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Research article

Association between the superior longitudinal fasciculus and perceptual organization and working memory: A diffusion tensor imaging study

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ABSTRACT

The superior longitudinal fasciculus (SLF) is a white matter structure that has long bidirectional projections among the prefrontal, temporal, occipital, and parietal cortices and extends over a wide area in a human brain. Recently, anatomical details of the SLF have been clarified using a diffusion tensor imaging (DTI) template of subjects from the Human Connectome Project. However, the neurobehavioral functions of the SLF have not been fully elucidated. It is speculated that the SLF contributes to a broad cognitive domain including visuospatial nonverbal cognitive ability and verbal memory ability because of its anatomical location; however, previous findings in imaging studies are inconsistent. Showing the contribution of the SLF to cognitive function may be important for improving our understanding of the functional role of white matter structures in the human brain. This study aimed to identify the relationship between DTI indices of the SLF and the Verbal Comprehension, Perceptual Organization, Working Memory and Processing Speed Indices of the Wechsler Adult Intelligence Scale-Third Edition using regression analysis, accounting for the effects of age, sex and scanner type in 583 healthy volunteers. We showed significant correlations between the fractional anisotropy of the left SLF and the Perceptual Organization Index ($\beta = 0.21$, $p = 4.5\times10^{-4}$) and Working Memory Index ($\beta = 0.19$, $p = 4.0\times10^{-4}$). These findings may have implications for the rehabilitation of cognitive function in patients with neurological disorders.

1. Introduction

The superior longitudinal fasciculus is a white matter structure that connects the prefrontal, temporal and occipital cortices via the posterior parietal cortex and has long bidirectional projections among these regions covering a wide area in the human brain [11,21,30]. Recently, anatomical details of the superior longitudinal fasciculus have been shown using a diffusion tensor imaging (DTI) template of subjects from the Human Connectome Project, which represents the largest and highest quality data set available to date [1,7,37]. However, the neurobehavioral functions of the superior longitudinal fasciculus have not been fully elucidated.

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Since the superior longitudinal fasciculus has anatomical connectivity with the frontal, temporal and occipital areas, it is speculated that the superior longitudinal fasciculus contributes to a broad range of cognitive functions, including visuospatial cognitive ability and verbal memory ability. Evidence linking the superior longitudinal fasciculus to visuospatial cognitive ability has been inconsistent in clinical imaging studies [2,19]. According to Hoeft et al. [9], increased fractional anisotropy (FA) in the superior longitudinal fasciculus is associated with poor visuospatial abilities in Williams syndrome, a neurodevelopmental disorder caused by a hemizygous deletion of up to 28 genes on chromosome 7q11.23 [8]. Moreover, Galli et al. [5] showed that the FA of the superior longitudinal fasciculus was significantly decreased in children with cerebral palsy and cognitive-visual deficits relative to children with cerebral palsy without cognitive-visual deficits. Conversely, associations between the superior longitudinal fasciculus and working memory have been relatively consistent [20,22,23,32,36]. Structure-function relationships between the superior longitudinal fasciculus and visuospatial ability and/or verbal memory ability in healthy adults may be important for understanding the organization of white matter tracts as they relate to cognition and they may have implications for the development of neuromodulatory interventions for patients with neurological disorders.

Few studies have investigated the association between the superior longitudinal fasciculus and nonverbal cognitive function in healthy human subjects [33,35]. A previous study including children, adolescents and young adults (aged 8–30 years old) assessed relationships between white matter integrity and crystalized intelligence as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) [39]; they found that lower white matter integrity in the superior longitudinal fasciculus was correlated with lower performance IQ scores [33]. This study focused on brain developmental processes, and adult subject sample sizes were limited. Furthermore, the association between the white matter integrity in the superior longitudinal fasciculus and nonverbal cognitive function in human adults has not been evaluated.

Therefore, the current study aimed to identify the relationship between DTI indices in the superior longitudinal fasciculus and nonverbal and verbal cognitive function in human adults in a relatively large sample size. We evaluated DTI indices, including: FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), of the superior longitudinal fasciculus. DTI indices of the corticospinal tract, which are almost exclusively associate with motor function, were used to demonstrate the relative specificity of the association between cognitive function and the superior longitudinal fasciculus. For the assessment of cognitive function, we used the Verbal Comprehension, Perceptual Organization, Working Memory and Processing Speed Indices of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [38].

