Received: 1 May 2025 | Revised: 2 July 2025 | Accepted: 20 July 2025

DOI: 10.1002/alz.70598

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Neural basis of motor symptoms in Alzheimer's disease: role of regional tau burden and cognition

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Funding information
Korea Health Technology R&D Project; Korea Health Industry Development Institute (KHIDI); Ministry of Health & Welfare, Republic of Korea, Grant/Award Number: RS-2023-00266536; Yonsei University College of Medicine, Grant/Award Number: 6-2022-0073

Abstract

INTRODUCTION: With accumulating evidence that motor manifestations in Alzheimer's disease (AD) may emerge from AD pathology independent of other copathologies, we investigated the neural basis of motor dysfunction under the amyloid/tau/neurodegeneration (ATN) framework.

METHODS: This study included 125 patients with AD, excluding individuals with severe leukoaraiosis or comorbid Lewy body features beyond Parkinsonism. Associations of ATN burden with motor dysfunction were tested using multivariate regression models, followed by mediation analyses exploring the cognitive contribution to these associations.

RESULTS: Tau burden in the prefrontal, sensorimotor, and parietal regions was associated with motor dysfunction independent of amyloid or neurodegeneration. The effect of parietal tau on motor function was fully mediated by visuospatial dysfunction, whereas prefrontal/sensorimotor tau exerted direct effects without cognitive mediation.

DISCUSSION: Increased tau burden in the sensorimotor and frontoparietal association cortices may elicit motor dysfunction in AD through either cognition-dependent or cognition-independent mechanisms, with effects depending on the affected regions.

KEYWORDS
Alzheimer's disease, cognitive dysfunction, motor deficits, positron emission tomography, tau proteins

Highlights

- Tau burden was intimately associated with motor symptoms independent of Aβ or atrophy.
- Tau in sensorimotor and frontoparietal association cortices may elicit motor symptoms.

Han Soo Yoo and Chul Hyoung Lyoo contributed equally to this work.

- Prefrontal/sensorimotor tau exerted cognition-independent effects on motor symptoms.
- Parietal tau indirectly influenced motor symptoms through visuospatial dysfunction.
- Parietal tau-related motor dysfunction may be partly explained by apraxic features.

1 | BACKGROUND

Apart from cognitive impairment, which is the hallmark symptom of Alzheimer's disease (AD), there is growing appreciation for motor dysfunction, another commonly observed yet long overlooked clinical aspect of AD.[1–7] Although the frequency and severity of motor symptoms are known to increase with disease progression,[2–4] motor symptoms are not exclusive to the advanced stages of AD, but can also be observed in earlier stages.[1] Given that motor symptoms tend to be associated with a poorer prognosis,[4–7] a better understanding of motor deficits in the AD population is imperative.

The neuropathological basis of motor symptoms in AD remains incompletely understood, with ongoing debate regarding whether these symptoms emerge from intrinsic AD-related neuropathological changes (ADNC) or coexistent pathologies. Conventionally, motor symptoms in AD have been regarded as manifestations attributable to concomitant cerebrovascular or Lewy body pathology.[8–12] Earlier *post mortem* studies implicated Lewy body pathology as a primary contributor to motor dysfunction, based on its frequent coexistence (25% to 55%) in AD patients who exhibited motor symptoms during their lifetime.[8–10] Nevertheless, these findings indicate that at least half of AD patients with motor manifestations may not harbor Lewy body pathology, even at a far advanced stage. Similarly, recent reports indicate that parkinsonian symptoms frequently occur in patients with AD even without substantial cerebrovascular lesions,[13,14] suggesting that vascular copathology may not fully explain the motor manifestations in AD.

These findings indicate that motor symptoms may not necessarily originate from coexistent non-AD pathologies but rather imply that they may, at least partly, originate from ADNC itself.[13–20] While several attempts have been made to explore the contribution of ADNC to motor deficits,[15–20] most of these studies were limited to small autopsy-based investigations, making it difficult to elucidate clinico-pathological associations in vivo.[16–19] Moreover, they mainly focused on the involvement of ADNC in the nigrostriatal pathway, which failed to correlate with the extent of nigral neuronal loss[16–19] or dopamine transporter availability,[13,21] suggesting that motor dysfunction in AD alone may not account for a deficit in the nigrostriatal pathway, but it may also originate from brain regions elsewhere. Although the advent of tracers targeting amyloid and tau has improved insights into the pathophysiology of cognitive impairment under the amyloid/tau/neurodegeneration (ATN) framework,[22–25] the current understanding of the motor role in AD pathology still lags far behind these advances, especially in terms of tau.[13–15]

Investigating motor dysfunction in the AD population is often challenging, as cognitive and motor processes are mutually dependent.[1,26–28] In addition to motor deficits arising from ADNC involving regions shared by motor and cognitive circuits, patients with AD may also exhibit higher-order motor dysfunctions such as apraxia, even without involvement of classic motor structures (e.g., primary motor cortex or basal ganglia).[29–34] In this regard, elucidating whether motor dysfunction is indeed driven by ADNC involving the motor circuit or whether motor impairment is a downstream effect of cognitive impairment is important for understanding the pathophysiology underlying motor manifestations in AD.

To address this knowledge gap, we sought to identify the potential neural basis of motor manifestations in biomarker-confirmed patients with AD under the ATN framework. Specifically, we aimed to (1) investigate which of the three biomarkers was most closely related to motor symptom burden, (2) delineate the neuroanatomical correlates of motor dysfunction related to the regional burden of ATN biomarkers, and (3) elucidate whether ATN biomarkers exerted their effect on motor symptoms directly or indirectly through cognitive dysfunction.

2 | METHODS

2.1 | Study participants

A detailed selection process for eligible participants for this study is presented in the Supporting Information (Figure S1). Participants were selected from an AD imaging cohort enrolled at the Movement and Memory Disorder Clinic in Gangnam Severance Hospital between January 2015 and July 2022. As part of the cohort enrollment protocol described previously,[22] all participants underwent apolipoprotein E (APOE) genotyping and ATN biomarker evaluation based on positron emission tomography (PET) scans (^{18}F-Flortaucipir [FTP] and ^{18}F-Florbetaben [FBB]) and brain magnetic resonance imaging (MRI) with three-dimensional T1-weighted images. Within this cohort, individuals satisfying the following criteria were considered as potential candidates for the present study: (1) amyloid positivity confirmed by FBB PET; (2) participants with cognitive impairment who fulfilled the diagnostic criteria for prodromal AD (i.e., mild cognitive impairment [MCI]) and AD dementia[35,36]; and (3) Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) assessment performed within 6-month interval from ATN evaluation.

