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Correlation Between Speech Repetition Function and the Arcuate Fasciculus in the Dominant Hemisphere Detected by Diffusion Tensor Imaging Tractography in Stroke Patients with Aphasia

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Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

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Background: Repetition disorder can be used as an important criterion for aphasia classification, and damaged arcuate fasciculus in the dominate hemisphere has been reported to be closely related to repetition disorder, but the underlying neurological mechanism remains unclear.

Material/Methods: Fifteen stroke patients with poststroke aphasia and 9 healthy controls were included in the study. The value of fractional anisotropy (FA) in the dominate arcuate fasciculus in stroke patients and healthy controls were measured using DTI. We also assessed their repetition dysfunction with the Aphasia Battery of Chinese (ABC) assessment and calculated the correlation between the FA values in the dominate arcuate fasciculus and ABC scores of word repetition and sentence repetition.

Results: There was a moderate correlation between the total score of repetition evaluation and the FA value of injured arcuate fasciculus in the dominant hemisphere ($r=0.551$, $P=0.033$). We found no correlation between the score of word repetition and the FA value of injured arcuate fasciculus in the dominant hemisphere ($r=0.330$, $P=0.230$), but there was a strong correlation between the score of sentence repetition and the FA value of injured arcuate fasciculus in the dominant hemisphere ($r=0.795$, $P\leq 0.001$).

Conclusions: We found that unintegrated left arcuate fasciculus might be related to the repetition dysfunction after stroke, especially sentence repetition deficit, which suggests that sentence repetition evaluation could be used to indicate the integrity of the arcuate fasciculus in the dominant hemisphere after stroke.

MeSH Keywords: **Aphasia • Diffusion Tensor Imaging • Stroke**

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Background

About 21–38% of acute stroke patients and 10–18% of chronic stroke patients are reported to have aphasia [1–3]. Repetition disorder is a common symptom of aphasia, such as Wernicke aphasia, Broca aphasia, conduction aphasia, and complete aphasia, and may have various degrees of repetition deficit. Moreover, a repetition disorder could be used as an important criterion for aphasia classification. However, the neurological mechanism underlying repetition disorder in stroke patients with aphasia remains unclear.

Arcuate fasciculus (AF) is a white-matter bundle connecting the frontal, temporal, and parietal cortical areas [4]. The direct pathway (known as the classic pathway, which connects the temporal cortex to the prefrontal cortex) has been linked to phonetics production [5], whereas the indirect pathway (including the anterior segment connecting the inferior parietal cortex and Broca's area and a posterior segment connecting temporal and parietal regions) has been linked to verbal comprehension (semantic/phonological transcoding, complex syntactic processing) [6]. Most previous research has shown that individuals with impaired repetition have underlying damaged AF in the dominant hemisphere [7–9]. Lichtheim et al. [10] believed that a broken connection between the auditory speech center and the spoken expression center was the physiological basis of the repetition dysfunction and that the main structure connecting the 2 language centers is the AF in the dominant hemisphere. Other researches have shown that preservation of the left AF is associated with positive language outcome [11,12]. However, occasional case reports show that this association between the AF and repetition performance has not been consistently upheld. Selnes et al. reported a patient with dominant hemisphere AF lesion presenting normal repetition performance by diffusion tensor imaging (DTI) [13]. Also, repetition is a complex process in which word repetition and sentence repetition involve different pathways. For example, after speech therapy, a stroke patient with aphasia had significant word repetition function improvement, while sentence repetition improvement was not obvious [14]. Thus, whether repetition deficits are related to a lesion of the AF remains an open question. Furthermore, if there is a correlation between these, which subtypes of the repetition performance (word repetition or sentence repetition) are more easily affected?

