

# Functional MRI Evidence of an Abnormal Neural Network for Pitch Processing in Congenital Amusia

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**Congenital amusia (tone deafness) is a lifelong disorder that prevents typically developing individuals from acquiring basic musical skills. Electrophysiological evidence indicates that congenital amusia is related to a musical pitch deficit that does not seem to arise from a dysfunction of the auditory cortex but rather from an anomaly along a frontotemporal auditory pathway. In order to better localize the neural basis of this pitch disorder, here we conducted a functional magnetic resonance imaging (fMRI) study. Congenital amusic adults and “musically intact” controls were scanned while passively listening to pure-tone melodic-like sequences in which the pitch distance between consecutive tones was varied parametrically. In both amusics and controls, brain activity increased as a function of increasing pitch distance, even for fine pitch changes, in both the left and right auditory cortices. These results support prior electrophysiological work showing that the auditory cortex of amusic individuals responds normally to pitch. In contrast, the right inferior frontal gyrus showed an abnormal deactivation in the amusic group, as well as reduced connectivity with the auditory cortex as compared with controls. These fMRI data are highly consistent with previous gray and white matter anomalies found in amusics in the auditory and inferior frontal cortices, as well as reduced white matter connections between these 2 regions.**

**Keywords:** brain, connectivity, fMRI, music, tone deafness

## Introduction

Music engagement is universal and present early in life. However, about 4% of the general population experiences a lifelong deficit in music perception and production that cannot be explained by hearing loss, brain damage, intellectual deficiencies, or lack of exposure to music. This musical disorder, commonly known as tone deafness and now termed congenital amusia, mostly affects the melodic pitch dimension (Peretz et al. 2002; Foxtan et al. 2004; Hyde and Peretz 2004). Amusics are impaired in detecting fine pitch deviations that are less than 1 semitone apart (that corresponds to adjacent notes on a keyboard) in the context of tone pairs (Foxtan et al. 2004), and of monotonic sequences (Hyde and Peretz 2004), but have no problems to detect time deviations in the same sequences (Hyde and Peretz 2004). Such a fine-grained pitch deficit could lead to problems in musical processing because most Western melodies and those from other cultures are constructed with pitch intervals in the order of 1 semitone (Dowling and Harwood 1986).

This pitch disorder is associated with gray and white matter abnormalities in the auditory cortex and inferior frontal cortex (Hyde et al. 2006, 2007; Mandell et al. 2007; Loui et al. 2009). More specifically, in a voxel-based morphometry (VBM) study, we found that amusics had reduced white matter (and increased gray matter) concentration in the right inferior frontal gyrus (IFG) relative to controls (Hyde et al. 2006). In a second study conducted with the same participants, we found that amusic participants had thicker cortex in this same right IFG region and in the right auditory cortex (Hyde et al. 2007). An independent VBM study also demonstrated gray matter abnormalities in the IFG and auditory cortex of amusics, but in the left hemisphere (Mandell et al. 2007). These gray matter differences suggest the presence of cortical malformations in the amusic brain that may have compromised the normal development of a right frontotemporal pathway. Supporting evidence has recently been provided by a diffusion tensor imaging study, showing that amusics have an abnormal lack of fiber connectivity along the arcuate fasciculus—a fiber tract that connects the auditory and inferior frontal cortices—mostly on the right side of the brain (Loui et al. 2009). These anatomical anomalies in the amusic brain were found to be correlated with their behavioral deficits on pitch-based musically relevant tasks (Hyde et al. 2006, 2007; Mandell et al. 2007; Loui et al. 2009).

There is, however, an inherent uncertainty with regard to the conclusions that can be drawn from anatomical studies in the absence of functional measures. It is important that anatomical measurements be supported by functional investigations in order to demonstrate that anatomical anomalies are related to the behavioral deficits of interest. To this aim, Peretz et al. (2005) measured electrical brain potentials (ERP) in amusic individuals while they were monitoring 5-tone sequences for the presence of a pitch change. The amusic brain did not respond to pitch deviances smaller than 1 semitone, whereas the normal controls did so reliably. In contrast, the amusic brain “overreacted” to large pitch changes by eliciting an N2 (that was not present in normals) and a P3 that was almost twice as large as that observed in controls’ brains. This altered pattern of electrical activity did not seem to arise from an anomalous functioning of the auditory cortex because the N1 component appeared to be normal. Rather, the enhanced N2-P3 complex in amusics might reflect difficulties that occur in later processing stages along the auditory pathway that involves frontal regions because it seems to be related to the attentional demands of the task.

Attentional requirements seem to play a key role in the neural manifestation of congenital amusia. In recent studies,

Moreau et al. (2009) and Peretz et al. (2009) demonstrated that the amusic brain can track quarter-tone (50 cents) pitch differences in melodies and eighth-tone (25 cents) pitch differences, as evidenced by their early right-lateralized negative brain response. This early negativity, or mismatch negativity (MMN), was obtained while participants ignored the sounds in 1 condition (Moreau et al. 2009) and when amusics failed to detect the pitch change at a behavioral level (Peretz et al. 2009). These findings indicate near-normal neural processing of fine-grained pitch differences in congenital amusia but without awareness of this ability. Thus, the amusic brain might be equipped with a normally functioning auditory cortex. What may distinguish the amusic brain from the normal brain is a reduced connectivity between the auditory cortex and the IFG that would be required to consciously or cognitively process pitch in a sequential context. This idea is plausible because the inferior frontal cortex has been consistently activated in tasks requiring the conscious detection of musical key violations (Maess et al. 2001; Tillmann et al. 2003).

