Journal of NeuroEngineering and Rehabilitation

RESEARCH

Open Access

Diffusion tensor imaging biomarkers for assessing cognitive and physical function in aging

Jungsoo Lee[1*], Woohee Han[1] and Hyunjin Kim[1]

Abstract

Background As the global population ages, the decline in cognitive and physical functions presents significant challenges for individuals and healthcare systems. In older adults, conventional assessment methods are often subjective, time-consuming, and influenced by external factors, highlighting the need for objective and efficient evaluation tools. Neuroimaging biomarkers, particularly diffusion tensor imaging (DTI) metrics, offer promising insights into brain structure and function, potentially serving as reliable indicators of functional decline.

Methods This study examines the relationship between DTI-derived metrics and cognitive and physical functions in older adults ($n = 106$). Four primary diffusion metrics, such as fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, were analyzed to assess their strength of association with functional decline. To enhance this association, principal component analysis (PCA) was applied, integrating multiple diffusion features. Age, sex, and educational level were included as covariates to control for their potential confounding effects.

Results Neuroimaging biomarkers were significantly associated with both cognitive and physical functions in older adults. Key neural pathways, including the corpus callosum, anterior and retrolenticular internal capsule, fornix, and superior fronto-occipital fasciculus, showed strong associations across domains. PCA combining metrics enhanced these associations, highlighting integrated patterns of white matter contributions. Models selecting multiple neural tracts demonstrated increased predictive accuracy, especially when adjusting for age, sex, and education. Distinct tract-function relationships were observed across physical and cognitive subdomains, emphasizing the complex and domain-specific roles of white matter in functional outcomes.

Conclusions The findings highlight the potential of neuroimaging biomarkers as objective tools for evaluating functional decline in aging. Identifying key neural pathways linked to cognitive and physical functions may contribute to early diagnosis and targeted interventions. The integration of multiple neuroimaging features enhances the strength of associations, suggesting that advanced neuroimaging techniques could play a crucial role in aging research and clinical applications.

Keywords Neuroimaging biomarkers, Diffusion tensor imaging, Cognitive function, Physical function, Aging, White matter integrity

*Correspondence:
Jungsoo Lee
jungsoo0319@gmail.com

[1]Department of Biomedical Engineering, Kumoh National Institute of Technology, 350-27 Gumi-Daero, Gumi, Gyeongbuk 39253, Republic of Korea

Introduction

With the global trend of an aging population, the decline in cognitive and physical functions among the elderly has become a critical issue. When such deterioration reaches severe levels, it affects individuals and creates significant societal challenges, increasing the burden on healthcare systems and caregivers [1]. As aging progresses, the prevalence of degenerative and vascular brain diseases rises, making early diagnosis and accurate assessment crucial for timely intervention and management [2, 3].

However, accurately assessing and tracking changes in physical and cognitive functions in the elderly presents substantial challenges. Conventional evaluation methods are often time-consuming, require active participation, and may be hindered by physical limitations or fluctuating health conditions. Additionally, motivation and environmental factors play a role in the variability of assessment outcomes, reducing the reliability of longitudinal tracking [4]. Thus, the need for objective, efficient, and reproducible assessment tools has become increasingly evident.

Neuroimaging biomarkers have demonstrated significant potential in providing objective insights into brain function and pathology. Previous studies have established significant correlations between neuroimaging features—such as cortical atrophy, white matter hyperintensities, and functional connectivity alterations—and aging [5–7]. If neuroimaging biomarkers can reliably reflect cognitive and physical function, they could serve as valuable tools for assessment. Moreover, neuroimaging is crucial in identifying pathological functional decline caused by brain diseases. Distinct neuroimaging patterns have been found to differentiate Alzheimer's disease from vascular dementia, helping clinicians determine the underlying causes of cognitive impairment and design targeted treatment strategies [8]. These findings highlight the importance of advancing neuroimaging-based assessments, which could improve diagnostic accuracy and facilitate personalized therapeutic interventions for the aging population.

Among the various neuroimaging techniques, diffusion tensor imaging (DTI) has emerged as a powerful tool for investigating white matter integrity and microstructural changes in the aging brain. DTI enables the extraction of key diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), each of which provides critical insights into white matter properties. FA reflects the directional coherence of water diffusion and is associated with white matter integrity, while MD represents the overall magnitude of diffusion and is often linked to neurodegenerative changes. AD quantifies diffusion along the principal axis of white matter tracts, whereas RD measures diffusion perpendicular to this axis, offering valuable information about axonal damage and demyelination [9]. By utilizing these DTI-derived metrics, researchers can better understand how white matter status relates to cognitive and physical function in the elderly.

In this study, we aim to investigate the associations between neuroimaging biomarkers, particularly DTI-derived metrics, and cognitive and physical functions in older adults. By extracting and analyzing key diffusion metrics, we will assess their associations with functional decline and propose methods to enhance their explanatory capability. Additionally, we will identify key neuroimaging indicators relevant to specific cognitive and physical functions, facilitating more precise evaluations and interventions. Through this research, we expect to provide valuable insights that can help researchers and clinicians better understand age-related functional decline, ultimately contributing to the advancement of diagnostic and therapeutic strategies for aging populations.

Methods

Participants and experiment design

One hundred and twenty elderly persons participated in this prospective cohort study. This study was designed to predict functional decline due to aging and establish strategies for functional improvement by longitudinally collecting multimodal data, including physical and cognitive function levels, and brain imaging, from community-dwelling older adults with physical or cognitive impairments. The inclusion criteria for this study were as follows: (1) community-dwelling older adults aged 55 to 84 years and (2) individuals with mild cognitive impairment, defined as a score of 6 or higher on the Korean Dementia Screening Questionnaire-Cognition (KDSQ-C), or those with physical impairment, defined as a score of 9 or lower on the Short Physical Performance Battery (SPPB). The exclusion criteria were as follows: (1) individuals with severe visual field defects, fractures, or brain diseases that prevent independent walking; (2) those with a history of musculoskeletal disorders, such as fractures, that could affect physical function within six months prior to recruitment; (3) individuals with severe cognitive impairment who were unable to understand the study and provide voluntary consent; (4) those with a history of major psychiatric disorders, such as schizophrenia or bipolar disorder; and (5) individuals for whom MRI was contraindicated due to the presence of a pacemaker, claustrophobia, or metallic implants in the skull.

