White matter integrity in right hemisphere predicts pitch-related grammar learning

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ABSTRACT

White matter plays an important role in various domains of cognitive function. While disruptions in white matter are known to affect many domains of behavior and cognition, the ability to acquire grammatical regularities has been mostly linked to the left hemisphere, perhaps due to its dependence on linguistic stimuli. The role of white matter in the right hemisphere in grammar acquisition is yet unknown. Here we show for the first time that in the domain of pitch, intact white matter connectivity in right-hemisphere analogs of language areas is important for grammar learning. A pitch-based artificial grammar learning task was conducted on subjects who also underwent diffusion tensor imaging. Probabilistic tractography using seed regions of interest in the right inferior frontal gyrus and right middle temporal gyrus showed positive correlations between tract volume and learning performance. Furthermore, significant correlations were observed between learning performance and FA in white matter underlying the supramarginal gyrus, corresponding to the right temporal–parietal junction of the arcuate fasciculus. The control task of recognition did not correlate with tract volume or FA, and control tracts in the left hemisphere did not correlate with behavioral performance. Results show that the right ventral arcuate fasciculus is important in pitch-based artificial grammar learning, and that brain structures subserving learning may be tied to the hemisphere that processes the stimulus more generally.

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Introduction

White matter is required for efficient communication within the human brain, and variability in white matter structures has been linked with various cognitive domains encompassing memory, creativity, and intelligence (Chiang et al., 2009; Johansen-Berg, 2010; Mabbott et al., 2009; Sasson et al., 2010; Jung et al., 2010). In the language domain, inter-subject variability in white matter connectivity, especially in the left hemisphere, has been related to reading ability and grammar learning in patients who suffer from stroke as well as the normal population (Flöel et al., 2009; Meinzer et al., 2010; Klingberg et al., 2000; Johansen-Berg, 2010). These reports of functional correlates of white matter variations suggest that the inter-individual differences in white matter architecture might reflect learning potential in various domains including linguistic and auditory-oralmotor competence.

The arcuate fasciculus (AF) is a white matter fiber tract that connects the perisylvian cortex in the posterior frontal, inferior parietal, and superior temporal lobes within each hemisphere (Catani et al., 2005; Catani and Mesulam, 2008a). Patients with lesions affecting the left-hemisphere AF are long known to have trouble reading and repeating words, in a condition known as conduction aphasia

(Lichtheim, 1885; Geschwind, 1965; Catani et al., 2005; Rauschecker et al., 2009). More recent structural and functional neuroimaging results have shown substantial individual differences in the AF morphology, with at least three portions of the AF including direct connections between frontal and temporal lobes as well as indirect connections from temporal lobe to inferior parietal lobe, and then from inferior parietal lobe to frontal lobe (Catani and Mesulam, 2008a). Furthermore, the different portions of the AF may be related to different abilities. Specifically, the fronto-parietal portion of the left AF has been linked to reading and mental arithmetic skills (Klingberg et al., 2000; Deutsch et al., 2005; Tsang et al., 2009). In contrast, the temporal-lobe endpoints of the left AF are anatomically dissociated between the superior temporal gyrus (dorsal branch) and middle temporal gyrus (ventral branch). These two regions and their major connections are thought to be specialized in phonological and lexical-semantic processing respectively (Glasser and Rilling, 2008; Friederici, 2009; Hickok and Poeppel, 2007).

The AF is generally larger in the left hemisphere than in the right hemisphere, with substantial variability existing in size and morphology between individuals (Glasser and Rilling, 2008; Nucifora et al., 2005; Rodrigo et al., 2007). Previous studies have hypothesized that the leftward asymmetry of the AF is associated with the functional dominance of the left hemisphere for language, and may reflect a structural adaptation for linguistic processing, but this hypothesis has also been questioned by others (Nucifora et al., 2005; Rodrigo et al., 2007; Vernooij et al., 2007). In recent years, the question of

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how the left AF mediates behavior has received considerable interest, especially in relation to aspects of language ability. In addition to studies that have related white matter to reading skills (Deutsch et al., 2005; Klingberg et al., 2000), one of the landmark studies on Artificial Grammar Learning (Friederici et al., 2006) showed that the left hemisphere AF is associated with processing and learning phrase-structure grammar, as compared to the inferior longitudinal fasciculus and tracts passing through frontal operculum which are associated with finite-state grammar. In another study, Artificial Grammar Learning (AGL) task performance was shown to be significantly correlated with white matter integrity in the left frontal lobe, especially Broca's area (Flöel et al., 2009).

While the role of the left AF has been explored in various studies (Catani et al., 2005; Rilling et al., 2008; Friederici, 2009; Friederici et al., 2006), relatively little is known about the AF in the right hemisphere. Based on neuropsychological research with neglect patients, the right AF is putatively involved in visuospatial processing (Doricchi et al., 2008) and some aspects of language such as prosody and semantics (Catani and Mesulam, 2008b; Glasser and Rilling, 2008). Among the normal population, however, little is known about the role that the right AF may play in perceptual and/or cognitive ability. One population that has a noted disruption in right AF connectivity is people who are tone-deaf, also known as congenital amusics, who have difficulties perceiving and producing pitch (Loui et al., 2008; Foxton et al., 2004; Peretz et al., 2002) as well as subtle anomalies in speech prosody discrimination, identification, and imitation (Liu et al., 2010). Tone-deaf individuals possess structural and functional differences in temporal and frontal regions in the right hemisphere (Hyde et al., 2007, in press), with pitch discrimination abilities specifically being correlated with the volume of the right dorsal AF which connects the inferior frontal gyrus and the superior temporal gyrus in the right hemisphere (Loui et al., 2009a).

Given that the left AF is involved in language grammar learning (Friederici et al., 2006; Flöel et al., 2009) whereas the right AF is related to pitch-discrimination disabilities (Loui et al., 2009a), we ask the question of whether white matter in the right hemisphere, especially in branches of the right AF, might be sensitive to learning potential in a system that requires predominantly right-hemisphere processing functions. Specifically, since pitch information has been linked to a right-hemispheric rather than a left-hemispheric dominance, especially in musically naïve subjects (Zatorre and Samson, 1991; Zatorre et al., 1994, 2002; Klostermann et al., 2009), we hypothesize that learning a pitch-based grammatical structure is related to variability in white matter connectivity in the right hemisphere. According to this hypothesis, individuals who are superior at learning an artificial system of pitch patterns should show a difference in right temporo-frontal connectivity as observable by diffusion tensor imaging, compared to people who are unable to learn a system of pitches, i.e. individuals with a pitch-related learning disability. To compare pitch-related learning abilities between individuals, we adopted a pitch-based artificial grammar learning task that was shown to be sensitive to grammar learning ability in previous studies (Loui et al., 2009b, 2010; Loui and Wessel, 2008). This artificial grammar system consists of pitches that are different from existing musical systems, so that participants could not rely on pre-existing knowledge or long-term memory to succeed in the behavioral tasks. By assessing learning and memory implicitly through generalization and recognition tests, we relate the between-subject variability of learning abilities to between-subject variability in white matter structure as assessed using DTI.

