The Arcuate Fasciculus: Analysis of White Matter Connection in Thai Language System Using Diffusion Tensor Imaging and Feasibility in Lateralization of the Dominant Hemisphere

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ABSTRACT

Objective: The arcuate fasciculus (AF) is classically described as white matter connecting Broca's and Wernicke's area, which is important for language processing in human. In a previous study, lateralization of the AF to the left in normal healthy people was described. However, using the AF for lateralization of the dominant hemisphere in Thai speakers with Thai mother tongue language has not been studied. The purpose of this study was to demonstrate any feasibility that AF (by diffusion tensor imaging (DTI)) could be used to lateralize the dominant hemisphere in native-Thai speakers.

Methods: Ten normal official Thai speakers with Thai mother tongue language (5 males, 5 females, mean age 24.9 years old; range 22-37 years old) were studied with DTI by 3T MRI using deterministic method in post processing software. The fractional anisotropy, relative fiber density index (RFD) and asymmetry index (AI) were analyzed to determine the dominant hemisphere. Comparison to functional hemispheric language lateralization from functional magnetic resonance imaging (fMRI) was done.

Results: Slightly higher fractional anisotropy (FA) values for the left AF as compared with the right AF in all subjects were noted. The lateralization of RFD to the right were found in 5 subjects, to the left in 3 subjects and no definite lateralization in 2 subjects. The lateralization of AI to the right was found in 5 subjects, to the left in 3 subjects and no definite lateralization in 2 subjects. The lateralization from the fMRI language paradigm using visual analysis of all subjects were to the left. The anterior end of the AF tract was at par opercularis in 6, par triangularis in 3 and middle frontal gyrus in 5 subjects. The posterior end of the AF was at superior temporal gyrus in 7, middle temporal gurus in 9 and angular gyrus in 4 subjects. The area of termination of the AF was not correlated with activation from fMRI in 6 subjects when fused with word paradigm and in 7 subjects when fused with verb paradigm.

Conclusion: The way to reconstruct the AF is feasible with practical method and software. However its clinical value to determine the dominant hemisphere in Thai subjects needs to be explored more with more advanced and promising technique.

Keywords: Arcuate fasciculus, diffusion tensor imaging, Thai language, dominant hemisphere

Abbreviations: [AF: Arcuate fasciculus; **DTI:** Diffusion tensor imaging; **FA:** Fractional anisotropy; **MD:** Mean diffusivity; **AD:** Axial diffusivity; **RFD:** Relative fiber density index; **AI:** Asymmetry index; **fMRI:** Functional magnetic resonance imaging]

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INTRODUCTION

The AF was originally described as white matter pathway connecting inferior posterior frontal lobe (Broca's area) and posterior superior temporal lobes (Wernicke's area) which is a bundle of great importance for language processing. Conduction aphasia is described if this connection is disrupted. Fluent speech with phonemic paraphasia and self correction with reasonably good comprehension is presented but the repetition of long words and sentences is disrupted.

Currently, the AF is proposed to be part of dorsal stream in the dual-stream pathway model of language connection for mapping auditory speech sounds to articulation.[1-10] The dorsal stream comprises of the superior longitudinal fasciculus and AF. However there are some different opinions about the origins, terminations and extent of these particular fiber pathways.

The non-invasive study such as fMRI and DTI were used for studying the relationship between functional hemispheric lateralization of language and structural asymmetry of the AF. Besides direct pathology study or other invasive study, current data support fMRI using blood oxygenation level dependent (BOLD) techniques as a valid alternative to the intracarotid amobarbital procedure.[11] For DTI, the degree of anisotropy with directional movement of water molecules in the particular white matter fiber can be derived and measured from DTI to be FA, ADC, fiber tractography and RFD can be calculated for comparing differences in both sides of hemispheres.[12-15] In fMRI, cooperation of the patients is needed, but for young patients or those with neurological deficit and non-cooperation, DTI may be more useful for dominant hemispheric lateralization in this clinical setting.

Many previous studies have demonstrated more prominence at the left side of the AF in healthy humans by using advanced MRI technique. DTI has demonstrated more FA and RFD with lateralization to the left cerebral hemisphere of the AF.[12,13,16,17,18] However, these studies are English language base analyses which are probably not suitable in routine use for Thai native speaker people. Thai language is a tonal language in which different pitch have different meaning. Therefore, a feasibility of difference in thinking and processing the verbal sounds for speaking as compared with other language is proposed.

