

# Bridging Reduced Grip Strength and Altered Executive Function: Specific Brain White Matter Structural Changes in Patients with Alzheimer's Disease

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**Objective:** To investigate the correlation between specific fiber tracts and grip strength and cognitive function in patients with Alzheimer's disease (AD) by fixel-based analysis (FBA).

**Methods:** AD patients were divided into AD with low grip strength (AD-LGS, n=29) and AD without low grip strength (AD-nLGS, n=25), along with 31 normal controls (NC). General data, neuropsychological tests, grip strength and cranial magnetic resonance imaging (MRI) scans were collected. FBA evaluated white matter (WM) fiber metrics, including fiber density (FD), fiber cross-sectional (FC), and fiber density and cross-sectional area (FDC). The mean fiber indicators of the fiber tracts of interest (TOI) were extracted in cerebral region of significant statistical differences in FBA to further compare the differences between groups and analyze the correlation between fiber properties and neuropsychological test scores.

**Results:** Compared to AD-nLGS group, AD-LGS group showed significant reductions in FDC in several cerebral regions. In AD patients, FDC values of bilateral uncinate fasciculus and left superior longitudinal fasciculus were positively correlated with Clock Drawing Test scores, while FDC of splenium of corpus callosum, bilateral anterior cingulate tracts, forceps major, and bilateral inferior longitudinal fasciculus were positively correlated with the Executive Factor Score of Memory and Executive Screening scale scores.

**Conclusion:** Reduced grip strength in AD patients is associated with extensive impairment of WM structural integrity. Changes in FDC of specific WM fiber tracts related to executive function play a significant mediating role in the reduction of grip strength in AD patients.

**Keywords:** Alzheimer disease, grip strength, white matter, fixel-based analysis, cognition function

Alzheimer's disease (AD) is the most prevalent type of dementia worldwide, characterized by the progressive cognitive decline as the main clinical symptoms of neurodegenerative disease. Although pharmacological treatment options for AD remain limited, early intervention targeting modifiable risk factors could prevent or delay up to 40–50% of dementia cases.<sup>1</sup> Given the long period preceding the onset of AD pathology and early symptoms, identifying and intervening with modifiable risk factors becomes crucial.

Recently, studies have demonstrated that reduced grip strength is a risk factor of early cognitive dysfunction and dementia in older adults.<sup>2</sup> Stronger grip strength is correlated with better cognitive processing speed, memory, executive function, as well as less cortical atrophy in brain regions closely related to these cognitive processes, such as the hippocampus, temporal lobe, ventral striatum and thalamus.<sup>3</sup> From a neuroimaging perspective, in addition to cortical atrophy, which is a distinctive feature of AD, structural or functional abnormalities in the white matter (WM) fiber tracts,

which serve as important network pathways connecting various cerebral regions, are also closely associated with the risk and progression of AD.<sup>4</sup> Persistent damage to brain WM fiber pathways not only disrupts functional brain network connectivity and information dissemination but also accelerates abnormal changes in oxidative stress, excitotoxicity, and pathological protein deposition.<sup>5</sup> Previous research utilizing animal models for AD suggested that some degree of axonal and myelin damage existed prior to  $\beta$ -amyloid protein (A $\beta$ ) deposition and neurofibrillary tangle formation in cortex,<sup>6</sup> accentuating that structural changes in the WM may occur before or even at an earlier stage of cognitive decline, which deserves attention and emphasis.<sup>7</sup> A cohort study of 190,406 adult patients discovered that each 5kg decrease in grip strength was linked to higher WM hyperintensities (WMH) volume and a greater risk of dementia development in the future,<sup>8</sup> suggesting that decreased grip strength and abnormalities in WM structure or function may be one of the early risk markers for the development of AD. To address the question of what role specific structural alterations in WM play in mediating reduced grip strength and altered cognitive function in AD patients is the primary aim of this research.

At present, diffusion-weighted imaging (DWI) based on the diffusion tensor imaging model (DTI) is a popular non-invasive technique for studying the structure of WM fiber tracts. However, the DWI technique has several limitations that can significantly affect a study's value and reliability, including biased acquisition of data, pre- and post-processing of data, quantitative analysis, and result interpretation.<sup>9</sup> Furthermore, its capability in handling complex crossed WM fiber tracts is restricted, and variations in the presence of WM voxels pose challenges in accurately attributing them to specific fiber pathways,<sup>10</sup> but WM changes manifest in multiple forms in neurodegenerative diseases, such as fiber atrophy and demyelination. However, a recently proposed diffusion model,<sup>11</sup> fixel-based analysis (FBA) can remedy these deficiencies where "fixels" refers to all specific WM fiber tracts within a voxel with different orientations.<sup>12</sup> FBA characterizes multiple WM fiber orientations within voxels by analyzing DWI data using constrained spherical inverse fold products,<sup>10</sup> detecting structural changes in specific WM fiber tracts. FBA related metrics include fiber density (FD), fiber cross-section (FC) and fiber density and cross-section (FDC).<sup>11</sup> FD reflects the microstructure of fiber tracts, FC reflects the macrostructural properties of fiber tracts, and FDC represents the combined impact of these two metrics, reflecting the microscopic and macroscopic variations that co-occur during neurodegeneration.<sup>13</sup> A recent study using FBA technology found that patients with early-onset AD exhibited more extensive damage in WM microstructure and poorer cognitive function than patients with late-onset AD, suggesting potential differences in neuropathological mechanisms of WM damage between the two types of AD.<sup>14</sup> This highlights the superiority of FBA technique in observing and interpreting structural changes of WM tracts in AD or neurodegenerative diseases.

Applying the latest FBA technique for assessing WM structure, this study attempted to provide a deeper comprehension of how changes in WM fiber tracts influence grip strength and cognitive function in AD patients by examining microscopic and macroscopic alterations in WM structure. We hypothesized that structural changes of some specific WM fiber tracts in AD patients may mediate the reduced grip strength and cognitive function decline through the damage of brain network connections. This provides a theoretical basis for further attention to structural and functional changes in WM, which may help prevent or delay the occurrence and progression of AD.

