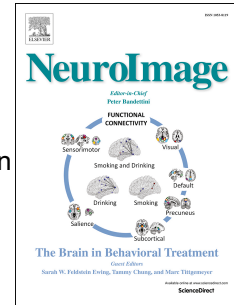


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White-matter structural connectivity predicts short-term melody and rhythm learning in non-musicians

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WHITE-MATTER STRUCTURAL CONNECTIVITY PREDICTS SHORT-TERM MELODY AND RHYTHM LEARNING IN NON-MUSICIANS

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Abbreviated title: Structural connectivity predicts music learning.

Conflict of interest: the authors declare no competing financial interests.

Abstract

Music learning has received increasing attention in the last decades due to the variety of functions and brain plasticity effects involved during its practice. Most previous reports interpreted the differences between music experts and laymen as the result of training. However, recent investigations suggest that these differences are due to a combination of genetic predispositions with the effect of music training. Here, we tested the relationship of the dorsal auditory-motor pathway with individual behavioural differences in short-term music learning. We gathered structural neuroimaging data from 44 healthy non-musicians (28 females) before they performed a rhythm- and a melody-learning task during a single behavioural session, and manually dissected the arcuate fasciculus (AF) in both hemispheres. **The macro- and microstructural organization of the AF (i.e., volume and FA) predicted the learning rate and learning speed in the musical tasks, but only in the right hemisphere.** Specifically, the volume of the **right** anterior segment predicted the synchronization improvement during the rhythm task, the FA in the **right** long segment was correlated with the learning rate in the melody task, and the volume and FA of the **right** whole AF predicted the learning speed during the melody task. This is the first study finding a specific relation between different branches within the AF and rhythmic and melodic materials. Our results support the relevant function of the AF as the structural correlate of both auditory-motor transformations and the feedback-feedforward loop, and suggest a crucial involvement of the anterior segment in error-monitoring processes related to auditory-motor learning. These findings have implications for both the neuroscience of music field and second-language learning investigations.

Keywords: arcuate fasciculus, feedback-feedforward loop, music learning, non-experts, predispositions, error-monitoring.

Highlights

- Structural connectivity markers predict behavioural individual differences.
- The arcuate fasciculus supports the dorsal pathway crucial in language and music.
- Structural markers in this tract differ between musicians and non-musicians.
- To rule-out experience, music learning and arcuate were explored in non-musicians.
- We found rhythm and melody learning related to different branches of the right arcuate.

1. Introduction

Research in the last decades has consistently described anatomical differences in auditory-motor regions in expert musicians compared to non-musicians (Schneider et al., 2002; Gaser and Schlaug, 2003; Bermudez et al., 2009; Halwani et al., 2011). Specifically, music training engages and elicits plastic changes in a network comprising primary and secondary auditory cortices (Koelsch, 2005, 2010; Schneider et al., 2005a, b), inferior frontal gyrus, parietal and somatosensory cortices, premotor, and primary and supplementary motor regions (Bangert et al., 2006; Chen et al., 2012; Grahn, 2012; Herholz et al., 2015; for a review see Zatorre et al., 2007). Music practice requires a close communication between these cortical regions which are connected through the arcuate fasciculus (AF), part of the dorsal auditory pathway that has been linked to perception and production of both speech and music (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; Patel, 2014). This pathway is thought to form a feedback-feedforward loop (Brown et al., 2015), underlying the integration of auditory, motor and somatosensory information, allowing the system to create predictions for upcoming movements, to integrate feedback and to correct errors if needed. Importantly, the AF seems to be the crucial white-matter tract supporting these auditory-motor feedback-feedforward functions (Cunillera et al., 2009; Rodríguez-Fornells et al., 2009). Furthermore, previous studies have found that AF microstructure differs between musicians and non-musicians (Halwani et al., 2011), and is associated with faster melody learning in non-musicians (Engel et al., 2014). However, none of these studies used deterministic tractography approaches, which allow the adaptation of the pathway-reconstruction to the individual anatomical differences, in a short-term training protocol to examine predictors of multiple aspects of music learning.

Previously observed brain structural differences between musicians and non-experts are likely the result of a combination between pre-existing individual differences and training effects (Seither-Preisler et al., 2014; Ullén et al., 2016; de Manzano & Ullén, 2018). Recent reports suggest that the genetic component underlying music abilities and predispositions to training cannot be ignored, despite the potential causal effects of music training on the

neuroplastic changes observed (Drayna et al., 2001; Mosing et al. 2014; Mosing, Madison et al., 2014; Seesjärvi et al., 2016; Macnamara et al., 2014, 2016). Moreover, neuroanatomical differences have been described at the beginning of any training and hence, reflect neural predisposing factors that may influence the learning process (Foster and Zatorre, 2010; Herholz and Zatorre, 2012; Zatorre, 2013). Still, most previous reports using cross-sectional and interventional designs interpret the differences as training-induced effects (Stewart et al., 2003; Lahav et al., 2007, 2013; Ripollés et al., 2016). In order to rule out the training component, a few recent investigations with non-musicians looking for baseline brain measures that could predict learning, have been carried out. Specifically, BOLD-activity in the right auditory cortex during pre-training listening (Herholz et al., 2015) and fractional anisotropy (FA) values in the right superior longitudinal fasciculus (SLF) –or anterior segment of the AF– (Engel et al., 2014) were found to predict learning rate and speed of learning of piano melodies.

Here we investigated in a large sample of non-musicians to which extent the macro- and microstructural properties of the AF could predict participants' success in a short-term music training protocol (i.e., one single session). Differently from the existing study regarding melody learning in non-musicians (Engel et al., 2014), we performed deterministic tractography instead of a whole-brain DTI approach, with a focus on the dorsal auditory-motor pathway. Also, we independently evaluated rhythm and melody learning instead of choosing one of these domains. Although melody and rhythm processing have classically been **considered** as separate functional modules (Peretz & Coltheart, 2003; Phillips-Silver et al., 2013; Sihvonen et al., 2016), previous reports suggest that both facets are highly intertwined in the brain (Brown et al., 2013) and a similar pattern of damage to auditory-motor-related white-matter pathways can be found for both pitch- and rhythm-amusia (Sihvonen et al., 2017). Shedding light on this modularity question, as well as studying any specificity within the AF for these two domains, are secondary goals of the present investigation.

