Is function paired with structure in the musician brain?

A DTI-TBSS study with left-handed musicians

MASTER'S THESIS

MASTER'S DEGREE IN RESEARCH ON BRAIN AND BEHAVIOUR

UNIVERSIDAD JAUME I

2019 – 2020

AUTHOR : NATALIA MORENO MAESTRE NIF: 21702936-K

TUTOR: CÉSAR ÁVILA RIVERA

Abstract – Brain differences between musicians and non-musicians have been found mainly in the primary auditory and motor cortex of the right hemisphere, as well as in their connections. Some previous investigations attempting to describe the peculiarities of the musician's brain have focused in the Corpus callosum (CC), being the common result of most of these investigations a larger anterior CC and overall thicker CC in the musician's brain. However, differences have also been found in the way their brains work, showing that musicians have less inter-hemispherical functional connectivity between the primary motor cortices associated to the movement of the upper limbs. Thus, the aim of our study was to investigate whether structural connectivity between these regions is also different in musicians by measuring white matter (WM) tracts using Diffusion MRI in a left-handed sample of 29 musicians and 43 non-musicians. As expected, it was found that musicians present lower FA than non-musicians in the callosal tracts connecting the upper limbs' primary motor cortices, suggesting more independence between both hands.

Keywords: handedness, musician, primary motor cortices, structural connectivity, diffusion tensor imaging.

INTRODUCTION

The musician's brain presents certain peculiarities when it is compared to the brain of a non-musician. These differences are found mainly in the primary auditory and motor cortices of the right hemisphere, as well as in their connections (Zatorre et al., 2007). In the auditory domain, structural magnetic resonance imaging has shown a greater volume of auditory cortex in professional musicians compared to non-musicians (Gaser & Schlaug, 2003). In the motor domain, musicians have a higher concentration of gray matter in the motor cortex (Gaser & Schlaug, 2003). These structural differences correlate with the age at which they began their musical training and the hours dedicated to it, since they are more evident the earliest and more intensive the musical training was (Gaser & Schlaug, 2003; Zatorre et al., 2007; Palomar-García et al., 2017).

Differences in musicians have been found not only in their brain structure, but also in the way their brain functions. Palomar-García et al. (2017) described a higher auditory-motor functional connectivity in the right hemisphere of musicians; that is, their right auditory and motor cortices presented a higher functional coupling at rest. Moreover, this was concordant with previous diffusion-weighted imaging results showing that musicians present a higher fractional anisotropy (FA) of the right arcuate fasciculus, a white matter (WM) tract responsible for auditory-motor connectivity (Halwani et al., 2011).

Importantly, Palomar-García et al. (2017) also found that musicians have less inter-hemispherical functional connectivity between the primary motor cortices associated to the movement of the upper limbs; that is, the brain activity at rest in motor regions corresponding to both hands would be less related to each other. This result would be consistent with the idea that the motor control of the hands in the musician's brain is much more independent between both hemispheres. In fact, they found that (1) musicians whose instrument did not involve bimanual coordination (trumpeters) did not present this difference, and (2) the more self-reported hours of musical practice musicians had over their lifetime, the less functional connectivity they showed. So, the more practice with a bimanual instrument, the more independence there was between the spontaneous motor activity related to each hand.

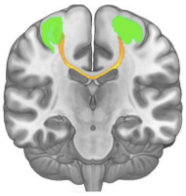


Fig. 1. Population-wise inter-hemispherical tractograms between upper limbs' primary motor cortices. (Domin & Lotze., 2019).

Then, if the upper limbs' primary motor cortices are less functionally connected in the musician's brain: are they also less structurally connected? Several studies attempting to describe the peculiarities of the musician's brain have focused in the Corpus callosum (CC), the largest interhemispheric WM fiber bundle. The CC, which contains more than 300 million axons, connects most of the cortical areas of the brain, being responsible for connecting both cerebral hemispheres and improving inter-hemispheric communication. Its function is to distribute perceptual, motor and cognitive information between the two hemispheres of the brain, facilitating interactions and integration of learned information between both (Chao et al., 2009; Cover et al., 2017).