Notably, patients with features suggestive of atypical AD variants (e.g., logopenic aphasia or posterior cortical atrophy), atypical parkinsonian syndromes, and severe white matter hyperintensities

(WMHs) were excluded a priori by the cohort enrollment protocol.[22] To minimize other factors contributing to motor symptoms, we further excluded patients with the following conditions: (1) patients who had or developed any of the core clinical features established in the diagnostic criteria for dementia with Lewy bodies (DLB) other than parkinsonism (i.e., rapid eye movement sleep behavior disorder, cognitive fluctuation with pronounced variations in attention/alertness, and recurrent formed visual hallucination)[37] in an attempt to exclude amyloid-positive DLB patients mislabeled as AD ($n = 18$); (2) patients with significant musculoskeletal disorders ($n = 7$, spinal cord disorders confirmed by spinal cord MRI or computed tomography (CT), fracture, and severe arthritis, which may affect gait disturbance); (3) drug-induced parkinsonism or use of neuroleptics within 6 months from UPDRS-III evaluation ($n = 6$); and (4) other systemic illnesses that may significantly affect the patient's general condition ($n = 1$). Furthermore, one AD patient with a PSEN1 mutation was excluded, considering the distinct clinical manifestations of autosomal dominant and sporadic AD. Finally, 125 amyloid-positive patients with prodromal AD ($n = 51$) or AD dementia ($n = 74$) were included in the study.

To account for age-related minor motor features that may occur independently of neurodegenerative pathology, this study included cognitively unimpaired participants as a control group. Among individuals who completed ATN evaluation and comprehensive neuropsychological assessment during the same period as AD participants (January 2015 to July 2022), those who met the following criteria were selected: (1) cognitively unimpaired individuals, including healthy participants who met Christensen's criteria[38] and individuals with subjective cognitive decline without objective impairment on neuropsychological assessments; (2) those without a history of neurological/psychiatric illness or other conditions that may affect motor function (e.g., musculoskeletal disorders or exposure to offending medications); (3) negative amyloid PET imaging; (4) UPDRS assessment performed within 6 months of ATN biomarker evaluation; and (5) age $\geq$ 60 years, to match the age distribution of the AD cohort. Finally, a total of 46 individuals (19 healthy controls and 27 with subjective cognitive decline) were included. All participants underwent a detailed clinical interview and neurological examination along with a systematic investigation of their medical history and vascular risk factors.[22,39]

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Board of Gangnam Severance Hospital approved this study (No. 3-2025-0044).

2.2 | Assessment of motor symptoms

The severity of motor deficits was evaluated using the UPDRS-III, assessed by two movement disorder experts (C.H.L. and H.S.Y.) within a 6-month interval from the ATN biomarker evaluation. The cardinal motor symptoms included in the UPDRS-III were categorized into four subdomains: tremor (items 20 and 21), rigidity (item 22), bradykinesia (items 23 to 26), and axial symptoms (items 18, 19, 27 to 30). To detect subclinical rigidity, an induced method (the Froment activation maneuver) was routinely used when rigidity was equivocal. In cases showing clear oppositional (Gegenhalten) or facilitatory (Mitgehen) paratonia, the symptom was not scored as rigidity.

Study participants were classified into three groups based on their motor symptom severity: "none or subtle," "mild Parkinsonian signs (MPS)," and "overt Parkinsonism" (Figure 1). Herein, we categorized participants without any motor signs (UPDRS-III = 0) and those exhibiting subtle motor signs (UPDRS-III > 0) but insufficient to meet the criteria for subthreshold parkinsonism (UPDRS-III $\leq$ 3, excluding action tremor [postural/kinetic tremor] items) into a single group defined as "none/subtle motor signs." The rationale underlying this definition was based on the established criteria,[40–42] which define MPS only for individuals presenting with motor deficits exceeding the cut-off (UPDRS-III > 3, excluding action tremor items). According to this framework, motor symptoms below this threshold are considered to have limited clinical significance, as such subtle deficits are also commonly observed in the general elderly population.[40–42] Participants with UPDRS-III total score > 3 (excluding action tremor items) were further classified as follows: Patients were categorized as having "overt parkinsonism" if the patient fulfilled the definition for parkinsonism (i.e., presence of bradykinesia, in combination with at least one of rest tremor or rigidity[43]), while the others were defined as having MPS.

RESEARCH IN CONTEXT

1. **Systematic review**: Although motor symptoms in AD have traditionally been attributed to copathologies, recent evidence suggests that they may also originate from AD pathology. However, only a few studies have comprehensively investigated their neural basis within the ATN framework, particularly with respect to tau.
2. **Interpretation**: Among ATN biomarkers, tau was most intimately associated with concurrent motor dysfunction. Increased tau burden in the sensorimotor and frontoparietal association cortices was identified as the substrate underlying motor dysfunction, with tau exerting effects either directly or through cognition-dependent mechanisms, depending on the affected regions.
3. **Future directions**: Our findings provide evidence that motor symptoms may, at least in a subset of individuals, represent intrinsic manifestations of AD. This highlights the need for cautious interpretation of motor symptoms in AD, as they may arise from either AD pathology or other comorbid conditions, necessitating further studies elucidating their respective contributions to motor dysfunction.

