

White Matter Structure Changes as Adults Learn a Second Language

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Abstract

■ Traditional models hold that the plastic reorganization of brain structures occurs mainly during childhood and adolescence, leaving adults with limited means to learn new knowledge and skills. Research within the last decade has begun to overturn this belief, documenting changes in the brain's gray and white matter as healthy adults learn simple motor and cognitive skills [Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., et al. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*, 48, 3878–3883, 2010; Taubert, M., Draganski, B., Anwander, A., Müller, K., Horstmann, A., Villringer, A., et al. Dynamic properties of human brain structure: Learning-related changes in cortical areas and associated fiber connections. *The Journal of Neuroscience*, 30, 11670–11677, 2010; Scholz, J., Klein, M. C., Behrens, T. E. J., & Johansen-Berg, H. Training induces changes in white-matter architecture. *Nature Neuroscience*, 12, 1370–1371, 2009; Draganski, B., Gaser, C., Busch, V., Schuirer, G., Bogdahn, U., & May, A. Changes in grey matter induced by training. *Nature*, 427, 311–312, 2004]. Although the

significance of these changes is not fully understood, they reveal a brain that remains plastic well beyond early developmental periods. Here we investigate the role of adult structural plasticity in the complex, long-term learning process of foreign language acquisition. We collected monthly diffusion tensor imaging scans of 11 English speakers who took a 9-month intensive course in written and spoken Modern Standard Chinese as well as from 16 control participants who did not study a language. We show that white matter reorganizes progressively across multiple sites as adults study a new language. Language learners exhibited progressive changes in white matter tracts associated with traditional left hemisphere language areas and their right hemisphere analogs. Surprisingly, the most significant changes occurred in frontal lobe tracts crossing the genu of the corpus callosum—a region not generally included in current neural models of language processing. These results indicate that plasticity of white matter plays an important role in adult language learning and additionally demonstrate the potential of longitudinal diffusion tensor imaging as a new tool to yield insights into cognitive processes. ■

INTRODUCTION

Language processing has traditionally been modeled as a primarily left-hemispheric cortical network involving a frontal language production region known as Broca's area and a temporal language-understanding region known as Wernicke's area. Recent neuroimaging research has challenged this view by uncovering a widespread network of language processing areas in both hemispheres of the brain (Price, 2010; Glasser & Rilling, 2008). Current models identify several distinct areas whose complex interactions enable the understanding and production of phonology, semantics, syntax, and prosody (Price, 2010; Friederici, 2009).

A sensitive period is thought to exist during which children can learn multiple languages with relative ease compared with adults, but little is known about the neural bases of these developmental changes in learning ability (Thomas & Johnson, 2008). Some studies have suggested that these differences may in part be explained by differences in the learning strategies employed by children and

adults (Hudson Kam & Newport, 2005). Imaging studies have found differences between how native and second languages are processed in children and adults (Kim, Relkin, Lee, & Hirsch, 1997, but see Stowe & Sabourin, 2005) and regions whose activity may influence language learning (Tan et al., 2011; Wang, Sereno, Jongman, & Hirsch, 2003). Additionally, neural changes have been found to occur with adult acquisition of reading skills (Kwok et al., 2011; Carreiras et al., 2009). These results provide a glimpse into functional changes that arise with acquisition of a new language, but the role of structural plasticity in adult language learning is unknown.

To investigate this, we used longitudinal diffusion tensor imaging (DTI) to track the structural white matter changes that occur with language learning. We found changes in white matter both within and beyond those regions identified in current neural models of language processing.

