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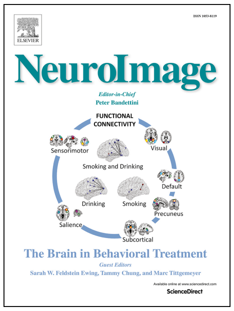

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Subcortical and cortical correlates of pitch discrimination: evidence for two levels of neuroplasticity in musicians

Abbreviated title: Subcortical and cortical plasticity in musicians

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Conflict of interest

Hartwig R. Siebner has served on a scientific advisory board for Lundbeck A/S, Valby Denmark, and has received honoraria as speaker from Biogen Idec, Denmark A/S, Genzyme, Denmark and MerckSerono, Denmark, has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, has received travel support from MagVenture, Denmark, and has received a research fund from Biogen-idec. The remaining authors have no conflicts of interest.

Abstract

Musicians are highly trained to discriminate fine pitch changes but the neural bases of this ability are poorly understood. It is unclear whether such training-dependent differences in pitch processing arise already in the subcortical auditory system or are linked to more central stages. To address this question, we combined psychoacoustic testing with functional MRI to measure cortical and subcortical responses in musicians and non-musicians during a pitch-discrimination task. First, we estimated behavioral pitch-discrimination thresholds for complex tones with harmonic components that were either resolved or unresolved in the auditory system. Musicians outperformed non-musicians, showing lower pitch-discrimination thresholds in both conditions. The same participants underwent task-related functional MRI, while they performed a similar pitch-discrimination task. To account for the between-group differences in pitch-discrimination, task difficulty was adjusted to each individual's pitch-discrimination ability. Relative to non-musicians, musicians showed increased neural responses to complex tones with either resolved or unresolved harmonics especially in right-hemispheric areas, comprising the right superior temporal gyrus, Heschl's gyrus, insular cortex, inferior frontal gyrus, and in the inferior colliculus. Both subcortical and cortical neural responses predicted the individual pitch-discrimination performance. However, functional activity in the inferior colliculus correlated with differences in pitch discrimination across all participants, but not within the musicians group alone. Only neural activity in the right auditory cortex scaled with the fine pitch-discrimination thresholds within the musicians. These findings suggest two levels of neuroplasticity in musicians, whereby training-dependent changes in pitch processing arise at the collicular level and are preserved and further enhanced in the right auditory cortex.

Keywords: musical training, pitch discrimination, auditory cortex, inferior colliculus, task difficulty, harmonic resolvability

1. INTRODUCTION

Natural sounds, like speech and music, contain harmonic structures that typically elicit a pitch percept corresponding to the fundamental frequency (F_0) (e.g., Licklider, 1956; Schouten, 1962; de Cheveigné, 2005). Hence, the human auditory system is typically exposed to harmonic sounds in everyday acoustic environments. Musicians are, however, specifically trained to retrieve the pitch of harmonic complex stimuli with high accuracy, since sounds produced by musical instruments are generally harmonic tones. Although musicians' superior ability to discriminate fine pitch changes has been shown in numerous behavioral investigations (Spiegel and Watson, 1984; Kishon-Rabin et al., 2001; Micheyl et al., 2006; Allen and Oxenham, 2014; Bianchi et al., 2016a), the neural bases of this enhanced performance are poorly understood. Many studies have reported that long-term musical training leads to structural and functional changes at both cortical (e.g., Pantev et al., 1998; Schneider et al., 2002; Bermudez et al., 2009; Hyde et al., 2009; Foster and Zatorre, 2010; Seither-Preisler et al., 2014) and subcortical (Musacchia et al., 2007; Wong et al., 2007; Parbery-Clark et al., 2009) stages along the auditory pathway (for a review see Herholz and Zatorre, 2012). However, evidence suggesting that this plasticity begins already at the subcortical level stem from electrophysiological measures that have recently been shown to reflect both subcortical and cortical contributions (Coffey et al., 2016; 2017). Hence, the extent to which training-dependent changes in musicians originate at subcortical vs. cortical stages of the auditory system needs to be re-considered. To address this question, the present study examined the origin of the musicians' enhanced performance for pitch discrimination using functional MRI.

The ability to discriminate pitch changes is assumed to be limited by the frequency resolution of the peripheral auditory system, often modeled in terms of auditory-filter bandwidth (e.g., Bernstein and Oxenham 2006, Moore and Glasberg 2011). The harmonic overtones of a complex tone are said to be *resolved* when they are processed within distinct auditory filters, and *unresolved* when neighbouring harmonics interact within the same filter (see Fig. 1). Since the auditory-filter bandwidth increases with frequency (Glasberg and Moore, 1990), lower-numbered harmonics are typically resolved while high-numbered harmonics are unresolved (Plack et al., 2005). Experimental investigations suggest that harmonics below the 6th are typically resolved and elicit a salient pitch percept (depicted in blue in Fig. 1), while harmonics above the 12th are unresolved and elicit a less salient pitch (depicted in red in Fig. 1, Plack et al., 2005). Cortical responses to resolved and unresolved complex tones have been investigated in previous neuroimaging studies (Penagos et al., 2004; Hall and Plack, 2009; Garcia et al., 2010; Barker et al., 2011; Norman-Haignere et al., 2013). It has been suggested that cortical pitch-sensitive regions are located in anterolateral regions of the auditory cortex (Griffiths et al., 1998; Patterson et al., 2002) that respond more strongly to tones with resolved harmonics as compared to tones containing only unresolved harmonics (Penagos et al., 2004; Norman-Haignere et al., 2013). These neuroimaging findings are consistent with neurophysiological studies in marmoset monkeys reporting that the response of pitch-sensitive neurons in the anterolateral border of primary auditory cortex increases with the salience of the pitch percept (Bendor and Wang, 2005; Fishman et al., 2013). However, it is still unclear whether neural responses to resolved and unresolved complex tones may change as a consequence of musical training.

In this study, psychoacoustic measures and functional magnetic resonance imaging (fMRI) were combined to examine differences in musicians' cortical and subcortical responses to resolved and unresolved complex tones, and to clarify whether these neural responses are related to the individual pitch-discrimination abilities. As previous studies have suggested a specialization of the right auditory cortex for fine pitch processing (e.g., Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Hyde et al., 2008; Coffey et al., 2016), it was hypothesized that an enhanced pitch representation in musicians would be associated with a stronger right-lateralized response to complex tones compared to non-musicians. In a first behavioral experiment, pitch-discrimination thresholds were measured for tones containing either resolved or unresolved harmonics to estimate the musicians' benefit in pitch-discrimination performance relative to the non-musicians. In a second experiment, an fMRI paradigm was used with the same listeners and a similar pitch-discrimination task. To avoid confounding differences in neural responses between musicians and non-musicians with differences in task demands, the task difficulty was adjusted according to the individual behavioral thresholds from the first experiment and, thus, matched across participants. Additionally, this novel paradigm allowed dissociation of the effect of harmonic resolvability from task difficulty, which would otherwise increase for the less salient unresolved tones. Hence, this is the first study to examine subcortical and cortical changes in pitch processing between musicians and non-musicians via fMRI independently of differences in task difficulty across conditions and participants.

-------- Figure 1 about here -------

2. MATERIALS AND METHODS

2.1 Participants

Thirty-one healthy listeners, aged from 22 to 30 years, were initially recruited for this study. Sixteen participants (median age: 26 years, ten females) were musically trained listeners who had at least eight years of formal musical education (formally enrolled at music schools and/or undergone private lessons). On average, the musicians started their musical education at the age of 7 and were formally enrolled at music schools or had lessons for 12.4 years. Five musicians were string players, three were classical percussionists, three were singers, three played a keyboard instrument, and two played woodwinds. One musician reported to have absolute pitch. Fifteen participants (median age: 25 years, seven females) had no formal musical education and had never played a musical instrument. One non-musician was excluded after Experiment I due to inability to discriminate one-semitone intervals (mean thresholds of 11% and 19% for resolved and unresolved complex tones, respectively). All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) except for one musician, who reported to be ambidextrous and had a Laterality Index of -20 (Middle decile). This musician was excluded from Experiment II. Hence, 30 listeners were included in Experiment I (16 musicians, 14 non-musicians) and 29 in Experiment II (15 musicians, 14 non-musicians). All participants had hearing thresholds of less than 20 dB hearing level (HL) at all audiometric frequencies between 125 Hz and 8 kHz. All experiments were approved by the Ethics Committee of the Capital Region of Denmark (H-3-2014-143 and H-3-2013-004) and were conducted in accordance with the Declaration of Helsinki.

2.2 Experiment I: Behavioral pitch-discrimination of complex tones

The first experiment was performed in a double-walled soundproof booth at the Technical University of Denmark. The ability to discriminate the pitch of resolved and unresolved complex tones was assessed by determining the just-noticeable difference in fundamental frequency F_0 (difference limen for F_0; F_0DL). An adaptive three-alternative forced-choice (3 AFC) paradigm was used in combination with a weighted up-down method (Kaernbach, 1991) to determine the different points on the psychometric function at which subjects perceived a difference in pitch in 60%, 75%, and 90% of the trials. This method is a modification of the simple up-down method. By using a varying step size to adjust the tracking variable after each response, it can converge to any desired point on the psychometric function. In each trial, three complex tones were presented to the listener (see Fig. 2b). Two complex tones served as a reference and had a fixed fundamental frequency F_0 at either 100 Hz or 500 Hz and one complex tone (i.e., the target) had a larger F_0 ($F_0 + \Delta F_0$). The position of the target was randomized across trials. Participants had to select the target tone with a higher pitch than the two reference tones (chance level of 33%). Reaction times were not measured in this first experiment. The initial difference in F_0 between reference and target, ΔF_0, was set to 20% and was then logarithmically decreased after a correct response or increased after an incorrect response by a varying step size. For each run, F_0 was roved from trial to trial from a ±5% uniform distribution around the nominal value. A random level perturbation of ±2.5 dB was applied to each interval to prevent the listener from using loudness as a cue. The threshold for each run was obtained as the geometric mean of the last six reversals. Before the actual test, the listeners performed three repetitions as training. The final pitch-discrimination threshold (F_0DL) was calculated from the mean of three repetitions.

