



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

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*Published in:*  
NeuroImage

*Link to article, DOI:*  
[10.1016/j.neuroimage.2017.07.057](https://doi.org/10.1016/j.neuroimage.2017.07.057)

*Publication date:*  
2017

*Document Version*  
Peer reviewed version

[Link back to DTU Orbit](#)

*Citation (APA):*  
Bianchi, F., Hjortkjær, J., Santurette, S., Zatorre, R. J., Siebner, H. R., & Dau, T. (2017). Subcortical and cortical correlates of pitch discrimination: Evidence for two levels of neuroplasticity in musicians. *NeuroImage*, 163, 398-412. <https://doi.org/10.1016/j.neuroimage.2017.07.057>

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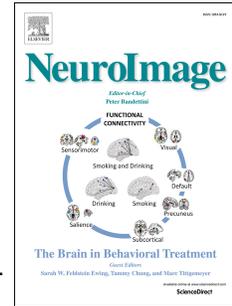
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# Accepted Manuscript

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

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PII: S1053-8119(17)30638-9

DOI: [10.1016/j.neuroimage.2017.07.057](https://doi.org/10.1016/j.neuroimage.2017.07.057)

Reference: YNIMG 14222

To appear in: *NeuroImage*

Received Date: 3 May 2017

Revised Date: 11 July 2017

Accepted Date: 27 July 2017

Please cite this article as: Bianchi, F., Hjortkjær, J., Santurette, Sé., Zatorre, R.J., Siebner, H.R., Dau, T., Subcortical and cortical correlates of pitch discrimination: Evidence for two levels of neuroplasticity in musicians, *NeuroImage* (2017), doi: [10.1016/j.neuroimage.2017.07.057](https://doi.org/10.1016/j.neuroimage.2017.07.057).

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

3                   Abbreviated title: Subcortical and cortical plasticity in musicians

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20                  Number of figures: 8

21                  Number of tables: 1

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**1 Conflict of interest**

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

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**1 Abstract**

2 Musicians are highly trained to discriminate fine pitch changes but the neural bases of  
3 this ability are poorly understood. It is unclear whether such training-dependent  
4 differences in pitch processing arise already in the subcortical auditory system or are  
5 linked to more central stages. To address this question, we combined psychoacoustic  
6 testing with functional MRI to measure cortical and subcortical responses in musicians  
7 and non-musicians during a pitch-discrimination task. First, we estimated behavioral  
8 pitch-discrimination thresholds for complex tones with harmonic components that were  
9 either resolved or unresolved in the auditory system. Musicians outperformed non-  
10 musicians, showing lower pitch-discrimination thresholds in both conditions. The same  
11 participants underwent task-related functional MRI, while they performed a similar  
12 pitch-discrimination task. To account for the between-group differences in pitch-  
13 discrimination, task difficulty was adjusted to each individual's pitch-discrimination  
14 ability. Relative to non-musicians, musicians showed increased neural responses to  
15 complex tones with either resolved or unresolved harmonics especially in right-  
16 hemispheric areas, comprising the right superior temporal gyrus, Heschl's gyrus, insular  
17 cortex, inferior frontal gyrus, and in the inferior colliculus. Both subcortical and cortical  
18 neural responses predicted the individual pitch-discrimination performance. However,  
19 functional activity in the inferior colliculus correlated with differences in pitch  
20 discrimination across all participants, but not within the musicians group alone. Only

1 neural activity in the right auditory cortex scaled with the fine pitch-discrimination  
2 thresholds within the musicians. These findings suggest two levels of neuroplasticity in  
3 musicians, whereby training-dependent changes in pitch processing arise at the  
4 collicular level and are preserved and further enhanced in the right auditory cortex.

5

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

8

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## 1        1. INTRODUCTION

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

1 the auditory system needs to be re-considered. To address this question, the present  
2 study examined the origin of the musicians' enhanced performance for pitch  
3 discrimination using functional MRI.

4 The ability to discriminate pitch changes is assumed to be limited by the frequency  
5 resolution of the peripheral auditory system, often modeled in terms of auditory-filter  
6 bandwidth (e.g., Bernstein and Oxenham 2006, Moore and Glasberg 2011). The  
7 harmonic overtones of a complex tone are said to be *resolved* when they are processed  
8 within distinct auditory filters, and *unresolved* when neighbouring harmonics interact  
9 within the same filter (see Fig. 1). Since the auditory-filter bandwidth increases with  
10 frequency (Glasberg and Moore, 1990), lower-numbered harmonics are typically  
11 resolved while high-numbered harmonics are unresolved (Plack et al., 2005).  
12 Experimental investigations suggest that harmonics below the 6<sup>th</sup> are typically resolved  
13 and elicit a salient pitch percept (depicted in blue in Fig. 1), while harmonics above the  
14 12<sup>th</sup> are unresolved and elicit a less salient pitch (depicted in red in Fig. 1, Plack et al.,  
15 2005). Cortical responses to resolved and unresolved complex tones have been  
16 investigated in previous neuroimaging studies (Penagos et al., 2004; Hall and Plack,  
17 2009; Garcia et al., 2010; Barker et al., 2011; Norman-Haignere et al., 2013). It has  
18 been suggested that cortical pitch-sensitive regions are located in anterolateral regions  
19 of the auditory cortex (Griffiths et al., 1998; Patterson et al., 2002) that respond more  
20 strongly to tones with resolved harmonics as compared to tones containing only

1 unresolved harmonics (Penagos et al., 2004; Norman-Haignere et al., 2013). These  
2 neuroimaging findings are consistent with neurophysiological studies in marmoset  
3 monkeys reporting that the response of pitch-sensitive neurons in the anterolateral  
4 border of primary auditory cortex increases with the salience of the pitch percept  
5 (Bendor and Wang, 2005; Fishman et al., 2013). However, it is still unclear whether  
6 neural responses to resolved and unresolved complex tones may change as a  
7 consequence of musical training.

8 In this study, psychoacoustic measures and functional magnetic resonance imaging  
9 (fMRI) were combined to examine differences in musicians' cortical and subcortical  
10 responses to resolved and unresolved complex tones, and to clarify whether these neural  
11 responses are related to the individual pitch-discrimination abilities. As previous studies  
12 have suggested a specialization of the right auditory cortex for fine pitch processing  
13 (e.g., Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Hyde et al., 2008;  
14 Coffey et al., 2016), it was hypothesized that an enhanced pitch representation in  
15 musicians would be associated with a stronger right-lateralized response to complex  
16 tones compared to non-musicians. In a first behavioral experiment, pitch-discrimination  
17 thresholds were measured for tones containing either resolved or unresolved harmonics  
18 to estimate the musicians' benefit in pitch-discrimination performance relative to the  
19 non-musicians. In a second experiment, an fMRI paradigm was used with the same  
20 listeners and a similar pitch-discrimination task. To avoid confounding differences in

1 neural responses between musicians and non-musicians with differences in task  
2 demands, the task difficulty was adjusted according to the individual behavioral  
3 thresholds from the first experiment and, thus, matched across participants.  
4 Additionally, this novel paradigm allowed dissociation of the effect of harmonic  
5 resolvability from task difficulty, which would otherwise increase for the less salient  
6 unresolved tones. Hence, this is the first study to examine subcortical and cortical  
7 changes in pitch processing between musicians and non-musicians via fMRI  
8 independently of differences in task difficulty across conditions and participants.

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

## 10 **2. MATERIALS AND METHODS**

### 11 **2.1 Participants**

12 Thirty-one healthy listeners, aged from 22 to 30 years, were initially recruited for this  
13 study. Sixteen participants (median age: 26 years, ten females) were musically trained  
14 listeners who had at least eight years of formal musical education (formally enrolled at  
15 music schools and/or undergone private lessons). On average, the musicians started  
16 their musical education at the age of 7 and were formally enrolled at music schools or  
17 had lessons for 12.4 years. Five musicians were string players, three were classical  
18 percussionists, three were singers, three played a keyboard instrument, and two played  
19 woodwinds. One musician reported to have absolute pitch. Fifteen participants (median

1 age: 25 years, seven females) had no formal musical education and had never played a  
2 musical instrument. One non-musician was excluded after Experiment I due to inability  
3 to discriminate one-semitone intervals (mean thresholds of 11% and 19% for resolved  
4 and unresolved complex tones, respectively). All participants were right handed  
5 according to the Edinburgh Handedness Inventory (Oldfield, 1971) except for one  
6 musician, who reported to be ambidextrous and had a Laterality Index of -20 (Middle  
7 decile). This musician was excluded from Experiment II. Hence, 30 listeners were  
8 included in Experiment I (16 musicians, 14 non-musicians) and 29 in Experiment II (15  
9 musicians, 14 non-musicians). All participants had hearing thresholds of less than 20 dB  
10 hearing level (HL) at all audiometric frequencies between 125 Hz and 8 kHz. All  
11 experiments were approved by the Ethics Committee of the Capital Region of Denmark  
12 (H-3-2014-143 and H-3-2013-004) and were conducted in accordance with the  
13 Declaration of Helsinki.

## 14 **2.2 Experiment I: Behavioral pitch-discrimination of complex tones**

15 The first experiment was performed in a double-walled soundproof booth at the  
16 Technical University of Denmark. The ability to discriminate the pitch of resolved and  
17 unresolved complex tones was assessed by determining the just-noticeable difference in  
18 fundamental frequency  $F_0$  (difference limen for  $F_0$ ;  $F_0DL$ ). An adaptive three-alternative  
19 forced-choice (3 AFC) paradigm was used in combination with a weighted up-down  
20 method (Kaernbach, 1991) to determine the different points on the psychometric

1 function at which subjects perceived a difference in pitch in 60%, 75%, and 90% of the  
2 trials. This method is a modification of the simple up-down method. By using a varying  
3 step size to adjust the tracking variable after each response, it can converge to any  
4 desired point on the psychometric function. In each trial, three complex tones were  
5 presented to the listener (see Fig. 2b). Two complex tones served as a reference and had  
6 a fixed fundamental frequency  $F_0$  at either 100 Hz or 500 Hz and one complex tone (i.e.,  
7 the target) had a larger  $F_0$  ( $F_0 + \Delta F_0$ ). The position of the target was randomized across  
8 trials. Participants had to select the target tone with a higher pitch than the two reference  
9 tones (chance level of 33%). Reaction times were not measured in this first experiment.  
10 The initial difference in  $F_0$  between reference and target,  $\Delta F_0$ , was set to 20% and was  
11 then logarithmically decreased after a correct response or increased after an incorrect  
12 response by a varying step size. For each run,  $F_0$  was roved from trial to trial from a  
13  $\pm 5\%$  uniform distribution around the nominal value. A random level perturbation of  
14  $\pm 2.5$  dB was applied to each interval to prevent the listener from using loudness as a  
15 cue. The threshold for each run was obtained as the geometric mean of the last six  
16 reversals. Before the actual test, the listeners performed three repetitions as training.  
17 The final pitch-discrimination threshold ( $F_0DL$ ) was calculated from the mean of three  
18 repetitions.  
19

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

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

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

### 9 ***2.2.1 Behavioral data analysis***

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

### 14 **2.3 Experiment II: Functional MRI during pitch discrimination**

15 The MRI experiment was performed at the Danish Research Center for Magnetic  
16 Resonance, Copenhagen University Hospital Hvidovre using a 3 Tesla whole-body  
17 scanner and a 32-channel head coil (Philips Achieva, Best, The Netherlands).  
18 Functional whole-brain MRI used a T2\*-weighted echo-planar imaging sequence (TR =  
19 10 s, TE = 30 ms; flip angle, 90°). Thirty-eight slices (slice thickness of 3 mm; isotropic

1 voxel size of  $3 \times 3 \times 3 \text{ mm}^3$ ) oriented parallel to the lateral sulcus were acquired. A sparse  
2 imaging approach (Hall et al., 1999) was adopted, whereby the sound stimuli were  
3 presented in the silent period between two volume acquisitions (see Fig. 2c). The  
4 acquisition time of one volume was of 2.5 s (black boxes in Fig. 2c) separated by a 7.5 s  
5 period without scanning. After the fMRI session, T1-weighted high-resolution  
6 anatomical images of the whole brain were acquired (inversion time, 1000 ms; TR,  
7 6056 ms; TE 2.78 ms; flip angle,  $0^\circ$ , scan resolution,  $288 \times 288$ ; slice thickness, 0.850  
8 mm).

