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SHORT REPORT

Alzheimer's disease biomarker burden in primary motor cortices is associated with poorer dexterity performance

Lily Gupta[1,2] | **Yue Ma**[1,2] | **Akshay Kohli**[1,2] | **Kao Lee Yang**[1,2] | **Jennifer M. Oh**[1,2] | **Tobey J. Betthauser**[1,2] | **Nathaniel A. Chin**[1,2] | **Ozioma C. Okonkwo**[1,2] | **Mary-Elizabeth Pasquesi**[1,2] | **Veena Nair**[1,2] | **Vivek Prabhakaran**[1] | **Shi-Jiang Li**[3] | **Barbara Bendlin**[1,2]

[1]Wisconsin's Alzheimer's Disease Research Center, Madison, Wisconsin, USA

[2]Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin, USA

[3]Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Correspondence
Barbara Bendlin, Wisconsin's Alzheimer's Disease Research Center, 600 Highland Ave, J5/1 Mezzanine, Madison, WI, USA.
Email: bbb@medicine.wisc.edu

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Abstract

INTRODUCTION: Motor function has correlated with longevity and functionality; however, there is limited research on those with Alzheimer's disease (AD). We studied the association between motor functionality and AD pathology in primary motor and medial temporal cortices.

METHODS: A total of 206 participants with a clinical diagnosis of cognitively healthy, AD, or mild cognitive impairment (MCI) underwent imaging and motor assessment. Linear regressions and analyses of variance were applied to test the prediction from AD imaging biomarkers to motor performance and the diagnosis group differences in motor performance.

RESULTS: Increased neurodegeneration was associated with worsening dexterity and lower walking speed, and increased amyloid and tau were associated with worsening dexterity. AD and MCI participants had lower motor performance than the cognitively healthy participants.

DISCUSSION: Increased AD pathology is associated with worsening dexterity performance. The decline in dexterity in those with AD pathology may offer an opportunity for non-pharmacological therapy intervention.

KEYWORDS

Alzheimer's disease pathology, dexterity performance in clinical and preclinical Alzheimer's disease, magnetic resonance imaging, motor decline in Alzheimer's disease, motor function, physiotherapy, positron emission tomography imaging

Highlights

- Noted worsening dexterity performance was associated with greater Alzheimer's disease (AD) pathology (tau, amyloid beta, and neurodegeneration) in primary motor cortices.
- Similarly, increased neurodegeneration and tau pathology in parahippocampal, hippocampal, and entorhinal cortices is associated with worsening dexterity performance.

- Motor performance declined in those with clinical and preclinical AD among an array of motor assessments.

1 | INTRODUCTION

Alzheimer's disease (AD) has been known to negatively affect motor functions including speech and facial expressions, rigidity, gait, and posture, leading to bradykinesia and tremor.[1] Although these have traditionally been thought to manifest late in the disease course, improvements in motor assessment tools and earlier disease diagnosis have contributed to increasing awareness of early motor performance decline in mild to moderate AD.[2] Moreover, motor function decline in AD may impact disease morbidity and caretaker fatigue. Motor decline is a ubiquitous, though variable, process as individuals age. Studies have shown that various motor function assessments may be good predictors of elderly longevity and functionality in those with normal cognitive status.[3,4] Early motor performance decline may also be related to the accrual of AD pathology, such as amyloid beta (Aβ) plaques and tau tangles, which accumulate decades prior to the onset of clinical symptoms.[5] However, few studies have examined the pathological correlates of motor decline among those with impaired cognition, particularly in those with mild cognitive impairment (MCI) and AD. Existing studies on various motor dexterity, strength, and agility assessments have limited generalizability, as they have incorporated only a small number of participants, often with clinically diagnosed AD or MCI.[6–13] As such, we sought to address this gap in knowledge and examine the association between AD pathology and clinical motor function using a large cohort that is well characterized along the AD clinicopathologic spectrum.