This study's ethical approval (202306-HR-004) was obtained from the Institutional Review Board (IRB) of Kumoh National Institute of Technology, Gumi, Republic of Korea. This study was registered with the Clinical Research Information Service (CRIS, Korea, https://cris.nih.go.kr; registration number: KCT0008569). Participant

recruitment began in September 2023. All participants provided written informed consent prior to their enrollment in the study, and all procedures were conducted in compliance with the approved study protocol.

Table 1 Baseline characteristics in participants

Characteristics	Participants ($n=106$)
Demographic information	
Age (years)	72.63 (5.69)
Sex (male / female)	40 / 66
Educational level (years)	8.35 (3.73)
Screening test	
SPPB (pt)	11.53 (1.09)
KDSQ-C (pt)	6.95 (1.47)
Physical function	
10MWT_comfort (m/s)	1.25 (0.20)
10MWT_fast (m/s)	1.55 (0.28)
TUG (sec)	7.91 (2.02)
FSST (sec)	8.05 (1.76)
6MWT (meter)	412.50 (78.00)
9HPT Rt. (sec)	18.52 (2.19)
9HPT Lt. (sec)	19.93 (2.82)
Cognitive function	
Attention	
DST forward (n)	6.75 (1.60)
DST backward (n)	3.30 (1.35)
Language	
S-K-BNT (n)	11.42 (2.44)
Repetition (n)	14.17 (1.28)
Visuospatial	
RCFT copy (pt)	25.28 (6.97)
RCFT time (sec)	170.03 (83.65)
Memory	
SVLT-E IR (n)	17.28 (4.63)
SVLT-E DR (n)	5.16 (2.45)
SVLT-E recognition (pt)	20.85 (2.07)
Executive	
Go-no go (n)	38.18 (3.87)
DSC (n)	41.80 (17.68)
COWAT semantic (n)	14.75 (4.48)
COWAT phonemic (n)	6.14 (3.82)
K-TMT-E part A (sec)	31.86 (19.05)
K-TMT-E part B (sec)	95.79 (96.15)
K-CWST WR (n)	82.22 (24.81)
K-CWST CR (n)	33.06 (13.92)

Continuous values are presented as means (standard deviation)

SPPB, Short Physical Performance Battery (physical impairment defined as a score of 9 or lower); KDSQ-C, Korean Dementia Screening Questionnaire-Cognition (mild cognitive impairment defined as a score of 6 or higher); 10MWT, 10-Meter Walk Test; TUG, Timed Up and Go Test; FSST, Four-Square Step Test; 6MWT, 6-Minute Walk Test; 9HPT Lt., Nine-Hole Peg Test (Left); 9HPT Rt., Nine-Hole Peg Test (Right); DST, Digit Span Test; S-K-BNT, Seoul-Korean Boston Naming Test; RCFT, Rey Complex Figure Test; SVLT-E, Seoul Verbal Learning Test - Episodic; IR, Immediate Recall; DR, Delayed Recall; DSC, Digit Symbol Coding; COWAT, Controlled Oral Word Association Test; K-TMT-E, Korean Trail Making Test - Executive; K-CWST, Korean Color Word Stroop Test; pt, point

One hundred and six participants' physical and cognitive function data and DTI data were analyzed for this study. The participants ranged in age from 57 to 84 years (mean age: 72.63 years), and the sample included 40 males and 66 females. In accordance with the purpose of this study, 14 participants were excluded due to a diagnosis of neurological disorders such as stroke, Parkinson's disease, or unstable conditions during the MRI scanning process. Table 1 shows the baseline characteristics of participants.

Physical and cognitive function assessments

A battery of standardized tests was employed to assess physical function. The 10-Meter Walk Test (10MWT) was conducted at both comfortable and fast walking speeds to evaluate gait speed and walking ability, with shorter completion times indicating better performance [10]. The Timed Up and Go (TUG) Test measured functional mobility by recording the time taken for participants to stand up from a chair, walk 3 m, turn around, walk back, and sit down, with shorter times reflecting better mobility [11]. The Four Square Step Test (FSST) assessed dynamic balance and agility by measuring the time taken to step in four quadrants in a specific sequence, where shorter completion times indicated better balance and coordination [12]. The Six-Minute Walk Test (6MWT) evaluated aerobic endurance and functional exercise capacity by measuring the total distance walked in six minutes, with longer distances indicating better physical endurance [13]. Finally, the Nine-Hole Peg Test (9HPT) assessed fine motor coordination and dexterity of the upper extremities by recording the time taken to place and remove nine pegs from holes, with shorter completion times indicating better manual dexterity [14].

Cognitive function was assessed across various subdomains using standardized tests. For the attention function, the Digit Span Test (DST) Forward and Backward was used. The DST forward assessed attention and short-term memory by requiring participants to repeat a sequence of digits in the same order, while the DST backward evaluated attention and working memory by having participants repeat the sequence in reverse order [15]. To evaluate language function, the Seoul-Korean Boston Naming Test (S-K-BNT) was administered, which involved naming visually presented objects, with a higher number of correct responses indicating better language function [16]. Additionally, a Repetition Task was used to assess verbal fluency and language processing by asking participants to repeat a series of sentences [17]. The visuospatial function was assessed using the Rey Complex Figure Test (RCFT), where participants were required to copy and later recall a complex figure from memory [18]. For the assessment of memory function,

the Seoul Verbal Learning Test - E (SVLT-E) was used, which measured participants' ability to learn and recall a list of words after multiple trials [19]. Lastly, the executive function was assessed using several tasks, including the Go-No-Go Task to measure inhibitory control and impulsivity [20], the Digit Symbol Coding (DSC) task to evaluate processing speed and working memory capacity [15], and the Controlled Oral Word Association Test (COWAT) to assess verbal fluency by asking participants to generate as many words as possible beginning with a specific letter in one minute [21]. The Korean Trail Making Test– E (K-TMT-E) was used to evaluate cognitive flexibility and executive function, with participants connecting a series of numbers and letters alternately [22], and the Korean Color Word Stroop Test (K-CWST) was used to assess cognitive inhibition and processing speed by asking participants to name the color of words that were either congruent or incongruent with the meaning of the word [23].