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

1 runs were carried out per participant, resulting in a total of 36 trials per condition. The  
2 total duration of the fMRI experiment was of about 42 minutes (252 trials).  
3  
4 The time line of three sample trials is illustrated in Fig. 2c. Two identical reference  
5 complex tones with a fixed  $F_0$  (either 100 or 500 Hz) and one target tone with a larger  
6  $F_0$  (either the first, second or third tone) were presented during the silent period without  
7 concurrent scanning. Acoustic stimulus presentation lasted for 1.7 s and started 2 - 3 s  
8 after the acquisition of the previous volume. The fMRI data acquisition of a single brain  
9 volume started 2.8 - 3.8 s after the end of the stimulus presentation and lasted 2.5 s.  
10 This time jitter in the onset of the signal was introduced to account for the inter-subject  
11 variability of the BOLD hemodynamic response (Aguirre, 1998) and to introduce  
12 variation in the timing of stimulus presentation. Participants performed a 3 AFC task,  
13 where they had to identify the target tone by pressing either the first, second or third  
14 button on a response box, according to the target's position (i.e., first, second or third  
15 tone presented). The target position was pseudorandomized across trials and runs. The  
16 participants were instructed to press the response button during the following volume  
17 acquisition, even for the noise-only conditions (any button in this case). For one  
18 participant, button presses could not be recorded due to a technical failure of the  
19 response box. The difficulty of the pitch-discrimination task was defined by the  
20 difference in  $F_0$  between the reference and target tone (i.e.,  $\Delta F_0$ ). Critically, this

1 difference was adjusted for each participant according to the individual thresholds  
2 measured in Experiment I (60% detection probability: high difficulty; 75% detection  
3 probability: medium difficulty; 90% detection probability: low difficulty) to match the  
4 task in terms of difficulty.

5

### 6 ***2.3.1 Neuroimaging data analysis***

7 Data analyses were performed with the statistical parametric mapping software (SPM8,  
8 Wellcome Trust Centre for Neuroimaging, London, UK). Data processing consisted of  
9 realignment, coregistration, spatial normalization to MNI standard space as  
10 implemented in SPM8, and smoothing with an 8-mm full-width at half-maximum  
11 isotropic Gaussian kernel. Data analysis was performed using a general linear model  
12 (GLM) approach. At the single subject level, separate regressors were defined for each  
13 experimental condition (seven regressors) to model the onset of the sound stimulus.  
14 Correct and incorrect responses were also modeled as additional regressors. Movement  
15 parameters estimated from the realignment were entered as six additional regressors of  
16 no-interest. Low frequency drifts in the BOLD signal were removed by a high-pass  
17 filter with a cut-off period of 128 s. Group level analysis for the HF conditions  
18 employed a full-factorial 2x2x2 ANOVA model. The design matrix included three main  
19 factors: group (musicians and non-musicians), task difficulty (two levels: 60% and 90%  
20 probability of correct target detection), and resolvability (two levels: unresolved and

1 resolved harmonics). Additionally, a 2x3x2 ANOVA was used to model the HF and LF  
2 conditions together. The design matrix included three main factors: group (musicians  
3 and non-musicians), task difficulty (three levels: 60%, 75% and 90% probability of  
4 correct target detection), resolvability (two levels: unresolved and resolved harmonics).  
5 Finally, six t-tests were carried out to clarify the effect of harmonic resolvability  
6 (Condition 1 vs. Condition 2; Control Condition 1 vs. Control Condition 2; Condition 1  
7 vs. Control Condition 1). The hypothesis was that an effect of harmonic resolvability  
8 would result from the contrasts Condition 2 (resolved) > Condition 1 (unresolved) and  
9 Control condition 1 (resolved) > Condition 1 (unresolved), while no differential  
10 activation should result from the contrasts Control condition 2 (resolved) > Control  
11 condition 1 (resolved). All peak p-values reported in this study were obtained from  
12 whole brain analysis, applying a corrected p-value of 0.05 as statistical threshold. The  
13 p-values for the contrast 60%>90% (effect of task difficulty) were obtained from a  
14 small volume correction (20 mm-sphere around peak value). Correction for multiple  
15 non-independent comparisons used the family-wise error (FWE) correction method at  
16 the voxel level as implemented in SPM8.

17

#### 18 **2.4 Correlation between behavioral and neuroimaging data**

19 Correlations between the individual pitch-discrimination performance from Experiment  
20 I and the cortical neural activation from Experiment II were carried out for the 15

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

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

17 Finally, since the inferior frontal gyrus (IFG) has been found to play an important role  
18 for active pitch-retention tasks (e.g., Zatorre et al., 1994; Griffiths et al., 1999; Albouy  
19 et al., 2013), a ROI comprising the right and left pars opercularis was defined using the  
20 SPM Anatomy toolbox (Broca's area 44; Eickhoff et al., 2005) and used to relate the

1 functional activation in the IFG with the listeners' performance (i.e., % correct target  
2 identification). This anatomical mask was applied to the individual contrasts obtained  
3 for each pitch condition relative to the noise. The mean activation of the voxels within  
4 the inclusive mask was calculated for each participant and used to correlate with  
5 performance. Correlation p-values lower than 0.025 (after Bonferroni correction with  $n$   
6 = 2) was considered significant.

7

### 8 **3. RESULTS**

#### 9 **3.1 Experiment I: Pitch-discrimination of complex tones**

10 Figure 3a shows the mean pitch-discrimination thresholds ( $F_0$ DLs) for the four HF  
11 conditions with either unresolved harmonics (Condition 1) or with resolved harmonics  
12 (Condition 2), and for the two LF conditions with resolved harmonics (Control  
13 conditions; grey-shaded area in Fig. 3a) for the 16 musicians (filled symbols) and 14  
14 non-musicians (open symbols). The performance for all listeners was more accurate in  
15 the presence of resolved harmonics (mean  $F_0$ DLs of musicians: 0.76%; mean  $F_0$ DLs of  
16 non-musicians: 1.9%) than unresolved harmonics (mean  $F_0$ DLs of musicians: 3.4%;  
17 mean  $F_0$ DLs of non-musicians: 5.9%), consistent with a more salient pitch percept  
18 evoked by the resolved than the unresolved harmonics (e.g., Houtsma and Smurzynski,  
19 1990; Shackleton and Carlyon, 1994; Bernstein and Oxenham, 2006). Compared to the  
20 non-musicians, the musically trained listeners had significantly lower thresholds in all

1 conditions, indicating a more accurate pitch-discrimination performance for both  
2 resolved and unresolved complex tones. The musicians' performance was enhanced  
3 relative to non-musicians, on average, by a factor of 2.5 for the resolved conditions, but  
4 only by a factor of 1.7 for the unresolved conditions. Additionally, as expected from  
5 estimating a higher point on the psychometric function, the thresholds of both musicians  
6 and non-musicians were larger for the 90% condition than those for the 60% condition.  
7 The effect of musical training was greater for the easy-task conditions (90% point of the  
8 psychometric function) as compared to the difficult-task conditions (60%).

9 The mixed-model ANOVA on the HF conditions confirmed a significant effect of the  
10 three main factors: group [ $F(1, 84) = 26.31$ ;  $p < 0.0001$ ], resolvability [ $F(1, 84) = 369.5$ ;  
11  $p < 0.0001$ ] and probability of correct target detection at threshold [ $F(1, 84) = 531.06$ ;  $p$   
12  $< 0.0001$ ], as well as a significant interaction between group and resolvability [ $F(1, 84)$   
13  $= 14.47$ ;  $p = 0.0003$ ] and group and probability of detection [ $F(1, 84) = 5.13$ ;  $p = 0.026$ ].  
14 No interaction was found between resolvability and probability of detection [ $F(1, 84) =$   
15  $1.12$ ;  $p = 0.292$ ] nor among the three factors [ $F(1, 84) = 0.02$ ;  $p = 0.891$ ].

16 Figure 3b shows the individual pitch-discrimination thresholds (16 musicians: filled  
17 symbols; 14 non-musicians: open symbols), averaged for the two unresolved conditions  
18 (HF; left panel) and the four resolved conditions (LF and HF; right panel) as a function  
19 of years of musical training. A marginally significant trend was observed for the  
20 resolved conditions (right panel; one-tailed Pearson's correlation:  $R^2 = 0.18$ ;  $p = 0.052$ ),

1 whereby performance increased with overall years of musical training. However, there  
2 was no correlation between pitch-discrimination performance and years of musical  
3 training for the unresolved conditions (left panel; one-tailed Pearson's correlation:  $R^2 =$   
4 0.04;  $p = 0.239$ ).

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

## 6 **3.2 Experiment II: Functional brain activation during a pitch-discrimination task**

### 7 **3.2.1 Behavioral performance**

8 The behavioral responses obtained during fMRI are summarized in Fig. 4a, showing the  
9 accuracy for target identification in the musician (filled symbols) and non-musician  
10 groups (open symbols). As mentioned above, task difficulty was adjusted to the  
11 individual pitch-discrimination ability to match performance across participants and  
12 groups. Thus, as expected from the experimental design, the ANOVA revealed no  
13 significant group nor subject effects on the behavioral responses to the HF conditions  
14 [Group:  $F(1,437) = 2.32$ ;  $p = 0.14$ ; Subject (nested in group):  $F(26,437) = 1.18$ ;  $p =$   
15  $0.292$ ]. There was also no interaction between group and difficulty [ $F(1,437) = 0.88$ ;  $p =$   
16  $0.356$ ] nor of group and resolvability [ $F(1,437) = 2.18$ ;  $p = 0.152$ ], suggesting that task  
17 difficulty and harmonic resolvability were similar in the two groups of participants.  
18 Additionally, a significant effect of resolvability [ $F(1,437) = 7.1$ ;  $p = 0.013$ ] and task  
19 difficulty [ $F(1,437) = 59.86$ ;  $p < 0.0001$ ] was found on the behavioral responses, together  
20 with an interaction between difficulty and resolvability [ $F(1,437) = 17.06$ ;  $p < 0.0001$ ],

1 suggesting a stronger effect of difficulty obtained for the resolved conditions. The  
2 ANOVA revealed a significant effect of runs [ $F(5,437) = 2.61$ ;  $p = 0.028$ ], whereby  
3 performance increased over the first three runs of the experiment until reaching a  
4 plateau for the last three runs (Fig. 4a, right panel). No interactions were found between  
5 the effect of runs and any of the other factors. The obtained levels of performance were  
6 slightly higher than the targeted levels (i.e., 60%, 75% and 90%). This may have been  
7 due to an effect of training over the six runs (Fig. 4a, right panel) or to the non-adaptive  
8 procedure used in Experiment II vs. the adaptive procedure of Experiment I. This effect  
9 was, however, consistent across groups and conditions, as confirmed by the absence of  
10 interactions between group and difficulty and group and resolvability.

