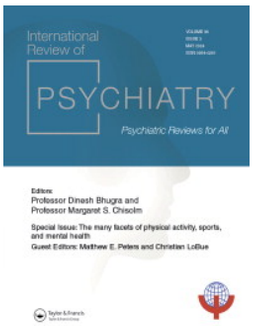

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RESEARCH ARTICLE

Impact of motor dysfunction on neuropsychiatric symptom profile in patients with autopsy-confirmed Alzheimer's disease

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ABSTRACT

Motor dysfunction, which includes changes in gait, balance, and/or functional mobility, is a lesser-known feature of Alzheimer's Disease (AD), especially as it relates to the development of neuropsychiatric symptoms (NPS). This study (1) compared rates of NPS between autopsy-confirmed AD patients with and without early-onset motor dysfunction and (2) compared rates of non-AD dementia autopsy pathology (Lewy Body disease, Frontotemporal Lobar degeneration) between these groups. This retrospective longitudinal cohort study utilized National Alzheimer's Coordinating Center (NACC) data. Participants ($N=856$) were required to have moderate-to-severe autopsy-confirmed AD, Clinical Dementia Rating-Global scores of ≤1 at their index visit, and NPS and clinician-rated motor data. Early motor dysfunction was associated with significantly higher NPI-Q total scores ($T=4.48$, $p<.001$) and higher odds of delusions (OR [95%CI]: 1.73 [1.02–2.96]), hallucinations (2.45 [1.35–4.56]), depression (1.51 [1.11–2.06]), irritability (1.50 [1.09–2.08]), apathy (1.70 [1.24–2.36]), anxiety (1.38 [1.01–1.90]), nighttime behaviors (1.98 [1.40–2.81]), and appetite/eating problems (1.56 [1.09–2.25]). Early motor dysfunction was also associated with higher Lewy Body disease pathology (1.41 [1.03–1.93]), but not Frontotemporal Lobar degeneration (1.10 [0.71–1.69]), on autopsy. Our results suggest that motor symptoms in early AD are associated with a higher number and severity of NPS, which may be partially explained by comorbid non-AD neuropathology.

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Motor dysfunction; neuropsychiatric symptoms; Alzheimer's disease

Introduction

Alzheimer's Disease (AD) is a leading cause of public health burden in older persons and families worldwide (GBD 2016 Neurology Collaborators, 2019). Recent evidence suggests that motor symptoms may be one of the first presentations of AD (Albers et al., 2015). Moreover, nearly half of patients with AD present with motor symptoms at some point in their disease course (Scarmeas et al., 2004). Common motor symptoms in AD include slowing of gait, decline in functional mobility, poor balance, and reduced grip strength (Koppelmans et al., 2022). Presence of motor symptoms in AD is associated with increased risk for cognitive and functional decline, institutionalization, and death (Scarmeas et al., 2004; Siokas et al., 2022). Beyond poor outcomes in patients, motor disturbance and poor patient mobility are known to increase the burden and decrease the quality of life for caregivers (Gómez-Gallego & Gómez-Gallego, 2021; Vu et al., 2022).

While archival case reports suggest that early clinical motor signs in patients with AD may be associated with more severe post-mortem AD pathology in the motor cortex (Horoupian & Wasserstein, 1999), more research is needed to characterize the long-term trajectories of these patients. In particular, the relationship between motor symptoms and non-cognitive neuropsychiatric symptoms (NPS) is an important area of study given preliminary research suggesting that motor symptoms and hyperactive NPS (i.e. agitation, disinhibition) may be associated with common neuroimaging alterations such as increased functional connectivity in the anterior cingulate cortex and right insula areas of the salience network (Balthazar et al., 2014; Chen et al., 2021). A recent study suggested that motor signs in

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both AD and vascular dementia patients may be associated with agitation, depressed mood, and hallucinations, but the study did not consider the timing of the onset of motor symptoms in relation to dementia progression and was not specific to AD patients (Al-Harrasi et al., 2021). Given that NPS are associated with more severe clinical and neuropathological outcomes in dementia patients (Canevelli et al., 2017; Shaw et al., 2024), more research is needed to characterize the prevalence and severity of non-cognitive NPS in patients with motor dysfunction in early AD (Canevelli et al., 2017; Shaw et al., 2024).