2. Material and methods

2.1. Participants

Five hundred eighty-three healthy volunteer subjects [sex ratio M/F, 325/258; the mean age (standard deviation, SD) was 30.8 (13.2) years (18–68 years)] participated in this study. Some of the subjects have participated in previously published neuroimaging and behavioral studies [3,4,13–18,24–28]. We recruited the participants through local advertisements at Osaka University and evaluated them using a non-patient version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition to exclude subjects who had current or past contact with psychiatric services or who had received psychiatric medication. We also excluded the participants who had neurological or medical conditions that could affect the central nervous system potentially, including intellectual disability, substance-related disorders, atypical headaches, active cancer, kidney disease, chronic lung disease, cerebrovascular disease, thyroid disease, chronic hepatic disease, epilepsy, seizures, or head trauma with loss of consciousness. Before participation, we obtained written informed consent from each subject. The Ethical Committee of the Faculty of Medicine, the University of Tokyo and the research Ethical Committee of Osaka University approved the current study.

2.2. Image acquisition

DTI data were acquired from two MRI scanners. Two hundred thirty-seven subjects were scanned [sex ratio M/F, 131/106; the mean age (SD) was 31.3 (13.2) years (18–65 years)] with one MRI scanner (Osaka A), and 346 subjects were scanned [sex ratio M/F, 194/152; the mean age (SD) was 30.5 (13.2) years (18–68 years)] with another MRI scanner (Osaka B). Using an eight-channel head coil, we performed whole-brain axial DTI scanning on a 3.0 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI) with the following parameters in the Osaka A group: two-dimensional diffusion-weighted spin-echo echo planar imaging (EPI), repetition time (TR) = 15 s, echo time (TE) =82.9 ms, acquisition matrix = 96 × 96, reconstruction matrix = 256 × 256, asset acceleration factor = 2, field of view (FOV) = 260 × 260 mm, slice thickness = 3 mm, voxel size = 1.015 × 1.015 × 3 mm, and number of slices = 48. We applied a diffusion sensitization gradient with 15 noncollinear gradient directions. We used a b value of 1000s/mm^2 and obtained one non-diffusion-weighted scan.

Using an HNS coil, we performed whole-brain axial DTI scanning on a 3.0 T GE DISCOVERY 750 scanner (GE Healthcare, Milwaukee, WI) with the following parameters in the Osaka B group: two-dimensional diffusion-weighted spin-echo EPI, TR = 15 s, TE =61.1 ms, acquisition matrix = 128 × 128, reconstruction matrix = 256 × 256, asset acceleration factor = 2, FOV = 240 × 240 mm, slice thickness = 2.6 mm, voxel size = 0.94 × 0.94 × 2.6 mm, and number of slices = 60. A diffusion sensitization gradient with 15 noncollinear gradient directions was applied. A b value of 1000s/mm^2 was used, and one non-diffusion-weighted scan was obtained.

2.3. Image analysis

Two independent MRI researchers visually inspected the original T1-weighted images in the quality control, and excluded images with any abnormal findings (e.g. cavum septum pellucidum and large cerebellar cysts). We included head motion and eddy current correction using eddy_correct (FSL 5.0) in the DTI image processing steps. We estimated the DTI indices (FA, MD, AD and RD) using dti_fit (FSL 5.0). We applied TBSS to extract local values of the DTI indices based on ENIGMA-DTI protocols (http://enigma.ini.usc.edu/protocols/dti-protocols/) using the JHU region of interests (ROIs) and the ENIGMA-DTI template. We confirmed that there were no outliers exceeding ±4 SD of the DTI indices. The FA indicates the underlying characteristics of white matter microstructure: the myelin sheath thickness and the density, directionality and diameter of axonal fibers. The FA is derived from the degree of the anisotropy of the eigenvalues of the diffusion tensor: λ_1, λ_2, and λ_3. The AD (the largest eigenvalue: λ_1) is considered an indicator of axonal injury. The RD (the average of the two smaller eigenvalues λ_2 and $\lambda_{3)}$ is a possible marker for myelin damage. The MD is the average of all three eigenvalues. The four ROIs were as follows: superior longitudinal fasciculus (right and left), right superior longitudinal fasciculus, left superior longitudinal fasciculus, and corticospinal tract (right and left).