### 11 **3.2.2 Effect of musical training**

12 Figure 4b depicts the differential activation maps for all HF conditions relative to the  
13 noise condition in musicians and non-musicians. Both groups of listeners showed task-  
14 related activations in the right and left superior temporal gyri (STG), with stronger  
15 activations in the musician group especially in the posterior division of the STG ( $x, y, z$   
16  $= 51, -22, 1$ ;  $t = 20.43$ ), Heschl's gyrus (HG;  $x, y, z = 51, -20, 3$ ;  $t = 18.39$ ), and planum  
17 polare (PP;  $x, y, z = 51, -7, -3$ ;  $t = 17.35$ ). Additionally, bilateral activations in  
18 musicians were observed in the inferior frontal gyri (IFG, pars opercularis) at the border  
19 with the precentral gyrus ( $x, y, z = 51, 8, 22$ ;  $t = 8.62$ ), in the lingual and occipital  
20 fusiform gyri ( $x, y, z = 9, -85, -5$ ;  $t = 7.32$ ), in the cerebellum ( $x, y, z = -27, -64, -26$ ;  $t =$

1 9.16), and in the inferior colliculi (IC;  $x, y, z = -10, -28, -10$ ;  $t = 6.54$ ) during the pitch-  
2 discrimination task. Figure 4c illustrates the differential activation map of musicians  
3 relative to non-musicians for all tested pitch conditions (LF and HF combined).  
4 Musicians showed a significantly stronger BOLD response during pitch discrimination  
5 in a set of cortical and subcortical areas (all peak-level coordinates and t-values are  
6 listed in Table 1). The largest cluster of enhanced activation in musicians comprised the  
7 posterior division of the right STG at the border of HG ( $x, y, z = 51, -22, 1$ ;  $t = 7.42$ ;  
8 Fig. 4c), extending to the insular cortex and frontally to the IFG (pars opercularis;  $x, y,$   
9  $z = 51, 8, 22$ ;  $t = 7.27$ ; Fig. 4c). The second largest cluster of enhanced activation in  
10 musicians was in the brainstem, and comprised dorsal parts of the midbrain, including  
11 the IC ( $x, y, z = -3, -34, -11$ ;  $t = 7.25$ ; Fig. 4c). The left planum temporale (PT;  $x, y, z =$   
12  $-63, -19, 7$ ;  $t = 6.92$ ) and the left lateral occipital cortex ( $x, y, z = -27, -82, 34$ ;  $t = 7.74$ )  
13 were also significantly more activated in the musicians. Additionally, the analysis  
14 revealed a significantly larger BOLD response in the non-musicians relative to the  
15 musicians in the right and left hippocampi (Table 1). No interaction between group and  
16 difficulty, group and resolvability, nor of group, difficulty and resolvability was found.

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

### 18 **3.2.3 Effect of task difficulty**

1 The ANOVA on the HF conditions revealed a significant effect of task difficulty (Fig.  
2 5a). The difficult conditions (60%) showed stronger task-related activation relative to  
3 the easy conditions (90%) in the left frontal operculum and insular cortex ( $x, y, z = -36,$   
4  $23, 1; t = 4.31$ ; Table 1), left IFG ( $x, y, z = -51, 11, 4; t = 4.03$ ; Table 1) and right frontal  
5 orbital and insular cortex ( $x, y, z = 33, 29, 4; t = 4.36$ ; Table 1). The two insert panels in  
6 Fig. 5a depict the effect of task difficulty for musicians and non-musicians, separately.  
7 The two panels in Fig. 5b depict the mean contrast estimates for musicians (filled  
8 squares) and non-musicians (open circles) in the left (left panel) and right (right panel)  
9 frontal operculum and insular cortex. The effect of task difficulty (60%>90%) was  
10 present for both unresolved and resolved conditions and for both groups of listeners, as  
11 confirmed by the absence of interactions between group and difficulty. However, non-  
12 musicians showed stronger task-related activations than musicians in the left frontal  
13 operculum and insular cortex (Fig. 5a, insert panels; Fig. 5b, left panel).

14 Additionally, the mean task-related BOLD signal within the anatomical mask defined  
15 for the IFG (pars opercularis, shown in Fig. 6) was calculated for each pitch condition  
16 (relative to noise) and each participant. Figure 6 depicts the mean contrast estimates for  
17 the musicians (filled symbols) and non-musicians (open symbols) in the left and right  
18 IFG (left and right panels, respectively) as a function of the behavioral performance (%  
19 correct target detection). The increase in activation in both the left and right pars  
20 opercularis was significantly correlated with a decrease in the behavioral performance

1 for both groups of listeners. Thus, increasing the difficulty of the pitch-discrimination  
2 task (i.e., decreasing the  $\Delta F_0$  between reference and target tones) resulted in a similar  
3 bilateral task-related activation in the IFG for both groups of listeners.

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

### 5 **3.2.4 Effect of harmonic resolvability**

6 The ANOVA on the HF conditions revealed a small main effect of resolvability in the  
7 posterior end of the right HG ( $x, y, z = 42, -28, 7$ ;  $F = 14.1$ ;  $p < 0.001$  uncorrected).  
8 However, the change in the resolvability of the harmonics was associated with a change  
9 in the  $F_0$  from 100 Hz to 500 Hz. Hence, additional t-tests were performed on the HF  
10 conditions, as well as on the control conditions to disentangle the two effects. The t-  
11 tests on the HF conditions revealed differential activation of resolved and unresolved  
12 tones in the anterior and posterior parts of the AC. Figure 7a depicts the contrasts of  
13 unresolved conditions (Condition 1,  $F_0$  of 100 Hz, red scale) and resolved conditions  
14 (Condition 2,  $F_0$  of 500 Hz, blue scale) relative to the noise for all 29 participants.  
15 Bilateral activation in HG extended anteriorly for the resolved tones while responses to  
16 the unresolved conditions extended more posteriorly into the PT region. This pattern  
17 was seen more strongly for musicians, but was similarly present in non-musicians (see  
18 insert panels of Figure 7a for the 15 musicians and 14 non-musicians). Directly  
19 contrasting the resolved and unresolved conditions showed that this pattern was more

1 pronounced in the right AC (see Fig. 7b). Activity in the right anterior HG and planum  
2 polare ( $x, y, z = 45, -10, -5$ ;  $t = 4.12$ ;  $p = 0.051$  FWE corrected) was stronger for the  
3 resolved conditions compared to the unresolved, while the unresolved conditions  
4 activated the posterior end of the right ( $x, y, z = 42, -25, 7$ ;  $t = 6.04$ ;  $p = 0.001$  FWE  
5 corrected) and left HG ( $x, y, z = -33, -31, 10$ ;  $t = 6.57$ ;  $p < 0.0001$  FWE corrected) and  
6 the left anterior PT ( $x, y, z = -63, -25, 13$ ;  $t = 4.39$ ;  $p = 0.028$  FWE corrected).  
7 Additional contrasts between the control conditions were run to clarify whether the  
8 differential activation seen in Fig. 7b was the result of a change in harmonic  
9 resolvability or a change in  $F_0$ . Similar as for the HF-filtered tones, the LF-filtered tones  
10 showed higher activity for the lower pitch ( $F_0 = 100$  Hz, control condition 1) relative to  
11 the higher pitch condition ( $F_0 = 500$  Hz, control condition 2) in the posterior parts of the  
12 AC (Fig. 7c, the posterior HG-PT border on the right  $x, y, z = 42, -28, 10$ ,  $t = 7.68$ ,  
13  $p < 0.0001$  FWE corrected; and left  $x, y, z = -39, -34, 16$ ,  $t = 7.47$ ,  $p = 0.001$  FWE  
14 corrected). No differential activation was found for the higher pitch (control condition  
15 2) relative to the lower pitch (control condition 1). Thus, the contrast unresolved >  
16 resolved (Fig. 7b, red scale, HF conditions) and the contrast between the resolved  
17 control conditions (Fig. 7c) were both seen to activate the posterior end of HG and the  
18 left PT. Hence, other factors than harmonic resolvability per se could be driving these  
19 contrasts (e.g., the change in the  $F_0$  from 100 to 500 Hz). Supporting this, no differential

1 activation was found between conditions with different harmonic resolvability but same  
2  $F_0$  (Condition 1 and Control condition 1).

3 --- Figure 7 about here ----

4

### 5 **3.3 Correlation of pitch-discrimination performance and cortical vs. subcortical** 6 **responses**

7 Figure 8a shows the correlation between the mean BOLD responses in the right and left  
8 AC and the behavioral  $F_0$ DLs (i.e., the pitch-discrimination performance from  
9 Experiment I) for the 15 musicians (filled symbols) and the 14 non-musicians (open  
10 symbols). After Bonferroni correction for multiple comparisons ( $n = 6$ , significance for  
11  $p < 0.0083$ ), a significant correlation for the musicians was observed in the right AC for  
12 the resolved conditions (top and middle right panels in Fig. 8a; Spearman's correlation:  
13  $r = -0.70$ ,  $p = 0.005$ ) but not in the left AC. Thus, finer discrimination of the resolved  
14 complex tones in the musically-trained listeners was associated with stronger neural  
15 responses to resolved tones in the right AC. No correlation was found for the  
16 unresolved conditions. Additionally, no correlation was present for the non-musicians'  
17 in either the right or left AC.

18 Figure 8b shows the correlation between the pitch-discrimination thresholds and the  
19 mean responses in the IC. Although no significant correlation was found within the

1 group of musicians nor non-musicians, a strong correlation was seen when pooling all  
2 listeners, reflecting a group difference in magnitude of response. Significant  
3 correlations between responses in the IC and the behavioral pitch thresholds were seen  
4 only for the resolved LF-filtered tones (top panel; Spearman's correlation:  $r = -0.68$ ,  $p <$   
5  $0.001$ ), and not for the unresolved conditions (bottom panel).