The acoustic stimuli were presented diotically through equalized headphones (Sennheiser HD 650). All signals were generated digitally in MATLAB (The Mathworks Inc., Natick, MA, USA) at a sampling rate of 48 kHz and consisted of 300-ms complex tones with harmonic components added in sine phase and embedded in broadband threshold equalizing noise (TEN, Moore et al., 2000). The sound pressure level (SPL) of the TEN was set to 45 dB per equivalent rectangular bandwidth (ERB, Glasberg and Moore, 1990) to mask the combination tones. Cochlear non-linearities can, in fact, introduce audible distortion products that are not present in the original sound (Goldstein, 1967). The level of each harmonic component was fixed at 50 dB SPL. Figure 2a depicts the conditions used in this study. Conditions of varying resolvability were achieved by band-pass filtering the complexes in a high-frequency region (HF filter: 1500-3500 Hz, red region in Fig. 2a), with 50 dB/octave slopes, and by using an F_0 of either 100 Hz (leading to unresolved harmonics, Condition 1) or 500 Hz (resolved harmonics, Condition 2). Two control conditions with complexes filtered in a low-frequency region (LF filter: 300-1500 Hz, grey region in Fig. 2a) and F_0s of either 100 or 500 Hz (resolved conditions) were used to control for changes in F_0 (Penagos et al., 2004). In fact, while Conditions 1 and 2 differed both in F_0 and in terms of the resolvability of the harmonics, Control conditions 1 and 2 only differed in F_0. For the HF-filtered complexes, two different points on the psychometric function were estimated at 60% and 90% probability for correct performance (see Fig. 2b). The 60%

point corresponded to a difficult pitch-discrimination task, and the 90% point corresponded to an easy task. For the LF-filtered complexes, only the 75% point on the psychometric function was estimated, resulting in a task of medium difficulty (Fig. 2b). Thus, six conditions were tested in total (summarized in Fig. 2c): Conditions 1 (60% and 90%; unresolved conditions), Conditions 2 (60% and 90%; resolved conditions), Control condition 1 at 100 Hz (75%; resolved condition) and Control condition 2 at 500 Hz (75%; resolved condition).

------- Figure 2 about here -------

2.2.1 Behavioral data analysis

A mixed-model ANOVA with three fixed factors (group, resolvability, and probability of correct target detection) and listeners as a random factor nested in group was performed on the 2x2x2 full factorial design for the HF conditions. The data analysis was performed in MATLAB.

2.3 Experiment II: Functional MRI during pitch discrimination

The MRI experiment was performed at the Danish Research Center for Magnetic Resonance, Copenhagen University Hospital Hvidovre using a 3 Tesla whole-body scanner and a 32-channel head coil (Philips Achieva, Best, The Netherlands). Functional whole-brain MRI used a T2*-weighted echo-planar imaging sequence (TR = 10 s, TE = 30 ms; flip angle, 90°). Thirty-eight slices (slice thickness of 3 mm; isotropic voxel size of 3x3x3 mm^3) oriented parallel to the lateral sulcus were acquired. A sparse imaging approach (Hall et al., 1999) was adopted, whereby the sound stimuli were presented in the silent period between two volume acquisitions (see Fig. 2c). The acquisition time of one volume was of 2.5 s (black boxes in Fig. 2c) separated by a 7.5 s period without scanning. After the fMRI session, T1-weighted high-resolution anatomical images of the whole brain were acquired (inversion time, 1000 ms; TR, 6056 ms; TE 2.78 ms; flip angle, 0°, scan resolution, 288 x 288; slice thickness, 0.850 mm).

We used an event-related fMRI design to delineate the blood oxygen level-dependent (BOLD) signal change evoked during a pitch-discrimination task. The experiment included the six pitch conditions tested behaviorally in Experiment I (summarized in Fig. 2c), which consisted of four HF-filtered complex tones and two LF-filtered complex tones (control conditions) with a level of 50 dB SPL per harmonic and embedded in TEN at 45 dB SPL/ERB (Fig. 1b). A noise-only condition with broadband TEN (45 dB SPL/ERB) was used as baseline condition. The stimuli were presented diotically to the participants during the inter-scan interval through equalized MRI-compatible insert earphones (Sensimetrics S14, Sensimetrics Corporation, Malden, MA, USA). All seven conditions were pseudorandomly presented six times in a single fMRI run which consisted of a total of 42 trials and lasted approximately 7 min. Six fMRI runs were carried out per participant, resulting in a total of 36 trials per condition. The total duration of the fMRI experiment was of about 42 minutes (252 trials).

The time line of three sample trials is illustrated in Fig. 2c. Two identical reference complex tones with a fixed F_0 (either 100 or 500 Hz) and one target tone with a larger F_0 (either the first, second or third tone) were presented during the silent period without concurrent scanning. Acoustic stimulus presentation lasted for 1.7 s and started 2 - 3 s after the acquisition of the previous volume. The fMRI data acquisition of a single brain volume started 2.8 - 3.8 s after the end of the stimulus presentation and lasted 2.5 s. This time jitter in the onset of the signal was introduced to account for the inter-subject variability of the BOLD hemodynamic response (Aguirre, 1998) and to introduce variation in the timing of stimulus presentation. Participants performed a 3 AFC task, where they had to identify the target tone by pressing either the first, second or third button on a response box, according to the target's position (i.e., first, second or third tone presented). The target position was pseudorandomized across trials and runs. The participants were instructed to press the response button during the following volume acquisition, even for the noise-only conditions (any button in this case). For one participant, button presses could not be recorded due to a technical failure of the response box. The difficulty of the pitch-discrimination task was defined by the difference in F_0 between the reference and target tone (i.e., ΔF_0). Critically, this difference was adjusted for each participant according to the individual thresholds measured in Experiment I (60% detection probability: high difficulty; 75% detection probability: medium difficulty; 90% detection probability: low difficulty) to match the task in terms of difficulty.

2.3.1 Neuroimaging data analysis

Data analyses were performed with the statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). Data processing consisted of realignment, coregistration, spatial normalization to MNI standard space as implemented in SPM8, and smoothing with an 8-mm full-width at half-maximum isotropic Gaussian kernel. Data analysis was performed using a general linear model (GLM) approach. At the single subject level, separate regressors were defined for each experimental condition (seven regressors) to model the onset of the sound stimulus. Correct and incorrect responses were also modeled as additional regressors. Movement parameters estimated from the realignment were entered as six additional regressors of no-interest. Low frequency drifts in the BOLD signal were removed by a high-pass filter with a cut-off period of 128 s. Group level analysis for the HF conditions employed a full-factorial 2x2x2 ANOVA model. The design matrix included three main factors: group (musicians and non-musicians), task difficulty (two levels: 60% and 90% probability of correct target detection), and resolvability (two levels: unresolved and resolved harmonics). Additionally, a 2x3x2 ANOVA was used to model the HF and LF conditions together. The design matrix included three main factors: group (musicians and non-musicians), task difficulty (three levels: 60%, 75% and 90% probability of correct target detection), resolvability (two levels: unresolved and resolved harmonics). Finally, six t-tests were carried out to clarify the effect of harmonic resolvability (Condition 1 *vs.* Condition 2; Control Condition 1 *vs.* Control Condition 2; Condition 1 *vs.* Control Condition 1). The hypothesis was that an effect of harmonic resolvability would result from the contrasts Condition 2 (resolved) > Condition 1 (unresolved) and Control condition 1 (resolved) > Condition 1 (unresolved), while no differential activation should result from the contrasts Control condition 2 (resolved) > Control condition 1 (resolved). All peak p-values reported in this study were obtained from whole brain analysis, applying a corrected p-value of 0.05 as statistical threshold. The p-values for the contrast 60%>90% (effect of task difficulty) were obtained from a small volume correction (20 mm-sphere around peak value). Correction for multiple non-independent comparisons used the family-wise error (FWE) correction method at the voxel level as implemented in SPM8.

2.4 Correlation between behavioral and neuroimaging data

Correlations between the individual pitch-discrimination performance from Experiment I and the cortical neural activation from Experiment II were carried out for the 15 musicians and 14 non-musicians that participated in both experiments. To clarify the effect of pitch-discrimination performance in the right and left auditory cortex (AC), a region of interest (ROI) comprising primary and non-primary AC (Te1.0, Te1.1, Te1.2 and Te3) was defined in the right and left hemisphere using the SPM Anatomy toolbox (Eickhoff et al., 2005). For each listener, the mean response of the voxels within the ROI was estimated for each pitch condition relative to the noise (four resolved conditions and two unresolved conditions). The correlation between the mean contrast estimates in the right and left AC relative to the individual pitch-discrimination performance was evaluated. The correlation was considered significant for *p*-values lower than 0.0083 (after Bonferroni correction with n = 6 comparisons).

To investigate subcortical correlates of pitch performance, an additional ROI was anatomically defined as a 12-mm sphere (centered at x, y, z = 1 -26 -14), comprising the inferior colliculus (IC) and the dorsal part of the midbrain. The correlation between the mean subcortical activation and the individual pitch-discrimination performance was evaluated. The correlation was considered significant for *p*-values lower than 0.017 (after Bonferroni correction with n = 3 comparisons).

Finally, since the inferior frontal gyrus (IFG) has been found to play an important role for active pitch-retention tasks (e.g., Zatorre et al., 1994; Griffiths et al., 1999; Albouy et al., 2013), a ROI comprising the right and left pars opercularis was defined using the SPM Anatomy toolbox (Broca’s area 44; Eickhoff et al., 2005) and used to relate the functional activation in the IFG with the listeners' performance (i.e., % correct target identification). This anatomical mask was applied to the individual contrasts obtained for each pitch condition relative to the noise. The mean activation of the voxels within the inclusive mask was calculated for each participant and used to correlate with performance. Correlation p-values lower than 0.025 (after Bonferroni correction with n = 2) was considered significant.

3. RESULTS

3.1 Experiment I: Pitch-discrimination of complex tones

Figure 3a shows the mean pitch-discrimination thresholds (F_0DLs) for the four HF conditions with either unresolved harmonics (Condition 1) or with resolved harmonics (Condition 2), and for the two LF conditions with resolved harmonics (Control conditions; grey-shaded area in Fig. 3a) for the 16 musicians (filled symbols) and 14 non-musicians (open symbols). The performance for all listeners was more accurate in the presence of resolved harmonics (mean F_0DLs of musicians: 0.76%; mean F_0DLs of non-musicians: 1.9%) than unresolved harmonics (mean F_0DLs of musicians: 3.4%; mean F_0DLs of non-musicians: 5.9%), consistent with a more salient pitch percept evoked by the resolved than the unresolved harmonics (e.g., Houtsma and Smurzynski, 1990; Shackleton and Carlyon, 1994; Bernstein and Oxenham, 2006). Compared to the non-musicians, the musically trained listeners had significantly lower thresholds in all conditions, indicating a more accurate pitch-discrimination performance for both resolved and unresolved complex tones. The musicians' performance was enhanced relative to non-musicians, on average, by a factor of 2.5 for the resolved conditions, but only by a factor of 1.7 for the unresolved conditions. Additionally, as expected from estimating a higher point on the psychometric function, the thresholds of both musicians and non-musicians were larger for the 90% condition than those for the 60% condition. The effect of musical training was greater for the easy-task conditions (90% point of the psychometric function) as compared to the difficult-task conditions (60%).

