Brain Neurorehabil. 2022 Mar;15(1):e6
https://doi.org/10.12786/bn.2022.15.e6
pISSN 1976-8753·eISSN 2383-9910

Brain & NeuroRehabilitation

Original Article

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Correlation of Hemispatial Neglect with White Matter Tract Integrity: A DTI Study

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Received: Dec 27, 2021
Revised: Mar 14, 2022
Accepted: Mar 22, 2022
Published online: Mar 24, 2022

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HIGHLIGHTS

- Neglect group has low tract volume in the inferior fronto-occipital fasciculus(IFOF).
- The fractional anisotropy of right white matter tract was low in the neglect group.

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Correlation of Hemispatial Neglect with White Matter Tract Integrity: A DTI Study

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OPEN ACCESS

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ABSTRACT

We investigated the diffusion tensor image (DTI) parameters of superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (IFOF), and their relationships with hemispatial neglect. Thirteen patients with first-ever ischemic stroke who had the right hemispheric lesion were included. Neglect was assessed using the Albert test and figure discrimination test of Motor-free Visual Perception Test 3 (MVPT-3). The SLF and IFOF were separated by diffusion tensor tractography (DTT) and tract volume (TV) was calculated. We measured the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in the total area, seed region of interest (ROI), and target ROI, respectively. Among thirteen patients, seven demonstrated signs of hemispatial neglect on neglect test. Tractography reconstruction showed significantly low TV of the right IFOF in patients with hemispatial neglect. FA values of the right SLF and the right IFOF were significantly lower in neglect patients. ADC values were not significantly different in two groups. This study suggests that damage of SLF and IFOF is associated with hemispatial neglect in right hemispheric stroke patients. DTI may be useful for predicting the severities of hemispatial neglect using values such as TV and FA of each tract.

Keywords: Stroke; Hemispatial Neglect; Diffusion Tensor Imaging

INTRODUCTION

Although previous studies have suggested that some specific brain lesions are associated with hemispatial neglect, which is signs of neglect in the left side of their space or their body (e.g. the posterior parietal cortex, the superior parietal lobule, and the premotor and prefrontal area around the frontal eye field etc.) [1,2], hemispatial neglect is a syndrome that is functionally heterogeneous, incorporating various aspects of cognitive deficits such as decreased spatial attention and perception, and even non-lateralized deficits such as an impairment of spatial working memory and reduced arousal [3-5]. Therefore, it might not be conducive to investigate hemispatial neglect to search for precise anatomo-clinical correlations suggesting a single locus as the source of the condition. Hemispatial neglect

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Funding
None.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

is more likely to result from a disruption of tracts distributed beyond the single locus in the parietal or in the frontal lobe [4,6].

Geschwind suggested a disconnection framework that describes how higher cognitive function deficits result from white matter lesions or lesions of the association cortices [7], and this framework helped to develop contemporary distributed network theories of brain function [8]. Catani and his colleague [8] assumed that the voxels of maximum overlap correspond to the cortical correlate of the neurological deficit. However, considering that neglect is more likely the result of relatively large lesions and caused by the disruption of tracts, the lesion overlapping method might be inappropriate to investigate the brain network of neglect [5]. Concurrent with this, recent studies adopted diffusion tensor imaging (DTI) tractography combined with lesion overlapping methods [5,9]. In a pathway-based approach to behavioral neurology, lesions along the trajectory of a white matter pathway were found to impair the integrated functioning of the cortical network connected by that pathway [10]. Visual orientation is related to pathways as well as networks. Functional magnetic resonance imaging (fMRI) studies revealed that orienting of spatial attention depends on the coordinated activity of fronto-parietal networks [2,11].

Previous studies reported that the middle cerebral artery (MCA) territories of the right hemisphere, particularly the inferior parietal lobule (IPL), the superior temporal gyrus (STG) [12,13], and the temporoparietal junction (TPJ) [14,15], have affected hemispatial neglect. Moreover, it is known that the brodamann area 6,44, and 46 were associated with hemispatial neglect [16]. However, hemispatial neglect is functionally heterogeneous and incorporates various aspects of cognitive deficits that could hardly be explained by a single brain lesion. Recent studies are more focused on distributed cortical networks or subcortical lesions [17-20].