6 --- Figure 8 about here ----

## 7 **4. DISCUSSION**

### 8 **4.1 Pitch-discrimination performance for resolved and unresolved harmonics**

9 Our behavioral data (Experiment I) revealed that the musicians outperformed the non-  
10 musicians in pitch-discrimination performance with a factor of about 2.5 for the  
11 resolved conditions, and a factor of 1.7 for the unresolved conditions (Fig. 3a).  
12 Additionally, a trend was found between pitch-discrimination performance and overall  
13 years of musical training for the resolved but not for the unresolved conditions (Fig.  
14 3b). These findings point towards a training-dependent effect in musicians that was  
15 more prominent for stimuli containing resolved harmonics. Although musical sounds  
16 generally contain both resolved and unresolved harmonics, a larger benefit of musicians  
17 for resolved tones is reasonable considering that the resolved harmonics provide the  
18 most salient cue for pitch retrieval (e.g., Houtsma and Smurzynski, 1990; Shackleton  
19 and Carlyon, 1994; Bernstein and Oxenham, 2006). However, musicians still showed

1 better pitch-discrimination performance than non-musicians in the unresolved  
2 conditions, despite not being specifically trained on stimuli containing only unresolved  
3 harmonics. This finding is in agreement with previous studies showing that learning is  
4 only partly resolvability-specific (Grimault et al, 2002; Carcagno and Plack, 2011b).  
5 Grimault et al. (2002) showed that listeners trained with a particular resolved tone  
6 obtained larger improvements when tested on other resolved tones than when tested on  
7 unresolved tones. Thus, although learning generalized to the untrained condition, the  
8 transfer of learning to a stimulus with a different resolvability was not complete.  
9 Similarly, Pantev et al. (1998) and Micheyl et al. (2006) showed that the musicians'  
10 advantage in pitch discrimination was larger for complex tones than for pure tones  
11 consistent with an incomplete generalization of learning for unfamiliar sounds (Demany  
12 and Semal, 2002).

13  
14 While some studies have suggested that experience-dependent changes in musicians  
15 emerge already at the level of the cochlea in terms of sharper tuning of cochlear filters  
16 (Soderquist, 1970; Bidelman et al., 2014b; Bidelman et al., 2016), previous behavioral  
17 studies did not find evidence for differences in musicians at the peripheral level (Fine  
18 and Moore 1993; Oxenham et al., 2003; Bianchi et al., 2016a). If the musicians' finer  
19 pitch discrimination, as observed behaviorally in the present study (Fig. 3), were  
20 exclusively ascribed to sharper peripheral frequency selectivity, then no advantage in

1 pitch-discrimination would be expected for the unresolved tones. In fact, narrower  
2 peripheral filters would lead to less salient envelope cues at the output of cochlear  
3 stages as a consequence of fewer harmonics interacting within the same filter (Bianchi  
4 et al., 2016b). Hence, our behavioral findings, showing enhanced pitch-discrimination  
5 abilities in musicians that extend to the unresolved tones, cannot be solely explained by  
6 sharper cochlear tuning (Bidelman et al., 2016) and point to an enhanced  $F_0$   
7 representations along the auditory system at stages beyond the cochlea. This  
8 behavioural enhancement for both resolved and unresolved tones could be ascribed to  
9 an increased neural synchrony in the auditory brainstem of musicians (e.g., Wong et al.,  
10 2007; Musacchia et al., 2007; Parbery-Clark, 2009) and/or to plasticity at the cortical  
11 level (e.g., Schneider, 2002; Bermudez et al., 2009; Hyde et al., 2009; Foster and  
12 Zatorre, 2010; Seither-Preisler et al., 2014; Coffey et al., 2016).

#### 13 **4.2 Subcortical and cortical responses to pitch in musicians**

14 The fMRI results (Experiment II) revealed both stronger cortical and subcortical  
15 responses in musicians for resolved as well as for unresolved complex tones. By  
16 adjusting the task to the individual pitch-discrimination abilities, we ensured that the  
17 observed differences in task-related activation were not caused by differences in task  
18 difficulty across participants. Neural responses in musicians were especially enhanced  
19 in right-hemispheric areas, comprising the right STG, HG, insular cortex, IFG (pars

1 opercularis), superior and middle frontal gyri (Fig. 4c, Table 1), and in the auditory  
2 midbrain. The stronger right-lateralized responses in musicians (relative to non-  
3 musicians) in the AC are in agreement with our initial hypothesis and support the notion  
4 that the right AC is more specialized than the left AC in fine pitch processing (e.g.,  
5 Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Zatorre et al., 2002;  
6 Hyde et al., 2008). These findings provide additional evidence of enhanced neural  
7 responses in musicians in a right fronto-temporal network that is assumed to be  
8 involved in pitch processing and tonal working memory (Zatorre and Samson, 1991;  
9 Zatorre et al., 1994; Albouy et al., 2013). Connectivity between the right superior  
10 temporal gyrus and the frontal cortex has been suggested to be part of a distributed  
11 neural network responsible for maintaining pitch into auditory working memory  
12 (Zatorre and Samson, 1991; Perry, 1993; Zatorre et al., 1994). The higher activation in  
13 musicians in the right STG, right IFG and insular cortex (Fig. 4c, Table 1) can be  
14 interpreted as a stronger involvement in neural resources to extract, maintain, and  
15 compare pitch information (e.g., Maess et al., 2001; Koelsch et al., 2005). Together,  
16 these findings suggest a right-hemispheric cortical network for pitch extraction and  
17 manipulation that is more developed in musicians (Koelsch et al., 2005; Zatorre et al.  
18 1994; Schulze et al., 2011).

19 Additionally, the auditory midbrain (including the IC, Fig. 4c) showed significantly  
20 higher activation in the musicians compared to the non-musicians. Pitch-related

1 activation in the midbrain occurred in both inferior colliculi suggesting that the  
2 asymmetry favoring right-hemispheric regions arises cortically in musicians (Griffiths  
3 et al. 2001; Coffey et al., 2016). Our findings show that stronger  $F_0$  encoding of  
4 resolved and unresolved complex tones was already present at the subcortical level,  
5 consistent with previous electrophysiological studies suggesting a higher degree of  
6 phase synchrony in the musicians' brainstem in response to harmonic complex sounds  
7 (e.g., Wong et al., 2007; Musacchia et al., 2007; Parbery-Clark 2009; Bidelman et al.,  
8 2011; Carcagno and Plack, 2011a).

#### 9 **4.3 Pitch-discrimination performance and functional activation**

10 Both at the cortical and subcortical level, the mean task-related responses to resolved  
11 complex tones were correlated with the individual pitch-discrimination thresholds (Fig.  
12 8). The increase in functional activity in the right AC predicted a finer pitch-  
13 discrimination performance of musicians for resolved complex tones (Fig. 8a, top and  
14 middle panels). However, at the subcortical level, neural responses in the IC reflected  
15 the pitch-discrimination performance across the two groups of subjects, but not within  
16 the musicians group alone (Fig. 8b, top panel). These findings suggest a hierarchical  
17 model of pitch extraction whereby the sensitivity to the harmonic structure of a sound is  
18 already present in subcortical auditory neurons, which may then provide inputs of  
19 harmonic templates to the AC (Wang et al., 2013). The existence of such harmonic  
20 templates was previously observed within the primary AC in different species (bat,

1 Fitzpatrick et al., 1993; cat, Sutter and Schreiner, 1991; marmoset, Kadia and Wang,  
2 2003; Bendor et al., 2012), where some neurons exhibited multi-peaked spectral tuning  
3 to the harmonics of complex tones. Related findings were also reported in humans,  
4 where cortical neurons exhibited sensitivity to harmonically related frequencies (Moerel  
5 et al., 2013, 2015). Such harmonic templates can provide sufficient spectral cues to  
6 extract the pitch of resolved harmonics and may be formed even earlier in the auditory  
7 system than the brainstem (Shamma and Klein, 2000; Bendor et al., 2012). The AC may  
8 then not only inherit these harmonic inputs but also shape and further enhance the  
9 sensitivity to the resolved harmonics following musical training. The presence of group  
10 differences in this hierarchical plasticity seems to confirm that the relative contribution  
11 of subcortical and cortical responses changes in an experience-dependent manner  
12 (Bidelman et al., 2014a).

13 Additionally, our results revealed increased subcortical and cortical responses in  
14 musicians to the unresolved complex tones. Given that the pitch of unresolved  
15 harmonics is assumed to be encoded using temporal envelope cues (de Cheveigné,  
16 2005; Oxenham et al., 2009), these findings suggest an enhanced synchrony to the  
17 temporal envelope of complex tones with high-order harmonics in musicians. However,  
18 this enhancement did not scale with the individual performance of musicians neither at  
19 the subcortical nor cortical level. Since complex-tones filtered in a high-frequency  
20 region are unnatural sounds, which musicians are neither trained nor exposed to, it may

1 be that the increased behavioral performance of musicians cannot be directly explained  
2 by a training-dependent plasticity reflected in the functional activations. As discussed  
3 earlier, the enhanced performance of musicians for unresolved complex tones may be  
4 related to an incomplete generalization of learning (Grimault et al., 2002; Carcagno and  
5 Plack, 2011b).

6 Previous studies have investigated subcortical plasticity in musicians in relation to pitch  
7 discrimination and reported somewhat inconclusive results. Wong et al. (2007) found a  
8 correlation between frequency-following responses (FFRs) to pitch contours in a falling  
9 Mandarin tone with an  $F_0$  around 100 Hz and pitch discrimination performance.  
10 However, at such low  $F_0$ s, FFRs have been shown to reflect a cortical contribution in  
11 addition to responses originating in the auditory brainstem (Coffey et al. 2016). No  
12 correlation was found for tones with  $F_0$ s above 110 Hz, which may suggest a greater  
13 degree of cortical contribution in the responses that are modulated by behavior.  
14 Musacchia et al. (2007) found no correlation between  $F_0$  encoding in the brainstem FFR  
15 and pitch discrimination and argued that subcortical encoding enhancement is not linked  
16 to performance but rather to persistence of practice. Bidelman et al. (2011) found a  
17 significant correlation between FFRs in response to mistuned chords and  $F_0$ DLs in  
18 musicians, but not in tone-language speakers nor in non-musicians. In their study, FFRs  
19 were measured in response to a fixed mistuning of 4%. Hence, in contrast to our study,  
20 the discrimination difficulty of the chords during the FFR experiment changed from

1 participant to participant, making the mistuning easier to detect for the musicians than  
2 for the non-musicians. Additionally, Carcagno and Plack (2011a) found a correlation  
3 between subcortical FFRs and F<sub>0</sub>DLs for a subset of pitch conditions when pooling  
4 trained and untrained listeners. Finally, Lau et al. (2017) found no correlation with  
5 subcortical measures and concluded that cortical responses may be more reflective of  
6 training-induced plasticity.

7 Our findings corroborate and, possibly, reconcile previous findings on plasticity in  
8 musicians. Using fMRI to directly compare subcortical and cortical activations vs.  
9 individual pitch-discrimination performance, we provide further evidence to disentangle  
10 the contributions along the auditory pathway. Our results demonstrate that training-  
11 dependent plasticity at the subcortical level reflects coarse differences in pitch-  
12 discrimination performance between musicians and non-musicians, while the enhanced  
13 activation in the right AC adds a second layer of sensitivity to F<sub>0</sub> encoding, predicting  
14 fine individual differences in pitch-discrimination within musicians (Schneider et al.,  
15 2002; Puschmann et al., 2013; Coffey et al. 2016). Overall, our findings are consistent  
16 with an enhanced neural synchrony to resolved and unresolved complex tones in the  
17 brainstem of musicians (e.g., Wong et al., 2007; Musacchia et al., 2007; Parbery-Clark,  
18 2009; Carcagno and Plack, 2011a; Bidelman et al., 2011), but they also stress the role of  
19 a right-hemispheric cortical plasticity to account for the perception of fine pitch

1 differences of resolved complex tones (e.g., Zatorre, 1988; Johnsrude et al., 2000;  
2 Zatorre and Belin, 2001; Hyde et al., 2008).