The mixed-model ANOVA on the HF conditions confirmed a significant effect of the three main factors: group [F(1, 84) = 26.31; $p < 0.0001$], resolvability [F(1, 84) = 369.5; $p < 0.0001$] and probability of correct target detection at threshold [F(1, 84) = 531.06; $p < 0.0001$], as well as a significant interaction between group and resolvability [F(1, 84) = 14.47; $p = 0.0003$] and group and probability of detection [F(1, 84) = 5.13; $p = 0.026$]. No interaction was found between resolvability and probability of detection [F(1, 84) = 1.12; $p = 0.292$] nor among the three factors [F(1, 84) = 0.02; $p = 0.891$].

Figure 3b shows the individual pitch-discrimination thresholds (16 musicians: filled symbols; 14 non-musicians: open symbols), averaged for the two unresolved conditions (HF; left panel) and the four resolved conditions (LF and HF; right panel) as a function of years of musical training. A marginally significant trend was observed for the resolved conditions (right panel; one-tailed Pearson's correlation: $R^2 = 0.18$; $p = 0.052$), whereby performance increased with overall years of musical training. However, there was no correlation between pitch-discrimination performance and years of musical training for the unresolved conditions (left panel; one-tailed Pearson’s correlation: $R^2 = 0.04$; $p = 0.239$).

------- Figure 3 about here -------

3.2 Experiment II: Functional brain activation during a pitch-discrimination task

3.2.1 Behavioral performance

The behavioral responses obtained during fMRI are summarized in Fig. 4a, showing the accuracy for target identification in the musician (filled symbols) and non-musician groups (open symbols). As mentioned above, task difficulty was adjusted to the individual pitch-discrimination ability to match performance across participants and groups. Thus, as expected from the experimental design, the ANOVA revealed no significant group nor subject effects on the behavioral responses to the HF conditions [Group: $F(1,437) = 2.32$; $p = 0.14$; Subject (nested in group): $F(26,437) = 1.18$; $p = 0.292$]. There was also no interaction between group and difficulty [$F(1,437) = 0.88$; $p = 0.356$] nor of group and resolvability [$F(1,437) = 2.18$; $p = 0.152$], suggesting that task difficulty and harmonic resolvability were similar in the two groups of participants. Additionally, a significant effect of resolvability [$F(1,437) = 7.1$; $p = 0.013$] and task difficulty [$F(1,437) = 59.86$; $p<0.0001$] was found on the behavioral responses, together with an interaction between difficulty and resolvability [$F(1,437) = 17.06$; $p < 0.0001$], suggesting a stronger effect of difficulty obtained for the resolved conditions. The ANOVA revealed a significant effect of runs [F(5,437) = 2.61; p = 0.028], whereby performance increased over the first three runs of the experiment until reaching a plateau for the last three runs (Fig. 4a, right panel). No interactions were found between the effect of runs and any of the other factors. The obtained levels of performance were slightly higher than the targeted levels (i.e., 60%, 75% and 90%). This may have been due to an effect of training over the six runs (Fig. 4a, right panel) or to the non-adaptive procedure used in Experiment II vs. the adaptive procedure of Experiment I. This effect was, however, consistent across groups and conditions, as confirmed by the absence of interactions between group and difficulty and group and resolvability.

3.2.2 Effect of musical training

Figure 4b depicts the differential activation maps for all HF conditions relative to the noise condition in musicians and non-musicians. Both groups of listeners showed task-related activations in the right and left superior temporal gyri (STG), with stronger activations in the musician group especially in the posterior division of the STG (x, y, z = 51, -22, 1; t = 20.43), Heschl’s gyrus (HG; x, y, z = 51, -20, 3; t = 18.39), and planum polare (PP; x, y, z = 51, -7, -3; t = 17.35). Additionally, bilateral activations in musicians were observed in the inferior frontal gyri (IFG, pars opercularis) at the border with the precentral gyrus (x, y, z = 51, 8, 22; t = 8.62), in the lingual and occipital fusiform gyri (x, y, z = 9, -85, -5; t = 7.32), in the cerebellum (x, y, z = -27, -64, -26; t =

9.16), and in the inferior colliculi (IC; x, y, z = -10, -28, -10; t = 6.54) during the pitch-discrimination task. Figure 4c illustrates the differential activation map of musicians relative to non-musicians for all tested pitch conditions (LF and HF combined). Musicians showed a significantly stronger BOLD response during pitch discrimination in a set of cortical and subcortical areas (all peak-level coordinates and t-values are listed in Table 1). The largest cluster of enhanced activation in musicians comprised the posterior division of the right STG at the border of HG (x, y, z = 51, -22, 1; t = 7.42; Fig. 4c), extending to the insular cortex and frontally to the IFG (pars opercularis; x, y, z = 51, 8, 22; t = 7.27; Fig. 4c). The second largest cluster of enhanced activation in musicians was in the brainstem, and comprised dorsal parts of the midbrain, including the IC (x, y, z = -3, -34, -11; t = 7.25; Fig. 4c). The left planum temporale (PT; x, y, z = -63, -19, 7; t = 6.92) and the left lateral occipital cortex (x, y, z = -27, -82, 34; t = 7.74) were also significantly more activated in the musicians. Additionally, the analysis revealed a significantly larger BOLD response in the non-musicians relative to the musicians in the right and left hippocampi (Table 1). No interaction between group and difficulty, group and resolvability, nor of group, difficulty and resolvability was found.

--- Figure 4 and Table 1 about here ----

3.2.3 Effect of task difficulty

The ANOVA on the HF conditions revealed a significant effect of task difficulty (Fig. 5a). The difficult conditions (60%) showed stronger task-related activation relative to the easy conditions (90%) in the left frontal operculum and insular cortex (x, y, z = -36, 23, 1; t = 4.31; Table 1), left IFG (x, y, z = -51, 11, 4; t = 4.03; Table 1) and right frontal orbital and insular cortex (x, y, z = 33, 29, 4; t = 4.36; Table 1). The two insert panels in Fig. 5a depict the effect of task difficulty for musicians and non-musicians, separately. The two panels in Fig. 5b depict the mean contrast estimates for musicians (filled squares) and non-musicians (open circles) in the left (left panel) and right (right panel) frontal operculum and insular cortex. The effect of task difficulty (60%>90%) was present for both unresolved and resolved conditions and for both groups of listeners, as confirmed by the absence of interactions between group and difficulty. However, non-musicians showed stronger task-related activations than musicians in the left frontal operculum and insular cortex (Fig. 5a, insert panels; Fig. 5b, left panel).

Additionally, the mean task-related BOLD signal within the anatomical mask defined for the IFG (pars opercularis, shown in Fig. 6) was calculated for each pitch condition (relative to noise) and each participant. Figure 6 depicts the mean contrast estimates for the musicians (filled symbols) and non-musicians (open symbols) in the left and right IFG (left and right panels, respectively) as a function of the behavioral performance (% correct target detection). The increase in activation in both the left and right pars opercularis was significantly correlated with a decrease in the behavioral performance for both groups of listeners. Thus, increasing the difficulty of the pitch-discrimination task (i.e., decreasing the ΔF_0 between reference and target tones) resulted in a similar bilateral task-related activation in the IFG for both groups of listeners.

----- Figure 5 and 6 about here -----

3.2.4 Effect of harmonic resolvability

The ANOVA on the HF conditions revealed a small main effect of resolvability in the posterior end of the right HG (x, y, z = 42, -28, 7; F = 14.1; $p < 0.001$ uncorrected). However, the change in the resolvability of the harmonics was associated with a change in the F_0 from 100 Hz to 500 Hz. Hence, additional t-tests were performed on the HF conditions, as well as on the control conditions to disentangle the two effects. The t-tests on the HF conditions revealed differential activation of resolved and unresolved tones in the anterior and posterior parts of the AC. Figure 7a depicts the contrasts of unresolved conditions (Condition 1, F_0 of 100 Hz, red scale) and resolved conditions (Condition 2, F_0 of 500 Hz, blue scale) relative to the noise for all 29 participants. Bilateral activation in HG extended anteriorly for the resolved tones while responses to the unresolved conditions extended more posteriorly into the PT region. This pattern was seen more strongly for musicians, but was similarly present in non-musicians (see insert panels of Figure 7a for the 15 musicians and 14 non-musicians). Directly contrasting the resolved and unresolved conditions showed that this pattern was more pronounced in the right AC (see Fig. 7b). Activity in the right anterior HG and planum polare (x, y, z = 45, -10, -5; t = 4.12; p = 0.051 FWE corrected) was stronger for the resolved conditions compared to the unresolved, while the unresolved conditions activated the posterior end of the right (x, y, z = 42, -25, 7; t = 6.04; p = 0.001 FWE corrected) and left HG (x, y, z = -33, -31, 10; t = 6.57; p<0.0001 FWE corrected) and the left anterior PT (x, y, z = -63, -25, 13; t = 4.39; p = 0.028 FWE corrected). Additional contrasts between the control conditions were run to clarify whether the differential activation seen in Fig. 7b was the result of a change in harmonic resolvability or a change in F_0. Similar as for the HF-filtered tones, the LF-filtered tones showed higher activity for the lower pitch (F_0 = 100 Hz, control condition 1) relative to the higher pitch condition (F_0 = 500 Hz, control condition 2) in the posterior parts of the AC (Fig. 7c, the posterior HG-PT border on the right x, y, z = 42, -28, 10, t = 7.68, p<0.0001 FWE corrected; and left x, y, z = -39, -34, 16, t = 7.47, p = 0.001 FWE corrected). No differential activation was found for the higher pitch (control condition 2) relative to the lower pitch (control condition 1). Thus, the contrast unresolved > resolved (Fig. 7b, red scale, HF conditions) and the contrast between the resolved control conditions (Fig. 7c) were both seen to activate the posterior end of HG and the left PT. Hence, other factors than harmonic resolvability per se could be driving these contrasts (e.g., the change in the F_0 from 100 to 500 Hz). Supporting this, no differential activation was found between conditions with different harmonic resolvability but same F_0 (Condition 1 and Control condition 1).

--- Figure 7 about here ----

3.3 Correlation of pitch-discrimination performance and cortical vs. subcortical responses

Figure 8a shows the correlation between the mean BOLD responses in the right and left AC and the behavioral F_0DLs (i.e., the pitch-discrimination performance from Experiment I) for the 15 musicians (filled symbols) and the 14 non-musicians (open symbols). After Bonferroni correction for multiple comparisons ($n = 6$, significance for $p < 0.0083$), a significant correlation for the musicians was observed in the right AC for the resolved conditions (top and middle right panels in Fig. 8a; Spearman's correlation: $r = -0.70$, $p = 0.005$) but not in the left AC. Thus, finer discrimination of the resolved complex tones in the musically-trained listeners was associated with stronger neural responses to resolved tones in the right AC. No correlation was found for the unresolved conditions. Additionally, no correlation was present for the non-musicians' in either the right or left AC.

