

Tone Deafness: A New Disconnection Syndrome?

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Communicating with one's environment requires efficient neural interaction between action and perception. Neural substrates of sound perception and production are connected by the arcuate fasciculus (AF). Although AF is known to be involved in language, its roles in non-linguistic functions are unexplored. Here, we show that tone-deaf people, with impaired sound perception and production, have reduced AF connectivity. Diffusion tensor tractography and psychophysics were assessed in tone-deaf individuals and matched controls. Abnormally reduced AF connectivity was observed in the tone deaf. Furthermore, we observed relationships between AF and auditory-motor behavior: superior and inferior AF branches predict psychophysically assessed pitch discrimination and sound production perception abilities, respectively. This neural abnormality suggests that tone deafness leads to a reduction in connectivity resulting in pitch-related impairments. Results support a dual-stream anatomy of sound production and perception implicated in vocal communications. By identifying white matter differences and their psychophysical correlates, results contribute to our understanding of how neural connectivity subserves behavior.

Introduction

Survival depends on the brain's ability to perceive and act on various features of the environment. Neural computations that enable humans to interact with their environment require efficient connectivity in white matter fibers of the brain, specifically between primary sensory areas and action-selection and execution areas. Although brain-imaging and neuropsychological evidence converge on a coupling between frontal motor-related areas and primary sensory cortices in maintaining the perception-action network, the anatomical pathways of communication within the network are as yet unidentified. One prominent candidate highway of white matter connectivity in the human brain is the arcuate fasciculus (AF), a fiber tract connecting temporal and frontal brain regions (Catani and Mesulam, 2008). Right-handed individuals who suffer disrupted connectivity (e.g., attributable to ischemic stroke, hemorrhage, or brain trauma) to the left AF, known as conduction aphasics, are unable to repeat words/phrases spoken to them (Lichtheim, 1885; Parker et al., 2005), implicating a vital role of the AF in language function. However, other roles of the AF, including its control of feedforward and feedback mechanisms (Tourville et al., 2008) and non-linguistic functions, are yet unexplored.

Although known white matter disconnection syndromes (such as conduction aphasia) can be profoundly debilitating to everyday life, deficits in pitch perception and production, also known as tone deafness or congenital amusia, are accompanied by normal peripheral hearing and only subtle anomalies in

speech perception (Patel et al., 2008). Tone-deaf individuals exhibit impaired pitch perception, inaccurate pitch production, and notable mismatches between perception and production abilities, suggesting an impairment in the action-perception brain network (Peretz et al., 2002; Foxton et al., 2004; Loui et al., 2008). This perception-action network is implicated in various domains, including vision (Goodale and Milner, 1992), hearing (Kohler et al., 2002), speech (Tourville et al., 2008), music (Lahav et al., 2007), and language (Pulvermüller, 2005) and may be a critical component of the putative mirror-neuron network in the mammalian brain (Rizzolatti et al., 1996).

Recent studies on the tone-deaf brain have implicated structural and functional anomalies in high-order perceptual processes in superior temporal brain areas, as well as in action-selection regions in the inferior frontal cortex (Peretz et al., 2005; Hyde et al., 2007; Mandell et al., 2007). Simultaneously observed abnormalities in gray and white matter in these two regions may result from abnormal connectivity between the regions or from one abnormally developed region (e.g., as a result of a migration disorder) affecting the other via mutually connecting white matter pathways.

We hypothesized that tone-deaf individuals may have structural abnormalities in their action-perception network, as observable by disrupted connectivity in branches of the AF and by correlations between AF tract volume and psychophysically defined perception and production abilities. Diffusion scans were obtained from tone-deaf individuals ($n = 10$) and matched controls ($n = 10$), and tractography was performed using atlas-defined (Mori and van Zijl, 2007; Lawes et al., 2008) seed regions of interest (ROI) in the endpoints of the AF in each hemisphere: posterior superior temporal gyrus (pSTG), posterior middle temporal gyrus (pMTG), and posterior inferior frontal gyrus (pIFG).