Thus, the electrophysiological findings converge with the brain anatomical anomalies observed along the auditory-frontal pathway in the amusic brain, with the exception of the auditory cortex. As described above, brain structural abnormalities have been found in the auditory cortex of amusics (Hyde et al. 2007; Mandell et al. 2007); however, the ERP studies (Peretz et al. 2005, 2009) did not reveal any functional abnormality in the auditory cortex of amusics in the processing of fine-grained pitch changes. These above ERP studies may not have been able to localize a potential functional brain anomaly in the auditory cortex of amusics due to the fact that such electrophysiological measures of brain activity (though sensitive to temporal brain dynamics) have poor spatial resolution.

In order to gain further information about the responsiveness of the auditory cortex to fine pitch differences in amusia, here we conducted a functional magnetic resonance imaging (fMRI) study, which has superior spatial resolution as compared with the ERP technique. We used a design that previously demonstrated the sensitivity of auditory cortex to fine-grained pitch changes in normals (Hyde et al. 2008). As in the study of Hyde et al. (2008), here participants were scanned while passively listening to pure-tone melodic-like patterns in which the successive tones differed in small steps from 0 to 2 semitones. Based on prior findings, we predicted that the auditory cortex would be responsive to an eighth-tone (25 cents) pitch difference but that there would be an abnormal functional connectivity between the auditory and inferior frontal cortices in amusics.

## Materials and Methods

### Participants

Nine amusic participants and 9 musically intact controls, matched in age, education, and handedness, took part in the fMRI experiment. All participants had been thoroughly evaluated on previous testing sessions (Ayotte et al. 2002; Hyde et al. 2006, 2007), and their characteristics are presented in Table 1. All participants had normal intellectual, memory, and language skills and normal hearing with respect to their age as determined by audiometric testing, and none of the participants had any previous neurological or psychiatric history. All participants were right handed as assessed by an adapted form of the Edinburgh inventory (Oldfield 1971). Participants were considered amusic if they performed 2 standard deviation below the global mean

control performance on the Montreal Battery of Evaluation of Amusia (MBEA), a battery of music perception and memory tests used to diagnose congenital amusia (Peretz et al. 2003). The global MBEA scores (averaged over 6 tests) for the amusics and controls that participated in the present study are summarized in Table 1. Most amusic participants ( $n = 7$  who had participated in Hyde and Peretz 2004, see Fig. 1) were also impaired relative to controls in detecting a small pitch deviation (including the semitone distance) in a 5-tone monotonic and isochronous sequence, whereas they performed as controls in detecting time deviations in the same context (Hyde and Peretz 2004). All participants gave informed written consent for a protocol approved by the MNI Ethics Review Board.

### Stimuli

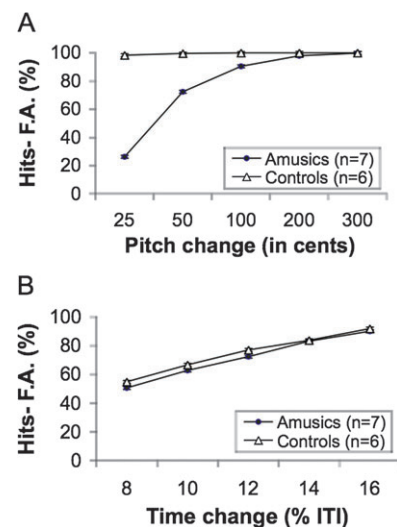
The stimuli consisted of 14 melodic-like sequences, each made of 21 pure tones (Fig. 2). All sequences had the same pitch contour starting at 1046 Hz (corresponding to the musical note C6) and were presented at one of the following 7 pitch distances between tones (from smallest to largest): 0 (fixed pitch), 6.25, 12.5, 25, 50, 100, or 200 cents (where 1 cent is a unit of equal log frequency separation; 1 semitone = 100 cents). The center value for all sequences was 1046 Hz. Instead of using tone durations of 100 ms as in our prior study (Hyde et al. 2008), each pure tone lasted 340 ms (with 10 ms between each tone) so as to increase the duration of auditory stimulation while

**Table 1**

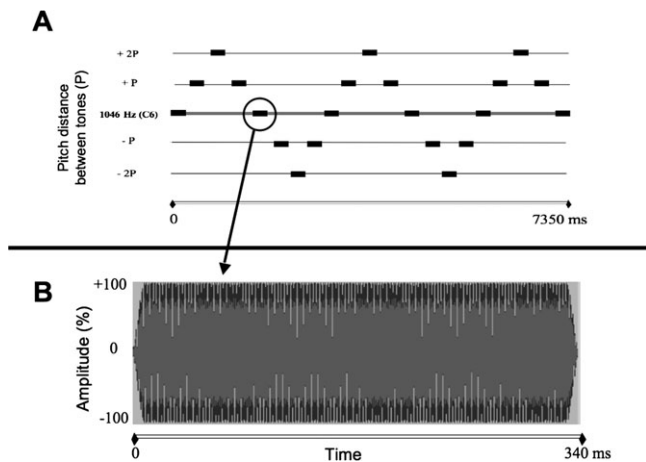
Characteristics of the participants

Characteristics	Amusics ( $n = 9$ )	Controls ( $n = 9$ )	<i>t</i> -Test
Age in years	56.7 (7.0)	53.1 (5.9)	NS
Gender	7F, 2M	5F, 4M	—
Education in years	16.0 (1.3)	16.0 (2.0)	NS
Musical battery (MBEA)	64.2 (5.9)	88.4 (6.6)	$P < 0.001$