Diffusion tensor imaging data acquisition and processing

DTI data were acquired using a Siemens MAGNETOM Skyra 3T MR scanner (Siemens Healthcare, Erlangen, Germany) of the K-MEDI hub. The DTI data were acquired with the following settings: $b = 1000$ s/mm^2, 64 non-colinear gradient directions, 80 axial slices, slice thickness = 2 mm (no gap), matrix size = 232×232, repetition time = 9600 ms, echo time = 82 ms, and field of view = 230×230 mm.

To extract the status of major neural pathways throughout the brain, DTI data were preprocessed using FMRIB's Diffusion Toolbox (FDT) from the FSL software package (version 6.0.7.9, FMRIB Software Library, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl). Corrections for eddy currents, head motion, and skull stripping were applied. The DTIfit algorithm, commonly used to quantify white matter integrity, was employed to fit a tensor model and reconstruct maps of FA and MD. AD and RD maps were generated by calculating the eigenvalues of the diffusion tensor. FA maps were spatially normalized by registering individual FA maps to the Montreal Neurological Institute (MNI) standard space (FMRIB58_FA standard space image) using nonlinear registration algorithms from the Tract-Based Spatial Statistics (TBSS) technique. Additionally, MD, AD, and RD maps were warped to the standard space using the registration information from the native FA map to the standard FA map.

The 50 tracts derived from the Johns Hopkins University White Matter Atlas (JHU ICBM-DTI-81) [24] were utilized to assess the status of major neural pathway. All tracts were binarized and masked onto the spatially normalized FA, MD, AD, and RD maps. The FA, MD, AD, and RD values were calculated by averaging within the regions corresponding to the 50 tracts.

Statistical analysis

In this study, linear regression was employed to examine the strength of association between neuroimaging metrics (FA, MD, AD, and RD) and physical and cognitive functions, with the coefficient of determination (R^2) used to quantify effect size. Additionally, to incorporate all four neuroimaging metrics, principal component analysis (PCA) was applied, and linear regression assessed the association of each function with the principal components. "PCA1" represents the model using only the first principal component, whereas "PCA2" includes both the first and second principal components. To account for multiple comparisons, the false discovery rate (FDR) correction was applied with a threshold of $q < 0.05$. Finally, multiple linear regression was then conducted to develop predictive models, incorporating age, sex, and educational level as covariates alongside neuroimaging metrics. Neuroimaging metrics were used to select between one and five tracts in order of their strength of association for each function, with the models designated as "Model 1" through "Model 5" based on the number of tracts included. In this selection process based on the strength of association, the "without covariance" condition measured the coefficient of determination using only neuroimaging metrics as variables, while the "with covariance" condition included age, sex, and educational level as covariates when measuring the coefficient of determination of the neuroimaging metrics. To validate the models, 10-fold cross-validation was performed.

Results

The strength of association between the four DTI metrics and physical and cognitive functions was examined (Fig. 1). Overall, neuroimaging metrics showed significant associations with both domains, with functions strongly associated in one domain tending to show stronger associations in the other. Across all metrics, associations with cognitive functions were generally slightly stronger than those with physical functions. Within physical functions, lower-limb measures showed higher effect sizes than upper-limb measures, while executive function exhibited the strongest associations among cognitive subdomains.

More specifically, the four neuroimaging metrics exhibited distinct patterns of association strength across the white matter tracts. In the case of FA, anterior tracts generally showed stronger associations than other tracts. The genu of the corpus callosum (CC) showed the strongest association with both physical and cognitive functions, followed by the anterior limb of the internal capsule (ALIC), fornix, and the splenium and body of the CC. For MD, compared to the FA pattern, the role of the cerebellar peduncle (CbP) was reduced, while the contributions of the retrolenticular part of the internal capsule