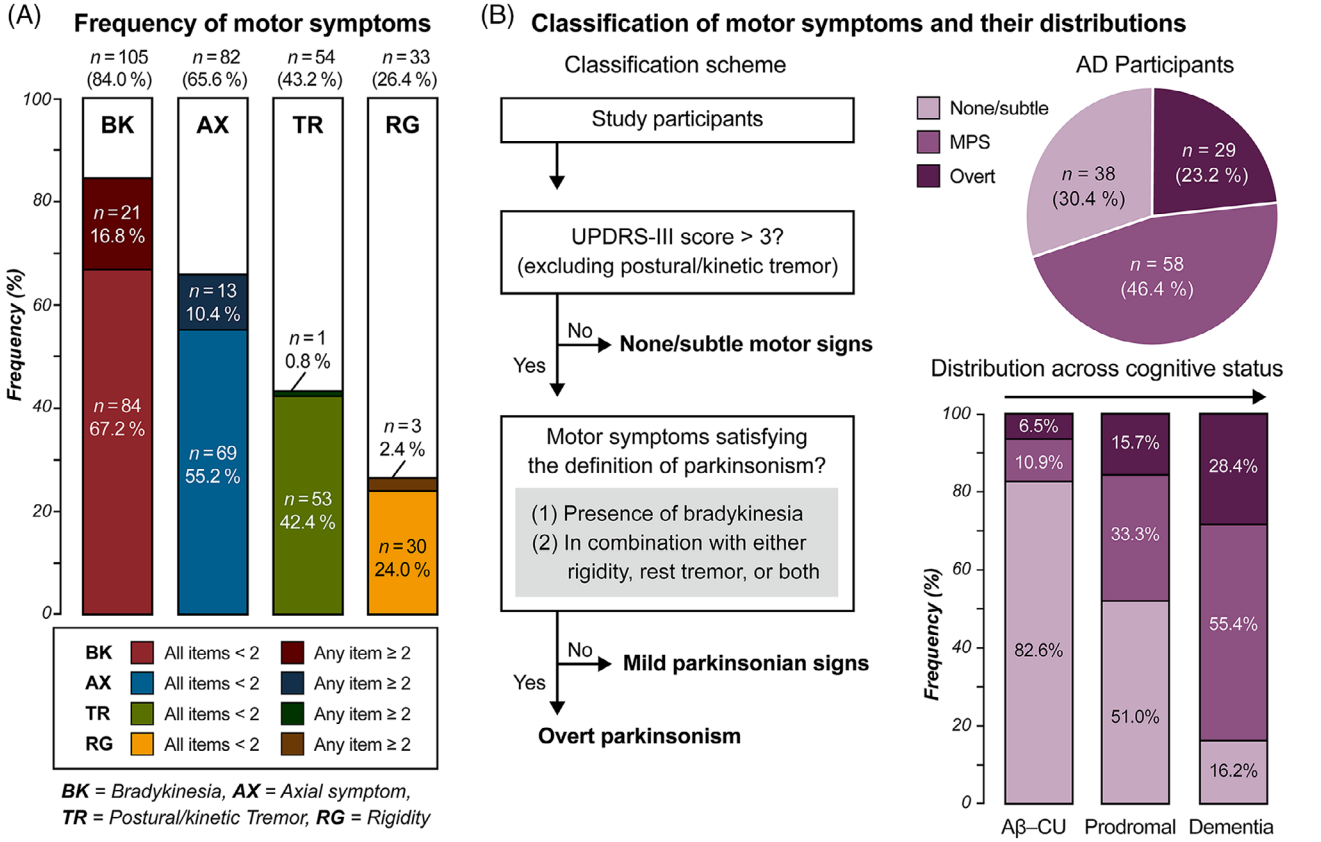

FIGURE 1 Frequency and profiles of motor symptoms in AD. (A) Bar graphs showing percentage of presence of motor symptoms in each motor subdomain. (B) According to the classification scheme presented, participants were classified into three groups: no or subtle motor signs, mild parkinsonian signs, and overt parkinsonism. The severity of motor symptoms increased in accordance with the level of cognitive impairment in the order of amyloid-negative controls, prodromal AD, and AD dementia (p for trend < 0.001). AD, Alzheimer's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

2.3 | Neuropsychological assessment

Along with Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) score, participants underwent a comprehensive neuropsychological assessment using the Seoul Neuropsychological Screening Battery (SNSB), which evaluates five cognitive domains: attention, language, memory, visuospatial function, and frontal/executive function (Method S1 in Supporting Information).[44,45] Based on scorable subtests with available age- and education-matched normative data, domain-specific composite scores were derived by averaging standardized z-score values of the subtests comprising each cognitive domain for the attention, memory, and frontal/executive domains. Meanwhile, standardized z-scores of the Korean version of the Boston Naming Test (K-BNT) and the Rey–Osterrieth Complex Figure Test (RCFT) copy were used to represent language and visuospatial performance, respectively.

Of the 125 patients, 122 completed the neuropsychological battery at the time of ATN evaluation. The remaining three patients had previously been diagnosed with dementia based on the SNSB but were unable to complete the assessment at the time of ATN evaluation due to severe cognitive impairment or lack of cooperation.

2.4 | Assessment of apraxia

Study participants were not systematically assessed by means of standardized instruments specifically designed for comprehensive apraxia evaluation. However, the SNSB included brief subtests for praxis evaluation.[45] Accordingly, we derived ideomotor (five items) and buccofacial praxis scores (four items) from these available subtests for analysis. Moreover, the SNSB offers dichotomized classifications for both ideomotor and buccofacial praxis (normal [≥16th percentile] or impaired [<16th percentile]) based on normative data from age- and education-matched healthy individuals. These classifications were used to determine the presence of apraxia in our study participants. Detailed information is described in Supporting Information (Method S2).

2.5 | Acquisition and quantitative analyses of PET/magnetic resonance images

Detailed protocols used for the acquisition of ^{18}F-FTP PET, ^{18}F-FBB PET, and MRI are described in the Supporting Information

(Method S3).[22,39] All PET images were obtained using a Biograph mCT PET/CT scanner (Siemens Medical Solutions, Malvern, PA, USA). This study employed two different MRI scanners: A 3T Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI, USA) was used to obtain MR images for 63 patients (50.4%), while the remaining 62 patients (49.6%) underwent MRI scanning using a 3T MAGNETOM Vida scanner (Siemens Healthcare, Erlangen, Germany).

Detailed image processing steps and quantitative analyses of PET images are outlined in the Supporting Information (Method S4).[22] Briefly, participant-specific volume-of-interest (VOI) images with the cortical regions were obtained by processing T1-weighted magnetic resonance images using FreeSurfer version 5.3 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu). PET images were co-registered to individual magnetic resonance images within the FreeSurfer space, and the standardized uptake value ratios (SUVRs) of each VOI were obtained using the cerebellar crus as a reference region. SUVRs were extracted from the whole-brain cortical gray matter and eight predetermined composite regions of interest (ROIs): prefrontal, sensorimotor, medial and lateral parietal, medial and lateral temporal, insula, and occipital cortex.[25] The voxel counts in each region were considered to be regional volumes. Details on WMH assessment are provided in the Supporting Information (Method S5).

2.6 | Statistical analysis

For comparisons of demographic and clinical characteristics, Student's *t*-test or ANOVA was used for continuous variables. Categorical variables were compared using chi-squared or Fisher's exact tests, as appropriate. A linear-by-linear association test was conducted to assess whether the severity of motor symptoms (none/subtle, MPS, and overt parkinsonism) increased in accordance with the level of cognitive impairment (controls, prodromal AD, and AD dementia).

Associations between UPDRS-III total scores and each of the global ATN biomarkers (global ^{18}F-FBB SUVR, global ^{18}F-FTP SUVR, total intracranial volume-corrected cortical gray matter volume [cGMV]) were explored by employing multivariate linear regression models adjusted for age, sex, education years, disease duration, APOE ε4 allele carrier, total Fazekas score,[46] and MRI scanner type (Model 1). To investigate which of the three ATN biomarkers independently contributed to motor symptoms, Model 2 incorporated all three ATN biomarkers simultaneously, in addition to covariates used in Model 1. Furthermore, a four-factor serial mediation model was constructed based on the previously proposed sequential hypothesis of ATN biomarkers (amyloid → tau → neurodegeneration → clinical symptoms),[47] using global ^{18}F-FBB SUVR as the independent variable, UPDRS-III total score as the dependent variable, and the other two ATN biomarkers as mediators (global ^{18}F-FTP SUVR and cGMV), adjusting for covariates used in Model 1.

Associations between the regional burden of ATN biomarkers in eight composite ROIs and motor symptom severity (UPDRS-III total and subdomain scores) were tested using multivariate linear regression analyses, adjusting for the global measures for the other two components of ATN biomarkers in addition to covariates used in Model 1. For example, when assessing the association between regional amyloid burden and motor symptoms, the following variables were used as covariates: global measures for tau and neurodegeneration (i.e., global ^{18}F-FTP SUVR and total cGMV), age, sex, education years, disease duration, APOE ε4 allele carrier, total Fazekas score, and MRI scanner type. The analyses were repeated for four motor subdomain scores. To address the issue of multiple comparisons, the family-wise error corrected *p*-value (P_{FWE}) < 0.05 was considered statistically significant.

To further investigate whether cognitive dysfunction played an intermediary role in the association between ATN biomarkers and motor symptoms, we examined the potential cognitive contribution using two complementary approaches. First, the mediating role of global cognition was tested by incorporating the MMSE score as an additional mediator in the serial mediation model (independent variable: global ^{18}F-FBB SUVR; dependent variable: UPDRS-III total score; three mediators: global ^{18}F-FTP SUVR, cGMV, and MMSE score; covariates: age, sex, education years, disease duration, APOE ε4 allele carrier, total Fazekas score, and MRI scanner type). Second, path analyses were performed to evaluate whether specific cognitive function mediated the association between regional tau burden and motor symptom severity in cases where regional ^{18}F-FTP SUVR, cognitive performance, and UPDRS-III total scores (or subdomain scores) demonstrated significant associations. In these mediation analyses, the following covariates were used: global measures for amyloid and neurodegeneration (global ^{18}F-FBB SUVR and total cGMV), age, sex, education years, disease duration, APOE ε4 allele carrier, total Fazekas score, and MRI scanner type.

