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Localization of specific language pathways using diffusion-weighted imaging tractography for presurgical planning of children with intractable epilepsy

Jeong-Won Jeong^{*,†,‡}, Eishi Asano^{*,†}, Csaba Juhász^{*,†,‡}, and Harry T. Chugani^{*,†,‡}

^{*}Carman and Ann Adams Department of Pediatrics, School of Medicine, Wayne State University, Detroit, Michigan, U.S.A.

[†]Department of Neurology, School of Medicine, Wayne State University, Detroit, Michigan, U.S.A.

[‡]Translational Imaging Laboratory, Children's Hospital of Michigan, Detroit, Michigan, U.S.A.

Summary

Objective—To examine whether diffusion-weighted imaging (DWI) tractography can detect multiple white matter pathways connected to language cortices, we employed a maximum a posteriori probability (MAP) classification method, which has been recently validated for the corticospinal tract.

Methods—DWI was performed in 12 normally developing children and 17 children with intractable focal epilepsy who underwent subsequent two-stage epilepsy surgery with intracranial functional mapping. First, whole-brain DWI tractography was performed to identify unique pathways originating from Broca's area, premotor area, and Wernicke's area on functional magnetic resonance imaging (fMRI) of normal children and intracranial electrical stimulation mapping (ESM) of children with epilepsy. Group averaging of these pathways based on fMRI was performed to construct the probability maps of language areas in standard MRI space. These maps were finally used to design a DWI-MAP classifier, which can automatically sort individual fibers originating from fMRI language areas as well as ESM language areas.

Results—In normally developing children, the DWI-MAP classifier predicted language-activation areas on fMRI with up to 77% accuracy. In children with focal epilepsy, the DWI-MAP classifier also showed high accuracy (up to 82%) for the fibers terminating in proximity to essential language areas determined by ESM. Decreased volumes in DWI-MAP-defined pathways after epilepsy surgery were associated with postoperative language deficits.

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Address correspondence to Jeong-Won Jeong, Departments of Pediatrics and Neurology, PET Center, Children's Hospital of Michigan, Wayne State University School of Medicine, 3901 Beaubien St., Detroit, MI 48201, U.S.A. jeongwon@pet.wayne.edu.

Disclosure

The authors declare no conflict of interest.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. DWI-MAP classifier.

Significance—This study encourages further investigations to determine if DWI-MAP analysis can serve as a noninvasive diagnostic tool during pediatric presurgical planning by estimating not only the location of essential language cortices, but also the underlying fibers connecting these cortical areas.

Keywords

Language pathways; Diffusion MRI tractography; Classification; Functional MRI; Epilepsy surgery; Children

The ultimate goal of epilepsy surgery is to achieve permanent seizure freedom while causing no or minimal post-operative functional deficits. This requires presurgical identification and preservation of “eloquent” cortex, including essential language areas, which are highly variable in their exact location among individuals.¹ Postoperative speech therapy for new language deficits is lengthy and expensive, and recent reports suggest that not all young children can fully recover from language deficits acquired after epilepsy surgery.^{2,3}

The current gold standard for identifying essential language areas during presurgical evaluation is observation of language disruption induced by direct electrical stimulation mapping (ESM) to the cerebral cortex. Yet, ESM is not an ideal gold standard method, since it carries an inherent risk of electrically induced seizures, and sometimes fails to replicate language symptoms in children.^{4,5} Furthermore, subdural electrodes cannot be placed over the whole brain surface, and electrical stimuli cannot be delivered to unsampled areas. Thus there is a clear need in presurgical planning to predict noninvasively the language areas to prevent postoperative deficits in children with intractable focal epilepsy. An alternative approach to ESM is functional magnetic resonance imaging (fMRI), which is noninvasive but highly susceptible to movement artifacts and demands patient cooperation during scanning. Thus it is challenging to perform fMRI studies in young children with focal epilepsy (success rate <60% at age 4–6 years old).⁶