Materials and methods

Participants

Sixteen healthy volunteers (7 males, 9 females, average age = 27, age range = 20–38) participated in this study. All participants were right-handed and had no hearing impairment and no neurological or psychiatric disorders. Informed consent was obtained from all participants as approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. Shipley verbal and abstract scaled composite scores (Shipley, 1940) were used to assess IQ and found that all participants were within the average range (see Results section). To determine whether grammar learning performance was related to perceptual attributes, subjects were also evaluated for their pitch discrimination thresholds using the three-up-one-down psychophysical staircase procedure around the center frequency of 500 Hz (Loui et al., 2009a; Cornsweet, 1962).

Stimuli

Five hundred tone sequences were constructed as stimuli. Each tone sequence contained eight tones and consecutive tone sequences were separated by a 500 ms silent gap. Each tone was 500 ms in duration, including rise and decay times of 10 ms each. The frequency of each tone was determined by an artificial phrase-structure grammar system which is based on the Bohlen–Pierce scale, a novel musical scale that differs from existing musical systems such as Western classical music in its mathematical ratios (Mathews et al., 1988; Sethares, 2004; Krumhansl, 1987). Previous studies have used artificial grammars generated from the Bohlen–Pierce scale to assess grammar learning in the domain of pitch (Loui and Wessel, 2008; Loui et al., 2009b, 2010). Further descriptions of the Bohlen–Pierce scale, and of the artificial grammars generated from this scale, are given in Fig. 1.

Procedure

Behavioral testing

Participants were seated in a comfortable chair in a sound-attenuated room. All testing was done on a Dell PC desktop with JVC HA-M300V headphones using customized software written in MaxMSP 4.6 (Zicarelli, 1998). All auditory stimuli were presented at a level of approximately 70 dB. Behavioral testing was conducted in two phases. The first phase was the *exposure phase*, during which subjects listened to tone sequences that were generated from the artificial grammar. The exposure phase lasted 30 min, during which 400 grammatical melodies were presented. Participants were told to listen passively but attentively to the tone sequences, without overanalyzing their content.

The second phase of behavioral testing was the *test phase*, during which subjects were given a two-alternative forced choice test to assess their implicit learning of the artificial grammar. Twenty test trials were presented in this two-alternative forced choice test. In each trial, two tone sequences were presented, and participants were told to choose the sequence that sounded most familiar, and to indicate their response via button-press.

Ten of the twenty test trials were *generalization* trials that assessed grammar learning. In each generalization trial, neither of the two tone sequences in the trial belonged to the set that had been presented in the exposure phase, but one of the sequences obeyed the rules of the grammar, whereas the other sequence violated the grammatical rules (Fig. 1d). Responses were considered correct if participants chose the sequence that followed the grammar, thus demonstrating sensitivity to the rules of the grammar.

The remaining ten out of twenty test trials were *recognition* trials that assessed rote memory for items presented during exposure. These trials served as a control task for grammar learning. In the recognition trials, one of the tone sequences had been presented during the exposure phase, whereas the other sequence had not been presented during exposure (Fig. 1e). Responses were considered correct if participants chose the previously presented sequence as being more familiar — i.e. a memory task.
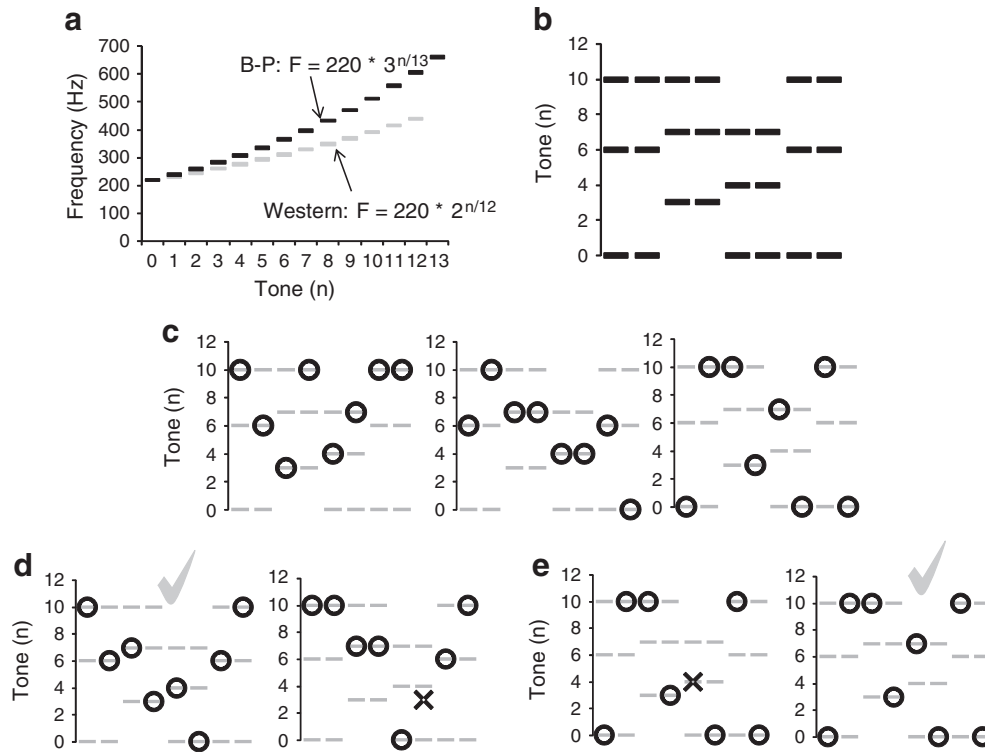
Fig. 1. Schematic representation of behavioral tasks. a) The frequency of each tone from which the musical grammar was generated. Dark lines represent tones in the Bohlen–Pierce (B–P) scale ($F = 220 * 3^{n/13}$); light grey lines represent tones in the Western scale ($F = 220 * 2^{n/12}$). b) Visual representation of the musical grammar. Each possible tone in the grammar is represented as a black line. The height of the line represents its tone, which maps onto a frequency as shown in Fig. 1a. c) Three examples of grammatical tone sequences presented during exposure. Each "o" represents one presented tone within a sequence. The grammar dictating possible pitches at each location (from Fig. 1b) is shown as light grey lines to illustrate the grammaticality of each tone in each sequence. d) One example of a generalization trial, where each "o" represents a presented pitch. The ungrammatical pitch, which deviates from the grammar as shown by the light grey lines, is represented as "x". e) One example of a recognition trial. The previously presented pitches are shown as "o" and the new (non-exposed) pitch is represented as "x". The grey check-marks indicate target choices for the generalization and recognition trials in d) and e) respectively.