Due to the size of the CC, it is divided into smaller regions based on the organization of its fibers. These regions are usually associated with certain areas of the cortex, corresponding to specific functions of the brain. The parcellation of the CC is divided into 5 parts: region I, the most anterior segment refers to fibers projecting into the prefrontal region; region II contains fibers projecting to premotor and supplementary motor cortical areas, and is located at the rest of the anterior half of the CC; region III, which comprises fibers projecting into the primary motor; region IV, which contains the primary sensory fibers and region V, including parietal, temporal, and occipital fibers (Hofer & Frahm, 2006; Cover et al., 2017)

The neuronal tracts connecting the primary motor cortices (Brodmann area 4) corresponding to the lower and upper limbs pass through the CC's posterior midbody, and are therefore necessary for the realization of manual movements (Chao et al., 2009; Domin et al., 2019).

Studies conducted with right-handed musicians such as Schlaug's et al. (1995) showed that the anterior half of the CC, which contains premotor fibers, had a larger volume in musicians when compared to non-musicians. Lee et al. (2002) found similar results, although the effect was only evident in men. Differences in CC thickness favoring musicians have also been described in both the anterior (premotor fibers) and posterior halves (which has projections of the somatosensory and posterior parietal areas) of the CC, and in the CC as a whole (Öztürk et al., 2002). However, this study used manual-drawing measures that did not correct by TIV. Although these volumetric studies seem to point in the same direction (musicians having a larger anterior CC and overall thicker CC), they share a limitation: regions measured were too extensive, having little concretion for motor tracts; in fact, only Öztürk et al. (2002) found differences in a region that at least contained the posterior midbody CC.

Diffusion tensor imaging (DTI), a mapping technique that measures the microstructural integrity of WM, has also been used in the study of the musician's brain. Schmithorst et al. (2002) found that musicians, when compared to non-musicians, presented a higher FA in the genu of the CC. Steele et al. (2013) measured FA in non-musicians and musicians, further divided in early-trained (ET), training begun before the age of 7 years, and late-trained (LT), which training begun after the age of 7 years. Their findings showed that ET musicians had higher FA in the CC's posterior midbody, containing tracts that connect to the sensorimotor cortices in the two hemispheres. However, LT musicians did not differ from non-musicians in this region.

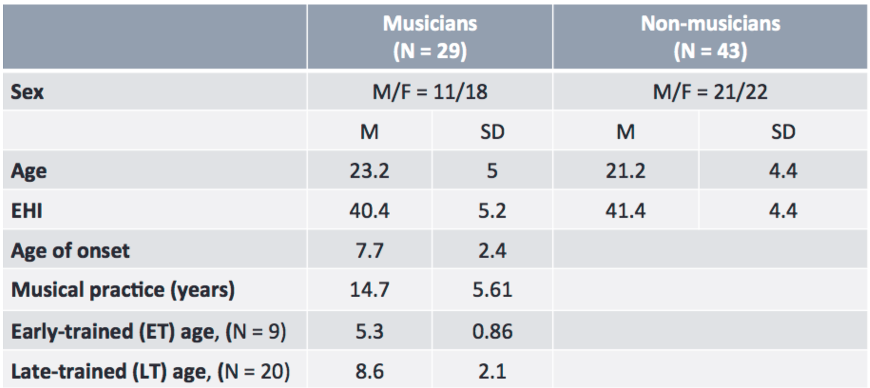
Therefore, our aim was to further study the possibility that structural connectivity between these motor regions is different in left-handed musicians. The findings of some studies showed an increased prevalence of left-handers in students of music (Götestam, 1990) and a small increase in the proportion of left-handers in profesional musicians compared to general population (Aggleton, Kentridge & Good, 1994). Aggleton et al., (1994) also found significant interactions between handedness and being musician, and between degree of handedness and being musician, suggesting that these effects were due to a greater proportion of left-handed musicians and to a relative loss of "strongly" handed musicians. Some studies have shown that left–handed musicians have some advantages in tasks such as sight-reading (Kopiez et al., 2006) or playing melodies in a reversed keyboard (Smit & Sadakata, 2018). Importantly for the present study, most of the left-handed musicians use to play the instrument as right-handers, including the requirement of use their non-dominant right hand as the main to interpret the music. Thus, our hypothesis is that the motor and sensitive part of the corpus callosum will be involved in the ability of left-handed musicians to play music.

