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A Sensitive Diffusion Tensor Imaging Quantification Method to Detect Language Laterality in Children: Correlation With the Wada Test

Vijay Narayan Tiwari, MD, PhD^{1,2}, Jeong-Won Jeong, PhD^{1,2}, Eishi Asano, MD, PhD^{1,2,3}, Robert Rothermel, PhD⁴, Csaba Juhasz, MD, PhD^{1,2,3}, and Harry T. Chugani, MD^{1,2,3}

¹Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan

²PET Center, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan

³Department of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan

⁴Department of Psychiatry, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan

Abstract

Using diffusion tensor imaging tractography and color-coded anisotropy map quantification, we investigated asymmetry of the arcuate fasciculus to determine language laterality in children and compared it with the Wada test. Arcuate fasciculus volume and fractional anisotropy were measured after tractography. We also quantified the fiber orientation distribution in the arcuate fasciculus region, ie, the fraction of arcuate fasciculus fibers oriented in the anteroposterior and mediolateral directions. A Laterality Index was calculated for each of the measured parameters. Volumetric analysis of the arcuate fasciculus showed asymmetry favoring the language dominant hemisphere ($P = .02$), while fractional anisotropy showed no significant asymmetry ($P = .07$). The mean anteroposterior and mediolateral components on the language dominant side were significantly higher than on the nondominant side ($P = .003$ and $.002$, respectively). The Laterality Index values were concordant with the Wada test results except for 1 case. Fractional anisotropy also falsely lateralized language in 1 case.

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Corresponding Author: Harry T. Chugani, MD, Children's Hospital of Michigan, Pediatric Neurology and PET Center, 3901 Beaubien Blvd., Detroit MI 48201, hchugani@pet.wayne.edu.

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Author Contributions

VNT: participated in the formulation of the hypothesis, acquired and analyzed the DTI data, and wrote the first draft of the manuscript. J-WJ: performed quantitative analysis and revised the first draft of the manuscript. EA: participated in the design of the study and revised the first draft of the manuscript. RR: performed the neuropsychological testing and revised the first draft of the manuscript. CJ: participated in the formulation of the hypothesis and revised the first draft of the manuscript. HTC: recruited the patients using the inclusion and exclusion criteria and extensive revision of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Human Investigations Committee at Wayne State University granted permission for the retrieval and analysis of de-identified DTI and outcome data that had been obtained clinically for these children.

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Keywords

Wada test; diffusion tensor imaging; arcuate fasciculus; language laterality

Language is one of the highest cognitive functions of the human brain and lateralization of language function is well defined. The left hemisphere plays a dominant role relative to the right in language functions in more than 95% of right-handed healthy individuals.^{1,2} Accurate determination of language lateralization is critical before resective brain surgery potentially affecting language-related cortical and subcortical structures. To avoid postsurgical functional impairment, the intracarotid sodium amytal (Wada) test has been a gold standard method to define language dominance as well as the integrity of memory function in functional neurosurgery.³ Once the injection of sodium amytal is made, the dominant hemisphere is identified based on the patient's responses to a variety of neuropsychological tests of language functions.⁴ However, it remains an invasive procedure and some risk factors are known to be associated with it.⁵ In addition, patient cooperation is required in the Wada test so that it is impractical and unreliable in the very young or uncooperative subject. Therefore, the development of alternative, noninvasive language lateralization techniques to replace the Wada test would be considered an important advance.

Recently, noninvasive magnetic resonance imaging techniques such as functional magnetic resonance imaging and diffusion tensor imaging have been increasingly used to delineate language areas and pathways. Diffusion tensor imaging has been used successfully to map the structure and asymmetry of white matter fiber tracts implicated in human language function.^{6–9} Language network tracts, particularly the arcuate fasciculus, play a major role in language function. However, the utility of diffusion tensor imaging for predicting hemispheric laterality, a prominent feature of language organization in the human brain, has not been explored in greater detail.

On the other hand, there has been greater emphasis on functional assessments of language laterality using functional magnetic resonance imaging (MRI) during language tasks, the results of which have shown good correlation with results of the Wada test.^{10–13} Since diffusion tensor imaging does not require patient participation, it can be better suited for the study of language lateralization when functional magnetic resonance imaging is not feasible.