Therefore, the aim of this study is to investigate the superior longitudinal fasciculus (SLF) and the inferior fronto-occipital fasciculus (IFOF) by using DTI tractography to identify the relationship between white matter tract disruptions and clinical signs of hemispatial neglect.

MATERIALS AND METHODS

Participants

We screened the patients with right hemisphere infarction admitted or transferred to the department of rehabilitation medicine between August 2010 and April 2013. The patients were included as follows: 1) age 18 to 80 years, 2) presence of an ischemic stroke in the right hemisphere, and 3) absence of other etiologies including infratentorial lesions, traumatic brain injury, hypoxic brain damage, and brain tumors. Exclusion criteria were the following: 1) previous stroke, 2) impaired comprehension, 3) psychiatric disorders, and 4) altered vigilance. All patients had Neuropsychological evaluation and brain magnetic resonance imaging (MRI) at least 4 weeks after stroke onset. We divided patients into groups with and without hemispace neglect by albert test and Motor-Free Visual Perception Test 3 (MVPT-3). Hemispatial neglect was regarded as 'suggest or indicate' in MVPT-3 or less than 70% in percent deviation (PD) in the Albert test [21,22].

All patients or their legally authorized representatives provided written informed consent before inclusion in this study. The study protocol was approved by the Institutional Review Board of Konkuk University Hospital.

Table 1. Diagnostic criteria of MVPT-3 suggesting or indicating hemispatial neglect

Age (yr)	Lt. side response			Rt. side response		
	Normal	Suggest	Indicate	Normal	Suggest	Indicate
18–49	≥ 18	17–10	9–0	≥ 12	11–7	6–0
50–69	≥ 18	17–10	9–0	≥ 11	10–6	5–0
70–80	≥ 17	16–9	8–0	≥ 10	9–6	5–0

MVPT-3, Motor-Free Visual Perception Test 3.

Measurement

Hemispatial neglect evaluation

Hemispatial neglect was assessed using the Albert test and the figure discrimination test of MVPT-3. The Albert test consists of 40 lines 2.5 cm long on a 20 × 26 cm^2 sheet [22]. The severity of neglect was assessed by calculating the PD (%) as follows: number of eliminated lines divided by 36 × 100 (%). For the MVPT-3 test, a visual stimulus was presented to the patients, and they were then asked to select the same stimulus from a subsequently presented answer sheet with four different stimuli placed directly in front of them. The correct answers in the MVPT-3 test are placed on the right side in 15 questions and on the left side in 21 questions [21]. Response behavior for each side was counted respectively, and the patients' performance was considered to indicate or suggest hemispatial neglect following the criteria presented in **Table 1**. A diagnosis of neglect was based on pathological performance in either the Albert test or the MVPT-3.

DTI data acquisition

All imaging was performed on a 3.0 Tesla MRI system (SignaHDxt, GE Medical System, Milwaukee, WI, USA) with a standard 8-channel phase array head coil. For each 15 noncollinear and noncoplanar diffusion-sensitizing gradients, we acquired about 70 contiguous slices parallel to the anterior commissure-posterior commissure line. Imaging parameters were as follows: matrix = 120 × 120, field of view = 240 × 240 mm^2, TE = 84 ms, TR = 16,000 ms, and b = 800 mm^2/s at a slice thickness of 2 mm. In addition to diffusion tensor images, conventional T2 fluid attenuated inversion recovery (FLAIR) images were obtained.

DTI analysis

Raw image data were transferred in DICOM format. All DTI images were corrected for eddy current-induced images distortions using the FSL software (The Image Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl). The DTI analyses for 13 patients were performed by an experienced rehabilitation medicine doctor using DTI studio (Johns Hopkins Medical Institute, Baltimore, MD, USA; www.mristudio.org). Two white matter tracts, the SLF and the IFOF, were reconstructed for each group (**Fig. 1**). The threshold values for the termination of the fiber tracking were less than 0.2 for FA and greater than 45° for the trajectory angles [5,23,24]. For the seed region of interest (ROI) of the SLF, the lowest axial level in which the fornix can be identified was selected, and then a coronal slice was selected at the middle of the posterior limb of the internal capsule. For the target ROI, a coronal slice was selected at the splenium of the corpus callosum (**Fig. 2**) [25]. For the seed ROI of the IFOF, a coronal slice was identified at the middle point between the posterior edge of the cingulum and the posterior edge of the parieto-occipital sulcus. For the target ROI, a coronal slice was selected at the anterior edge of the genu of the corpus callosum and the entire hemisphere was delineated (**Fig. 2**) [25]. The volume of each tract was recorded as the number of voxels. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values for the total tract as well as for each ROI were extracted from tractography.