DTI, as an effective neuroimaging technique for identification of white-matter fibers in the living brain, can be used to evaluate the integrity of AF in the dominant hemisphere [15]. In this study, we attempted to explore the relationship between the integrity of AF in the dominant hemisphere and repetition function (not only the whole repetition performance, but also including the word repetition and sentence repetition) using DTI technology in poststroke aphasia patients. We also aimed to identify clinical predictors for aphasia stroke patients.

Material and Methods

Subjects

The stroke patients with poststroke aphasia (the aphasia group) were recruited from the Department of Rehabilitation and the Department of Neurology in the First Affiliated Hospital of Jinan University between 2015 and 2016.

Inclusion criteria were: 1) stroke, as defined by the classification and diagnosis of cerebrovascular diseases in the Fourth National Conference in China on Cerebrovascular Diseases (1995) [16], with DTI examination clearly indicating infarction or bleeding lesions in the AF in the dominant hemisphere (left hemisphere), but not in the nondominant hemisphere; 2) patients diagnosed with aphasia with repetition dysfunction based on the Aphasia Battery of Chinese (ABC) assessment [17]; 3) first-ever stroke(s) within 6 months of onset; 4) between 40 and 75 years old, with education of more than 6 years; 5) all patients were right-handed, as assessed by the Edinburgh Handedness Questionnaire [18]; 6) patients who were able to complete the ABC assessment and MRI image scanning.

Exclusion criteria were: 1) mental illnesses, organic changes, or other diseases affecting brain function; 2) a severe hearing impairment, visual impairment, or dysarthria; 3) contraindications for magnetic resonance examination, such as vascular stents, cardiac pacemakers, and metal implants; 4) unstable condition, such as heart failure and pulmonary insufficiency.

Nine healthy right-handed subjects with age and years of education matched with the patient group participated in this study as the healthy control (HC) group (3 females, 6 males; mean age, 53.4 ± 9.3 years; demographic information shown in Table 1), who could complete the MRI image scanning and had no brain organic disease, history of psychotropic drug abuse, speech disorders, or cognitive impairments.

Our study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (No. 2014-022), and informed consent was obtained from all subjects or their families.

Repetition function assessment

The ABC was used to evaluate the language function of 15 patients in our study, which is based on the cultural specificity of the Chinese and the Western Aphasia Battery (WAB) [19]. The reliability and validity testing were well performed in the Chinese population [20]. The ABC includes 9 subdomains for investigating the speech abilities involved in question and answer, comprehension, repetition, naming, reading, writing, structure and space, ability for use, and calculation. The repetition sub-item includes 2 parts: word repetition, and sentence repetition. The scores of total repetition performance (100 points),

Table 1. Subject demographics and diffusion tensor imaging data of the arcuate fasciculus.

Items	Aphasia group (n=15)	Control group (n=9)	P value
Age (years)	52.73±11.71	53.44±9.38	0.879
Sex			
Male	13	6	
Female	2	3	
Handedness	Right-handed	Right-handed	
Educational level (years)	11.200±4.074	10.444±3.245	0.345
Time from the stroke onset (months)	2.77±1.26	NA	
FA values of arcuate fasciculus			
Average FA value (left/dominated side)	0.290±0.108*	0.512±0.025	0.000
Average FA value (right/dominated side)	0.512±0.061	0.511±0.022	0.931
P value	0.000	0.923	

Values are presented as number or mean (±standard deviation). FA – fractional anisotropy; NA – not applicable. * Significantly differences between the Aphasia group and control group at $p < 0.05$.

word repetition performance (24 points), and sentence repetition performance (76 points) were used as observation indicators in our study. All assessments were completed by the same leading speech therapist in our hospital.

DTI data acquisition and processing

DTI was acquired on a 3.0 T Magnetic Resonance Imaging System (General Electric Discovery 750), as well as T1-weighted images and T2-weighted images. Scanning parameters were as follow: T1-weighted images (echo time, 30 ms; rotation angle, 15°; flip time, 4500 ms; slice thickness, 1 mm; voxel, 0.93×0.93×1 mm³; number of slices, 164), T2-weighted images (repetition time, 8000 ms; echo time, 165 ms; slice thickness/slice spacing, 1 mm/1.5 mm); DTI (repetition time/echo time, 5000 ms/68.0 ms; reconstructed to matrix, 128×128; field of view, 25.6×25.6 cm²; number of excitations, 1; b=1000 s/mm²; 25 dispersion-sensitive gradients; slice thickness/slice spacing=3 mm/0 mm).

