International Journal of Aging

Int J Agin 2025;3:e9125
doi:10.34172/ija.9125
http://ijage.com

Original Article

Association of Aging and Structure Connectome With Cognitive Performance: A Systematic Review

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Article History:
Received: August 1, 2025
Revised: September 17, 2025
Accepted: October 1, 2025
ePublished: December 17, 2025

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Abstract

Objectives: To systematically review evidence on the association between aging-related alterations in the structural connectome, particularly white matter microstructure, and cognitive performance.

Design: Systematic review.

Participants: Older adults without clinically diagnosed neurological disorders from 24 eligible studies.

Outcome Measures: Diffusion tensor imaging (DTI)-derived indices of white matter microstructure, including fractional anisotropy and mean diffusivity, and cognitive outcomes encompassing working memory, attention, processing speed, and executive function.

Results: The majority of included studies demonstrated that advancing age was associated with reduced white matter integrity. These alterations were consistently linked to poorer performance across multiple cognitive domains, particularly processing speed, executive function, and working memory. Multimodal studies integrating DTI with functional MRI further suggested that aging weakens structural–functional coupling and reduces network efficiency, which may contribute to less effective cognitive and spatial processing. However, substantial heterogeneity in sample characteristics, imaging protocols, and analytic approaches limited direct comparison across studies.

Conclusions: The current evidence supports a robust association between age-related white matter microstructural changes and cognitive decline. These alterations may represent early markers of cognitive vulnerability and could help identify individuals at increased risk for future cognitive impairment or dementia. Larger longitudinal studies with standardized acquisition and analytic methods are needed to clarify the predictive value of these markers and strengthen causal inference.

Keywords: Aging, Cognition, Diffusion tensor imaging, White matter, Brain connectome

Please cite this article as follows: Zahmatyar M, Heidari P, Motamedi A, Abbasi F, Ilkhani S, Rahnemayan S, et al. Association of aging and structure connectome with cognitive performance: a systematic review. Int J Aging 2025;3:e9125. doi:10.34172/ija.9125

Introduction

The proportion of older adults is rapidly increasing globally.[1] Cognitive changes associated with aging are influenced by various factors, including genetic background, lifestyle, and environmental exposures.[2] Even in the lack of overt neurological or neurodegenerative diseases, advancing age is commonly accompanied by declines in several cognitive domains, including working memory, learning and memory, attention, executive functioning, and processing speed.[3-5] Cognitive abilities that tend to diminish with age are often described as fluid cognition, whereas those that remain stable or improve are referred to as crystallized cognition.[6] Moreover, cognitive impairments in later life have been linked to increased hospitalization, higher readmission rates, mortality, reduced mobility, and eventual loss of independence.[7,8]
Population aging has placed increasing pressure on healthcare systems, thereby rising costs and capacity limitations.[9] According to neuroimaging research, aging is associated with structural brain alterations that increase vulnerability to disease and cognitive decline. Although brain aging is a universal phenomenon, the degree to

which cognitive abilities are preserved varies markedly across individuals. Measures such as gait speed, pulmonary function, grip strength, and cognitive performance have all been related to brain aging trajectories.[10,11] It is noteworthy that the cerebellum plays a compensatory role in aging-related neural changes and may serve as a functional reserve. Therefore, improved understanding of cerebellar and other brain structures is essential for advancing knowledge of cognitive aging and age-related diseases.[12]

Research on cognitive aging using diffusion tensor imaging (DTI) has largely focused on elucidating relationships between age, white matter integrity, most commonly assessed using fractional anisotropy (FA) and mean diffusivity (MD), and cognitive performance. Evidence indicates that specific white matter pathways, including the cingulum bundle and uncinate fasciculus, exhibit distinct age-related alterations and may be further influenced by genetic factors (e.g., catechol-O-methyl transferase polymorphisms). Additionally, aging has generally been associated with reductions in FA, along with increases in MD and radial diffusivity within these tracts.[13] Advances in imaging approaches, including measures of cerebral parenchymal cerebrospinal fluid fraction and DTI-ALPS, have enabled the assessment of perivascular space pathology and cerebrospinal fluid dynamics in relation to brain aging [14], potentially facilitating early detection of Alzheimer's disease and amnestic mild cognitive impairments.[15] Moreover, combined DTI and functional magnetic resonance imaging (MRI) studies have shown that aging influences the efficiency of allocentric and egocentric spatial coding mediated by the fronto-parietal and dorsal attention networks.[16] In addition, DTI has been applied to distinguish individuals with subjective cognitive decline who subsequently progress to mild cognitive impairments from those who remain stable, with a particular emphasis on hippocampal–cingulum pathways.[17]

Accordingly, the present systematic review aims to synthesize existing evidence on age-related microstructural brain changes (i.e., alterations in white matter integrity, cortical organization, and neural connectivity) and their associations with cognitive performance. By integrating findings of different studies, this review seeks to provide consolidated evidence, identify potential imaging biomarkers, and highlight methodological considerations relevant to future research on and intervention development in cognitive aging.