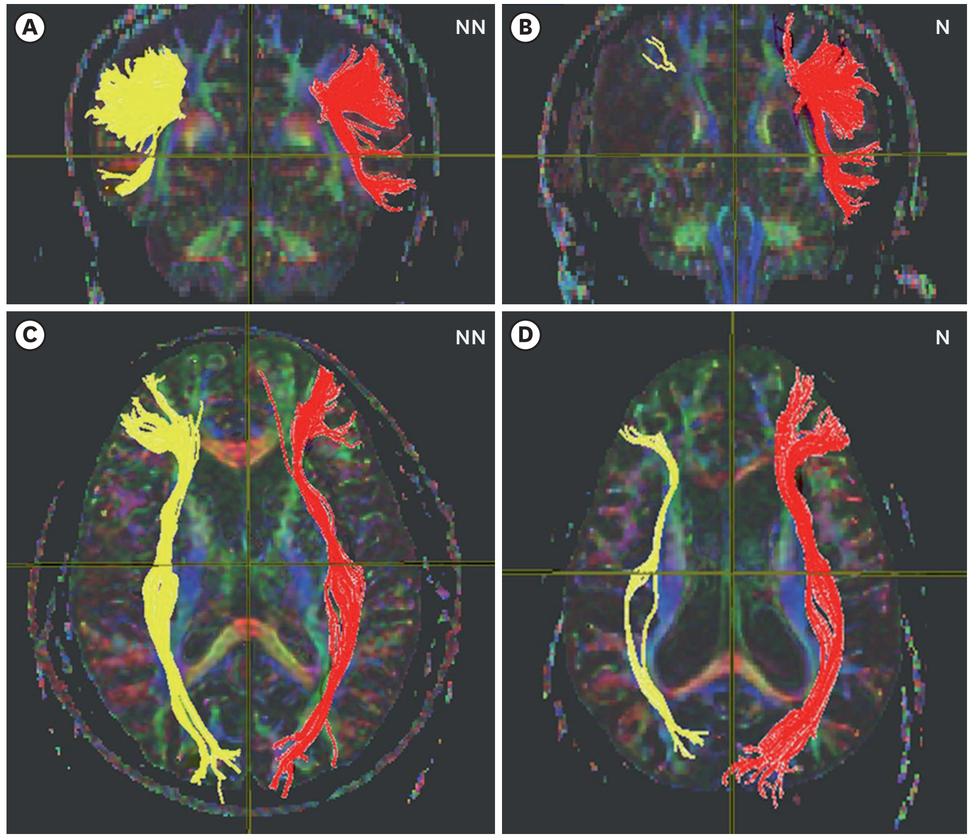

Fig. 1. Two white matter tracts, the SLF and the IFOF, were reconstructed for each group. (A) SLF in a patient without neglect. (B) SLF in patient with neglect. (C) IFOF in a patient without neglect. (D) IFOF in a patient with neglect (left: red fibers, right: yellow fibers).
SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; NN, non-neglect; N, neglect.

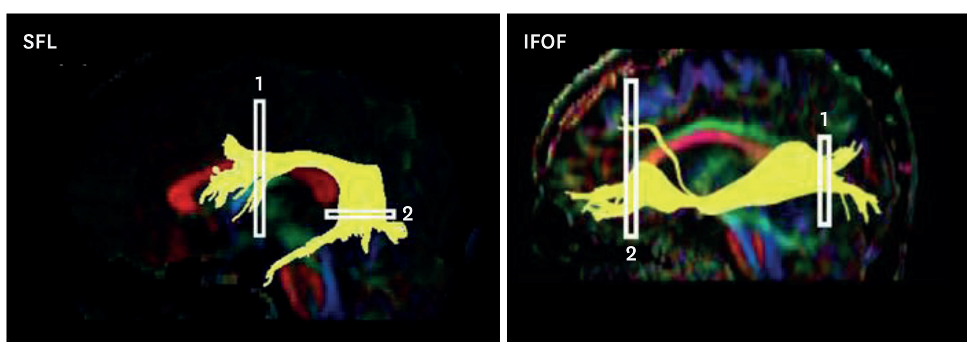

Fig. 2. The seed and target ROI of SLF and IFOF (1: seed ROI, 2: target ROI).
ROI, region of interest; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus.