Taking into account the possible differences that we could find in our results when dealing with a left-handed sample, we will use DTI to investigate structural differences between left-handed musicians and non-musicians. We will focus our analysis on the CC segment that connects the primary motor cortices responsible for the upper limbs' movement. Our hypothesis was that musicians would differ from non-musicians, in accordance to previous functional connectivity and DTI results, and that age in which the training begun would modulate the results.

EXPERIMENTAL PROCEDURES

Participants

Seventy-two participants took part in the study. All participants were left-handed or ambidextrous, according to the Edinburgh Handedness Inventory/EHI (Bryden, 1977; Oldfield, 1971). The subjects were separated into two groups according to their musical training (29 musicians and 43 non-musicians). The condition for being classified as a musician was having received musical training (at an official music school) for at least 5 years. The data on the history of music training was obtained through a detailed self-report. It included estimates of weekly music practice hours for each phase of their musical activities. The most common primary instruments were string instruments (such as violin, viola and guitar, (N = 16) and woodwind instruments (such as oboe, transverse flute and clarinet, (N = 12). Non-musicians, on the other hand, had never played a musical instrument or received musical training beyond basic school education In the group of musicians, 11 subjects were male and 18 female. Their mean age was 23.2 (SD = 5), their mean EHI was 40.4 (SD = 5.2), their mean age of onset was 7.7 (SD = 2.4), and their musical practice, estimated in years, was 14.7 (SD = 5.61). The non-musicians group had 21 female and 22 male subjects. Their mean age was 21.1 (SD = 4.4) and their mean EHI was 41.4 (SD = 4.4). No significant between-groups differences were found in sex (p>0.05), age (p>0.05) or EHI (p>0.05).



	Musicians (N = 29)		Non-musicians (N = 43)	
Sex	M/F = 11/18		M/F = 21/22	
	M	SD	M	SD
Age	23.2	5	21.2	4.4
EHI	40.4	5.2	41.4	4.4
Age of onset	7.7	2.4		
Musical practice (years)	14.7	5.61		
Early-trained (ET) age, (N = 9)	5.3	0.86		
Late-trained (LT) age, (N = 20)	8.6	2.1		

Table 1. M and SD for sex, age and EHI for all participants and musical practice, age of ET and LT for musicians.

None of the participants had suffered any neurological or psychiatric disorders or had a history of head injury with loss of consciousness. Written informed consent was obtained from all participants following a protocol approved by the Jaume I University. All methods were carried out in accordance with approved guidelines and regulations.

MRI acquisition

MRI data acquisition was performed on a 3-T MRI scanner (General Electrics Signa Architect). Participants were placed inside the scanner in a supine position, and their heads were immobilized with cushions. Axial DTI were acquired with an echo-planar imaging sequence (EPI) with 25 gradient directions. The scan parameters used were the following: TR = 12000 ms, TE = 80 ms, b0/b = 0/1000s/mm^2, FOV = 256 mm, matrix = 128x128, flip angle = 90º, number of slices = 60, slice thickness = 2 mm, gap = 0mm.

DTI processing and statistical analysis

All DTI data were processed using the FMRIB Software Library (FSL). First, diffusion weighted images were corrected for eddy current distortions using *eddycorrect*. Brain extraction and deletion of non-brain tissue were performed using *bet* (Brain Extraction Tool). Then, *dtifit* was applied to extract FA.

FA indicates the degree of directionality of water diffusion. In WM, FA reflects to what extent the movement of water molecules is limited by the WM's tracts. That is, the greater the increase in the organization of the CC's tracts, the greater the increase in FA values. This would be an indicator of WM integrity at the microstructural level of WM, hard to get through other means *in vivo* (Schmithorst et al., 2002).

Voxelwise statistical analysis of FA data was carried out using Tract-Based Spatial Statistics (TBSS). This included non-linear registration of all FA individual images to a common space (MNI152), using the FMRIB58_FA atlas. Next, a mean FA skeleton was created and thinned in order to represent the center of all tracts common to the subjects, with a threshold = 0.2. Finally, each subject's aligned FA data were projected onto this skeleton. The resulting data were used for voxelwise cross-subject statistics.

Between-group comparisons, including sex and age as covariates, were conducted with a two sample *t-test* applied with *randomise.* The threshold-free cluster enhancement (TFCE) statistic was estimated, and statistical significance was determined using permutation-based nonparametric inference (1000 permutations per analysis) at a threshold of $p < 0.05$, family-wise error (FWE) corrected. All analyses were restricted to a mask of a specific region of the CC, responsible for inter-hemispherically connecting the upper limbs' primary motor cortices (Domin & Lotze., 2019).