## Materials and Methods

### Participants

A total of 54 AD patients diagnosed in the Memory Disorders Clinic of the Department of Neurology of the Second Hospital of Soochow University from January 2021 to December 2022 were recruited after approval by the Ethics Committee of the Second Hospital of Soochow University (JD-LK-2021-049-01), and informed consent was obtained from both the subjects and their caregivers. Additionally, 31 normal controls (NC) with normal cognition and grip strength were included. The inclusion criteria for AD patients include: (1) met the core diagnostic criteria based on the National Institute on Aging and the Alzheimer's Association (NIA/AA) workgroups in 2011 by the current physician or previously confirmed.<sup>15</sup> (2) an age range of 55 to 90 years and right-hand dominance. (3) craniocerebral magnetic resonance imaging (MRI) examination did not show occupying lesions and age-inappropriate periventricular and deep WM lesions.<sup>16</sup> (4) Hachinski ischemia score  $\leq 4$ . (5) no medication with effects on cognitive function and mental status within 1 month prior to enrollment. (6) clinical information was complete and understand the involved scales. The

exclusion criteria for AD patients include: (1) other diseases that cause cognitive impairment, such as cerebrovascular disease and brain tumors. (2) serious medical diseases, such as cardiopulmonary, hepatic and renal insufficiency, hypothyroidism, malignancy and other chronic wasting diseases. (3) severe depression, schizophrenia and other psychiatric diseases. (4) those who are unable to perform bioelectrical impedance and MRI examination due to metal placement. (5) those who have motor system disorders or balance dysfunction diseases affecting limb movements, such as lumbar disc herniation, history of fracture, diabetic foot, osteoarthritis, etc. (6) combined motor system symptoms, such as complaints of subjective fatigue, muscle weakness, muscle atrophy, and signs of cone system and extrapyramidal damage on physical examination. (7) mini nutritional assessment (MNA) score  $\leq 24$ .<sup>17</sup>

The inclusion criteria for NC include: (1) an age range of 55 to 90 years and right-hand dominance. (2) Montreal Cognitive Assessment (MoCA) score  $\geq 26$  points. (3) normal WM on MRI examination and no central nervous system disease. (4) no medications with effects on cognitive function and mental status within 1 month before enrollment. (5) normal grip strength was  $\geq 28$  kg for men and  $\geq 18$  kg for women. Exclusion criteria were the same as those for AD patients.

## Demographics Data

Gender, age, years of education, hypertension, diabetes, hyperlipidemia, coronary heart disease, history of smoking and alcohol consumption, height, weight were recorded. Body Mass Index (BMI) was calculated as weight (kg)/height ( $\text{m}^2$ ). The activity level was assessed based on the amount of weekly walking. Less than 120 minutes of walking per week for females and less than 150 minutes per week for males were considered low physical activity.<sup>18</sup> Participants were asked to squeeze the dynamometer (WCS-100, Nantong, China) as hard as possible with each hand. Grip strength was measured for a total of three trials and the maximum value was recorded. The cut-off was defined as  $<28$  kg for men and  $<18$  kg for women.<sup>19</sup> Based on whether there was a reduction in grip strength, AD patients were divided into 25 AD patients with low grip strength (AD-LGS) and 29 AD patients without low grip strength (AD-nLGS).

## Neuropsychological Assessments

The assessors who had received specialized and consistent training in administering assessment scales conducted neuropsychological tests on the subjects in a quiet room, including evaluations of both cognitive and non-cognitive functions. The cognitive function tests included MoCA, Clock Drawing Test (CDT), Memory and Executive Screening scale (MES), and Digit Symbol Substitution Test (DSST). MoCA assess overall cognitive function. The total score of MES (MES-T) includes the Memory Factor Score (MES-M) to assess situational memory and the Executive Factor Score (MES-E) to assess executive function. The Verbal Fluency Task (VFT) assesses verbal function. Non-cognitive tests include the Activities of Daily Living (ADL) scale, which assesses activities of daily living, and the 17-item Hamilton Depression Scale-17 (HAM-D-17), which assesses depression level.

## Magnetic Resonance Imaging (MRI) Acquisition and Preprocessing

A total of 65 volumes (DWI 60 gradient direction  $b=2000\text{s/mm}^2$  and 5 images  $b=0\text{s/mm}^2$ ) were acquired by the same 3.0T (Siemens, Germany, Prisma) MRI scanner with the following parameters: repetition time/echo time = 6600/86 ms, 2.2 mm isotropic voxels, phase encoding direction = AP. The DWI acquisition time was 0–9 min. The preprocessing and analysis steps of a state-of-the-art FBA were employed.<sup>20</sup> All diffusion MRI data were preprocessed using MRtrix3. The preprocessing steps included denoising, Gibbs ringing correction, correction for eddy current-induced distortions, with subsequent bias field correction applied. Response functions for single-fiber WM as well as gray matter (GM) and cerebrospinal fluid (CSF) were estimated from the data using an unsupervised approach. Next, single-shell 3-tissue constrained spherical deconvolution was employed to obtain WM-like fiber orientation distributions as well as GM and CSF-like compartments across all voxels. The MRtrix3Tissue software (<https://3Tissue.github.io>), a fork of MRtrix3, was utilized for this step. The obtained WM-like fiber orientation distribution (FOD), GM-like, and CSF-like images were used for multi-tissue informed log-domain intensity normalization. A cubic b-spline interpolation was further employed to upsample the WM fiber orientation distribution images to 1.3 mm isotropic voxels. A study-specific template was subsequently generated using the WM FOD images from 31 NC and all subjects' FOD images were non-linearly

registered to it. Finally, the WM FOD template was utilized to generate a whole-brain probabilistic tractogram that was filtered from 20 million tracts to 2 million tracts to mitigate reconstruction bias.

## Fixel-Based Metrics

We employed the FBA framework to calculate FD and FC at the level of a “fixel”,<sup>11</sup> which refers to a population of fibers within a voxel. This means that even when multiple fibers are crossing in the same voxel, each fiber still has its own individual measurements of FD and FC. (1) FD, obtained from FOD images because the integration of FOD along a particular direction is proportional to the volume within the axons aligned along that direction. Therefore, FD values are particularly sensitive to changes in the level of microstructure within the voxel. (2) FC, a loss of the axons results in shrinkage of the fiber tract across its cross-section, implying a reduction in the extent of space occupied by that fiber tract, leading to changes in macrostructure.<sup>11</sup> Using nonlinear distortion to calculate the spatial normalization of the subject image to the template image, structural differences can be estimated for each FC (in a plane perpendicular to the fixed direction). (3) FDC, the product of the above two metrics and provides information about the combined pathology of microstructural and macrostructural changes, increasing sensitivity to the overall ability of the fiber population to transmit information between connected cerebral regions.

## Statistical Analysis

SPSS26.0 software package was used for statistical analysis. Normally distributed continuous variables were presented as means  $\pm$  standard deviation (SD) and analyzed using Analysis of Variance (ANOVA;  $F$  value). Post-hoc tests with Bonferroni corrections for multiple comparisons were conducted when a statistically significant variable was identified in ANOVA. Non-normally distributed continuous variables were reported as medians (interquartile range) and analyzed by the Kruskal–Wallis  $H$ -test ( $H$  value). Categorical variables were expressed as percentages, and inter-group comparisons were conducted using the  $\chi^2$  test or Fisher’s exact test ( $\chi^2$  value). Bonferroni correction was employed to indicate significant group differences.  $P < 0.05$  was considered a statistically significant difference.