Note: Characteristics of participants, percentage of global score (averaged over 6 tests) on MBEA, and significance levels on corresponding *t*-tests; "NS" refers to a nonsignificant difference. Standard deviations are in parentheses.



**Figure 1.** Performance of the amusic and control groups in the pitch and time discrimination tasks from Hyde and Peretz (2004). Performance is expressed as the mean percentage of hits (correct detection of a change) minus false alarms (FA) (detection of a change when all tones were the same) in each group of participants, for each level of (A) pitch change in cents, and (B) time change as a percentage of intertone interval (ITI) of 350 ms. Error bars represent standard errors. Scores are averaged over 7 amusic participants and 6 controls who participated both in the present fMRI study and the study of Hyde and Peretz (2004).



**Figure 2.** Schematic of a pitch pattern used in the fMRI study. In (A) is a pure-tone melodic-like sequence, where each black square corresponds to 1 tone, and the pitch distance between consecutive tones ( $P$ ) in cents is shown along the vertical axis from a center pitch of 1046 Hz corresponding to the musical note C6. In (B) is a waveform of a single pure tone of 1046 Hz, where amplitude is represented along the  $y$ -axis as a percentage (from  $-100\%$  to  $+100\%$ ), and the time window is represented in milliseconds (ms) along the  $x$ -axis.

maintaining the intertone interval of 350 ms for comparison with our previous studies (Hyde and Peretz 2004; Hyde et al. 2008). Thus, each melodic-like sequence was 7350 ms in duration. All tones were generated using MITSYN software.

### Task Design

Participants were scanned while passively listening to the stimuli. A passive paradigm was used so as to optimize both the comparison of results to our prior study done with students (Hyde et al. 2008) and the automatic activation of the auditory cortex in the amusic brain (Moreau et al. 2009; Peretz et al. 2009). Participants heard the stimuli binaurally at a level of  $\sim 80$  dB sound pressure level via Siemens MR-compatible pneumatic sound transmission headphones. There were 2 stimulus “conditions”—a pitch condition with patterns including either fixed pitch at 0 cents between tones or “pitch change” at each of 6 levels: 6.25, 12.5, 25, 50, 100, or 200 cents and a baseline condition of silence. On each “trial,” one of these stimulus conditions (pitch or silence) was presented. Each “run” comprised 80 trials: 16 trials for the fixed pitch level, 48 for pitch-change trials (8 trials for each of the 6 pitch-change levels), and 16 silence trials. For each participant, there were 2 runs (with 80 trials each), and the 80 trials were presented in a randomized order within and across the 2 runs using Media Control Functions software (Digivox). Each run lasted about 18 min, each scan acquisition lasted 2 s, and each trial (lasting 7.35 s) was presented 0.4 s after each acquisition. A long interacquisition time of 10 s was used in order to minimize the noise artifact from the scanner on the participants’ ability to hear the stimuli (Belin et al. 1999). This also serves to avoid scanner noise contamination of the blood oxygenation level-dependent (BOLD) response on the stimuli in the auditory cortices.

### fMRI Parameters and Analysis

Scanning was performed on a Siemens Vision 1.5-T MRI scanner at the MNI. A high-resolution  $T_1$ -weighted anatomical scan was obtained for anatomical localization for each participant (echo time [TE], 9.2 ms; repetition time [TR], 22 ms; matrix size,  $256 \times 256$ ; voxel size,  $1 \times 1 \times 1$  mm), followed by 2 series of 136  $T_2^*$  gradient echo-planar images. A headcoil was used to obtain 20 interleaved slices spanning the whole brain and oriented along the Sylvian fissure (TE, 50 ms; TR, 10 s; matrix size,  $64 \times 64$ ; voxel size,  $5 \times 5 \times 5$  mm).

In-house software (Collins et al. 1994) was used in the pre-processing of the BOLD images. The images were first spatially smoothed using a 12-mm “full-width at half-maximum” Gaussian

blurring kernel, corrected for motion, and then were linearly transformed into standard stereotaxic space corresponding to the Montreal Neurological Institute (MNI)/Talairach ICBM152 template (Collins et al. 1994). Next, statistical analysis based on a general linear model with correlated errors was performed on the BOLD data using FMRISTAT software (Worsley et al. 2002). For each group, covariate analyses considering the BOLD response over all 7 pitch distances were performed in order to investigate which brain areas showed activity that correlated in a linear fashion with increasing changes in pitch. In order to test for a nonlinear relationship between BOLD activity and pitch distance, subtraction analyses, including 2 contrasts, were performed for each group as follows: 1) a contrast of all pitch-change conditions versus fixed pitch was performed in order to isolate the brain areas responsive to changing pitch information and 2) all pitch conditions were summed and compared with silence as a control contrast. The same covariate and subtraction analyses were then performed between groups to compare patterns of BOLD activity between amusics and controls.