There are many studies about the AF with diseased patients. Both MD and FA were less lateralized in the autistic group.[19] The less lateralization of the AF appears to affect poorer language function. Another study in schizophrenia patients had shown abnormal FA and AD lateralization as compared with healthy controls which were found to be associated with psychotic symptoms.[20]

In this study we were interested in the AF as its importance in language network. To the best of our knowledge, a practical method to reconstruct the AF is available and more robust from the other fiber tracts in the language pathway. No study in normal healthy patients in Thai people about this interesting language pathway has been done. The objective of this study was to demonstrate any feasibility that the AF (by DTI) could be used to lateralize the dominant hemisphere in native-Thai speakers.

MATERIALS AND METHODS

This study was part of the study evaluating Thai language paradigm for fMRI to lateralize dominant hemisphere. The study was approved by The Siriraj Institutional Review Board (Si.482/2012) and written informed consent was given from all subjects. Ten normal official Thai speakers with Thai mother tongue language (5 males and 5 females, mean age 24.9 years; range 22-37 years) and educated to at least primary school level 6, were called for participation. A group of right-handedness adults was initially identified by using the Edinburgh's handedness questionnaire and rapidly confirmed by the Vase-Face test. After ruling out ones who had visual problem, the rest were screened for hearing with auditory Screening Test (Whispered Voice Test), and then administered with Language Screening Test (ALPS: Aphasia-Language Performance Scales, full score = 40) and Communication Checklist. None of the subjects had a known history of neurological disease.

Imaging was performed on a 3.0-T MRI (Archieva, Philips, the Netherlands). An 8-channel head coil was used for reception of the signal. For fMRI, a T2*-weighted gradientecho echo-planar imaging (EPI) sequence, sensitive to BOLD contrast, and covering the entire brain was used (TR = 3,000 ms, TE = 35 ms; acquisition matrix 64×63; FOV 24 cm; 32 contiguous slices with slice thickness of 5 mm). Thai Language paradigm for fMRI were performed by using words (presented in Thai language) and verb generation shown as picture in the monitoring software. Block design was used, each task = 300 sec or 5 min for word and verb generation (30x2 sec (rest/activate) x 5 blocks). Acquisition time was 5:09 minutes, which included 9 seconds of dummy scans that were discarded from further analysis. DTI study was performed with a single shot, diffusion weighted spin echo EPI sequence; 32 diffusion encoding directions; diffusion weighting factor b=800 s/mm^2 in addition to a single reference image (b=0); acquisition matrix 112x110; FOV 22.4 cm; voxel size = 2 mm x 2 mm with 60 contiguous slices with slice thickness of 2.3 mm; TR = 10371 ms; TE = 54 ms; flip; and angle = 90°. Acquisition time was 12:42 minutes. DTI data were processed to perform diffusion tractography of the AF and analyzed with extended MR Workspace (Release 2.6.3.3, 2011; Philips, medical systems, the Netherlands).

Method to draw ROI (region-of-interest) was reviewed from previous literatures such as from Nucifora et al.[12], Fletcher et al.[19], Catani et al.[21], and Akiko Hosomi et al.[22] In the present study, we chose the seeding and target ROI based on paths between two ROI methods. The automatic volumetric segmentation of the AF required as input a manual delineation of the endpoint regions of the tract in the DTI. The ROIs were manually outlined on color images of the major diffusion tensor eigenvector (red=left/right, green=anterior/posterior, and blue=superior/inferior). The first ROI was placed in the coronal view of the AF which is the most obvious green color fiber tract adjacent to the blue color of the corticospinal tract (Fig 1A). The second ROI was placed in the sagittal view where the AF curved infero-laterally (purple to blue color as it curved) (Fig 1B). Deterministic method of tractography was done (Fig 2) with threshold of FA value at least 0.15 and threshold angle of 60°.[20] The average value of FA was calculated. The RFD (defined as left fiber density – right fiber density)/ (left fiber density +right fiber density) value ranged from -1 to + 1; when RFD ≥0.10 was predetermined as left-sided lateralization and RFD ≤-0.10 was predetermined as right-sided lateralization. The AI was defined as $((voxel_L \times FA_L) - (voxel_R \times FA_R)) / ((voxel_L \times FA_L) + (voxel_R \times FA_R))$, where $voxel_L$/ $voxel_R$ and FA_L/ FA_R were the number of voxels and FA values of the AF on the left and right side respectively. The AI was used to quantify the degree of asymmetry for each participant and the values range from -1 to + 1, when an AI ≥0.10 was determined as left-sided lateralization or an AI ≤-0.10 as right-sided lateralization.