## Whole-Brain Fixel-Based Analysis

To identify regions with altered FD, FC and FDC in the AD-LGS, AD-nLGS and NC groups, we first compared metrics based on whole-brain FBA. A general linear model was used to statistically compare FD, FC, and FDC in the AD-LGS, AD-nLGS, and NC groups. Age and gender were used as covariates to compare differences in fixel levels using the connectivity-based fixel enhancement (CFE). The utilization of smoothing in CFE primarily focuses on applying it along structurally connected fixels. This approach guarantees that fixel-based metrics undergo local smoothing alongside fixels that are part of the same fiber tract. Allocated Family-wise error rate (FWE)-corrected  $P$ -values to each fixel using non-parametric permutation testing conducted over 5000 permutations.<sup>21</sup>

Significant fixels (FWE-corrected  $P$ -value  $< 0.05$ ) were visualized using the *mrview* tool in MRtrix3. To enhance the understanding of the implicated fiber pathways, significant fixels were overlaid on the template-derived tractogram. This approach involved isolating only those fixels that held significance and displaying corresponding streamlines. The visualization utilized color-coded streamlines based on their orientations (anterior-posterior: green, left-right: red, superior-inferior: blue).

## Tract of Interest (TOI) Analysis

We performed a further TOI analysis to investigate the potential degeneration of selective fiber pathways in the AD-LGS group. All fixels that demonstrated significant differences in the FDC metric among the three groups upon whole-brain FBA were classified into 21 distinct WM tracts based on JHU brain WM atlas. Mean FDC values for each fiber tract were extracted, including bilateral anterior thalamus radiation (ATR), corticospinal tract (CST), anterior cingulate tract, posterior cingulate tract, uncinate fasciculus (UF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), genu of corpus callosum (GCC), body of corpus callosum (BCC), splenium of corpus callosum (SCC), forceps major, and forceps minor.

PALM (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM>) was used in MATLAB to count the group differences of FDC values in all fiber tracts on the basis of correction for age and gender. Correlation analysis was performed between FDC values of the fiber tracts and neuropsychological scale scores, controlling for age, gender and years of education. The above statistics were calculated by permutation testing to calculate the *P*-FEW values.

## Results

### Comparison of General Clinical Characteristics Among the Three Groups

As demonstrated in Table 1, the NC group included 15 males and 16 females, aged ( $68.45 \pm 8.90$ ) years with 11.0 (9.0,16.0) years of education. The AD-nLGS group included 10 males and 19 female patients, aged ( $67.86 \pm 8.63$ ) years with 9.0 (3.0,12.0) years of education. The AD-LGS group included 3 males and 22 female patients, age ( $76.88 \pm 6.79$ ) years with 6.0 (2.0,12.0) years of education. The height, weight, grip strength and MTA scores were statistically significant differences (all  $P < 0.05$ ). Compared to the NC and AD-nLGS groups, the AD-LGS group had poorer grip strength and higher MTA scores (all  $P < 0.01$ ).

### Comparison of Neuropsychological Characteristics Among the Three Groups

As demonstrated in Table 2, compared with the NC group, the AD group had lower scores for MoCA, CDT, MES-T, MES-M, MES-E, DSST, FDST, BDST, VFT, and higher scores for ADL and HAMD-17 (all  $P < 0.05$ ); compared with the AD-nLGS group, the AD-LGS group had lower scores for CDT, MES-E and DSST ( $P < 0.05$ ).

### Comparison of FD, FC and FDC in TOI Among Three Groups

As demonstrated in Figure 1, adjusting for age and gender, streamline segments associated with fixels that had a significant (FWE-corrected  $P$ -value  $< 0.05$ ) decrease between the three groups in FC, FD, and FDC of BCC, GCC, SCC, bilateral ATR, forceps major, forceps minor, bilateral IFOF, bilateral UF, bilateral anterior cingulate tract and bilateral ILF; there were also significant differences among the three groups in FC and FDC of bilateral ILF, bilateral CST and right posterior cingulate tract, and significant differences among the three groups in FDC of the left posterior cingulate tract.

**Table 1** Comparison of General Clinical Characteristics Among the Three Groups

Index	NC (n = 31)	AD-nLGS (n = 29)	AD-LGS (n = 25)	<i>F</i> / <i>H</i> / $\chi^2$	<i>P</i>
Male, n (%)	15 (48.4)	10 (34.5) <sup>†</sup>	3 (12.0) <sup>‡</sup>	8.342 <sup>c</sup>	0.015*
Age (y)	68.45 $\pm$ 8.90	67.86 $\pm$ 8.63	76.88 $\pm$ 6.79 <sup>‡§</sup>	9.904 <sup>a</sup>	0.000**
Years of education (y)	11.0 (9.0,16.0)	9.0 (3.0,12.0)	6.0 (2.0,12.0) <sup>‡</sup>	8.567 <sup>b</sup>	0.014*
Hypertension, n (%)	13 (41.9)	15 (51.7)	14 (56.0)	1.189 <sup>c</sup>	0.552
Diabetes, n (%)	6 (19.4)	3 (10.3)	7 (28.0)	2.72 <sup>c</sup>	0.284
Dyslipidemia, n (%)	5 (16.1)	6 (20.7)	8 (32.0)	2.079	0.354
Coronary artery disease, n (%)	3 (9.7)	4 (13.8)	6 (24.0)	2.165	0.358
Current smoking, n (%)	6 (19.4)	4 (13.8)	1 (4.0)	2.889 <sup>c</sup>	0.233
Alcohol drinking, n (%)	5 (16.1)	4 (13.8)	2 (8.0)	0.852 <sup>c</sup>	0.663
Height (cm)	161.38 $\pm$ 8.62	158.63 $\pm$ 7.70	151.61 $\pm$ 6.54 <sup>‡§</sup>	11.432 <sup>a</sup>	0.000**
Weight (kg)	64.55 $\pm$ 10.63	60.40 $\pm$ 10.25	52.54 $\pm$ 7.57 <sup>‡§</sup>	10.775 <sup>a</sup>	0.000**
BMI (kg/m <sup>2</sup> )	24.73 $\pm$ 3.21	23.97 $\pm$ 3.53	22.83 $\pm$ 2.82	2.40 <sup>a</sup>	0.097
Low physical activity, n (%)	8 (25.8)	9 (31.0)	13 (52.0)	4.507	0.105
Grip strength (kg)	28.20 (21.95,33.7)	26.80 (21.90,31.80)	17.60 (14.90,17.80) <sup>‡§</sup>	39.837 <sup>b</sup>	0.000**
MTA	1.0 (0.0,1.0)	2.0 (1.0,2.0) <sup>†</sup>	2.0 (2.0,2.0) <sup>‡</sup>	23.906 <sup>c</sup>	0.000**

**Notes:** <sup>a</sup>Normally distributed variable is expressed as mean  $\pm$  standard deviation and analyzed by ANOVA of three groups (*F* value). <sup>b</sup>Non-normally distributed variable is expressed as median (interquartile range) and analyzed by Kruskal–Wallis *H*-test of three groups (*H* value). <sup>c</sup>Categorical variables are expressed as frequency (percent;  $\chi^2$  value). <sup>†</sup>AD-nLGS significantly different from NC ( $P < 0.05$ ); <sup>‡</sup>AD-LGS significantly different from NC ( $P < 0.05$ ); <sup>§</sup>AD-LGS significantly different from AD-nLGS ( $P < 0.05$ ). \* $P < 0.05$ ; \*\* $P < 0.01$ .