2. Methods

2.1. Participants

44 healthy native Spanish-Catalan speakers (mean age: 22.16 ± 2.56 ; 28 females) participated in this experiment. None reported any neurological, psychiatric or auditory disorder. All were non-musicians, with no more than 3 years of music lessons or experience (at least 10 years ago), or less than one consecutive year of experience (less than 10 years ago). Although all of them were non-musicians, were not currently playing, and did not master performance in any instrument, all participants had introductory music lessons at school (about 2 hours per week) during primary and secondary school. Participants were screened for Amusia using the Montreal Battery of Evaluation of Amusia (MBEA, Peretz et al., 2003), and none scored below the cutoff (i.e., 23). Participants were naïve to the hypothesis of the study, gave their written informed consent, and received monetary compensation. All procedures were approved by the Ethics Committee of the Hospital Universitari de Bellvitge, Barcelona (PR181/13).

2.2. Experimental Procedure

Participants first underwent an MRI session in which T1-weighted and DTI data was obtained, followed by a behavioural testing session in which they completed the rhythm and melody learning tasks (counterbalanced across participants). Behavioural sessions were always scheduled on a different date and after the MRI session. **The behavioural protocol included a neuropsychological battery that, due to time constraints, only contained proxy measures of verbal and non-verbal IQ (Wechsler Adult Intelligence Scale-III's Vocabulary test, Wechsler, 1999; and Raven Progressive Matrices test, Raven, 1989), and auditory working memory (WAIS-III's Digit Span). A short analysis to explore the relationship of these three cognitive variables with the music learning tasks is included here.**

2.2.1. Music learning tasks

Rhythm learning task

The Rhythm Learning task (RLT; Figure 1A and 1B) was an adaptation of the Rhythm Synchronization task (Chen et al., 2008 a, b; Bailey and Penhune, 2010) developed in our laboratory (Padrão et al., 2014). In this task, participants reproduced five different auditory rhythmic sequences across 12 consecutive trials. Rhythms varied in difficulty and were always presented in the same order, from easier to harder. Each rhythm consisted of 11 woodblock notes with the same pitch, with a total duration of 6 seconds. Rhythms differed in their temporal structure, so the interval following each sound varied such that five different musical durations (onset-to-onset) were created. Each rhythm contained: five eighth notes (each 250 ms), three quarter-notes (each 500 ms), one dotted quarter-note (750 ms), one half-note (1000 ms) and one dotted half-note (1500 ms).

Each trial was divided into two steps: *Listen* and *Listen and Imitate*. During the *Listen* part of the trials, participants were instructed to listen carefully without moving or marking the beat with any part of their bodies; during *Listen and Imitate*, they were instructed to tap in synchrony with the rhythm as accurately as possible, using the right index finger on the left button of a PC-mouse. The beginning of each trial was signaled with a warning tone presented 500 ms before the target sequence. Participants were instructed to perform the rhythmic sequences without stopping to correct errors and to try to follow the rhythm even when they were unsure. Before the start of learning, participants were given two trials of practice with two rhythms not included in the learning protocol, to familiarize them with the stimuli and what they were expected to do. No feedback was administered after this initial familiarization block, but the number of the current trial and rhythm was displayed on the screen with every change of trial and rhythm respectively.

Performance and learning were evaluated through two different variables: (i) the percentage correct (PC) responses, calculated as the percentage of responses (taps) made within

half of the onset-to-onset interval before and after a woodblock note (model tap or inter-stimulus interval); (ii) the absolute value of mean asynchrony (mASY), calculated only on correct responses (see Figure 1B).

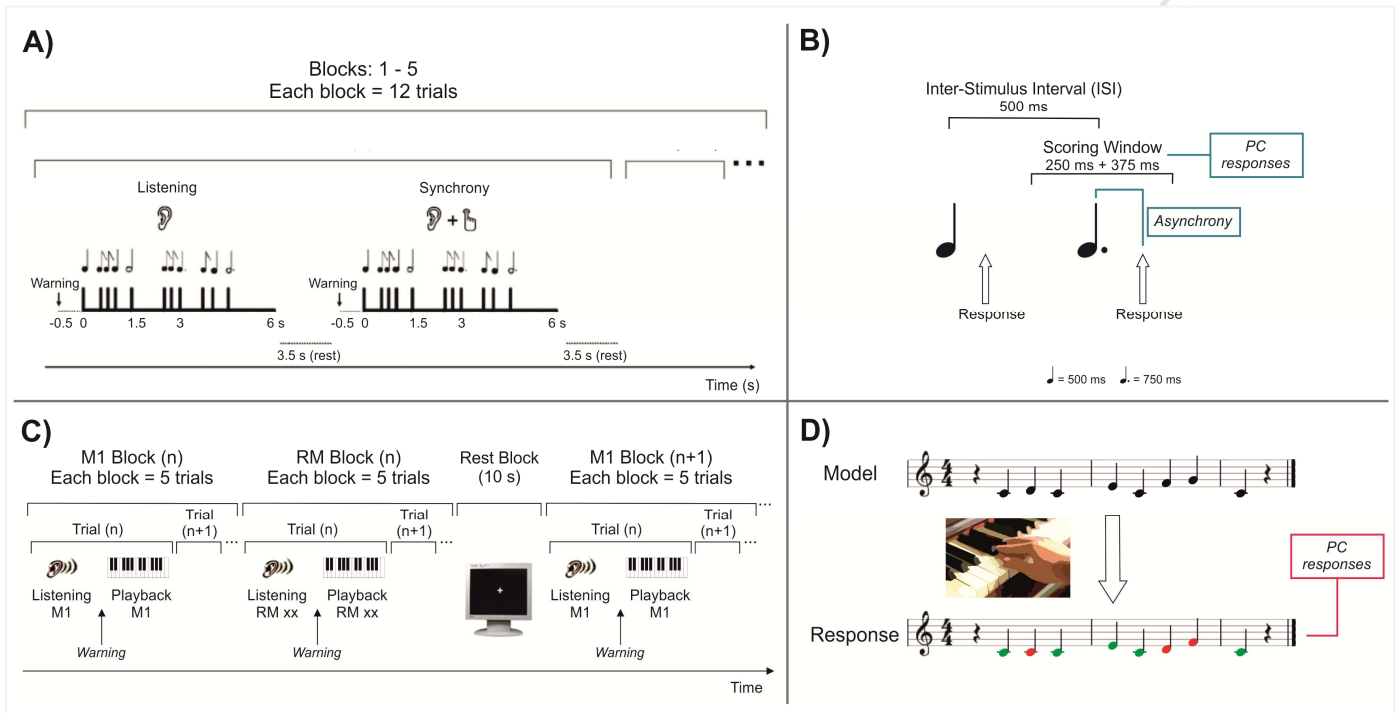


Figure 1. Schematic representation of the musical tasks and their measures of learning (top row corresponds to the rhythm learning task or RLT, bottom row pertains to piano-melody learning task or MLT). **A)** Scheme of the RLT: each block contained only one of the rhythms, and there were 12 consecutive trials per block. **B)** Parameters extracted for the RLT. **C)** MLT's scheme: blocks of the trained melody (M1) and random melodies (RM: control condition) were intercalated, with resting breaks of 10 seconds after each pair of M1 and RM blocks; this scheme was repeated until reaching block number 8, both for the M1 and the RM. **D)** Responses in the melody learning task and measure extracted. Abbreviations: M1, trained melody; RM; random melody; PC, percentage correct responses.