DTI measures the magnitude and direction of water diffusion. Such diffusion is isotropic in regions where water can move unimpeded, as in the brain's ventricles, and is anisotropic in regions that restrict diffusion in one direction more than others. Diffusion is typically anisotropic in the axon bundles of the brain's white matter tracts

because intracellular water moves more freely along an axon than across an axonal cell membrane. Several parameters linked to aspects of white matter organization and development can be reconstructed from multi-directional diffusion tensor data. At a given brain location, these data can be reduced to a single scalar, fractional anisotropy (FA), that quantifies the degree to which water diffuses equally in all directions (FA = 0) or only along a line (FA = 1) while ignoring the magnitude and direction of that diffusion. FA has been associated with variations in axon count, density of axonal packing, and myelination. In contrast, mean diffusivity (MD) is a tensor-derived scalar that characterizes the overall magnitude of diffusion (water in a fluid-filled ventricle would have high MD whereas that in bone would have low MD). MD generally decreases with increased myelination. Another tensor-derived scalar, axial diffusivity (λ_{\parallel}), characterizes freedom of diffusion along the principal axis of diffusion and is associated with axon diameter, count, and density. Finally, radial diffusivity (λ_{\perp}) characterizes freedom perpendicular to the principal axis of diffusion and decreases with increased myelination (Beaulieu, 2011).

METHODS

Participants

The study was approved by the Dartmouth Committee for the Protection of Human Subjects. Fifteen female and 12 male healthy Dartmouth students gave informed consent according to the institutional review board policy. All participants were right-handed as assessed by self-report. Mean participant age was 20.05 years ($SD = 1.89$ years). All 27 participants were regularly enrolled college students. Eleven participants took a three-term intensive Modern Standard Chinese language course during the study period, whereas the 16 control participants did not study a language. Experimental and control groups were matched for GPA and identical general linear model (GLM) analyses on age- and gender-matched subgroups yielded results matching those described in the text.

Language Course

The 9-month Dartmouth language course served as an introduction to spoken and written Modern Standard Chinese for students with no prior background in the language. Classes met nine times (7.5 hr) per week and focused on pronunciation, basic patterns of speech, spoken language drills, and reading and writing traditional and simplified characters. Students were assigned extensive homework in the course as well.

Imaging

MR imaging data were acquired on a 3T Philips Achieva Intera scanner with an eight-channel sense head coil. One T1-weighted structural image was acquired for each partici-

pant during the course of the study using a magnetization-prepared rapid acquisition gradient-echo sequence (repetition time = 9.9 msec; echo time = 4.6 msec; flip angle = 8°; field of view = 240 × 240 mm; 160 sagittal slices; voxel size = 0.9375 × 0.9375 × 1 mm; acquisition time = 6.78 min). A median of 8 (195 total) diffusion-weighted scans were collected for each subject, with a mean of 33.11 days ($SD = 11.00$ days) in between each scan (32 directions; $b = 1000$ sec/mm², repetition time = 9.014 sec, echo time = 91 msec, flip angle = 90°, field of view = 240 × 240 mm, 70 axial slices, voxel size = 1.875 × 2 × 1.875 mm, one additional $b = 0$ sec/mm² image, acquisition time = 5.42 min).

Analysis

Data were analyzed using a combination of FMRIB Software Library (FSL) analysis package (Smith et al., 2004), the FreeSurfer image analysis suite (Dale, Fischl, & Sereno, 1999), and MATLAB software developed in-house. Two analyses were conducted: a whole-brain GLM and a tract-based GLM.

Whole-brain GLM

Diffusion parameters (FA, MD, λ_{\parallel} , and λ_{\perp}) for each diffusion-weighted data set were reconstructed, z -transformed by data set to reduce the effect of potential equipment changes over time, and normalized to a standard 2 × 2 × 2 mm³ template in Montreal Neurological Institute space via FSL's FNIRT nonlinear registration tool. Each diffusion parameter was then analyzed across participants using the GLM described in Results. Only data from white matter were analyzed, as determined by FreeSurfer's automatic segmentation algorithm. Additionally, each voxel location in standard space was only included in the analyses if at least 75% of participants had white matter at that location. Even for locations that passed the 75% threshold, data from non-white matter at those locations were excluded from the analyses. This allowed for as much of the white matter data as possible to be included without risking errors due to potential misregistration between white matter and non-white matter regions. t Contrasts were calculated for each diffusion parameter to test for voxels with $m_E > m_C$ and $m_E < m_C$ using FSL's permutation-based nonparametric inference tool (randomise; 5000 permutations within-participant only). Threshold-free cluster enhancement was used to find significant clusters (Smith & Nichols, 2009). All reported p values are false detection rate (FDR) corrected. *Time course*: For each participant, the same GLM analysis was performed on FA data excluding that subject. The subject's FA data at voxels with $p < .05$ (uncorrected) under this analysis were then averaged to compute one mean value for each time point. Excluding the data to be averaged from the voxel selection step prevented Type I errors. Results for each participant were converted to percentage change from the $t = 0$ value of a best-fit line for that subject's data. All data were

then binned by month and plotted along with a best-fit line.