Mean FA value from between-group significantly different voxels was extracted for every participant, and the following correlation analyses were carried out: (1) Pearson's correlation coefficient with handedness score, separately for musicians and non-musicians; (2) Spearman's correlation coefficient with age of onset of musical training, in musicians; and (3) Spearman's correlation coefficient with amount of musical training, in musicians. Age of onset was self-reported by each musician, whereas we calculated the amount of musical training based on self-reports of how many hours per week they had practiced music during different age ranges.

An ANCOVA's were conducted to compare differences in mean FA using as a function of Type of Instrument (string instruments and wind instruments) and using age of training onset as covariate .

RESULTS

Differences in DTI

Using the mask of the CC that only included the tracts connecting the upper limbs' primary motor cortices, it was found that non-musicians exhibited higher FA in this specific region compared to musicians ($p < 0.05$, TFCE-FWE corrected).

No significant correlations were found between mean FA value in this region and handedness (musicians: $r = -0.2$, $p = 0.29$; non-musicians: rs = -0.22; p = 0.15), or amount of musical training ($r_s = -0.09$, p = 0.64).

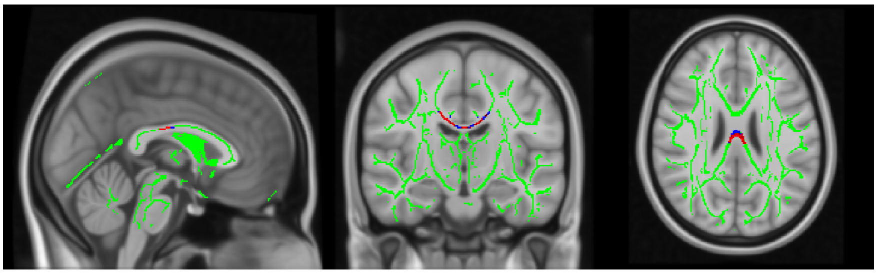


Fig. 2. Differences in FA in the inter-hemispherical upper limbs' motor tracts between non-musicians and musicians (p<0.05, TFCE-FWE corrected). Green: skeleton tracts; blue: restrictive mask corresponding to upper motor limbs' tracts; and red: tracts within the mask with significantly higher FA in non-musicians compared to musicians.

Differences between musicians groups

In the ANCOVA for groups of instrument (string instruments vs. wind instruments), our analysis showed a significant effect of age of onset (p = 0.04) and a trend of higher FA for strings than wind instruments (p = 0.62). The FA mean for string instruments was 0.68 (SD = 0.52) and for wind instruments 0.65 (SD = 0.47), and age of the onset correlated negatively with mean FA value.

DISCUSSION

Our results showed that left-handed musicians present lower FA than non-musicians in the callosal tracts connecting the upper limbs' primary motor cortices. This suggests that the musician's brain may undergo changes due to their training. In this study, the FA decrease between inter-hemispherical upper limbs' motor tracts, suggesting more independence between both hands. Nevertheless, the correlation in these tracts between mean FA value and handedness was no significant. This result suggests that these structural changes occur regardless the strength of handedness. Moreover, no significant correlation between mean FA and amount of training was found. Results were modulated by type of instrument (with high FA values for string than wind instruments and for age of onset of training, with early training producing higher FA values than late training.

To date, several studies have been conducted focusing their analysis on the CC of musicians. Using *in vivo* magnetic resonance morphometry, which measures thickness and volume of the WM, Schlaug et al. (1995) found differences in the anterior CC comparing groups of musicians and non-musicians, being larger the anterior CC of the first group and suggesting that their results indicate a difference in interhemispheric communication. This increase from the anterior CC was significantly higher in musicians with early commencement of musical training compared to musicians beginning later.

Similar results were found using also *in vivo* magnetic resonance morphometry, showing significant differences in the anterior CC in musicians compared to non-musicians (Öztürk et al., 2002; Lee et al., 2002), but these method to measure the size of the CC have large variability and are prone to bias (Lee et al., 2002). Moreover, a DTI study showed greater FA in the CC's genu in musicians compared to non-musicians, relating these differences as a consequence of the cognitive and motor effects of the musical training (Schmithorst's et al., 2002).