The present study applies diffusion-weighted imaging (DWI) tractography to develop an automatic classification of *separate* language pathways, called a maximum a posteriori probability (MAP) classifier, which can delineate different streamline pathways associated with each of the essential language areas (i.e., expressive and receptive language areas), which may be potentially located close to the epileptogenic zone. We have recently validated this approach to detect function-specific segments of the primary motor pathways.^{7,8} In the present study, we used the proposed MAP classifier to localize distinctive cortical areas associated with separate language pathways and also to measure the extent of these pathways before and after epilepsy surgery. If successful, this approach could be instrumental in optimizing surgical tailoring and predicting the occurrence of postoperative language deficits in children with intractable focal epilepsy. Therefore, this study may be of practical value in providing a more accurate assessment of benefit–risk analysis prior to surgical intervention.

Methods

Study subjects

Twelve normally developing children with no history of neuropsychiatric disorders (age: mean $11.0 \pm$ one standard deviation 5.3, 8–18 years, eight boys) and 17 children with a diagnosis of focal epilepsy (age: mean $9.6 \pm$ one standard deviation 3.2, 4–17 years, eight boys) were investigated. All participants were right-handed. The patients with epilepsy were selected by using the following inclusion criteria: (1) a history of intractable focal epilepsy scheduled for extraoperative electrocorticography (ECoG) recording as a part of the surgical procedure at Children's Hospital of Michigan, Detroit; and (2) coverage of presumed language areas and mapping of essential language functions using ESM via subdural electrodes. Exclusion criteria consisted of the following: (1) presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly), which could confound anatomic landmarks for the central sulcus and sylvian fissure; and (2) history of previous neurologic surgery. All children with epilepsy underwent comprehensive neuropsychology testing before surgery to evaluate verbal and nonverbal cognitive functions. All studies were performed in accordance with the policies of the Wayne State University Institutional Review Board with written informed consent obtained from the parents or guardians. Table 1 summarizes clinical data and imaging abnormalities obtained from all children with focal epilepsy.

MRI acquisition

All MRI scans were performed on a 3T GE-Signa scanner (GE Healthcare, Milwaukee, WI, U.S.A.) equipped with an eight-channel head coil and array spatial sensitivity encoding technique (ASSET). DW-MRI was acquired with a multi-slice single-shot diffusion weighted echo-planar-imaging (EPI) sequence at repetition time (TR) = 12,500 msec, echo time (TE) = 88.7 msec, field of view (FOV) = 24 cm, 128×128 acquisition matrix (nominal resolution = 1.89 mm), contiguous 3 mm thickness in order to cover entire axial slices of whole brain using 55 isotropic gradient directions with $b = 1,000 \text{ s/mm}^2$, one $b = 0$ acquisition, and number of excitations (NEX) = 1. Whole brain fMRI data were acquired from the normally developing children using T2*-weighted EPI sequence at TR = 2,000 msec, TE = 30 msec, matrix = 64×64 , FOV = 24 cm, thickness = 4 mm. For anatomic reference, a three-dimensional fast spoiled gradient-recalled echo (FSPGR) sequence was acquired for each participant at TR/ TE/TI of 9.12/3.66/400 msec, slice thickness of 1.2 mm, and planar resolution of $0.94 \times 0.94 \text{ mm}^2$.

Experimental fMRI protocol of language fMRI

To map semantic language areas, three different patterns (square, triangle, and circle) were randomly displayed every 5 s in a 30-s block. Subjects were instructed to tag one of two buttons (yes, no) at every 5 s in response to six auditory questions to ask about how three patterns were spatially arranged in the screen (ON 30-s activation block) or six visual pattern comparisons to tag “yes,” only if identical patterns were displayed in the screen (OFF 30-s baseline block). These ON-OFF blocks were repeated four times with different questions, resulting in a 4-min session. The fMRI activations were recorded for Broca's area (anatomically defined as BA 44/45), Wernicke' area (BA 22), premotor area (BA 6), and

inferior-parietal area (BA 39) in the left hemisphere and utilized as a binary mask to sort out relative language pathways from DW-MRI tractography (Fig. 1).