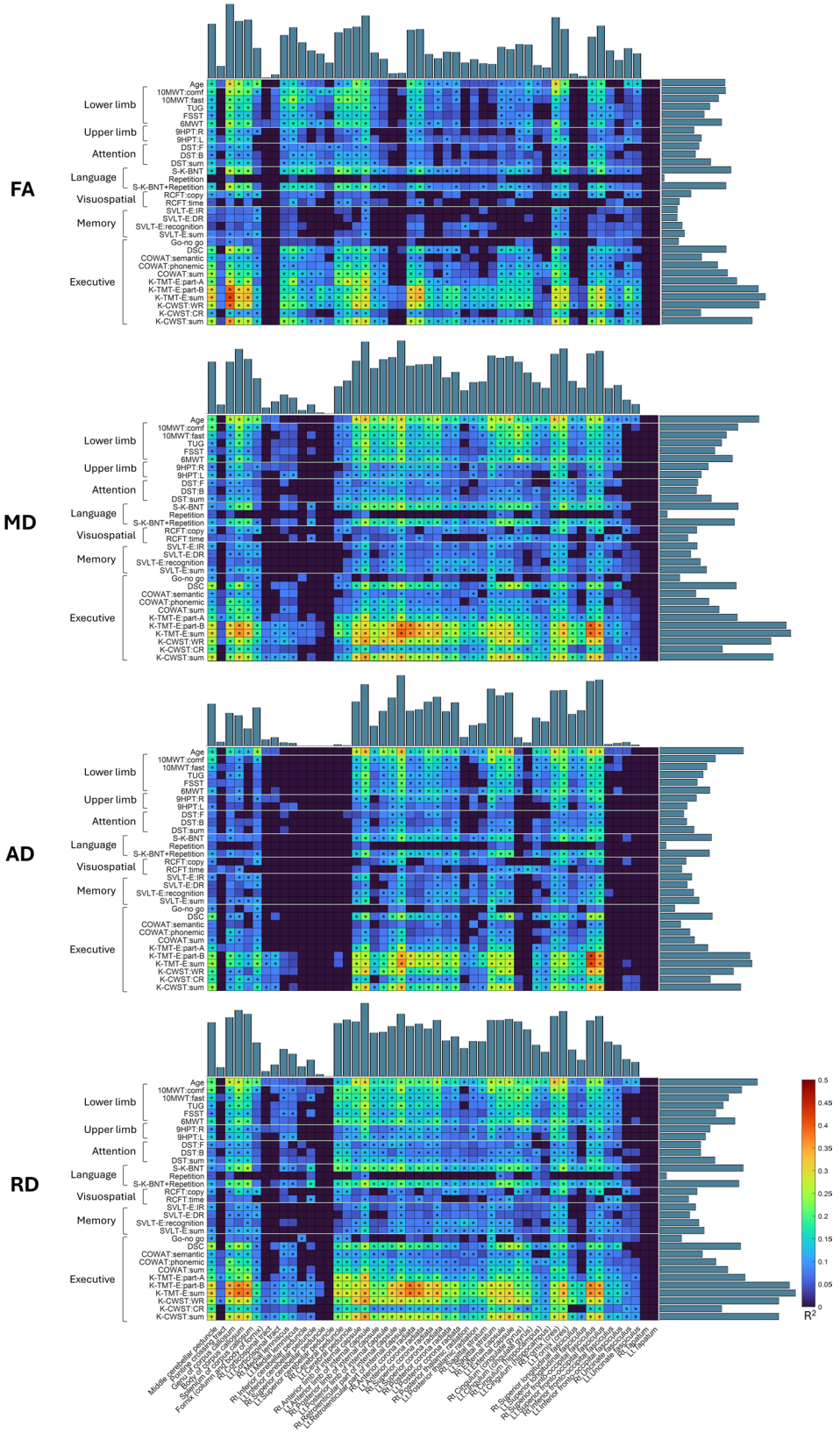

Fig. 1 (See legend on next page.)

(See figure on previous page.)

Fig. 1 The strength of association of four DTI metrics for physical and cognitive functions. Statistically significant results are highlighted in color, and the colorbar represents the coefficient of determination (R^2). The vertical and horizontal bar graphs are drawn to relatively compare the sum of the coefficients of determination for the corresponding columns and rows. An asterisk indicates statistical significance after FDR correction. **FA**, fractional anisotropy; **MD**, mean diffusivity; **AD**, axial diffusivity; **RD**, radial diffusivity; 10MWT, 10-meter walk test; TUG, timed up and go; FSST, four square step test; 6MWT, 6-minute walk test; 9HPT, 9-hole peg test; DST, digit span test; S-K-BNT, Seoul-Korean Boston naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; DSC, digit symbol coding; COWAT, controlled oral word association test; K-TMT-E, Korean trail making test– E; K-CWST, Korean color word Stroop test

(RLIC) and the superior longitudinal fasciculus (SLF) increased. RLIC showed the strongest association with physical and cognitive functions, followed by ALIC, fornix, the body of the CC, and the superior fronto-occipital fasciculus (SFO). For AD, relative to the FA pattern, the contributions of the medial lemniscus (ML), CbP, cerebral peduncle (CP), inferior fronto-occipital fasciculus (IFO), and uncinate fasciculus (UF) were reduced. Similar to MD, RLIC showed the strongest association with both physical and cognitive functions, followed by SFO, ALIC, sagittal stratum (SS), and fornix. For RD, the overall pattern was similar to that of MD, with ALIC showing the strongest association for both physical and cognitive functions. This was followed by the body of the CC, fornix, the splenium of the CC, and RLIC.

Additionally, PCA was applied to incorporate the characteristics of all four neuroimaging metrics, and linear regression was used to assess the strength of association for each function (Fig. 2). The first principal component (PCA1) accounted for 81.0% of the variance. In this case, the strength of association was generally higher than when using the four individual DTI metrics separately. PCA1 captured a pattern that integrated the varying association strengths of the individual metrics. For PCA2, which incorporated both the first and second principal components, the variance accounted for increased to 99.6%. This approach effectively captured the distinct association strength distributions of the four DTI metrics in a more comprehensive manner. PCA2 integrated the strengths of different metrics while compensating for areas where certain metrics had low or no association strength, resulting in an overall higher strength of association compared to using individual metrics. The genu of the CC was the neural pathway most strongly associated with both physical and cognitive functions, followed by the ALIC, RLIC, fornix, the splenium and body of the CC, and the SFO.

To develop models that effectively explain functional outcomes using neuroimaging metrics, neural pathways with high association strength were selected in order, ranging from one to five tracts, and their effect size and cross-validation performance were assessed (Fig. 3). The overall strength of association of the models tended to increase with the number of neural pathways included. Additionally, PCA2 showed greater effect size than PCA1, and selecting tracts while controlling for covariates (age, sex, and educational level) resulted in higher association strength compared to models without covariate control (Fig. 3A). Since this trend may be influenced by the increased number of variables, cross-validation was conducted for confirmation (Fig. 3B and C). The results indicated that controlling for covariates improved the strength of association, with the optimal model consisting of two selected neural pathways for PCA1 and one selected tract for PCA2.

