo et al. 2012; Fauvel et al. 2014; Klein et al. 2016) and likely reflects the extensive training of the musicians recruited in our study, as shown also by the positive correlation between years of training and strength of rs-FC.

The relevant issue in this study is that changes obtained in rs-FC may be mediated via the experience-dependent structural changes that occur in WM pathways that interconnect particular functional networks, which in turn may reflect changes in

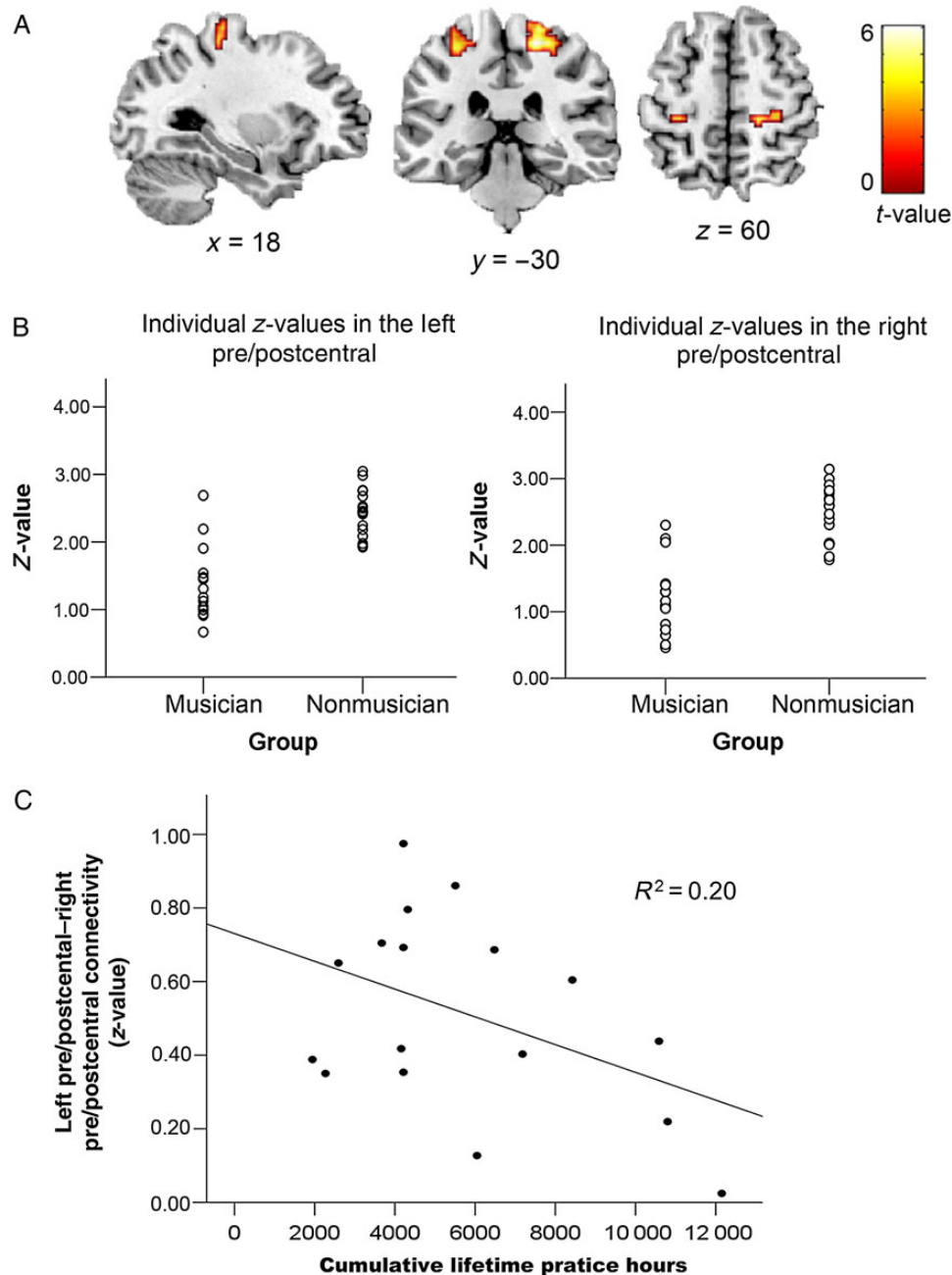


Figure 4. (A) Differences in the SMN when comparing the nonmusician with the musician group ($P < 0.05$, cluster-corrected with an auxiliary uncorrected threshold of $P < 0.001$, cluster size = 30 voxels). The right side of the image is the right side of the brain. (B) Individual z-values in the right pre/postcentral and in the left pre/postcentral for musicians and nonmusicians. (C) The scatter plot shows that the connectivity between the right pre/postcentral and the left pre/postcentral (z-value) correlated negatively with the cumulative lifetime practice hours.

myelination or axonal architecture (Markham and Greenough 2004; Zatorre et al. 2012). Although we did not obtain anatomic connectivity measures in this study, our results are consistent with a proposed role for the AF in the connectivity between auditory and premotor regions. Halwani et al. (2011) detected higher FA values in the arcuate when learning to connect actions with sounds. These results suggest that musical training produces structural changes in that portion of the AF that connects the auditory and premotor regions. It is noteworthy that these authors found that instrumentalists showed specific changes in the right AF, whereas singers showed bilateral changes. Thus,

the findings of Halwani et al. (2011) complement our results as it has shown that instrumental musical training is associated with structural and functional changes in the connectivity between the right auditory and motor regions. As in Halwani et al.'s study, we detected no significantly increased functional connectivity between left-hemisphere auditory and premotor areas in the musician group, although the trend was in a similar direction. This was not entirely unexpected as these areas in the left hemisphere have been related to mapping heard speech sounds, such as phonemes, onto articulatory representations (Wilson et al. 2004; Pulvermüller et al. 2006; Meister et al. 2007).