Processing of fMRI data

Statistical Parametric Mapping (SPM, www.fil.ion.ucl.ac.uk/spm/) general linear model with hemodynamic response function was used to identify the voxels corresponding to the hemodynamic activations of semantic language tasks. Statistical inferences were carried out at $p < 0.001$ based on an uncorrected p-value and an extent threshold >10 . The resulting language-related clusters in “Broca’s area,” “Wernicke’s area,” “premotor area,” and “inferior parietal area” were subsequently coregistered to the b0 image. The registered clusters were finally used as regions of interest that seed (or sort out) corresponding language pathways.

Stereotactic probability maps of language pathways using ICA+BSM and fMRI

We have recently established a novel method called “independent component analysis with ball and stick model (ICA+BSM)” to solve the intravoxel problem in clinical DWI data measuring water diffusion at lower spectral resolution.⁹ Unlike with the stand-alone ball and stick model (BSM) to guess initial orientations of multiple tensor orientations randomly, ICA+BSM adapts an ICA approach to isolates independently attenuated diffusion profiles from “neighboring voxels.”^{9–11} The orientations of the resulting profiles were then used as initial guesses of multiple tensor orientations in the framework of stand-alone BSM.^{10,11} In vivo, the crossing of prominent fiber tracts is most likely observable in the cluster of neighboring voxels. Thus, the independent diffusion processes existing in the cluster can be better estimates of multiple tensor orientations than those multiple tensor orientations randomly selected for a single voxel, that are feasibly suited to be trapped at local minimum and that also require computational complexity in the overall fitting procedure of stand-alone BSM. Via computer simulations and human studies, we have demonstrated that ICA+BSM provides the highest accuracy and reproducibility to resolve the orientation of crossing fiber bundles (up to three) in clinical DWI data. ICA+BSM outperformed other conventional methods in resolving correct orientations of corticospinal tracts (CSTs) and arcuate fasciculus (AF) crossing in the lateral region of the central sulcus.^{9,12}

In the present study, whole brain tractography was performed using ICA+BSM to reconstruct up to three crossing streamlines at voxels of fractional anisotropy (FA) >0.20 .^{9,12} At every voxel, the first eigenvectors of the resulting stick components having FA >0.20 were considered as the reconstructed fiber orientations and then utilized for the streamline tractography at step size = 0.2 voxel width, turning angle threshold = 60 degrees, and length constraint = 80–150 mm.

For each participant, the following five projections of white matter pathways connecting two distant fMRI clusters were investigated: (1) Broca’s area-Wernicke’s area, (2) Broca’s area-premotor area, (3) premotor area-Wernicke’s area, (4) premotor-inferior parietal area, and (5) Wernicke’s area-inferior parietal area. For each pathway, all voxels of the first cluster area were used as the seeding region where 100 seed points were uniformly distributed per

voxel. Those of the second cluster area were then used to sort out stream-lines terminating in the corresponding pathway (Fig. 2).

To construct the probability maps of the five language pathways probably associated with different language functions including phonology, lexical-semantic processing, and prosodic processing,¹³ the percentage overlap map of each pathway was obtained by counting the number of fibers intersecting each voxel. The percentage overlap maps of the five pathways were separately normalized into Montreal Neurological Institute (MNI) space using SPM diffeomorphic anatomical registration through exponential lie algebra (DARTTEL, a toolbox of SPM 8 available at www.fil.ion.ucl.ac.uk/spm/software/) where b0 images of individual subjects were utilized to optimize both group average template and spatial normalization field minimizing inter-subject variation of brain geometry (size and shape).^{14,15} The normalized maps were then group-averaged across participants to generate the probability maps, $C_i = 1,2,3,4,5$ (x,y, z) of “C₁: Broca’s area-Wernicke’s area,” “C₂: Broca’s area-premotor area,” “C₃: premotor area-Wernicke’s area,” “C₄: premotor-inferior parietal area,” and “C₅: Wernicke’s area-inferior parietal area,” which represent the probability of individual pathways at every voxel (Fig. 3). We constructed the group-averaged maps, P_c (x,y,z| $C_i = 1,2,3,4,5$), using 12 normal controls and then examined their variation across 17 patients with focal epilepsy using the DWI-MAP classifier.^{7,8}