Statistical analysis

We retrospectively analyze the DTI parameters of patients with and without hemispatial neglect. Statistical analysis was performed using SPSS for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). Comparison of tract volume (TV) and FA values of the 2 groups was performed with the Mann-Whitney U test. In the white matter tract related to the severity of unilateral neglect, the correlation between the DTI parameters of SLF and IFOF and Albert's PD value was confirmed by Spearman's correlation. The level of significance was set to $p < 0.05$.

https://doi.org/10.12786/bn.2022.15.e6

Table 2. Characteristics of the neglect patients and the non-neglect patients

No.	Lesion site	Gender	Age	Education (years of schooling)	Onset of stroke (days)
N1	SPL, IPL, ANG, SMG, TPJ, STG, IFG, MFG	Male	53	9	40
N2	ANG, Insula, BG	Female	80	6	23
N3	TPJ, STG, IFG, MFG, Insula, BG	Male	56	16	31
N4	SPL, IPL, ANG, SMG, TPJ, STG, IFG, MFG, Insula, BG	Male	58	9	34
N5	SMG, TPJ, STG, IFG, MFG, Insula, CR, BG	Female	69	6	27
N6	SMG, IFG, MFG, Precentral gyrus	Female	73	6	25
N7	IFG, MFG, Insula, BG, Precentral gyrus	Female	66	12	33
N-N1	SPL, IPL, Precentral gyrus, Postcentral gyrus, MTG	Male	68	9	15
N-N2	CR, BG	Female	44	12	29
N-N3	BG	Female	50	12	27
N-N4	STG, IFG, MFG, Insula, BG	Male	28	12	30
N-N5	CR, BG	Female	71	9	34
N-N6	CR, BG	Male	52	9	27

N, neglect; NN, non-neglect; SPL, superior parietal lobule; IPL, inferior parietal lobule; ANG, angular gyrus; SMG, supramarginal gyrus; TPJ, temporoparietal junction; STG, superior temporal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; CR, corona radiata; BG, basal ganglia.

RESULTS

We enrolled total 13 patients with first-ever infarction in right hemisphere (6 males, 7 females; mean age [mean ± standard deviation], 59.08 ± 14.06 years, **Table 2**). Among 13 patients, 7 presented signs of left hemispatial neglect (abbreviate to neglect) (65.00 ± 9.83 years), while the remaining 6 did not sign of hemispatial neglect (abbreviate to non-neglect) (52.17 ± 15.88 years). The lesion site and degree of cognitive impairment of all patients are described at **Table 3**. In the neglect group, 6 patients were identified as 'Indicate', and a patient 'suggest' in MVPT-3 (**Table 3**). In the non-negligence group, all patients performed normally in the albert test and MVPT-3.

The FA value of the right SLF significantly decreased in the comparison between the neglected group and the non-neglect group (**Table 4**). SLF seed and target ROI's FA were significantly decreased in the neglect group. ADC values were significantly higher than in the non-neglect group. In the IFOF comparison between the 2 groups, there was a significant difference in total TV and FA value, but there was no significant difference in FA and ADC of the target ROI. There was no significant difference between two groups of left SLF and IFOF (**Table 5**). The white matter tracts related to the severity of unilateral neglect were right SLF and IFOF (**Table 6**).

Table 3. Degree of neglect symptoms in the neglect patients and the non-neglect patients

No.	MMSE	Albert test, PD (%)	MVPT-3, Response behavior
N1	11	75 (5/10/12)	7 (indicate)
N2	10	50 (0/6/12)	1 (indicate)
N3	21	69 (1/12/12)	3 (indicate)
N4	19	50 (0/6/12)	0 (indicate)
N5	21	25 (0/0/9)	0 (indicate)
N6	16	86 (7/12/12)	0 (indicate)
N7	22	100 (12/12/12)	14 (suggest)
N-N1	28	100 (12/12/12)	21 (normal)
N-N2	27	100 (12/12/12)	21 (normal)
N-N3	30	100 (12/12/12)	21 (normal)
N-N4	30	100 (12/12/12)	21 (normal)
N-N5	26	100 (12/12/12)	21 (normal)
N-N6	21	100 (12/12/12)	21 (normal)

MMSE, Mini-Mental State Examination; PD, percent deviation; MVPT-3, Motor-Free Visual Perception Test 3; N, neglect.