Materials and Methods

Participants. Ten tone-deaf and 10 matched control adult subjects participated in the study. Each of the tone-deaf and control groups consisted

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of five males and five females with an age range of 21–55 (tone-deaf group, 22–55; control group, 21–55). All subjects were right handed and had normal audiometry. Mean IQ, as assessed by Shipley's verbal and abstract scaled composite score (Shipley, 1940), was equal in normal and tone-deaf individuals (normals: mean = 117, range = 109–123; tone deaf: mean = 118, range = 105–124). Subjects were recruited from online advertisements and were screened using a psychophysical three-up-one-down adaptive staircase procedure for pitch discrimination. All participants provided written informed consent, which was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center.

Tone-deaf individuals showed an average pitch discrimination threshold of 51 Hz around a center frequency of 500 Hz (SD, 3.4 Hz), significantly larger than control subjects' average threshold of 3 Hz (SD, 0.27 Hz), as confirmed by a two-tailed *t* test comparing pitch discrimination thresholds between groups: $t_{(18)} = 4.0$, $p < 0.001$. Pitch interval production thresholds were also collected in all subjects using the three-up-one-down psychophysical procedure combined with online pitch tracking [same as Loui et al. (2008)]. Results replicated our previous report in showing a mismatch between perception and production abilities in tone-deaf individuals but no mismatch in non-tone-deaf individuals (Loui et al., 2008).

To confirm that these subjects were tone deaf using multiple measures, the contour subtest of the Montreal Battery of Amusia (Peretz et al., 2003) was also administered. Results reconfirmed the pitch discrimination test by showing that the tone-deaf subjects scored an average of 66%, over two SDs below the published norm and below the cutoff of 71% for congenital amusia. Thus, the current group of subjects met both psychophysical and psychometric criteria for tone deafness.

Procedure. Structural MRI with diffusion tensor imaging (DTI) was performed using a 3-Tesla General Electric scanner. Anatomic images were acquired using a T1-weighted, three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo volume acquisition with a voxel resolution of $0.93 \times 0.93 \times 1.5$ mm. DTI was performed using a diffusion-weighted, single-shot, spin-echo, echo-planar, imaging sequence (TE1 = 86.9 ms, relaxation time = 10,000 ms, field of view = 240 mm, matrix size 94×94 voxels, slice thickness = 2.5 mm, no skip, NEX = 1, axial acquisition). Thirty noncollinear directions with a *b* value of 1000 s/mm² and six volumes with a *b* value of 0 s/mm² were acquired. Fractional anisotropy (FA) values, a measure of the degree of directional preference of water diffusion (Basser, 1995), were calculated within each brain voxel.

Data analysis. Tractography was applied to the DTI data to reconstruct white matter tracts by successively following the path of preferred direction of water diffusion (Jones et al., 1999; Mori et al., 1999; Basser et al., 2000). Using MedINRIA software version 1.7 (Fillard et al., 2007), diffusion tensors were calculated from all voxels within the brain. Fiber tracts were calculated by connecting adjacent voxels with similar principal eigenvectors, using a threshold FA value of 0.2 and a smoothness factor [a parameter ranging from 0 to 1 corresponding to the straightness of each fiber (Weinstein et al., 1999)] of 0.2 for continuous fiber reconstruction (Thomas et al., 2005). Only fibers with lengths of >10 mm were included. These parameters were similar to those used by others who applied a fiber assignment by continuous tracking algorithm (Weinstein et al., 1999; Schaechter et al., 2008).

To constrain fiber tracts and to determine regional FA values, regions of interest were drawn on one sagittal slice for each hemisphere on each brain by a single coder, who was blind to the status of the participants, in white matter underlying the pSTG, pMTG, and pIFG. See Figure 1 for region location and region size. Fibers were reconstructed using the pSTG/pMTG and each of the ipsilateral pIFG ROIs in two stages. First, voxels of the pSTG or pMTG served as seeds, and the pIFG ROIs served as the target; then voxels of the pIFG ROI served as seeds, and the pSTG or pMTG served as targets. These regions of interest were defined according to published DTI atlases (Wakana et al., 2004; Lawes et al., 2008) and