Methods

Literature Search

We conducted a comprehensive literature search in PubMed, Scopus, and Web of Science from database inception to January 5, 2024, to identify studies examining associations between aging, structural brain connectome measures, and cognitive performance. We also manually screened the first ten pages of Google Scholar to capture grey literature. No restrictions were applied with respect to publication date, study design, or language. In addition, we performed backward and forward citation tracking for all included studies to identify further eligible articles. The initial search was carried out by the first author (M.Z.) and independently verified by two co-authors (A.M. and S.I.). Search terms combined concepts related to aging and diffusion imaging, including (Aging OR Senescence) AND (Diffusion Tensor Magnetic Resonance Imaging OR Diffusion Tensor MRI). The detailed search strategies for each database are provided in Supplementary File, Supplementary file, Table S1. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (Figure 1).

Study Selection

All records were imported into EndNote (Clarivate Analytics, version 2025), and duplicates were removed. Two reviewers (S.H. and S.I.) independently screened titles and abstracts to identify potentially relevant studies. The same reviewers then assessed the full texts of selected articles against predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion or, when needed, by consulting additional reviewers.

We excluded studies that: (1) reported DTI measures without any cognitive assessment; (2) assessed cognition but did not include neuroimaging data; or (3) used DTI exclusively to study processes unrelated to aging. After removal of duplicates, 1,482 records remained. Following title and abstract screening, 1,441 records were excluded. Forty-one full-text articles were assessed for eligibility, of which 17 were excluded, resulting in 24 studies included in the final synthesis.

Data Extraction

Data were extracted using standardized, predesigned forms created in Google Sheets. Two reviewers (A.M. and S.I.) independently extracted information from each included study. Extracted variables comprised: (1) general study characteristics (title, first author, country, and year of publication); (2) participant characteristics (study population, sample size, age, sex, cognitive measures, imaging modality, and DTI parameters); and (3) cognitive outcomes, including the extent and severity of performance changes. Discrepancies were resolved through consensus-based discussion and, when necessary, by consulting a third reviewer (M.Z.).

Quality Assessment

Two reviewers (S.H. and M.Z.) independently assessed methodological quality using the Joanna Briggs Institute Critical Appraisal Checklist, which evaluates study design, risk of bias, validity, and overall rigor. Overall risk of bias was determined for each study, and any disagreements were resolved by consensus or consultation with a third reviewer (A.M.). Cross-sectional studies are summarized in Supplementary file, Table S2, and cohort studies are presented in Supplementary file, Table S3.

Results

Study Selection

The systematic search identified 1,636 records. After the removal of 154 duplicates, 1,482 titles and abstracts were screened. Forty-one studies underwent full-text evaluation (Figure 1). Of this number, 17 articles were excluded due to insufficiently detailed data or review design, leaving 24 studies for inclusion in the final analysis.[19-42]

Quality Assessment

The risk of bias related to randomization, deviations from intended interventions, and missing data was generally low among the included studies. In contrast, bias associated with outcome measurement and selective reporting was rated as high or of some concern in several studies. However, methodological quality was generally deemed adequate to support inclusion in the review.

Study Characteristics

All included studies investigated older adult populations, although a subset also included younger comparison groups.[21,25-27,29,31,36,40,42] In addition, most studies (16 of 24) employed cross-sectional designs.[24,25,30,33,35,37,43] Further, the United States contributed the largest number of studies in this field (8 articles).[21-24,26,31,34,35]

Furthermore, sample sizes varied substantially, ranging from 25 participants[37] to 731 participants,[30] with a mean sample size of approximately 149 individuals across studies.

Main Results

The proportion of older adults has globally increased steadily since 1990 due to declining mortality rates, reaching 617 million individuals aged 65 years and older (8.5%) in 2016, with projections indicating growth