Lastly, given that UPDRS-III scores may also reflect higher-order motor dysfunctions such as apraxia, which is also associated with cortical tau pathology,[29–31] we repeated the aforementioned analyses for apraxia to examine its potential contribution to the tau–motor relationship.

For mediation analyses, the PROCESS MACRO version 4.2 was implemented in SPSS (version 28.0; IBM, Armonk, NY, USA) with bias-corrected bootstrapping (n = 5000).[48] Visualization of regional associations was conducted using MATLAB (version R2019b; MathWorks, Natick, MA, USA). All other analyses were performed using R Statistics (version 4.2.2; Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Demographic and clinical characteristics

The demographic and clinical characteristics of the study participants are summarized in Table 1. Compared to patients with prodromal AD, patients with AD dementia had longer disease duration, worse cognition in terms of MMSE scores and CDR-SB, and higher UPDRS-III scores (p < 0.001). Moreover, patients with AD dementia had higher global ^{18}F-FBB and ^{18}F-FTP burden, but lower cGMV compared to those with prodromal AD. Meanwhile, age, distribution of gender,

TABLE 1 Clinical characteristics of study participants.

	Prodromal AD ($n = 51$)	AD dementia ($n = 74$)	Total ($n = 125$)	p value
Characteristics				
Sex, male, *n* (%)	21 (41.2)	23 (31.1)	44 (35.2)	0.245
Age (years)	72.4 ± 6.7	74.6 ± 8.8	73.7 ± 8.1	0.123
Onset age (years)	69.0 ± 7.4	70.1 ± 8.4	69.6 ± 8.0	0.460
Disease duration (years)	3.4 ± 2.0	4.5 ± 2.5	4.1 ± 2.4	0.008
Education (years)	11.9 ± 3.7	10.5 ± 5.3	11.1 ± 4.8	0.077
APOE ε4 carrier, *n* (%)	30 (58.8)	40 (54.1)	70 (56.0)	0.598
MMSE score	26.1 ± 2.7	19.2 ± 5.8	22.0 ± 5.8	<0.001
CDR-SB	1.5 ± 0.8	5.1 ± 3.5	3.6 ± 3.3	<0.001
Motor symptoms				
UPDRS-III Total score	4.57 ± 3.97	9.54 ± 7.21	7.51 ± 6.55	<0.001
UPDRS-III Bradykinesia	2.53 ± 2.41	5.97 ± 4.59	4.57 ± 4.20	<0.001
UPDRS-III Axial	1.06 ± 1.30	1.91 ± 1.92	1.56 ± 1.74	0.007
UPDRS-III Tremor	0.51 ± 0.83	0.91 ± 0.97	0.74 ± 0.93	0.019
UPDRS-III Rigidity	0.47 ± 1.41	0.76 ± 1.55	0.64 ± 1.49	0.294
Motor subgroups				<0.001
None or subtle, *n* (%)	26 (51.0)	12 (16.2)	38 (30.4)	
MPS, *n* (%)	17 (33.3)	41 (55.4)	58 (46.4)	
Overt Parkinsonism, *n* (%)	8 (15.7)	21 (28.4)	29 (23.2)	
Ideomotor praxis score	4.23 ± 0.97	3.13 ± 1.56	3.59 ± 1.45	<0.001
Imaging markers				
Global ^{18}F-FBB SUVR	1.92 ± 0.28	2.08 ± 0.29	2.01 ± 0.29	0.003
Global ^{18}F-FTP SUVR	1.25 ± 0.21	1.52 ± 0.34	1.41 ± 0.32	<0.001
Cortical GMV (% of TIV)	28.35 ± 2.28	27.17 ± 2.10	27.65 ± 2.25	0.003
Total Fazekas score	2.61 ± 1.25	2.80 ± 1.30	2.72 ± 1.28	0.418
DWMH grade	1.31 ± 0.71	1.30 ± 0.72	1.30 ± 0.71	0.899
PWMH grade	1.29 ± 0.70	1.51 ± 0.78	1.42 ± 0.75	0.110

Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; DWMH, deep white matter hyperintensity; GMV, gray matter volume; FBB, florbetaben; FTP, flortaucipir; MMSE, Mini-Mental State Examination; MPS, mild Parkinsonian signs; PWMH, periventricular white matter hyperintensities; SUVR, standardized uptake value ratio; TIV, total intracranial volume; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

education years, frequency of APOE e4 allele carrier, and WMH burden did not reveal a significant difference across cognitive status.

3.2 | Motor profiles

The frequency, number of motor subdomains involved, motor profile, and severity of the motor symptoms are presented in Figures 1 and S2. Among the 125 patients, 119 (95.2%) exhibited motor symptoms to at least a subtle degree (UPDRS-III total score > 0). Among the motor subdomains, bradykinesia was the most frequent symptom (84.0%), followed by axial symptoms (65.6%), postural or kinetic tremor (43.2%), and rigidity (26.4%). None of the patients included in our study revealed rest tremor. Of note, eight patients who satisfied the diagnostic criteria for prodromal AD or AD dementia had rest tremors, but they were excluded during the selection process for the following reasons: presence of core clinical features of DLB ($n = 6$, with three of the six patients also exposed to neuroleptics at the point of UPDRS evaluation) and drug-induced parkinsonism ($n = 2$, Figure S1).

In the classification of the AD participants based on the severity of motor symptoms, 38 patients (30.4%) were classified as having no/subtle motor signs (none, $n = 6$ [4.8%]; subtle, $n = 32$ [25.6%]; UPDRS-III, 2.03 ± 1.62), 58 as having MPS (48.0%; UPDRS-III, 7.47 ± 2.78), and 29 as having overt parkinsonism (23.2%; UPDRS-III, 15.33 ± 8.72). AD participants with no or subtle motor signs exhibited lower ideomotor apraxia burden (higher ideomotor praxis scores, 4.26 ± 1.08) compared to those with MPS (3.24 ± 1.47) or overt parkinsonism (3.37 ± 1.57). Detailed clinical characteristics of AD participants within each motor subgroup are presented in the Supporting Information (Table S1).

When compared to amyloid-negative controls, AD participants revealed significantly higher UPDRS-III scores (7.51 ± 6.55 vs 2.37 ± 2.68, $p < 0.001$). Notably, the distribution of motor subgroups differed markedly across control, prodromal AD, and AD dementia groups, demonstrating an increasing trend in motor symptom severity (no/subtle, MPS, overt parkinsonism) in accordance with cognitive decline (p for trend < 0.001) (Figure 1B). Detailed information is available in Supporting Information (Table S2).