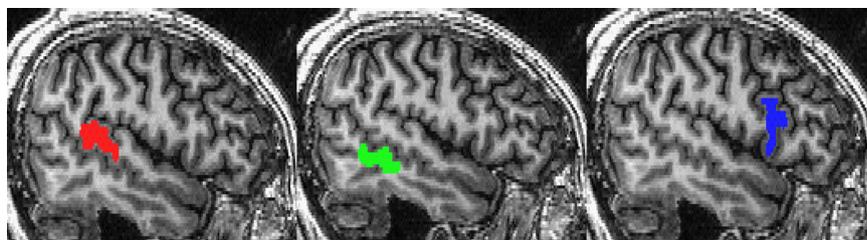


Figure 1. Anatomical locations of regions of interest superimposed on a T1 image. Red, pSTG; green, pMTG; blue, pIFG.

were identifiable in all individuals in the sagittal slice of the FA-weighted image. As the AF has been identified as a large fiber tract connecting the pIFG to both the pSTG and pMTG (Mori and van Zijl, 2007; Glasser and Rilling, 2008; Sundaram et al., 2008), we labeled the connection between the pIFG and pSTG as the superior AF and the connection between pIFG and pMTG as the inferior AF.

A mean FA value was calculated for each ROI of each subject by averaging the mean FA values in all voxels. Region of interest volume was calculated by multiplying the number of voxels included in each ROI by the voxel size. Tone-deaf and control groups were matched in volumes of each ROI (mean volume: tone deaf = 214 mm³, control = 202 mm³, two-tailed *t* test $t_{(18)} = 0.72$, $p = 0.48$) and regional FA values (mean: TD = 0.27, control = 0.28, two-tailed *t* test $t_{(18)} = 1.11$, $p = 0.28$). After applying tractography, the identified fiber bundles were compared for tract volume and regional FA values. Although the exact relationship between axonal counts and identified tracts is yet unclear, volume and FA data of identified tracts provide information on myelination and white matter connectivity of fiber tracts within neural tissue.

Results

Unidentified superior arcuate fasciculus among tone-deaf individuals

Fiber tracking reliably identified both the superior and inferior AF bilaterally in normal subjects. In contrast, only the inferior AF was identifiable bilaterally in all tone-deaf individuals (Fig. 2). Within the tone-deaf group, the superior AF was unidentifiable in the right hemisphere for 9 of 10 subjects and in the left hemisphere for one subject. A χ^2 test for tract detection (detected vs undetected) by group (tone deaf vs control) was highly significant ($\chi^2 = 55.0$, $p < 0.0001$), confirming that, using the imaging parameters mentioned below, tone-deaf individuals had a lower rate of successful detection of the superior AF by blinded observers. A three-way ANOVA with AF fiber volume (in mm³) as the dependent variable, with factors of group (tone deaf vs control), tract (superior vs inferior), and hemisphere (left vs right) revealed a significant effect of group ($F_{(1,84)} = 10.3$, $p = 0.002$), confirming that tone-deaf subjects had less fiber volume overall than controls. Additionally, a three-way interaction between the factors of group, hemisphere, and tract was significant ($F_{(1,84)} = 23.2$, $p < 0.0001$), supporting the observation that the right superior AF was diminished in TD individuals relative to controls. FA values in a region of interest drawn bilaterally around the midpoint of the AF (see Materials and Methods) were significantly lower in TD individuals than in controls ($t_{(18)} = 3.16$, $p < 0.01$), confirming that the structure of the AF is disrupted in tone-deaf individuals, resulting in an impaired perception-action network.

In addition to the main effect of group (tone deaf vs control) on tract volume, a main effect of hemisphere was also observed in the AF of all subjects ($F_{(1,84)} = 9.4$, $p = 0.003$), with more fiber volume in left hemisphere than in the right hemisphere. This is consistent with previous studies showing larger AF volume in the left hemisphere regardless of gender, handedness, and functional