Melody learning task

The Melody Learning task (MLT) was based on the melody learning paradigm used in a fMRI study by Chen and colleagues (2012) in which participants learned to play an eight-note melody (M1) across 40 trials of practice (Figure 1C and 1D). Performance on the learned melody was compared to performance of similar melodies that were only repeated once, and thus could not be learned (RM: random melodies). Random melodies contained the same

pitches as the M1, but the order of them was unique and different in every trial. All melodies were isochronous and contained 8 quarter notes from the middle octave of the piano, C4-D-E-F-G (duration of each quarter note: 730 ms; 51.43 ms of inter-stimulus interval; total duration of the melody: 6600 ms, including 200 silent ms at the beginning and the end of each clip).

The task was divided into two steps: (1) *Familiarization*: participants listened to and played 2 repetitions of 5 practice sequences. These sequences increased progressively in difficulty, from simple sequences of repeated keys to more complex combinations. (2) *Training phase*, containing 8 blocks with 5 repetitions of each of the conditions in each block: (i) *Melody Listen and Melody Imitation* first, participants had to listen to M1 and, after that, they had to play it by memory after hearing a warning tone; (ii) *Random melody Listen and Random melody Imitation*, which is an interesting condition that could reinforce the auditory association with each pitch, but not the learning of the M1 contour. (iii) *Rest* in silence for 10 seconds. These three steps were fixed and the only aspect that changed was the Random melody Listen and Imitation condition, since the order of the random melodies (RM) presented in those blocks were randomized across participants. **The** performance was measured by calculating the percentage of correct notes per trial for the trained melody (M1) and for the random melodies (RM) (see Figure 1D).

For both musical tasks, the auditory stimuli were delivered through stereo headphones at a comfortable intensity level, adjusted for each participant. For the melody task, a Yamaha PSR-E343 MIDI keyboard was used as the response device. In order to avoid visual feedback, the keyboard was covered by a box (similar to that used by Engel and collaborators, 2014). For the rhythm task, a computer mouse was used for recording participants' performance. The rhythm learning task was implemented in Presentation (Neurobehavioral Systems) and the melody task in EventIDE (Okazolab Ltd, 2012). Both tasks were run on a PC computer.

2.2.2. *Imaging acquisition and analyses*

Diffusion Tensor Imaging (DTI: spin echo diffusivity sequence) data was obtained from a 3.0 T Discovery mr750w General Electric scanner (Alomar Medic Centre, Barcelona, Spain). Imaging parameters for the DTI sequence were: TR = 12825.00 ms, TE = 9ms; FOV = 128 x 128 x 57 mm; matrix size = 128 x 57; slice thickness = 2.0 mm; no gap; 57 axial slices; voxel size was 2 x 2 x 2 mm. Diffusion was measured along 72 non-collinear directions, using a b value of 1000 s/mm², and including a b=0 as the first volume of the acquisition as well as 8 additional b=0 intercalated each 8 volumes.

DTI - preprocessing and manual dissection

To pre-process the diffusion-weighted images, first, the brain was virtually separated from the rest of the head using FSL's Brain Extractor Tool (Smith, 2002; Smith et al., 2004; Woolrich et al., 2009). Afterwards, motion and eddy-current correction was performed using FMRIB's Diffusion Toolbox (FDT), part of the FMRIB Software Library (FSL 5.0.1 www.fmrib.ox.ac.uk/fsl/). The b-vectors gradient matrix was then rotated in order to take into account the corrections made at the previous stage, by using the *fdt_rotate_bvecs* software included in the FMRIB Software Library. The diffusion tensors were then reconstructed using Diffusion Toolkit's least-square estimation algorithm for each voxel, and Fractional Anisotropy (FA) was calculated (Ruopeng Wang, Van J. Wedeen, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, <http://www.trackvis.org/>).

Whole-brain deterministic tractography was performed in Diffusion Toolkit, using an interpolated streamlines algorithm, with a maximum curvature threshold of 35 degrees and a minimum FA threshold of 0.2. The fibre direction is assumed to correspond to the principal eigenvector (the eigenvector with the largest eigenvalue). This vector was colour coded (green for anterior–posterior, blue for superior–inferior and red for left–right directions) in order to generate a colour–coded FA map. Dissections were carried out for each subject in the native space and in both hemispheres, using Trackvis software. The regions of interest (ROIs) were

defined on the FA and FA colour-coded maps according to individual anatomical landmarks, instead of atlas-based constraints which neglect individual differences (López-Barroso et al., 2013).

The three segments of the AF were dissected by LV using three main manually defined ROIs as described in previous studies (Catani et al., 2005, 2007; López-Barroso et al., 2013). Specifically, a first ROI was delineated in the coronal view, anterior to the central sulcus, encompassing the fibres going to the inferior frontal gyrus (IFG, including Broca's area; Brodmann's areas 44 and 45, and parts of the medial frontal gyrus). Then, in the axial view, a second ROI was depicted covering the WM underlying the medial and superior temporal gyrus (STG, embracing the fibers traveling to Wernicke's territory; Brodmann's areas 22p, 41 and 42). Finally, a third ROI was drawn on the sagittal view, covering supramarginal and angular gyri and encompassing the fibers traveling to Geschwind's territory (Brodmann's areas 39 and 40). These ROIs were combined to encompass the three rami of the AF: the long (between IFG-Broca's and STG-Wernicke's areas), the anterior (linking IFG-Broca's and Geschwind's territories) and the posterior (connecting Wernicke's and Geschwind's territories) segments. Artefactual fibers were removed using exclusion ROIs. See Figure 2 for a dissection example in one of our participants.