Tract-based GLM

To define tracts of interest (TOIs) for the tract-based analysis, probabilistic tractography was performed between each pairing of the 38 language-related areas identified in Table 1 (703 tracts) and for each subject. FSL's *bedpostx* tool was used to model up to two crossing white matter fibers per voxel (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). A connectivity index (C) for the tracts computed for each pair of areas was defined as the fraction of tractography samples that connected the seed masks multiplied by the average length of each connecting

sample. Values were normalized across all calculated tracts and thresholded at $C \geq 0.1$ to determine which TOIs showed the strongest evidence of sharing direct connectivity and were therefore suitable for analysis. One hundred eleven of the 703 tracts analyzed passed this threshold (see Figure 3A). For each data set, weighted mean FA, MD, λ_{\parallel} , and λ_{\perp} were calculated for each of these 111 TOIs along with 38 TOIs resulting from single-seed tractography from each area (all TOIs individually defined for each subject). A GLM analysis was performed as above on each of the 149 TOIs, with results FDR-corrected for multiple comparisons and shown in Figure 3B. The tract-based approach allowed all analyses to be performed in native space, without the potential for noise added by interpolating data to a standard space.

Table 1. Language Areas in Tract-based Analysis

Area	Abbreviation	Reported Functions
Transverse frontopolar gyrus and sulcus	TFPG	Supervisory attentional gateway (Burgess, Dumontheil, & Gilbert, 2007); retrieval of long-term memories (Kroll, Markowitsch, Knight, & von Cramon, 1997)
Frontomarginal gyrus and sulcus	FMGS	Supervisory attentional gateway (Burgess et al., 2007); retrieval of long-term memories (Kroll et al., 1997)
Inferior middle BA 9 (from middle frontal gyrus)	imBA9	Lexical-semantic production (Glasser & Rilling, 2008)
BA 47 (from orbital part of inferior frontal gyrus [IFG] and portions of orbital gyrus)	BA47	Lexical-semantic production (Glasser & Rilling, 2008); semantic recall (Wagner, Paré-Blagoev, Clark, & Poldrack, 2001)
BA 45 (triangular part of IFG)	BA45	Lexical-semantic production (Glasser & Rilling, 2008)
BA 44 (opercular part of IFG)	BA44	Phoneme production (Glasser & Rilling, 2008); hierarchical structure processing (Friederici, 2009)
Inferior BA 6 (from precentral gyrus)	iBA6	Phoneme production (Glasser & Rilling, 2008); hierarchical structure processing (Friederici, 2009)
Caudate nucleus	CN	Lexical-semantic control (Crinion et al., 2006); predicts language learning ability (Tan et al., 2011)
BA 41 and BA 42 (from temporal transverse gyrus)	BA41/2	Increased activity after lexical tone training (Wang et al., 2003)
Planum polare	PP	Connectivity with aSTG (Friederici, 2009)
Anterior superior temporal gyrus	aSTG	Phrase structure, syntactic violations, high temporal details of speech (Friederici, 2009)
Middle temporal gyrus	MTG	Lexical-semantic processing (Glasser & Rilling, 2008)
Inferior temporal gyrus	IFG	Lexical-semantic processing (Glasser & Rilling, 2008)
Posterior superior temporal gyrus	pSTG	Syntactic/semantic integration, semantic violations (Friederici, 2009)
Planum temporale	PT	Connectivity with pSTG (Friederici, 2009)
BA 40 (from supramarginal gyrus)	BA40	Phoneme processing, phonological working memory (Glasser & Rilling, 2008)
BA 39 (from angular gyrus)	BA39	Semantic processing (Glasser & Rilling, 2008)
Intraparietal sulcus	IPS	Hierarchical structure processing (Friederici, 2009)
Fusiform gyrus	FusiG	Selective filtering of visual attention; predicts language learning ability (Tan et al., 2011)