Figure 8b shows the correlation between the pitch-discrimination thresholds and the mean responses in the IC. Although no significant correlation was found within the group of musicians nor non-musicians, a strong correlation was seen when pooling all listeners, reflecting a group difference in magnitude of response. Significant correlations between responses in the IC and the behavioral pitch thresholds were seen only for the resolved LF-filtered tones (top panel; Spearman’s correlation: $r = -0.68$, $p < 0.001$), and not for the unresolved conditions (bottom panel).

--- Figure 8 about here ----

4. DISCUSSION

4.1 Pitch-discrimination performance for resolved and unresolved harmonics

Our behavioral data (Experiment I) revealed that the musicians outperformed the non-musicians in pitch-discrimination performance with a factor of about 2.5 for the resolved conditions, and a factor of 1.7 for the unresolved conditions (Fig. 3a). Additionally, a trend was found between pitch-discrimination performance and overall years of musical training for the resolved but not for the unresolved conditions (Fig. 3b). These findings point towards a training-dependent effect in musicians that was more prominent for stimuli containing resolved harmonics. Although musical sounds generally contain both resolved and unresolved harmonics, a larger benefit of musicians for resolved tones is reasonable considering that the resolved harmonics provide the most salient cue for pitch retrieval (e.g., Houtsma and Smurzynski, 1990; Shackleton and Carlyon, 1994; Bernstein and Oxenham, 2006). However, musicians still showed better pitch-discrimination performance than non-musicians in the unresolved conditions, despite not being specifically trained on stimuli containing only unresolved harmonics. This finding is in agreement with previous studies showing that learning is only partly resolvability-specific (Grimault et al, 2002; Carcagno and Plack, 2011b). Grimault et al. (2002) showed that listeners trained with a particular resolved tone obtained larger improvements when tested on other resolved tones than when tested on unresolved tones. Thus, although learning generalized to the untrained condition, the transfer of learning to a stimulus with a different resolvability was not complete. Similarly, Pantev et al. (1998) and Micheyl et al. (2006) showed that the musicians' advantage in pitch discrimination was larger for complex tones than for pure tones consistent with an incomplete generalization of learning for unfamiliar sounds (Demany and Semal, 2002).

While some studies have suggested that experience-dependent changes in musicians emerge already at the level of the cochlea in terms of sharper tuning of cochlear filters (Soderquist, 1970; Bidelman et al., 2014b; Bidelman et al., 2016), previous behavioral studies did not find evidence for differences in musicians at the peripheral level (Fine and Moore 1993; Oxenham et al., 2003; Bianchi et al., 2016a). If the musicians' finer pitch discrimination, as observed behaviorally in the present study (Fig. 3), were exclusively ascribed to sharper peripheral frequency selectivity, then no advantage in pitch-discrimination would be expected for the unresolved tones. In fact, narrower peripheral filters would lead to less salient envelope cues at the output of cochlear stages as a consequence of fewer harmonics interacting within the same filter (Bianchi et al., 2016b). Hence, our behavioral findings, showing enhanced pitch-discrimination abilities in musicians that extend to the unresolved tones, cannot be solely explained by sharper cochlear tuning (Bidelman et al., 2016) and point to an enhanced F_0 representations along the auditory system at stages beyond the cochlea. This behavioural enhancement for both resolved and unresolved tones could be ascribed to an increased neural synchrony in the auditory brainstem of musicians (e.g., Wong et al., 2007; Musacchia et al., 2007; Parbery-Clark, 2009) and/or to plasticity at the cortical level (e.g., Schneider, 2002; Bermudez et al., 2009; Hyde et al., 2009; Foster and Zatorre, 2010; Seither-Preisler et al., 2014; Coffey et al., 2016).

4.2 Subcortical and cortical responses to pitch in musicians

The fMRI results (Experiment II) revealed both stronger cortical and subcortical responses in musicians for resolved as well as for unresolved complex tones. By adjusting the task to the individual pitch-discrimination abilities, we ensured that the observed differences in task-related activation were not caused by differences in task difficulty across participants. Neural responses in musicians were especially enhanced in right-hemispheric areas, comprising the right STG, HG, insular cortex, IFG (pars opercularis), superior and middle frontal gyri (Fig. 4c, Table 1), and in the auditory midbrain. The stronger right-lateralized responses in musicians (relative to non-musicians) in the AC are in agreement with our initial hypothesis and support the notion that the right AC is more specialized than the left AC in fine pitch processing (e.g., Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Zatorre et al., 2002; Hyde et al., 2008). These findings provide additional evidence of enhanced neural responses in musicians in a right fronto-temporal network that is assumed to be involved in pitch processing and tonal working memory (Zatorre and Samson, 1991; Zatorre et al., 1994; Albouy et al., 2013). Connectivity between the right superior temporal gyrus and the frontal cortex has been suggested to be part of a distributed neural network responsible for maintaining pitch into auditory working memory (Zatorre and Samson, 1991; Perry, 1993; Zatorre et al., 1994). The higher activation in musicians in the right STG, right IFG and insular cortex (Fig. 4c, Table 1) can be interpreted as a stronger involvement in neural resources to extract, maintain, and compare pitch information (e.g., Maess et al., 2001; Koelsch et al., 2005). Together, these findings suggest a right-hemispheric cortical network for pitch extraction and manipulation that is more developed in musicians (Koelsch et al., 2005; Zatorre et al. 1994; Schulze et al., 2011).

Additionally, the auditory midbrain (including the IC, Fig. 4c) showed significantly higher activation in the musicians compared to the non-musicians. Pitch-related activation in the midbrain occurred in both inferior colliculi suggesting that the asymmetry favoring right-hemispheric regions arises cortically in musicians (Griffiths et al. 2001; Coffey et al., 2016). Our findings show that stronger F_0 encoding of resolved and unresolved complex tones was already present at the subcortical level, consistent with previous electrophysiological studies suggesting a higher degree of phase synchrony in the musicians' brainstem in response to harmonic complex sounds (e.g., Wong et al., 2007; Musacchia et al., 2007; Parbery-Clark 2009; Bidelman et al., 2011; Carcagno and Plack, 2011a).

4.3 Pitch-discrimination performance and functional activation

Both at the cortical and subcortical level, the mean task-related responses to resolved complex tones were correlated with the individual pitch-discrimination thresholds (Fig. 8). The increase in functional activity in the right AC predicted a finer pitch-discrimination performance of musicians for resolved complex tones (Fig. 8a, top and middle panels). However, at the subcortical level, neural responses in the IC reflected the pitch-discrimination performance across the two groups of subjects, but not within the musicians group alone (Fig. 8b, top panel). These findings suggest a hierarchical model of pitch extraction whereby the sensitivity to the harmonic structure of a sound is already present in subcortical auditory neurons, which may then provide inputs of harmonic templates to the AC (Wang et al., 2013). The existence of such harmonic templates was previously observed within the primary AC in different species (bat, Fitzpatrick et al., 1993; cat, Sutter and Schreiner, 1991; marmoset, Kadia and Wang, 2003; Bendor et al., 2012), where some neurons exhibited multipeaked spectral tuning to the harmonics of complex tones. Related findings were also reported in humans, where cortical neurons exhibited sensitivity to harmonically related frequencies (Moerel et al., 2013, 2015). Such harmonic templates can provide sufficient spectral cues to extract the pitch of resolved harmonics and may be formed even earlier in the auditory system than the brainstem (Shamma and Klein, 2000; Bendor et al., 2012). The AC may then not only inherit these harmonic inputs but also shape and further enhance the sensitivity to the resolved harmonics following musical training. The presence of group differences in this hierarchical plasticity seems to confirm that the relative contribution of subcortical and cortical responses changes in an experience-dependent manner (Bidelman et al., 2014a).

Additionally, our results revealed increased subcortical and cortical responses in musicians to the unresolved complex tones. Given that the pitch of unresolved harmonics is assumed to be encoded using temporal envelope cues (de Cheveigné, 2005; Oxenham et al., 2009), these findings suggest an enhanced synchrony to the temporal envelope of complex tones with high-order harmonics in musicians. However, this enhancement did not scale with the individual performance of musicians neither at the subcortical nor cortical level. Since complex-tones filtered in a high-frequency region are unnatural sounds, which musicians are neither trained nor exposed to, it may be that the increased behavioral performance of musicians cannot be directly explained by a training-dependent plasticity reflected in the functional activations. As discussed earlier, the enhanced performance of musicians for unresolved complex tones may be related to an incomplete generalization of learning (Grimault et al., 2002; Carcagno and Plack, 2011b).

Previous studies have investigated subcortical plasticity in musicians in relation to pitch discrimination and reported somewhat inconclusive results. Wong et al. (2007) found a correlation between frequency-following responses (FFRs) to pitch contours in a falling Mandarin tone with an F_0 around 100 Hz and pitch discrimination performance. However, at such low F_0s, FFRs have been shown to reflect a cortical contribution in addition to responses originating in the auditory brainstem (Coffey et al. 2016). No correlation was found for tones with F_0s above 110 Hz, which may suggest a greater degree of cortical contribution in the responses that are modulated by behavior. Musacchia et al. (2007) found no correlation between F_0 encoding in the brainstem FFR and pitch discrimination and argued that subcortical encoding enhancement is not linked to performance but rather to persistence of practice. Bidelman et al. (2011) found a significant correlation between FFRs in response to mistuned chords and F_0DLs in musicians, but not in tone-language speakers nor in non-musicians. In their study, FFRs were measured in response to a fixed mistuning of 4%. Hence, in contrast to our study, the discrimination difficulty of the chords during the FFR experiment changed from participant to participant, making the mistuning easier to detect for the musicians than for the non-musicians. Additionally, Carcagno and Plack (2011a) found a correlation between subcortical FFRs and F_0DLs for a subset of pitch conditions when pooling trained and untrained listeners. Finally, Lau et al. (2017) found no correlation with subcortical measures and concluded that cortical responses may be more reflective of training-induced plasticity.

Our findings corroborate and, possibly, reconcile previous findings on plasticity in musicians. Using fMRI to directly compare subcortical and cortical activations *vs.* individual pitch-discrimination performance, we provide further evidence to disentangle the contributions along the auditory pathway. Our results demonstrate that training-dependent plasticity at the subcortical level reflects coarse differences in pitch-discrimination performance between musicians and non-musicians, while the enhanced activation in the right AC adds a second layer of sensitivity to F_0 encoding, predicting fine individual differences in pitch-discrimination within musicians (Schneider et al., 2002; Puschmann et al., 2013; Coffey et al. 2016). Overall, our findings are consistent with an enhanced neural synchrony to resolved and unresolved complex tones in the brainstem of musicians (e.g., Wong et al., 2007; Musacchia et al., 2007; Parbery-Clark, 2009; Carcagno and Plack, 2011a; Bidelman et al., 2011), but they also stress the role of a right-hemispheric cortical plasticity to account for the perception of fine pitch differences of resolved complex tones (e.g., Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Hyde et al., 2008).