One of the most commonly used analytical approaches in diffusion tensor imaging is to extract white matter tracts using tractography, and, in fact, some recent studies have used diffusion tensor imaging tractography successfully for lateralizing language.^{14,15} In the present study, we combined tractography with direct quantification of the diffusion tensor imaging color-coded orientation maps to determine language laterality more objectively. In addition, the present language laterality study is performed in a younger population as compared to previous diffusion tensor imaging tractography studies involving adult populations.^{14,15}

Methods

Subjects included 13 children (mean age, 12.1 years; age range, 2–18 years; 10 males; 11 right-handed) who underwent the intracarotid sodium amytal (Wada) test, as part of their presurgical evaluation due to intractable epilepsy, and were found to have unilateral language dominance (Table 1). Unilateral language dominance was defined by (1) sustained initial speech arrest (usually for > 1 min) observed predominantly on injection of the amytal to 1 hemisphere and (2) dysphasia or paraphasia, if present, on injection to the same

hemisphere.¹⁶ Patients with bilateral language representation in whom speech arrest was observed for > 1 min after sequential injection to both hemispheres were excluded from this study. No patients showed language impairment on neurological examination. Handedness was assessed using the Edinburgh Inventory.¹⁷

Diffusion Tensor Imaging Acquisition Protocol

Magnetic resonance imaging scans were performed using a GE system with 3 Tesla scanner. Diffusion tensor images were acquired in the axial plane with diffusion sensitization gradients applied in 55 noncollinear directions with a b-value of 1000 s/mm². The same imaging parameters were used to acquire T2 weighted (b ~ 0 s/mm²) images to use as a reference image and to measure signal attenuation. Double refocusing pulse was used to reduce eddy-current artifacts. In addition, array spatial sensitivity encoding technique (ASSET) was used to further reduce geometric distortion due to the sequence design. The echo time was 79 milliseconds, and the repetition time was approximately 10 seconds. A set of minimum 34 axial slices of 3 mm thickness without gap were acquired with a matrix size of 128 × 128 which were later reconstructed to 256 × 256 matrixes covering the whole brain, including the cerebellum. Field of view was 240 × 240 mm² and the approximate scanning time for the diffusion tensor imaging acquisition was 9 minutes. Because the scans were clinical magnetic resonance imaging studies, sedation was used as necessary by the sedation team at Children's Hospital of Michigan.

Tensor Calculation and Tractography

Acquired diffusion sensitized and reference image sets were transferred to an Intel Pentium, Microsoft windows based operating system for further data analysis. Tensor calculation and tractography were performed using diffusion tensor imaging studio software version 2.40.¹⁸ Tractography was carried out based on Fiber Assignment by Continuous Tracking algorithm,^{19,20} with fiber propagation starting at fractional anisotropy threshold value of 0.2. The fiber propagation was stopped at a fractional anisotropy threshold less than 0.2 or an angle threshold greater than 60 degrees.

Isolation of the Arcuate Fasciculus

The arcuate fasciculus was identified on the diffusion tensor imaging color-coded map as described previously.²¹ Briefly, the first region of interest was placed in the coronal plane at the level of the posterior tip of the putamen using the "OR" operator lateral to the superior aspect of the corona radiata. A second region of interest in the axial plane was then placed using the "AND" operator at the level just below the Sylvian fissure where the arcuate fasciculus can be discretely identified.

Region-Based Quantification Analysis

The direction of individual fibers in diffusion tensor imaging data can be quantified by the color-coded anisotropy maps. In diffusion tensor imaging color-coded maps, the 3 components of the eigenvector v_1 along with the largest eigenvalue are color-coded based on conventional red-blue-green components. These components are symmetric with respect to all color axes. The color axes are aligned with the patient coordinate system (green: anteroposterior; red: mediolateral). As a direct metric to quantify a measure of directional fiber volume in the arcuate fasciculus fibers, we summed up anteroposterior components (v_{1y} , green component of the color-coded anisotropy map) and mediolateral components (v_{1x} , red component of the color-coded anisotropy map) at the color-coded anisotropy map of the arcuate fasciculus region.

The quantification was achieved by the region of interest based analysis described previously.²² Figure 1 illustrates the overall procedure of this analysis. The color-coded anisotropy map of individual subjects was masked by the region of interest that was objectively transformed from the region of interest of Montreal Neurological Institute space. The operator delineated 2 binary regions of interest in Montreal Neurological Institute space. Each region of interest covered the voxels of left or right arcuate fasciculus. Each drawn region of interest was then transformed back into the native space of the individual subject by means of an inverse deformation field (ie, $M_i^{-1}(x,y,z)$, the inverse of the transformation that maps the fractional anisotropy map of an individual subject to the fractional anisotropy template of the Montreal Neurological Institute space). This method is efficient to evaluate a large amount of data in a systematic manner since the $M_i^{-1}(x,y,z)$ allows a free deformation to match the regions of template space to those of the i^{th} subject's space, the size and location of the transformed region of interest can be extended or contracted depending on the size and structure of the i^{th} subject's brain. Thus, the total number of anteroposterior and mediolateral components inside the transformed region of interest provides an objective measure of the arcuate fasciculus fiber connection existing in anteroposterior and mediolateral directions, which do not depend on any experimental variability. Five different operators demarcated the region of interest of bilateral arcuate fasciculus in Montreal Neurological Institute space. To assess inter-rater variability, we used the average of 5 component values for further analysis.