DWI-MAP classifier to detect language pathways without placement of regions of interest

Based on the stereotactic probability maps of five language pathways, $P(x,y,z|C_i = 1,2,3,4,5)$, a MAP classifier was extended to make a classification of a given tract into six classes of interest, $C_i = 1,2,3,4,5,6$, where C₆: other area consists of streamlines not belonging to any of $C_i = 1,2,3,4,5$ (see details in Supporting Information). Briefly, the first step of the MAP classifier is to transfer the maps of $P(x,y,z|C_i = 1,2,3,4,5,6)$ into individual subject’s space via spatial deformation obtained between the subject’s b0 image and MNI b0 template using SPM DARTTEL package. The resulting maps were then used to approximate the conditional probability maps of a given voxel (x,y,z), $P(x,y,z|C_i)$ for individual language pathways. Finally, we evaluated the a posteriori probability, $P(\text{fiber}_j|C_i = 1,2,\dots,6)$, that a given fiber streamline fiber_j (x,y,z) belongs to $C_i = 1,2, \dots, 6$, under an equal prior of $C_i = 1,2,3,4,5,6$. The argument of i having the most probable a posteriori probability $P(\text{fiber}_j|C_i)$ determines the membership of the fiber_j . To validate the accuracy of the proposed DW-MAP classifier, we compared the locations of ESM-defined essential language areas (as the gold standard) with cortical terminals of individual fibers in $C_i = 1,2,3,4,5$ of the pediatric epilepsy group.

Clinical language mapping with ESM

ESM was performed using a method similar to those described previously.^{5,7,16,17} A pulse-train of repetitive electrical stimuli was delivered to subdural electrode pairs, using the Grass constant-current stimulator (Astro-Med, Inc, West Warwick, RI, U.S.A.). The stimulus frequency was 50 Hz, the pulse duration was 300 μ s, and the train duration ranged from 5 to 10 s. Initially, stimulus intensity was set to 3 mA, and intensity was increased up to 9 mA in a stepwise manner until a clinical response or after discharge was observed. During each period of stimulation, each patient was asked to answer brief auditory questions such as “What flies in the sky?” Other tasks such as picture naming, counting, and reciting ABCs

were performed, as needed. Sites at which stimulation reproduced auditory perceptual changes, failure to verbalize correct responses, or sensorimotor symptoms involving the mouth or throat were determined by at least two investigators, always including at least one clinical neuropsychologist, who was blinded to results of the DWI analyses. When the patient failed to answer a question or complete the assigned task during a stimulation period, he/she was asked why he/she failed to do so. Brain regions at which stimulation consistently elicited a clinical response were declared eloquent for a given function. When after discharge without an observed clinical response or when neither clinical response nor after discharge was elicited by the maximally intense stimuli, the region was declared to have not been proven eloquent. Electrode sites responding to speech arrest, expressive aphasia, or receptive aphasia were identified as essential language areas. Finally, these ESM electrodes were spatially registered to the b0 image using a multi-modal registration method.⁷ Only the voxels representing the interface of the gray matter and white matter inside of the 8 mm sphere were included in the final electrode mask to represent the nearest possible fiber termination sites.

Study design

First, we demonstrated the correspondence between language sites defined by the DWI-MAP classification versus ESM in individual children with epilepsy. We then analyzed the performance (sensitivity, specificity and accuracy) of the DWI-MAP classifier as compared to fMRI and ESM language sites between the normal group (fMRI) and epileptic children (ESM), while using five different criteria based on the distance between abnormalities of DWI-MAP and fMRI or ESM abnormalities (from 0 [direct contact] to 20 mm distance, in 5 mm steps). Finally, we evaluated the relation between resection extent of selected language pathways, defined by DWI-MAP, and postoperative language function in seven children with left hemispheric epilepsy surgery, who had undergone preoperative and postoperative language assessment. Presence of expressive and/or receptive language deficits was evaluated both before and after surgery as part of the neurologic evaluation. The outcome measure in the present study included postoperative language deficit, which was not explained by the effects of medications or altered consciousness and which required speech therapy.¹⁸ Disturbance in verbal comprehension, naming, repetition, articulation, or fluency was evaluated by the speech therapist as well as a parent or legal guardian of the patient.