To test the relationship between AD pathology and motor function, we leveraged data from the National Institutes of Health (NIH)–funded Alzheimer's Disease Connectome Project (ADCP). Participants in the ADCP underwent comprehensive neuroimaging, neuropsychological testing, and motor function assessments of grip strength, walking speed, and dexterity performance with the NIH Toolbox.[14] We hypothesized that those with greater AD pathology in primary motor cortices would have poorer motor performance overall. A secondary analysis tested whether motor performance was associated with worse clinical status along the AD continuum. We hypothesized that worse motor function would be associated with worse cognitive status.

2 | METHODS

2.1 | Participants

Participants along the AD clinical and biologic continuum were enrolled in the ADCP, which collected data across two academic centers (University of Wisconsin and Medical College of Wisconsin), recruiting from established cohorts as well as from the surrounding community. Exclusion criteria included those under age 55, non-English speakers, magnetic resonance (MR) imaging exclusionary biohardware or body habitus, inability to complete motor assessments, those without a secondary informant, and those with an additional non-AD neurological condition such as Parkinson's, chronic migraine, multiple sclerosis, meningitis, hydrocephalus, and so forth. A total of 206 participants were included in this study.

2.2 | Clinical diagnosis

Participants completed the majority of components of the National Alzheimer's Coordinating Center (NACC) Uniform Data Set[15] including self-reported demographic information, and extensive cognitive function tests including the Montreal Cognitive Assessment[16] (MoCA), the Craft Story 21 Immediate and Delayed Recall, category fluency tests, Trail Making Test Parts A and B, Neuropsychiatric Inventory Questionnaire (NPI-Q), Geriatric Depression Scale (GDS), and a functional assessment after interviewing a secondary informant on participants' independence and ability to complete activities of daily living (ADL) and instrumental activities of daily living (IADL). Participants also completed the NIH Toolbox motor, cognitive, and emotional assessments. Participant diagnosis of MCI, AD, or cognitively healthy was determined per the National Institute on Aging–Alzheimer's Association criteria,[17,18] and reviewed by a team of physicians, neuropsychologists, and nurse practitioners at a consensus diagnosis conference.

2.3 | AD imaging biomarker assessment

All 206 participants underwent T1-weighted MR imaging. A subgroup of 61 and 58 participants underwent additional [C-11] Pittsburgh compound B (PiB) positron emission tomography (PET) and [F-18]Flortaucipir PET to assess Aβ and tau pathology, respectively. MR imaging was completed concurrently with cognitive and motor assessment visits. PET imaging was collected within a year of MR imaging and motor assessments. T1-weighted scans were processed using FreeSurfer v6.0 to estimate regional cortical thickness as an indicator of neurodegeneration.[19] [C-11]PiB distribution volume ratios (DVR) were estimated using Logan graphical analysis with cerebellar gray matter (GM) as the reference region. Amyloid positivity was defined as the average cortical PiB DVR $\geq$1.19 using a global composite from the following brain regions: bilateral anterior and posterior cingulate cortex, the precuneus, the angular gyrus, supramarginal gyrus, middle

and superior temporal gyrus, and the frontal medial orbital gyrus.[20] [F-18]Flortaucipir standardized uptake value ratios (SUVR; inferior cerebellar GM reference region) were assessed. Tau positivity was determined to be ≥ 1.29 using the threshold of two standard deviations (SDs) above the volume weight means of the anterior parahippocampal SUVRs within our amyloid negative cohort. Regions of interest (ROIs) to assess neurodegeneration included: entorhinal, parahippocampal, and precentral cortices. To further assess tau and amyloid burden we used hippocampal, parahippocampal, and precentral ROIs.

2.4 | Motor function assessment

Motor function was assessed using NIH Toolbox tests including the 2-minute walking, 9-hole pegboard, and dynamometer grip assessments.[14] These assessments were used to analyze walking speed, dexterity, and strength, respectively. Participants did not have to complete all three motor assessments to be included in the analysis. Motor performance was analyzed using participants' uncorrected standardized scores from participant-reported dominant hand performance, with higher scores indicating better performance.