Participants were not informed as to whether each trial was a recognition or generalization trial. As was demonstrated in previous studies (Loui et al., 2009b, 2010), the correct identification of novel grammatical sequences was an appropriate test of grammar learning, and is indicative of the ability to generalize learned structures into new instances.

Image acquisition

Structural MRI and DTI were performed using a 3-Tesla General Electric scanner. Anatomical images were acquired using a T1-weighted, three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo (MPRAGE) volume acquisition with a voxel resolution of $0.93 \times 0.93 \times 1.5$ mm. Diffusion images were acquired using a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (TE1 = 86.9 ms, TR = 10,000 ms, FOV = 240 mm, slice thickness = 2.5 mm resulting in a voxel size of 2.5 mm^3, no skip, NEX = 1, axial acquisition, 30 noncollinear directions with b-value of 1000 s/mm^2, 6 volumes with a b-value of 0 s/mm^2). Fractional anisotropy (FA) values, a measure of the degree of directional preference of water diffusion (Basser, 1995), were calculated within each brain voxel.

Image analysis. Images were processed using tools from FSL (www.fmrib.ox.ac.uk) and correlational analysis was done in SPM5. Images were corrected for eddy current and head motion (Jenkinson and Smith, 2001), and non-brain tissue was removed using the brain-extraction tool (BET) in FSL (Smith, 2002). A diffusion tensor model was fit to the data for each brain using dti_fit, generating an FA (fractional anisotropy) map for each subject. A probability distribution of fibre directions was then calculated for each voxel (Behrens et al., 2003). Estimates of two directions per voxel were modelled to account for crossing fibers (Behrens et al., 2007).

ROI definition

Regions of interest were drawn in the white matter underlying the posterior inferior frontal gyrus (IFG, BA 44 and 45), posterior superior temporal gyrus (STG, BA 22), and posterior middle temporal gyrus (MTG, BA 37) in each hemisphere. Regions were defined according to published DTI atlases (Wakana et al., 2004; Lawes et al., 2008) and were drawn on each individual subject's FA image by a single coder who was blind to the behavioral performance of each subject. Average and standard deviation of ROI volumes (number of voxels times the size of each voxel) and locations (xyz coordinates of the center of gravity) of each ROI are shown in Table 1 and average ROIs are shown in the T1 template brain in Fig. 2.

DTI tractography

Probabilistic tractography was initiated using seed regions of interest defined in each hemisphere of each individual brain in native diffusion image space. Tractography was initiated from frontal seed regions (LIFG, RIFG) to the ipsilateral superior temporal (LSTG, RSTG) and middle temporal (LMTG, RMTG) ROIs as waypoint masks. The

Table 1
Mean (standard error) in volumes and x y z coordinates (locations) of each region of interest.

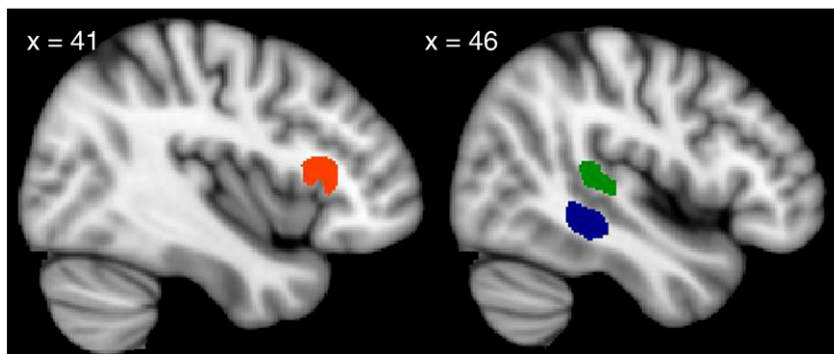|	Volume (mm^3)	x (mm)	y (mm)	z (mm)
LIFG	138.8 (11.3)	−46 (1.1)	21 (1.8)	8 (0.5)
LMTG	161.2 (13.2)	−49 (0.8)	−33 (1.9)	−10 (0.5)
LSTG	109.1 (7.2)	−49 (0.8)	−27 (1.6)	3 (0.4)
RIFG	112.3 (8.6)	41 (1.0)	20 (1.8)	8 (0.6)
RMTG	166.1 (20.1)	46 (1.0)	−31 (2.2)	−8 (0.4)
RSTG	112.1 (5.8)	46 (1.0)	−22.5 (1.9)	5 (0.5)

Fig. 2. ROI locations. Average volume and locations of the right-hemisphere ROIs: red = RIFG; green = RSTG; and blue = RMTG.

resulting tracts were labeled as dorsal arcuate fasciculus (IFG to STG) and ventral arcuate fasciculus (IFG to MTG) in each hemisphere, in accordance with previous studies (Glasser and Rilling, 2008; Friederici, 2009; Loui et al., 2009a). Tracts identified in each step were thresholded at their median intensity level to minimize extraneous tracts. Tract volume was computed as the number of voxels in the thresholded tract multiplied by the voxel size. The volume of each tract was exported for statistical comparisons.

To allow images to be visualized and compared directly between subjects, all subjects' tracts and FA images were aligned and normalized to the FSL 1 mm FA template using both linear registration (FLIRT) (Jenkinson and Smith, 2001) and nonlinear registration tools (FNIRT) in the FSL library. To enable a correlational analysis with behavioral variables across all subjects, tracts were summed between subjects and a robust threshold of 10% of the tract intensity was then applied to remove extraneous tracts with intensities that fell below the threshold. The resulting "canonical" tract, representing a robust estimate of each tract in the entire group of subjects, was binarized and then converted to Analyze format for analysis in SPM5. A regression analysis was done on all subjects' normalized FA images in SPM5 using the canonical tract as an explicit mask, with the regressors of generalization scores, recognition scores, and IQ performance. This regression analysis yielded voxels with FA values that were significantly correlated with behavioral performance at a corrected level. The use of the canonical tract as a mask improves statistical power by reducing the number of statistical comparisons to the hypothesized search space, while avoiding biasing our between-subject comparisons by constraining the search space to be the same for all subjects.