Table 4. Comparison of TV, FA, ADC of right SLF and IFOF between neglect group and non-neglect group

Right side	Neglect (n = 7)	Non-neglect (n = 6)	p value
SLF			
TV	1,697.14 ± 2,209.78	4,769.17 ± 2,130.27	0.059
FA	0.3977 ± 0.0764	0.4697 ± 0.0860	0.039*
ADC	0.7084 ± 0.0857	0.7193 ± 0.1604	0.415
FA of seed ROI	0.22 ± 0.04	0.29 ± 0.04	0.007**
FA of target ROI	0.22 ± 0.06	0.32 ± 0.02	0.000**
ADC of seed ROI	1.13 ± 0.15	0.84 ± 0.04	0.000**
ADC of target ROI	1.01 ± 0.21	0.78 ± 0.07	0.014*
IFOF			
TV	633.86 ± 786.62	3,031.33 ± 1,348.16	0.002**
FA	0.4541 ± 0.0511	0.5230 ± 0.0344	0.014*
ADC	0.8218 ± 0.1716	0.7164 ± 0.0488	0.161
FA of seed ROI	0.25 ± 0.04	0.28 ± 0.03	0.238
FA of target ROI	0.22 ± 0.02	0.28 ± 0.01	0.000**
ADC of seed ROI	0.87 ± 0.10	0.78 ± 0.09	0.119
ADC of target ROI	1.15 ± 0.12	0.96 ± 0.04	0.000**

TV, tract volume; FA, fractional anisotropy; ADC, apparent diffusion coefficient; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ROI, region of interest.
Mann-Whitney U test, *$p < 0.05$, **$p < 0.01$.

Table 5. Comparison of TV, FA, ADC of left SLF and IFOF between neglect group and non-neglect group

Left side	Neglect (n = 7)	Non-neglect (n = 6)	p value
SLF			
TV	4,693.29 ± 1,825.68	5,058.17 ± 3,010.13	0.894
FA	0.4929 ± 0.0288	0.5029 ± 0.0203	0.415
ADC	0.6767 ± 0.0493	0.6607 ± 0.0425	0.687
FA of seed ROI	0.27 ± 0.03	0.29 ± 0.03	0.412
FA of target ROI	0.30 ± 0.02	0.31 ± 0.02	0.451
ADC of seed ROI	0.98 ± 0.14	0.86 ± 0.05	0.118
ADC of target ROI	0.86 ± 0.08	0.80 ± 0.06	0.180
IFOF			
TV	3,001.43 ± 1,778.49	3,369.17 ± 1,924.27	0.789
FA	0.5255 ± 0.0351	0.5483 ± 0.0295	0.339
ADC	0.7188 ± 0.0569	0.7064 ± 0.0498	0.789
Seed ROI	0.26 ± 0.04	0.28 ± 0.02	0.371
Target ROI	0.28 ± 0.02	0.30 ± 0.02	0.201
ADC of seed ROI	0.84 ± 0.11	0.78 ± 0.07	0.413
ADC of target ROI	1.00 ± 0.13	0.92 ± 0.05	0.414

TV, tract volume; FA, fractional anisotropy; ADC, apparent diffusion coefficient; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ROI, region of interest.
Mann-Whitney U test, *$p < 0.05$, **$p < 0.01$.

The severity of hemispatial neglect was evaluated on the basis of the PD of the Albert test; a PD of 100% was recorded when a subject crossed all 36 lines on the sheet. High integrity means that the FA value is close to 1. Severe neglect was significantly correlated with decreased TV of right IFOF and FA values of IFOF and SLF (**Table 6**).