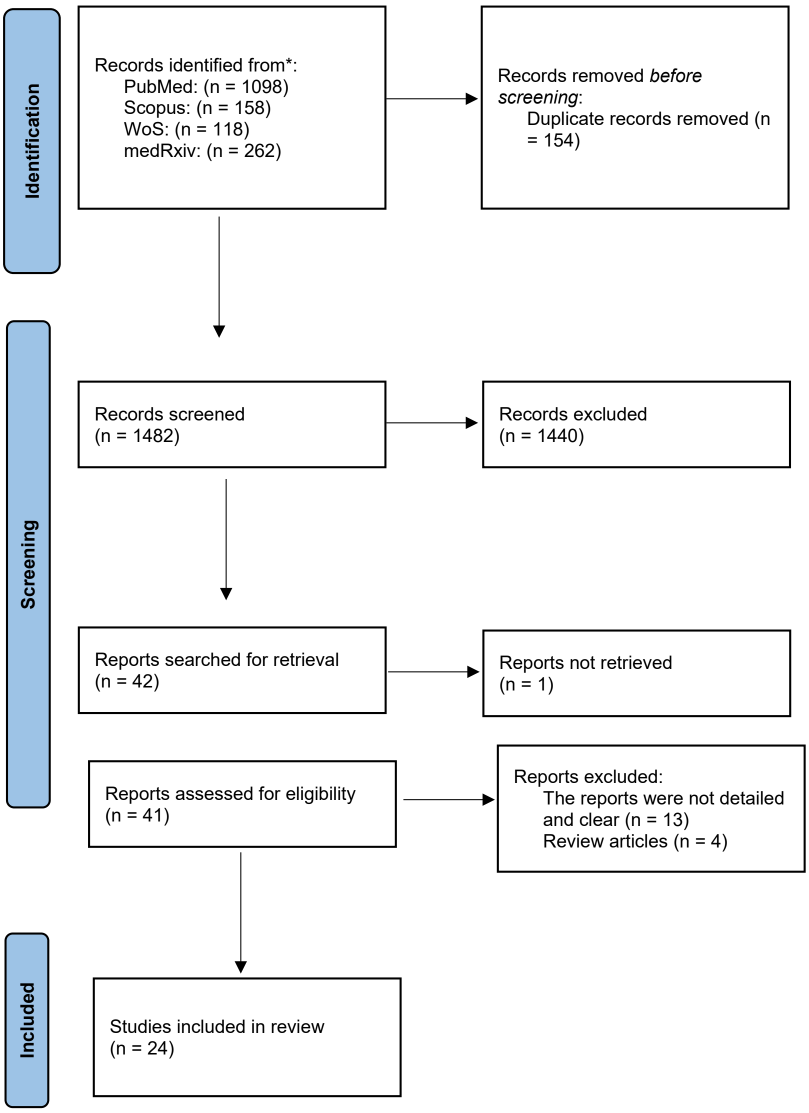

Figure 1. PRISMA 2020 Flow Diagram (Study Selection Process)
Note. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

to approximately 1.6 billion (17%) by 2050 [44]. Nearly all included studies reported significant associations between aging and white matter integrity as indexed by FA and MD, implying that advancing age is accompanied by microstructural white matter alterations. [20-29,36,37,39-42] These changes were consistently linked to functional impairments in cognitive and executive domains, including reduced processing efficiency, working memory, and information processing speed.[20-23,26-31,36-42] Consequently, older adults exhibiting greater white matter degeneration were more likely to demonstrate cognitive disorders (e.g., Alzheimer's and Parkinson's disease) compared with cognitively healthy peers.[23,29,33,37,40] Collectively, the evidence indicates a direct association between white matter integrity and cognitive and executive functioning, with progressive degeneration accompanying advancing age and contributing to worsening cognitive outcomes.[20-29,36,37,39-42] Deficits in working memory, in particular, emerged as robust predictors of subsequent cognitive decline.[20-23,26-31,33,36-42]

However, some studies reported more nuanced findings. For example, independent factor models revealed voxel-wise correspondence exceeding 60%, whereas cognitive mediation models accounted for approximately 16% of variance,[19] indicating that associations between white matter integrity and cognition are not uniform across the brain. Cognitive performance mediated the relationship between age and white matter measures in a limited number of cases,[36] while other studies reported no significant association between white matter integrity and cognitive outcomes.[32] Figure 1 displays the study selection process. Baseline study characteristics are presented in Supplementary file, Table S4. Baseline characteristics of the included studies are presented in Supplementary file, Table S4, while detailed diffusion tensor imaging (DTI) characteristics of the included studies are provided in Supplementary file, Table S5.

Discussion

This systematic review provided an integrated overview of the relationship between DTI metrics and cognitive performance in the context of brain aging. The findings emphasize the complexity of these associations and underscore several key observations warranting further consideration.

Numerous investigations have examined structural brain alterations in neurodegenerative disorders (e.g., Alzheimer's, Parkinson's, and Huntington's disease) using different approaches, including DTI, tensor-based morphometry, and voxel-based morphometry.[45-49] Compared with morphometric techniques, DTI offers greater specificity for assessing white matter organization and integrity through metrics such as FA, MD, axial diffusivity, and radial diffusivity.[50,51] In Parkinson's disease, increased MD and reduced FA, particularly within the corpus callosum, have been linked to deficits in executive function, memory, attention, and global cognition.[58] In Alzheimer's disease, reductions in white matter integrity have been observed in tracts critical for memory processing, which aligns with reports of concurrent gray and white matter alterations.[52,53]Although white matter hyperintensities have been associated with neurological and neuropsychological symptoms, their relationship with global cognitive impairment has been inconsistent.[54] Disruption of large-scale brain connectivity contributes to cognitive deterioration in Alzheimer's disease,[53] with executive performance correlating with DTI-derived white matter measures.[55] Associations between white matter integrity and physical measures, such as grip strength, have also been reported.[56] In Huntington's disease, early microstructural changes detected by DTI have shown strong associations with both cognitive and motor declines.[57-59]