3.3 | Association of global ATN burden with motor symptoms

We investigated whether motor deficits were associated with ATN biomarkers. The UPDRS-III total score was significantly associated with each of the global measures for amyloid (global ^{18}F-FBB; $\beta = 0.363$, $p < 0.001$), tau (global ^{18}F-FTP; $\beta = 0.601$, $p < 0.001$), and brain atrophy (cGMV; $\beta = -0.509$, $p < 0.001$) individually (Model 1). However, in a multivariate linear regression model incorporating all three ATN biomarkers (Model 2), only global ^{18}F-FTP SUVR showed a significant association with the UPDRS-III total score ($\beta = 0.460$, $p < 0.001$), whereas amyloid ($\beta = 0.084$, $p = 0.174$) and brain atrophy ($\beta = -0.186$, $p = 0.078$) lost their statistical significance (Figure 2A).

Path analysis showed that the association between global amyloid burden and motor dysfunction was completely mediated by the global tau burden (Figure 2B). When incorporating global cognition (MMSE) into the serial mediation model as an additional mediator, the amyloid–motor relationship was mediated either by the tau-mediated pathway (Aβ → tau → motor symptom) or the tau-/cognition-mediated pathway (Aβ → tau → general cognition → motor symptom) (Figure S3).

3.4 | Association of regional ATN burden with motor symptoms

We then investigated the regions of amyloid accumulation, tau accumulation, or cortical gray matter atrophy that were associated with motor symptoms to identify the neural correlates of motor deficits in AD. In regression analyses examining the association between the regional tau burden in eight ROIs and motor dysfunction, the ^{18}F-FTP burden in the prefrontal ($\beta = 0.461$, $P_{FWE} < 0.001$), sensorimotor ($\beta = 0.453$, $P_{FWE} < 0.001$), lateral parietal ($\beta = 0.433$, $P_{FWE} < 0.001$), and medial parietal cortices ($\beta = 0.375$, $P_{FWE} = 0.002$) exhibited significant associations with the UPDRS-III total score (Figure 3). Although the regional ^{18}F-FBB SUVR showed diffuse positive correlations with UPDRS-III total scores in all ROIs except the medial temporal region, the associations were no longer significant after further adjustment for global ^{18}F-FTP burden and cGMV. Similarly, regional cGMV in the prefrontal, sensorimotor, parietal, and lateral temporal cortices positively correlated with the UPDRS-III total score, but the significance was not retained after further adjustments for global ^{18}F-FBB and ^{18}F-FTP uptake (Figure S4).

When investigating the regional correlates of each of the UPDRS-III subdomain scores, the bradykinesia subdomain score showed a significant positive association with ^{18}F-FTP uptake in the prefrontal, sensorimotor, lateral parietal, and medial parietal cortices, whereas the axial subdomain scores positively correlated with ^{18}F-FTP uptake in the prefrontal and sensorimotor cortices (Figure S5).

3.5 | Cognitive influence on tau–motor relationship

Multivariate linear regression analyses were performed to assess the association between the cognitive performance and the ^{18}F-FTP SUVR in the four ROIs, which revealed a significant association with motor symptoms. The tau burden in all four ROIs was significantly associated with the RCFT copy score and the composite score of the frontal/executive domain (Table S3). When evaluating the association between cognitive performance and motor symptoms, the UPDRS-III total scores were significantly associated with visuospatial (RCFT copy; $\beta = -0.427$, $P_{FWE} < 0.001$) and frontal/executive domain ($\beta = -0.293$, $P_{FWE} = 0.049$), but not with attention ($\beta = -0.128$, $P_{FWE} > 0.999$), language (K-BNT; $\beta = -0.188$, $P_{FWE} = > 0.999$), or memory ($\beta = -0.212$, $P_{FWE} = 0.500$). When repeating the analysis for UPDRS-III subdomain scores, frontal/executive dysfunction ($\beta = -0.301$, $P_{FWE} = 0.033$) and the performance of the RCFT copy test revealed a significant association with the bradykinesia subdomain score. (Table S4).

To examine the cognitive influence on the relationship between regional tau and motor symptoms, mediation analyses were performed using the regional ^{18}F-FTP SUVR in the four ROIs as predictors, the UPDRS-III total score as the outcome, and cognitive performance as the potential mediator (the RCFT copy score or composite score for the frontal/executive domain). Mediation analyses revealed that the association between lateral/medial parietal tau burden and motor dysfunction was fully mediated by visuospatial dysfunction (RCFT copy score) but not by frontal/executive dysfunction (Figure 4). Meanwhile, tau burden in the prefrontal and sensorimotor cortices exerted a direct effect on motor dysfunction without the indirect effect of frontal/executive or visuospatial dysfunction. Even with secondary analyses using anatomically refined parcellation of the prefrontal and sensorimotor subregions, they failed to demonstrate significant cognitive mediation effects across all models (Figure S6). Regarding the UPDRS-III subdomain scores, path analyses showed that the association between the lateral/medial parietal tau burden and the bradykinesia subdomain score was fully mediated by visuospatial dysfunction (RCFT copy score), whereas the association between bradykinesia and prefrontal/sensorimotor tau was not mediated by either visuospatial or frontal/executive dysfunction (Figure S7).

3.6 | Association between regional tau burden, apraxia, and motor symptoms

Among the 122 patients who completed praxis subtests, ideomotor apraxia was identified in 63 patients (51.6%) based on performance