DISCUSSION

We confirmed integrity of SLF and IFOF in right hemisphere correlated with symptom and severity of hemispatial neglect. The FA values of the right SLF and IFOF in the neglect group were significantly decreased. There have been many attempts to find out roles of white matter networks [13,26-29]. Golay and colleagues [29] found that spatial attention is subserved by a distributed network of cortical and subcortical regions involving the IPL, the

Table 6. Correlations between DTI parameters and neglect severity

DTI parameters	Albert test, PD (%)	
	Correlation coefficient	p value
Tract volume		
Lt. SLF	−0.012	0.969
Rt. SLF	0.449	0.124
Lt. IFOF	0.099	0.748
Rt. IFOF	0.691	0.009**
Fractional anisotropy		
Lt. SLF	0.404	0.171
Rt. SLF	0.586	0.035*
Lt. IFOF	0.144	0.640
Rt. IFOF	0.679	0.011*
Apparent diffusion coefficient		
Lt. SLF	−0.057	0.854
Rt. SLF	0.015	0.961
Lt. IFOF	−0.057	0.854
Rt. IFOF	−0.162	0.598

DTI, diffusion tensor image; PD, percent deviation; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus.
Spearman's correlation, *$p < 0.05$, **$p < 0.01$.

STG, the prefrontal cortex, and the insula [30]. Urbanski and colleagues [31] used a lesion overlapping method, and found the maximum overlap not in the cortex but in the white matter, based on a topological method; their results showed that the SLF III and the IFOF are significantly involved in neglect [5]. Previous lesion overlapping studies reported that the subcortical lesions of patients with neglect invariably overlapped near the SLF, in the major frontoparietal network [18,31]. Urbanski's study provided evidence of a disconnection of the IFOF in the major rostro-caudal white matter pathway in patients with neglect [31]. Although most of the studies using DTI tractography suggested disconnection of white matter tracts, they did not assess other DTI parameters such as FA or ADC values, which represent structural integrity.

In this study, the SLF and IFOF were reconstructed by DTI tractography and disconnection of the pathway was evaluated based on the TV of each network. Furthermore, FA and ADC values were extracted from the tractography for assessing the integrity of the pathways. Patients with neglect had a significantly smaller TV of the right IFOF, and lower FA values in the right SLF as well as in the right IFOF when compared to non-neglect. The TV of the SLF was also decreased in the neglect group, but there was no significant difference due to the large deviation between patients.

The ADC mean range for normal white matter is known to be $0.84 \pm 0.11 \times 10^{-3}$ mm^2/s [32]. The seed and target ROI's ADC of out of the normal ADC mean were also significantly different in comparison between the two groups. In the ADC comparison of the IFOF's ROI, there was a significant difference only in the target ROI. The seed ROI and target ROI of IFOF are marked in the occipital lobe and frontal lobe, respectively. Previous studies reported that the right dorsolateral prefrontal cortex and deep temporal lobe regions were associated with the severity of neglect [30]. In this respect, significant differences in ADC in the target ROI of IFOF are related to the severity of neglect.

Two patients in the non-neglect group (C1, C4) who had cortical lesions in the IPL and the STG respectively — conventionally believed to be associated with spatial neglect—but sparing the SLF and the IFOF, did not present signs of neglect. On the contrary, three

https://doi.org/10.12786/bn.2022.15.e6

patients with neglect (N2, N5, and N7) who had no cortical lesions that had previously been suggested as critical cortical loci but showed disruptions of the SLF and the IFOF, presented signs of neglect. The present results suggest that apart from cortical lesions, damage of the SLF and the IFOF can be associated with hemispatial neglect. Previous studies using DTI tractography also support our current findings that Fiber tracts projecting from the SLF and the IFOF are associated with neglect [33].

Although the results of this study are clinically meaningful, there are some limitations. First, the neglect test battery used in this study included only the Albert test and the MVPT-3. Although in severe cases signs of neglect are obvious and can be detected by simple observation, in most patients, neglect is not clinically apparent and specific testing is needed to reveal the disorder. More precise neglect batteries composed of various neglect tests are therefore necessary to diagnose neglect.

Second, a general decline in cognitive function could influence the results of the neglect test; patients with neglect showed significantly lower the Mini-Mental State Examination (MMSE) scores in this study. Although we excluded patients who did not adhere to the instructions of the test properly, the possibility remains that cognitive decline may have influenced the test results.

In conclusion, this study suggests that damage of the SLF and the IFOF with or without cortical lesions is associated with hemispatial neglect in patients with right hemispheric stroke. DTI may be useful for predicting the severities of hemispatial neglect using parameters such as TV and FA values of each tract.

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