2.5 | Statistical analysis

Independent two-sample *t* test was used to compare the precentral, parahippocampal, and hippocampal biomarker burden between the biomarker (Aβ or tau) positive versus negative groups. Linear regression models were used to assess the relationships between the underlying cortical burden of AD biomarker pathology in primary motor cortices and the medial temporal lobe and participants' performance in each NIH motor assessment. Initial models included all participants regardless of diagnosis or biomarker status. Subsequent linear regression was performed only in the cognitively healthy cohort to determine whether relationships were present in individuals with no clinical impairment. The age and sex of participants were treated as covariates for these models. Due to high correlations between the ROIs, each ROI was included in a regression model separately. The Benjamini–Hochberg false discovery rate (FDR) method[21] was applied to adjust for the inflated type I error associated with multiple tests. One-way analysis of variance (ANOVA) and post hoc Tukey tests were used to compare motor assessment performances among the consensus-designated cognitive groups (cognitively healthy, MCI, and AD).

3 | RESULTS

3.1 | Sample characteristics

This study included data from 206 participants, aged 55 to 90 years (mean = 66.9, SD = 8.1). Participants were mostly female (*n* = 113, 54.9%), self-identified as White (*n* = 187, 90.8%), and cognitively healthy (*n* = 122, 59.2%). Ten participants (4.9%) self-identified as Black and two (1.0%) self-identified as Asian. Twenty-three (37.7%) of the 61 participants who underwent the PiB PET were Aβ positive, and 13 (22.4%) of the 58 participants who underwent the tau PET were tau positive. The sample characteristics of the study cohort and each Aβ and tau subgroup are summarized in Table 1.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed existing literature using online publishing databases (e.g., PubMed) to investigate the current understanding of motor function decline in those with Alzheimer's disease (AD). These relevant citations are included. We noted a pattern of declining motor functions with worsening cognition status and a dearth of research into the AD pathology presence in brain cortices and its relation to motor function.
2. **Interpretation**: Our findings led to a hypothesis that the greater presence of underlying AD pathology, particularly in primary motor cortices, was associated with declining motor performance. This hypothesis is consistent with non-clinical and clinical findings currently in the public domain.
3. **Future directions**: The article proposes a framework for the generation of hypotheses and additional studies. Examples include investigating: (a) the pathophysiology time course of AD pathology deposition in motor cortices and (b) the utility of physiotherapy treatment for motor function deficits in those with AD.

3.2 | AD biomarkers

Lower thickness in the precentral, parahippocampal, and entorhinal cortex was associated with worse dexterity (p value = 0.0029, 0.0036, 0.000, respectively; see Table 2). Neurodegeneration in the precentral gyrus was associated with slower walking speed (p value = 0.0013); however, this relationship was not observed in the parahippocampal gyrus or entorhinal cortex ROIs. Grip strength did not show statistically significant predictive outcomes with underlying cortical atrophy. There was no relationship observed between grip strength, walking speed, nor dexterity and neurodegeneration in the precentral or parahippocampal gyri or entorhinal cortex ROIs for those with healthy cognition (Table 3).

There was a significant difference in precentral Aβ pathology between the amyloid positive and negative groups (*t*-statistic: 10.7, p value: < 0.0001). Of the 23 Aβ positive participants, the average precentral Aβ burden within primary motor cortices was increased (DVR mean ± SD = 1.3 ± 0.2) compared to their AD pathology negative peers (DVR mean ± SD = 1.0 ± 0.0). Increased Aβ burden in primary

TABLE 1 Participant demographics of each imaging cohort.