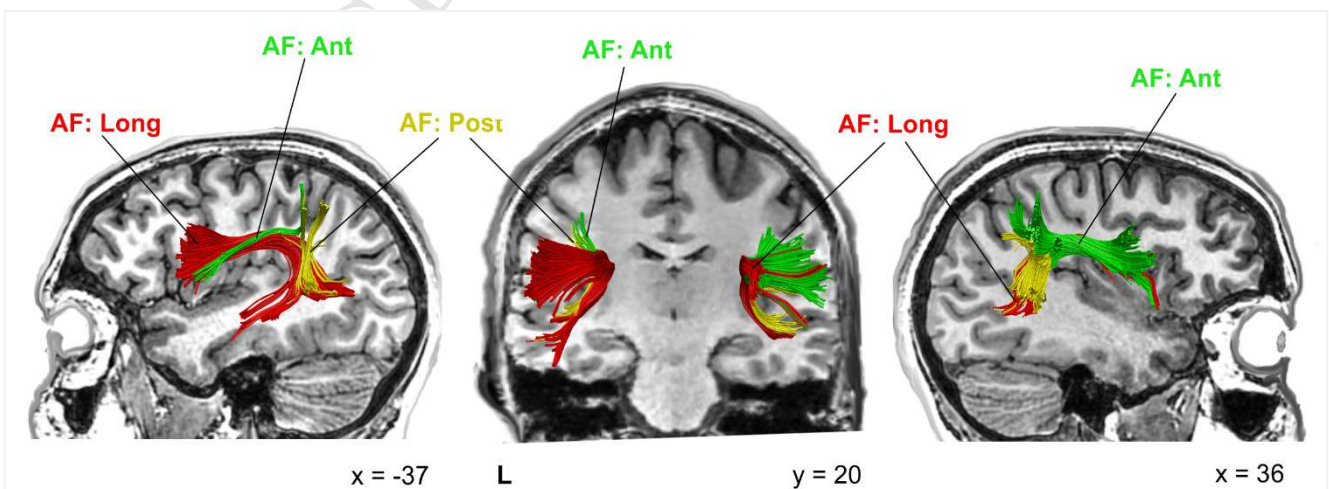


Figure 2. Depiction of the bilateral dissection of the AF in an example subject. Colour code: red, long segment of the AF; green, anterior segment of the AF; yellow, posterior segment of the AF. Abbreviations: AF: arcuate fasciculus; Ant: anterior segment; Post: posterior segment.

2.3. Statistical analysis

We restricted our statistical analysis to FA and volume measures since recent investigations have shown that these WM parameters are very sensitive to individual differences (Saygin et al., 2013; Ocklenburg et al., 2014; Sreedharan et al., 2015; Vaquero et al., 2016). We extracted the volume and the FA from the bilateral whole AF (summing up the values from each of the three AF segments, Vaquero et al., 2016), as well as for the three rami of the AF separately in each hemisphere. Pearson correlations between the WM related measurements and the music learning values, both for RLT and MLT, were performed, always controlling for the self-reported number of hours of music lessons. These correlations were run using IBM SPSS Statistics 24. Correlations were run in two steps: firstly, we run the analysis with the AF as a whole; and secondly, we run the correlations separating by AF segments. FDR-corrections were made at the two steps of analysis separately (whole AF, AF segments), differentiating also by type of task (RLT, MLT). FDR-corrections were applied using Matlab 2012b. Thus, correlations were considered significant for p -values below 0.05 after FDR correction with $n = 12$ comparisons for the RLT and $n = 8$ comparisons for the MLT for the whole-AF analysis, and $n = 36$ comparisons for the RLT and $n = 24$ comparisons for the MLT for the AF-segments comparison. P -values were adjusted for non-sphericity using the Greenhouse-Geisser test when appropriate.

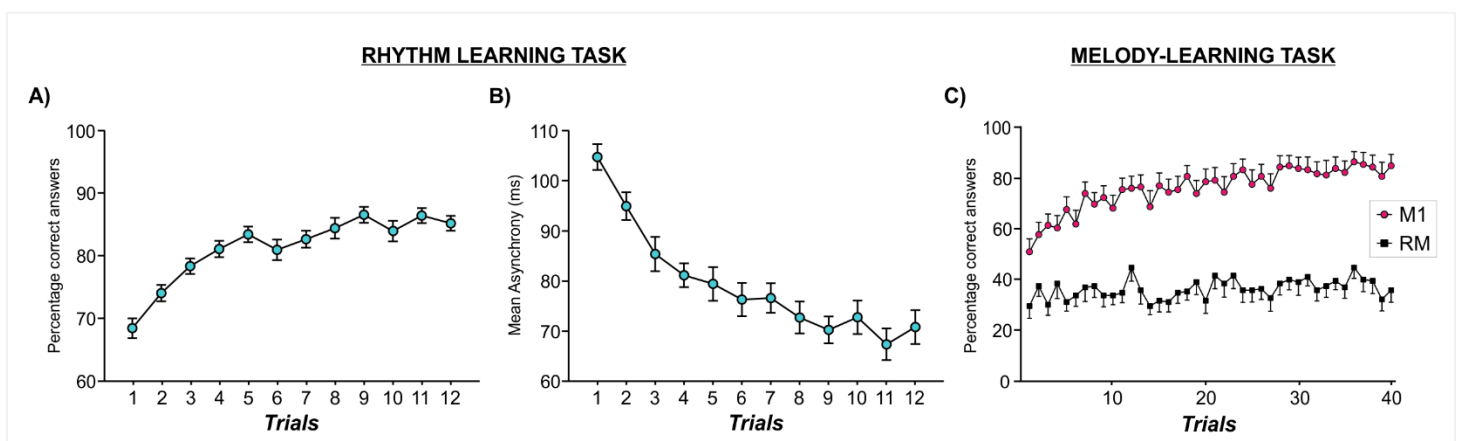


Figure 3. Learning curves depicting the mean performance across subjects in each trial. First two graphs from the left correspond to the RLT (all four rhythms are collapsed and depicted trial by trial). **A)** Percentage correct (PC) responses in the rhythm task: PC increases trial by trial. **B)** Mean absolute values of asynchrony: asynchrony is reduced throughout the task. The last graph on the right (**C)** corresponds to the MLT: pink circles show the learning curve for melody 1 or M1 (the only melody that was repeated throughout the task and was targeted for learning), black squares show the performance for the random melodies (RM); performance for the M1 increased trial by trial, while there was no indicator of improvement for the RM across trials.

3. Results

3.1. Behavioural results: learning of musical tasks

3.1.1. Rhythm task

The thirty-five participants who completed this task and also had usable DTI data were included in this analysis. In addition, when correcting this task, we observed that “rhythm 4” was extremely difficult and no single participant was able to learn it. Consequently, we decided to remove this rhythm and focus our analyses on the average of the remaining four rhythms (i.e., 1, 2, 3, and 5).

As shown in Figure 3 (panels A, B), a repeated-measures ANOVA determined that performance improved across the 12 trials of learning for both mean asynchrony ($F(11, 374) = 28.96, p < .0001$) and percentage correct ($F(11, 374) = 24.16, p < .0001$). See Table 1 for correlation values among rhythm measures.