Results

Comparison of the MAP classifier with ESM in individual children with epilepsy

A typical example of the DWI-MAP classifications ($C_i = 1,2,3,4,5$) is presented in Figure 4, as compared with three language areas determined by ESM. This example shows clinical case where three types of language symptoms— expressive aphasia, expressive aphasia, and speech arrest—were successfully induced during the ESM procedures. The DWI-MAP method successfully localized individual streamlines of language pathways terminating in the areas of ESM associated with receptive aphasia (C_1 :Broca's area-Wernicke's area, C_3 :premotor area-Wernicke's area, C_4 :premotor area-inferior parietal area), speech arrest (C_2 : Broca's area-premotor area, C_3 :premotor area-Wernicke's area), and expressive aphasia (C_1 :Broca's area-Wernicke's area, C_2 :Broca's area-premotor area), suggesting that the

DWI-MAP method may delineate functional language areas and pathways connecting these areas in individual patients with epilepsy.

Performance analysis of the MAP classifier to detect language areas determined by fMRI and ESM

We assessed how accurately the proposed DWI-MAP classification can detect the localizations of semantic language activation areas defined by fMRI (in 12 healthy control children) and essential language areas determined by ESM (in 14 children with epilepsy of left-hemispheric origin). The group percentage overlap maps of fMRI activations and ESM regions were obtained in MNI space (left column images of Fig. 5). The group percentage overlap maps of three pathways ($C_i = 1,2,3$) by DWI-MAP classifier were also obtained in MNI space from healthy controls and children with epilepsy, respectively (right column images of Fig. 5). Note that the present study assessed the accuracy of DWI-MAP method only using $C_i = 1,2,3$, that were terminated at expressive aphasia (C_1 : Broca's area-Wernicke's area), speech arrest (C_2 : Broca's area-premotor area), and receptive aphasia (C_3 : premotor area-Wernicke's area).

The receiver operating characteristic (ROC) curves of sensitivity, specificity, and accuracy of data are also shown in two plots of Fig. 5. The sensitivity of the DWI-MAP classifier over fMRI combined across all normal children increased from 17% (contact) to 46% (5 mm), 63% (10 mm), 77% (15 mm), and 88% (20 mm), as the criterion changed gradually from contact to 20 mm away from the outer boundary of fMRI activation. For children with epilepsy, sensitivity of the DWI-MAP over ESM increased from 20% (contact) to 57% (5 mm), 72% (10 mm), 90% (15 mm), and 97% (20 mm), respectively, as the criterion changed from contact to 20 mm away from the centroid of the electrode. Specificity of the DWI-MAP classifier across normal children decreased from 98% (contact) to 94% (5 mm), 91% (10 mm), 87% (15 mm), and 81% (20 mm) as the criterion was relaxed from contact to 20 mm. Similarly, specificity of the DWI-MAP classifier across epilepsy children decreased from 99% (contact) to 96% (5 mm), 94% (10 mm), 89% (15 mm), and 85% (20 mm).

In normally developing children, the DWI-MAP classifier predicted language areas as localized with fMRI with high accuracy: 58% (contact), 70% (5 mm), 77% (10 mm), 82% (15 mm), and 84% (20 mm). In children with focal epilepsy, the DWI-MAP classifier also found high accuracy for the fibers terminating in the proximity to three language areas determined by ESM: 59% (contact), 76% (5 mm), 82% (10 mm), 90% (15 mm), and 91% (20 mm).