We aimed to fill this gap by using data from the National Alzheimer's Coordinating Center (NACC). Our retrospective cohort analysis sought to (1) compare rates of non-cognitive NPS between autopsy-confirmed AD patients with and without motor dysfunction early in their disease course and (2) compare rates of comorbid neuropathology consistent with non-AD dementias, such as Lewy Body disease and Frontotemporal Lobar degeneration, between these groups. An exploratory aim was to examine the relationship between specific presenting motor symptoms (gait disorder, falls, tremors, and slowness) and the presence of NPS.

With respect to our first objective, we hypothesized that patients who presented with motor dysfunction early in their AD course would have more severe non-cognitive NPS compared to patients who did not present with motor dysfunction. Furthermore, based on prior research (Cerejeira et al., 2012), we hypothesized that specific NPS such as agitation and disinhibition would be elevated in early-AD patients with motor dysfunction. Finally, we hypothesized that patients who presented with early motor dysfunction in AD would have higher rates of co-occurring Lewy Body disease and Frontotemporal Lobar degeneration on autopsy, given their association with non-cognitive NPS in early AD (Palmqvist et al., 2023; Shaw et al., 2024). By providing a better understanding of the NPS profile in patients with motor dysfunction in early AD, our findings may help inform both the prognosis of the disease course and more targeted and personalized intervention in this patient group.

Methods

Participants and study design

This retrospective longitudinal cohort study utilized participant data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). We analyzed clinical and neuropathological data from 37 past and present Alzheimer's Disease Research Centers (ADRCs) funded by the National Institute on Aging collected between March 6, 2015, and August 2023, between which data on clinician-rated motor symptoms were available. All contributing ADRCs were required to obtain written informed consent from their participants and obtain approval from their institutional review board before submitting data to the NACC. In-person and telephone data were collected by clinical personnel and trained physicians used a standardized evaluation protocol. See Figure 1 for a comprehensive overview of inclusion and exclusion criteria at all levels of analysis leading to the final study groups included in this analysis.

Alzheimer's Disease (AD) and Dementia neuropathologic data

Participants were included in this study if they had 'intermediate' or 'high' ratings of AD-related neuropathology on the NIA-AA AD Neuropathologic Change score (ABC score of 2–3, NACC variable NPADNC), which was used to define AD diagnosis (Montine et al., 2012). The ABC score is a composite of three components of AD pathology: amyloid-β deposits ('A' for Amyloid), neurofibrillary degeneration ('B' for Braak stage), and neuritic plaques ('C' for CERAD rating of plaque distribution). These three components are combined, and cases are identified as having high, intermediate, or low AD neuropathological change. The ABC score is rated on a scale of 0–3 and is associated with cognitive decline in older adults (Serrano-Pozo et al., 2016). AD measures from the NACC neuropathologic dataset show good agreement across centers (average weighted κ =.88) (Montine et al., 2016).

Other neuropathologic variables included assessments of Frontotemporal Lobar and Lewy Body neuropathologic change. 827 (96.5%) of study participants had data for at least one of these measures of neuropathology. To measure Frontotemporal Lobar degeneration, the NACC variable NPFTDTAU was utilized, which assesses for the presence of Tau pathology, one of the most common pathologic classes of Frontotemporal Lobar Dementia (Bahia et al., 2013). Lewy Body disease pathology was measured by the NACC variable NACCLEWY, which assesses for the presence of Lewy Bodies in the brainstem, limbic system, neocortex, and other unspecified regions. In line with current criteria for positive diagnosis of Lewy Body pathology (Attems