Patient characteristics for each imaging cohort			
	MRI	**Aβ**	**Tau**
Participants, *n*	206	61	58
Sex, *n* (%)			
Female	113 (54.9)	27 (44.3)	34 (58.6)
Male	93 (45.1)	34 (55.7)	24 (41.4)
Age (Years)	69.9 ± 8.0	69.4 ± 8.4	69.7 ± 8.3
Race			
White	187 (90.8)	57 (93.4)	54 (93.1)
Black	10 (4.9)	2 (3.3)	3 (5.2)
Asian	2 (1.0)	0 (0.0)	0 (0.0)
Other	7 (3.3)	2 (3.3)	1 (1.7)
Cognitive diagnosis			
Healthy	129 (62.6)	35 (57.4)	33(56.9)
MCI	41 (19.9)	17 (27.9)	17 (29.3)
AD	36 (17.5)	9 (14.8)	8 (13.8)
Other			
Assessment performance (Avg ± SD)			
Grip strength	96.9 ± 10.9	98.1 ± 10.6	97.8 ± 10.5
Walking speed	92.1 ± 13.6	91.4 ± 13.3	89.7 ± 12.0
Dexterity	94.0 ± 13.9	93.3 ± 18.9	92.2 ± 13.0
Biomarker positive *n*, (%)	–	23 (37.7)	13 (22.4)
Biomarker burden, SUVR, (Avg ± SD)			
Precentral cortex	–	1.1 ± 0.1	0.98 ± 0.1
Parahippocampus	–	1.1 ± 0.2	1.2 ± 0.2
Hippocampus/entorhinal cortex	–	1.1 ± 0.1	1.3 ± 0.2
Cortical thickness in ROIs, mm, (Avg ± SD)			
Precentral cortex	2.46 ± 0.1	2.45 ± 0.1	2.44 ± 0.1
Parahippocampus	2.58 ± 0.2	2.60 ± 0.2	2.60 ± 0.2
Hippocampus/entorhinal cortex	3.22 ± 0.4	3.22 ± 0.4	3.23 ± 0.4

Note: All 206 study participants underwent MR imaging. Cognitive diagnosis was determined in lieu of pathology imaging within categories: cognitively healthy, MCI, and AD. Each PET imaging cohort represents a subset of participants who underwent additional PET imaging.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; MR, magnetic resonance; PET, positron emission tomography; ROI, region of interest; SD, standard deviation; SUVR, standardized uptake value ratio.

motor cortices was associated with worse participant dexterity (Table 2: p value = 0.0010). Interestingly, increased parahippocampal (p value = 0.0461, $\alpha < 0.017$) and hippocampal (0.5213, $\alpha < 0.019$) Aβ burden was not associated with reduced dexterity. Increased Aβ burden in hippocampal, parahippocampal, or primary motor ROIs did not show significant predictive relationships to walking speed or grip strength. There was no relationship observed between grip strength, walking speed, nor dexterity and Aβ burden in precentral, parahippocampal, or hippocampal ROIs for those with healthy cognition (Table 3).

There was a significant difference in precentral tau burden between the tau positive and negative groups (t-statistic: 5.1, p value < 0.0001). Of the 13 tau-positive participants, the average precentral tau burden within primary motor cortices was increased (SUVR = 1.1 ± 0.2) compared to their AD pathology-negative peers (SUVR = 0.9 ± 0.1). Increased tau burden in primary motor, parahippocampal, and hippocampal ROIs was associated with worse dexterity (Table 2: p value < 0.0001, = 0.0002, and = 0.0111, respectively). Increased tau burden in primary motor, parahippocampal, and hippocampal ROIs was not significantly associated with worse performance in either walking speed or grip strength assessments. There was no relationship observed between grip strength, walking speed, nor dexterity and tau burden in precentral, parahippocampal, or hippocampal ROIs for those with healthy cognition (Table 3).

TABLE 2 This table includes results from linear regression analysis using motor performance as the predictor and biomarker burden in select ROIs as outcomes.

Linear regression analysis predicting each NIH motor assessment outcome by ROI biomarker burden						
	Grip		Walking speed		Dexterity	
Neurodegeneration	*β*	*p*	*β*	*p*	*β*	*p*
Precentral cortex	0.003	0.957	0.227	**0.001**	0.213	**0.003**
Parahippocampus	0.109	0.054	0.087	0.232	0.212	**0.004**
Entorhinal cortex	0.079	0.166	0.127	0.082	0.278	**0.0001**
Aβ burden						
Precentral cortex	0.071	0.464	0.191	0.157	0.426	**0.001**
Parahippocampus	0.080	0.403	0.185	0.166	0.263	0.046
Hippocampus	0.059	0.532	0.114	0.391	0.085	0.521
Tau burden						
Precentral cortex	0.105	0.256	0.101	0.474	0.530	**<0.0001**
Parahippocampus	0.045	0.623	0.010	0.945	0.477	**0.0002**
Hippocampus	0.124	0.182	0.012	0.932	0.341	**0.011**