2.4. Neuropsychological measures

We employed the 4 indices of the WAIS-III to assess cognitive function: the Verbal Comprehension Index (consisting of subscales of Vocabulary, Similarities and Information), the Perceptual Organization Index (Picture Completion, Block Design and Matrix Reasoning), the Working Memory Index (Arithmetic, Digit Span and Letter-Number Sequencing) and the Processing Speed Index (Digit Symbol-Coding and Symbol Search) [38]. We scaled the raw scores of the WAIS-III to

normalize for age. The WAIS-III subscale scores range from 1 to 19. Higher scores indicate higher ability.

2.5. Statistical analysis

Regression analysis was performed adjusting for the effects of age, sex, and scanner type on the model to show the relationship between the DTI indices and the WAIS-III indices, as outlined below:

(WAIS-III index) = $\beta_0+\beta_1\times$age$+\beta_2\times$sex$+\beta_3\times$scanner$+\beta_4\times$(DTI index)$+\varepsilon$

A p-value of < 0.0008 [0.05/(4 ROIs × 4 DTI indices × 4 WAIS-III indices)] was considered statistically significant according to the Bonferroni correction.

3. Results

The mean (SD) of the Verbal Comprehension Index was 113.8 (12.6), that of the Perceptual Organization Index was 108.9 (13.4), that of the Working Memory Index was 113.0 (15.1) and that of the Processing Speed Index was 110.9 (13.9) in healthy volunteer subjects.

The results of the correlation analyses are shown in Table 1. The FA of the superior longitudinal fasciculus (right and left; Fig. 1) was significantly correlated with the Perceptual Organization Index ($\beta = 0.20$, $p = 4.6\times10^{-4}$). The FA ($\beta = 0.21$, $p = 4.5\times10^{-4}$) and AD ($\beta = 0.17$, $p = 7.0\times10^{-4}$) of the left superior longitudinal fasciculus were significantly correlated with the Perceptual Organization Index. The FA ($\beta = 0.19$, $p = 4.0\times10^{-4}$) of the left superior longitudinal fasciculus was significantly correlated with the Working Memory Index. There were no significant correlations between any of the DTI indices of the corticospinal tract (right and left) and the WAIS-III indices.

4. Discussion

In the current study, we examined the association between regional DTI indices and the 4 WAIS-III indices using regression analysis, accounting for the effects of age, sex and scanner type, and we showed significant correlations between the FA and AD of the left superior longitudinal fasciculus and the Perceptual Organization Index and a significant correlation between the FA of the left superior longitudinal fasciculus and the Working Memory Index in healthy human adults. Furthermore, none of the DTI indices of the corticospinal tract were shown to be significantly correlated with any of the 4 WAIS-III indices.

Our results, showing the correlation between the integrity of the superior longitudinal fasciculus and visuospatial cognitive function [33,35] and working memory performance [20,22,23,32,33,36], are consistent with previous studies. A previous study assessing the relationships between the superior longitudinal fasciculus and performance IQ (estimated from the subtests Matrix Reasoning and Block Design abilities) in adolescents and young adults (aged 8–30 years old) found that lower FA and higher RD of the left superior longitudinal fasciculus were correlated with lower performance IQ scores [33]. Our study showed significant correlations between the FA and AD of the superior longitudinal fasciculus and the Perceptual Organization Index. The difference between RD and AD may be caused by a difference in subjects' ages across the studies, which were between the mean age of 17.7 years (8.2–30.8 years) and the mean age of 30.8 years (18–68 years); this difference may be influenced by the dynamic neurodevelopmental process of the nervous system. AD is a possible marker for axonal injury, and RD is considered an indicator of myelin damage; myelin formation may be immature during development, and aging may damage axons. These white matter alterations may have caused differences in the results. Regarding the correlation between the FA of the superior longitudinal fasciculus and working memory performance, our study in healthy adults showed similar results to those of previous studies in children or adolescents [20,22,23,32,36]. The association between the superior longitudinal fasciculus and working memory performance may be common among children, adolescents and adults.