RESULTS

We collected monthly DTI scans from each participant and performed whole-brain longitudinal analyses for each of the above diffusion parameters to localize areas with parametric increases or decreases among language learners when compared with controls. We constructed a univariate GLM with independent x intercepts for each participant and independent slopes for experimental and control groups (m_E and m_C , respectively). The independent x intercepts were included to account for any preexisting differences in white matter that may have existed between participants, whereas any observed differences in slope between the two groups would indicate an effect of language learning. During the course of the intervention, language learners exhibited significant increases in FA ($m_E > m_C$) along with decreases in λ_{\perp} ($m_E < m_C$) in several areas (Figure 1; $p < .05$, after FDR correction for multiple comparisons). Participants were matched for GPA, and further analyses controlled for age and gender (see Methods). No voxels in the other tests on FA, MD, λ_{\parallel} , or λ_{\perp} reached significance. Widespread increases in FA were evident along left-hemisphere tracts between language areas and in the temporal region of the right hemisphere. However, the most highly significant FA increases occurred in frontal axonal tracts that cross the genu of the corpus callosum. This is surprising, as this region is not typically implicated in language use. In addition, left-hemisphere frontal regions of language learners experienced a significant decrease in λ_{\perp} .

By collecting data regularly over a long duration, we were able to investigate the temporal dynamics of the observed learning-related white matter changes. For each subject, we averaged FA data from voxel locations showing significant $m_E > m_C$ in a GLM analysis with that participant excluded ($p < .05$, uncorrected). These data were binned by month and time courses were plotted along with a best-fit line for each group (Figure 2). The

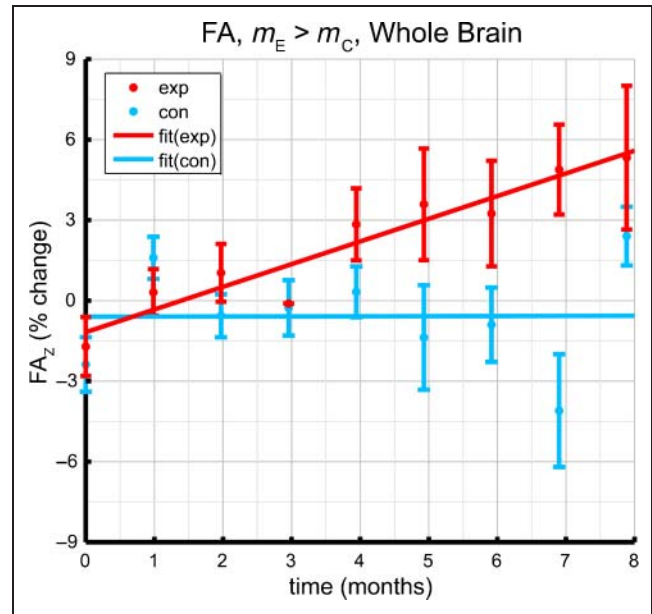
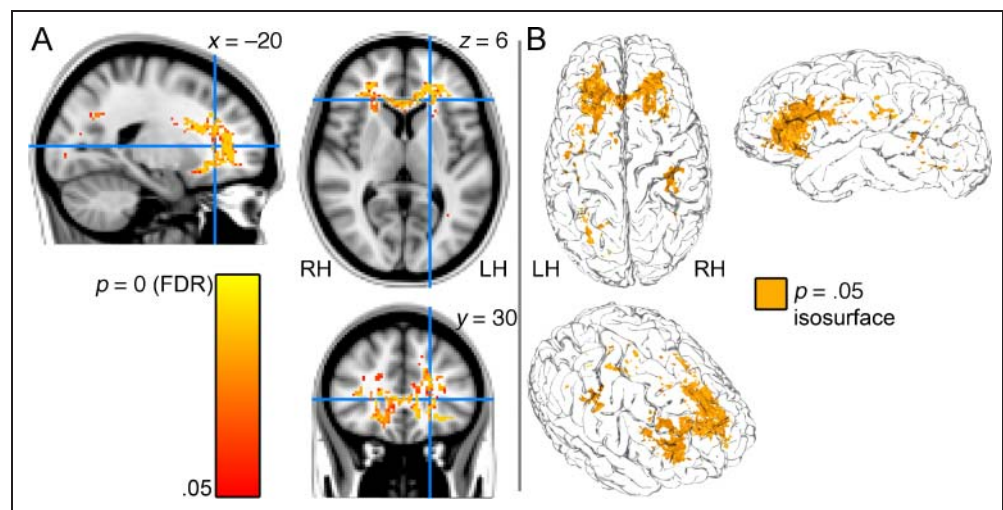