Note: All models controlled for participant age and sex and corrected for multiple comparisons using the Benjamini–Hochberg (1995) procedure. The NIH motor assessment outcomes included the grip strength dynamometer, 2-minute walking speed, and 9-hole peg dexterity tests.
Abbreviations: Aβ, amyloid beta; NIH, National Institutes of Health; ROI, region of interest. Statistically significant P values are bolded.

TABLE 3 This table includes results from linear regression analysis of our cognitively healthy subgroup using motor performance as the predictor and biomarker burden in select ROIs as outcomes.

Linear regression analysis predicting each NIH motor assessment outcome by ROI biomarker burden for those cognitively healthy						
	Grip		Walking speed		Dexterity	
Neurodegeneration	*β*	*p*	*β*	*p*	*β*	*p*
Precentral cortex	0.046	0.519	0.181	0.036	0.172	0.072
Parahippocampus	0.135	0.135	0.053	0.544	4.147	**0.015**
Entorhinal	0.053	0.462	0.111	0.212	0.283	0.003
Aβ burden						
Precentral cortex	−0.082	0.508	−0.205	0.294	−0.025	0.897
Parahippocampus	−0.165	0.173	−0.195	0.278	−0.158	0.408
Hippocampus	−0.059	0.622	0.091	0.686	0.021	0.911
Tau burden						
Precentral cortex	−0.120	0.321	−0.386	0.046	−0.065	0.754
Parahippocampus	−0.251	0.036	−0.195	0.276	−0.220	0.292
Hippocampus	−0.141	0.296	−0.173	0.440	−0.401	0.072

Note: All models were controlled for participant age and sex and corrected for multiple comparisons using the Benjamini–Hochberg (1995) procedure. The NIH motor assessment outcomes included the grip strength dynamometer, 2-minute walking speed, and 9-hole peg dexterity tests.
Abbreviations: Aβ, amyloid beta; NIH, National Institutes of Health; ROI, region of interest.

3.3 | Clinical diagnosis

Mean grip strength performance was significantly different between the cognitively healthy and MCI group (p value = 0.02, 95%). No significant difference was seen between the cognitively healthy and AD group (p value = 0.13), nor between the MCI and AD groups (p value = 0.79). Tukey honestly significant difference testing for multiple comparisons found that the mean value of walking speed was significantly different between cognitively healthy and MCI groups (p value = 0.019) and between cognitively healthy and AD groups (p value = 0.016). Similarly, dexterity motor assessments showed statistically significant differences in those with MCI and AD diagnosis relative to their cognitively healthy peers (p value = 0.0001, < 0.0001). No significant differences were found between the MCI and AD groups across all three motor performance measures (p value = 0.79, 1.0, 0.94). These findings are summarized in Figure 1.