### 3 **4.4 Effect of task difficulty in musicians and non-musicians**

4 While pitch processing appeared to be enhanced in musicians, the effect of task  
5 difficulty was present in both groups of listeners (as reflected by the absence of  
6 difficulty and group interactions). A direct comparison of the difficult (60%) vs. easy  
7 (90%) conditions appeared to elicit stronger responses in the left insular cortex and  
8 frontal operculum in the non-musicians (Fig. 5a). This could indicate higher processing  
9 effort involved in discriminating small pitch differences for non-trained listeners.  
10 Increased BOLD responses when the pitch-discrimination task increased in difficulty  
11 were also observed bilaterally in the IFG for both groups (Fig. 6). Larger BOLD  
12 responses in the IFG and insular cortex have previously been related to an increased  
13 involvement of auditory working memory during active pitch-retention tasks (Zatorre et  
14 al, 1994; Koelsch et al., 2005; Albouy, 2013). It is unlikely that the mean activation of  
15 the IFG was higher in musicians than non-musicians as a result of increased processing  
16 effort. As argued above, increased activation in the IFG in the musicians is likely to  
17 reflect involvement of auditory working memory to process and maintain pitch  
18 information (e.g., Zatorre et al, 1994; Maess et al., 2001; Koelsch et al., 2005). An  
19 extended neural network for pitch processing in musicians, rather than an increased  
20 processing effort, is further supported by a recent study (Bianchi et al., 2016a). Task-

1 related pupil dilations, as a measure of processing effort, were found to be smaller in  
2 musicians compared to non-musicians performing a pitch discrimination task at the  
3 same level of difficulty.

#### 4 **4.5 Neural correlates of resolvability**

5 Two previous studies have reported an effect of harmonic resolvability in anterior  
6 regions of the AC, where complex tones with resolved harmonics elicited stronger  
7 responses compared to complex tones containing only unresolved harmonics (Penagos  
8 et al., 2004; Norman-Haignere et al., 2013). Our analysis confirmed these findings and  
9 additionally revealed how differential activation maps of resolved and unresolved  
10 complex tones (relative to the noise) were similar in musicians and non-musicians, with  
11 larger clusters of activation in the musicians (Fig. 7a). Neural responses to the resolved  
12 tones extended from the right HG in anterolateral direction (Fig. 7a and 7b, blue scale),  
13 while responses to the unresolved tones extended posteriorly into the PT region (Fig. 7a  
14 and 7b, red scale). The activation of the anterior AC for resolved complex tones is likely  
15 to reflect the increase in pitch salience with increasing harmonic resolvability, in  
16 agreement with Penagos et al. (2004) and Norman-Haignere et al. (2013). The increased  
17 activation in the unresolved conditions (relative to the resolved tones) bilaterally in  
18 posterior regions of the secondary AC (Fig. 7b) is consistent with a role of the PT in  
19 temporal pitch processing (Griffiths et al., 2001; Patterson et al., 2002; Hall and Plack,  
20 2009; Barker et al., 2011). These results are in agreement with spectro-temporal models

1 of pitch extraction (Steinschneider et al., 1998; Bendor et al., 2012). The pitch of  
2 resolved complex tones may be extracted by harmonically related peaks in the  
3 tonotopical representation of the sound as a result of a hierarchical and right-  
4 hemispheric processing (Patterson et al., 2002). The pitch of unresolved complex tones  
5 is, on the other hand, extracted using temporal envelope cues (de Cheveigné, 2005;  
6 Oxenham et al., 2009). Given that the envelope phase-locking limit decreases when  
7 ascending the auditory pathway, envelope cues are more likely to be extracted earlier in  
8 the auditory system than the primary AC (Griffiths et al., 1998). However, a region  
9 posterior to the AC, bilaterally within the PT, may be involved in pitch processing of  
10 unresolved complex tones characterized by slow changes of temporal cues over time  
11 (Griffiths et al., 1998; Hall and Plack, 2009; Barker et al., 2011).

12  
13 Since a similar pattern of activation was observed for the two resolved control  
14 conditions in the posterior region of the HG (Fig. 7c), some considerations need to be  
15 addressed. First, in the current stimulus design, the sound level per harmonic was fixed,  
16 leading to the same signal-to-noise ratio (SNR) per harmonic in all conditions relative to  
17 the noise, but to a higher overall stimulus level for the unresolved conditions compared  
18 to the resolved conditions. Since correlates of overall sound level have been reported in  
19 the primary AC and PT (Ernst et al., 2008; Langers and van Dijk, 2012), it is possible  
20 that the contrast unresolved > resolved (Fig. 7b, red scale) could have been driven by

1 the increase in overall level. The increase in level could also potentially explain the  
2 effect of the contrast between the LF-filtered control conditions (Control condition 1 >  
3 Control condition 2 in Fig. 7c, green scale). However, the overall level also increased  
4 between the LF- and HF-filtered complex tones at  $F_0 = 100$  Hz, but the contrast between  
5 these conditions (Condition 1 > Control condition 1) did not reveal any differences.  
6 Hence, the observed differences between the unresolved and resolved conditions were  
7 probably not related to differences in the overall sound level.

8 A second point to consider is the larger  $\Delta F_0$  between reference and target in the  
9 unresolved conditions compared to the resolved conditions. The  $\Delta F_0$  between reference  
10 and target was adjusted according to the individual  $F_0$ DLs obtained in Experiment I.  
11 Thus, the unresolved conditions implied larger differences in  $F_0$  between the individual  
12 tones in a trial compared to the resolved conditions. Increasing the pitch interval size  
13 during a melody-discrimination task (Zatorre et al., 2012) or during passive listening of  
14 pure-tone melodies (Hyde et al., 2008) has been shown to increase the neural activation  
15 in the anterior and posterior STG and right PT. However, in Zatorre et al. (2012), the  
16 increase in frequency separation between tones was also associated with an increase in  
17 the behavioral performance, whereas the  $\Delta F_0$  in the current study was increased to elicit  
18 equal behavioral performance across conditions and participants. Additionally, in the  
19 current study, the increase in  $\Delta F_0$  between the LF- and HF-filtered conditions for  $F_0 =$   
20 100 (Condition 1 vs Control condition 1) did not reveal any significant differences. This

1 seems to rule out the effect of  $\Delta F_0$ . Hence, the most plausible explanation for the  
2 differential activations observed in the posterior HG for the contrasts unresolved >  
3 resolved conditions (Fig. 7b, red scale) and Control condition 1 > Control condition 2  
4 (Fig. 7c, green scale) seems to be the difference in pitch from an  $F_0$  of 100 to 500 Hz. It  
5 is possible that  $F_0$  representations coexist with frequency maps in the human auditory  
6 cortex (Pantev et al., 1989; Langner et al., 1997; Bendor and Wang, 2005, 2006; Moerel  
7 et al., 2013, 2015) and provide a representation of pitch for complex sounds.

8

## 9 **5. CONCLUSION**

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

1 resolvability was similarly present in musicians and non-musicians, with resolved  
2 complex tones eliciting more anterior responses in the right HG than the unresolved  
3 conditions.

4

#### 5 **ACKNOWLEDGMENTS**

6 This work was supported by the Technical University of Denmark and by the Erasmus  
7 Mundus fellowship in Auditory Cognitive Neuroscience. JH was supported by the  
8 Oticon Foundation (Oticon Centre of Excellence for Hearing and Speech Sciences).  
9 HRS was supported by the Lundbeck Foundation (Grant of Excellence "ContAct" R59  
10 A5399) and the Novo Nordisk Foundation (Interdisciplinary Synergy Programme Grant  
11 "BASICS" NNF14OC0011413). RJZ was supported by the Canadian Institutes of  
12 Health Research.

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16

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- 8  
9  
10

1 **FIGURE CAPTIONS**

2

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

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

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

16 **Figure 3 a.** Mean pitch-discrimination thresholds ( $F_0DL$ s) for the 14 non-musicians  
 17 (open circles) and 16 musicians (filled squares) who participated in the  
 18 behavioral experiment. Thresholds for Conditions 1 and 2 are reported at the  
 19 60% and 90% correct target detection, while the two control conditions (at either  
 20 100 or 500 Hz, gray-shaded area) refer to the 75% correct detection point. Error

1 bars depict the standard error of the mean. **b.** Individual pitch-discrimination  
2 thresholds for the 14 non-musicians (open circles) and 16 musicians (filled  
3 squares) as a function of years of musical training. The linear fit to the  
4 musicians' thresholds is reported as a dashed line. Left panel: mean thresholds  
5 for the unresolved conditions (Condition 1); Right panel: mean thresholds for all  
6 resolved conditions (Condition 2 and control conditions).

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

- 1 **Figure 5 a.** Main effect of task difficulty. Differential activation maps for the contrast  
2 60% (difficult task) > 90% (easy task) ( $p < 0.001$ , uncorrected) for all 29  
3 participants. The insert panels depict the contrast 60% > 90% for musicians and  
4 non-musicians, separately. All local peaks of the activation are listed in Table 1  
5 ( $p < 0.05$ , FWE corrected over a 20-mm sphere around maximum). The color  
6 scale refers to t-values. R: right, L: left, A: anterior; IFG: inferior frontal gyrus.
- 7 **b.** The insert panels depict the mean contrast estimates [A.u.] in the left frontal  
8 operculum and insular cortex ( $x = -36, y = 23, z = 1$ ; left panel) and right frontal  
9 orbital cortex ( $x = 33, y = 29, z = 4$ ; right panel), for musicians (filled squares)  
10 and non-musicians (open circles) in the four HF conditions. Error bars depict the  
11 standard error of the mean.
- 12 **Figure 6** Correlation between the mean contrast estimates in the right and left IFG and  
13 the behavioral performance for the six pitch conditions. The anatomical ROIs  
14 comprising the right and left IFG are shown in red and blue, respectively. Error  
15 bars depict the standard error of the mean. Dashed lines indicate the regression  
16 lines for both musicians and non-musicians.
- 17 **Figure 7 a.** Overlay of the contrasts resolved > noise (blue scale) and unresolved >  
18 noise (red scale) filtered in the HF region (Conditions 1 and 2) for all 29  
19 participants ( $p < 0.05$ , FWE corrected; t-values thresholded at  $t > 8$ ). The insert  
20 panels depict the differential activation maps for the 15 musicians (above) and

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

9 **Figure 8** Correlation between behavioral pitch discrimination and BOLD responses to  
10 the different pitch conditions (>noise). **a.** Mean contrast estimates [A.u.] for  
11 each pitch condition (relative to noise) in the right and left auditory cortex (AC)  
12 as a function of the individual pitch-discrimination thresholds from Experiment I  
13 ( $F_0$ DLs) for the 15 musicians (filled squares) and 14 non-musicians (open  
14 circles). The contrast estimates refer to the two LF control conditions (top  
15 panels), the two resolved HF conditions (Condition 2, middle panels) and the  
16 two unresolved conditions (Condition 1, bottom panels). Spearman's correlation  
17 coefficients and the p-values are reported for each panel, for the musicians alone  
18 and for all participants (significant correlations after Bonferroni correction with  
19  $n = 6$ ,  $p < 0.0083$ , are depicted by an asterisk and visualized by the linear  
20 regression line). **b.** Mean contrast estimates [A.u.] for each pitch condition