Results

Behavioral results

Average IQ, as assessed using Shipley verbal and abstract scaled composite scores (a measure which correlates highly with general intelligence (Paulson and Lin, 1970)), was 118.5 (range = 108–126). Pitch discrimination thresholds ranged from 1.75 Hz to 56 Hz around the center frequency of 500 Hz. Confirming previous results (Loui et al., 2009a, 2010), subjects were able to identify grammatical pitch sequences as being more familiar, demonstrating successful learning of the artificial grammar. On average, subjects performed reliably above chance at generalization (as confirmed by a one-sample t-test against the chance level of 50%: $t(15) = 6.2$, $p < 0.001$), but not at recognition ($t(15) = 1.8$, n.s.). Performance levels ranged from 30% to 80% correct in the recognition task and from 40% to 100% correct on the generalization task.

Tract volume predicts learning performance

The volume of tracts identified between RIFG and RMTG was significantly and positively correlated with performance on the gen-

eralization task ($r = 0.53$, $t(14) = 2.35$, $p = 0.03$, two-tailed, Fig. 3), confirming that better learners possessed larger volume in their right ventral AF. This correlation was not observed for the control task of recognition, for pitch discrimination, or for the baseline IQ test, confirming that between-subject differences in tract volume between RIFG and RMTG are related to individual differences in learning, rather than to memory, perceptual ability, or IQ more generally.

Consistent with previous results in the literature (Loui et al., 2009a), tract volume between RIFG and RSTG was significantly correlated with pitch discrimination threshold ($r_S = -0.50$, $p = 0.048$, two-tailed). However, tract volume between RIFG and RSTG was not significantly correlated with recognition or generalization. To tease apart the contributions of the RIFG–RSTG (dorsal) tract from the RIFG–RMTG (ventral) tract, voxels within the dorsal tract were subtracted from voxels within the ventral tract to remove the overlapping voxels between the dorsal and ventral AF, so that only voxels in the right ventral AF and not the right dorsal AF were included in further analysis. Tract volume in the resulting partial ventral tract was still significantly correlated with generalization scores ($r = 0.44$, $p < 0.05$), confirming that generalization ability is associated with tract volume in the right ventral AF.

Tract volume between left IFG and left MTG was significantly correlated with tract volume between right IFG and right MTG ($r = 0.59$, $t(14) = 2.73$, $p = 0.016$). However, no significant correlation was observed between tract volumes in the left hemisphere and generalization, recognition, pitch discrimination, or IQ scores. This disassociation confirms that homologous arcuate structures are mostly symmetrical, but also sensitive to differences that constitute hemispheric asymmetry, and that pitch-related learning abilities are more associated with the right than the left hemisphere.

FA in right ventral AF correlates with generalization

Having identified the right ventral AF as being related to generalization performance in volume, an additional step was to identify portions of the right ventral AF with FA values that were related to generalization scores. To identify voxels within the tract that were correlated with behavioral measures, the canonical tract (see Methods section) was used as a mask over each individual's FA image, so that the variable of FA was regressed on generalization scores for all voxels within the right ventral AF. The regression yielded a single cluster of nine voxels in the inferior parietal lobe, in white matter in the right temporal-parietal junction underlying the supramarginal gyrus (xyz coordinates 36, –49, and 27), where FA was significantly predicted by generalization scores at the $p < 0.05$ (FWE-corrected) level. Results from this regression analysis are shown in Fig. 4. The same analysis was not significant when using recognition or IQ scores as a regressor. The observation that FA in the right temporal-parietal junction is significantly correlated with a learning task, but not with a control memory task that appears similar but taps into different
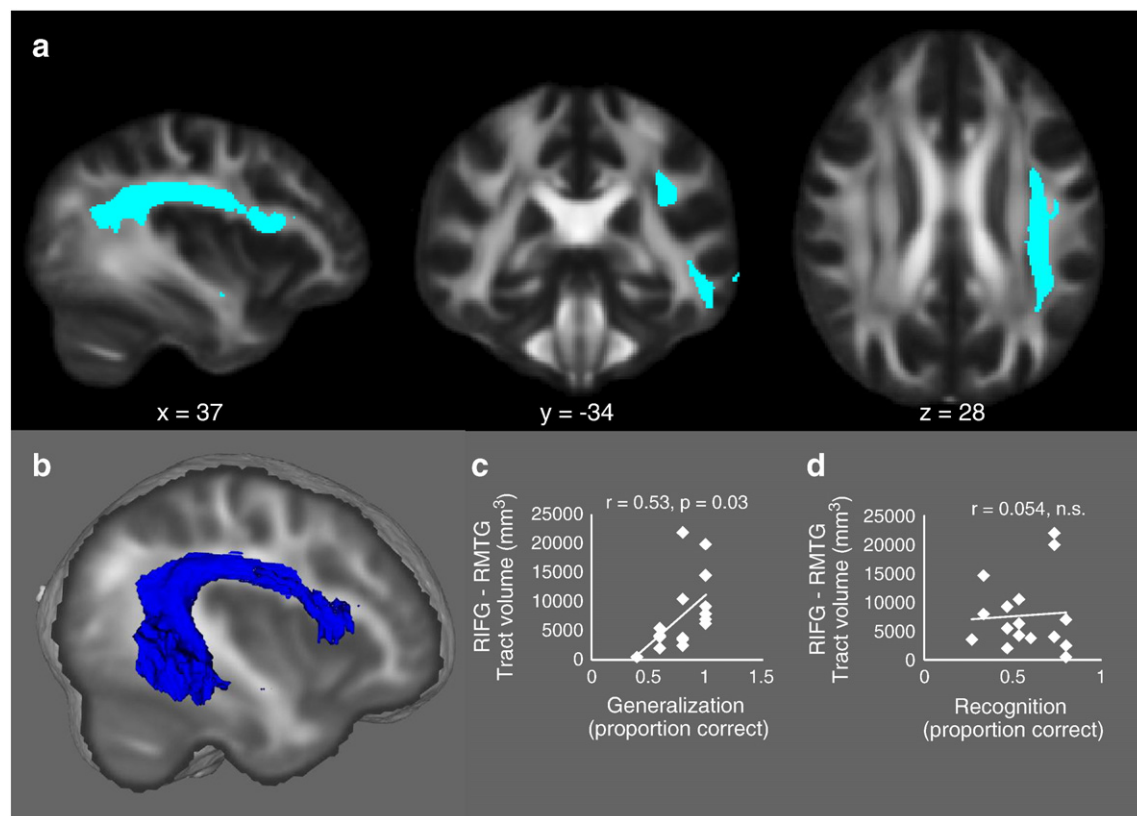
Fig. 3. AF volume correlates with grammar learning. a) Tracts identified between RIFG and RMTG in axial, coronal, and sagittal views overlaid on the FA template. b) 3D view of tracts identified between RIFG and RMTG. c) Tract volume and generalization performance, showing significantly positive correlation. d) In contrast to c), no significant relationship was observed between tract volume and performance on the control task of recognition.