As such, one would not necessarily expect musical training to directly influence this system, although there is evidence that under certain conditions musical training may enhance speech processing (Besson and Schön 2001; Samson et al. 2001; Parbery-Clark et al. 2009).

How is this differential connectivity between musicians and nonmusicians established? One possibility is that playing an instrument requires the association between the sound of a note and the effector used to produce that note. Interactions between auditory–motor systems can be elicited when direct learned mapping exists between sound and movement (Lahav et al. 2007). A second contribution stems from the ability to tap to the beat, a behavior that can be observed even in people with no musical training (Drake and Penel 2000; Snyder and Krumhansl 2001; Large and Palmer 2002). The listener must extract the appropriate temporal information from a complex auditory stimulus and make predictions that permit the planning and performance of sequential movements in a precisely timed way. Kung et al. (2013) used fMRI to study beat finding and tapping, and found a network including the basal ganglia (BG), superior temporal gyrus, premotor cortex (PMC), and ventrolateral prefrontal cortex (VLPFC). Of greatest relevance to the present findings, they reported that the right VLPFC enhanced its functional coupling with both the BG and right STG for rhythms with weak metrical structure, compared with highly metrical rhythms. The modulation in functional connectivity during processing of complex rhythms, which presumably would occur frequently in highly trained musicians, may thus lead to stable changes to the brain, which are then manifested in rs-FC between regions, especially auditory and premotor/frontal areas.

In relation to these mechanisms, our study offers some clues about the relationship between structural and functional changes. For all the subjects, we observed that those with more GM volume in the right AC had increased rs-FC between the right AC and the right vPMC. This result agrees with the results discussed above. In this case, the AC volume related to stronger audiomotor connectivity which, in turn, may lead to better musical ability. Future studies will need to determine the neural mechanism that allows these coordinated structural–functional changes to develop.