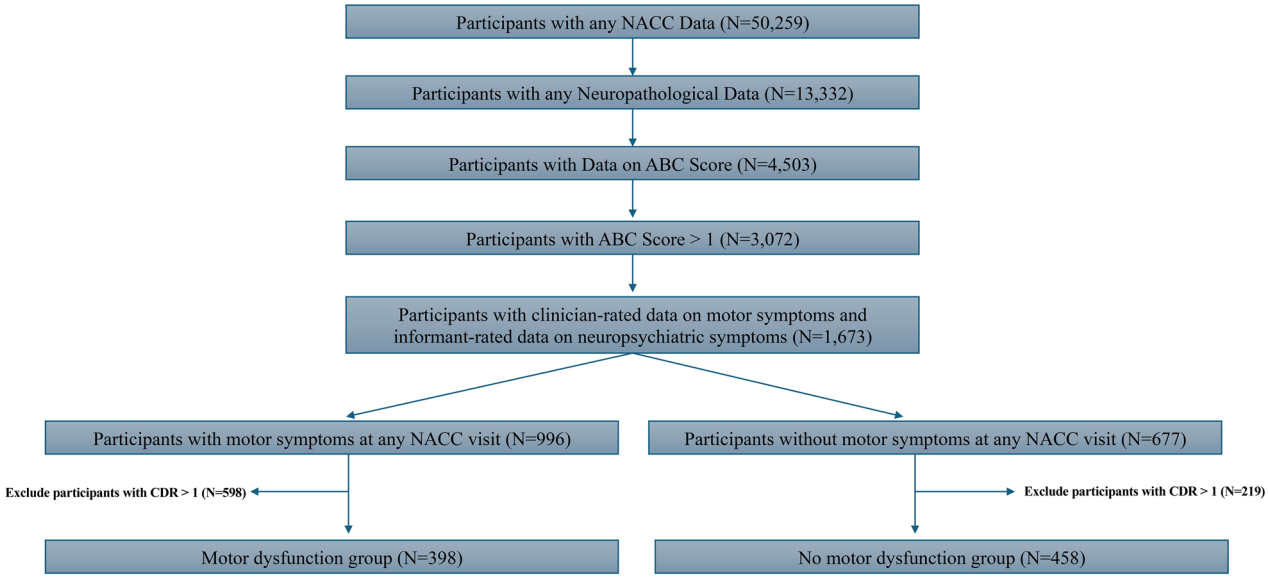

Figure 1. Eligibility criteria for NACC participants included in this analysis ($N = 856$). Participants were included if they (1) had moderate or severe Alzheimer's neuropathological change found on autopsy (ABC Score) and (2) scored ≤ 1 on the Clinical Dementia Rating-Global (CDR-G) at their index clinical visit.

et al., 2021; Mrak & Griffin, 2007), the NACCLEWY variable was dichotomized such that identification of Lewy Body neuropathologic change in the limbic system and/or neocortex was coded as positive for Lewy Body disease pathology.

Motor dysfunction symptoms

For inclusion in this study, participants were also required to have available NACC clinical data on clinician-defined motor symptoms. To measure motor dysfunction, the NACC variable DECCLMOT was used, a dichotomous yes/no clinician-rated variable using the prompt, 'Based on the clinician's judgement, is the subject currently experiencing any motor symptoms?' The motor symptoms that this variable was intended to assess included gait disorder, falls, tremor, and slowness. The first visit at which participants presented with clinician-defined motor symptoms was isolated, and these participants were included in the 'motor dysfunction group'. We further divided the motor dysfunction group into four groups (gait disorder, falls, tremor, and slowness) based on the NACC variable MOTF, for which clinicians 'Indicate the predominant symptom that was first recognized as a decline in the subject's motor function.' The Clinical Dementia Rating (CDR®) Dementia Staging Instrument (Morris, 1993) was completed by participants at all clinical visits, and we excluded participants whose first presentation with motor symptoms occurred at a visit in which they also received a CDR-Global (CDR-G) (Albers et al., 2015) score >1 to assess only those participants who presented with motor dysfunction earlier in the disease course before the onset of more severe cognitive decline. Participants who did not present with clinician-defined motor symptoms at any NACC visit were included in the 'no motor dysfunction group', and data from their initial clinical visit was utilized. Participants without motor dysfunction with a CDR-G > 1 at their initial clinical visit were also excluded.