Neural pathways with high association strength for each function were examined (Fig. 4). Regardless of covariate control, the fornix, ALIC, CC, and SFO exhibited strong associations with functional outcomes. When association strength was assessed using only neuroimaging metrics without controlling for covariates, the top two tracts for lower-limb function were the fornix and ALIC, while the same tracts also showed the strongest associations for upper-limb function. Among cognitive functions, the top two tracts were as follows: attention—SFO and RLIC; language—ALIC and external capsule (EC); visuospatial function—IFO and fornix; memory—fornix and ALIC; and executive function—CC and ALIC. When association strength was analyzed while controlling for covariates, different patterns emerged. For physical function, the lower-limb function was best explained by the fornix and cingulum, while the upper-limb function was best explained by the ML and fornix. Among cognitive functions, the top two tracts were attention—SFO and fornix; language—inferior cerebellar peduncle (ICP) and fornix; visuospatial function—IFO and fornix; memory—IFO and posterior thalamic radiation (PTR); and executive function—SFO and middle cerebellar peduncle (MCP).

Discussion

The present study examined the strength of association of DTI-derived metrics in relation to cognitive and physical functions in the elderly. Our findings demonstrated that neuroimaging biomarkers were significantly associated with both cognitive and physical functions in this population. Among the individual DTI metrics, FA, MD, AD, and RD showed distinct patterns in their association strength. The PCA-based approaches proposed in this study further enhanced the overall strength of association for both cognitive and physical functions by integrating complementary information from multiple DTI-derived metrics.

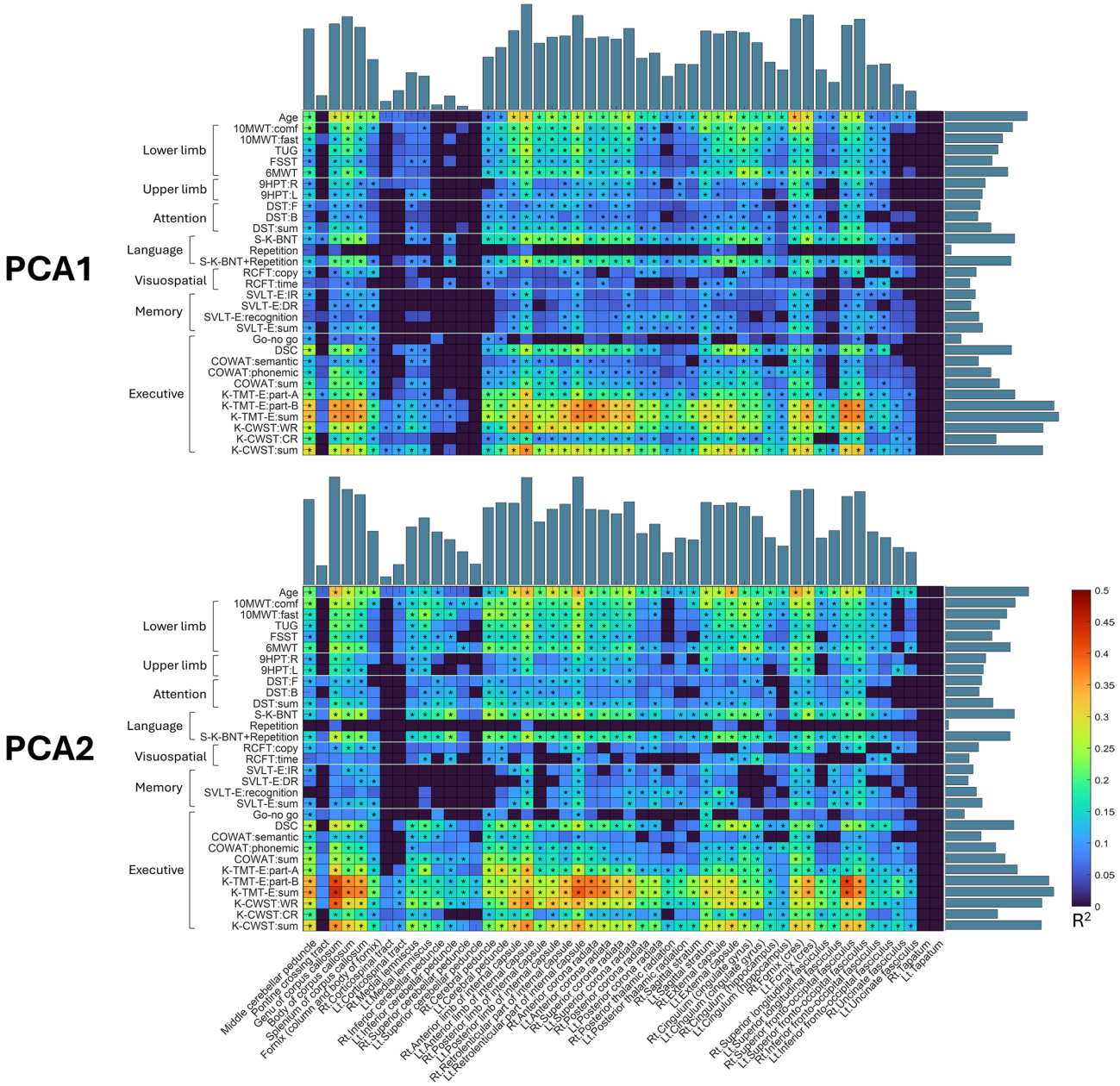

Fig. 2 The strength of association of four DTI metrics using PCA. **PCA1** represents the model using only the first principal component, whereas **PCA2** includes both the first and second principal components. Statistically significant results are highlighted in color, and the colorbar represents the coefficient of determination (R^2). The vertical and horizontal bar graphs are drawn to relatively compare the sum of the coefficients of determination for the corresponding columns and rows. An asterisk indicates statistical significance after FDR correction. 10MWT, 10-meter walk test; TUG, timed up and go; FSST, four square step test; 6MWT, 6-minute walk test; 9HPT, 9-hole peg test; DST, digit span test; S-K-BNT, Seoul-Korean Boston naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; DSC, digit symbol coding; COWAT, controlled oral word association test; K-TMT-E, Korean trail making test– E; K-CWST, Korean color word Stroop test

While previous research has demonstrated significant associations between a specific DTI metric and cognitive or physical functions, our study provides a more comprehensive analysis by systematically examining all four primary DTI metrics and their relationships with both cognitive and physical domains. This study extends previous work by systematically comparing multiple DTI metrics and employing PCA to enhance the overall strength of association, offering a broader understanding of white matter contributions to aging-related functional decline.