4.4 Effect of task difficulty in musicians and non-musicians

While pitch processing appeared to be enhanced in musicians, the effect of task difficulty was present in both groups of listeners (as reflected by the absence of difficulty and group interactions). A direct comparison of the difficult (60%) *vs.* easy (90%) conditions appeared to elicit stronger responses in the left insular cortex and frontal operculum in the non-musicians (Fig. 5a). This could indicate higher processing effort involved in discriminating small pitch differences for non-trained listeners. Increased BOLD responses when the pitch-discrimination task increased in difficulty were also observed bilaterally in the IFG for both groups (Fig. 6). Larger BOLD responses in the IFG and insular cortex have previously been related to an increased involvement of auditory working memory during active pitch-retention tasks (Zatorre et al, 1994; Koelsch et al., 2005; Albouy, 2013). It is unlikely that the mean activation of the IFG was higher in musicians than non-musicians as a result of increased processing effort. As argued above, increased activation in the IFG in the musicians is likely to reflect involvement of auditory working memory to process and maintain pitch information (e.g., Zatorre et al, 1994; Maess et al., 2001; Koelsch et al., 2005). An extended neural network for pitch processing in musicians, rather than an increased processing effort, is further supported by a recent study (Bianchi et al., 2016a). Task-related pupil dilations, as a measure of processing effort, were found to be smaller in musicians compared to non-musicians performing a pitch discrimination task at the same level of difficulty.

4.5 Neural correlates of resolvability

Two previous studies have reported an effect of harmonic resolvability in anterior regions of the AC, where complex tones with resolved harmonics elicited stronger responses compared to complex tones containing only unresolved harmonics (Penagos et al., 2004; Norman-Haignere et al., 2013). Our analysis confirmed these findings and additionally revealed how differential activation maps of resolved and unresolved complex tones (relative to the noise) were similar in musicians and non-musicians, with larger clusters of activation in the musicians (Fig. 7a). Neural responses to the resolved tones extended from the right HG in anterolateral direction (Fig. 7a and 7b, blue scale), while responses to the unresolved tones extended posteriorly into the PT region (Fig. 7a and 7b, red scale). The activation of the anterior AC for resolved complex tones is likely to reflect the increase in pitch salience with increasing harmonic resolvability, in agreement with Penagos et al. (2004) and Norman-Haignere et al. (2013). The increased activation in the unresolved conditions (relative to the resolved tones) bilaterally in posterior regions of the secondary AC (Fig. 7b) is consistent with a role of the PT in temporal pitch processing (Griffiths et al., 2001; Patterson et al., 2002; Hall and Plack, 2009; Barker et al., 2011). These results are in agreement with spectro-temporal models of pitch extraction (Steinschneider et al., 1998; Bendor et al., 2012). The pitch of resolved complex tones may be extracted by harmonically related peaks in the tonotopical representation of the sound as a result of a hierarchical and right-hemispheric processing (Patterson et al., 2002). The pitch of unresolved complex tones is, on the other hand, extracted using temporal envelope cues (de Cheveigné, 2005; Oxenham et al., 2009). Given that the envelope phase-locking limit decreases when ascending the auditory pathway, envelope cues are more likely to be extracted earlier in the auditory system than the primary AC (Griffiths et al., 1998). However, a region posterior to the AC, bilaterally within the PT, may be involved in pitch processing of unresolved complex tones characterized by slow changes of temporal cues over time (Griffiths et al., 1998; Hall and Plack, 2009; Barker et al., 2011).

Since a similar pattern of activation was observed for the two resolved control conditions in the posterior region of the HG (Fig. 7c), some considerations need to be addressed. First, in the current stimulus design, the sound level per harmonic was fixed, leading to the same signal-to-noise ratio (SNR) per harmonic in all conditions relative to the noise, but to a higher overall stimulus level for the unresolved conditions compared to the resolved conditions. Since correlates of overall sound level have been reported in the primary AC and PT (Ernst et al., 2008; Langers and van Dijk, 2012), it is possible that the contrast unresolved > resolved (Fig. 7b, red scale) could have been driven by the increase in overall level. The increase in level could also potentially explain the effect of the contrast between the LF-filtered control conditions (Control condition 1 > Control condition 2 in Fig. 7c, green scale). However, the overall level also increased between the LF- and HF-filtered complex tones at F_0 = 100 Hz, but the contrast between these conditions (Condition 1 > Control condition 1) did not reveal any differences. Hence, the observed differences between the unresolved and resolved conditions were probably not related to differences in the overall sound level.

A second point to consider is the larger ΔF_0 between reference and target in the unresolved conditions compared to the resolved conditions. The ΔF_0 between reference and target was adjusted according to the individual F_0DLs obtained in Experiment I. Thus, the unresolved conditions implied larger differences in F_0 between the individual tones in a trial compared to the resolved conditions. Increasing the pitch interval size during a melody-discrimination task (Zatorre et al., 2012) or during passive listening of pure-tone melodies (Hyde et al., 2008) has been shown to increase the neural activation in the anterior and posterior STG and right PT. However, in Zatorre et al. (2012), the increase in frequency separation between tones was also associated with an increase in the behavioral performance, whereas the ΔF_0 in the current study was increased to elicit equal behavioral performance across conditions and participants. Additionally, in the current study, the increase in ΔF_0 between the LF- and HF-filtered conditions for F_0 = 100 (Condition 1 vs Control condition 1) did not reveal any significant differences. This seems to rule out the effect of ΔF_0. Hence, the most plausible explanation for the differential activations observed in the posterior HG for the contrasts unresolved > resolved conditions (Fig. 7b, red scale) and Control condition 1 > Control condition 2 (Fig. 7c, green scale) seems to be the difference in pitch from an F_0 of 100 to 500 Hz. It is possible that F_0 representations coexist with frequency maps in the human auditory cortex (Pantev et al., 1989; Langner et al., 1997; Bendor and Wang, 2005, 2006; Moerel et al., 2013, 2015) and provide a representation of pitch for complex sounds.

5. CONCLUSION

Comparing individual pitch-discrimination performance of musicians and non-musicians and neural cortical and subcortical responses to complex tones with a different spectral resolvability, we provide evidence for two levels of plasticity following musical training. Enhanced pitch processing in musicians first emerged at the level of the inferior colliculus, whereby increased task-related activation was found in response to both resolved and unresolved complex tones. Neural responses in the inferior colliculus predicted the individual pitch-discrimination performance across all listeners, but not the fine pitch differences between the musicians alone. Only neural responses in the right auditory cortex correlated with the individual pitch-discrimination abilities of musicians, indicating a second level of training-dependent plasticity, where harmonic sensitivity is further enhanced. Additionally, the effect of harmonic resolvability was similarly present in musicians and non-musicians, with resolved complex tones eliciting more anterior responses in the right HG than the unresolved conditions.

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FIGURE CAPTIONS

Figure 1 Illustration of harmonic resolvability. The frequency resolution of the peripheral auditory system can be represented by auditory filters that increase in bandwidth with increasing frequency (in gray). The low-numbered harmonics (1-6, in blue) of a complex tone with a fundamental frequency F_0 are processed within distinct filters and are said to be ‘resolved’. Neighboring high-numbered harmonics (above the 12th, in red) interact within the same filter and are said to be ‘unresolved’.

Figure 2 a. Stimulus conditions used in Experiments I and II. Complex tones with a fundamental frequency F_0 of either 100 or 500 Hz were filtered in either a low-frequency region (LF filter: 300-1500 Hz, gray rectangle) or a high-frequency region (HF filter: 1500-3500 Hz, red rectangle), generating four conditions: Condition 1 (harmonic numbers: 15-35, unresolved), Condition 2 (harmonic numbers: 3-7, resolved), Control conditions 1 and 2 (both containing resolved harmonics). The control conditions served to disentangle the effects of resolvability and F_0. Each harmonic component was presented at 50 dB SPL and embedded in threshold equalizing noise. **b.** Behavioral paradigm for Experiment I. In each trial (depicted on the left panel), three tones were presented: two references with a fixed F_0 (either 100 or 500 Hz) and a target tone with a larger

F_0 (randomly presented among the references). An adaptive procedure was used to estimate the just noticeable difference in pitch between reference and target tones (F_0 difference limen; F_0DL). For conditions 1 and 2, the change in pitch (ΔF_0) yielding 60% and 90% correct target detection was estimated ($\Delta F_{0;\,60\%}$ and $\Delta F_{0;\,90\%}$; red dots on the right panel), while the 75% correct performance was estimated for the control conditions ($\Delta F_{0;\,75\%}$; gray dot). **c.** Imaging paradigm for Experiment II. As in Experiment 1, two identical reference tones and one target tone (1.7 s acoustic stimulation with jittered onset) were presented during the silent interval between two volume acquisitions. The difference in pitch between reference and target was set at the individual F_0DLs measured from Experiment I ($\Delta F_{0;\,60\%}$: small F_0 separation, difficult task; $\Delta F_{0;\,90\%}$: large F_0 separation, easy task;). In total, six pitch conditions (embedded in noise) were presented, two control conditions (left table; $\Delta F_{0;\,75\%}$: medium-difficult task) and four HF-filtered conditions (right table; $\Delta F_{0;\,60\%}$: difficult task; $\Delta F_{0;\,90\%}$: easy task), as well as a baseline condition with only noise.

Figure 3 a. Mean pitch-discrimination thresholds (F_0DLs) for the 14 non-musicians (open circles) and 16 musicians (filled squares) who participated in the behavioral experiment. Thresholds for Conditions 1 and 2 are reported at the 60% and 90% correct target detection, while the two control conditions (at either 100 or 500 Hz, gray-shaded area) refer to the 75% correct detection point. Error bars depict the standard error of the mean. **b.** Individual pitch-discrimination thresholds for the 14 non-musicians (open circles) and 16 musicians (filled squares) as a function of years of musical training. The linear fit to the musicians' thresholds is reported as a dashed line. Left panel: mean thresholds for the unresolved conditions (Condition 1); Right panel: mean thresholds for all resolved conditions (Condition 2 and control conditions).

Figure 4 a. Left panel: Mean behavioral performance during fMRI (% correct target detection) for the six pitch conditions (four HF; two LF in gray-shaded area) for musicians (filled squares) and non-musicians (open circles). **Right panel:** Mean behavioral performance for musicians and non-musicians as a function of the six fMRI runs (mean results across all conditions in each run). Error bars depict the standard error of the mean. **b.** Differential activation maps for the contrast pitch>noise (for the HF-filtered Conditions 1 and 2) for the 15 musicians and 14 non-musicians. Both maps are thresholded at t-values > 4.63 (FWE corrected, p<0.05). **c.** Main effect of musical training from the ANOVA modelling the HF and LF conditions together. Differential activation map to the contrast musicians > non-musicians (*p*<0.05, FWE corrected, voxel extent: 20). R: right, L: left, A: anterior; STG: superior temporal gyrus, HG: Heschl's gyrus; PT: planum temporale, IFG: inferior frontal gyrus, MFG: middle frontal gyrus, IC: inferior colliculus.