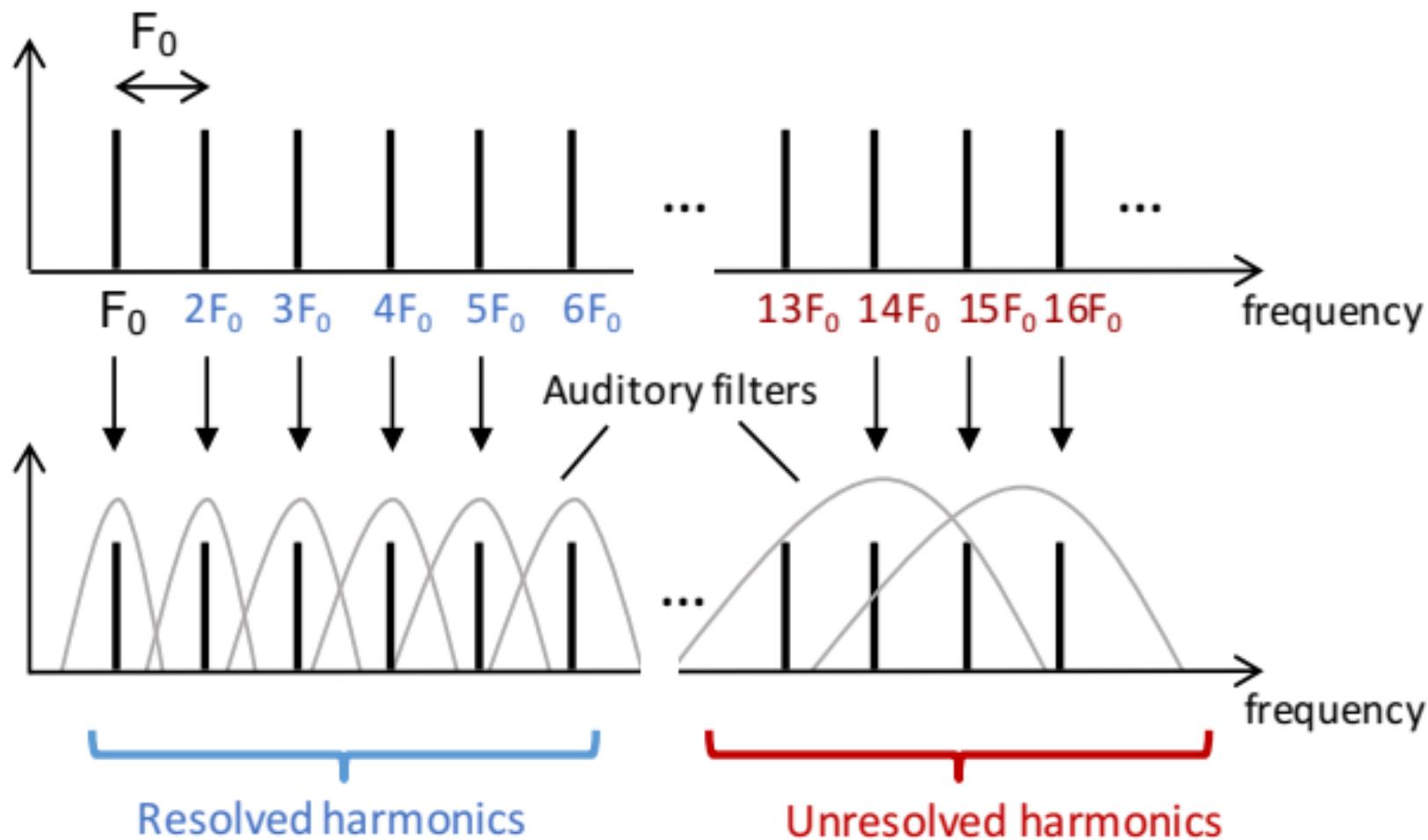
1 (relative to noise) in the inferior colliculus as a function of the individual pitch-  
2 discrimination thresholds from Experiment I ( $F_0$ DLs). The Spearman's  
3 correlation coefficients and the p-values are reported for each panel, for the  
4 musicians alone and for all participants (significant correlations after Bonferroni  
5 correction with  $n = 3$ ,  $p < 0.017$ ).

6

7

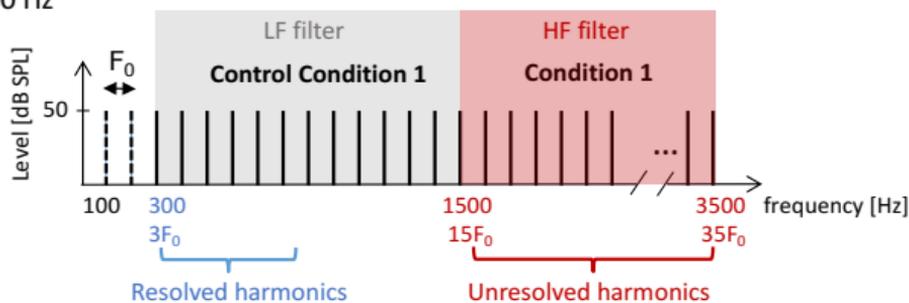
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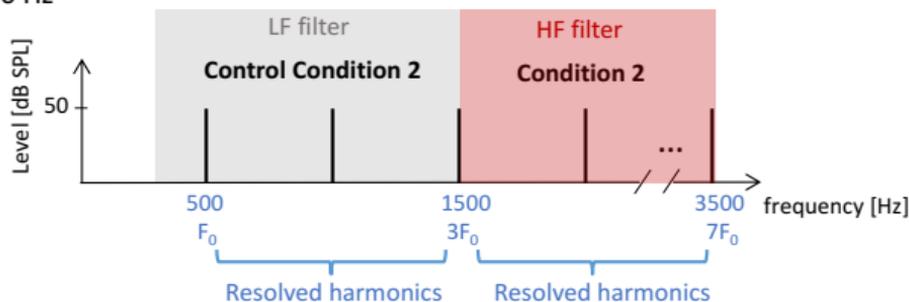


## a. Stimuli

$F_0 = 100$  Hz

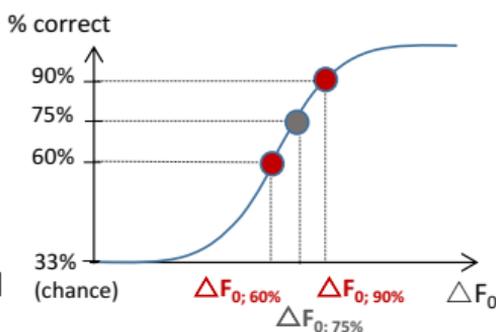
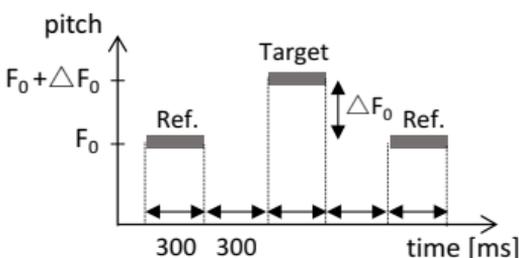


$F_0 = 500$  Hz



## b. Experiment I: Behavioral pitch discrimination

"Which tone is highest in pitch?"

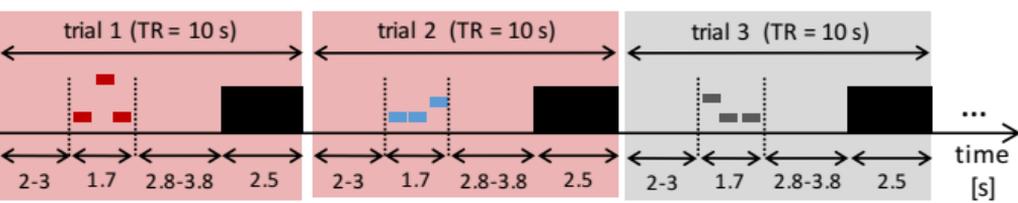


## c. Experiment II: functional MRI

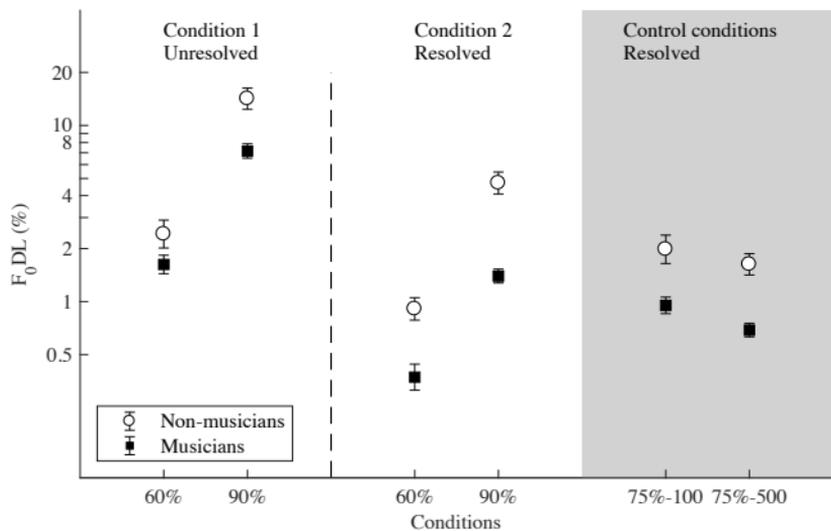
LF filter	Control 1 $F_0 = 100$ Hz	Control 2 $F_0 = 500$ Hz	HF filter	Condition 1 $F_0 = 100$ Hz	Condition 2 $F_0 = 500$ Hz
	Resolved Medium-difficulty task	Resolved Medium-difficulty task		Unresolved Difficult task	Resolved Difficult task
$\Delta F_{0;75\%}$			$\Delta F_{0;60\%}$		
			$\Delta F_{0;90\%}$	Unresolved Easy task	Resolved Easy Task