3.1.2. Melody task

The twenty-four participants with both usable behavioural and DTI data were included in this analysis. As depicted in Figure 3 (panel C), a condition (2: M1, RM) per trial (40) repeated-measures ANOVA showed an interaction of melody type per trial ($F(39, 897) = 1.93, p < .05$), such that there was a significant improvement between the first and the last trial for M1 but not for RM (paired t-test between first and last trials for M1: mean PC 1st trial = 51.04, SEM = 6.2, mean PC trial 40th = 84.9, SEM = 5.4; $t(23) = -5.2, p < .0001$; paired t-test between first and last

trials for RM: mean PC 1st trial = 29.69, SEM = 4.9, mean PC trial 40th = 35.94, SEM = 4.8;
 $t(23) = -1.2, p = 0.228$).

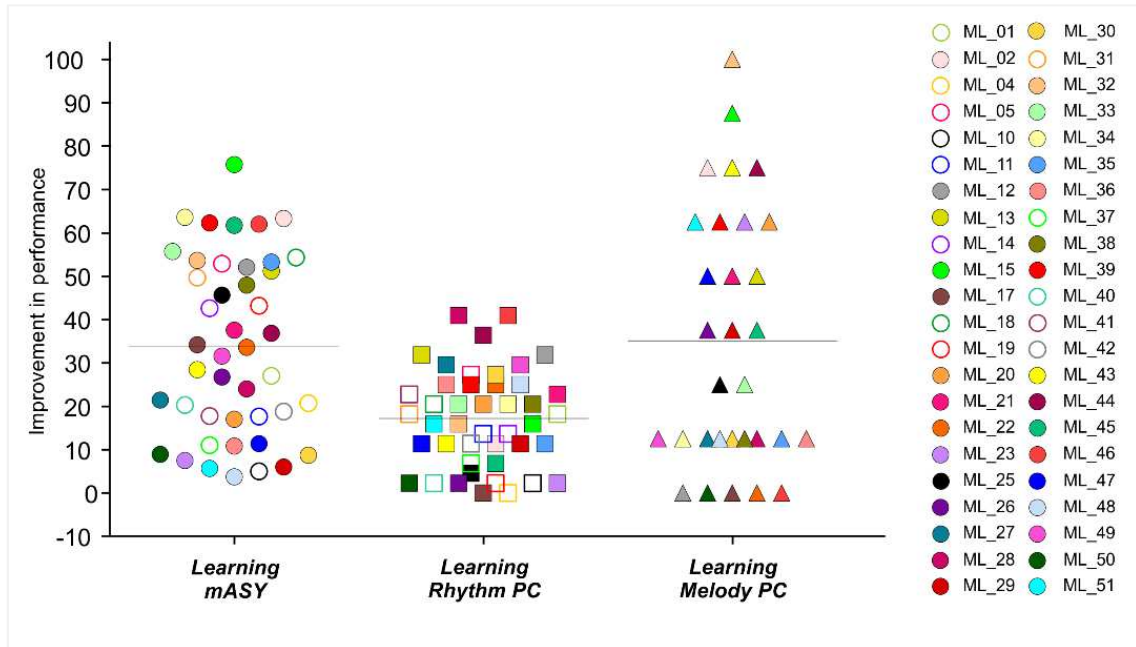


Figure 4. This graph depicts the distribution of our cohort in terms of change in performance throughout the task (learning rate) in the different aspects of our music learning paradigm. From left to right: circles correspond to learning in mASY (mean absolute values of asynchrony) in the RLT; squares show the distribution of improvement in percentage correct (PC) responses in the RLT; triangles correspond to the improvement in percentage correct responses in the MLT. Open figures (circles/squares) correspond to those participants who completed the rhythm task but not the melody task, filled figures show the participants who completed both the rhythm and the melody task; each subject is coded with a different colour. Horizontal lines depict the group means for each measure.

3.2. Calculation of individual learning measures

To assess the relationship between brain structure **or cognitive measures with the** individual differences in learning we extracted a score for both the Melody and Rhythm Learning tasks. To assess learning we used individual learning rate [(final performance – initial performance) / initial performance], which reflects the amount of change for each participant taking into account the baseline performance (see for a discussion Dimitrov and Rumrill, 2003). This measure of learning rate was calculated for percentage correct responses (in both MLT and

RLT) and for mASY in the RLT. See Figure 4 for a depiction of the distribution of learning in the different music-tasks variables.

In addition, to measure the speed of learning in the musical tasks, we computed the minimum number of trials needed by each participant to reach 70% correct responses (e.g., Golestani et al., 2002, 2004; Engel et al., 2014). In the case that the participant never reached 70% correct responses, we assigned a score corresponding to the maximum number of trials contained in the task, 12 for the RLT, and 40 for the MLT.

| | Learning rate for Rhythm PC | Learning rate for mASY | Learning Speed for Rhythm | Learning rate in Melody PC | Learning Speed in Melody |
|-----------------------------|----------------------------------|------------------------|----------------------------------|----------------------------|--------------------------|
| Learning rate for Rhythm PC | | | r = .84 p = .00 | | |
| Learning rate for mASY | | | | | r = -.34 p = .10 |
| Learning Speed for Rhythm | r = .84 p = .00 | | | r = -.24 p = .28 | |
| Learning rate in melody PC | | | r = -.24 p = .28 | | |
| Learning speed in Melody | | r = -.34 p = .10 | | | |

Table 1. Correlations across all the variables of learning for both music tasks (RLT and MLT). Bold letters show the significant correlations. Comparisons among the rhythm task parameters (white cells) have a sample size: $n = 35$; comparisons among the melody task parameters or for the rhythm compared to the melody task (violet-shaded cells) have a sample size: $n = 24$. All values are rounded to a maximum of two decimals, and only those correlations with $r \geq 0.25$ are shown. Abbreviations: PC, percentage correct; mASY, absolute values of mean asynchrony.

3.3. Behavioural results: relationship with cognitive variables

Pearson correlations were performed between the cognitive measures (i.e., general IQ and auditory working memory) and the learning rate and learning speed in both the RLT and the MLT for the final sample used in the rest of the analysis (participants who had usable DTI data and RLT and/or MLT data): for WAIS' Vocabulary and Digit Span subtests, $n = 35$; for Raven Progressive Matrices test, $n = 30$. No significant relationship was found for any of these correlations ($p > .14$), even after controlling for hours of music lessons. Thus, in the present sample, neither general IQ nor auditory working memory abilities influenced music learning, in either the RLT or the MLT.

3.4. Tractography correlations

For the 35 participants with rhythm data and the 24 participants with melody data, learning rate, and the index of learning speed for every measure in both RLT and MLT were included in the Pearson correlations carried out with the imaging data: for the total volume/FA of the arcuate fasciculus, first, and for the individual volumes/FA of each of the three segments of the AF, secondly. All correlations were controlled for the self-reported number of hours of music lessons.