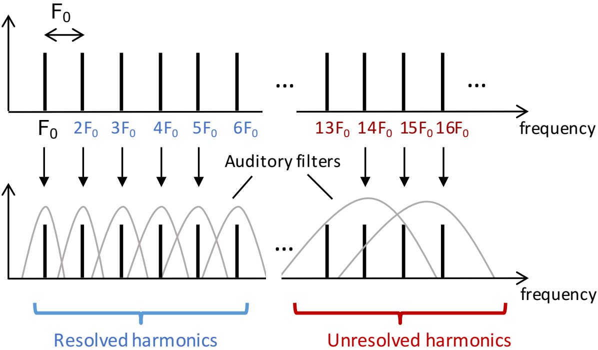
Figure 5 a. Main effect of task difficulty. Differential activation maps for the contrast 60% (difficult task) > 90% (easy task) (*p*<0.001, uncorrected) for all 29 participants. The insert panels depict the contrast 60% > 90% for musicians and non-musicians, separately. All local peaks of the activation are listed in Table 1 (p<0.05, FWE corrected over a 20-mm sphere around maximum). The color scale refers to t-values. R: right, L: left, A: anterior; IFG: inferior frontal gyrus. **b.** The insert panels depict the mean contrast estimates [A.u.] in the left frontal operculum and insular cortex (x = -36, y = 23, z = 1; left panel) and right frontal orbital cortex (x = 33, y = 29, z = 4; right panel), for musicians (filled squares) and non-musicians (open circles) in the four HF conditions. Error bars depict the standard error of the mean.

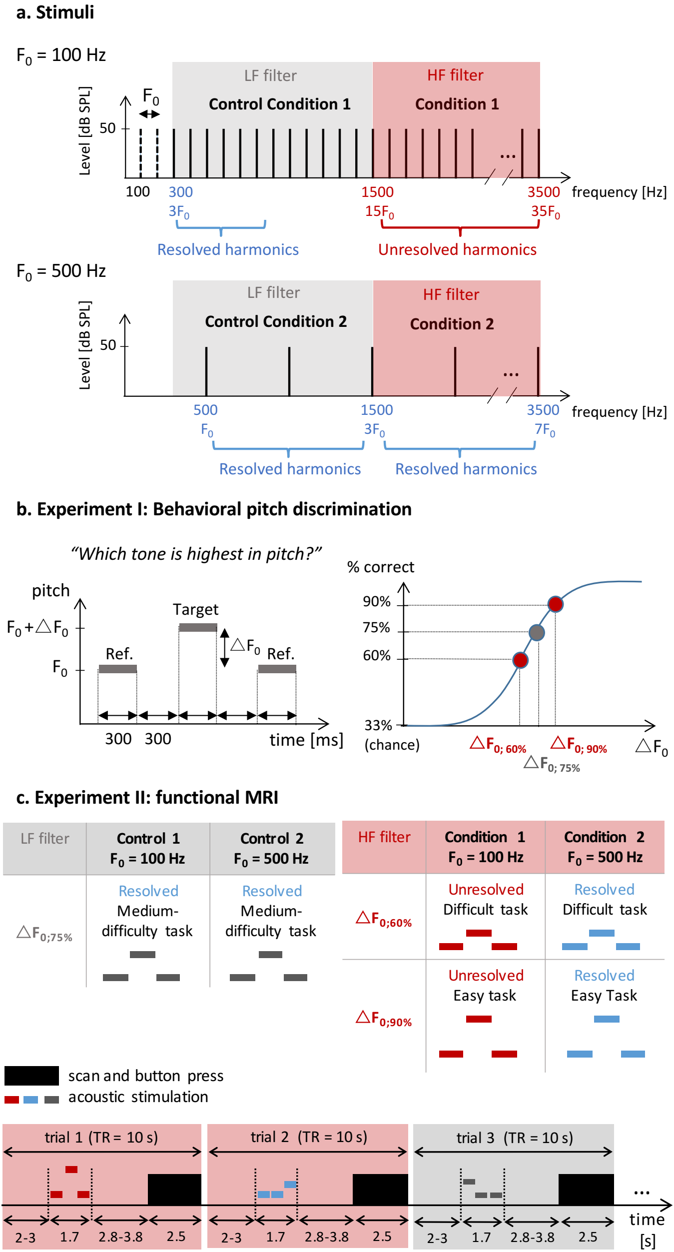
Figure 6 Correlation between the mean contrast estimates in the right and left IFG and the behavioral performance for the six pitch conditions. The anatomical ROIs comprising the right and left IFG are shown in red and blue, respectively. Error bars depict the standard error of the mean. Dashed lines indicate the regression lines for both musicians and non-musicians.

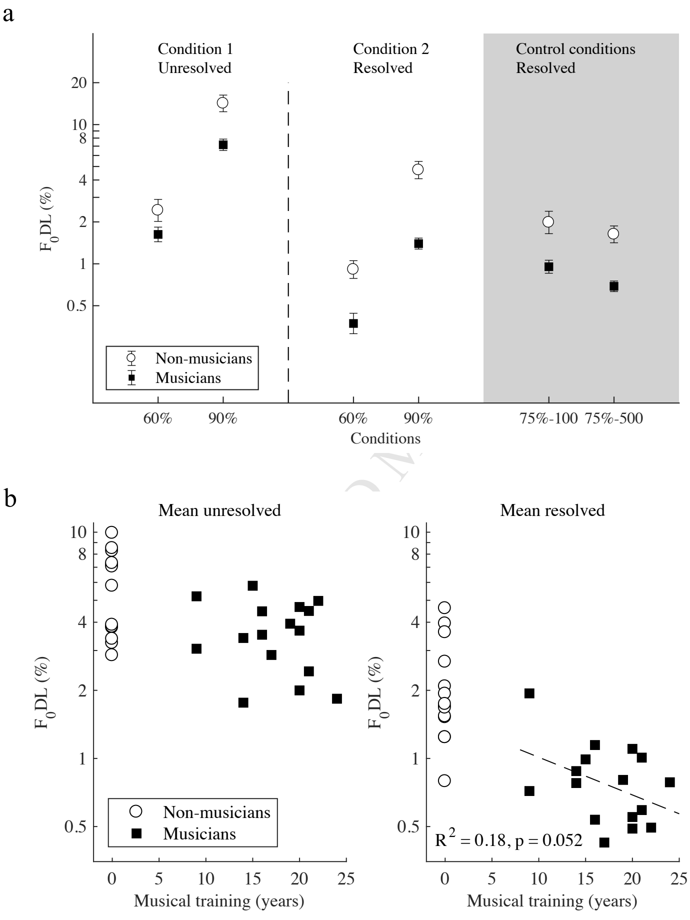
Figure 7 a. Overlay of the contrasts resolved > noise (blue scale) and unresolved > noise (red scale) filtered in the HF region (Conditions 1 and 2) for all 29 participants (p<0.05, FWE corrected; t-values thresholded at t > 8). The insert panels depict the differential activation maps for the 15 musicians (above) and

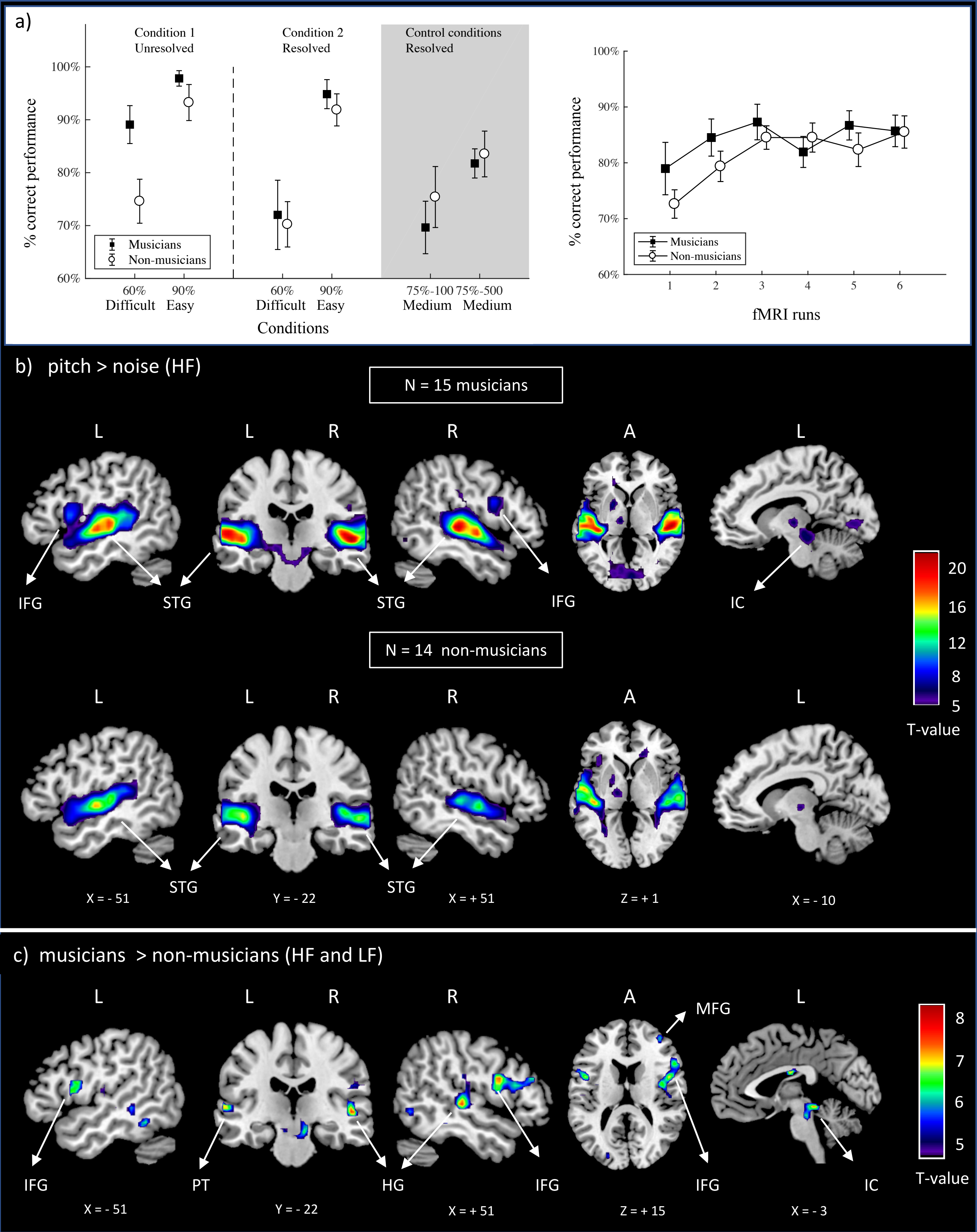
14 non-musicians (below) (thresholded at *t* > 3). **b.** Differential maps to the contrasts resolved > unresolved (blue scale) and unresolved > resolved (red scale) for all 29 participants. For ease of visualization, both maps were thresholded at $p < 0.001$ (uncorrected). **c.** Differential activation maps showing the contrast Control condition 1 (F_0 = 100 Hz, resolved) > Control condition 2 (F_0 = 500 Hz, resolved). For ease of visualization, both maps were thresholded at $p < 0.001$ (uncorrected). R: right, L: left, A: anterior; HG: Heschl's gyrus; PT: planum temporale; PP: planum polare.