Lastly, we conducted functional connectivity analysis on the fMRI data both within and between groups. In the within-group analysis, a functional connectivity map, which corresponds to the brain’s “residual” activity after factoring out the effect of the stimulus, was generated for each group as follows. First, the general linear model was fitted to account for the neural activity due to all pitch-change conditions versus the fixed pitch condition. Then, the remaining activity within a specific voxel (the “seed” voxel) was regressed on the activity within the rest of the brain on a voxel-by-voxel basis to determine where activity significantly covaried with the activity in that seed voxel (Worsley et al. 2005). We then performed a between-group analysis (amusics vs. controls) by comparing the functional connectivity maps that were generated for each group. The seed voxels were defined as the peak voxel in the left ( $x = -64$ ,  $y = -26$ ,  $z = 8$ ) and right ( $x = 62$ ,  $y = -18$ ,  $z = 0$ ) auditory cortices as obtained here for the contrast of all pitch-change conditions versus fixed pitch in controls (see Results below).

A minimum threshold for statistical significance was computed according to the random field theory, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al. 2002). We employed a whole-brain statistical threshold of  $t = 5.0$  for the within-group and  $t = 4.7$  for the between-group analyses, both at  $P < 0.05$  (corrected for multiple comparisons). In addition, we used a volume of interest (VOI) approach to maximize the chances to find predicted differences in BOLD activity between amusics and controls in the auditory cortex and the IFG. We defined an “auditory VOI” based on previous anatomical probability maps of left and right primary auditory cortices in medial Heschl’s gyrus (HG) (Penhune et al. 1996) and secondary auditory cortex in the planum temporale (PT) (Westbury et al. 1999). In addition, we defined a VOI in the pars orbitalis of the IFG (Brodmann area [BA] 47/11) centered at the location where we previously found abnormally increased cortical thickness in amusics in the right IFG ( $x = 45$ ,  $y = 28$ ,  $z = -11$ ; Hyde et al. 2007) and the equivalent VOI in the left IFG. The statistical thresholds applied for the auditory VOI ( $9301 \text{ mm}^3$ ) and the IFG VOI ( $2000 \text{ mm}^3$ ) were  $t = 3.5$  and  $t = 3.0$  for the within-group and  $t = 3.0$  and  $t = 2.7$  for the between-group analyses, each at the  $P < 0.05$  level, corrected for multiple comparisons based on random field theory (Worsley et al. 2002).

### Results

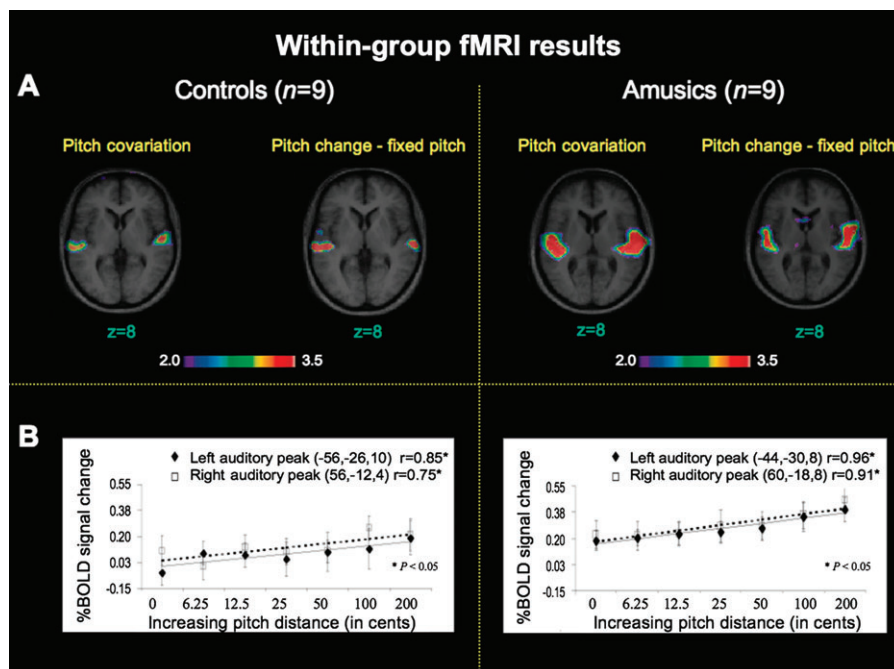
The pitch covariation analysis considering the BOLD response across the 7 pitch distances revealed significant increased BOLD responses bilaterally in auditory cortex (at the border of the PT and lateral HG) in both controls and amusics (Table 2 and Fig. 3A). The contrast of all pitch-change conditions versus fixed pitch also revealed significant activation in the PT/HG border region bilaterally in both groups and in the anterior superior temporal gyri (STG) (Table 2 and Fig. 3A). In addition, for the contrast of all pitch-change conditions versus fixed pitch, controls showed a near-significant BOLD increase in the