Figure 2. FA increases linearly during language learning over 9 months. For each participant, FA data were included from white matter locations that showed significantly greater slope in language learners over controls in a GLM analysis with that participant left out ($p < .05$, uncorrected). Data from language learners (red) and control participants (blue) are binned by month and plotted with a best-fit line. The y axis represents the percentage change of Z-transformed FA from time zero (see Methods). Error bars represent SEM. For language learners, $r^2 = .91$ for best-fit line to average binned data and the mean of r^2 s for individual participant best-fit lines is 0.42 ($SEM = 0.10$).

resulting time courses show a change in FA among language learners that is well described by an increasing, linear function ($r^2 = .91$ for best-fit line to average binned data while mean of r^2 s for individual participant best-fit lines is 0.42 [$SEM = 0.10$]). Additionally, we found a significant correlation between the individual participant slopes of FA changes and the degree of language learning as assessed by instructor evaluation ($r^2 = .41$, $p = .035$;

Figure 1. Results of whole-brain longitudinal GLM analysis of FA in language learning.

(A) A bihemispheric cluster shows increases in FA in the language learning group over controls. Statistical values were threshold-free cluster enhanced, FDR corrected, and thresholded at $p < .05$. Results are superimposed on a Montreal Neurological Institute template brain. (B) A $p = .05$ isosurface model from the same analysis projected onto one subject's glass brain. Additional clusters of significance can be seen along the left language pathway and in the right temporal lobe.



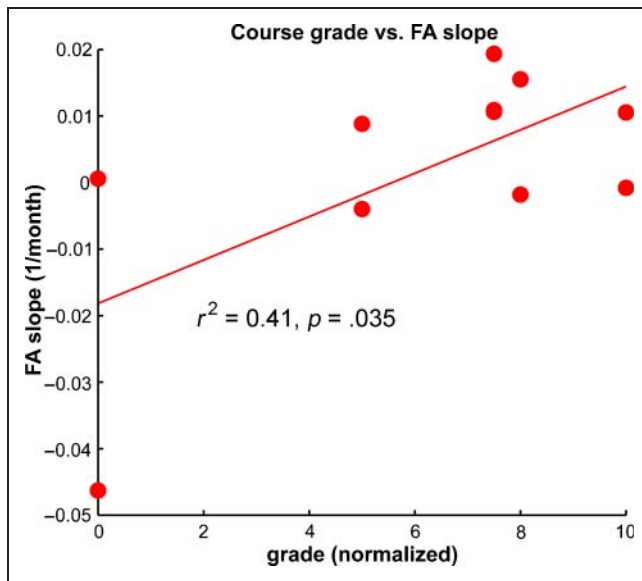


Figure 3. Correlation between learning outcome and change in FA. Best-fit FA slopes were calculated for each participant using the procedure described in Figure 2. A comparison of these slopes with participants' learning outcome as assessed by instructor evaluations reveals a significant correlation between the two ($r^2 = .41, p = .035$). Evaluations were normalized for the analysis and do not indicate absolute performance.

Figure 3). Thus, our data establish a clear link between increases in FA and language learning.