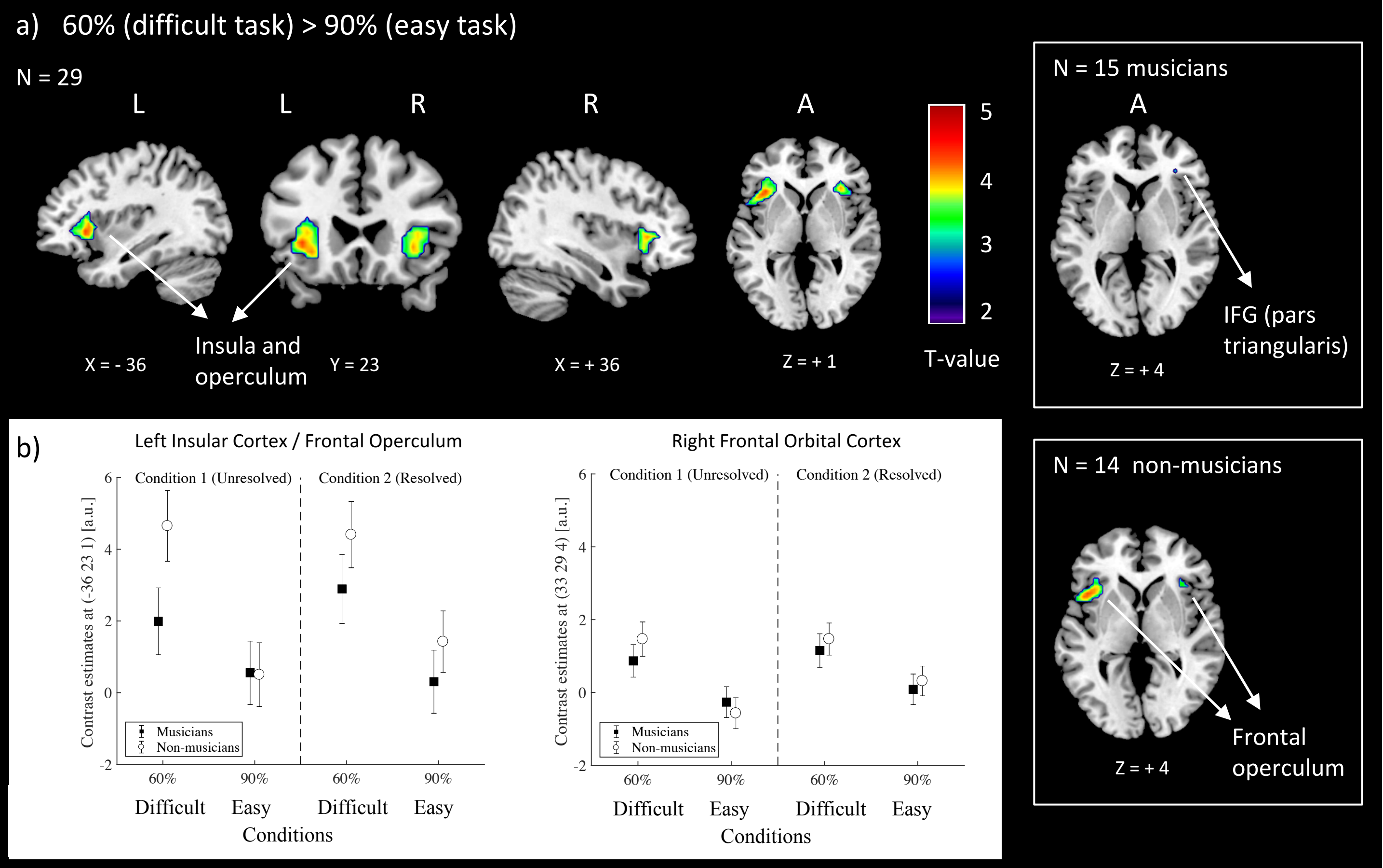
Figure 8 Correlation between behavioral pitch discrimination and BOLD responses to the different pitch conditions (>noise). **a.** Mean contrast estimates [A.u.] for each pitch condition (relative to noise) in the right and left auditory cortex (AC) as a function of the individual pitch-discrimination thresholds from Experiment I (F_0DLs) for the 15 musicians (filled squares) and 14 non-musicians (open circles). The contrast estimates refer to the two LF control conditions (top panels), the two resolved HF conditions (Condition 2, middle panels) and the two unresolved conditions (Condition 1, bottom panels). Spearman's correlation coefficients and the p-values are reported for each panel, for the musicians alone and for all participants (significant correlations after Bonferroni correction with $n = 6$, $p<0.0083$, are depicted by an asterisk and visualized by the linear regression line). **b.** Mean contrast estimates [A.u.] for each pitch condition (relative to noise) in the inferior colliculus as a function of the individual pitch-discrimination thresholds from Experiment I (F_0DLs). The Spearman's correlation coefficients and the p-values are reported for each panel, for the musicians alone and for all participants (significant correlations after Bonferroni correction with $n = 3$, $p<0.017$).

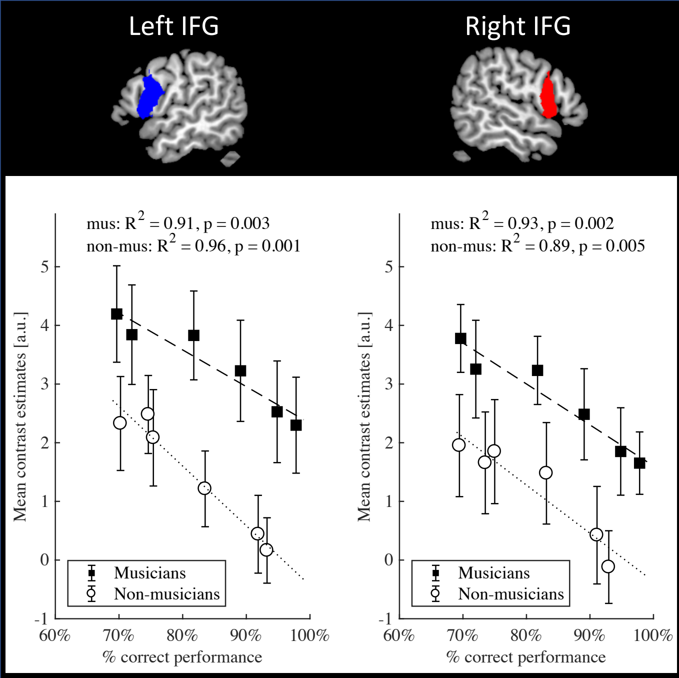

F0
F0
2F0
3F0
4F0
5F0
6F0
13F0
14F0
15F0
16F0
frequency
Auditory filters
frequency
Resolved harmonics
Unresolved harmonics


a. Stimuli
F0 = 100 Hz
LF filter
Control Condition 1
HF filter
Condition 1
Level [dB SPL]
50
F0
...
100
300
3F0
1500
15F0
3500
35F0
frequency [Hz]
Resolved harmonics
Unresolved harmonics
F0 = 500 Hz
LF filter
Control Condition 2
HF filter
Condition 2
Level [dB SPL]
50
...
500
F0
1500
3F0
3500
7F0
frequency [Hz]
Resolved harmonics
Resolved harmonics
b. Experiment I: Behavioral pitch discrimination
"Which tone is highest in pitch?"
pitch
F0+△F0
F0
Ref.
Target
△F0
Ref.
300
300
time [ms]
% correct
90%
75%
60%
33%
(chance)
△F0; 60%
△F0; 90%
△F0; 75%
△F0
c. Experiment II: functional MRI
LF filter
Control 1
F0 = 100 Hz
Control 2
F0 = 500 Hz
△F0;75%
Resolved
Medium-difficulty task
Resolved
Medium-difficulty task
HF filter
Condition 1
F0 = 100 Hz
Condition 2
F0 = 500 Hz
△F0;60%
Unresolved
Difficult task
Resolved
Difficult task
△F0;90%
Unresolved
Easy task
Resolved
Easy Task
scan and button press
acoustic stimulation
trial 1 (TR = 10 s)
trial 2 (TR = 10 s)
trial 3 (TR = 10 s)
2-3
1.7
2.8-3.8
2.5
2-3
1.7
2.8-3.8
2.5
2-3
1.7
2.8-3.8
2.5
...
time
[s]

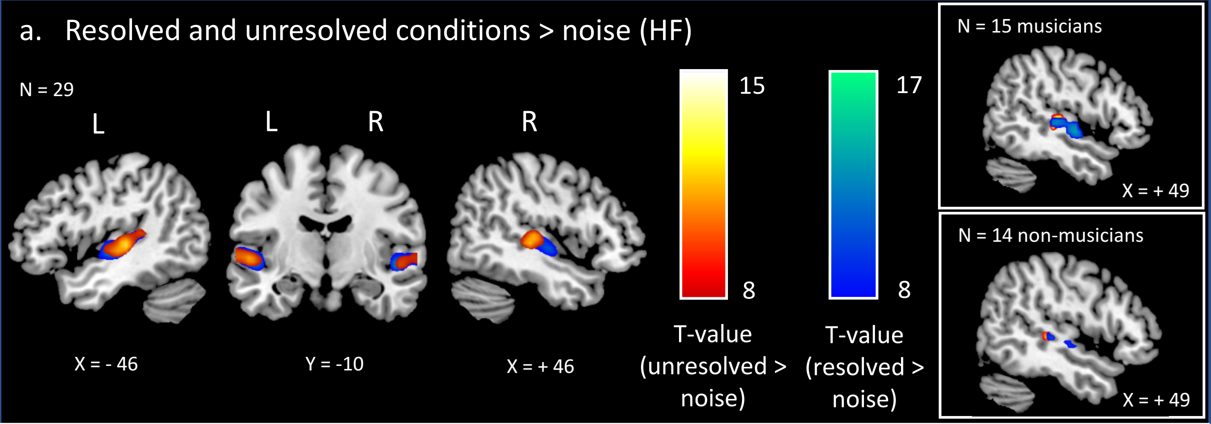

a
Condition 1
Unresolved
Condition 2
Resolved
Control conditions
Resolved
F_0DL (%)
20
10
8
4
2
1
0.5
Non-musicians
Musicians
60%
90%
60%
90%
75%-100
75%-500
Conditions
b
Mean unresolved
Mean resolved
F_0DL (%)
10
8
4
2
1
0.5
Non-musicians
Musicians
$R^2 = 0.18$, p = 0.052
0
5
10
15
20
25
Musical training (years)
Musical training (years)


a)
Condition 1
Unresolved
Condition 2
Resolved
Control conditions
Resolved
% correct performance
100%
90%
80%
70%
60%
Musicians
Non-musicians
60%
Difficult
90%
Easy
60%
Difficult
90%
Easy
75%-100
Medium
75%-500
Medium
Conditions
fMRI runs
1
2
3
4
5
6
b) pitch > noise (HF)
N = 15 musicians
N = 14 non-musicians
L
R
A
IFG
STG
IC
X = - 51
Y = - 22
X = + 51
Z = + 1
X = - 10
20
16
12
8
5
T-value
c) musicians > non-musicians (HF and LF)
MFG
PT
HG
X = - 51
Y = - 22
X = + 51
Z = + 15
X = - 3
8
7
6
5
T-value