scan and button press

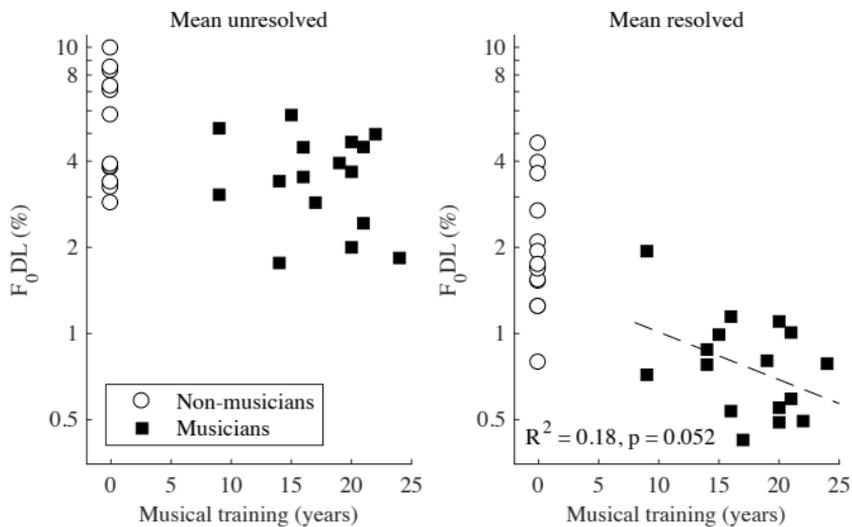
acoustic stimulation

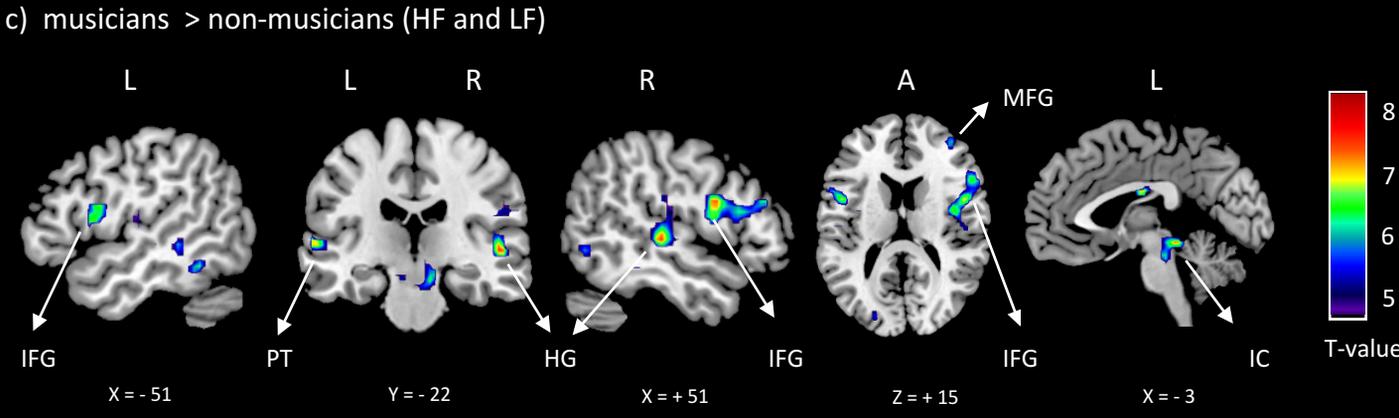
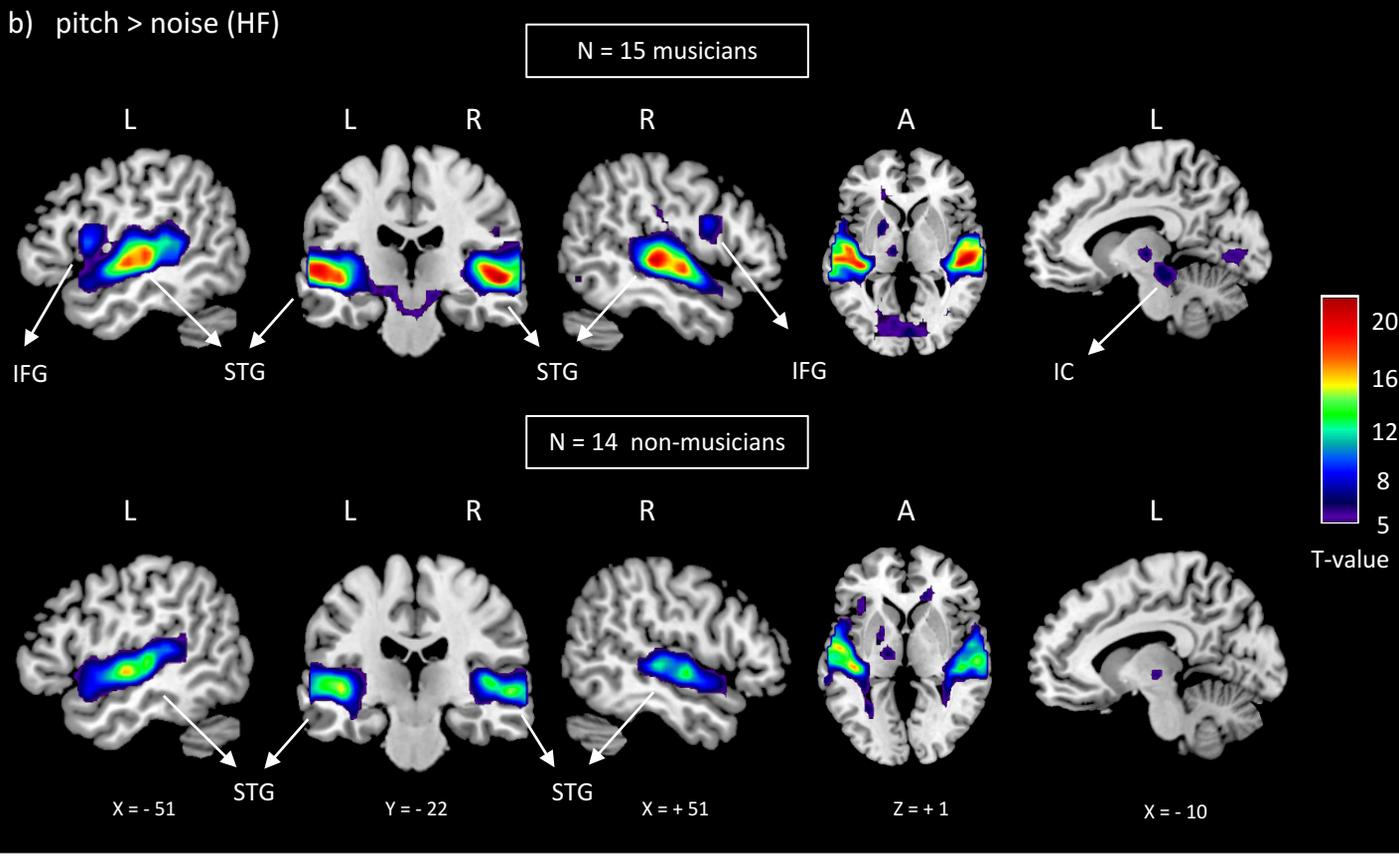
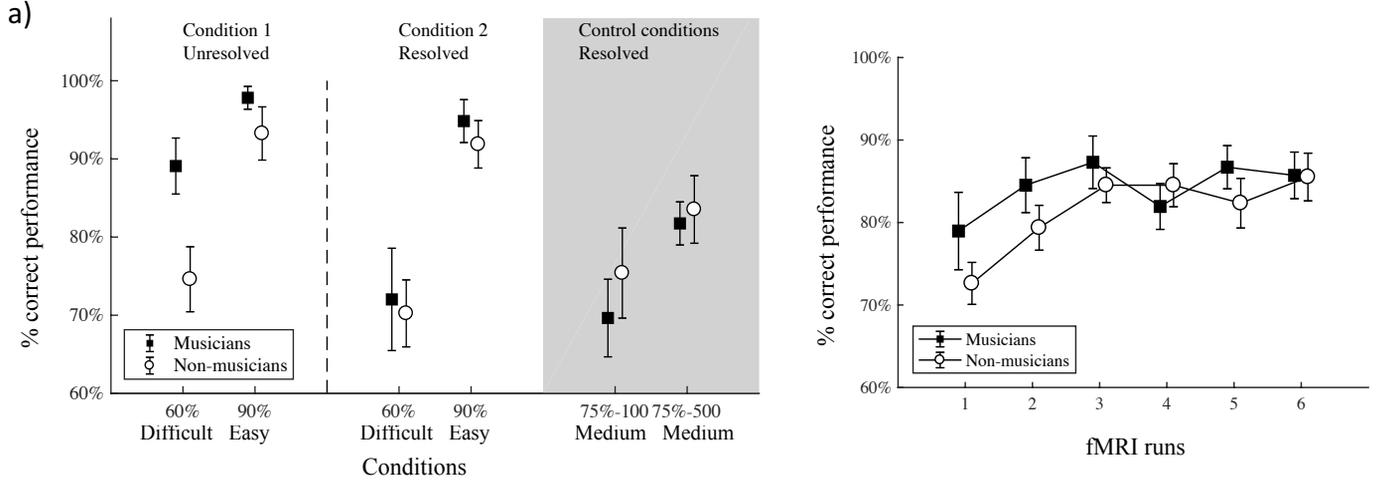


a



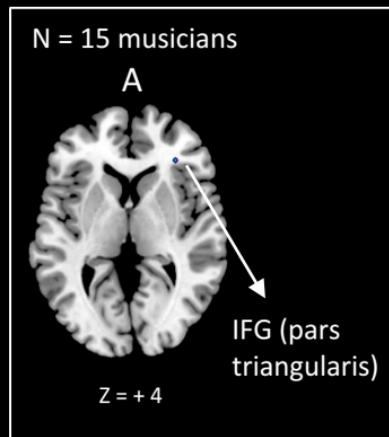
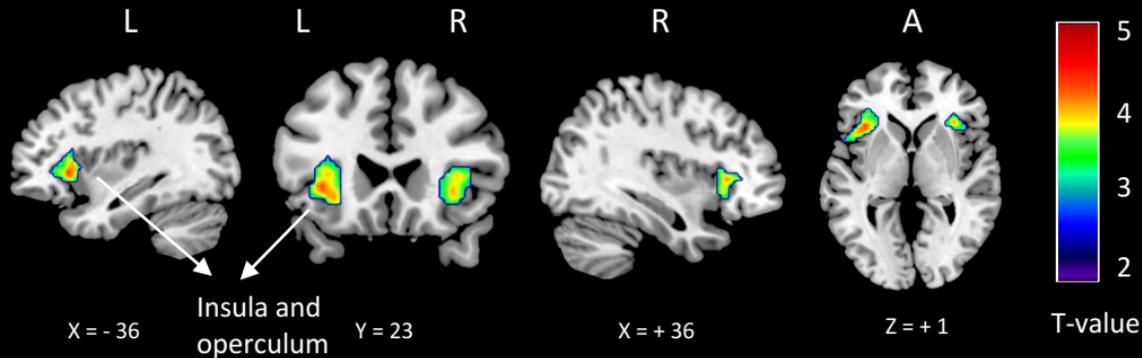
b



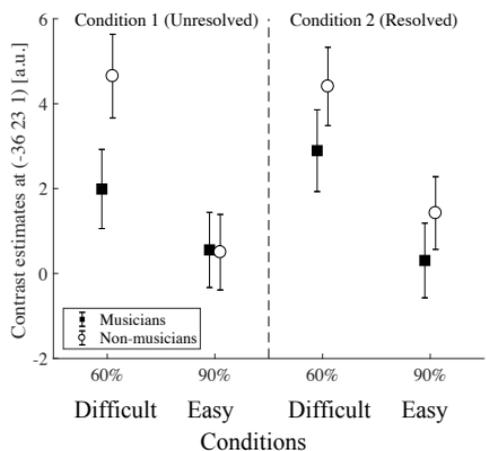


a) 60% (difficult task) > 90% (easy task)