Functool software (version 9.4.05a, General Electric Medical System) was used for DTI data processing, including three-dimensional reconstruction and the fractional anisotropy (FA) value measurement of the AF on the left hemisphere. The measurement site was placed underneath the inferior limbic gyrus (the position of the AF corner) (Figure 1A). Two regions of interest (ROIs) were selected to track left AF, ROI 1 on the posterior temporal lobe (Figure 1B), and ROI 2 on the posterior parietal lobe in the superior longitudinal fasciculus (Figure 1C) [21]. The area of ROI is 32 mm². The whole process

was performed by the same advanced radiologist. The FA values of the AF in each subject were measured 3 times, and the average was used in the analyses.

Statistical analysis

The data were statistically analyzed using SPSS 20.0 software. The continuous variables of 2 groups (the age, educational years, and FA value of AF in the dominant hemisphere) were measured by two-sample *t* test. The categorical variables (such as handedness and gender) were measured by the chi-square test. The correlation between the FA value of AF in the dominant hemisphere and the repetition performance (the word repetition score, the sentence repetition score, and the total score of repetition) were measured by Spearman correlation analysis. The statistical significance was accepted for *P* values <0.05.

Results

Fifteen stroke patients with aphasia (2 females and 13 males; mean age, 52.73±11.71 years) and 9 health subjects (3 females and 6 males; mean age, 53.44±9.38 years) were recruited to the aphasia group and control groups, respectively. There were no significant differences in age ($P=0.879$) and educational level ($P=0.345$) between the 2 groups. All stroke patients had left hemisphere stroke lesions: 8 were Broca aphasia, 2 were transcortical motor aphasia, 2 were transcortical mixed aphasia, 1 was nominal aphasia, and 2 were complete aphasia. They were all less than 6 months from the first stroke onset (mean

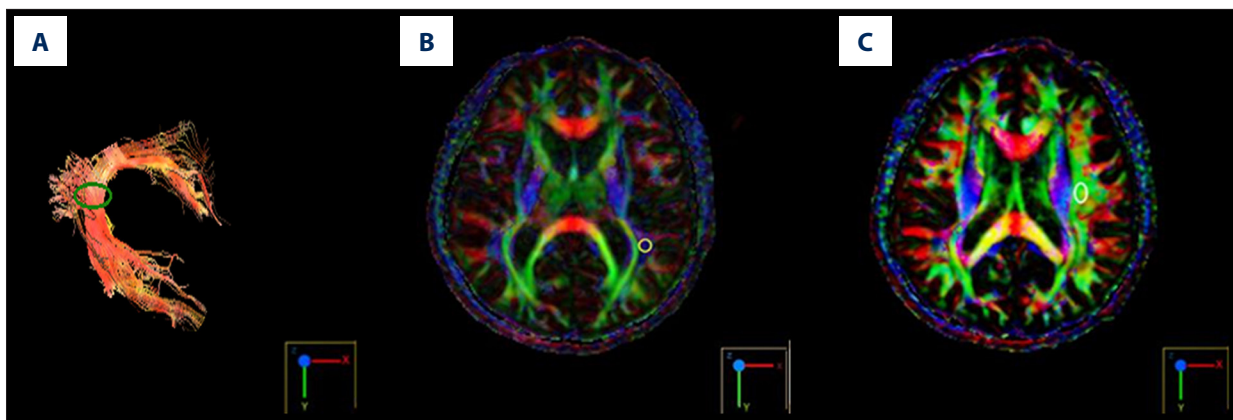


Figure 1. Diffusion tensor imaging of the arcuate fasciculus in the normal subject. (A) The FA value measurement point of the arcuate fasciculus (green circle); (B) The ROI 1 position (white circle); (C) The ROI 2 position (white circle). FA – fractional anisotropy; ROI – region of interest.