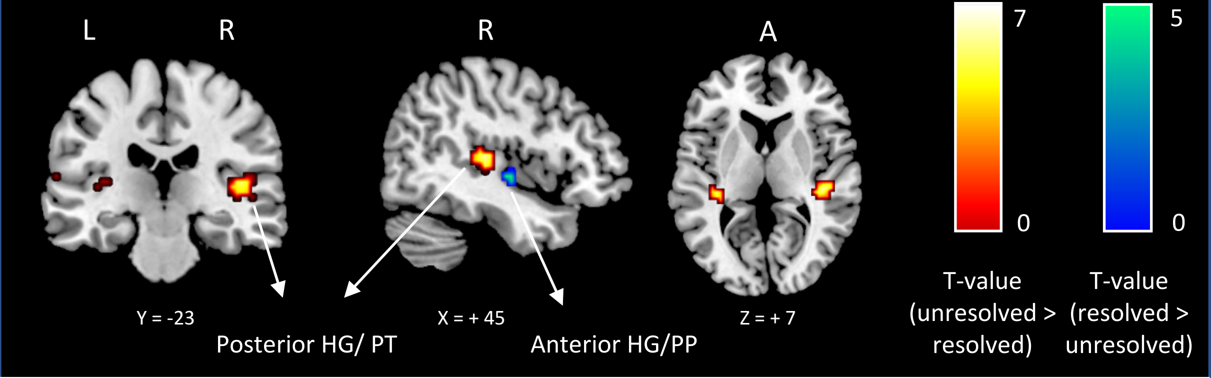

a) 60% (difficult task) > 90% (easy task)
N = 29
L
L
R
R
A
5
4
3
2
T-value
Insula and operculum
X = - 36
Y = 23
X = + 36
Z = + 1
N = 15 musicians
A
IFG (pars triangularis)
Z = + 4
N = 14 non-musicians
Frontal operculum
Z = + 4
b)
Left Insular Cortex / Frontal Operculum
Condition 1 (Unresolved)
Condition 2 (Resolved)
Contrast estimates at (-36 23 1) [a.u.]
6
4
2
0
-2
Musicians
Non-musicians
60%
Difficult
90%
Easy
60%
Difficult
90%
Easy
Conditions
Right Frontal Orbital Cortex
Condition 1 (Unresolved)
Condition 2 (Resolved)
Contrast estimates at (33 29 4) [a.u.]
6
4
2
0
-2
Musicians
Non-musicians
60%
Difficult
90%
Easy
60%
Difficult
90%
Easy
Conditions


Left IFG
Right IFG
mus: R² = 0.91, p = 0.003
non-mus: R² = 0.96, p = 0.001
mus: R² = 0.93, p = 0.002
non-mus: R² = 0.89, p = 0.005
Mean contrast estimates [a.u.]
-1
0
1
2
3
4
5
60%
70%
80%
90%
100%
% correct performance
Musicians
Non-musicians

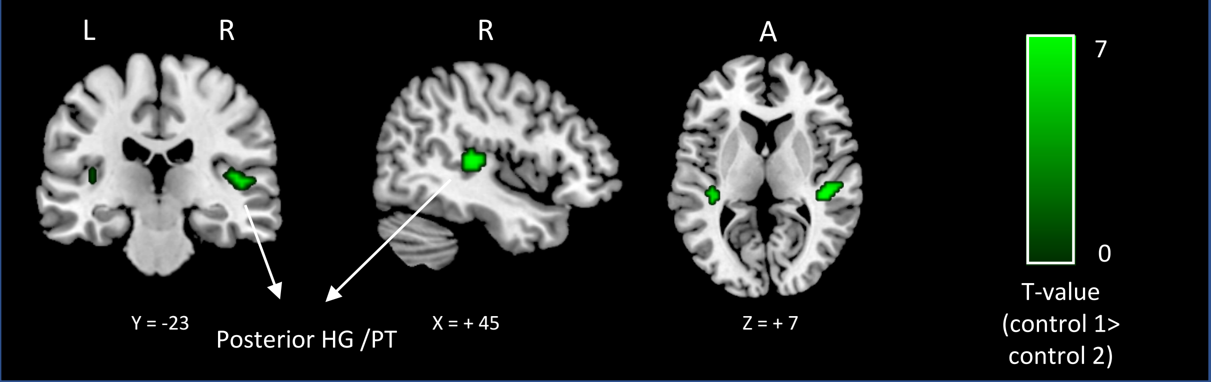
a. Resolved and unresolved conditions > noise (HF)

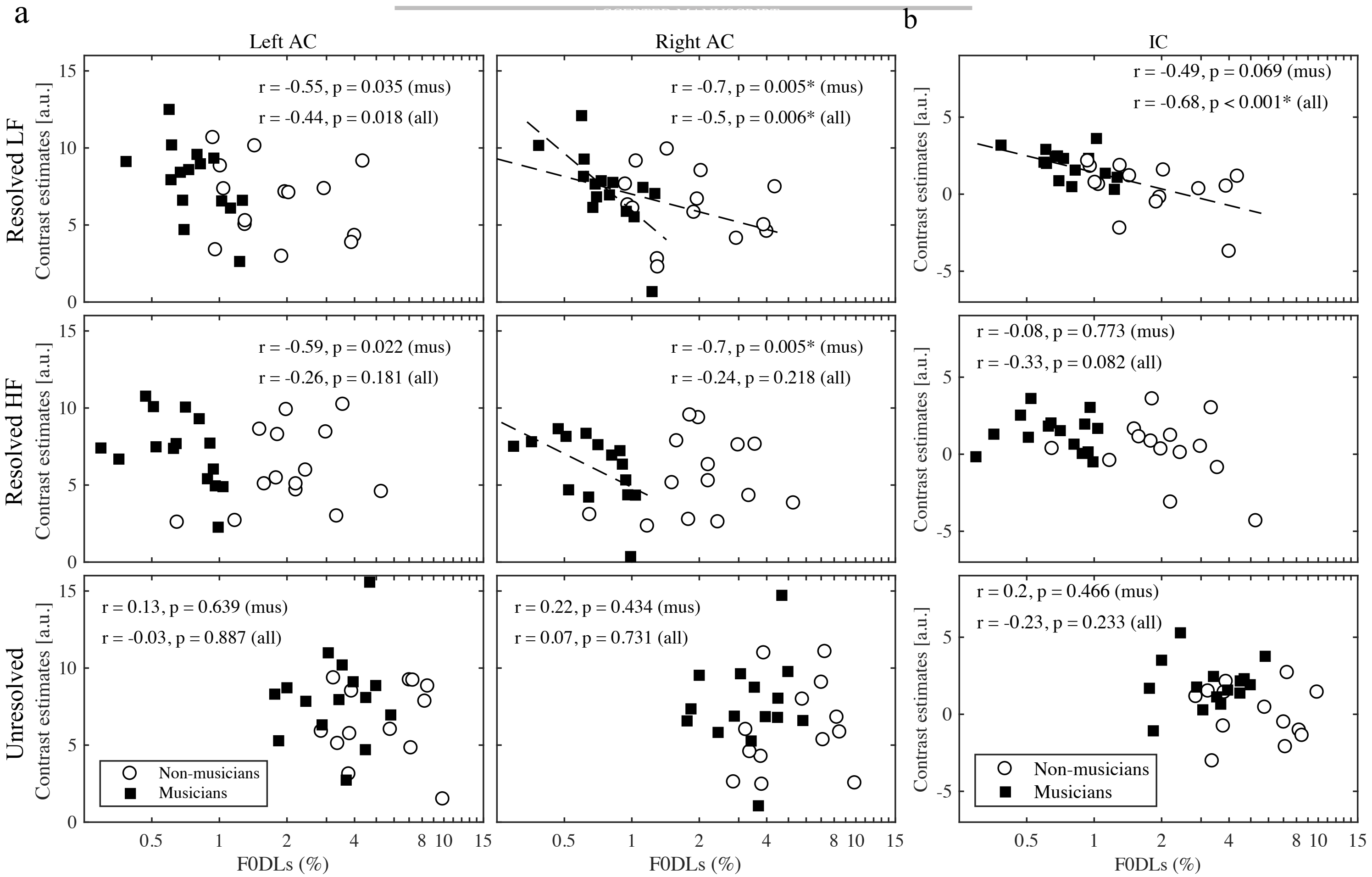


b. Resolved conditions *vs.* unresolved conditions (HF)



c. Control condition 1 > Control condition 2 (LF)




a
b
Left AC
Right AC
IC
Resolved LF
Resolved HF
Unresolved
Contrast estimates [a.u.]
r = -0.55, p = 0.035 (mus)
r = -0.44, p = 0.018 (all)
r = -0.7, p = 0.005* (mus)
r = -0.5, p = 0.006* (all)
r = -0.49, p = 0.069 (mus)
r = -0.68, p < 0.001* (all)
r = -0.59, p = 0.022 (mus)
r = -0.26, p = 0.181 (all)
r = -0.7, p = 0.005* (mus)
r = -0.24, p = 0.218 (all)
r = -0.08, p = 0.773 (mus)
r = -0.33, p = 0.082 (all)
r = 0.13, p = 0.639 (mus)
r = -0.03, p = 0.887 (all)
r = 0.22, p = 0.434 (mus)
r = 0.07, p = 0.731 (all)
r = 0.2, p = 0.466 (mus)
r = -0.23, p = 0.233 (all)
Non-musicians
Musicians
0
5
10
15
-5
0.5
1
2
4
8
10
15
F0DLs (%)