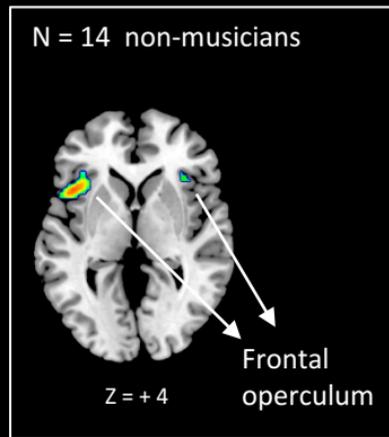
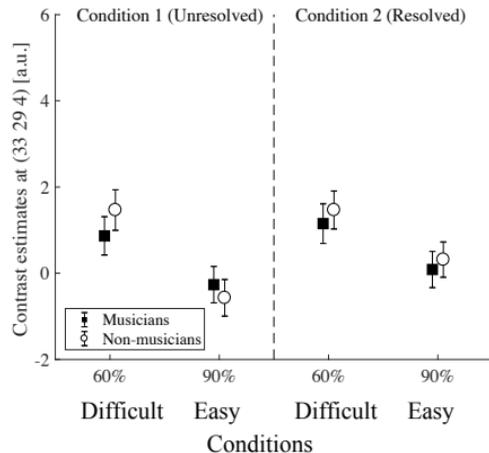
N = 29



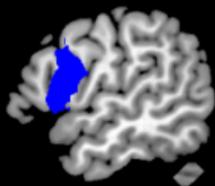
b) Left Insular Cortex / Frontal Operculum



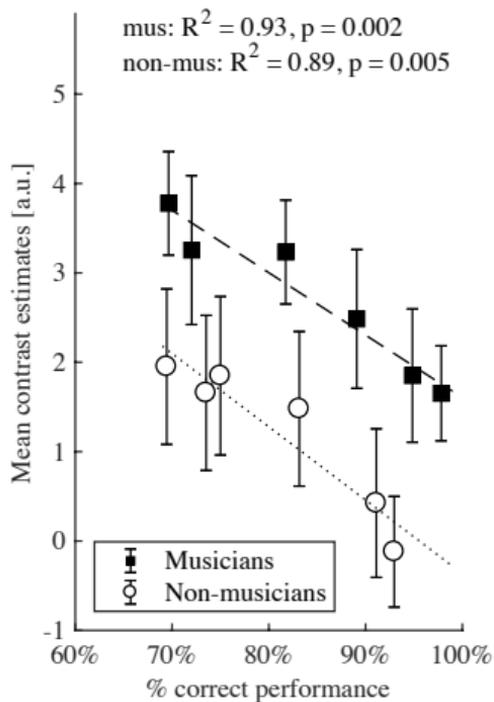
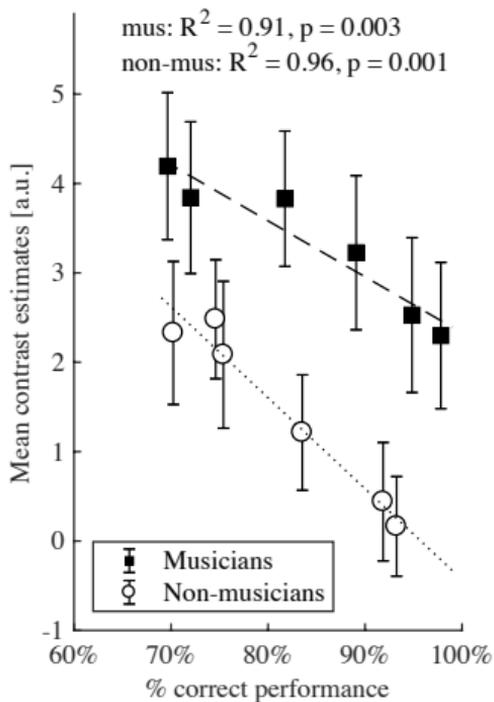
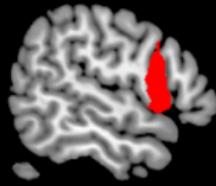
Right Frontal Orbital Cortex



## Left IFG

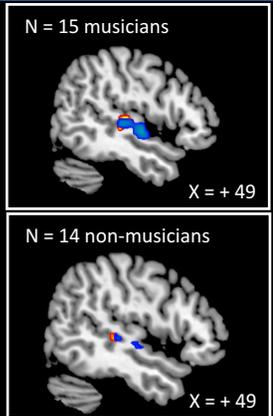
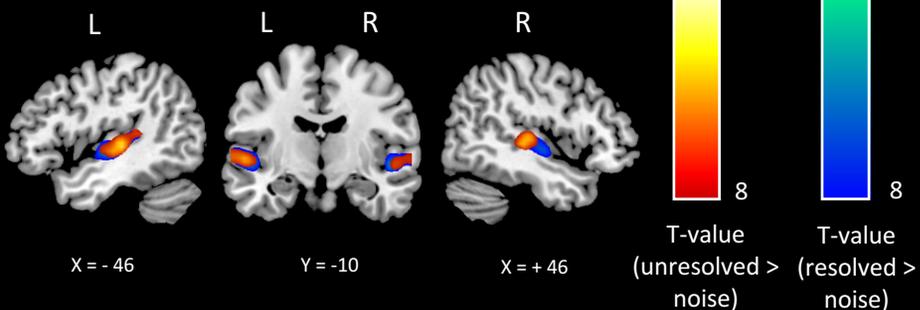


## Right IFG

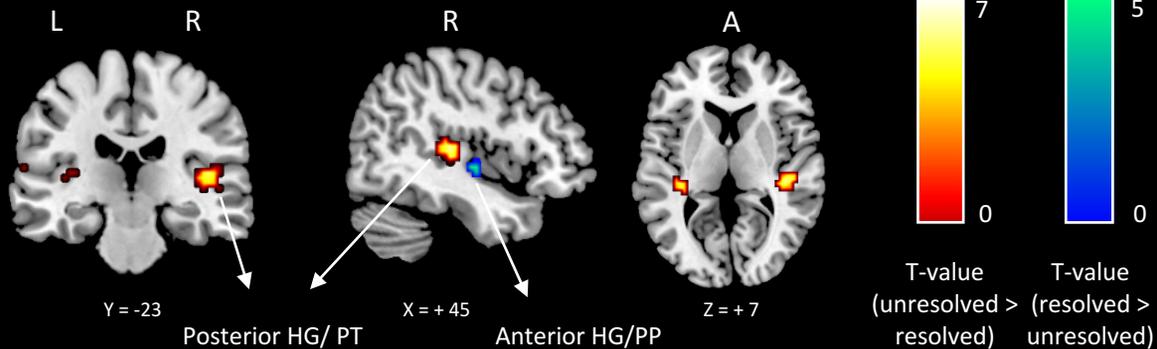


a. Resolved and unresolved conditions > noise (HF)

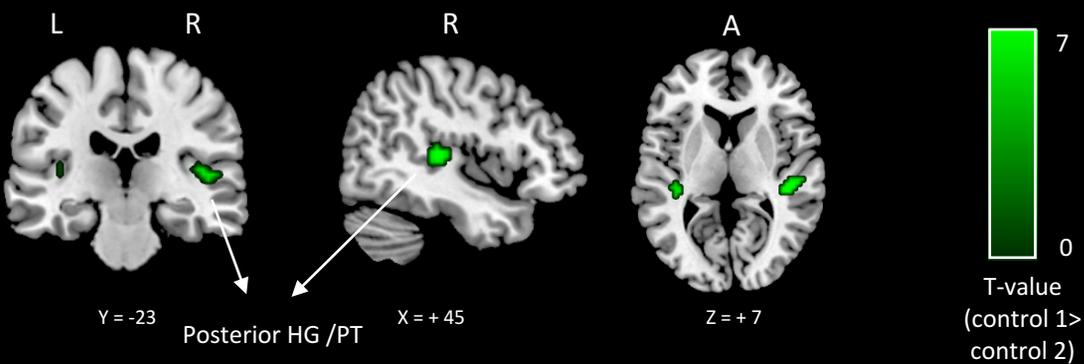
N = 29

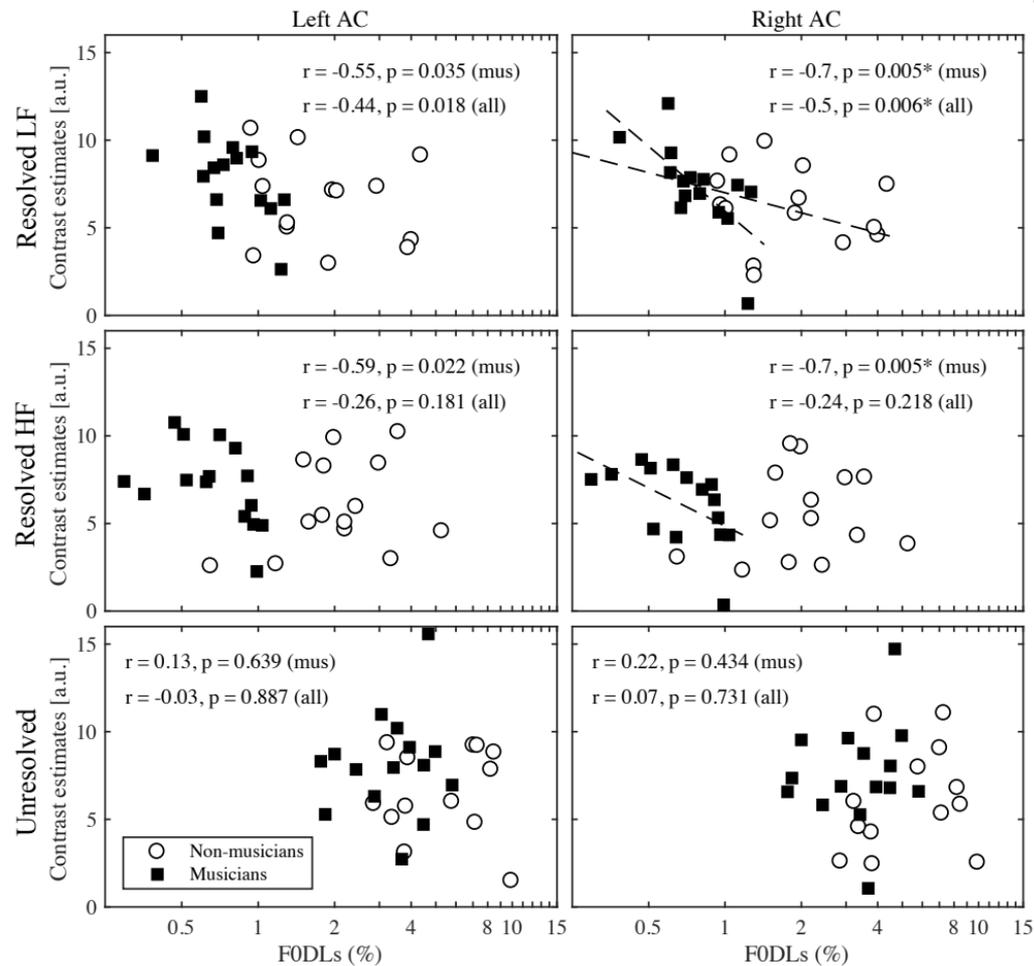


b. Resolved conditions vs. unresolved conditions (HF)



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



**a****b**