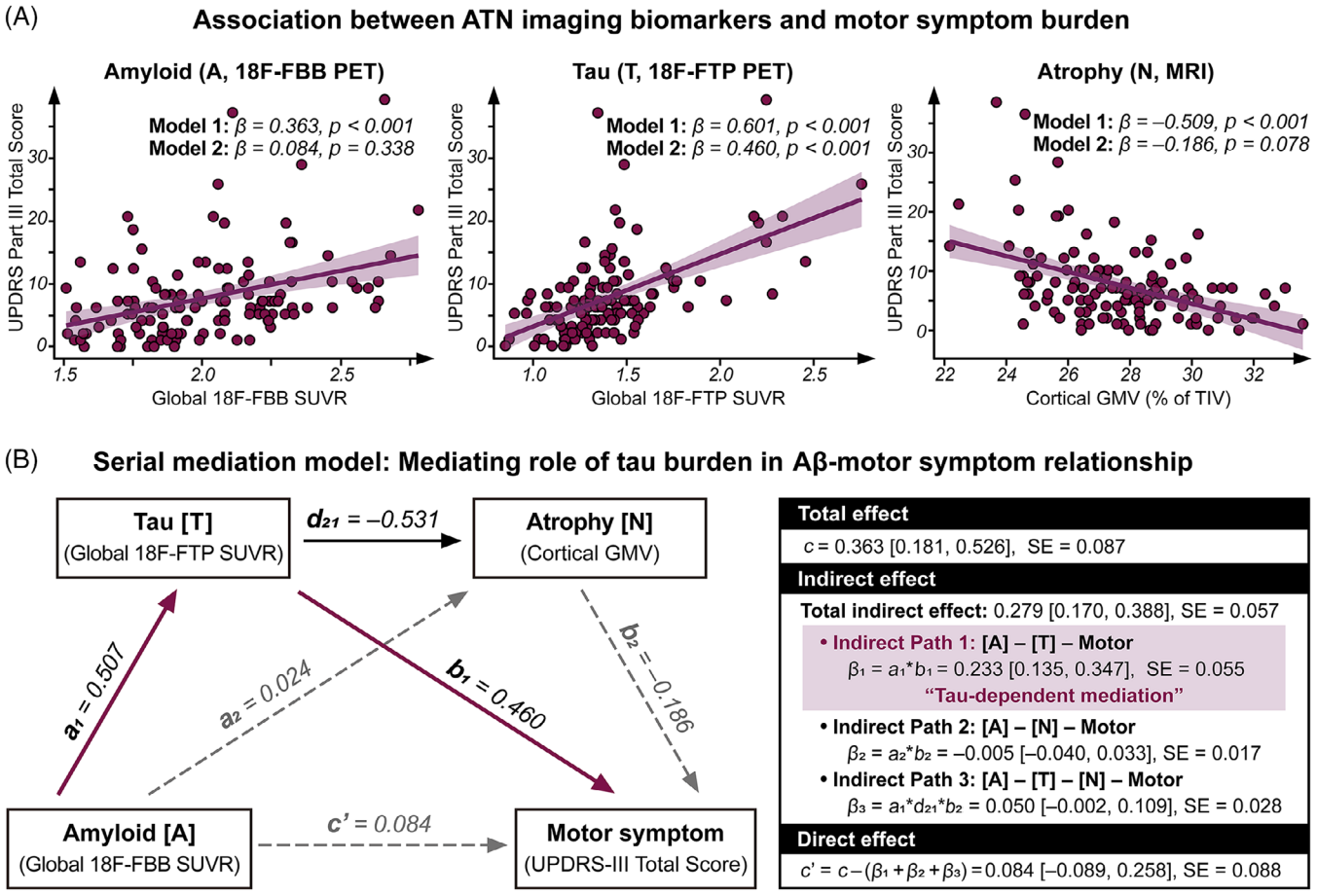

FIGURE 2 Association of motor symptoms with ATN biomarkers. (A) Linear regression models were conducted to investigate the associations between UPDRS-III total scores and global ATN biomarkers. Model 1 examined each ATN biomarker separately, while Model 2 included all three biomarkers simultaneously. (B) Serial mediation analysis of amyloid and motor symptom burden using two mediators (tau and neurodegeneration) reveals that the effect of amyloid on motor symptom is fully mediated via a tau-dependent pathway. All analyses (both regression models and mediation analyses) were adjusted for age, sex, education years, disease duration, presence of APOE ε4 allele, white matter hyperintensity burden (total Fazekas score), and MRI scanner type. Abbreviations: Aβ, amyloid-beta; FBB, florbetaben; FTP, flortaucipir; MRI, magnetic resonance imaging; SE, standard error; SUVR, standardized uptake value ratio; TIV, total intracranial volume; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

below age-/education-matched normative values. The prevalence of ideomotor apraxia showed a significant association with disease severity, being more frequent in AD dementia patients (45/71, 63.4%) compared to those with prodromal AD (18/51, 35.3%; $p = 0.002$). Of note, buccofacial apraxia was relatively rare, affecting only five patients (5/122; 4.1%), all of whom had dementia and concurrent ideomotor apraxia.

Given the rarity of buccofacial apraxia and its consistent co-occurrence with ideomotor apraxia, only ideomotor apraxia was included in the analyses exploring the associations between regional tau burden, praxis dysfunction, and motor symptom severity. Significant associations with ideomotor apraxia scores were observed for regional ^{18}F-FTP SUVR in the parietal cortex (lateral: $\beta = -0.377$, $P_{FWE} = 0.002$; and medial: $\beta = -0.312$, $P_{FWE} = 0.012$) and lateral temporal cortex ($\beta = -0.319$, $P_{FWE} = 0.017$). Furthermore, the performance of ideomotor praxis exhibited a significant association with motor symptom severity, in terms of UPDRS-III total scores ($\beta = -0.282$, $P_{FWE} = 0.012$) and bradykinesia subdomain scores ($\beta = -0.324$, $P_{FWE} = 0.003$). Mediation analyses further demonstrated that the severity of ideomotor apraxia partially mediated the effects of lateral and medial parietal tau burden on motor symptoms, for both UPDRS-III total scores and bradykinesia subdomain scores (Figure S8).

4 | DISCUSSION

This study investigated the association between motor symptoms and ATN biomarkers along with the influence of cognitive impairment on their association, offering three major findings. First, tau appears to be the main neuropathological substrate underlying motor symptoms among the ATN imaging hallmarks. Second, in terms of neuroanatomical correlates, the severity of motor dysfunction was associated with increased tau burden in the sensorimotor and frontoparietal association cortices. Third, the effect of tau deposition in the parietal regions

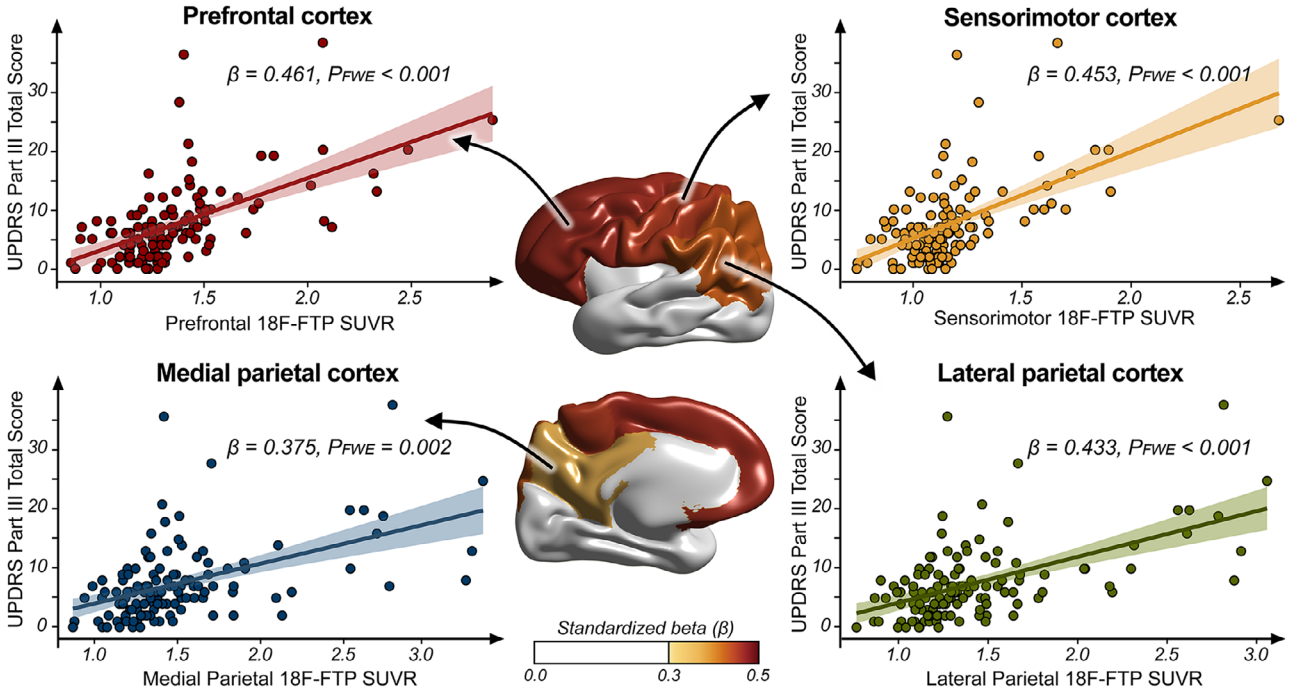

FIGURE 3 Associations between regional tau burden and motor symptom severity. Regional ^{18}F-Flortaucipir SUVR in the prefrontal, sensorimotor, lateral parietal, and medial parietal cortices revealed significant positive associations with UPDRS-III total scores based on multivariate linear regression models. Age, sex, education years, disease duration, presence of APOE ε4 allele, white matter hyperintensity burden, MRI scanner type, global amyloid burden, and cortical gray matter volume were used as covariates. MRI, magnetic resonance imaging; P_{FWE}, family-wise error corrected *p* value; UPDRS-III, Unified Parkinson's Disease Rating Scale.