**Table 2**

fMRI results for covariation and contrast analyses

	Controls ( <i>n</i> = 9)							Amusics ( <i>n</i> = 9)						
	Brain region	BA	<i>x</i>	<i>y</i>	<i>Z</i>	<i>t</i>	Significance	Brain region	BA	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	Significance
Pitch covariation	R PT/HG	22/41	56	-12	4	3.5	*	R PT	22	60	-18	8	8.2	**
	L PT	22	-56	-26	10	3.5	*	L PT/HG	22/41	-44	-30	8	6.7	**
All pitch-change conditions-fixed pitch	L PT	22	-64	-26	8	3.8	*	L PT/HG	22/41	-54	-14	6	5.7	**
	R PT	22	62	-18	0	3.6	*	R anterior STG	42	58	-8	6	4.5	*
	L PT/HG	22/41	-50	-24	6	3.5	*	L PT/HG	22/41	-54	-24	8	4.0	*
	L anterior STG	42	-58	0	-2	3.5	*	L PT/HG	22/41	-50	-28	10	4.0	*
	R IFG (pars orbitalis)	47/11	34	32	2	2.4		L anterior STG	42	-56	-6	4	3.9	*
								L anterior STG	42	-56	-6	14	3.8	*
All conditions-baseline of silence	R PT/HG	22/41	44	-30	16	5.5	**	L PT/HG	22/41	-56	-12	4	3.7	*
	R anterior STG	42	60	-8	2	4.7	*	R PT	22	44	-30	10	3.6	*
	R anterior STG	42	66	-8	2	4.7	*	R IFG (pars orbitalis)	47/11	40	24	3	-3.2	*
	R PT	22	64	-26	12	4.3	*	L HG	41	-38	-32	14	8.4	**
	L HG	41	-36	-30	16	3.7	*	R PT/HG	22/41	40	-30	12	8.3	**
								R PT	22	66	-28	14	6.6	**
							L HG	42	41	-14	4	5.9	**	
							L PT	22	-64	-16	2	5.1	**	

Note: For each peak, the stereotaxic coordinates are given in MNI/Talairach space (Collins et al. 1994) along with the corresponding brain region, BA, and *t* values. Table 2 reports the within-group fMRI results for the covariation and contrast analyses: for the subtractions, a positive *t* value reflects an increased BOLD response and a negative *t* value reflects a decreased BOLD response, and for the pitch covariation analyses, a positive *t* value reflects a positive linear trend of the BOLD signal as a function of increasing pitch distance. Results are significant at  $P < 0.05$  (corrected for multiple comparisons) at the whole-brain\* or VOI\*\* thresholds. L, left; R, right.



**Figure 3.** Within-group fMRI results. In (A) are the within-group fMRI results for the pitch covariation analysis and contrast of all pitch-change conditions versus fixed pitch, superimposed on the average anatomical MRI of the corresponding group, for the controls (left panel) and the amusics (right panel). Images are shown as horizontal sections and show the auditory activations in each brain image (left side of each brain image corresponds to the left side of the brain). In the covariation image, the activations demonstrate a positive linear trend of the BOLD signal with increasing pitch distance, and in the pitch-change conditions versus fixed pitch contrast, the activations consist of increased BOLD responses (see Table 2 for corresponding *t* statistics and stereotaxic coordinates). In (B) are the significant positive correlations of BOLD signal change as a function of increasing pitch distance at the peak voxels in the left and right auditory VOIs and corresponding Pearson *r* values.

vicinity of the pars orbitalis of the right IFG (BA 47/11), whereas amusics showed a significant BOLD decrease in this same region (Table 2). In both controls and amusics, the control contrast of all conditions versus silence showed extensive and significant BOLD responses bilaterally in auditory cortex, including HG, PT, and more anterior regions in the STG (Table 2). There were no other significant BOLD activations.

In order to investigate the percent BOLD signal change (as compared with silence) across all pitch distances, in each group, we extracted the BOLD signal at the peak voxel (with the highest *t* value) from the pitch covariation analyses within the right and left auditory VOIs, respectively (Fig. 3B). The correlation computed from these extracted values revealed a significant positive linear trend where the BOLD signal

increased as a function of increasing pitch distance at both the right and left auditory peak voxels in both controls (Fig. 3B, left panel) and amusics (Fig. 3B, right panel).

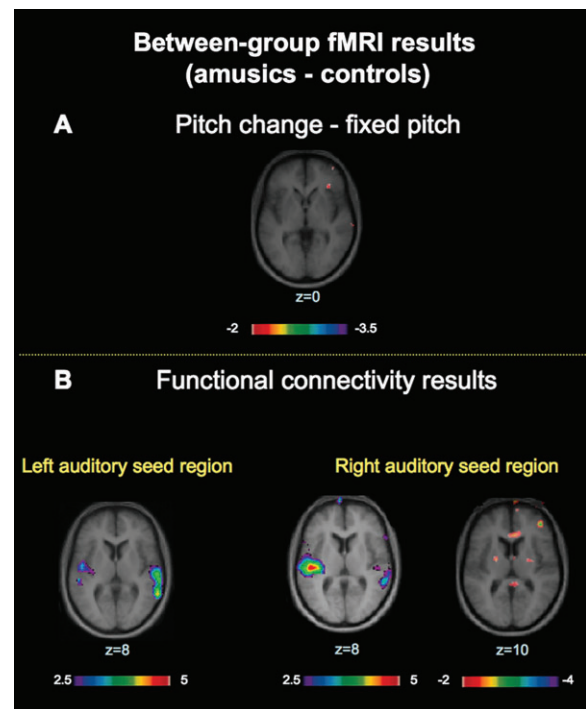
There were no significant between-group differences in the pitch covariation analyses. However, the analysis of the contrast for all pitch-change conditions versus fixed pitch revealed that amusics had significantly less BOLD activation relative to controls in the pars orbitalis of the right IFG, in the vicinity of BA 47 and 11 (Fig. 4A). There were no differences between groups at the level of the auditory cortex or any other significant between-group differences for the pitch covariation or pitch-change versus fixed pitch contrast.