To further localize the functional regions responsible for the observed effects, we performed a tract-based analysis of 38 areas (19 in each hemisphere) identified through a review of the literature as relevant to language processing (Table 1). We were particularly interested in the caudate nucleus, primary auditory cortex, left superior temporal gyrus, right inferior frontal gyrus, and fusiform gyrus as previous studies had found relationships between these

regions and language learning (Tan et al., 2011; Wang et al., 2003). Probabilistic tractography between each pair of areas identified 111 TOIs with high connectivity from among the 703 possible pairs (see Methods). An additional 38 TOIs were constructed using single-seed tractography from each area, resulting in a total of 149 TOIs. One weighted-mean FA, MD, λ_{\parallel} , and λ_{\perp} value was calculated for each TOI and subject, and the above GLM analysis was then performed for each TOI. Sixteen of 149 TOIs showed increases in FA in language learners ($p < .05$, FDR-corrected for multiple TOI comparisons). None showed decreases in FA. Interestingly, 5 of the 16 significant TOIs terminated in the caudate nucleus. Previous studies have shown that the caudate plays a role in language control and that activity levels in the left caudate before language learning predict how well a second language will be learned (Tan et al., 2011). Additionally, 10 TOIs between frontal and left-hemisphere language areas showed decreases in λ_{\perp} among language learners (Figure 4, FDR-corrected for multiple TOI comparisons).

DISCUSSION

In this longitudinal DTI study, we investigated the effects of language learning on the organization of white matter in the brain. We collected monthly DTI scans of participants who either participated in a 9-month intensive course in Modern Standard Chinese or who did not study a language during that period. Parametric changes in FA and radial diffusivity (λ_{\perp}) occurred in language learners over controls in traditional left-hemisphere language regions, their right hemisphere analogs, and also across the genu of the corpus callosum. Given increases in FA and decreases in λ_{\perp} , our data are most consistent with increases in myelination in these TOIs over the study period. Although MD is also associated with myelination, λ_{\perp} and MD are correlated and

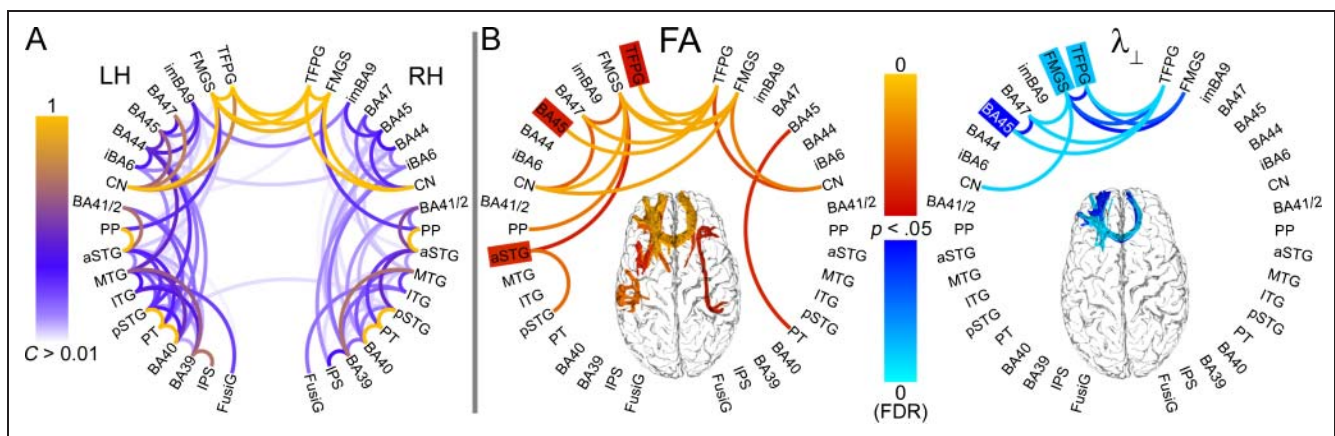


Figure 4. Results of tract-based analysis of FA and λ_{\perp} in language learning. (A) Tract candidates for analysis as determined by a probabilistic tractography connectivity index (C) (see Methods). See Table 1 for abbreviation key. Tracts are color-coded by connectivity index with yellow tracts having highest connectivity. Tracts with $C \geq 0.1$ were included in the tract-based analysis. (B) Results of longitudinal tract-based GLM analysis for FA and λ_{\perp} . Warm colors show tracts with significant increases in language learners over controls ($p < .05$, FDR corrected for multiple TOI comparisons). Cool colors show significant decreases. Colored boxes indicate single-seed tracts that reached significance. Tracts for one participant are shown as inset for reference.