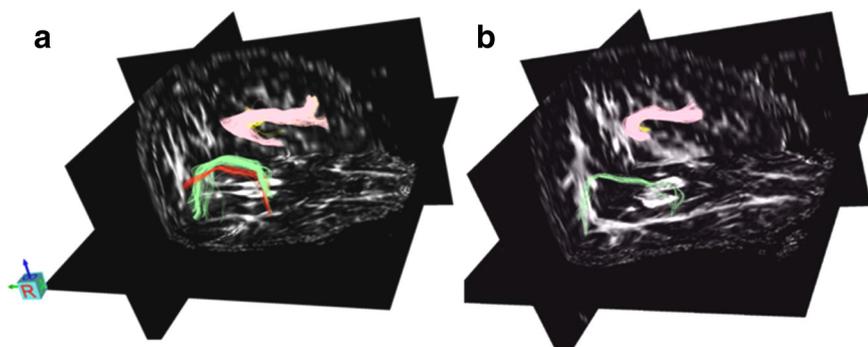


Figure 2. *a*, Tractography of a typical normal individual showing superior and inferior AFs bilaterally. Yellow, Left superior AF; pink, left inferior AF; red, right superior AF; green, right inferior AF. *b*, Tractography of a typical tone-deaf individual showing hemispheric asymmetry in the AF. Yellow, Left superior AF; pink, left inferior AF; green, right inferior AF. The right superior AF was not identified.

lateralization of language (Vernooij et al., 2007). A robust effect of tract was also observed ($F_{(1,84)} = 76.0, p < 0.0001$), showing more volume in the inferior branch overall; this is also consistent with previous studies on AF tractography (Glasser and Rilling, 2008) and converges with existing models of dorsal and ventral streams in language processing (Hickok and Poeppel, 2004).

Abnormal right-superior projections in tone deafness

To further explore the pathology of an altered or possibly missing right-superior AF in the tone-deaf population, tractography was initiated with only one region of interest in the right pSTG. Most resultant fibers in normal individuals projected toward the ipsilateral IFG. In contrast, tracts in the tone-deaf group projected dorsally toward the parietal lobe and/or transcallosally to the left hemisphere but not toward the ipsilateral IFG (Fig. 3*a,b*). This suggests that the right pSTG, as an endpoint of the AF, is not deficient in connections, per se, but rather lacking in its connectivity specifically toward the frontal lobe. A similar one-ROI analysis initiated from the right pIFG revealed massive posterior projections toward the temporal lobe (Fig. 3*c,d*), suggesting that the pSTG, not the pIFG, is the main origin of the pathology.

Behavioral correlates of superior and inferior AF tract volume

Having identified the bilateral branches of the arcuate fasciculus and their abnormalities in tone-deaf individuals, we sought to define behavioral correlates of these tracts to investigate the hypothesis that branches of the AF subserved behavioral differences indicative of tone deafness. We correlated the logarithmic pitch discrimination threshold with the volume of fiber tracts in the AF. The resultant correlation was significantly negative between right superior AF volume and logarithmic pitch discrimination threshold (Spearman rank order correlation, $r_s = -0.53, t_{(18)} = 2.66, p = 0.016$, two-tailed). In a subsequent analysis, tone-deaf individuals whose thresholds were beyond one semitone ($n = 8$) were excluded as their right superior AF fiber volumes were all at a floor level of zero, which would have resulted in a biased correlation (Vul et al., 2009). For the remaining subset of normal ($n = 10$) and borderline tone-deaf individuals ($n = 2$), results again showed a significant negative correlation of $r_s = -0.80$ (Spearman rank order correlation, $t_{(10)} = -4.21, p = 0.0018$ two-tailed) (Fig. 4*a*) between right superior AF volumes and pitch discrimination thresholds. In other words, considering both the entire set and an unbiased subset of participants, individuals with larger fiber tracts in the superior AF had better pitch discrimination

abilities (smaller thresholds), suggesting that the superior AF is a neural correlate of conscious pitch discrimination.

To further investigate the dichotomy between production and conscious perception, pitch production thresholds were obtained to assess the smallest interval at which subjects could correctly reproduce the direction of intervals. Previous work has shown that tone-deaf subjects have a perception-production mismatch as demonstrated by smaller production thresholds than perceptual thresholds (Loui et al., 2008), suggesting separate streams of processing for interval production and conscious pitch perception. We developed a metric of this perception-production mismatch by