**Abbreviations:** NC, normal controls; AD-nLGS, Alzheimer's disease without low grip strength; AD-LGS, Alzheimer's disease with low grip strength; BMI, body mass index; MTA, medial temporal atrophy.

**Table 2** Comparison of Neuropsychological Characteristics Among the Three Groups

Scale	NC (n = 31)	AD-nLGS (n = 29)	AD-LGS (n= 25)	P value	
				NC vs AD	AD-nLGS vs.AD-LGS
MoCA	27.0(26.0,27.0)	17.0(12.0,20.0)	15.0(11.0,16.0)	0.000**	0.137
CDT	3.0(3.0,3.0)	2.0(2.0,3.0)	2.0(1.0,2.0)	0.000**	0.010*
MES-T	89.0(84.5,95.5)	58.0(42.0,68.0)	52.0(40.0,61.0)	0.000**	0.152
MES-M	42.1 ± 4.2	20.5 ± 7.1	19.3 ± 3.2	0.000**	0.586
MES-E	49.0(45.5,50.0)	37.0(27.0,44.0)	35.0(23.0,36.0)	0.000**	0.027*
DSST	30.0(24.0,36.5)	14.0(10.0,23.0)	10.0(6.0,13.0)	0.000**	0.014*
DST					
FDST	8.0(8.0,9.0)	8.0(8.0,8.0)	8.0(6.0,8.0)	0.016*	0.465
BDST	5.0(4.0,5.0)	4.0(3.0,4.0)	3.0(2.0,4.0)	0.000**	0.259
VFT	33.6 ± 10.8	17.8 ± 6.3	15.8 ± 6.7	0.000**	0.255
ADL	20.0(20.0,20.0)	24.0(23.0,25.0)	25.0(23.0,31.0)	0.000**	0.155
HAMD-17	3.0(0.5,4.5)	5.0(2.0,6.0)	6.0(4.0,7.0)	0.000**	0.298

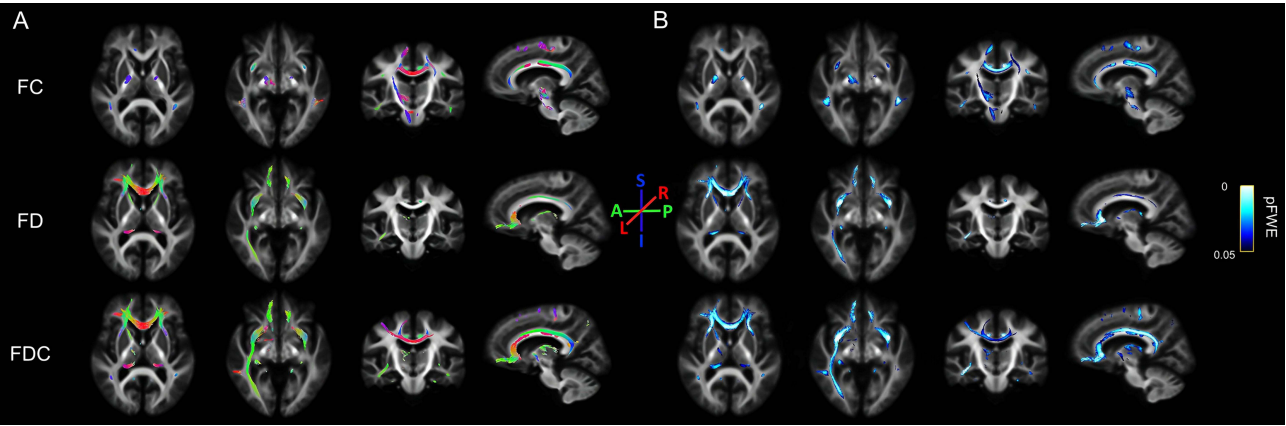
**Notes:** \* $P<0.05$ ; \*\* $P<0.001$ .  
**Abbreviations:** NC, normal controls; AD, Alzheimer's disease; AD-nLGS, Alzheimer's disease without low grip strength; AD-LGS, Alzheimer's disease with low grip strength; MoCA, Montreal cognitive assessment; CDT, Clock Drawing Test; MES-T, Total Score of MES; MES-M, Memory and Executive Screening scale; MES-M, Memory Factor Score of MES; MES-E, Executive Factor Score of MES; DSST, Digit Symbol Substitution Test; VFT, Verbal Fluency Task; ADL, Activities of Daily Living scale; HAMD-17, the 17-item Hamilton Depression Scale-17.

Two-by-Two Post Hoc Comparisons of FC, FD, and FDC of the Statistically Different TOI Among the Three Groups