Neuropsychiatric symptoms

The primary outcome variable was clinical data from the Neuropsychiatric Inventory-Questionnaire (NPI-Q), an informant-based brief assessment of neuropsychiatric symptomatology commonly used in routine clinical practice settings (Kaufer et al., 2000). The NPI-Q assesses the presence and severity of 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating. This study utilized both individual NPI-Q domain items assessing for the presence or absence of each NPS as well as a summation of severity scores (NPI-Q total severity score), which ranges from 0–36 and is representative of the total burden of neuropsychiatric symptoms. The NPI-Q has shown strong content and concurrent validity, interrater reliability, test-retest reliability, and

internal consistency in AD populations (Cummings et al., 1994; Lai, 2014). NPI-Q scores were assessed at the clinical visit coinciding with the emergence of motor symptoms in the motor dysfunction group, and at the first clinical visit for the no motor dysfunction group.

Statistical analysis

First, we examined the associations between presentation with motor dysfunction during early AD (CDR-G ≤ 1) and total severity of NPS. To compare total NPS between AD patients with and without early motor dysfunction, we performed a linear regression with total severity score on the NPI-Q as the outcome variable and motor dysfunction group as the predictor variable with covariables of sex, age at index clinical visit, education, and APOE ε4 genotype (number of alleles). Next, to compare rates of specific NPS between AD patients with and without early motor dysfunction, we performed a logistic regression with each specific NPS as the outcome variable (yes/no) and motor dysfunction group as the predictor variable with the same covariates as above. To compare rates of non-AD dementia pathologies between AD patients with and without early motor dysfunction, we performed a logistic regression with neuropathological evidence of Lewy Body disease and Frontotemporal Lobar degeneration (yes/no) as the outcome variables and motor dysfunction group as the predictor variable and the same covariates with the addition of age at death. Finally, to assess whether presence of specific motor symptoms (gait disorder, falls, tremor, and slowness) were associated with presence and severity of NPS, we performed linear regressions with total severity score on the NPI-Q as the outcome variable and presence of each motor symptom as the predictor variable and performed logistic regressions with each specific NPS as the outcome variable and presence of each motor symptom as the independent variable (with the same covariates as above). For these exploratory analyses, the Bonferoni of multiple testing correction approach was used (Noble, 2009).

For all analyses, the no motor dysfunction group was used as the reference group, and adjusted odds ratios were calculated for all dichotomous outcome variables. All hypothesis tests were two-sided and were performed at an overall alpha of 0.05. R, version 4.2.1 (R Foundation for Statistical Computing), was used for all analyses (RStudio Team, 2020).

Results

Demographics

Table 1 contains demographic characteristics of participants meeting eligibility criteria. A total of 856 participants were included in the analysis (403 women [47.1%] and 453 men [52.9%]; mean [SD] age, 79.7 [10.7] years). Most participants were white (93.9%) followed by black/African American (5.1%). The mean [SD] education of all participants was 16.1 [2.9] years. The mean [SD] number of NACC visits of all participants was 6.4 [3.7] and the mean [SD] time from index visit to autopsy was 3.4 [1.7] years. 46.3% of participants had at least one high risk APOE ε4 allele.