A more recent study conducted in 2013 by Steele et al. using DTI found FA differences in the posterior midbody/isthmus of the CC comparing white-matter organization between early and LT musicians, finding that ET had greater FA in that region. Thus, their findings showed a better connectivity in ET musicians between sensory and motor regions of the two hemispheres. In the current study we used also DTI and analyzed the same region of the CC, but comparing FA between musicians and non-musicians and focusing our analysis in the tracts that connects the primary motor cortices responsible for the upper limbs' movement. We have not replicate in our left-handed sample the difference between musicians and non-musicians, but early trained musicians had also greater FA values than late trained musicians.

Nevertheless, it was found reduced functional connectivity at rest (rs-FC) between the motor cortical regions that control both hands of musicians (Palomar-García et al., 2017), and it would be expected that functional and structural connectivity will be positively related (Skudlarski et al., 2008; Teipel et al., 2010). Thus, our result is consistent with this finding, showing lower FA in musicians than non-musicians and acting as its possible structural basis. It should also be noted that left-handed musicians, when playing instruments for righ-handed, use their non-dominant hand as the main to perform music. These requirements are greater for string than for wind instruments. This can lead to greater coordination between hands, as the right hand becomes the strong one. Moreover, right-handed musicians shown a lesser degree of hand skill asymmetry than non-musicians, being the reduced degree of right-hand superiority mainly due to a left-hand gain and not to a right-hand loss of skill, suggesting a better bihemispheric control of fine motor activity in musicians (Jäncke et al., 1997). Furthermore, the rs-FC between upper limbs' primary motor cortices is lower in musicians whose instrument did involve bimanual coordination and in whose with more self-reported hours of musical practice had over their lifetime, reflecting plastic changes (Palomar-García et al., 2017).

However, in a cross-sectional study such the present one, it cannot be confirmed that these structural changes are due only to musical training, and may also be the result of factors unrelated to training. In a study conducted with musicians found that in the auditory cortex a significant percentage of the relative pitch was explained by gray matter anatomical variation, independently of musical training (Foster & Zatorre, 2010). Thus, it seems that these differences would have both an innate and a training component. In this study the differences found in the WM did not correlate with music training –unlike Palomar's et al. (2017) study–, and this may be due to the fact that these differences probably also evoke an innate factor.

Future investigations should focus in confirming a possible linear relationship between both structural and functional connectivity differences present in musicians. For this purpose, Palomar's et al. (2017) study should be replicated with a sample of left-handed musicians, and a possible correlation between rs-FC and FA should be explored. A longitudinal design could also help with further defining the specific weight of training versus predisposition in our results.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGMENTS

I would like to thank the members of the Neuropsychology and Functional Neuroimaging research group of the Universidad Jaume I, Villar-Rodríguez, E. & Marín-Marín, L., their support and contribution in this study.

REFERENCES

Aggleton, J. P., Kentridge, R. W., & Good, J. M. M. (1994). Handedness and musical ability: A study of professional orchestral players, composers, and choir members. *Psychology of Music, 22*(2), 148–156. DOI: 10.1006/brcg.1997.0922.

Bryden, M. P. (1977). Measuring handedness with questionnaires. *Neuropsychologia, 15*(4-5), 617-624. DOI: 10.1016/0028-3932(77)90067-7.

Chao, Y-P., Cho, K-H., Yeh, C-H., Chou, K-H, Chen, J-H. & Lin, C-P. (2009). Probabilistic Topography of Human Corpus Callosum Using Cytoarchitectural Parcellation and High Angular Resolution Diffusion Imaging Tractography. *Human brain mapping, 30*(10), 3172-3187. DOI: 10.1002/hbm.20739.

Cover, G., Pereira, M., Bento, M., Appenzeller, S. & Rittner, L. (2017). Data-Driven Corpus Callosum Parcellation Method Through Diffusion Tensor Imaging. *IEEE access, 5*, 22421-22432. DOI: 10.1109/ACCESS.2017.2761701.

Domin, M. & Lotze, M. (2019). Parcellation of motor cortex-associated regions in the human corpus callosum on the basis of Human Connectome Project data. *Brain structure and function*, *224*(4), 1447-1455. DOI: 10.1007/s00429-019-01849-1.