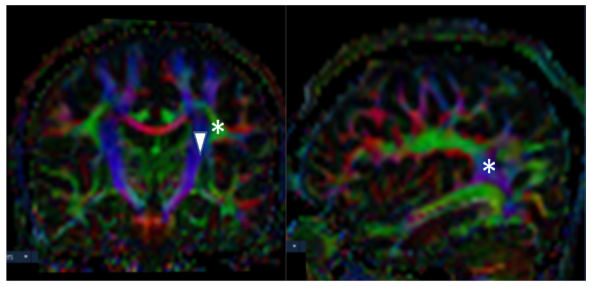

Fig 1. The first ROI was placed in coronal view of the AF (*) which was the most obvious green color fiber tract adjacent to the blue color of the corticospinal tract (∇) (Fig 1A). The second ROI was placed in sagittal view which the AF curving infero-laterally (purple to blue color as it curved) (Fig 1B).

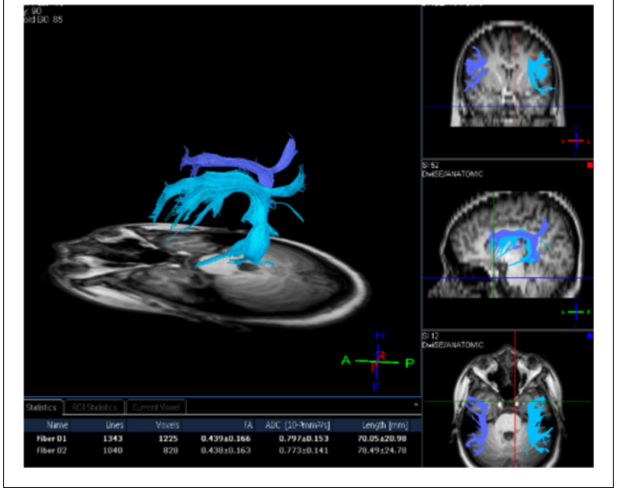

Fig 2. The left and right AF from diffusion tractography.

RESULTS

The patients' demographic data has been shown in Table 1. Slightly higher FA value for the left AF as compared with the right AF in all subjects was noted. (Table 2). The lateralization to the right of RFD was found in 5 subjects, to the left in 3 subjects and no definite lateralization

TABLE 1. Demographic data.

Number	Gender	Age	Education	Handedness	Auditory Screening Test (Whispered Voice Test)	Language Screening Test (ALPS) (Full Score = 40)	Communication Checklist
1	Female	37	Grade 9	Right	Normal	Normal (40)	Normal
2	Female	22	Post-graduate student	Right	Normal	Normal (39.5)	Normal
3	Male	23	Post-graduate student	Right	Normal	Normal (40)	Normal
4	Female	22	Post-graduate student	Right	Normal	Normal (40)	Normal
5	Female	22	Post-graduate student	Right	Normal	Normal (39)	Normal
6	Male	25	Post-graduate student	Right	Normal	Normal (38.5)	Normal
7	Male	26	Post-graduate student	Right	Normal	Normal (39.5)	Normal
8	Male	24	Post-graduate student	Right	Normal	Normal (40)	Normal
9	Female	29	Resident	Right	Normal	Normal (40)	Normal
10	Male	29	Post-graduate student	Right	Normal	Normal (38.5)	Normal

Abbreviation: ALPS: Aphasia-Language Performance Scales

TABLE 2. Relative fiber density index (RFD), Fractional anisotrophy (FA) and Asymmetry index (AI) in each subjects.

Subjects	RFD	FA		AI
		Left	Right	
1	-0.13	0.403	0.381	0.02
2	-0.55	0.405	0.381	-0.33
3	0.5	0.447	0.423	0.57
4	0.13	0.439	0.438	0.19
5	-0.40	0.416	0.407	-0.26
6	-0.06	0.432	0.414	0.07
7	0.001	0.429	0.386	0.08
8	-0.37	0.495	0.428	-0.21
9	-0.63	0.459	0.404	-0.31
10	-0.27	0.395	0.389	-0.23
		Mean 0.432	Mean 0.4051	

Abbreviations: RFD: Relative fiber density index; FA: Fractional anisotrophy; AI: Asymmetry index

in 2 subjects. The lateralization to the right of AI was found in 5 subjects, to the left in 3 subjects and no definite lateralization in 2 subjects (Table 3).