Previous studies have reported associations between FA reductions in motor-related tracts, such as the corticospinal tract, and declines in motor performance or

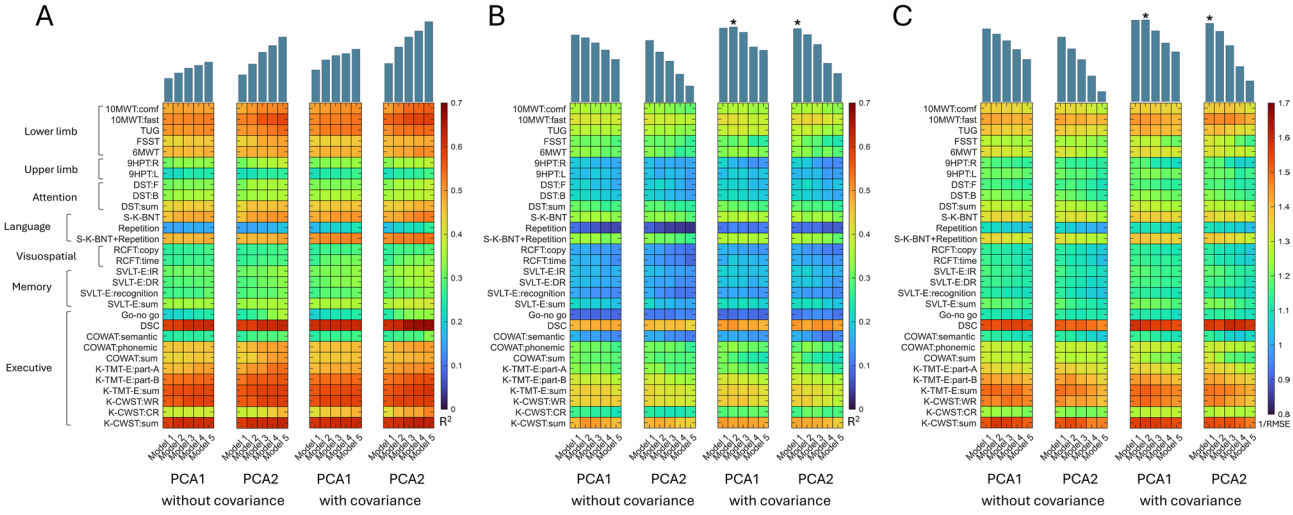

Fig. 3 (**A**) The strength of association (R^2) of the PCA-based model. (**B**) The cross-validation results (R^2). (**C**) The cross-validation results (1/RMSE). Model 1–5 represent regression models constructed by selecting one to five tracts in order of highest strength of association for each function. The process of selecting tracts in order of highest strength of association was examined both with and without the application of covariates. The vertical bar graphs provide a relative comparison of the summed cross-validation results for each column. An asterisk indicates the tallest vertical bar. RMSE, root mean square deviation; 10MWT, 10-meter walk test; TUG, timed up and go; FSST, four square step test; 6MWT, 6-minute walk test; 9HPT, 9-hole peg test; DST, digit span test; S-K-BNT, Seoul-Korean Boston naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; DSC, digit symbol coding; COWAT, controlled oral word association test; K-TMT-E, Korean trail making test– E; K-CWST, Korean color word Stroop test

gait stability in older adults [25, 26]. Other studies have reported that frontal white matter tracts, including the SLF and cingulum, are critical for executive function and attention [27, 28]. In our study, DTI metrics were associated with cognitive and physical functions. The trend among the four DTI metrics was that they tended to explain cognitive function slightly better than physical function. This is likely because cognitive assessments typically capture integrated neural network functions, whereas physical function measures often reflect composite outcomes influenced by both neural and peripheral physiological factors.

Within the physical function, the strength of association for the lower-limb function was higher than for the upper-limb function, whereas within the cognitive function, the executive function showed the strongest association among the cognitive subdomains. Lower-limb function depends on coordinated activity across widespread brain regions involved in balance, proprioception, and gait control—processes heavily reliant on white matter integrity in sensorimotor and cerebellar-thalamic pathways [29]. In contrast, upper-limb tasks may involve more localized cortical representations that are less dependent on long-range white matter connectivity. Executive function is primarily governed by the dorsolateral prefrontal cortex and anterior cingulate cortex, which are key hubs in large-scale neural networks responsible for cognitive control, decision-making, and working memory. These regions rely heavily on white matter tracts to facilitate efficient communication with other cortical and subcortical structures [30].

The integration of DTI metrics through PCA provided a more comprehensive representation of white matter integrity. PCA integrated the strengths of different metrics while compensating for areas where certain metrics had low or no association strength, resulting in an overall stronger association compared to using individual metrics. This approach not only improved the strength of association but also revealed that specific tracts, such as the CC, ALIC, fornix, RLIC, and SFO, play pivotal roles in both cognitive and physical domains. The CC facilitates interhemispheric integration crucial for executive functions and coordinated movement, and the ALIC supports error-monitoring and decision-making processes through its role in the fronto-cingulo-parietal cognitive control network [31]. The fornix, a key component of the limbic system, is essential for memory consolidation and emotional processing, with its integrity closely linked to cognitive function in conditions like Alzheimer's disease [32]. The RLIC plays a crucial role in visual and auditory processing, containing fibers of the optic radiation and auditory pathways, and its damage can result in specific sensory deficits [33]. The SFO is thought to facilitate visuospatial attention and cognitive flexibility by connecting frontal and parietal regions [34]. These tracts are primarily associated with cognitive and sensory functions, but they have also been found to relate to physical functions.