Foster, N. E. V. & Zatorre, R. J. (2010). Cortical structure predicts success in performing musical transformation judgments. *Neuroimage, 53*(1), 26-36. DOI: 10.1016/j.neuroimage.2010.06.042.

Gaser, C. & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *The Journal of Neuroscience*, *23*(27), 9240–9245. DOI: 10.1523/JNEUROSCI.23-27-09240.2003.

Götestam, K. O. (1990). Lefthandedness among students of architecture and music. *Perceptual and motor skills, 70*(3), 1323-1327. DOI: 10.2466/pms.1990.70.3c.1323.

Halwani, G. F., Loui, P., Rüber, T & Schlaug, G. (2011). Effects of practice and experience on the arcuate fasciculus: comparing singers, instrumentalists, and non-musicians. *Frontiers in psychology,* 2:156. DOI: 0.3389/fpsyg.2011.00156.

Hofer, S. & Frahm, J. (2006). Topography of the human corpus callosum revisited—Comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage, 32*(3), 989-994. DOI: 10.1016/j.neuroimage.2006.05.044.

Jäncke, L., Schlaug, G. & Steinmetz, H. (1997). Hand skill asymmetry in professional musicians. *Brain and cognition, 34*, 424-432. DOI: 10.1006/brcg.1997.0922.

Kopiez, R., Galley, N., & Lee, J. I. (2006). The advantage of a decreasing right-hand superiority: The influence of laterality on a selected musical skill (sight reading achievement). Neuropsychologia, 44(7), 1079–1087. DOI: 10.1016/j.neuropsychologia.2005.10.023.

Lee, D. J., Chen, Y. & Schlaug, G. (2002). Corpus callosum: musician and gender effects. *NeuroReport*, *14*(2), 205-209. DOI: 10.1097/00001756-200302100-00009

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1)*,* 97-112. DOI: 10.1016/0028-3932(71)90067-4.

Öztürk, A. H., Tasçioglu, B., Aktekin, M., Kurtoglu, Z. & Erden, I. (2002). Morphometric comparison of the human corpus callosum in professional musicians and non-musicians by using *in vivo* magnetic resonance imaging. *Journal of Neuroradiology*, *29*, 29-34. PMID: 11984475.

Palomar, M. A., Zatorre, R. J., Ventura, N., Bueichekú, E. & Ávila, C. (2017). Modulation of functional connectivity in auditory–motor networks in musicians compared with nonmusicians. *Cerebral Cortex*, *27*(5), 2768-2778. DOI: 10.1093/cercor/bhw120.

Schlaug, G., Jäncke, L., Huang, Y., Staiger, J. F. & Steinmetz, H. (1995). Increased corpus callosum size in musicians. *Neuropsychologia, 33*(8), 1047-1055. DOI: 10.1016/0028-3932(95)00045-5.

Schmithorst, V. J. & Wilke, M. (2002). Differences in white matter architecture between musicians and non-musicians: a diffusion tensor imaging study. *Neuroscience Letters, 321*, 57-60. DOI: 10.1016/S0304-3940(02)00054-X

Skudlarski, P., Jagannathan, K., Calhoun, V. D., Hampson, M., Skudlarska, B. A. & Pearlson, G. (2008). Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. *Neuroimage, 43*(3), 554-561. DOI: 10.1016/j.neuroimage.2008.07.063.

Smit, E. A. & Sadakata, M. (2018). The effect of handedness on spatial and motor representation of pitch patterns in pianists. PLoS ONE, 13(5). DOI: 10.1371/journal.pone.0195831

Steele, C. J., Bailey, J. A., Zatorre, R. J. & Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. *The Journal of Neuroscience, 33*(3), 1282-1290. DOI: 10.1523/JNEUROSCI.3578-12.2013.

Teipel, S. J., Bokde, A. L.W., Meindl, T., Amaro Jr., E., Soldner, J., Reiser, M. F., Herpertz, S. C., Möller, H.-J., Hampel, H. (2009) White matter microstructure underlying default mode network connectivity in the human brain. *NeuroImage*, *49*(3), 2021-2032. 10.1016/j.neuroimage.2009.10.067.

Zatorre, R. J., Chen, J. L. & Penhune, V. B. (2007). When the brain plays music: auditory–motor interactions in music perception and production. *Nature*, *8*, 547-558. DOI: 10.1038/nrn2152.