In fusion image with anatomical T1W (Table 4), the anterior end of the AF tract was at par opercularis in 6 subjects, par triangularis in 3 subjects and middle frontal gyrus in 5 subjects. There were 4 subjects with 2 separate anatomical points of anterior end. The posterior end of the AF tract was at superior temporal gyrus in 7 subjects, middle temporal gurus in 9 subjects and angular gyrus in 4 subjects. Only 3 subjects had one anatomical point of posterior end. Interestingly, 5 subjects had all or some part of anterior termination of the AF at the middle frontal gyrus which was not the classic Broca's area (par opercularis and/or par triangularis). Also findings of the posterior termination at middle temporal gyrus (9 subjects) and angular gyrus (4 subjects) were not the classic Wernicke's area (postero-superior temporal gyrus).

The lateralization from the language fMRI study by visual analysis of all volunteers was to the left. When fused with the fMRI from word paradigm, the termination of the AF did not correlate with the activation from fMRI in 6 subjects. When fused with verb paradigm, there were 7 subjects whose termination of AF did not correlate with activation from fMRI (Fig 3), (Table 5).

TABLE 3. Lateralization of Relative fiber density index (RFD), Fractional anisotrophy (FA) and asymmetry index (AI)

Lateralization	Number of subjects		
	RFD	FA	AI
Right	5	0	5
Left	2	10	2
No	3	0	3
No but slightly to the right *	2	-	0
No but slightly to the left **	1	-	3

*RFD or AI between 0.0 - 0.1, **RFD or AI between -0.1 - 0.0

Abbreviations: RFD: Relative fiber density index; FA: Fractional anisotrophy; AI: Asymmetry index

DISCUSSION

Many fiber tracts have been described to involve in language pathway such as AF, uncinate fasciculus, inferior occipitofrontal fasciculus, middle longitudinal fasciculus and superior longitudinal fasciculus. Currently, it is a practical way

TABLE 4. The termination of the AF when fusion with anatomical T1w

	Anterior termination			Posterior termination		
No.	PO	PTG	MFG	STG	MTG	AG
1	+		+	+	+	+
2			+			+
3		+		+	+	
4	+	+		+	+	+
5	+			+	+	
6	+			+	+	
7	+		+	+	+	+
8			+		+	
9	+	+			+	
10			+	+	+	
sum	6	3	5	7	9	4

PO : Par opercularis; PTG : Par triangularis; MFG : Middle frontal gyrus; STG : Superior temporal gyrus; MTG : Middle temporal gyrus; AG : Angular gyrus

Abbreviations: PO: Par opercularis; PTG: Par triangularis; MFG: Middle frontal gyrus; STG: Superior temporal gyrus; MTG: Middle temporal gyrus; AG: Angular gyrus

to reconstruct the AF as mentioned earlier. Therefore in this study, we intended to explore whether this tract could be used for lateralization of the dominant hemisphere in clinical setting and to examine its pathway related to the functional language anatomy.

In previous studies, the leftward lateralization of the AF included RFD and AI (included voxel size and FA) and were proposed.[12,13,16,17,18]

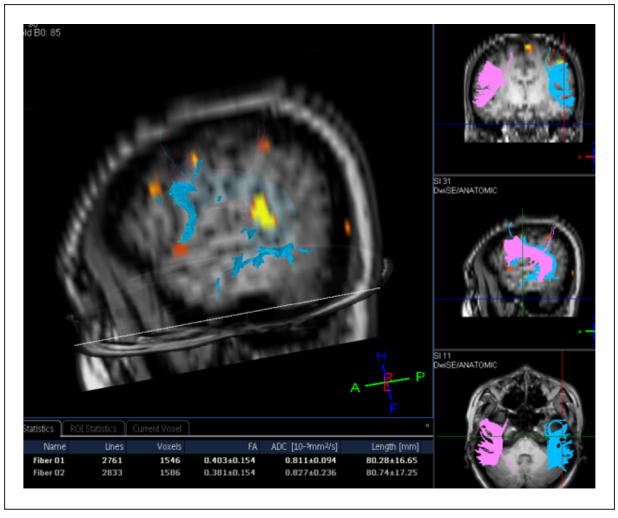

Fig 3. The AF termination when fusion and compare with activation from fMRI : Anterior termination of the AF at MFG and PO; Posterior termination of the AF at STG and MTG; Activation of the fMRI at PO, STG and AG; MFG : Middle frontal gyrus; PO : Par opercularis; STG : Superior temporal gyrus; MTG : middle temporal gyrus; AG : Angular gyrus, fMRI : Functional MRI