The within-group functional connectivity analysis for controls revealed a near-significant positive correlation in brain activity between the right auditory seed region and the right IFG/pars orbitalis and significant positive correlations between the left auditory seed region and the left IFG/pars orbitalis, as well as the right auditory cortex at the PT/HG border (Table 3). In amusics, brain activity in the right auditory seed region was negatively correlated (though nonsignificantly) with the right IFG/pars orbitalis and significantly positively correlated with the left auditory cortex at the PT/HG border and the right posterior PT/superior temporal sulcus (STS) border. Brain activity in the left auditory seed region was significantly negatively correlated with the left IFG/pars orbitalis (though more medial than the right IFG finding) and significantly positively correlated with the right auditory cortex at the PT/HG border and right posterior PT/STS border (Table 3). In order to test whether the 2 patterns seen in each group were significantly different, we conducted a between-group functional connectivity analysis. The between-group analysis revealed that amusics had significantly less functional connectivity relative to controls between the right auditory seed region and the right IFG/pars orbitalis (Table 3 and Fig. 4B) and that amusics have significantly greater functional connectivity between the right auditory seed region and the left and right auditory cortices (at the PT/HG border and right posterior PT/STS border) (Table 3 and Fig. 4B). In addition, amusics had significantly greater functional connectivity relative to controls between the left auditory seed region and the left and right auditory cortices (at the PT/HG border and right posterior PT/STS border) (Table 3 and Fig. 4B). The functional connectivity analyses did not reveal any other significant findings.

## Discussion

The present results show that the auditory cortex of amusic individuals can track fine pitch changes in melodic-like sequences. This finding supports the hypothesis that the amusic brain is equipped with the essential neural circuitry to process fine-grained pitch differences in melodies. A key distinguishing feature of the amusic from normals is a decreased functional connectivity between the auditory and inferior frontal cortices. The convergence between these functional data and previous anatomical abnormalities found in these same brain regions in amusics provides compelling support for considering congenital amusia as a disconnection syndrome.

Both amusic and control participants showed a positive linear BOLD response as a function of increasing pitch distance in bilateral auditory cortices (on the border of the PT and lateral HG). This linear response of the auditory cortex to the increasing pitch distances between successive tones is very



**Figure 4.** Between-group fMRI results (amusics–controls). Panel A shows the between-group fMRI results for the pitch-change versus fixed pitch contrast highlighting the right IFG (right IFG) where amusics have decreased activation relative to controls ( $x = 34, y = 32, z = 0, t = -2.7$ ). Panel B shows the between-group functional connectivity results for the left auditory seed region highlighting bilateral auditory cortex where amusics have greater functional connectivity relative to controls (panel B left image) and the results for the right auditory seed region highlighting the bilateral auditory cortex where amusics have greater functional connectivity relative to controls (panel B middle image) and the right IFG where amusics have less functional connectivity relative to controls (panel B right image) (see Table 3 for corresponding  $t$  statistics and stereotaxic coordinates). All fMRI results are superimposed on the average anatomical MRI of all participants and are shown as horizontal sections (left side of each brain image corresponds to the left side of the brain).

similar to that observed in our prior study with normal university students (Hyde et al. 2008). The linear effect of pitch distance on BOLD signal is open to several interpretations. One possibility is that auditory cortical neurons may undergo neural “adaptation” (or reduced responses to repeated presentation of a specific stimulus, see Grill-Spector et al. 2006) in response to the repeating tone sequences, which lasted for over 7 s. According to this account, adaptation would diminish as a function of increasing pitch distance. This is because increasing the pitch distance between tones results in a wider pitch range, thus activating a greater number of distinct frequency-tuned auditory neural populations that have not yet “adapted” to the auditory stimulus. At any rate, the fact that the BOLD signal increased linearly as a function of small pitch changes in a similar fashion in the amusic and normal brain provides evidence that the amusics’ auditory cortex is able to respond to small pitch differences.