taking the absolute value of the difference between logarithmic production and perception thresholds [$\log_2(\text{perceptual threshold}) - \log_2(\text{production threshold})$]. The resultant metric is low for normal individuals (whose pitch perception and production abilities are evenly matched) and higher for more severely tone-deaf individuals, resulting in a psychophysically defined index of production-perception mismatch in tone deafness (Loui et al., 2008). Correlating this index with tract volumes in the AF revealed a significant negative correlation between the right inferior AF volume and the tone-deafness index (Spearman rank order correlation, $r_s = -0.49, t_{(18)} = 2.39, p = 0.028$, two-tailed), confirming that individuals with a greater degree of perception-action mismatch tend to have a smaller inferior AF. The same correlation was observed using the same subset of subjects that was included in the aforementioned relationship between pitch discrimination and superior AF volume (Spearman rank order correlation, $r_s = -0.77, t_{(11)} = -3.78, p = 0.0036$, two-tailed) (Fig. 4*b*). No other correlations were observed between AF volume and pitch and production measurements obtained. Together, the findings of two brain-behavior correlations (1) between superior AF and pitch-perception threshold and (2) between inferior AF and perception-production mismatch implicate a dual-stream model of auditory function, where the superior branch is responsible for fine-grained discrimination, whereas the inferior branch is responsible for the automatic matching of a sound output to its target. Both the superior and inferior branches of AF are necessary for accurate perception and production.

Discussion

The study of vocal pitch abilities as they relate to pitch perception abilities is a relatively neglected area of investigation. Although previous documentation exists of individuals who can sing accurately despite poor perception (Ayotte et al., 2002), a systematic mismatch between perception and production has only recently been reported in a group of tone-deaf individuals (Loui et al., 2008). Using diffusion tensor tractography combined with perception and production psychophysics, we identified neuroanatomical disconnections in the tone-deaf population. Here, we show that people who are tone deaf are affected by a previously unknown disconnection of the AF. Diffusion tensor tractography (Mori et al., 1999) and psychophysical assessments (Patel et al., 2005) were performed on tone-deaf individuals who have impaired pitch perception (Foxton et al., 2004) and vocal pitch production (Loui et al., 2008) and matched controls. We identify a lack of neural

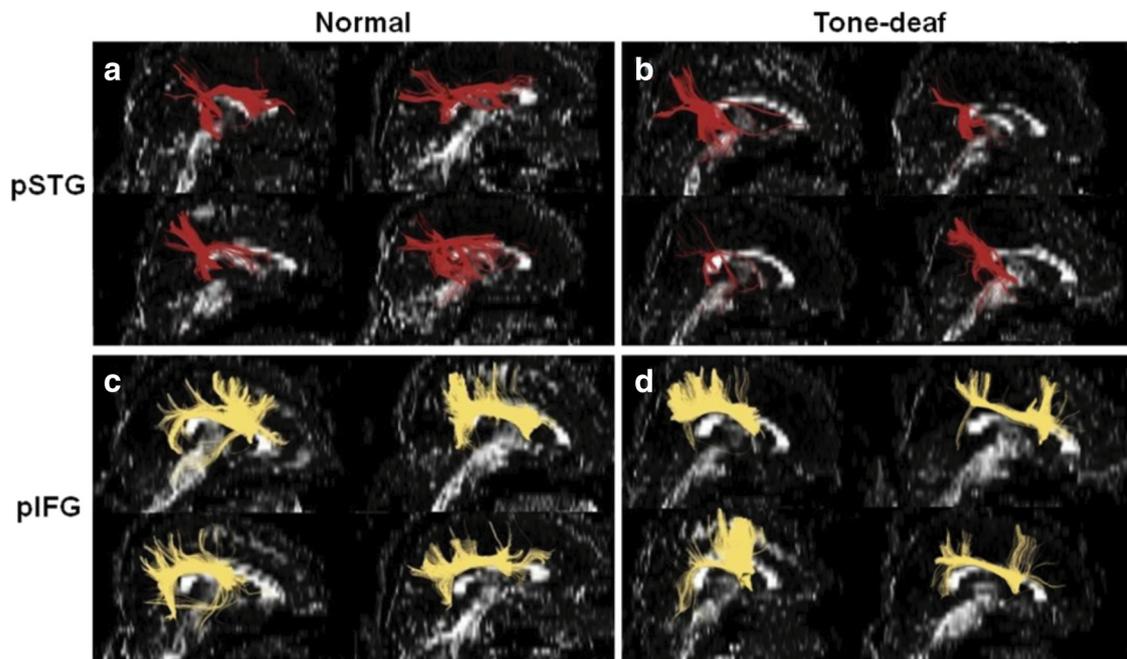


Figure 3. Comparison of tracts identified using one region of interest in normal and tone-deaf individuals superimposed on fractional anisotropy images. **a**, Tracts identified in normal individuals with one region of interest placed on the right posterior STG. **b**, Tracts identified in tone-deaf individuals with one region of interest placed on the right posterior STG, showing decreased tracts identified relative to controls. **c**, Tracts identified in normal individuals with one region of interest placed on the right posterior IFG. **d**, Tracts in tone-deaf individuals with one region of interest on the right posterior IFG, showing decreased connections to the superior temporal lobe relative to controls.