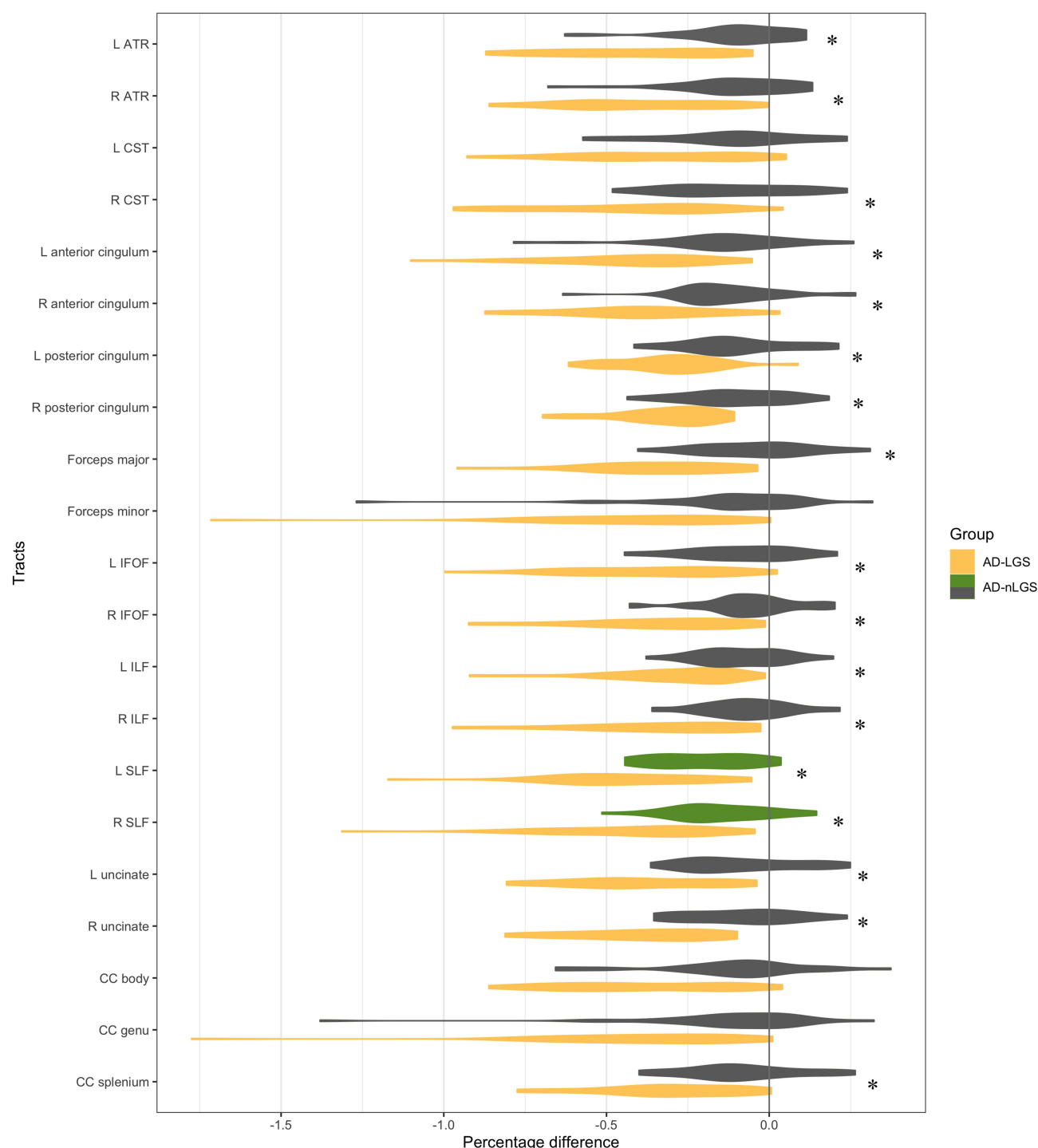
As demonstrated in Figure 2, post hoc test analysis showed that compared to the AD-nLGS group, FDC was significantly lower in the AD-LGS group in CC, SCC, bilateral IFOF, bilateral ILF, bilateral UF, bilateral ATR, right CST, bilateral anterior cingulate tract, left posterior cingulate tract, forceps major and bilateral SLF. FD was significantly lower in CC, SCC, bilateral IFOF, bilateral ILF, bilateral UF, bilateral ATR, bilateral anterior cingulate tract and forceps major. FC was significantly lower in CC, BCC, SCC, bilateral IFOF, bilateral ILF, bilateral UF, left ATR, bilateral anterior cingulate tract and bilateral SLF.

Correlation Between FDC and CDT, DSST, and MES-E Scores of Cerebral TOI with Statistically Differences Between Groups

As demonstrated in Table 3 and Figure 3, correlation analysis showed that after controlling for age, gender, and years of education, the FDC values of AD patients in the left UF ( $r=0.39$ ,  $P\text{-FWE}=0.016$ ), right UF ( $r=0.36$ ,  $P\text{-FWE}=0.034$ ), and



**Figure 1** Whole-brain FBA results. Fiber tract-specific differences among AD-nLGS, AD-LGS and NC are shown. Streamline segments were cropped from the template tractogram to include only those corresponding to fixels significant at family-wise error-corrected  $P<0.05$ . Streamlines were colored by (A) fiber direction (A-P indicates anterior-posterior, green; L-R, left-right, red; and S-I, superior inferior, blue.) and (B) family-wise error-corrected  $P$  value for fiber density (FD), fiber cross-section (FC), and combined fiber density and cross-section (FDC).



**Figure 2** Tract-of-interest results. Mean FDC within tracts of interest are displayed for AD-nLGS and AD-LGS, as a percentage difference from the NC mean, adjusted for age and gender. For each AD group vs NC group, significant tracts ( $P\text{-FWE} < 0.05$ ) are displayed in color, while non-significant are shown in grey. For AD-nLGS vs AD-LGS, significant tracts are labeled with asterisks (\*).

**Abbreviations:** AD-nLGS, AD patients with non-low grip strength; AD-LGS, AD patients with low grip strength; ATR, anterior thalamus radiation; CST, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; CC, corpus callosum; L, left; R, right.

left SLF ( $r=0.36$ ,  $P\text{-FWE}=0.033$ ) were positively correlated with CDT scores; the FDC values in the SCC ( $r=0.40$ ,  $P\text{-FWE}=0.016$ ), left anterior cingulate tract ( $r=0.35$ ,  $P\text{-FWE}=0.046$ ), right anterior cingulate tract ( $r=0.41$ ,  $P\text{-FWE}=0.01$ ), forceps major ( $r=0.47$ ,  $P\text{-FWE}=0.002$ ), left SLF ( $r=0.41$ ,  $P\text{-FWE}=0.01$ ), right SLF ( $r=0.37$ ,  $P\text{-FWE}=0.03$ ) were positively correlated with MES-E scores (all  $P < 0.05$ ).

**Table 3** Correlation Between FDC in Cerebral TOI That Were Statistically Different Between Groups with CDT, DSST and MES-E Scores