The Laterality Index was calculated to assess lateralization of the fractional anisotropy, volume, anteroposterior and mediolateral components between hemispheres: Laterality Index $x = (x \text{ language dominant hemisphere} - x \text{ nondominant hemisphere}) / (x \text{ language dominant hemisphere} + x \text{ nondominant hemisphere})$, where x is the volume, fractional anisotropy, anteroposterior or mediolateral component of the diffusion tensor imaging color-coded anisotropy map in the arcuate fasciculus region.

Statistical Analysis

Two-sample unpaired t tests were applied to compare the fractional anisotropy, volume, anteroposterior and mediolateral component between left and right hemispheres. A P value of less than .05 was considered as statistically significant.

Results

All but 1 patient (#2) had left hemisphere language dominance (Table 1) and this patient was correctly lateralized by diffusion tensor imaging tractography as well as color-coded map quantification (Figure 2). By conventional tractography, the arcuate fasciculus was identified in all 13 subjects. Volumetric analysis showed larger mean volume in the language dominant side ($P = .02$) while mean fractional anisotropy showed no significant asymmetry ($P = .07$), although there was a trend to be higher on the language dominant side (Table 2). Quantitative diffusion tensor imaging color-coded analysis showed that the mean anteroposterior and mediolateral components in the language dominant side were significantly higher than in the nonlanguage dominant side ($P = .003$; 0.002 , respectively) (Table 2). The Laterality Index was calculated for each parameter (volume, fractional anisotropy, anteroposterior and mediolateral components) and the results are summarized in Table 1. In patient 3, the fractional anisotropy falsely lateralized the language dominant hemisphere; however, volumetric analysis lateralized it correctly. Also, patient 11 showed false lateralization when anteroposterior and mediolateral components were quantified.

Discussion

The main finding of this study is an asymmetry of the arcuate fasciculus toward the language dominant hemisphere demonstrated by quantification of diffusion tensor imaging color-coded anisotropy maps. These results are also consistent with the diffusion tensor imaging tractographic approach. The findings were statistically significant in the group analysis for the quantitative method (anteroposterior and mediolateral components) of diffusion tensor imaging color-coded maps. Volumetric measurement performed after tractography showed a clear-cut asymmetry favoring a larger tract in the language dominant side. However, we could not find any significant difference in fractional anisotropy between the language dominant and language nondominant hemispheres, although fractional anisotropy showed a trend to be slightly higher in the language dominant side.

The need to accurately map language areas in children with epilepsy who are surgical candidates to avoid damaging key language areas is important. Early research showed that functional magnetic resonance imaging could be an important addition to Wada testing and cortical stimulation for children who are candidates for neurosurgical treatment potentially affecting language areas. High concordance rates (80%–90%) between functional magnetic resonance imaging and Wada test in determining language laterality have been reported in several studies.^{23–27} However, some disparity still exists between functional magnetic resonance imaging and Wada test results (10%–20%) and this could be attributed to procedural differences and tasks used in these methods. Studies of concordance between functional magnetic resonance imaging and cortical stimulation in healthy young adults demonstrate that functional magnetic resonance imaging has high sensitivity and can reliably identify critical language sites. However, functional magnetic resonance imaging specificity in determining language areas is not very high (50%–70%) as it can also show activations in brain areas not critical to language processing.^{23,24,26} Furthermore, functional magnetic resonance imaging requires patient cooperation. Still, functional magnetic resonance imaging continues to remain a useful noninvasive tool that can be used to map language areas.

Diffusion tensor imaging has been recently used to explore functional brain systems, and initial studies have demonstrated its potential clinical utility for language lateralization by assessing the asymmetry of the arcuate fasciculus. Vernooij and colleagues correlated language laterality findings with functional magnetic resonance imaging and diffusion tensor imaging in healthy adults and found excellent correlations between these 2 methods.²⁸ Subsequently, Ellmore and colleagues combined diffusion tensor imaging and functional magnetic resonance imaging to detect language laterality and showed good concordance of these methods with the Wada test (19 of 23 were lateralized correctly).¹⁵ Although the degree of mismatch between diffusion tensor imaging findings and Wada test has been variable in previous reports,^{14,15} diffusion tensor imaging still can have an important role in decision making and it can complement other modalities for further assessment of language lateralization. Previous diffusion tensor imaging studies to lateralize language used a tractographic approach. However, 1 disadvantage of the tractography procedure is that it is user dependent and subject to at least some individual bias. The present study combined tractography with diffusion tensor imaging color-coded map quantification to increase accuracy and objectivity. Moreover, previous studies mostly consisted of an adult population while we have investigated a much younger population in this study. Diffusion tensor imaging color-map quantification could potentially be a more robust method compared with tractography as it removes the subjective bias. Moreover, it defines the orientation of white matter tracts in different directions thereby detecting even subtler abnormalities which often go undetected by tractography.