Whereas in the study of Hyde et al. (2008) the linear brain response to increasing pitch changes was relatively lateralized to the right auditory cortex, in the present study, the linear response was bilateral. This finding may be due to the fact that the participants tested here (age range: 46–62 years) were considerably older relative to the university students tested in

**Table 3**  
fMRI functional connectivity results

	Amusics-controls							Controls ( <i>n</i> = 9)							Amusics ( <i>n</i> = 9)								
	Brain region	BA	<i>x</i>	<i>y</i>	<i>Z</i>	<i>T</i>	Significance	Brain region	BA	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	Significance	Brain region	BA	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	Significance		
Right auditory seed region ( <i>x</i> = 62, <i>y</i> = -18, <i>z</i> = 0)	L PT/HG	22/41	-50	-20	4	4.7	**	R IFG (pars orbitalis)	47/11	44	44	6	2.6		L PT/HG	22/41	-50	-18	4	6.3	**		
	L PT/HG	22/41	-62	-18	2	3.8	*								R PT/STS	22	58	-44	14	4.8	*		
	R HG	41	42	-24	-2	3.8	*								R PT/STS	22	66	-34	2	4.2	*		
	L PT/HG	22/41	-62	-14	0	3.8	*								L HG	41	-36	-34	14	4.2	*		
	R HG	41	-50	0	-2	3.7	*								R IFG (pars orbitalis)	47/11	44	31	15	-2			
	R HG	41	56	-14	2	3.3	*																
	R PT/STS	22	58	-44	12	3.3	*																
	R HG	41	60	-14	2	3	*																
	R IFG (pars orbitalis)	47/11	44	46	10	-3	*																
	R IFG (pars orbitalis)	47/11	38	34	-6	-2.7																	
Left auditory seed region ( <i>x</i> = -64, <i>y</i> = -26, <i>z</i> = 8)	R PT/STS	22	62	-48	16	5.4	**	R PT/HG	22/41	58	-32	16	3.3	*	R PT/STS	22	66	-46	14	6.4	**		
	R PT/STS	22	62	-52	6	4.9	**	L IFG (pars orbitalis)	47/11	-52	22	8	3.6	*	R PT/STS	22	-66	-34	10	6.1	**		
	R PT/HG	22/41	60	-22	0	4.9	**								R HG	41	54	-10	2	5.3	**		
	R PT/HG	22/41	56	-22	0	4.9	**								L IFG (pars orbitalis)	47/11	-18	36	-2	-3.4	*		
	L PT/HG	22/41	-56	-26	4	4.2	*																
	L PT/HG	22/41	-56	-32	8	4.1	*																
	L PT/HG	22/41	-54	-36	12	4	*																
	L HG	41	-50	-10	10	3.9	*																
	L HG	41	-42	-16	8	3.6	*																
	L PT/HG	22/41	-50	-38	14	3.1	*																

Note: For each peak, the stereotaxic coordinates are given in MNI/Talairach space (Collins et al. 1994) along with the corresponding brain region, BA, and *t* values. Table 3 reports the fMRI functional connectivity results between and within groups: a positive *t* value indicates that the BOLD response at that peak is positively correlated with the seed region, and a negative *t* value indicates that the BOLD response at that peak is negatively correlated with the seed region. Results are significant at  $P < 0.05$  (corrected for multiple comparisons) at the whole-brain\* or VOI\*\* thresholds. L, left; R, right.

our prior study (age range: 21–36 years; Hyde et al. 2008). Older adults typically exhibit reduced cortical asymmetry (Cabeza et al. 2002). It has been suggested that older adults counteract age-related neural decline through a functional brain compensation process, whereby, with diminished activity of the principal hemisphere, neurons in the opposite hemisphere are recruited and become responsive, resulting in a reduced cortical asymmetry (Cabeza et al. 2002). Thus, it is possible that in the present study, a similar process was at play, resulting in reduced asymmetry and more bilateral pattern of auditory brain activation in response to the changing pitch sequences. Although reduced cortical asymmetry has been typically observed in the context of cognitive tasks (e.g., Cabeza et al. 2002), the present findings may reflect new evidence for a brain functional compensation mechanism in older adults that occurs in the context of a passive listening fMRI study (and thus independently of a cognitive task). Although this idea remains to be further examined in future studies, our findings suggest that auditory cortical pitch processing may become more symmetrical with age. Nonetheless, these findings do not influence the conclusions with respect to amusia because neither the control nor the amusia group showed any significant asymmetry.

The relatively normal functioning of the auditory cortical responses to pitch changes in amusia suggests that the principal functional abnormality lies outside the auditory cortex, with the evidence pointing instead to the frontal cortex. Indeed, here we found 2 pieces of evidence that support this conclusion. First, we observed a global functional brain difference between groups in response to the changing pitch sequences versus fixed pitch in the pars orbitalis of the right IFG (BA 47/11). Whereas the control participants had a slight increased BOLD activation in the right IFG, the amusic participants showed a decreased BOLD activation in the same area. This abnormal decrease of activity in the right IFG in amusics may be related to a dysfunction of the right IFG in the conscious, attentive monitoring of pitch sequences. Support for this idea comes from findings implicating the IFG in tasks requiring the conscious detection of musical key violations in normals (Maess et al. 2001; Tillmann et al. 2003). Moreover, findings of an early right-lateralized negative (or MMN) brain response to pitch changes in the amusics (Moreau et al. 2009; Peretz et al. 2009) indicate near-normal neural processing of fine-grained pitch differences but without awareness of this ability. Second, the functional connectivity analyses revealed that the auditory cortex was functionally related to the right IFG in the normal brain but showed decreased functional connectivity in the amusic brain. These findings indicate an abnormal propagation of sequential pitch information between the auditory cortex (in the vicinity of the PT) and the right inferior frontal cortex in the amusic brain.