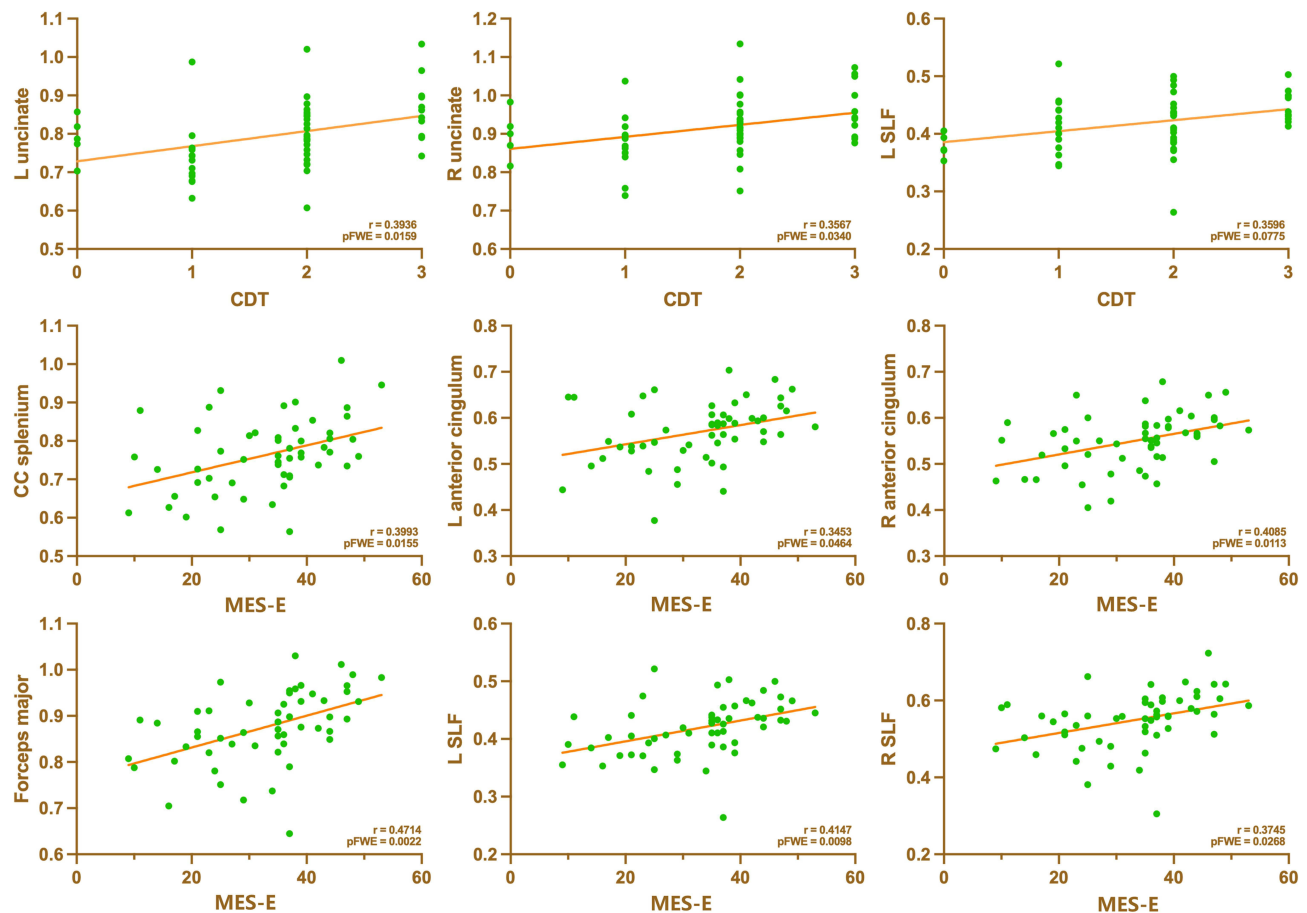
TOI	CDT			DSST			MES-E		
	<i>r</i>	<i>P</i> -FWE	<i>P</i> _Uncorrected	<i>r</i>	<i>P</i> -FWE	<i>P</i> _Uncorrected	<i>r</i>	<i>P</i> -FWE	<i>P</i> _Uncorrected
BCC	0.2327	0.2147	0.0429	0.1291	0.5482	0.1782	0.3005	0.095	0.0153
GCC	0.0747	0.7151	0.2951	0.1398	0.5129	0.1607	0.2363	0.2184	0.0447
SCC	0.2823	0.1172	0.019	0.2472	0.1904	0.0388	0.3993	<b>0.0155</b>	0.0017
Forceps minor	0.085	0.684	0.2664	0.1763	0.3897	0.1019	0.2478	0.189	0.0373
IFOF_L	0.3101	0.0757	0.0126	0.2734	0.1364	0.0214	0.3115	0.0806	0.0117
IFOF_R	0.2791	0.1224	0.022	0.2565	0.1701	0.0276	0.3355	0.0538	0.0082
ILF_L	0.0792	0.7018	0.2781	0.1363	0.5236	0.1662	0.0823	0.6888	0.2797
ILF_R	0.2211	0.2425	0.0534	0.1485	0.4824	0.1451	0.2221	0.254	0.055
UF_L	0.3936	<b>0.0159</b>	0.002	0.2801	0.124	0.0219	0.2034	0.3048	0.0687
UF_R	0.3567	<b>0.034</b>	0.0046	0.2675	0.1484	0.0276	0.2399	0.2112	0.0399
ATR_L	0.2484	0.1796	0.0355	0.222	0.2548	0.0557	0.3143	0.077	0.0119
ATR_R	0.2656	0.1452	0.0261	0.2324	0.2285	0.0466	0.2662	0.1485	0.0279
CST_L	0.2527	0.1726	0.0334	0.0892	0.6748	0.2624	0.2808	0.1227	0.0219
CST_R	0.2808	0.1196	0.0199	0.1286	0.5501	0.1818	0.2703	0.1413	0.0257
Anterior cingulum_L	0.2094	0.2751	0.0624	0.2299	0.2335	0.0499	0.3453	<b>0.0464</b>	0.0068
Anterior cingulum _R	0.2503	0.176	0.0316	0.2403	0.207	0.043	0.4085	<b>0.0113</b>	0.001
Posterior cingulum _L	0.2411	0.1955	0.0382	0.1464	0.4901	0.1491	0.3031	0.0901	0.0123
Posterior cingulum _R	0.315	0.0683	0.0095	0.1877	0.3562	0.0907	0.2629	0.1541	0.0293
Forceps major	0.2858	0.1109	0.0167	0.289	0.1104	0.0185	0.4714	<b>0.0022</b>	0.0001
SLF_L	0.3596	<b>0.0328</b>	0.0044	0.1544	0.4639	0.1329	0.4147	<b>0.0098</b>	0.001
SLF_R	0.3088	0.0775	0.012	0.2543	0.1747	0.0325	0.3745	<b>0.0268</b>	0.0031

**Notes:** The values present *r* (*p* value); *r*, correlation coefficient; correlation analysis adjusted for age, gender and education. *P* value was family-wise error-corrected (*P*\_uncorrected) for the correlation of FDC and CDT, DSST, MES-E scores. Bold values denote statistical significance (*P* < 0.05).

## Discussion

This study showed that compared to the AD-nLGS and NC groups, the damage to the structural WM integrity in the AD-LGS group was more extensive spatially, with more axonal loss in macroscopic and microscopic structures of certain specific WM tracts, such as SCC, BCC, forceps major, bilateral anterior cingulate tracts, bilateral SLF, bilateral UF, bilateral ATR, bilateral IFOF, bilateral ILF, right CST and bilateral posterior cingulate tracts. Compared to the AD-nLGS group, the AD-LGS group had extensive cognitive impairment and scored lower on the CDT, MES-E and DSST, indicating worse executive function, visuospatial ability and information processing speed. Notably, executive function in AD patients was more closely related to SCC, bilateral anterior cingulate tracts, forceps major, bilateral SLF, and bilateral UF, inferring that specific structural alterations of WM fiber tracts associated with executive function may be one of the mechanisms contributing to reduced grip strength in AD patients. These findings highlight the importance of monitoring and maintaining the normal structure and function of WM fiber tracts in AD to prevent or delay the occurrence and progression of the disease.