Auditory and Sensory–Motor Networks—Musicians Versus Nonmusicians

The pattern of RSNs obtained in our resting-state analysis confirmed the main networks found in previous studies (Beckmann et al. 2005; Damoiseaux et al. 2006; Shehzad et al. 2009) and confers validity to the analysis. In the present study, the ICA revealed training-related differences in the SMN but not in the auditory network. The SMN included correlation between the precentral and postcentral gyri, the lateral premotor cortex, and the SMA. In contrast to the enhancement in FC observed between auditory and motor areas, our study found diminished connectivity in the SMN in musicians versus nonmusicians, specifically between homologous areas in both precentral/postcentral gyri, close to the knob-like structure that is typically related to the hand motor area. Previous fMRI studies have related the activity of this region to voluntary finger movements (Grafton et al. 1992; Yousry et al. 1997; Indovina and Sanes 2001). Neuroimaging and electrophysiological studies in humans have shown that this motor hand area reveals adaptive modifications in response to learning, as well as acquisition of novel motor skills (Sanes and Donoghue 2000; Ungerleider et al. 2002; Sosnik et al. 2014), including music (Bangert and Schlaug 2006).

The bimanual coordination relevant for playing an instrument does not seem to lead to differences in the proportion of right handers between musicians and nonmusicians (Christman 1993; Jäncke et al. 1997). However, Jäncke's study reported that right-handed musicians who require bimanual coordination to play an instrument exhibit a lower degree of hand skill asymmetry. These differences have been interpreted as a sign of better bihemispheric control of fine motor activity in instrumentalists. Transcranial magnetic stimulation has revealed that left-to-right IHI of the motor cortex is stronger in musicians, reflecting greater independence of motor control over the 2 hands (Vollmann et al. 2014). The results of the present study are compatible with this concept of greater independence because we found lower functional connectivity between the 2 hand areas, and also because the spontaneous activity of each hand cortical area correlated less with the activity of the rest of motor network in musicians.

As in audiomotor interactions, previous studies have revealed an anatomic substrate for these effects. DTI studies have observed that an enhanced FA in the CC may be the neural basis for these intermanual differences (Halwani et al. 2011). In a recent study, Vollmann et al. (2014) reported a correlation between IHI and the FA in the medial part of the CC, suggesting that the functional effect is mediated via anatomic adaptations. This location in the CC is similar to the one identified by Steele et al. (2013) as showing greater FA as a function of start of music training. Thus, the result of the present study might reflect the plastic changes brought about by bimanual demands of the instruments on which musicians train, and of consecutively practicing complex, coordinated bimanual finger movements.

In consonance with this interpretation, our results also show that reduced rs-FC between both hands is greater in musicians who play instruments that entail bimanual coordination (the FC values were highest for the 3 trumpet players, whose instrument only requires one hand) and, more importantly, in musicians with more self-reported hours of practice throughout their life time. So the more practice, the more independence between the spontaneous activity of each hand. This result is in line with previous results which have shown that FA in the CC is associated with hours of practice (Vollmann et al. 2014) and that earlier commencement of training is associated with more efficient interhemispheric connections, measured by response times (Hughes and Franz 2007). Thus, for the overall data, we infer that IHI is a direct consequence of practice. Future studies should attempt to link rs-FC between both hands directly with bimanual task performance.

Limitations

The present research may comprise some limitations. A first issue is that the data are not completely acquired “at rest” because steady scanner noise is present. Thus, we cannot completely rule out the possibility that the audiomotor and motor differences found in our study may be biased by the different processing of this scanner noise in musicians and nonmusicians. This possibility is less likely because we found no differences in the auditory network between both groups. A recent study has also shown no differences in cortical RSNs when comparing standard continuous acquisition with sparse acquisition (Yakunina et al. 2016). The second issue is that behavioral correlations, such as those presented in Figures 1B and 3B, were based on a limited number of participants. Future studies should replicate these results in bigger samples.

Conclusion

We provide evidence that musical training is associated with changes in AC morphology, in enhancement of the functional coupling between auditory and motor regions, and in a reduction of the rs-FC in the motor regions that control both hands. Our results are consistent with the idea that the rs-FC reflects the impact of training on the brain since these effects were stronger in musicians who reported earlier and longer training.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

Funding

This work was supported by grants from the Spanish Ministry of Economy and Competitiveness (PSI2013-47504-R) and by a research stay grant from the Spanish Ministry of Economy and Competitiveness to M.-A.P.-G. (BES-2011-045789) developed at McGill University. Authors M.-A.P.-G. and E.B. was supported by pre-doctoral graduate program grants (National FPI to M.-A.P.-G.; and National FPU to E.B.).

Notes

Conflict of Interest: None declared.

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