Table 2. Repetition evaluation (the subtest score of the Aphasia Battery in Chinese) and diffusion tensor imaging data of the arcuate fasciculus.

Patient No.	Word repetition	Sentence repetition	Total repetition	Total ABC	Stroke type	Brain regions injured	FA value of abdominal AF
1	24/24	30/76	54/100	137	Infarct and hemorrhage	L Basal Ganglia, Corona Radiata	0.270
2	3/24	0/76	3/100	37	Hemorrhage	L Basal Ganglia, Frontal lobe, Temporal Lobe	0.216
3	24/24	35/76	59/100	241	Hemorrhage	L Frontal lobe, Insular Lobe, Temporal Lobe	0.405
4	24/24	2/76	26/100	69	Hemorrhage	L External Capsule, Temporal Lobe, Parietal Lobe	0.158
5	24/24	36/76	60/100	264	Hemorrhage	L Basal Ganglia, Corona Radiata	0.401
6	24/24	62/76	88/100	338	Infarction	L Basal Ganglia, Corona Radiata	0.389
7	12/24	5/76	17/100	79	Infarction	L Insular Lobe, Temporal Lobe, Frontal lobe	0.343
8	17/24	3/76	20/100	100	Hemorrhage	L Thalamus, Lateral Ventricles	0.159
9	24/24	17/76	41/100	101	Infarction	L Basal Ganglia, Parietal Lobe, Occipital Lobe	0.292
10	19/24	3/76	22/100	118	Infarction	L Frontal lobe, Parietal Lobe, Insular Lobe, Basal Ganglia,	0.130
11	24/24	38/76	62/100	331	Hemorrhage	L Frontal Temporal Lobe, Basal Ganglia,	0.343
12	6/24	5/76	11/100	11	Hemorrhage	L Basal Ganglia, Temporal and Parietal Lobe	0.219
13	15/24	3/76	18/100	116	Infarction	L Basal Ganglia, Frontal Temporal Parietal Lobe	0.196
14	21/24	33/76	54/100	186	Infarction	L Basal Ganglia, Frontal Temporal Lobe, Insular Lobe	0.495
15	13/24	3/76	16/100	84	Infarction	L Frontal lobe, Parietal Lobe	0.331

The total scores of the word repetition, the sentence repetition and total repetition are 24 points, 76 points, and 100 points respectively. L – left; FA – fractional anisotropy; AF – arcuate fasciculus.