Current studies on the relationship between grip strength and WM structure mainly rely on WMH and DTI techniques, which have certain limitations. However, WMH results can be influenced by factors such as imaging equipment, image processing methods and evaluator subjectivity, resulting in lack of consistency and specificity, and are unable to accurately assess specific nerve fiber tracts.<sup>22,23</sup> Kwak et al<sup>24</sup> evaluated nerve fiber tracts using DTI technique and found a significant correlation between decreased grip strength in elderly women and reduced CST volume. Nevertheless, DTI has limitations in identifying diffusion rates of complex intersecting fiber tract structures within up to 90% of WM voxels, reducing the reliability of results.<sup>10</sup> Various forms of microstructural and macro-structural changes in WM in neurodegenerative diseases can also make intersecting fibers more complex. If one type of intersecting fiber within a voxel decreases WM integrity while another increases connectivity, these two changes cannot be observed, so DTI is not inherently fiber-specific.<sup>25</sup> However, FBA technology can address these deficiencies by showing the direction of multiple WM fiber tracts within a voxel and provide quantitative indicators for macroscopic and



**Figure 3** Correlations between exacted values of mean FDC of AD patients and scores of CDT and MES-E.

microscopic changes in WM fibers.<sup>25</sup> The three FBA-related indicators included FD, FC and FDC. Decreased number or individual volume of axons may not affect macroscopic FC, as the extracellular matrix surrounding the axons becomes filled with inflammatory cells or proliferating glial cells. When extracellular matrix or cells surrounding the axons are cleared, fiber tracts may contract and result in decreased FC, suggesting that FD reduction may precede changes in FC.<sup>20</sup> FD is more sensitive to neurodegenerative lesions, while decreased FC indicates more severe neurodegeneration and structural atrophy. FDC, reflecting the combined lesion degree of microstructure and macrostructure changes, is noteworthy for its improved sensitivity to the early nerve fiber tract degeneration. This is also why the FDC was mainly utilized for inter-group comparisons and correlation analysis, which is one of the advantages of this study.

Considerable evidence suggests that reduced grip strength is an early risk factor of cognitive decline and dementia incidence in late life.<sup>26</sup> A cohort study of 340,212 cognitively normal elderly individuals found that every 5 kg increase in grip strength was associated with a reduced risk for all-cause dementia, AD, and vascular dementia.<sup>27</sup> Despite some evidence linking reduced grip strength to cognitive decline and dementia, there still lacks in-depth mechanistic studies. Notably, every 5 kg decrease in grip strength is associated with increased WMH volume and dementia incidence in older adults,<sup>8</sup> suggesting that abnormal WM changes may be one of the mechanisms linking cognitive decline and weaker grip strength. This may be due to that WM serves as the primary fiber pathway connecting cortical regions and plays a crucial role in transmitting information and maintaining normal cognitive or motor functions in the cortex. Abnormalities in WM connections can affect cortical function, which is closely related to grip strength. For example, Jiang et al<sup>3</sup> included 42,843 normal older adults and found that stronger grip strength was associated with increased hippocampus and temporal cortex volumes. Stronger grip strength in patients with amnesic mild cognitive impairment (MCI) was related to better executive function, possibly due to changes in the hippocampus-prefrontal network integrity.<sup>28</sup> This study found

that AD-LGS patients had extensive micro- and macrostructural changes in WM fiber tracts, accompanied by extensive cognitive decline, suggesting that changes in specific WM fiber pathways in AD patients may link cognitive decline and reduced grip strength. AD is characterized by large-scale brain network dysfunction associated with A $\beta$  deposition, neurofibrillary tangles, cortical atrophy, and functional disconnection between cortical areas. It exhibits a typical spatio-temporal change pattern<sup>13</sup> where WM plays a crucial role in maintaining normal function of cortical regions. Early microstructural WM changes in AD initially manifest in the UF and progressively involve short fiber tracts connecting lateral temporal-parietal lobes as well as long fiber tracts linking to the frontal lobe.<sup>29</sup> These WM fiber pathways connect cortical regions susceptible to AD pathology, like the default mode network (DMN), which underlies widespread cognitive decline.<sup>30</sup> Anatomically, the cingulate tract is a hub connecting the DMN, including the medial prefrontal cortex, posterior cingulate cortex and medial temporal lobe.<sup>31,32</sup> ILF and IFOF also connect to the DMN.<sup>33</sup> The UF links the ventral medial prefrontal cortex and hippocampus, while SCC connects the posterior inferior parietal cortex, posterior cingulate gyrus and posterior prefrontal cortex, all of which are important components of DMN. Therefore, the abnormal structural changes of specific WM fiber tracts in AD patients may mediate the decline of cognitive function and the decrease in grip strength by affecting the normal function of cerebral cortex.

A recent study found a positive correlation between stronger grip strength and higher CDT scores in older adults, particularly in men.<sup>34</sup> Weaker grip strength in patients with subjective cognitive decline and MCI was associated with worse baseline information processing speed and executive function but no longitudinal association was observed.<sup>35</sup> However, previous studies lack a mechanistic explanation for the correlation between grip strength and executive function. Similarly, this study also revealed that AD-LGS patients had lower CDT, DSST and MES-E scores compared to AD-nLGS patients, indicating poorer executive and visuospatial functions. Further analysis showed that CDT scores were correlated with FDC of bilateral UF and left SLF; MES-E scores were correlated with SCC, bilateral SLF, forceps major and bilateral anterior cingulate tracts. This suggests that structural alterations in specific WM fiber tracts associated with executive function are closely related to grip strength reduction in AD patients.