connectivity in the tone-deaf brain: robust decreases in AF volume were observed in tone-deaf individuals relative to matched controls. Furthermore, we demonstrate for the first time that the AF is a neural correlate of auditory–motor behavior: its superior and inferior branches predict psychophysically assessed pitch discrimination and sound production–perception abilities, respectively. This newly identified neural abnormality suggests that tone deafness is a new disconnection syndrome resulting in impaired pitch perception and vocal sound production. Results support a dual-stream anatomy of sound production and perception (Hickok and Poeppel, 2007) that may be required for all types of vocal communication. By identifying behavioral correlates of white matter differences observed via diffusion tensor imaging (Jones, 2008), results contribute to our understanding of the role of neural connectivity in human behavior.

Results from the present study converge with previous morphometric studies (Hyde et al., 2007; Mandell et al., 2007) showing frontotemporal gray matter differences between tone-deaf and control individuals. The finding of abnormal projections in the right hemisphere fits with Hyde et al. (2006), showing white matter morphometric abnormalities on the right hemisphere, although voxel-based morphometric studies focusing on gray matter differences have either shown strong left-hemisphere abnormalities in the frontotemporal network (Mandell et al., 2007) or found evidence for cortical thickness abnormalities in both hemispheres (Hyde et al., 2007). Although most of the observed effects in the current study are on the right hemisphere, the observed significance levels may be attributable to fiber volumes being smaller overall on the right (and thus to differences being

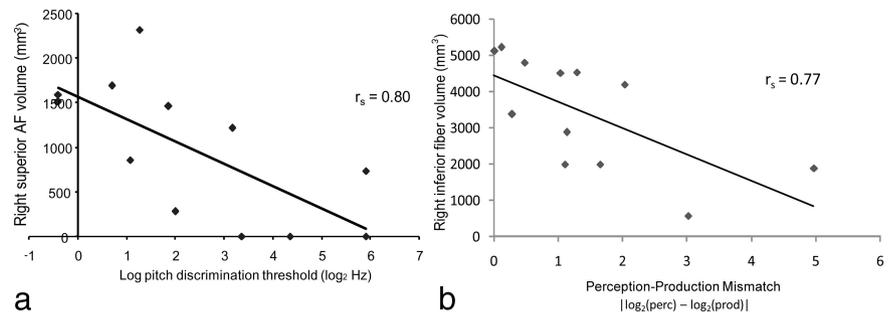


Figure 4. **a**, Correlation between volume of fiber tracts in the right superior AF and the pitch discrimination threshold. **b**, Correlation between volume of fiber tracts in the right inferior AF and the action-perception mismatch index.

more easily detectable) and thus may not be indicative of an exclusively right-hemispheric network subserving pitch perception and production. Future studies are needed to further explore the relationships between gray and white matter abnormalities within and between hemispheres in this interesting developmental disorder.

Compared with the normal population, tone-deaf individuals possessed fewer fibers in the arcuate fasciculus, with at least one of the superior AF branches being unidentified with the current imaging parameters. Furthermore, superior AF tract volume was a significant predictor of conscious pitch discrimination ability, whereas inferior AF volume predicted the degree of action-perception mismatch. Both of these correlations were observed even while excluding profoundly tone-deaf individuals with pitch discrimination thresholds of over one semitone so as to minimize the chances of an artificially boosted correlation. This may suggest that the neural correlates of conscious pitch discrimination and action-perception identified here are applicable not only to tone-deaf individuals but can be generalized to the normal population.