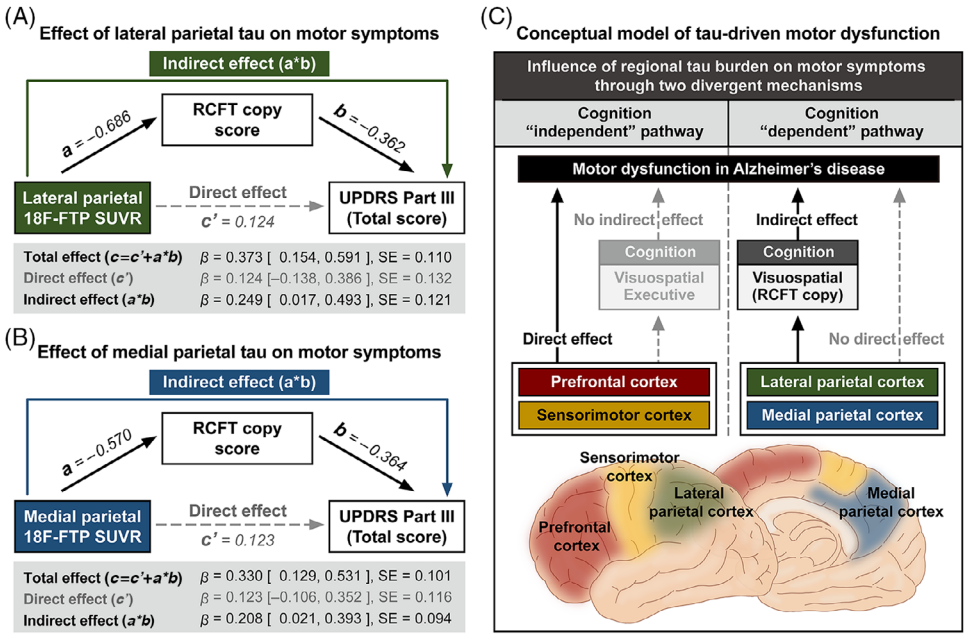

FIGURE 4 Mediation analyses of cognitive dysfunction on association between regional tau burden and motor symptom severity. (A and B) Effects of tau burden in lateral parietal (A) and medial parietal cortex (B) were fully mediated by visuospatial dysfunction. (C) Schematic illustration depicting divergent mechanisms for motor dysfunction elicited by regional tau. Prefrontal and sensorimotor tau directly influence motor dysfunction (cognition-independent pathway), while medial and lateral parietal tau exert their effect on motor dysfunction through a cognition-dependent pathway. Abbreviations: FBB, florbetaben; FTP, flortaucipir; SE, standard error; SUVR, standardized uptake value ratio; UPDRS-III, Unified Parkinson's Disease Rating Scale.

on motor symptoms was fully mediated by visuospatial dysfunction (i.e., cognition-dependent manner), whereas tau accumulation in the prefrontal/sensorimotor cortex influenced motor symptoms directly without mediation effects elicited by cognition. Altogether, our findings lend support that tau pathology may serve as the neural substrate for motor dysfunction in AD, with the mechanisms by which tau influences motor symptoms – whether through a cognition-dependent or cognition-independent pathway – depending on the affected brain regions.

Traditionally, motor symptoms in AD have been attributed to coexisting cerebrovascular or Lewy body pathology.[8–12] However, subsequent autopsy reports failed to confirm these copathologies in a substantial proportion of AD patients who presented motor symptoms during their lifetime,[16–19] prompting investigations into whether ADNC itself directly contributes to motor dysfunction.[13–20] One study proposed subcortical amyloid as a correlate of motor dysfunction in autosomal dominant AD,[15] although not replicated in sporadic AD.[13,14] Similarly, several neurophysiological studies have identified significant inter-relationships among reduced short-latency afferent inhibition, amyloid burden, and UPDRS-III scores, indicating that motor impairment in AD may arise from "amyloid-mediated cholinergic dysfunction."[49] Meanwhile, the potential contribution of tau pathology to motor dysfunction has received relatively limited attention, with only a few studies comprehensively examining all three ATN biomarkers to date.[29–31,50,51] In our analysis, although each ATN biomarker individually correlated with UPDRS-III scores, the multivariate model incorporating all three demonstrated that only tau revealed a significant association with UPDRS-III (Figure 2A). Furthermore, path analysis revealed that the effect of the amyloid burden on motor dysfunction was fully mediated through tau-mediated pathways, but not through atrophy (Figure 2B). These findings may partly be explained by the temporal dissociation of ATN biomarkers.[52] Amyloid deposition plateaus by the time clinical symptoms manifest, whereas atrophy represents a downstream consequence of diverse pathologies, obscuring symptom correlation. Meanwhile, tau pathology is known to exert direct neuronal toxicity through synaptic and cytoskeletal disruption, thereby contributing to clinical symptoms even before overt neuronal loss takes place.[23–25] Accordingly, tau pathology tends to exhibit a more intimate association with clinical symptomatology compared to amyloid or atrophy,[22–25] as observed in our study.

Our study identified tau accumulation in the prefrontal, sensorimotor, and medial and lateral parietal cortices as a potential neuroanatomical correlate of motor symptoms. These regions are integral components of the motor network, collectively subserving motor planning, execution, and higher-order control through cortico-subcortical and cortico-cortical interconnections.[26–28] However, since tau accumulation in the sensorimotor and frontoparietal association cortices typically occurs late in AD progression (Braak stage V/VI), their association with motor symptoms may be interpreted as a mere epiphenomenon of a more advanced neuropathological stage rather than a direct mechanistic link.[53,54] While this perspective aligns with previous reports indicating that motor symptoms tend to emerge later during AD,[2–4,53] such an explanation cannot fully account for the substantial proportion of patients manifesting with motor symptoms even at earlier stages (MPS, n = 17 [33.3%]; overt, n = 8 [15.7%]) or those without clinically meaningful motor symptoms even in dementia stage (n = 12; 16.2%).[1] The variability in motor symptom onset may be partly explained by the heterogeneity in tau spreading patterns across the AD spectrum.[55–58] While approximately half of AD patients follow the tau propagation pattern that adheres to the Braak staging scheme (typical AD), there exist patients revealing alternative patterns: hippocampal-sparing (pooled frequency; 17%) or limbic-predominant subtype (pooled frequency; 22%).[55] Notably, hippocampal-sparing AD subtype exhibits preferential tau accumulation in the frontoparietal cortex at earlier stages[55–57] and is characterized by an earlier age of onset, faster progression, and frequent atypical clinical presentations[55–57] – traits that mirror those observed in AD patients with early motor manifestations.[5–7]