3.4.1. Structural connectivity predictors of learning rate

When looking at FDR-corrected results for the whole AF in relation to learning rate values, no significant results held after the correction. However, there was a significant uncorrected correlation between white matter structure and learning rate for the RLT. Specifically, the

volume on the right whole AF was positively correlated with the learning rate of mASY ($r = 0.36, p < .05$ uncorrected). See Figure 5 – A1.

As a secondary step in the analysis, looking at the different segments of the AF separately we found that it was the right anterior segment the one driving the changes in mASY: volume in the right anterior segment was positively correlated with the learning rate of mASY ($r = 0.57, p < .001$ FDR-corrected). In other words, the greater the volume of the right AF (concretely, in the anterior segment), the higher the change between initial and final performance in the RLT. In addition, there was a significant positive correlation between the FA in right long segment and the learning rate in the MLT by means of PC ($r = 0.58, p < .05$ uncorrected). However, this result did not survive the FDR correction. See Figure 5 B and Table 2.

No significant correlations were found for the left AF, neither as a whole or separated by segments.

3.4.2. Structural connectivity predictors of learning speed

The macro- and microstructural organization of the right AF also predicted the minimum amount of trials needed for reaching 70% correct responses, specifically in the MLT. Learning speed in the MLT was negatively correlated both with volume ($r = -0.58, p < .005$, FDR corrected) and FA ($r = -0.52, p < .05$, FDR corrected) of the right whole AF (See Figure 5 – A2).

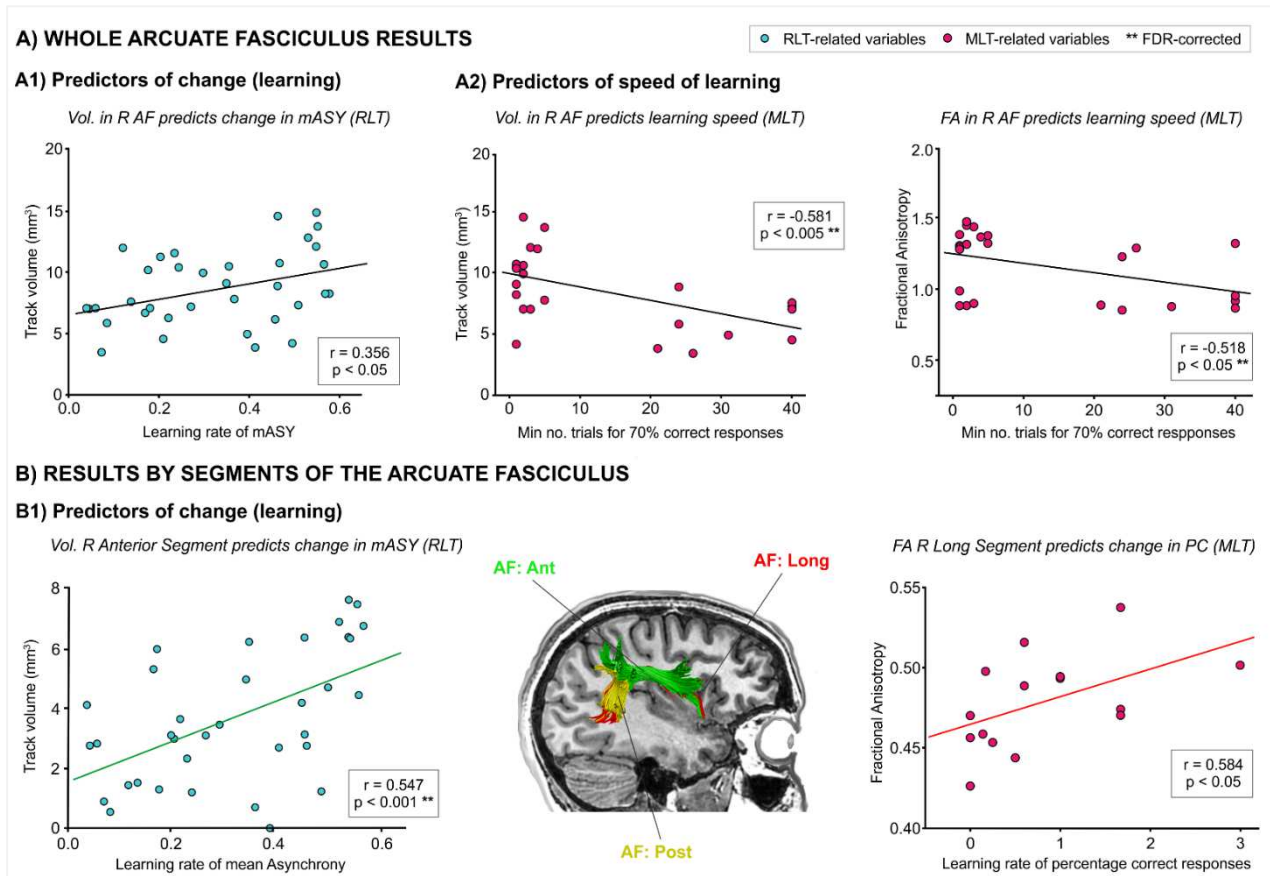


Figure 5. Scatterplots showing the significant correlations found between DTI measurements and learning in the musical tasks. Blue dots correspond to rhythm variables, pink dots show melody-related measures. **A)** Results for the analysis with the whole AF. **B)** Results for the analysis dividing the AF by segments. *Predictors of learning (change between the last and the first trials):* **A1)** Positive correlation between the volume in the right AF as a whole and the learning rate of mASY (RLT); uncorrected. **B1)** On the left: positive correlation between the volume in the right anterior segment of the AF and the learning rate of mASY (RLT); this result is FDR-corrected. On the right: positive correlation between FA in the right long segment of the AF and the learning rate of PC (MLT); uncorrected. *Predictors of learning speed:* **A2)** Negative correlations between volume and FA in the right AF as a whole and the learning speed in the MLT; these results are FDR-corrected. Abbreviations: AF: arcuate fasciculus; mASY: mean asynchrony (absolute values); Vol.: volume; FA: Fractional Anisotropy; R: right; RLT: rhythm learning task; MLT: melody learning task.