Of the 856 eligible participants, 46.5% of participants presented with clinician-defined motor symptoms early in their disease course (when CDR-G ≤ 1). Demographic characteristics of participants in the motor dysfunction group ($N = 398$) and no motor

Table 1. Demographic characteristics of NACC participants included in this analysis ($N = 856$). Continuous variables are presented as mean ± *SD*, while dichotomous variables are presented as column-based percentages. Visit age reflects the age at which participants first presented with motor symptoms (motor dysfunction group) and the age at first clinical visit (no motor dysfunction group).

	Motor dysfunction group ($N = 398$)	No motor dysfunction group ($N = 458$)	*T*-value or X^2 statistics	*P*-value
Total NACC visits (Mean ± SD)	6.9 ± 3.8	6.0 ± 3.7	3.4	<.01
Index visit age (Mean ± SD, years)	81.1 ± 10.2	78.5 ± 11.0	2.7	<.01
Age at death (Mean ± SD, years)	84.7 ± 10.1	82.7 ± 10.9	3.2	<.01
Education (Mean ± SD, years)	16.3 ± 2.9	15.8 ± 2.8	2.4	.02
Sex				
Males, *N* (%)	236 (59.3)	217 (47.4)	11.9	<.01
Females, *N* (%)	162 (40.7)	241 (52.3)		
Race				
White, *N* (%)	383 (96.2)	421 (91.9)	7.0	<.01
Black or African American, *N* (%)	13 (3.3)	31 (6.8)		
Asian, *N* (%)	0 (0.0)	3 (0.7)		
Other/Unknown, *N* (%)	2 (0.5)	3 (0.7)		
Number of APOE-ε4 alleles				
0 Alleles, *N* (%)	202 (50.8)	199 (43.5)	7.1	.03
1 Allele, *N* (%)	139 (34.9)	187 (40.8)		
2 Alleles, *N* (%)	25 (6.3)	45 (9.8)		
Predominant motor symptom				
Gait disorder, *N* (%)	130 (32.7)	–	–	–
Falls, *N* (%)	49 (12.3)	–	–	–
Tremor, *N* (%)	101 (25.4)	–	–	–
Slowness, *N* (%)	108 (27.1)	–	–	–

dysfunction group ($N = 458$) are presented in Table 1. Compared to participants without motor dysfunction, participants with early-onset motor dysfunction were found to be significantly older at their index clinical visit, older at death, and have a higher proportion of males. Participants with motor dysfunction were also found to have a lower number of APOE ε4 alleles and a higher number of NACC visits, proportion of white individuals, and years of education. We adjusted for age at index clinical visit, sex, education, number of APOE alleles, and age at death (for neuropathological outcomes) in our analyses. 6.3% of participants in the motor dysfunction group had clinical diagnoses of Parkinson's Disease (NACC variable: PARK) at the index visit.

Table 2. Comparison of informant-rated NPI-Q scores for Alzheimer's Disease participants with and without early motor dysfunction. *$p < .05$; **$p < .01$.

NPI-Q domains, *N* (%)	Motor dysfunction group ($N = 398$)	No motor dysfunction group ($N = 458$)	OR ± 95% CI	*P*-value
Delusions	41 (10.3%)	30 (6.6%)	1.73 ± 1.02 – 2.96*	.045
Hallucinations	36 (9.1%)	21 (4.6%)	2.45 ± 1.35 – 4.56**	<.01
Agitation	97 (24.4%)	109 (23.8%)	1.08 ± 0.76 – 1.52	.68
Depression	146 (36.7%)	132 (28.8%)	1.51 ± 1.11 – 2.06**	<.01
Elation	13 (3.3%)	20 (4.4%)	0.88 ± 0.40 – 1.86	.74
Irritability	130 (32.7%)	123 (26.9%)	1.50 ± 1.09 – 2.08*	.014
Apathy	144 (36.2%)	124 (27.1%)	1.70 ± 1.24 – 2.36**	<.01
Anxiety	136 (34.2%)	143 (31.2%)	1.38 ± 1.01 – 1.90*	.047
Disinhibition	70 (17.6%)	74 (16.2%)	1.25 ± 0.85 – 1.85	.25
Motor disturbance	55 (13.8%)	47 (10.3%)	1.56 ± 0.98 – 2.51	.062
Nighttime behaviors	114 (28.6%)	74 (16.2%)	1.98 ± 1.40–2.81**	<.01
Appetite/ eating problems	92 (23.1%)	83 (18.1%)	1.56 ± 1.09 – 2.25*	.016