Furthermore, our findings are supported by previous lesion mappings of cognitive abilities in patients with focal brain damage, showing structure-function relationships between lower Perceptual Organization Index scores and severe gray matter lesion volume in regions such as the temporal, parietal and occipital gyri; which are connected by the superior longitudinal fasciculus [6]. The patients also showed associations between lower working memory index scores and severe gray matter lesion volume in regions such as the frontal and temporal gyri [6]. The superior longitudinal fasciculus is composed of long bidirectional frontal-parietal-temporal-occipital projections among the prefrontal, temporal and occipital cortices via the posterior parietal cortex, and is

Table 1
Correlations between DTI indices of ROIs and the WAIS-III indices.

	Verbal Comprehension		Perceptual Organization		Working Memory		Processing Speed	
	β	p	β	p	β	p	β	p
Superior longitudinal fasciculus (left and right)								
FA	0.06	0.28	0.20	4.6×10^{-4}*	0.16	3.1×10^{-3}	0.07	0.21
MD	0.05	0.36	0.01	0.84	–0.06	0.29	–0.01	0.92
AD	0.08	7.2×10^{-2}	0.14	2.4×10^{-3}	0.04	0.41	0.03	0.48
RD	–0.001	0.99	–0.11	7.2×10^{-2}	–0.11	4.6×10^{-2}	–0.04	0.54
Right superior longitudinal fasciculus								
FA	0.03	0.55	0.15	2.4×10^{-3}	0.09	4.5×10^{-2}	0.03	0.52
MD	0.04	0.37	0.004	0.93	–0.03	0.49	–0.02	0.62
AD	0.06	0.14	0.10	2.2×10^{-2}	0.02	0.63	–0.01	0.87
RD	0.01	0.85	–0.08	0.13	–0.06	0.20	–0.03	0.58
Left superior longitudinal fasciculus								
FA	0.08	0.16	0.21	4.5×10^{-4}*	0.19	4.0×10^{-4}*	0.10	9.0×10^{-2}
MD	0.05	0.41	0.02	0.75	–0.09	0.17	0.02	0.73
AD	0.09	5.8×10^{-2}	0.17	7.0×10^{-4}*	0.05	0.28	0.08	0.12
RD	–0.01	0.82	–0.13	5.4×10^{-2}	–0.16	1.0×10^{-2}	–0.04	0.54
Corticospinal tract (right and left)								
FA	0.05	0.17	0.11	9.3×10^{-3}	0.04	0.34	0.03	0.54
MD	0.07	6.8×10^{-2}	–0.03	0.50	0.03	0.50	0.02	0.56
AD	0.11	5.9×10^{-3}	0.06	0.18	0.07	9.4×10^{-2}	0.04	0.37
RD	0.02	0.62	–0.10	2.2×10^{-2}	–0.02	0.63	–0.01	0.83

Legend: * Bonferroni corrected $p < 0.05$.
Abbreviations: DTI, diffusion tensor imaging; ROI, region of interest; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

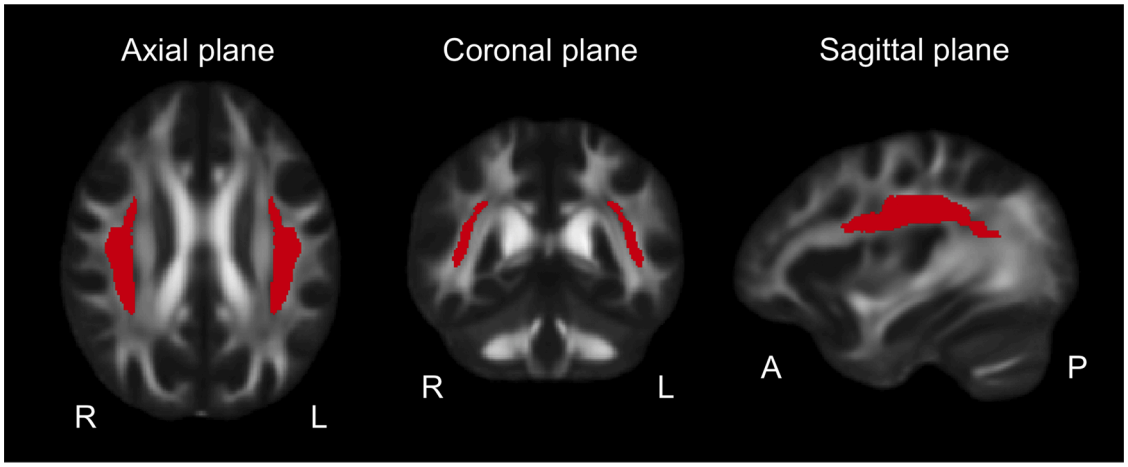

Fig. 1. Region of superior longitudinal fasciculus (right and left).
Legends: The superior longitudinal fasciculus is composed of long bidirectional occipito-temporal-parietal-frontal projections among the occipital, temporal and prefrontal cortices via the posterior parietal cortex.
Abbreviations: R, right; L, light.