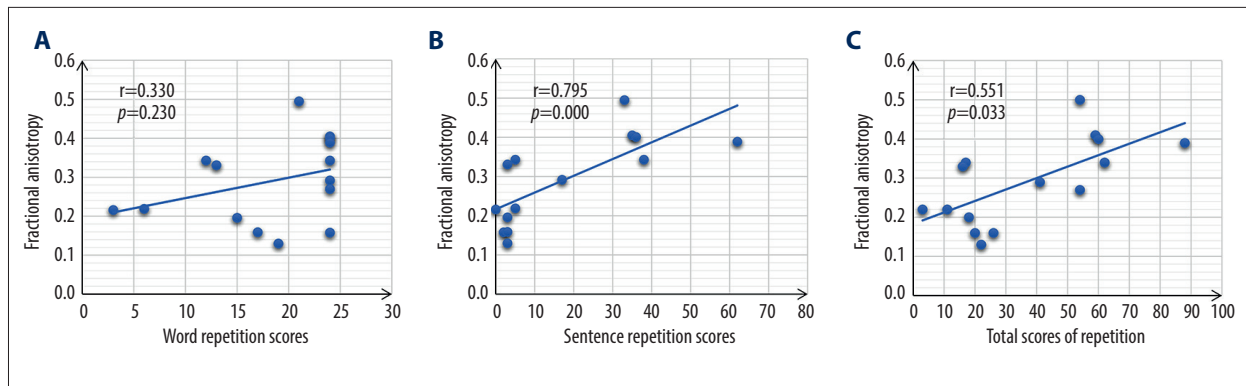


Figure 2. Correlation of DTI FA values of arcuate fasciculus and repetition outcomes. (A) The correlation of DTI FA values of the arcuate fasciculus and the word repetition scores. (B) shows the correlation of DTI FA values of the arcuate fasciculus in the dominant hemisphere and the sentence repetition scores. (C) The correlation of DTI FA values of arcuate fasciculus and the total scores of repetitions. R values (r) and p-values of the regression model are shown in the figures. DTI – diffusion tensor imaging; FA – fractional anisotropy.

time, 2.77 ± 1.26 months). The average FA value of AF in the dominant hemisphere in the patient group was significantly lower than that in the control group ($P \leq 0.001$), but no significant difference was found in the nondominant hemisphere between the 2 groups. The demographic information and FA values of AF in the dominant hemisphere of the 2 groups are shown in Table 1.

For the aphasia group, the speech repetition evaluation of ABC assessment (including word repetition scores, sentence repetition scores, and total repetition scores), the stroke types and injured brain regions, and the FA values of the AF in dominant hemisphere of 15 aphasia patients are shown in Table 2. There was a moderate correlation between the total score of repetition evaluation and the FA value of injured AF in the dominant hemisphere ($r=0.551$, $P=0.033$) (Figure 2C). Moreover, there was no correlation between the score of word repetition and the FA value of injured AF in the dominant hemisphere ($r=0.330$, $P=0.230$) (Figure 2A), whereas there was a strong correlation between the score of sentence repetition and the FA value of injured AF in the dominant hemisphere ($r=0.795$, $P \leq 0.001$) (Figure 2B).

Discussion

We explored repetition disorders and neural correlates using DTI in stroke patients with aphasia. Our results showed injured AF in the dominant hemisphere was more strongly associated with repetition dysfunction, especially sentence repetition deficit, which could help to understand subtypes of repetition ability and the involved neural structures.

Repetition deficit is a patient's difficulty repeating written or spoken words, and can be used in differential diagnosis of

aphasia. Most researches were focused on the single-word repetition [22,23] or sentence repetition as the clinical predictors of severity of stroke aphasia [24,25], but the correlation between stroke aphasia and repetition dysfunction (word/sentence/total repetition) has rarely been reported. Our study fills this gap in this field.

The Chinese edition of the ABC scale used in this study is the most widely used scale for screening and evaluating aphasia in clinical practice in China, and is based on the WAB test. The basic principles of the assessment are compiled in conjunction with the characteristics of the Chinese language [26]. The ABC scale as a clinical evaluation scale has the advantages of rapid and economical diagnosis of aphasia and remains the main assessment method for the differential diagnosis of aphasia [27]. Furthermore, the repetition sub-scale can be used to assess word repetition and sentence repetition ability of patients with aphasia. However, the ABC scale only works at the functional level, and understanding the anatomical level of damage and relevant relationship between the brain damage and functional deficit requires further imaging tests.