In our study, 5 subjects had right lateralization of the RFD and the AI which did not agree with the previous studies. The possible explanation of the different result might be: (1) Considering post processing technique; in terms of scanning technique, the present technique was comparable with the previous studies.[12,13,16,17,18] However, post processing DTI technique in this study was rather different. With methods of deterministic techniques, there were limitations at some points such as crossing fiber and the very curve fiber tract such as optic radiation, uncinate fasciculus and in our study, the AF. Most previous studies used more complex research tools for studying in voxel base analysis and probabilistic method with probably more accuracy for analysis of the crossing fiber, but currently, most of these softwares are not routinely used and still not widely available in clinical practice. Therefore, deterministic method is still widely available in commercial software and simple to use with reasonable results. Further study is probably needed to confirm clinical usefulness of deterministic technique in studying AF to determine the dominant hemisphere. (2) The studied population: The previous studies from Europe and the USA showed precise lateralization of the AF to the left which was not found in our study. Difference in features of the language may be the explanation. Thai language has a feature of tone or music and might be like

TABLE 5. The AF termination when fusion and compare with activation from fMRI.

No	Word				Verb				Lateralization
	Broca's area		Wernicke's area				Broca's area		Wernicke's area
1	POC		STG, AG		PTG	*NC*	STG, AG		L
2	-	*NC*	STG, AG		-	*NC*	STG, AG		L
3	PTG		STG		PTG		MTG		L
4	POC		STG, AG		PTG		STG, AG		L
5	-	*NC*	STG, AG		POC		AG	*NC*	L
6	-	*NC*	-	*NC*	POC		STG, MTG		L
7	POC		STG, MTG		-	*NC*	STG		L
8	PTG	*NC*	STG, MTG		PTG	*NC*	STG, MTG		L
9	PTG		STG	*NC*	POC		STG	*NC*	L
10	PTG	*NC*	STG		POC	*NC*	STG		L

Abbreviations: NC = Not correlate with the termination of the arcuate fasciculus; - = No activation in fMRI; PO : Par opercularis; PTG : Par triangularis; MFG : Middle frontal gyrus; STG : Superior temporal gyrus; MTG : Middle temporal gyrus; AG : Angular gyrus

a speech prosody when the Thai subjects think or process it. The prosody rises in pitch at end of a sentence when asking a question or the tone that represents emotional state.[23] In Thai language, the same word is different in meaning if pronounced in different pitch. Some previous studies have revealed more prominent activation from fMRI in a particular area of the right hemisphere such as activation in the right inferior frontal gyrus and right lateralized posterior temporal lobe in prosodic processing tasks when compared with non-prosodic tasks. Right hemisphere homologue of Broca's area involved in the production of speech prosody have been reported.[24-28] The previous study using fMRI revealed the posterior right middle temporal gyrus was involved in the representation of meaningful prosodic sequences and the right middle temporal gyrus was bilaterally connected to the frontal lobe.[29] However, currently no direct study about the AF correlated with the prosody task has been reported.

As mentioned, nearly equal accuracy was proposed by using fMRI for lateralization of the dominant hemisphere as compared with the gold standard Wada's test. A more non-invasive way to lateralize language dominant hemisphere is possible with lateralization index or visual analysis of the activated cortex. In the present study, evaluation from visual analysis showed that all of the subjects had left lateralization from the language paradigm fMRI, which was not concordant with lateralization from the RFD and the AI from the AF. It was indicated that the AF was processed from the available techniques and commercial software was not precise to determine lateralization.

In our study, most of the AF terminated anteriorly at inferior frontal gyrus (par triangularis and par opercularis) and there were some subjects with anterior termination of the AF at the middle frontal gyrus, which is premotor region. Some studies proposed the AF terminated in the more dorsal premotor and lateral prefrontal cortex distal to the classic language homologues.[2,5,30] For the posterior termination, the result varied as described in a previous study. Termination at posterior superior temporal gyrus, middle temporal gyrus, angular gyrus and supramarginal gyrus have been described in other studies and also in our study. Some of the AF terminations were not correlated with the activation from classic Broca's and Wernicke's area. It was not surprising according to the modern language model of dual stream pathway which mentioned multiple fiber pathways beyond the classic AF and classic area of the Broca's and Wernicke's involved in language system.[2] The dorsal ventral premotor area (area of middle frontal lobe) seen as anterior termination of the AF was the example that termination could be in other areas beyond the classic pars triangularis and pars opercularis of the inferior frontal gyrus.

CONCLUSION

The way to reconstruct the AF is feasible with practical method and software. However, its clinical value to determine the dominant hemisphere in Thai subjects needs to be explored more with more advanced and promising technique.

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