Correlation of streamline volume change and postoperative language deficit assessed using DWI-MAP classifier

Two children with left hemispheric resection (patients 13 and 14) had postoperative language deficit, which was transient but required speech therapy. Figure 6 summarizes the longitudinal changes of streamline volumes in two major language pathways: C_1 : Broca's area-Wernicke's area connecting the regions associated with expressive aphasia and receptive aphasia, which were obtained from seven children with focal epilepsy who had no or minimal presurgical language impairment. Five children without a postoperative language

deficit showed either no change or slightly increased streamline volume in C₁:Broca's area-Wernicke's area, likely reflecting normal development of these fibers (left plot of Fig. 6). In contrast, two children with postoperative language deficit (patients 13 and 14) showed a significantly reduced volume in C₁:Broca's area-Wernicke's area of DWI-MAP classification. One of these two children, an 8-year-old boy (patient 14), who had resection of the inferior portion of the left pre- and postcentral gyri, showed a marked deterioration of verbal fluency. The other, a 5-year-old boy (patient 13), who had a similar resection in addition to removal of the inferior parietal lobule, showed expressive dysphasia and poor articulation, which subsided 2 years after surgery. This observation supports our hypothesis that the proposed DWI-MAP method can effectively predict a postsurgical language deficit, and suggests that postsurgical language outcome may substantially differ according to the extent of white matter damage encompassing specific language pathways.

Discussion

By extending a maximum a posteriori probability (MAP) classification to localize different language pathways, the present study provided encouraging preliminary data to justify further studies aimed at determining whether DWI tractography can be used to detect multiple white matter pathways connecting language areas. Compared with fMRI and ESM, the proposed DWI-MAP classifier achieved high accuracies of 77% (fMRI) and 82% (ESM) to localize distinctive language areas within an error range of 10 mm (i.e., spatial resolution of ESM). This result has important implications for presurgical planning for children with intractable focal epilepsy or other neurologic conditions, without any extra cost of performing additional imaging.

Conventional ROI-based tractography approaches have focused mainly on the arcuate fasciculus, connecting Broca's area to Wernicke's region, the key white matter tract in language function. However, recent human studies, applying advanced neuroimaging (fMRI, DWI) and electrophysiologic techniques, have demonstrated that the anatomy of cortical language sites and pathways is more complex, and involves additional regions such as the premotor cortex as well as the inferior parietal region.^{19–21} This network of cortical nodes and white matter connections forms a complex language system distributed throughout three cerebral regions. Organization of this network can be even more complex and atypical in patients with chronic epilepsy, where some components of this network may be reorganized due to early brain injury or malformation.¹

The proposed DWI-MAP approach tested in this study may fulfill a clinical need by providing a new noninvasive, objective tool to localize different language areas and tracts in children with epilepsy without any added financial cost. With further validation, this classifier could be also useful for investigating different functional pathways that fMRI and/or ESM are not able to detect in young children with focal epilepsy. Another potential application of the proposed MAP classifier may be to improve prediction of postoperative language deficits. Our preliminary data suggest that postoperative reduction in the streamline volume of language pathways is associated with postoperative language deficits. Our data also demonstrate that the DWI-MAP classifier could efficiently monitor the longitudinal processes of white matter development. Further studies are required to evaluate

how reorganization of these pathways can be detected and how these compensatory changes in unresected pathway segments affect language function postoperatively.

DWI tractography in the presence of structural lesions requires careful consideration of data analysis to avoid the effect of pseudo-diffusion that can be created by slow blood flow in the lesion capillary bed, which could increase isotropic components in DWI signals. Our ICA +BSM has an isotropic ball compartment, which can provide a comprehensive model of water diffusion in the lesion environment, leading to better accuracy to resolve the orientations of CST and AF in the vicinity of a structural lesion.⁹ For instance, our previous study reported that the DWIMAP classifier could identify functional pathways of the primary motor tracts without any confound by structural lesions (i.e., accuracy of hand/leg CST = 77%/83% without lesion, 75%/88% with lesion), suggesting that the performance of DWI-MAP to localize accurate AF may not be significantly affected by structural lesions.⁷