| | Learning rate rhythmPC (n=35) | Learning rate mASY (n=35) | Learning speed Rhythm (n=35) | Learning rate Melody (n=24) | Learning speed Melody (n=24) |
|----------------------|-------------------------------------|-------------------------------------|------------------------------------|-----------------------------------|--------------------------------------|
| L whole AF volume | ACCEPTED MANUSCRIPT | | | | |
| L whole AF FA | | | | | |
| R whole AF volume | | r = .36 p = .04 | | | r = -.58 p = .00 ** |
| R whole AF FA | | | | | r = -.52 p = .01 ** |
| L Long volume | | | | r = -.3 p = .18 | |
| L Long FA | r = .29 p = .1 | | | | |
| L Ant volume | | | | | r = .31 p = .15 |
| L Ant FA | | | | | |
| L Post volume | | | | r = .34 p = .12 | |
| L Post FA | | | | r = .33 p = .14 | |
| R Long volume | | | | | r = -.25 p = .4 |
| R Long FA | | | | r = -.58 p = .03 | r = -.46 p = .1 |
| R Ant volume | | r = .57 p = .00 ** | | r = .41 p = .06 | |
| R Ant FA | | | | | |
| R Post volume | r = -.25 p = .15 | | | | |
| R Post FA | | | | | r = -.27 p = .21 |

Table 2. Details of the correlations between the DTI measures and the performance measurements from both the MLT and the RLT (sample size is given in brackets for each music-learning measure). Shaded cells and bold letters show those significant results at $p < 0.05$, after controlling for the number of hours of music lessons. Asterisks mark the correlations that hold after FDR-correction (see details of this correction in the main text, in the methods, section 2.2.2.). All values are rounded to a maximum of two decimals, and only those correlations with $r \geq 0.25$ are shown. Abbreviations: PC, percentage correct; mASY, absolute values of mean asynchrony; L, left; R, right; AF, arcuate fasciculus; Ant, anterior segment of the AF; Post, posterior segment of the AF; FA, fractional anisotropy.

As seen in Figure 5 (A2), the variable accounting for learning speed in the MLT, has a very polarized distribution that could be affecting the estimated correlation value. Hence, for explorative purposes, we decided to seek for differences between fast and slow learners of piano melodies. We divided our sample into two groups: fast melodic learners (minimum amount of trials to reach 70% of correct responses ≤ 20 , $n = 15$) and slow melodic learners (minimum amount of trials to reach 70% of correct responses > 20 , $n = 9$). Then, we performed a two-sample t-test in order to compare these two groups regarding their WM macro- and microstructure in the whole AF. Not surprisingly, we found that these two groups showed a specific significant difference in their mean right whole AF volume (mean volume in right whole AF for fast learners = 9.92, SD = 2.73; mean volume in right whole AF for slow learners = 5.98, SD = 1.87; $t(22) = 3.81$, $p < .001$) and FA (mean FA in right whole AF for fast learners = 1.24, SD = 0.21; mean FA in right whole AF for slow learners = 1.02, SD = 0.2, $t(22) = 2.53$, $p < .05$).

No significant correlations were found for learning speed in the RLT or for the left AF neither as a whole or separated by segments.

4. Discussion

In the present study, we examined white-matter structural correlates of individual differences in rhythm and melody learning abilities in non-musicians, using deterministic tractography. Our results showed that (i) volume of the right AF, particularly in the anterior segment, predicts rate of learning in the rhythm task, (ii) volume and FA in the right AF predict the speed of learning in the melody task, and (iii) FA in the right long segment also predicts melody learning rate. These results support the crucial role of the AF in auditory-motor learning and the involvement of feedback-feedforward loops during auditory-motor integration (Hickok and Poeppel, 2007; Zatorre et al., 2007; Rauschecker and Scott, 2009; Novembre and Keller,

2014; Patel, 2014). They also show for the first time specificity within the AF branches for different musical facets (i.e., melody and rhythm). **The strong lateralization showed by our results supports a role for the right dorsal auditory pathway in integrating auditory and motor information for music that parallels the role of the left in language (Hickok & Poeppel 2015; Rauschecker & Scott, 2009; Rodríguez-Fornells et al., 2009).** Furthermore, the strongest result, relating the volume in the anterior segment with improvements in synchronization ability, **points** out to a critical involvement of this pathway in the monitoring, prevention and minimization of errors during music learning (Rodríguez-Fornells et al., 2012; Padrão et al., 2014).

In the context of speech processing and auditory-motor integration, there is a predominant model characterizing the cortical and functional organization of language (but also music) in a dorsal and a ventral stream (Rauschecker & Tian, 2000; Hickok & Poeppel, 2000, 2004, 2007; Rauschecker & Scott, 2009). According to this dual-route description, there is (i) a *postero-dorsal stream* responsible of mapping acoustic signals to their articulatory-based representations, in other words, it would process auditory objects in relation to a sensorimotor internal model. The dorsal route encompasses the superior temporal gyrus (STG), the parieto-temporal boundary and posterior frontal regions (including IFG/Broca's area and premotor regions). On the other hand, there is (ii) an *antero-ventral stream* controlling the mapping of sounds to its corresponding meaning by recognizing the auditory objects in different degrees of complexity, creating then novel structures using conceptual combinations. This ventral stream includes the middle and superior temporal cortices, inferior temporal and anterior temporal pole regions, terminating in anterior and ventral parts of the IFG (Rauschecker & Tian, 2000; Hickok & Poeppel, 2000, 2004, 2007; Poeppel & Hickok, 2004; Rauschecker & Scott, 2009; Rodríguez Fornells et al., 2009; Hickock et al., 2011; Bornkessel-Schlesewsky et al., 2015). Two regions emerge as crucial in both streams: the superior temporal cortex, and the prefrontal cortex which according to a recent revision of this dual-route model, is viewed

as a cross-stream integration and top-down feedback controller between the two routes (Bornkessel-Schlesewsky et al., 2015). The three segments of the AF connect the auditory (STG), inferior parietal, premotor, motor, and prefrontal regions, which are all part of the dorsal stream. This dorsal auditory-motor pathway has been described as part of a feedback-feedforward loop important for both perception and production of speech (Hickok & Poeppel, 2015; Rauschecker & Scott, 2009). More generally, it is involved in the accurate perception of auditory stimuli (for instance, music), the creation of predictions of sensory consequences of motor actions, and the comparison with stored templates in order to correct for errors if needed (Zatorre et al., 1992; Warren et al., 2005; Cunillera et al., 2009; Rodríguez-Fornells et al., 2009; Rauschecker and Scott, 2009; Rauschecker, 2012; López-Barroso et al., 2013, 2015; Brown et al., 2015; Vaquero et al., 2016).