The findings of this study have important implications for both research and clinical applications. First, the identification of specific neural pathways associated with cognitive and physical functions, including various

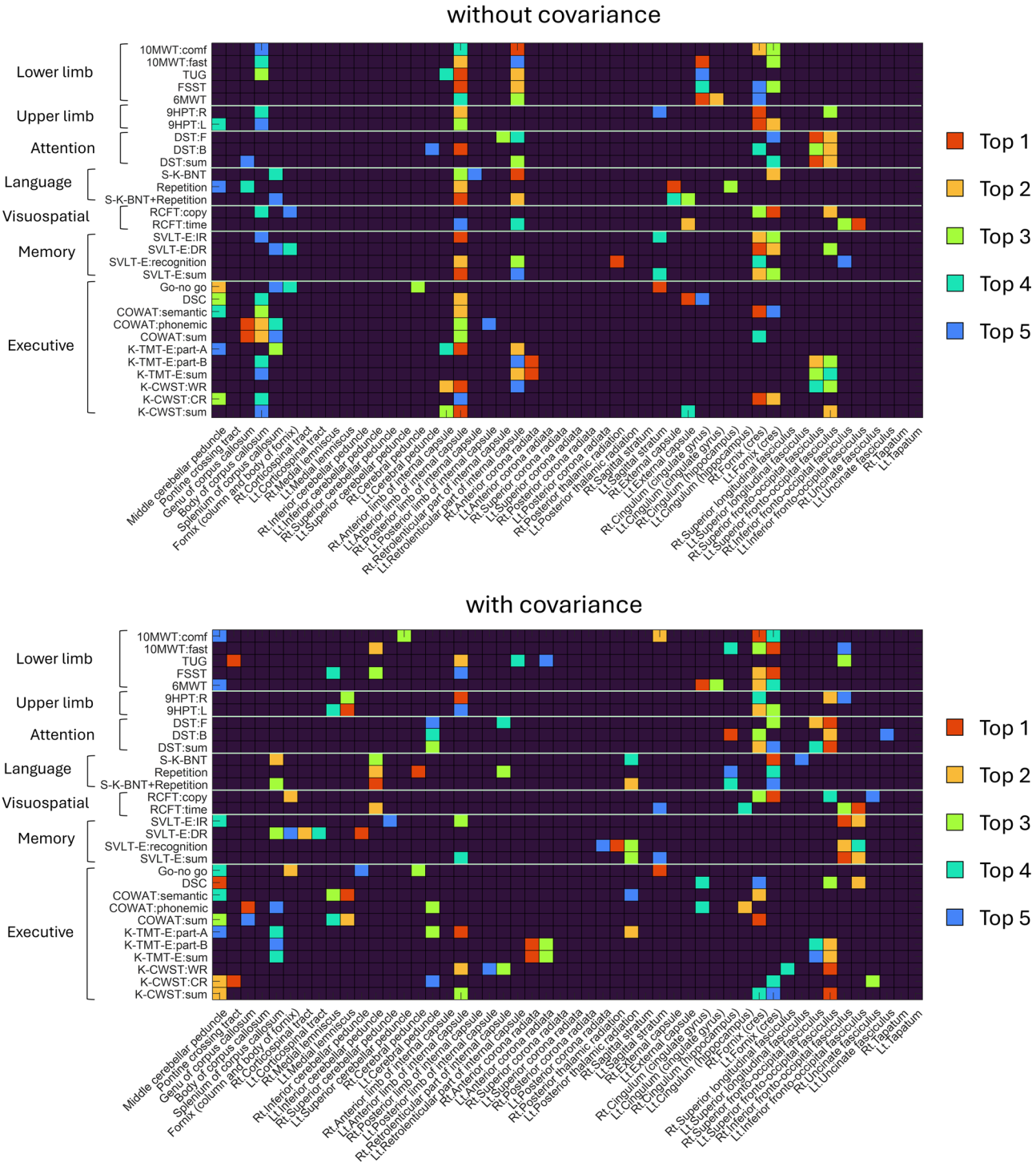

Fig. 4 Top five tracts with the highest strength of association for each function. 10MWT, 10-meter walk test; TUG, timed up and go; FSST, four square step test; 6MWT, 6-minute walk test; 9HPT, 9-hole peg test; DST, digit span test; S-K-BNT, Seoul-Korean Boston naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; DSC, digit symbol coding; COWAT, controlled oral word association test; K-TMT-E, Korean trail making test– E; K-CWST, Korean color word Stroop test

cognitive and physical subdomains, suggests that targeted interventions could be developed to preserve or enhance functional abilities in aging individuals. Second, our results highlight the potential of neuroimaging biomarkers as objective tools for tracking functional decline, which could improve early diagnosis and monitoring of age-related disorders. Additionally, the integration of PCA-based approaches demonstrates the

advantage of combining multiple neuroimaging metrics to improve the overall strength of association, which could lead to the development of more precise predictive models in future studies.

Despite its strengths, this study has several limitations. First, its cross-sectional design precludes causal inferences about the relationship between DTI metrics and functional outcomes. Longitudinal studies are needed to confirm these associations and explore their predictive value over time. Second, this study did not account for potential confounding factors such as comorbidities or lifestyle variables, which could influence both white matter integrity and functional outcomes. Although covariate control was applied for age, sex, and education level, further research should include a broader range of covariates to enhance generalizability.

In conclusion, this study provides compelling evidence that neuroimaging biomarkers, particularly DTI-derived metrics, are valuable tools for explaining variations in cognitive and physical functions in the elderly. The identification of key neural pathways associated with different functional domains underscores the potential of neuroimaging-based assessments for evaluating age-related decline. The integration of multiple neuroimaging metrics through PCA further enhances the overall strength of association, offering a promising avenue for future research and clinical applications. These findings highlight the potential of neuroimaging as an efficient and objective method for monitoring functional changes in aging populations, paving the way for more precise and personalized interventions.