Impact of motor dysfunction in early AD on neuropsychiatric symptoms

Participants with motor dysfunction in early AD had significantly higher total severity scores on the NPI-Q (mean [SD]: 3.9 [3.9]) than patients without motor dysfunction (3.0 [3.5]) ($T = 4.5$, $p < .001$). Relative odds of informant-rated presence of each NPS included on the NPI-Q is listed in Table 2 and illustrated in Figure 2. Motor dysfunction in early AD was associated with significantly higher odds of delusions, hallucinations, depression, irritability, apathy, nighttime behaviors, and appetite/eating problems. Presence of agitation, elation, disinhibition, and motor disturbance (repetitive behaviors such as pacing and punding) did not significantly differ between participants with and without early motor dysfunction.

Participants presenting with gait disorder (mean [SD]: 3.8 [3.6]), falls (3.8 [3.4]), tremor (3.6 [4.0]), and slowness (4.3 [4.3]) as their predominant motor symptom all had higher total scores on the NPI-Q compared to participants without motor dysfunction (3.0 [3.5]), three of which reached the threshold for statistical significance (gait disorder: $T = 2.9$, $p < .001$; falls $T = 3.3$, $p < .01$; tremor; $T = 1.7$, $p = .10$; slowness $T = 3.1$, $p < .01$). Table 3 shows the relationship between specific first motor symptoms (gait disorder, tremor, falls, slowness) in early AD and the presence of NPS.