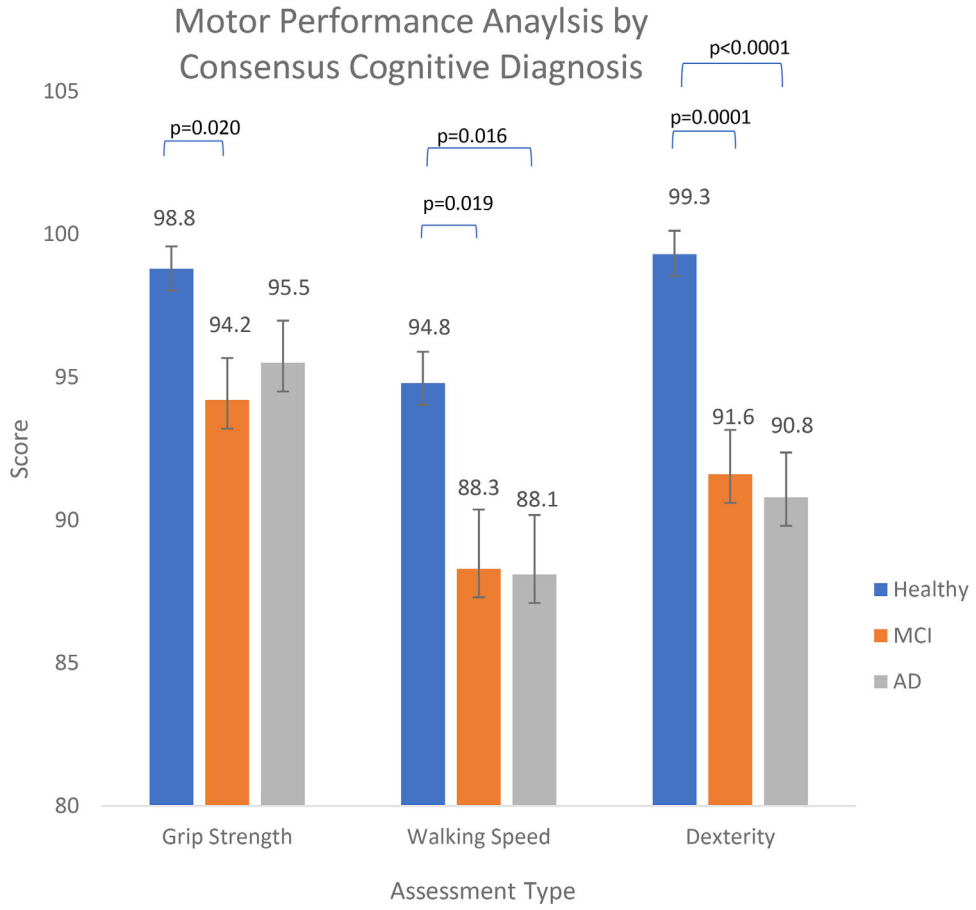

FIGURE 1 Analysis of variance least square means and Tukey pairwise comparison of motor assessment performance by each consensus cognition group: cognitively healthy, mild cognitive impairment (MCI), and Alzheimer's disease (AD) controlling for participant age and sex. National Institutes of Healthy motor assessments include grip strength dynamometer, 2-minute walking speed, and 9-hole dexterity. Our models demonstrated a statistically significant difference in grip strength, walking speed, and dexterity performance between the cognitive healthy and AD cohorts. Similarly, we see a statistically significant difference in walking speed and dexterity performance between the cognitively healthy and MCI cohorts.

4 | DISCUSSION

The present study found that the presence of tau and Aβ biomarker burden and neurodegeneration in primary motor cortices was associated with worse dexterity. In contrast to our hypotheses, tau and Aβ burden in primary motor cortices were not shown to be associated with walking speed and grip strength performance. Cortical neurodegeneration in primary motor regions was related to performance in both dexterity and walking speed assessments, such that increased cortical atrophy was associated with worse dexterity and walking speed. Grip strength was not shown to be associated with tau, Aβ, or cortical atrophy in primary motor cortices.

Our findings also showed that increases in neurodegeneration in entorhinal and parahippocampal ROIs and increases in tau pathological burden in hippocampal and parahippocampal regions were associated with worse dexterity. Motor task performance is complex and demands integration across a variety of cortical regions. Fine motor tasks likely mandate increased supplemental cortical input and executive cognitive functions including attention, working memory, and cognitive flexibility.[22,23] These functions are also known to be compromised in AD, and thus it is plausible that reduced dexterity in those with increased AD pathology is due to subtle disruptions in these higher order cognitive processes.[24] To this end, these associations were not mimicked when analyzing our cognitively healthy subgroup, suggesting that these higher order cognitive functions may still be intact for these individuals. This may also explain why we did not see a similar association in grip strength, a relatively straightforward task. Similarly, walking speed may be preserved given the large input from the cerebellum, a region that is largely spared from AD pathology until far later in the disease course.[22]