Fiber tracking with DTI is not directly analogous to studies using tracers such as horseradish peroxidase where the connectivity of axons is assured; here, the real number of axons within a tract relative to the number of reconstructed fibers is unknown (Johansen-Berg and Behrens, 2006). However, fiber tracking can be used to identify sufficiently large tracts of axons traveling in the same general direction, and tract-based statistics have been applied in various normal and diseased populations as a proxy for structural integrity and hemispheric asymmetry of major white matter pathways (Johansen-Berg and Behrens, 2006; Leh et al., 2006; Schaechter et al., 2008; Sundaram et al., 2008). In our results, the diminished number and volume of detectable superior AF fibers may not necessarily imply a complete absence of the tract but rather that the preferred directions of diffusion along the path readily detected in controls are discontinuous in tone-deaf subjects; this may be indicative of reduced fiber volume, decreased myelination along the tract direction, or abnormal development of fiber projections originating from one of the regions. Thus, the origin of this disorder could be in regionally abnormal neuronal migration leading to reduced structural connectivity, similar to what is observed in congenital prosopagnosia (Thomas et al., 2009), dyslexia (Deutsch et al., 2005), or global developmental delay (Sundaram et al., 2008). Furthermore, reduced connectivity in tone-deaf controls may not represent a categorical difference from the normal population but rather a quantitative difference in which the tone-deaf arcuate fasciculus represents the low end of a continuum. Relative to controls, the structural integrity of white matter tracts is so compromised in tone-deaf individuals as to preclude successful tracking of the superior branch of the arcuate fasciculus using currently available neuroimaging and analysis techniques.

Methodologically, the present data suggest that tractography methods can reveal structural integrity not only of white matter in general but of tracts that connect distributed nodes within a structural brain network (Jones et al., 1999). The directionality of these fiber tracts remains to be determined and presents a challenge for current diffusion tractographic methods. Another caveat in this relatively novel technique lies in the statistical inference of fiber volume from diffusion data. In that regard, the present analysis methods, involving the validation of fiber tracts connecting seed regions of interest, parallel those of recent studies comparing diffusion data with dissected postmortem brain tissue or across various neurological populations such as patients of diffuse axonal injury (Wang et al., 2008), children with global developmental delay (Sundaram et al., 2008), congenital prosopagnosics (Thomas et al., 2009), and hemispherectomized patients with and without blindsight (Leh et al., 2006).

Another question concerns directionality of the newly identified disconnection syndrome: whether the abnormality of tone deafness originates from the temporal or frontal regions. As a two-region of interest analysis does not yield information about whether fiber tracts were originating from or projecting to the temporal and frontal regions (Leh et al., 2006), we included a one-region of interest analysis, with seed regions placed at the endpoints of the arcuate fasciculus, to identify all tracts passing to or from the pSTG or pIFG. Resultant fibers showed selective hypoconnectivity from the pSTG to the pIFG, suggesting that the pSTG is the origin of the disorder (Fig. 3); however, as tract volume using one-ROI analyses cannot be constrained to specific branches of the fiber bundle, we report tract volume statistics from two-ROI analyses as the more accurate measure of specific branches of fiber tracts. Test–retest reliability of diffusion tractography has been established by comparing tracts obtained from

the same subjects using multiple sets of imaging parameters (Loui and Schlaug, 2009). Combined with threshold data for perception and vocal production obtained from each subject, the present results show for the first time that AF volume can be an effective predictor of vocal behavior.

Although pitch perception and production is a basic ability in humans and other animals, an estimated 17% of the normal population self-identifies as tone deaf (Cuddy et al., 2005). The present results show that this seemingly normal population possesses disrupted pathways bridging perception and action areas in the brain, resulting in an inability to discriminate and produce pitches to sing in tune. The data suggest that action and perception may arise from dissociated dorsal and ventral neural pathways that may be differentially affected in tone deafness. As the posterior inferior frontal gyrus (specifically Broca's area) was shown to be recruited in visuospatial processing involving sequentially manipulating mental objects (Sluming et al., 2007), the present finding of diminished connectivity to the posterior IFG might be related to recent reports of impaired mental rotation among tone-deaf people (Douglas and Bilkey, 2007). Furthermore, the dorsal and ventral pathways may be responsible for automatic, category-based sound analysis and conscious access to perceptual information, respectively, both of which are important in vocal communication. Results parallel existing dual-stream models of speech, language, and auditory processing (Hickok and Poeppel, 2004; Sridharan et al., 2007; Glasser and Rilling, 2008; Griffiths, 2008) and may provide the neurological basis for a domain-general neural framework that subsumes auditory and motor systems in the human brain.

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