Acknowledgements
We would like to thank the participants in the study. We acknowledge and thank the funding support from the National Research Foundation of Korea (NRF).

Author contributions
J.L. contributed to the design and conceptualization of the study, data acquisition and analysis, data interpretation, drafting the manuscript, and critical revision of the manuscript and final approval. H.K. and W.H. contributed to the data acquisition and interpretation, and critical revision of the manuscript. All authors have read and approved the final manuscript.

Funding
This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT, MSIT) (No. RS-2023-00208884) and the K-Brain Project of the NRF funded by the Korean government (Ministry of Science and ICT, MSIT) (No. RS-2023-00265824).

Data availability
The data are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
All participants recruited through Kumoh National Institute of Technology provided informed consent before participating in the study. Written informed consent was obtained from all participants before the experiments, in accordance with the Declaration of Helsinki, and this study protocol was approved by the ethics committee of the Kumoh National Institute of Technology Institutional Review Board (202306-HR-004).

Competing interests
The authors declare no competing interests.

Received: 7 April 2025 / Accepted: 4 July 2025
Published online: 10 July 2025

References

1. Jakovljevic M, Westerman R, Sharma T, Lamnisos D. Aging and global health. Handbook of global health. 2021:73–102.
2. Frisoni GB, Boccardi M, Barkhof F, Blennow K, Cappa S, Chiotis K, et al. Strategic roadmap for an early diagnosis of alzheimer's disease based on biomarkers. Lancet Neurol. 2017;16(8):661–76.
3. Markus HS, de Leeuw FE. Cerebral small vessel disease: recent advances and future directions. Int J Stroke. 2023;18(1):4–14.
4. Stolz E, Mayerl H, Freidl W. Fluctuations in frailty among older adults. Age Ageing. 2019;48(4):547–52.
5. Sala-Llonch R, Bartrés-Faz D, Junqué C. Reorganization of brain networks in aging: a review of functional connectivity studies. Front Psychol. 2015;6:663.
6. Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, et al. Brain atrophy in alzheimer's disease and aging. Ageing Res Rev. 2016;30:25–48.
7. Zhuang F-J, Chen Y, He W-B, Cai Z-Y. Prevalence of white matter hyperintensities increases with age. Neural Regeneration Res. 2018;13(12):2141–6.
8. Dubois B, von Arnim CA, Burnie N, Bozeat S, Cummings J. Biomarkers in alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. Alzheimers Res Ther. 2023;15(1):175.
9. Beaulieu C. The basis of anisotropic water diffusion in the nervous system–a technical review. NMR Biomedicine: Int J Devoted Dev Application Magn Reson Vivo. 2002;15(7–8):435–55.
10. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing. 1997;26(1):15–9.
11. Podsiadlo D, Richardson S. The timed up & go: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.
12. Dite W, Temple VA. A clinical test of stepping and change of direction to identify multiple falling older adults. Arch Phys Med Rehabil. 2002;83(11):1566–71.
13. Enright PL. The six-minute walk test. Respir Care. 2003;48(8):783–5.
14. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole Peg test of finger dexterity. Occup Therapy J Res. 1985;5(1):24–38.
15. Wechsler D. The measurement and appraisal of adult intelligence. Acad Med. 1958;33(9):706.
16. Kang Y, Kim H-H, Na DL. A short form of the Korean-Boston naming test (K-BNT) for using in dementia patients. Korean J Clin Psychol. 1999;18(2):125–38.
17. Luria AR. The working brain: An introduction to neuropsychology. 1976.
18. Rey A, Osterrieth PA. Rey-Osterrieth complex figure copying test. Psychological assessment. 1941.
19. Kang Y, Jahng S, Na D. Seoul neuropsychological screening battery-core (SNSB-C). Seoul: Human Brain Research & Consulting Co; 2015.
20. Donders FC. On the speed of mental processes. Acta Psychol. 1969;30:412–31.
21. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999;14(2):167–77.
22. Lee H-S, Chin JL, Hwa B, Kang Y, Na DL. Development & validation of Korean version of trail making test for elderly persons. Dement Neurocognitive Disorders. 2007;6(2):54–66.
23. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18(6):643.
24. Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. NeuroImage. 2008;40(2):570–82.
25. Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. Neurobiol Aging. 2010;31(3):464–81.

26. Gow AJ, Bastin ME, Muñoz Maniega S, Valdés Hernández MC, Morris Z, Murray C, et al. Neuroprotective lifestyles and the aging brain: activity, atrophy, and white matter integrity. Neurology. 2012;79(17):1802–8.
27. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. Front NeuroSci. 2013;7:32.
28. Mayo CD, Garcia-Barrera MA, Mazerolle EL, Ritchie LJ, Fisk JD, Gawryluk JR, et al. Relationship between DTI metrics and cognitive function in alzheimer's disease. Front Aging Neurosci. 2019;10:436.
29. Fling BW, Dutta GG, Schlueter H, Cameron MH, Horak FB. Associations between proprioceptive neural pathway structural connectivity and balance in people with multiple sclerosis. Front Hum Neurosci. 2014;8:814.
30. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology. 2022;47(1):72–89.
31. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci. 2012;12:241–68.
32. Senova S, Fomenko A, Gondard E, Lozano AM. Anatomy and function of the fornix in the context of its potential as a therapeutic target. J Neurol Neurosurg Psychiatry. 2020;91(5):547–59.
33. Nieuwenhuys R, Voogd J, Van Huijzen C. The human central nervous system: a synopsis and atlas. Springer Science & Business Media; 2007.
34. Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, De Crespigny AJ, et al. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain. 2007;130(3):630–53.

Publisher's note