Given that motor and cognitive processes cannot be completely set apart,[1,26–28] investigating whether motor dysfunction is truly driven by ADNC involving the motor circuit or whether it is a downstream effect of cognitive impairment is important for unravelling the pathophysiology underlying motor manifestations in AD. Our study identified two divergent mechanisms through which tau elicits motor dysfunction, contingent upon the affected anatomical regions (Figure 4C): (1) Prefrontal/sensorimotor tau directly influenced motor dysfunction without the mediating role of cognition (cognition-independent pathway) and (2) posterior parietal tau burden affected motor function, especially bradykinesia, indirectly through visuospatial dysfunction (cognition-dependent pathway). These findings may reflect the unique characteristics of the posterior parietal cortex in motor processes (i.e., "sensorimotor integration").[26–28] Unlike other regions directly engaged in motor processes, the posterior parietal cortex does not directly execute motor action but rather participates in higher-order aspects of motor control by integrating multimodal sensory inputs into information appropriate for action and relaying the processed information to the frontal cortex.[26–28,59–61] Given that the RCFT evaluates multiple dimensions encompassing visuospatial perception, fine-motor coordination, and planning/organization,[62–64] it may have served as an ideal measure reflective of "visuomotor integration" capacity, potentially explaining why RCFT performance completely mediated the effect of parietal tau on motor dysfunction.

In contrast, prefrontal/sensorimotor tau burden directly affected motor dysfunction without cognitive mediation, even with finer parcellation schemes (Figure S6). While these findings may indicate that motor deficits in AD are not merely downstream effects of cognitive decline, these results should be interpreted with caution, given the following methodological considerations. First, ROI-based approaches capture only isolated regional effects; merely correlating regional tau burden with UPDRS-III may not adequately capture the true cognitive contribution to the tau–motor relationship. As prefrontal/sensorimotor cortices participate in motor processes in a highly complicated manner through multiple parallel circuits[1,28,65] – some of which are associated with cognition and others functioning independently – interpreting motor dysfunction from a network perspective may be more appropriate than focusing on isolated regional

effects.[26–28,53,59–61,65] Second, UPDRS-III may be insufficient to fully characterize subtle motor deficits such as reduced dexterity, alteration in spatiotemporal gait parameters, and balance impairments commonly observed in AD.[51,66–68] Future investigations that incorporate functional MRI and more sensitive tools for evaluating AD-related motor symptoms (e.g., instrumented gait analyses or balance scales) are warranted to ascertain whether prefrontal/sensorimotor tau indeed affects motor function through cognition-independent pathways.

Another challenge in investigating motor dysfunction in AD lies in the heterogeneous nature of motor manifestations arising from the intricate interplay of multiple neural systems, ranging from parkinsonism to higher-order motor-cognitive disorders such as apraxia.[29–31] Given that the UPDRS cannot adequately distinguish parkinsonian from non-parkinsonian manifestations commonly observed in AD (e.g., paratonia, apraxia, and psychomotor slowing),[29–34] interpreting motor symptoms measured by UPDRS as "pure parkinsonism" may be inappropriate. In line with these concerns, our study found that ideomotor apraxia was significantly associated with parietal tau burden and motor symptom severity, particularly bradykinesia, with path analyses confirming that ideomotor apraxia partially mediated the parietal tau–motor relationship. While apraxia and bradykinesia represent distinct syndromic entities, differentiating between these phenomena can be challenging, as they inevitably influence each other.[32–34] Accordingly, the umbrella term "motor symptoms" was used throughout this study, despite its lack of specificity, as referring to these manifestations as "parkinsonism" would be misleading.

This study had several notable limitations. First, while we implemented strict patient selection criteria to minimize confounding from non-AD pathologies (e.g., excluding individuals with core clinical features of DLB beyond parkinsonism or those with severe WMHs), this may have constrained the generalizability of our findings. Second, even with such stringent selection, the possibility of Lewy body copathology cannot be entirely ruled out without confirmatory biomarkers (histopathology or α-synuclein seed amplification assays).[69–71] Third, the evaluation of motor symptoms relied solely on the UPDRS. Fourth, the ideomotor apraxia score used in this study reflects only a limited portion of the multifaceted syndromic entity of apraxia, warranting future studies employing validated instruments for comprehensive praxis assessment.[30,72,73] Fifth, UPDRS raters were not blinded to participants' clinical information, as the motor assessments were performed during routine clinical evaluations or as part of eligibility screening for cohort enrollment. However, since UPDRS-III was rated prior to imaging analyses, raters were effectively blinded to the ATN status of the participants. Lastly, contributions of striatal tau to motor symptoms could not be investigated due to the off-target binding of ^{18}F-FTP tracers in the basal ganglia.

Collectively, our findings demonstrate that motor dysfunction in AD may be driven by increased tau burden in the sensorimotor and frontoparietal association cortices, with tau exerting its effects either directly or through cognition-dependent mechanisms, varying across affected anatomical regions. Of note, we do not claim that motor symptoms in AD are solely attributable to tau pathology, nor do we disregard the contributions of other concomitant pathologies. Nevertheless, our findings provide preliminary evidence that motor symptoms do not necessarily require coexisting pathologies but may also arise as one of the intrinsic manifestations of AD, at least in a subset of patients. Subsequent research incorporating ADNC and multiple copathological aspects should be conducted to further elucidate the pathophysiology underlying motor dysfunction in AD.

AUTHOR CONTRIBUTIONS

Conception and design: Han Kyu Na, Han Soo Yoo, and Chul Hyoung Lyoo. *Acquisition, analysis, or interpretation of data*: Han Kyu Na, Hanna Cho, Hye Sun Lee, Han-Kyeol Kim, Sohoon Yoon, Young Hoon Ryu, Jae Hoon Lee, Han Soo Yoo, and Chul Hyoung Lyoo. *Drafting of the manuscript*: Han Kyu Na, Han Soo Yoo, and Chul Hyoung Lyoo. *Critical review of the manuscript for important intellectual content*: Han Kyu Na, Hanna Cho, Hye Sun Lee, Han-Kyeol Kim, Sohoon Yoon, Young Hoon Ryu, Jae Hoon Lee, Han Soo Yoo, and Chul Hyoung Lyoo. *Final approval of the manuscript*: Han Kyu Na, Hanna Cho, Hye Sun Lee, Han-Kyeol Kim, Sohoon Yoon, Young Hoon Ryu, Jae Hoon Lee, Han Soo Yoo, and Chul Hyoung Lyoo. *Obtained funding*: Han Soo Yoo and C.H.L. *Supervision*: Han Soo Yoo and Chul Hyoung Lyoo.

ACKNOWLEDGMENTS

This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant RS-2023-00266536); a faculty research grant from Yonsei University College of Medicine (Grant 6-2022-0073). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to this work. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Written informed consent was obtained from all participants. This study was conducted in accordance with the tenets of the 1964 Declaration of Helsinki and its subsequent amendments. The Institutional Review Board of Gangnam Severance Hospital approved this study (No. 3-2025-0044).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Na HK, Cho H, Lee HS, et al. Neural basis of motor symptoms in Alzheimer's disease: role of regional tau burden and cognition. *Alzheimer's Dement*. 2025;21:e70598. https://doi.org/10.1002/alz.70598