4.1 | Research in context

Despite the presence of amyloid and tau pathology in other cortical areas, primary motor cortices are generally spared from early amyloid and tau accumulation until the later stages of AD.[25,26] This may suggest that motor function would deteriorate as AD pathology accumulates

and cognition declines. Our study findings partially supported this hypothesis, as amyloid and tau pathology in the precentral gyrus, as well as tau burden in the hippocampus and parahippocampus, was associated with lower dexterity. Although we did not observe this relationship with regard to walking speed and grip strength, post hoc analysis showed that all indexed motor assessments differed between cognitively unimpaired individuals and those with MCI and AD. Our cognitively healthy subgroup analysis demonstrated a lack of association between motor assessment performance and underlying AD pathology and neurodegeneration, suggesting that this relative susceptibility of fine-motor function to AD pathology presence may be silent until early clinical disease. There is mounting evidence that fine-motor function decline is seen in tandem with clinically detectable cognitive decline for those with AD.[1,8,27–30] Our findings suggest a window of motor performance decline along the disease course, and a possible opportunity to implement treatment.

Non-pharmacologic therapeutic interventions, such as physiotherapy, have shown promise in improving motor performance and physical function in those with decreased motor function related to cognitive decline.[12,31–33] These studies also demonstrated an improvement in instrumental and non-instrumental activities of daily living (IADLs, ADLs) for those with AD. These limitations in I/ADLs are significant sources of AD treatment costs and caregiver fatigue.

Continued recognition of the decline in fine-motor function in those with clinical and pre-clinical AD is paramount. It could offer a novel opportunity to provide evidence-based, non-invasive treatment options to families that limit or slow functional decline. Further studies are needed to illuminate AD pathology progression and its role in motor function pathway disruptions.

4.2 | Limitations

Participant consensus diagnosis was determined without the use of MR and PET imaging data available. As such, diagnosis relied heavily on clinical cognitive and functional data, without knowledge of participant AD pathology. Additionally, participants who were unable to complete any of the studied motor assessments were excluded from our study cohort, likely underrepresenting participants who are severely frail or have gross motor deficits. The included motor assessments examined specific, simple motor tasks. They do not encompass the entirety of measurable motor task performance nor the holistic picture of motor performance change in AD or related dementias. Alternative motor tasks should be tested to elucidate if better-suited tasks are more valid.

Our PET imaging cohorts were smaller than our larger MR imaging cohort and thus may reduce the generalizability of these findings. Additionally, our PET imaging was collected within 1 year of motor assessments and thus there may be a slight variation in in vivo cortical biomarker burden at the time of motor assessments and imaging. Last, our data cohort comprised a predominantly White demographic distribution which is not representative of the AD population as a whole.

5 | CONCLUSION

Our study evaluated the underlying brain AD pathology burden and cortical structural changes in primary motor cortices and its relation to motor performance in individuals along the AD continuum. Our findings are in concordance with previous studies demonstrating worsening motor task performance is associated with underlying AD biomarker burden or neurodegeneration. Additionally, our results support previous studies[6–11] which demonstrate declining motor performance in those with AD or MCI diagnosis compared to their age-matched cognitively healthy peers.

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CONFLICT OF INTEREST STATEMENT

Dr. Barbara Bendlin has received precursors and tracers from AVID Radiopharmaceuticals including PET precursor for AV1451 which was used in the current study. She has also received honorariums from UC-Irvine, the University of Pittsburgh, the University of Illinois, and the Karolinska Institute for lectureships. Dr. Bendlin has received payment from New Amsterdam Inc. for consulting fees and from the Alzheimer's Association for attendance at their event. She serves as the chair of the ADRC research education national committee, the CLSA-Healthy Brains Healthy Aging/Weston Advisory Committee, and Rush's ADRC external advisory board committee. Dr. Nathaniel A. Chin has received consulting fees from New Amsterdam Inc. He also serves as a member of the Medical & Scientific Advisory Board of the Wisconsin Alzheimer's Association and Alzheimer's Foundation of America. Dr. Ozioma C. Okonkwo is currently the treasurer of the International Neuropsychological Society. Dr. Tobey J. Betthauser has received an honorarium from Intermountain Healthcare and the NIH. He has also received travel support from the University College London, the Alzheimer's Association, and the NIH. The remaining authors have no disclosures. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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