In addition to the change in temporofrontal connectivity, the amusics also showed increased functional connectivity between the right and left auditory cortices relative to controls. These findings of decreased and increased functional connectivity in different brain networks in amusia are similar to the pattern of increased and decreased functional connectivity observed in other developmental disorders such as dyslexia (Wolf et al. 2010) and attention deficit and hyperactivity disorder (Wolf et al. 2009). In particular, a recent fMRI connectivity study in dyslexic adults demonstrated that dyslexics had abnormally decreased functional connectivity within an

“executive” bilateral frontoparietal network (dorsolateral prefrontal and posterior parietal regions) but increased connectivity in a “phonological” left-lateralized network (prefrontal and inferior parietal regions) (Wolf et al. 2010). The authors posited that this latter abnormal increased functional connectivity could be related to a compensatory mechanism in reaction to impaired phonological processing in dyslexia. From this perspective, one possibility to explain the abnormally high connectivity in amusics between left and right auditory cortices is that it is related to a similar compensatory mechanism, whereby amusics compensate for an impoverished auditory cortical response in 1 hemisphere by recruiting the help of the opposite auditory cortex. This increased connectivity could therefore explain why the amusics demonstrated a similar auditory cortical response to controls. Another possibility is that this abnormally high functional connectivity between bilateral auditory cortices is merely symptomatic of amusia (rather than the result of a compensatory mechanism) and hence represents some type of inefficient redundancy. However, further research will be required to determine whether the increased connectivity we observed in amusic individuals is indeed compensatory or pathological in nature.

The functional brain differences in sequential pitch processing found here in amusia are consistent with prior electrophysiological findings (Peretz et al. 2005, 2009; Moreau et al. 2009). Electric brain responses to pitch changes are essentially normal in the first 200 ms but show drastic changes thereafter when attention and musical processing of pitch intervals are involved. The present fMRI data further show that this abnormal processing of pitch information likely results from an anomalous connectivity between the auditory and frontal cortices. This is important because it helps to understand how the structural brain differences (along the frontotemporal pathway) that distinguish an amusic from a normal brain affect brain function.

The location of VBM gray/white matter differences ( $x = 39$ ,  $y = 42$ ,  $z = -3$ ; Hyde et al. 2006) and increased cortical thickness ( $x = 45$ ,  $y = 28$ ,  $z = -11$ ; Hyde et al. 2007) previously found in the right IFG of amusics is close to the right IFG area found here ( $x = 34$ ,  $y = 32$ ,  $z = 0$ ) in which amusics showed an abnormal decrease of BOLD activation in response to the changing pitch sequences. Furthermore, the abnormal functional connectivity between the right auditory and frontal cortices in the amusic brain is consistent with the recently reported reduced connectivity in white matter tracts along the arcuate fasciculus in the amusic brain as measured with diffusion tensor tractography (Loui et al. 2009). However, whereas the present findings indicate reduced functional connectivity between right temporal and inferior frontal cortical areas along a ventral stream, in agreement with the prior VBM and cortical thickness data, the tractography data (Loui et al. 2009) suggest that only the dorsal tract is affected in amusia, a discrepancy that will have to be addressed in future studies.

Structural (gray matter) abnormalities have previously been observed in the auditory cortex of amusics (Hyde et al. 2007; Mandell et al. 2007), but this structural anomaly does not appear to lead to an abnormal functional response in the auditory cortex, at least for “low-level” or basic pitch discrimination as in the present study. One possibility that remains to be investigated is whether fMRI would reveal auditory cortical functional differences in the amusic brain in “higher level” processing such as detecting an anomalous “out-

of-key" note in a traditional Western melody that engages tonal knowledge. Thus, neither the present findings nor the ERP data rule out the possibility that auditory cortical responses in amusia will be normal under these musical, more abstract circumstances.

Another issue that remains to be tested in future research is whether differences in brain structure and function, particularly in the auditory cortex and IFG, are related across amusic individuals. Based on the behavioral heterogeneity observed across amusic individuals (e.g., Peretz et al. 2003), it seems plausible to predict that amusic individuals with more pronounced brain structural anomalies may have greater functional changes as well (i.e., a greater abnormal cortical thickness increase in the right auditory cortex or right IFG may be related to an increased BOLD response in the same areas). Whereas a preliminary attempt to correlate brain structure (i.e., cortical thickness and gray matter concentration) and function (i.e., fMRI BOLD response) in the present sample of  $n = 9$  amusics failed to yield any significant correlations, the same analyses conducted in larger samples may indeed yield significant correlations.

The previous anatomical and present functional brain anomalies found in congenital amusia may be related to a cortical malformation, just as in other developmental disorders such as dyslexia (Galaburda et al. 1985). Cortical malformations can interfere with white matter connectivity as a result of heterotopic nodules forming connections with each other and with overlying cortex, thereby disturbing brain connectivity (Kakita et al. 2002). Overall, the correspondence between the present functional brain differences and previous structural differences strengthen our conclusion that a disturbed frontotemporal network involving auditory and inferior frontal cortices is related to the musical impairments in congenital amusia (Hyde et al. 2007). Thus, the results are broadly compatible with the view that normal musical competence may depend on the structural integrity of a right frontotemporal pathway.

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