Among the above brain regions, the CC is particularly noteworthy as its atrophy is linked to cognitive impairment in MCI and AD patients, even before the onset of AD.<sup>36,37</sup> Composed of over 20 billion fibers,<sup>38</sup> the CC serves as the largest WM fiber tract responsible for transmitting and integrating information between cerebral hemispheres, affecting executive function, visual-motion integration, spatial attention and complex motor control.<sup>39</sup> It has four parts: the rostrum and genu form the front portion, BCC makes up the central portion and SCC is the posterior part. Few studies explored the relationship between the CC and grip strength in AD patients, with most research focusing on manual dexterity and coordination. Notably, the SCC connects both hemispheres' primary motor cortex, associated with hand movements and coordination,<sup>40</sup> and also links the bilateral parietal lobes and posterior cingulate cortex, which are closely related to grip strength<sup>41</sup> and form a network structure associated with executive function.<sup>42</sup> This study also found that AD-LGS patients had a smaller FDC in the SCC, which was associated with executive function. Garnier-Crussard et al<sup>43</sup> propose that WMH of SCC is the core feature of AD, present in the early stage and associated with poor overall cognitive performance and executive function, independent of cortical A $\beta$  deposition, cortical and hippocampal atrophy. SCC is more involved in AD and located near cortical regions more vulnerable to AD pathological proteins (eg, posterior cingulate cortex and posterior hippocampus),<sup>44</sup> while GCC is more susceptible to cerebrovascular injury factors. Consequently, SCC may be a specific WM fiber tracts affecting grip strength and executive function decline in AD patients. It also sends out a large fiber tract as forceps major to the occipital lobe, forming a CC swelling in the medial wall of the atrial and occipital angle.<sup>45</sup> Forceps major's microstructure integrity is correlated with executive function, visual space and working memory,<sup>46</sup> and abnormalities in the activity of the attached occipital visual cortex have also been strongly associated with decreased information processing speed.<sup>47</sup> The combination of WM integrity in forceps major with perceptual speed and hippocampal volume (AUC = 0.911) was found to be the most predictive model for AD,<sup>48</sup> indicating forceps major as another specific site of WM degeneration in AD.

AD-LGS patients also show significant axonal loss in the microstructure and macrostructure of the anterior cingulate fasciculus, associated with executive function. This crucial cingulate fasciculus connects the limbic system, cingulate gyrus and DMN,<sup>49</sup> including short fiber tracts connecting to the cingulate gyrus and long fiber tracts to the prefrontal, parietal and temporal cortices, controlling cognitive functions like executive function and memory.<sup>50</sup> While few studies

explored the relationship between the anterior cingulate tract and grip strength, some have shown cortical regions connected by this tract are related to hand motor performance and coordination.<sup>51</sup> Cordani et al<sup>52</sup> found that hand motor performance decline in multiple sclerosis patients was associated with the left anterior cingulate gyrus atrophy and the right CST structural abnormalities, possibly because the anterior cingulate gyrus is instrumental in attention and modulating supplementary motor cortical areas during movement tasks. Stronger non-dominant side grip strength in AD patients was associated with larger hippocampal volume, while stronger dominant side grip strength was correlated with larger frontal cortical volume.<sup>53</sup> Therefore, we speculate that structural alterations in the anterior cingulate tract in AD patients affect its connectivity to cortical regions related to executive function (eg, frontal lobe, anterior cingulate gyrus), mediating the relationship between the reduced grip strength and diminished executive function. Proliferating studies have also demonstrated that the anterior cingulate gyrus exhibits anatomical and functional abnormalities in amnesic MCI and AD, predicting the progression from amnesic MCI to AD. Normal connectivity of the anterior cingulate gyrus relies on the integrity of the anterior cingulate tract,<sup>54</sup> so structural alterations in this tract may be a characteristic WM fiber tract involved in executive function decline and grip strength reduction in AD patients.

In addition, this study revealed that the higher the FDC of the left SLF and bilateral UF in AD-LGS group, the higher the CDT score, suggesting that SLF and UF are related to visuospatial and executive functions. Disruption of the SLF in AD patients can cause hypofunction of the DMN, sensorimotor and frontoparietal cortices, accompanied by decreased motor and executive abilities,<sup>55</sup> as the SLF connects the frontal, parietal, temporal and occipital lobes that are vital for language, visuospatial function and metacognitive function.<sup>56,57</sup> For example, in clinical pre-AD patients with a family history of dementia or carrying APOE  $\epsilon 4$ , damage to the WM integrity of SLF, UF, CC and cingulum serve as an important predictor of poorer visual-motor integration ability,<sup>58</sup> which can impact grip strength performance.<sup>59</sup> MCI patients have more A $\beta$  and tau protein deposition<sup>60</sup> and microstructural WM damage in UF is also related to memory and executive function in AD and amnesic MCI patients.<sup>61</sup> It connects with some limbic systems (eg, the hippocampus and amygdala) and the orbitofrontal cortex,<sup>62</sup> which are vulnerable to A $\beta$  and tau protein accumulation,<sup>63</sup> and related to grip strength.<sup>64</sup> Therefore, we should also consider the specific role of SLF and UF in the grip strength and executive functions of AD patients.

## Conclusion

This study found that AD-LGS patients had more extensive structural alterations in WM macroscopically and microscopically, and a broad cognitive function decline compared to NC and AD-nLGS patients. Compared to AD-nLGS patients, AD-LGS patients performed worse in executive and visuospatial functions. Notably, specific structural alterations in WM fiber tracts associated with executive functions may mediate reduced grip strength in AD patients, such as SCC, bilateral anterior cingulate tracts, forceps major, left SLF and bilateral UF tracts. Grip strength may indicate micro- or macrostructural alterations in WM and executive function impairment in AD patients. These findings broaden our comprehension of the structural changes in WM fiber tracts – executive function alterations – grip strength reduction pathway. Targeted interventions for WM structural or functional changes may contribute to delaying AD progression and have some clinical implications for effective screening and treatment.

This study still has shortcomings: 1. It is a cross-sectional study, and future longitudinal studies are required to confirm the causal relationship between WM fiber tracts, grip strength and cognitive function. 2. The sample size is relatively small (especially for men), and more AD and MCI patients are needed for a stratified analysis by gender and age. Compared with the NC and AD-nLGS groups, the proportion of females and age in the AD-LGS group were significantly higher. The explanation was not only due to the small sample size but also that older age and female were the characteristics and major influencing factors for grip strength weakening in AD patients. Similarly, Jian et al<sup>65</sup> included 2623 older Americans and found that weak grip strength was associated with female, older age and lower educational levels. To minimize potential confounding effects of age and gender, we made adjustments in imaging management accordingly. Therefore, the results can still provide some theoretical basis for the mechanism of grip strength decline and cognitive function impairment in AD patients. 3. Subjects were all right-handed, making the left CST more dominant than the right CST for grip strength.<sup>66</sup> This may explain why the FDC of CST differ only on the right side among groups. Maximum grip strength of both hands should be collected for a stratified analysis. 4. Given that some studies have confirmed the effects of vitamin D levels, dipeptidyl peptidase-4 inhibitors, and renin-angiotensin-aldosterone system blockers on muscle strength,<sup>67–69</sup> it is necessary to collect these

indicators in future research. 5. Multi-shell data and higher b-value data allow for a more accurate assessment of fiber orientation, but data with a single b-value can also produce relatively robust results.<sup>10</sup> Future research methods can be further refined using multi-shell MRI.

## Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

## Ethical Approval

The study was performed in accordance with the guidelines of the 1964 Declaration of Helsinki and was approved by the ethics committee of the Second Affiliated Hospital of Soochow University (JD-LK-2021-049-01). All patients provided written informed consent prior to the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no competing interests relevant to the content of this work.

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