FA values can be used to reflect changes in directionality (or shape) of diffusion, with values ranging from 0 (isotropic diffusion; indicative of WM damage) to 1 (highly directional, anisotropic diffusion; reflecting WM integrity) [28]. The crucial role of AF in the correct transfer of information and conversion of sounds (phonology) into articulatory output patterns (language production) has been used to study the repetitive functions in patients with aphasia. Thus, the FA value has been used for evaluating the occurrence or severity of the AF injury in stroke patients with aphasia [29,30]. In our study, we chose the FA values to represent the degree of directionality of the microstructures [31], while a decrease of FA values might indicate injury of the AF tract. First, we compared the FA values of AF

in the dominant and nondominant hemispheres both in intra-groups and in inter-groups (between aphasia group and normal control group), and found that the FA values of AF in the dominant hemisphere in the aphasia group were significantly lower than those in the normal control group, whereas no significant differences were found in the nondominant hemisphere neither in intra-groups or in inter-groups. These results suggested that aphasia in patients after stroke might be more related to the integrity of AF in the dominant hemisphere than in nondominant hemisphere, which appeared to coincide with findings from previous studies. Other previous studies also found that the AF in the dominant hemisphere (usually in the left) supports some language skills, especially semantic comprehension, speech production, and repetition [4,11,32]. However, further studies reported different strategies of network reorganization in aphasic patients to compensate for impaired repetition performance [33]; for example, some patients recruit networks surrounding the infarction in the left hemisphere [34], whereas others mediated the right hemisphere [23].

Moreover, we analyzed the correlation between the DTI findings of AF and the repetition performance in stroke patients with aphasia and found that there was a strong positive correlation with sentence repetition performance but no significant correlation with word repetition performance.

A possible mechanism for this is the different pathways for word and repetition processing. Sentence repetition appears to be a valuable tool for language assessment because it draws upon a wide range of language processing skills [25]. Compared with sentence repetition, word repetition might not require more cognitive processing or semantic processing, and information might be directly transmitted to the language output processing center through direct phonological access [35]. Meanwhile, the ability of repetition is affected by the memory span. With the increase of repetition content, the repetition error rate of aphasia patients might also be increased, demonstrating that sentence repetition requires higher ability than word repetition, and sentence repetition function depends on a more complicated brain mechanism [36]. Functional magnetic resonance studies have also found that more brain regions need to be involved in sentence repetition, whereas only the frontal and temporal regions were activated during word repetition [37]. During the repetition processing, phonetic information input through the auditory pathway and the lexical-semantic processing and syntactic integration of this phonetic information are performed. Whether based on phonetic processing or semantic processing analysis, the mechanism of sentence repetition is expected to be more complicated than that of word repetition. Sentence repetition requires functional activation of the relevant brain regions and the brain inter-structure connection.

Our results appear to coincide with findings from previous studies. Chernoff et al. [9] observed that a brain tumor patient developed specific difficulty with repeating sentences toward the end of the surgery, after resection of the tumor and partial transection of left AF. But other studies reported different results. Sierpowska et al. [4] found monitoring nonword intraoperatively could permit better preservation of the important language production functions subserved by the AF. Another possible reason for the inconsistency between our results and those of other studies is the different target language used. Most studies involved English language, while the present study involved Chinese language. There is different phonological and semantic processing in alphabetic languages (such as English) and logographic languages (such as Chinese) [38]. The oral spelling process for logographic languages (Chinese) is intrinsically different from alphabetic languages. Chinese phonological identities (i.e., component names) do not always correspond to the sound of the whole characters.

Therefore, these underlining mechanisms likely account for our findings of different correlations between FA values of AF in the dominant hemisphere and word repetition versus sentence repetition in aphasia patients after stroke.

Limitations

This study has a few limitations. The sample size was relatively small due to a high examination fee for the DTI data collection. Moreover, there was heterogeneity among stroke patients with aphasia recruited in the patient group. Finally, it is hard to completely rule out the effect of eventual physiological improvement on speech performances. Future studies need to recruit more subjects to the patient group and perform hierarchical statistical analysis based on the type of aphasia or degree of repetition deficit.

Conclusions

We found that injured AF in the dominant hemisphere might be related to repetition dysfunction, especially sentence repetition deficit. Our results suggest that facilitation of the AF in the dominant hemisphere could be an important strategy in neuro-rehabilitation for stroke patients with aphasia, so that the patients with the sentence repetition deficit might benefit more than the patients with word repetition deficit.

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