In the present study, using the quantitative diffusion tensor imaging color-coded map method, we found false lateralization of the language dominant hemisphere in only 1 (subject #11) of the 13 patients. On the other hand, the tractographic approach also falsely lateralized 1 (subject #3) of the 13 patients, but this subject was different from the 1 who was falsely lateralized using the quantitative method. Importantly, diffusion tensor imaging with the applied approach correctly lateralized 1 patient who had right-sided language dominance. Since, in this study, we had 12 patients who had left-sided language dominance and only 1 patient with right-sided dominance, we could not assess effects of pathology on language lateralization.

Methodological Issues and Limitations

One of the main limitations of this study is the small sample size and the lack of additional patients with right hemispheric language lateralization as defined by the Wada test. Further studies involving a larger sample size will be necessary. From a technical perspective, use of the tensor model in the present study is limited in that it cannot accurately model crossing fibers. Fortunately, for this study, the focus was on a tract (arcuate fasciculus) which is not particularly susceptible to the problem of crossing fibers (as opposed to tracts such as the corona radiata); moreover, we complemented the tractographic approach with quantitative analysis of diffusion tensor imaging color-coded anisotropy maps. Finally, since it is not possible to administer the Wada procedure to healthy controls, one cannot say conclusively that asymmetry in the highly anisotropic arcuate fasciculus is predictive of language laterality in the normal population.

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Figure 1.

Automatic quantification of color-coded anisotropy map in bilateral arcuate fasciculus regions of native space. A single region of interest to enclose core voxels of bilateral arcuate fasciculus (orange colored contour of left panel) was manually delineated on the Montreal Neurological Institute fractional anisotropy template (gray scaled image in left panel). This region of interest was then transferred to individual color-coded anisotropy maps (colored images in right panel) by means of corresponding $M^{-1}(x,y,z)$. At each transferred region of interest, the sum of anteroposterior (green) and mediolateral (red) components were calculated and compared across the subjects to quantify the degree of white matter development in bilateral arcuate fasciculus.

Figure 2. Arcuate fasciculus of patient 2 (L = Left; R = Right). Arcuate fasciculus is more lateralized to right compared with left.

Table 1

Patient Profile, Language Dominance Defined by Wada Test and Laterality Indices Determined by Various Parameters

Pt. no.	Handedness	Age	Sex	Seizure focus	Wada result	FA LI	Vol. LI	AP LI	ML LI
1	R	16	F	L	L	0.029	0.028	0.243	0.069
2	L	5	M	L	R	-0.031	-0.37	-0.007	-0.020
3	R	15	M	L	L	-0.097	0.032	0.241	0.176
4	R	10	F	L	L	0.032	0.103	0.083	0.297
5	R	15	F	L	L	0.047	0.438	0.216	0.247
6	R	14	M	L	L	0.021	0.153	0.291	0.318
7	R	2	M	L	L	0.011	0.430	0.019	0.101
8	R	16	M	R	L	0.008	0.105	0.016	0.205
9	R	11	M	L	L	0.035	0.033	0.332	0.161
10	R	18	M	L	L	0.015	0.500	0.544	0.464
11	R	16	M	R	L	0.034	0.044	-0.151	-0.153
12	R	10	M	L	L	0.036	0.238	0.013	0.009
13	L	10	M	L	L	0.025	0.405	0.498	0.355

Abbreviations: FA, fractional anisotropy; Vol., volume of arcuate fasciculus (cc); LI, laterality index; AP, anteroposterior component of diffusion tensor imaging color-coded maps; ML, mediolateral component of diffusion tensor imaging color-coded maps

Table 2

Mean Values of Various Parameters (Fractional Anisotropy, Volume, Anteroposterior, and Mediolateral Summed Components)^a

	Left	Right	<i>P</i> value
Anteroposterior component	25380 (2159)	17379 (1638)	.003
Mediolateral component	28237 (2086)	19941 (1793)	.002
Fractional anisotropy	51.5 (4.2)	48.2 (4.6)	.07
Volume (cc)	5715.4 (602.5)	3765.3 (396.4)	.02

^aValues are displayed as mean (SE).