critical for appropriate visual-spatial functioning in humans [19,5,12]. These studies are consistent with the results of our study and underscore the specificity of the relationship between cognitive function and the superior longitudinal fasciculus.

An interesting observation is that our study did not reveal any correlations between the DTI indices of the superior longitudinal fasciculus and the Processing Speed Index. Processing Speed Index (Digit Symbol-Coding and Symbol Search) is a nonverbal cognitive functional indexed by the WAIS-III, that is widely used to support fluent execution of perceptual, cognitive and motor processes [38]. A functional magnetic resonance imaging (fMRI) study showed that better performance on the Digit-Symbol test is associated with higher activity in Brodmann area 40 (i.e., supramarginal gyrus) [31]. Turken et al. [34] reported that Digit-Symbol performance was positively correlated with fractional anisotropy of the superior and inferior longitudinal fasciculi, and furthermore, they also reported that lesions in the supramarginal (i.e., Brodmann area 40) and angular gyri (i.e., Brodmann area 39) were associated with impaired processing speed performance. The finding is supported by neuroanatomical studies showing the effect of posterior parietal lesions extending into white matter on perceptual processing speed [6,29]. While it is evident that the superior longitudinal fasciculus is implicated in various neurocognitive functions, including processing speed; it is worth noting that its structural connectivity is distributed among several neuroanatomical subregions and white matter tracts (i.e., I, II, III and the arcuate fascicle). The superior longitudinal fasciculus II extends from the angular gyrus to the caudal dorsolateral prefrontal regions; the superior longitudinal fasciculus III extends from the supramarginal gyrus to ventral prefrontal regions [10,21,37]. The present study did not divide the parts of the superior longitudinal fasciculus. Therefore, our results might not have the necessary resolution to detect relationships between the DTI indices of the superior longitudinal fasciculus and the Processing Speed Index.

Our study should be considered in light of certain limitations. First, as mentioned above, we did not divide the superior longitudinal fasciculus into subregional compartments in the current study. Future studies that account for these anatomic branch points may provide better spatial and functional resolution of specific associations with the neurocognition. Second, the DTI indices such as the FA are unable to resolve regions of crossing white matter pathways. Since the superior longitudinal fasciculus contains many those regions, these points need to be considered when interpreting the results. Third, the current study was a cross-sectional study; thus, a causal relationship between DTI indices and nonverbal cognitive function cannot be drawn.

5. Conclusions

We demonstrate that the white matter integrity of the superior longitudinal fasciculus may contribute to visuospatial ability and working memory performance in healthy adult humans. This finding may have implications for neuromodulation therapies for individuals with neurological disorders associated with impaired cognitive functioning.

CRediT authorship contribution statement

Daisuke Koshiyama: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft. **Masaki Fukunaga:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation. **Naohiro Okada:** Data curation, Investigation, Resources. **Kentaro Morita:** Data curation, Investigation, Validation. **Kiyotaka Nemoto:** Data curation, Investigation, Methodology, Software, Visualization. **Fumio Yamashita:** Data curation, Investigation. **Hidenaga Yamamori:** Data curation, Investigation, Resources. **Yuka Yasuda:** Data curation, Investigation, Resources. **Junya Matsumoto:** Data curation, Investigation, Resources. **Michiko Fujimoto:** Data curation, Investigation, Resources. **Noriko Kudo:** Data curation, Investigation, Resources. **Hirotsugu Azechi:** Data curation, Investigation, Resources. **Yoshiyuki Watanabe:** Data curation, Investigation, Resources. **Kiyoto Kasai:** Conceptualization, Funding acquisition, Supervision, Project administration, Writing - review & editing. **Ryota Hashimoto:** Conceptualization, Data curation, Investigation, Resources, Funding acquisition, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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