λ_{\perp} more precisely reflects the changes in diffusion that would result from myelinating processes. Therefore, the lack of significance on MD measures may have simply been due to lack of statistical power.

In the CNS, oligodendrocytes extend processes that wrap myelin sheaths around axons (Baumann & Pham-Dinh, 2001). Myelin prevents ions from entering or leaving the axon and serves as insulation that reduces signal decay while enhancing the speed of action potential propagation. Myelination could increase as oligodendrocytes increase in size, packing, or number or as their processes wrap additional myelin around axons. Axonal activity could induce myelination given a glial-axonal communication mechanism that increases oligodendrocyte growth or migration as nearby axons carry an increased number of action potentials. Although this mechanism is not fully understood, studies have reported signaling pathways whereby neuronal electrical activity triggers myelinogenesis (Demerens et al., 1996), which is mediated by astrocytes (Ishibashi et al., 2006). Plasticity realized in such mechanisms could play a more prominent role in adult learning as modifications are made to existing processing structures. In comparison, processes in childhood such as synaptic pruning and apoptosis may be more responsible for the initial formation of linguistic neural circuitry (Thomas & Johnson, 2008). Adult learners will also likely exhibit forms of synaptic plasticity associated with long-term potentiation and depression that DTI is unable to detect.

Wang et al. (2003) investigated changes in functional activity as native English speakers completed a lexical tone training program as part of a course in Mandarin. Improvement in performance was correlated with the expansion and emergence of activity in left hemisphere language areas along with the emergence of activity in a right hemisphere analogue. The right hemisphere analogs of left hemisphere language areas are thought to play a role in the processing of prosody (see Price, 2010) and so could have been recruited by the English-speaking participants while attempting to learn a tonal language. The expansion of activity to new regions found by Wang et al. suggests that new connections developed between the nodes of the language processing network. This possibility is supported by the changes in white matter connectivity we found in left- and right-hemisphere language areas.

Tan et al. (2011) measured brain activity as children engaged in a lexical decision task both before and after learning a second language. They found that activity in the left caudate and fusiform regions predicted how well the second language would be learned, in line with evidence that these regions mediate switching and competition between languages. In the current study, five of the white matter tracts that demonstrated changes as a result of language learning terminated in the left or right caudate, supporting the view that the caudate is an important node in the network responsible for language learning.

In summary, we observed systematic, learning-dependent changes in white matter tracts between known language processing regions and additionally in a bihemispheric frontal network whose axons pass through the genu of the corpus callosum as adult English speakers took an intensive course in spoken and written Modern Standard Chinese. These findings indicate that structural plasticity plays a role in language learning even among adults. The changes observed between frontal cortical hemispheres and caudate nuclei support previous findings that language learning entails the development of control networks to mediate switching between languages (Filippi et al., 2011; Tan et al., 2011). Moreover, our data demonstrate that longitudinal DTI can provide new insights into the neural circuits underlying cognition that are not attainable using BOLD fMRI. The BOLD signal correlates with changes in neural activity in gray matter but is relatively insensitive to neural activity in white matter. Longitudinal DTI, in contrast, provides an orthogonal measure of the neural circuitry underlying cognition via learning-induced modification of the axonal tracts that connect cortical regions. This axonal plasticity may serve as a signature of neural information processing that cannot be resolved using currently established methods. Consistent with previous findings, our data suggest that these structural changes may occur through use-dependent myelination. Additional work is needed to discover the significance of white matter plasticity for language learning and other developmental processes recently observed in gray matter (Taubert et al., 2010; Draganski & May, 2008). Our data support the emerging view that the adult brain retains a robust capacity for reorganization with learning. Like a muscle that grows with use, the brain appears capable of expanding the functionality of networks involved in learning by altering the underlying anatomy through myelination.

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