cognitive mechanisms, suggests that the right ventral AF may have a different structure in low learners compared to high learners, and provides further support for the role of the right AF in supporting pitch-related grammar learning. Furthermore, the positive relationship between generalization score and FA in the significant cluster remained significant at the FWE level even after the contribution of frequency discrimination thresholds was partialled out using partial correlation ($r = 0.90$, $p < 0.05$ FWE), suggesting that white matter underlying the right temporal–parietal junction is necessary for pitch-related grammar learning independent of individual differences in pitch discrimination skills.

Fig. 5 illustrates the location of the significant FA cluster relative to the right dorsal and ventral AF. The significant FA cluster was

within the ventral tract and not the dorsal tract (Figs. 5a and b). The FA cluster was within the right ventral AF even after the overlapping voxels between dorsal and ventral tracts were subtracted from the ventral tract (as described in Tract volume predicts learning performance section; Fig. 5c), thus demonstrating that white matter in the right ventral AF, rather than in overlapping regions between dorsal and ventral AF, is predictive of performance on the grammar generalization task.

Discussion

The present study showed that white matter connectivity in the right ventral AF is important for grammar learning in the domain of
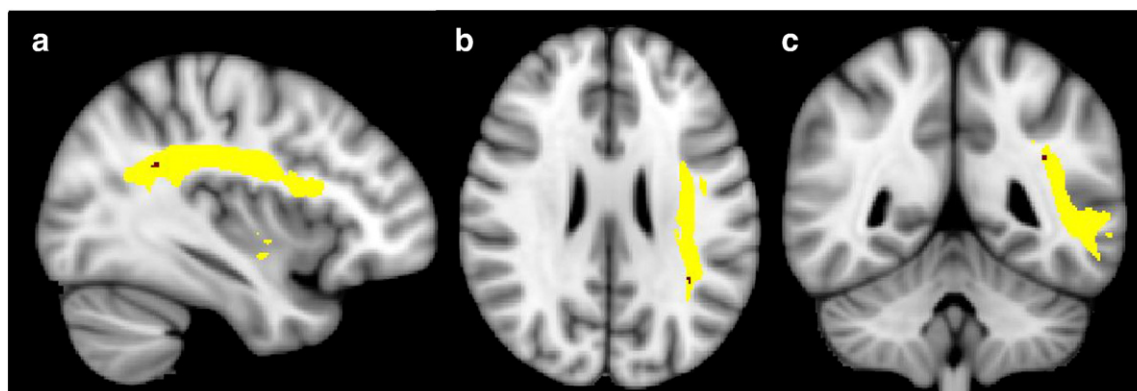

Fig. 4. Results from the regression analysis overlaid on the T1 template. The canonical tract mask is shown in yellow, and voxels with FA values that are significantly correlated with generalization scores at the $p < 0.05$ (FWE corrected) level are shown in dark red.
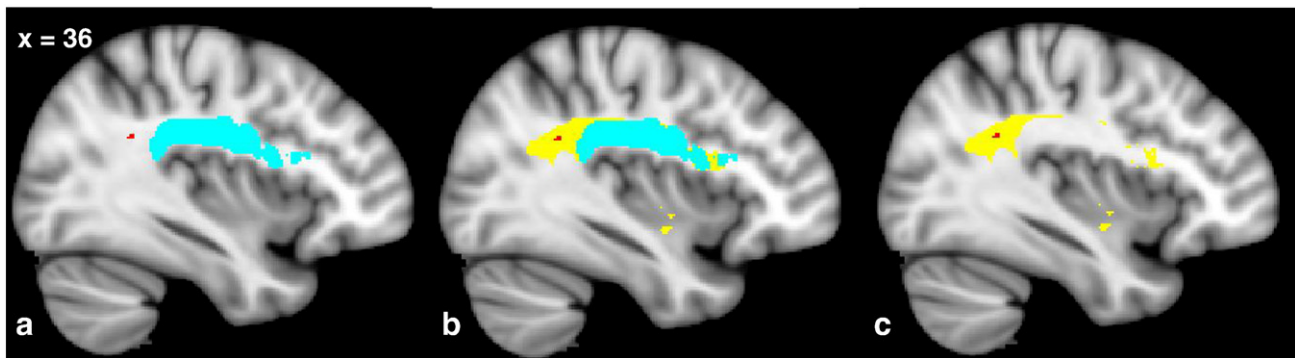
Fig. 5. FA cluster in right ventral AF. a) The cluster of voxels with FA values that are significantly correlated with generalization behavior (red), overlaid on the T1 template with RIFG–RSTG (dorsal) tracts (blue) and RIFG–RMTG (ventral) tracts (yellow), showing some overlap between dorsal and ventral tracts. b) The same FA cluster (red) overlaid on the T1 template with right dorsal tracts only (blue), showing that the significant region is outside the dorsal tract space. c) The same significant cluster overlaid on the T1 template with partial ventral tracts (yellow) that remain after the voxels that overlap with the dorsal tract are subtracted from the ventral tract, demonstrating that the region with significant FA correlation is in the right ventral AF.

pitch. The associations between behavioral performance and tract volume and FA in the right ventral AF suggest that grammar learning, at least in the domain of pitch, can rely on intact white matter connectivity in the right hemisphere. As the grammar used in this study consists of individual pitches that are embedded into chord structures, the stimuli follow the rules of a phrase structure grammar where pitches are organized in hierarchical levels. In that regard, our results are congruent with previous reports of the role of connectivity to Broca's area in learning a phrase structure grammar (Friederici et al., 2006), except that the materials used here are musical pitches rather than linguistic syllables. As musical pitch is a domain that is previously shown to be biased for right-hemisphere processing (Hyde et al., 2008; Zatorre et al., 2002; Zatorre and Samson, 1991; Klostermann et al., 2009), the right-hemisphere effects may be due to the pitched stimuli used in this study. Through a series of behavioral and DTI correlations, our data show that people with reduced connectivity in the right hemisphere are impaired in acquiring grammatical structure in the domain of pitch. This grammar acquisition ability can be independent in its neural substrates from pitch memory, pitch discrimination, or general intelligence, as shown by our recognition control task (which is a similar task on the surface but assesses a different type of knowledge from generalization tests) as well as baseline tests for IQ and pitch discrimination.