However, the proposed DWI-MAP classifier has several limitations for clinical translation. First, the accuracy of DWI-MAP is critically affected by all potential errors in both spatial normalization (native space vs. atlas template) and registration (ESM vs. MRI). In the present study, the SPM DARTEL package was used to transfer the maps of $P(x,y,z|C_i = 1,2,3,4,5,6)$ into individual subject's space. Other sophisticated methods such as fast diffeomorphic landmark-free registration should be investigated to improve the accuracy of spatial normalization in large cohorts.^{22,23} and examine whether the performance of the DWI-MAP classifier may be affected by the age-related variation of brain geometry and maturation. In addition, future studies are warranted to determine how the performance of the DWI-MAP classifier is affected by the size and location of lesions observed in patients with focal epilepsy. Second, the current fMRI assessment of "semantic language areas" activated by audio signals could preferentially highlight receptive language regions. This experimental confound, where fMRI seems more calibrated for receptive language function, is a major problem, especially since the DWI-MAP classifier is based on fMRI data as the gold standard. Thus to minimize potential discrepancy between fMRI and ESM, ESM-based DWI-MAP classifiers should be tested with fMRI-based DWI-MAP classifiers. Finally, the present study failed to recruit any ESM cases localizing the language area of BA 39 (see "ESM: epilepsy" in Fig. 5 lacking overlap percentage in the vicinity of BA 39). Furthermore, other language areas such as basal temporal area were not included.²⁴ Thus, current DWI-MAP classifier was limited to detect a part of language system associated mainly with direct/indirect AF segments in left hemisphere, but can be feasibly extended if sufficient ESM cases are available. We did not investigate the effect of distance between the determined language cortex and resection boundary on postoperative language deficit because this was beyond the scope of the present study. We will investigate this in a future study as we collect additional postoperative language outcome data.

In conclusion, the present study reports preliminary results to provide proof-of-concept data on the utility of the DWI-MAP classifier to detect specific language tracts in children. It is clear that this approach needs to be tested further and the results need to be confirmed in a much larger sample, and in prospective studies evaluating changes in specific language tracts and associated changes in language functions postoperatively.

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Biography

Dr. Jeong-Won Jeong is an Assistant Professor and MRI physicist at Wayne State University Medical School, Detroit, MI, U.S.A.

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Figure 1.

Group average maps of semantic fMRI activations obtained from 12 typically developing children. Broca's area (BA 44/45 at $MNI_{xyz} = [-48\ 20\ -7]$), Wernicke's area (BA 22 at $MNI_{xyz} = [-60\ -12\ 1]$), premotor area (BA 6 at $MNI_{xyz} = [-41\ -2\ 43]$), and inferior-parietal area (BA 39 at $MNI_{xyz} = [-26\ -76\ 45]$) were presented from left to right.

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Figure 2.

A representative example of five different language pathways in a typically developing children obtained from ICA+BSM tractography combined with fMRI. Seed regions were defined by cortical areas determined by fMRI activations, in “Wernicke’s area” (burgundy), “Broca’s area” (cyan), “premotor area” (blue), and inferior parietal area (green). Each pair of two activation areas was applied to sort out individual language pathways, “Broca’s area-Wernicke’s area” (green), “Broca’s area-premotor area” (red), “premotor area-Wernicke’s area” (yellow), “premotor area-inferior parietal area” (magenta), and “Wernicke’s area-inferior parietal area” (blue).

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Figure 3.

DWI-driven probability representation of “ C_1 :Broca’s area-Wernicke’s area,” “ C_2 :Broca’s area-premotor area,” “ C_3 :premotor area-Wernicke’s area,” “ C_4 :premotor area-inferior parietal area,” “ C_5 :Wernicke’s area-inferior parietal area,” and “ C_6 :other region.” Each map shows the probability of a voxel that belongs to each pathway in 12 healthy children.

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Figure 4.