Aging-related factors may modulate the extent of white matter degeneration. Prior work has confirmed significant associations between DTI measures and executive function, memory, and overall cognitive status, highlighting relationships between advancing age, cognitive deficits, and white matter deterioration.[60] Age-related group differences in FA and MD have been consistently observed.[61] Additionally, genetic influences, particularly involving dopamine-related genes, have been involved in shaping white matter integrity and working memory performance.[62,63]

In addition, the integration of DTI with functional MRI has clarified how aging affects functional connectivity within cognitive networks. Older adults typically display reduced functional connectivity density and white matter integrity across most networks, with the notable exception of preserved connectivity within the default mode network.[64] Moreover, higher white matter integrity within the corpus callosum has been associated with superior memory performance.[65]

Overall, the present findings are consistent with prior literature, indicating that age-related white matter degeneration substantially contributes to cognitive decline observed in later life. Based on the findings of different studies, diffusion MRI markers, most consistently reduced FA, increased MD, and elevated free water, have shown robust associations with declines in processing speed, executive control, episodic memory, and fluid intelligence.[19,23,25,27,33,37,38] Vulnerable pathways frequently include fronto-parietal and fronto-striatal tracts, the cingulum, corpus callosum, and medial temporal structures (e.g., the fornix and perforant path).[21,24,26,29,34,35,42] Network-level analyses further demonstrate reduced structural efficiency and disrupted cortico-striatal connectivity, with multimodal studies revealing parallel reductions in functional coupling that track behavioral performance.[28,35,41]

Importantly, studies of cognitively normal older adults, including those with subjective complaints, indicate that even subtle microstructural alterations can have measurable cognitive consequences.[24,27,31,41] Longitudinal evidence strengthens these observations, showing that deterioration in tract integrity predicts subsequent cognitive impairments and that synchronized changes in white matter and cognitive abilities unfold over time.[26,31,33,40] Modifiable factors, such as physical activities, have been associated with more preserved structural and functional connectivity, suggesting potential avenues for interventions.[39]

In general, the evidence represents that aging exerts a graded, system-wide influence on white matter microstructure and brain network organization. These changes are quantifiable, regionally specific, and significantly predictive of cognitive performance in later life.[20,23,27,33]

Study Limitations

Several limitations were identified across the included studies. Most investigations employed cross-sectional designs, limiting causal inference and characterization of longitudinal trajectories.[20-24,26,27,29-32,34,35,38,39,41,42] In addition, sample sizes were often modest, and participant heterogeneity was common.[19,22-24,27-29,33,34,37,39-42] Moreover, methodological constraints included reliance on single diffusion models, fixed slice thickness, and primary use of FA and MD as indices of white matter integrity.[19,20,22,25,28,30,32,34,37] Further, DTI measures are susceptible to noise, artifacts, and partial volume effects.[19,21,25,28,31,33,36,37,42] Additionally, several studies lacked direct physiological validation of free-water measures[33,34] or did not correct for multiple comparisons, increasing the risk of false-positive findings.[20,38,40] Furthermore, some researchers acknowledged that their analyses provided descriptive models of aging-related brain changes rather than definitive mechanistic explanations.[19,23,24,27,36] Likewise, generalizability was limited by potential confounding factors, such as vascular risk, comorbidities, genetic influences, medication use, education, and lifestyle variables.[20,21,26,29,30,32,34-36,38,40-42]

Conclusion

This systematic review evaluated how diffusion tensor imaging (DTI) measures relate to brain aging and cognitive performance. The available evidence indicates a consistent association between age-related white matter changes and cognitive decline, although several methodological limitations temper the strength of these conclusions. Future work should emphasize longitudinal designs, larger and more heterogeneous samples, inclusion of younger comparison groups, and the use of more advanced imaging and analytic techniques (such as tractography and probabilistic fiber tracking). These strategies will be crucial for clarifying the contribution of specific white matter pathways to cognitive aging and for establishing the predictive value of DTI markers for subsequent cognitive decline and dementia.

Acknowledgments

The authors would like to appreciate the Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran, for their cooperation in conducting this research.

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Funding

This research received no external funding

Data Availability Statement

The data presented in this study are available on request from the corresponding author

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Conflicts of Interests

The authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT (OpenAI) to assist with language editing and improving the clarity of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Supplemententray file

Supplementary file contains Table S1-S5.

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