Our behavioral and DTI results demonstrate substantial individual variability in the ability to learn new grammatical structures, which are localized to the right ventral AF. Grammar learning is a complex and demanding task that may require multiple brain systems (such as perceptual analysis, categorization, attention, working memory, recursion, and sensitivity to statistical regularities) that are assessed by the generalization task used here. While the present volume and FA results show that white matter in the right ventral AF is correlated with the generalization task, whether the white matter connects a network of grey matter hubs that subserve one or more of these functions, or whether the white matter subserves activity in a single grey matter region that may be uniquely linked to grammar learning, is still an open question. Nevertheless, because of our control tests of recognition, pitch discrimination, and IQ testing, we believe that the present findings in the right ventral AF and the right temporal–parietal junction are fairly independent of working memory and perceptual ability. We believe that the current paradigm was effective in capturing grammar learning ability in the domain of pitch, which is reflected in the white matter integrity of the right ventral AF. This learning ability may be analogous to the statistical learning mechanism that is well documented in language learning literature (Saffran et al., 1996). It is now well-established that infants are able to extract the statistical properties (frequencies and probabilities) of sounds in the environment (Saffran et al., 1996), and this ability is thought to be

important for various aspects of language learning, from word segmentation (Aslin et al., 1998) to higher-order aspects of language such as syntax and semantics (Hudson Kam and Newport, 2005). In the domain of music, especially of musical pitch, the ability to learn from statistical regularities has been shown in adults as well as eight-month-old infants (Saffran et al., 1999), and is sensitive to gestalt cues (Creel et al., 2004) and the combination of syllables with pitches as in song (Schön et al., 2008). This statistical learning system is closely related to the implicit learning mechanism that is assessed using artificial grammars (Reber, 1967; Perruchet and Pacton, 2006). This type of implicit learning is tied to the dopaminergic system as shown in pharmacological studies (de Vries et al., 2010), and is related to the Broca's area as shown in neuroimaging and brain-stimulation studies (Petersson et al., 2003; Forkstam et al., 2006; Floel et al., 2008, 2009; de Vries et al., 2009; Friederici et al., 2006). By using a novel system of pitch sequences, our experiment design ensures that all sound stimuli presented during the study are novel and relatively unaffected by long-term memory or prior associations. Given that the learning process took place within an hour, it is unlikely that subjects could have developed white matter changes within such a short time window. Thus, we believe that the white matter differences observed between high and low learners reflect neurobiological differences in learning ability.

Previous studies have shown that FA and diffusivity measures in homologous white matter structures between left and right hemispheres are highly (but not perfectly) correlated (Wahl et al., 2010). Despite significant symmetry between homologous tract volumes in our data, left-hemisphere tract volumes were not correlated with generalization performance in our results, suggesting that pitch-related learning abilities are tied to inter-subject variability in white matter of the right hemisphere that is unexplained by homologous variability in the left hemisphere.

FA is a measure of the degree of directional preference in water diffusion (Basser, 1995), and has been associated with myelination, coherence of fibers, and axonal membrane integrity (Jones, 2008; Beaulieu, 2002). The present results show that FA values in the right hemisphere underlying the supramarginal gyrus, along the course of the AF, were significantly correlated with the ability to acquire language-like grammatical structure from pitched sequences. Although the present methods cannot tease apart possible biological explanations for observed FA effects in the right temporal–parietal junction, we suspect that high learners may have more myelination or more direct fibers between frontal and temporal lobes, in comparison to low learners who may have lower myelination or a different morphology such as more indirect fibers terminating in the parietal lobe, thus resulting in morphological differences of the right ventral arcuate fasciculus between high learners and low learners. Catani

et al. have documented that tractography-defined pathways in the arcuate fasciculus have multiple segments. Some of these segments run directly between frontal and temporal lobes (passing through the parietal lobe), whereas other segments run indirectly between terminations in the parietal lobe and the frontal or temporal lobes (Catani et al., 2005; Catani and Thiebaut de Schotten, 2008). It is also documented that the arcuate fasciculus differs in morphology between individuals, but how individual variability in AF morphology may subserve behavioral differences is not yet well understood. On the other hand, performing accurately in the present generalization task requires a conjunction of the cognitive processes previously shown to involve the supramarginal gyrus and right temporal–parietal junction, such as word learning in a second language (Jeong et al., 2010; Veroude et al., 2010; Raboyeau et al., 2010), pitch memory (Vines et al., 2006), and mathematical processing (Wu et al., 2009). Based on the present data in combination with previous literature on the AF and on the supramarginal gyrus and right temporal–parietal junction, we believe that the temporal portion of the arcuate fasciculus may be more directly and preferentially connected with the frontal lobe through this region in high learners, resulting in more efficient connectivity between frontal and temporal areas, which gives rise to better learning ability. The same efficient fronto-temporal connectivity has also been shown to lead to larger electrophysiological signatures of pitch processing in superior learners as observed in previous studies (Alho et al., 1994; Alain et al., 1998; Loui et al., 2009b).

Conclusions

Taken together, the present results indicate that nonlinguistic grammar learning is not solely a left-lateralized process: white matter in the right hemisphere, specifically in the right ventral arcuate fasciculus, is important for pitch-based grammar learning. The ability to generalize in the domain of pitch is specifically correlated with tract volume of the right ventral arcuate fasciculus and with white matter integrity underlying the right temporal–parietal junction. By identifying neural correlates of individual learning differences in the domain of pitch, the present results demonstrate a role of the right hemisphere in grammar learning. The present results suggest that individual variability in white matter integrity of the right ventral AF may have implications for language learning and development.

Acknowledgments

References

Alain, C., Woods, D.L., Knight, R.T., 1998. A distributed cortical network for auditory sensory memory in humans. Brain Res. 812, 23–37.

Alho, K., Woods, D.L., Algazi, A., Knight, R.T., Naatanen, R., 1994. Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalogr. Clin. Neurophysiol. 91, 353–362.

Aslin, R., Saffran, J.R., Newport, E., 1998. Computation of conditional probability statistics by 8-month old infants. Psychol. Sci. 9, 321–324.

Basser, P.J., 1995. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed. 8, 333–344.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system — a technical review. NMR Biomed. 15, 435–455.