The functions of the dorsal pathway that are mediated by the AF may be especially relevant early in auditory-motor learning, when multisensory feedback is crucial to establish and refine the link between motor actions and sensory consequences (Kleber et al., 2013; James et al., 2014; Qi et al., 2015; Mamiya et al., 2016). Recent investigations found a critical involvement of the AF during music training in non-musicians. Specifically, better micro- and macrostructural organization of the right AF / SLF were related to faster learning rates in a melody task (Engel et al., 2014) and to the ability to learn the structure of musical phrases (Loui et al., 2011). Also, FA within the left AF was related to more synchronized tapping (Blecher et al., 2016), and a sequential engagement of some of the areas linked by the AF in the early stages of rhythm learning (i.e., prefrontal, parietal and premotor regions) was described (Ramnani & Passingham, 2001). In addition, damage to the right AF was found to be associated with congenital (Loui et al., 2009) and acquired (Sihvonen et al., 2017) amusia, highlighting the importance of this structure in music processing.

In the present study, the right AF was found to be crucially involved in music learning, but the micro- and macrostructural organization of specific branches were differentially related to learning rhythms or melodies. Specifically, we found a relation between volume of

the right AF and learning rate in the rhythm learning task (RLT) that was specifically driven by the anterior segment. Following the AF's characterization used in the present study (Catani et al., 2005; Vaquero et al., 2016), the anterior segment links the IFG with the inferior parietal region. Thus, improvements in asynchrony were related to individual differences in the ability to detect and correct for errors, and to update the internal representation of the auditory-motor map that is being created. In line with this, Padrão and colleagues (2014) observed a P3-like centroparietal ERP component for errors committed during the late stages of rhythm learning, which magnitude was associated with individual differences in synchronization. Hence, a strong direct connection between multisensory-integration parietal regions and premotor and motor areas that can plan and modify the motor commands, adjusting the synchronization, seem to be crucial to improve the performance in the present RLT. On a different note, it is important to acknowledge the lack of consensus regarding AF's anatomical division, functions and terminology, and how, in some studies, the AF can include some of the SLF rami –SLF III as Anterior segment, mainly– (Dick and Tremblay, 2012; Fernández-Miranda et al., 2015; Wang et al., 2016; Petrides et al., 2012; Bozkurt et al., 2016).

On the other hand, learning speed in the melody learning task (MLT) was strongly related to the volume and FA of the right AF as a whole, but no strong relationship with one of the three branches emerged from our analysis. This may be pointing out to the nature of this measure, learning speed, as a more general index of how difficult was the task of relating specific sounds with the corresponding key-presses. Thus, a strong general connection between the three main regions connected by the AF could be the key. **Previous** research suggested a domain-general involvement of the right AF in activities requiring matching sounds with actions (Halwani et al., 2011). Despite this view, we observed a trend in the long segment, connecting the IFG with superior and middle temporal regions (Catani et al., 2005; Vaquero et al., 2016), as being the branch driving the relationship with learning rate in the melody learning task (MLT). Hence, learning in the MLT was related to individual differences in the ability to link auditory and motor information, for which a direct connection between auditory and motor

regions seems crucial. Moreover, the right auditory cortex has been previously related to pitch **and melodic** processing (Loui et al., 2011; Albouy et al., 2013; Sihvonen et al., 2016). This correlation may have not been stronger due to the high number of individuals in which the long segment was missing on the right hemisphere, in line with previous reports (Catani et al., 2007; Catani & Mesulam, 2008). In summary, our results showing a differential involvement of the anterior segment for rhythmic learning and of the long segment for melodic learning suggests a **somewhat modular view** for music **processing**, although this question would need further investigation.

The global right lateralization of the findings is in line with previous reports: at the level of primary auditory cortex, it is hypothesized that the right hemisphere is more sensitive to pitch and spectral information, while the left hemisphere is more sensitive to very rapid temporal changes (10-20 msec range) that are important for speech (Poehpel, 2003; Boemio et al., 2005; Zatorre et al., 1992; Zatorre et al., 2002; Zatorre et al., 2007). The temporal dynamics of the rhythms learned in this study are well outside this range (shortest notes were 250 ms and longest notes were 1500 ms), and studies using similar stimuli have found either right-sided or bilateral activation for rhythm processing (Chen et al., 2008 a,b; Grahn & Rowe, 2009; Brown et al., 2013). Further, patients with right auditory cortex lesions show deficits in rhythm imitation (Penhune et al, 1999). Also, this hemispheric asymmetry by which the right auditory regions are preferentially involved in the processing of both rhythm and melody, seems to be influenced by music training (Bermudez et al., 2009; Angulo-Perkins et al., 2014; Elmer et al., 2016; Serrallach et al., 2016), but it is still observed in non-musicians adults and even in newborns (see Brown et al., 2015, and Herholz & Zatorre, 2012 for reviews; Perani et al., 2010; Telkemeyer et al., 2009).

In addition, the present results support recent views regarding the presence of pre-existing structural traits that may explain individual differences in musical abilities (Schneider et al., 2005b; Foster & Zatorre, 2010; Seither-Preisler et al., 2014). These individual differences have

been recently suggested to be the result of a combination of genetic and environmental components (Ullén, Hambrick & Mosing, 2016; de Manzano & Ullén, 2018). Interestingly for the present topic, a strong genetic contribution has been observed on pitch perception, as well as on music training (Drayna et al., 2001; Mosing et al. 2014; Ullén et al., 2016; Seesjärvi et al., 2016). In addition, different contributions of environmental and genetic factors have been described to influence the three rami of the AF, with the long segment maturing early, being left lateralized and being mostly affected by shared environmental or familial factors; the anterior branch being lateralized to the right before adolescence and being determined to a similar degree by familial and pure environmental factors; and the posterior segment being the most affected by pure environmental factors (especially on the right hemisphere; Budisavljevic et al., 2015). This description suggests that the parietal/indirect branches of the AF may be more affected by training and life experiences than the long/direct segment. This may point out to an advantage in the RLT for those individuals with greater musical experience or who are more engaged in musical activities in their daily lives. However, we controlled for the number of hours of music lessons attended in the participants' lifetime, and thus this experience is partially ruled out. **Further** investigation on the contribution of genetic and environmental factors on brain predispositions would be necessary **and, in the future, a better control for music experience, direct or indirect exposure to music, and general use and engagement in music (as assessed by questionnaires like the Goldsmith Musical Sophistication Index, Müllensiefen et al., 2014), would be highly recommendable.**

In conclusion, the present findings endorse the AF as the crucial white-matter bundle supporting the dorsal route classically described for speech and language processing, and recently proposed for music processing (Brown et al., 2015). In addition, our results point out to the AF as the structure performing the important transformations described for the feedback-feedforward loop needed in both language and music learning and performance. Especially, the anterior branch and the inferior parietal regions that it connects to the IFG seem to be the key to keep the audio-to-motor representations updated and to control performance, via error

monitoring processes. Future studies may try to reconcile previous functional findings and the present structural results by combining DTI with EEG, MEG or resting state connectivity data.

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