Automatic detection of five language pathways using the DWI-MAP classifier obtained from four children with focal epilepsy. To demonstrate the reliability of the MAP classification, five pathways including C₁:Broca's area-Wernicke's area (green), C₂:Broca's area-premotor area (red), C₃:premotor area-Wernicke's area (yellow), C₄:premotor area-inferior parietal area (magenta), and C₅:Wernicke's area-inferior parietal area (blue) are shown with corresponding ESM clusters (burgundy: receptive aphasia, cyan: speech arrest, blue: expressive aphasia).

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Figure 5.

Comparison of DWI-MAP classification with fMRI and ESM. Group comparisons of fMRI ($n = 12$ normal children) and ESM ($n = 14$ children with a diagnosis of focal epilepsy of left-hemispheric origin, patients 1–14) were performed with corresponding DWI-MAP classifications of C₁:Broca's area-Wernicke's area, C₂:Broca's area-premotor area, and C₃:premotor area-Wernicke's area. To assess the accuracy of localization provided by DWI-MAP classifier, ROC curves of healthy children (◆) and epilepsy children (■) were plotted

at five different levels of Euclidean distance from cortical terminal of individual fibers in $C_i = 1,2,3$ to either its nearest fMRI cluster or ESM electrode.

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Figure 6.

Fiber volumes in C₁:Broca's area-Wernicke's area of two longitudinal DWI data obtained from before and after surgery (n = 7, five epilepsy children with no postoperative language impairment and two epilepsy children who developed postoperative aphasia). The month of surgery is indicated by 0.

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Clinical data, imaging, and surgical pathology findings of the 17 children with focal epilepsy

Table 1

Patient number	Age/gender	Duration of epilepsy (year)	Seizure type	Seizure onset lobe(s)	FDG-PET	MRI (pathology)	Presurgical cognitive function
1	12/M	8	Focal	Lt T	↓	Dysplasia (dysplasia)	Regular education class
2	17/M	12	Focal	Lt T	↓	Increased FLAIR signal (tumor)	Regular education class
3	11/F	10	Focal	Lt T	↓	Increased FLAIR signal (gliosis)	Special education class
4	4/M	1	Focal	NA (Frequent spikes in Lt T)	↓	Cavernoma (cavernoma)	Preschool; normal development
5	9/F	1	Focal	Lt T	↓	Increased FLAIR signal (tumor)	Regular education class
6	6/F	4	Focal and sGTC	Lt T	↓	Nonlesional (hippocampal sclerosis)	Regular education class
7	10/F	3	Focal	Lt T	↓	Increased FLAIR signal (tumor)	Regular education class
8	12/F	3	Focal	Lt T	↓	Nonlesional (hippocampal sclerosis)	Regular education class
9	14/F	2	Focal	Lt T	↓	Increased FLAIR signal in Lt F (hippocampal sclerosis)	Regular education class
10	15/F	2	Focal	Lt T	↓	Increased FLAIR signal (tumor)	Regular education class
11	5/F	1	Focal and sGTC	Lt FT	↓	Cortical atrophy (gliosis and inflammation)	Regular education class
12	15/F	1	Focal and sGTC	NA (lesion in Lt P)	↓	Increased FLAIR signal (tumor)	Regular education class
13	5/M	3	Focal and sGTC	NA (Frequent spikes in Lt PFT)	↑	Nonlesional (gliosis)	Preschool; (+) speech delay
14	8/M	2	Focal and sGTC	Lt P	↓	Cortical atrophy (gliosis and inflammation)	Regular education class; (+) developmental delay
15	4/M	3	Focal	Rt PT	↓	Cortical tuber (cortical tuber)	Preschool; (+) developmental delays
16	6/M	5	Focal and sGTC	Rt PO	↓	Ulegyria (gliosis)	Preschool; (+) developmental delays
17	10/M	9	Focal and sGTC	Rt P	↓	Dysplasia (dysplasia)	Special education class

M, male; F, female; sGTC, secondarily generalized tonic-clonic; Lt, left; Rt, right; F, frontal; T, temporal; P, parietal; O, occipital; ↓, hypometabolism; ↑, hypermetabolism; FLAIR, fluid-attenuated inversion recovery.