Behrens, T.E., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M., Smith, S.M., 2003. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn. Reson. Med. 50, 1077–1088.

Behrens, T.E., Berg, H.J., Jbabdi, S., Rushworth, M.F., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage 34, 144–155.

Catani, M., Mesulam, M., 2008a. The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. Cortex 44, 953–961.

Catani, M., Mesulam, M., 2008b. What is a disconnection syndrome? Cortex 44, 911–913.

Catani, M., Thiebaut de Schotten, M., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44, 1105–1132.

Catani, M., Jones, D.K., ffytche, D.H., 2005. Perisylvian language networks of the human brain. Ann. Neurol. 57, 8–16.

Chiang, M.-C., Barysheva, M., Shattuck, D.W., Lee, A.D., Madsen, S.K., Avedissian, C., Klunder, A.D., Toga, A.W., McMahon, K.L., de Zubicaray, G.I., Wright, M.J., Srivastava, A., Balov, N., Thompson, P.M., 2009. Genetics of brain fiber architecture and intellectual performance. J. Neurosci. 29, 2212–2224.

Cornsweet, T.N., 1962. The staircase-method in psychophysics. Am. J. Psychol. 75, 485–491.

Creel, S.C., Newport, E.L., Aslin, R.N., 2004. Distant melodies: statistical learning of nonadjacent dependencies in tone sequences. JEP Learn. Mem. Cogn. 30, 1119–1130.

de Vries, M.H., Barth, A.C., Maiworm, S., Knecht, S., Zwitserlood, P., Floel, A., 2009. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J. Cogn. Neurosci. 22, 2427–2436.

de Vries, M.H., Ulte, C., Zwitserlood, P., Szymanski, B., Knecht, S., 2010. Increasing dopamine levels in the brain improves feedback-based procedural learning in healthy participants: an artificial-grammar-learning experiment. Neuropsychologia 48, 3193–3197.

Deutsch, G.K., Dougherty, R.F., Bammer, R., Siok, W.T., Gabrieli, J.D., Wandell, B., 2005. Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex 41, 354–363.

Doricchi, F., Thiebaut de Schotten, M., Tomaiuolo, F., Bartolomeo, P., 2008. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. Cortex 44, 983–995.

Floel, A., Rosser, N., Michka, O., Knecht, S., Breitenstein, C., 2008. Noninvasive brain stimulation improves language learning. J. Cogn. Neurosci. 69, 32–40.

Flöel, A., de Vries, M.H., Scholz, J., Breitenstein, C., Johansen-Berg, H., 2009. White matter integrity in the vicinity of Broca's area predicts grammar learning success. Neuroimage 47, 1974–1981.

Forkstam, C., Hagoort, P., Fernandez, G., Ingvar, M., Petersson, K.M., 2006. Neural correlates of artificial syntactic structure classification. Neuroimage 32, 956–967.

Foxton, J.M., Dean, J.L., Gee, R., Peretz, I., Griffiths, T.D., 2004. Characterization of deficits in pitch perception underlying 'tone deafness'. Brain 127, 801–810.

Friederici, A.D., 2009. Pathways to language: fiber tracts in the human brain. Trends Cogn. Sci. 13, 175–181.

Friederici, A.D., Bahlmann, J.r., Heim, S., Schubotz, R.I., Anwander, A., 2006. The brain differentiates human and non-human grammars: functional localization and structural connectivity. Proc. Natl. Acad. Sci. U.S.A. 103, 2458–2463.

Geschwind, N., 1965. Disconnexion syndromes in animals and man. I. Brain 88, 237–294.

Glasser, M.F., Rilling, J.K., 2008. DTI tractography of the human brain's language pathways. Cereb. Cortex 11, 2471–2482.

Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8, 393–402.

Hudson Kam, C., Newport, E., 2005. Regularizing unpredictable variation: the roles of adult and child learners in language formation and change. Lang. Learn. Dev. 1, 151–195.

Hyde, K.L., Lerch, J.P., Zatorre, R.J., Griffiths, T.D., Evans, A.C., Peretz, I., 2007. Cortical thickness in congenital amusia: when less is better than more. J. Neurosci. 27, 13028–13032.

Hyde, K.L., Peretz, I., Zatorre, R.J., 2008. Evidence for the role of the right auditory cortex in fine pitch resolution. Neuropsychologia 46, 632–639.

Hyde, K.L., Zatorre, R.J., Peretz, I., in press. Functional MRI evidence of an abnormal neural network for pitch processing in congenital amusia. Cereb. Cortex. May 21 (Electronic publication ahead of print).

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5, 143–156.

Jeong, H., Sugiura, M., Sassa, Y., Wakusawa, K., Horie, K., Sato, S., Kawashima, R., 2010. Learning second language vocabulary: neural dissociation of situation-based learning and text-based learning. Neuroimage 50, 802–809.

Johansen-Berg, H., 2010. Behavioural relevance of variation in white matter microstructure. Curr. Opin. Neurol. 23, 351–358.

Jones, D.K., 2008. Studying connections in the living human brain with diffusion MRI. Cortex 44, 936–952.

Jung, R.E., Grazioplene, R., Caprihan, A., Chavez, R.S., Haier, R.J., 2010. White Matter Integrity, Creativity, and Psychopathology: Disentangling Constructs with Diffusion Tensor Imaging. PLoS ONE 5, e9818.

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J.D., Moseley, M.E., Poldrack, R.A., 2000. Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron 25, 493–500.

Klostermann, E.C., Loui, P., Shimamura, A.P., 2009. Activation of right parietal cortex during memory retrieval of non-linguistic auditory stimuli. Cogn. Affect. Behav. Neurosci. 9, 242–248.

Krumhansl, C.L., 1987. General properties of musical pitch systems: some psychological considerations. In: Sundberg, J. (Ed.), Harmony and Tonality. Royal Swedish Academy of Music, Stockholm.

Lawes, I.N.C., Barrick, T.R., Murugam, V., Spierings, N., Evans, D.R., Song, M., Clark, C.A., 2008. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. Neuroimage 39, 62–79.

Lichtheim, L., 1885. On aphasia. Brain 7, 433–484.

Liu, F., Patel, A.D., Fourcin, A., Stewart, L., 2010. Intonation processing in congenital amusia: discrimination, identification and imitation. Brain 133, 1682–1693.

Loui, P., Wessel, D.L., 2008. Learning and liking an artificial musical system: effects of set size and repeated exposure. Musicae Scientiae 12, 207–230.

Loui, P., Guenther, F.H., Mathys, C., Schlaug, G., 2008. Action-perception mismatch in tone-deafness. Curr. Biol. 18, R331–R332.

Loui, P., Alsop, D., Schlaug, G., 2009a. Tone-deafness: a disconnection syndrome? J. Neurosci. 29, 10215–10220.

Loui, P., Wu, E.H., Wessel, D.L., Knight, R.T., 2009b. A generalized mechanism for perception of pitch patterns. J. Neurosci. 29, 454–459.

Loui, P., Wessel, D.L., Hudson Kam, C.L., 2010. Humans rapidly learn grammatical structure in a new musical scale. Music Percept. 27, 377–388.

Mabbott, D.J., Rovet, J., Noseworthy, M.D., Smith, M.L., Rockel, C., 2009. The relations between white matter and declarative memory in older children and adolescents. Brain Res. 1294, 80–90.

Mathews, M.V., Pierce, J.R., Reeves, A., Roberts, L.A., 1988. Theoretical and experimental explorations of the Bohlen–Pierce scale. J. Acoust. Soc. Am. 84, 1214–1222.

Meinzer, M., Mohammadi, S., Kugel, H., Schiffbauer, H., Flöel, A., Albers, J., Kramer, K., Menke, R., Baumgärtner, A., Knecht, S., Breitenstein, C., Deppe, M., 2010. Integrity of the hippocampus and surrounding white matter is correlated with language training success in aphasia. Neuroimage 53, 283–290.

Nucifora, P.G., Verma, R., Melhem, E.R., Gur, R.E., Gur, R.C., 2005. Leftward asymmetry in relative fiber density of the arcuate fasciculus. NeuroReport 16, 791–794.

Paulson, M.J., Lin, T., 1970. Predicting WAIS IQ from Shipley–Hartford scores. J. Clin. Psychol. 26, 453–461.

Peretz, I., Ayotte, J., Zatorre, R.J., Mehler, J., Ahad, P., Penhune, V.B., Jutras, B., 2002. Congenital amusia: a disorder of fine-grained pitch discrimination. Neuron 33, 185–191.

Perruchet, P., Pacton, S., 2006. Implicit learning and statistical learning: one phenomenon, two approaches. Trends Cogn. Sci. 10, 233–238.

Petersson, K.M., Forkstam, C., Ingvar, M., 2003. Artificial syntactic violations activate Broca's region. Cogn. Sci. 28, 383–407.

Raboyeau, G., Marcotte, K., Adrover-Roig, D., Ansaldo, A.I., 2010. Brain activation and lexical learning: the impact of learning phase and word type. Neuroimage 49, 2850–2861.

Rauschecker, A.M., Deutsch, G.K., Ben-Shachar, M., Schwartzman, A., Perry, L.M., Dougherty, R.F., 2009. Reading impairment in a patient with missing arcuate fasciculus. Neuropsychologia 47, 180–194.

Reber, A.S., 1967. Implicit learning of artificial grammar. J. Verbal Learn. Verbal Behav. 6, 855–863.

Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., Behrens, T.E., 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nat. Neurosci. 11, 426–428.

Rodrigo, S., Naggara, O., Oppenheim, C., Golestani, N., Poupon, C., Cointepas, Y., Mangin, J.F., Le Bihan, D., Meder, J.F., 2007. Human subinsular asymmetry studied by diffusion tensor imaging and fiber tracking. AJNR Am. J. Neuroradiol. 28, 1526–1531.

Saffran, J.R., Aslin, R.N., Newport, E., 1996. Statistical learning by 8-month-old infants. Science 274, 1926–1928.

Saffran, J.R., Johnson, E.K., Aslin, R.N., Newport, E.L., 1999. Statistical learning of tone sequences by human infants and adults. Cognition 70, 27–52.

Sasson, E., Doniger, G.M., Pasternak, O., Assaf, Y., 2010. Structural correlates of memory performance with diffusion tensor imaging. Neuroimage 50, 1231–1242.

Schön, D., Boyer, M., Moreno, S., Besson, M., Peretz, I., Kolinsky, R., 2008. Songs as an aid for language acquisition. Cognition 106, 975–983.

Sethares, W., 2004. Tuning Timbre Spectrum Scale. Springer-Verlag.

Shipley, W.C., 1940. A self-administering scale for measuring intellectual impairment and deterioration. J. Psychol. 9, 371–377.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.

Tsang, J.M., Dougherty, R.F., Deutsch, G.K., Wandell, B.A., Ben-Shachar, M., 2009. Frontoparietal white matter diffusion properties predict mental arithmetic skills in children. Proc. Natl. Acad. Sci. 106, 22546–22551.

Vernooij, M.W., Smits, M., Wielopolski, P.A., Houston, G.C., Krestin, G.P., van der Lugt, A., 2007. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. Neuroimage 35, 1064–1076.

Veroude, K., Norris, D.G., Shumskaya, E., Gullberg, M., Indefrey, P., 2010. Functional connectivity between brain regions involved in learning words of a new language. Brain Lang. 113, 21–27.

Vines, B.W., Schnider, N.M., Schlaug, G., 2006. Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. NeuroReport 17, 1047–1050.

Wahl, M., Li, Y.-O., Ng, J., LaHue, S.C., Cooper, S.R., Sherr, E.H., Mukherjee, P., 2010. Microstructural correlates of white matter tracts in the human brain. Neuroimage 51, 531–541.

Wakana, S., Jiang, H., Nagae-Poetscher, L.M., van Zijl, P.C., Mori, S., 2004. Fiber tract-based atlas of human white matter anatomy. Radiology 230, 77–87.

Wu, S.S., Chang, T.T., Majid, A., Caspers, S., Eickhoff, S.B., Menon, V., 2009. Functional heterogeneity of inferior parietal cortex during mathematical cognition assessed with cytoarchitectonic probability maps. Cereb. Cortex 19, 2930–2945.

Zatorre, R.J., Samson, S., 1991. Role of the right temporal neocortex in retention of pitch in auditory short-term memory. Brain 114 (Pt 6), 2403–2417.

Zatorre, R.J., Evans, A.C., Meyer, E., 1994. Neural mechanisms underlying melodic perception and memory for pitch. J. Neurosci. 14, 1908–1919.

Zatorre, R.J., Belin, P., Penhune, V.B., 2002. Structure and function of auditory cortex: music and speech. Trends Cogn. Sci. 6, 37–46.

Zicarelli, D., 1998. An extensible real-time signal processing environment for Max. Proceedings of the International Computer Music Conference. University of Michigan, Ann Arbor, USA.