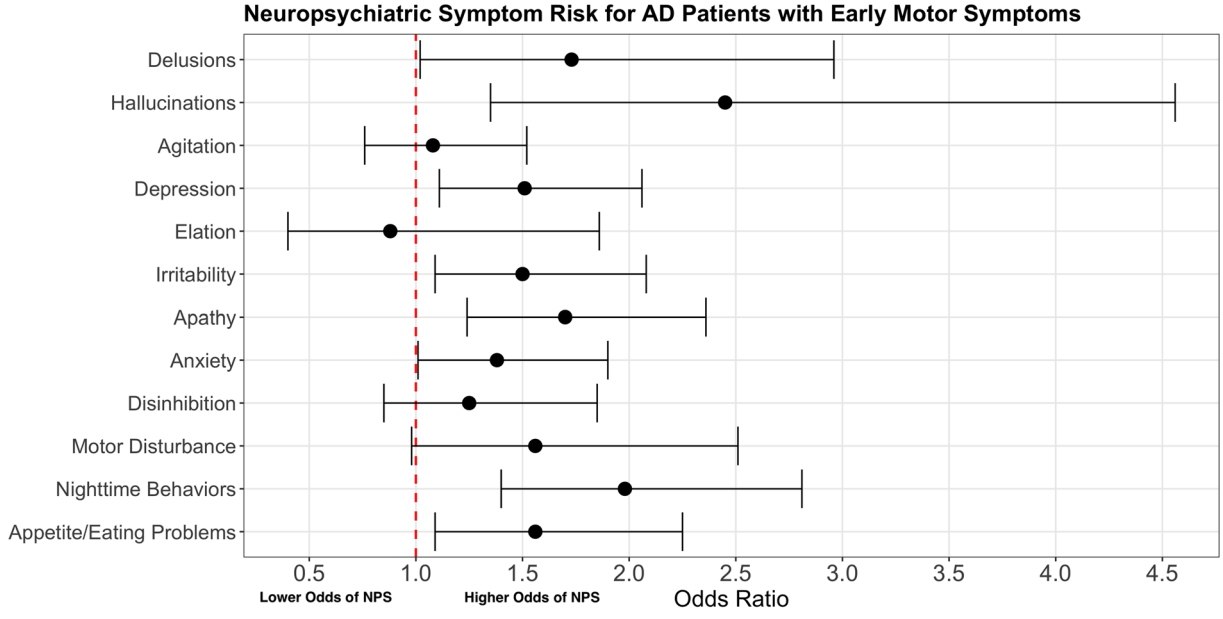

Figure 2. Adjusted odds of presence of neuropsychiatric symptoms (NPS) in participants with clinician-rated motor symptoms in early Alzheimer's Disease (AD). The No motor dysfunction group was used as the reference group (red dotted line).

Table 3. Comparison of neuropsychiatric symptoms (NPS) by first presenting motor symptom group. All percentages are presented as column-based representing the proportion of participants in each motor symptom group with corresponding NPS. *$p < .05$ at the nominal level; **significant after correction for multiple comparisons across all outcomes in this exploratory analysis, $p < .0011$.

NPI-Q domains, *N* (%)	No motor dysfunction group (*N* = 458)	Gait disorder (*N* = 130)	Gait Disorder OR ± 95% CI, *p*-value	Falls (*N* = 49)	Falls OR ± 95% CI, *p*-value	Tremor (*N* = 101)	Tremor OR ± 95% CI, *p*-value	Slowness (*N* = 108)	Slowness OR ± 95% CI, *p*-value
Delusions	30 (6.6%)	18 (13.8%)	2.86 ± 1.42–5.67, .0028*	4 (8.2%)	1.75 ± 0.48–4.99, 0.34	7 (6.9%)	1.22 ± 0.44–2.95, .68	11 (10.2%)	1.74 ± 0.76–3.74, .17
Hallucinations	21 (4.6%)	11 (8.5%)	2.33 ± 0.95–5.42, .054	5 (10.2%)	2.77 ± 0.84–7.83, .068*	8 (7.9%)	2.62 ± 1.0–6.46, .041*	12 (11.1%)	3.14 ± 1.35–7.04, .006*
Agitation	109 (23.8%)	32 (24.6%)	1.14 ± 0.68–1.86, .62	8 (16.3%)	0.77 ± 0.30–1.74, .56	23 (22.8%)	0.93 ± 0.52–1.62, .82	28 (25.9%)	1.09 ± 0.63–1.82, .76
Depression	132 (28.8%)	50 (38.5%)	1.63 ± 1.03–2.56, .036*	20 (40.8%)	2.50 ± 1.29–4.81, .006*	34 (33.7%)	1.50 ± 0.92–2.43, .10	40 (37%)	1.47 ± 0.91–2.37, .11
Elation	20 (4.4%)	7 (5.4%)	1.58 ± 0.59–3.87, .33	0 (0.0%)	–	2 (2%)	0.23 ± 0.01–1.13, .15	3 (2.8%)	0.71 ± 0.16–2.18, .59
Irritability	123 (26.9%)	45 (34.6%)	1.71 ± 1.07–2.72, .024*	14 (28.6%)	1.59 ± 0.76–3.18, .20	33 (32.7%)	1.31 ± 0.77–2.17, .31	34 (31.5%)	1.47 ± 0.89–2.39, .13
Apathy	124 (27.1%)	41 (31.5%)	1.43 ± 0.88–2.31, .14	19 (38.8%)	**3.19 ± 1.60–6.34. <.001****	37 (36.6%)	1.57 ± 0.94–2.58, .080	44 (40.7%)	1.70 ± 1.04–2.75, .03*
Anxiety	143 (31.2%)	46 (35.4%)	1.43 ± 0.89–2.26, .13	14 (28.6%)	1.20 ± 0.58–2.39, .61	32 (31.7%)	1.24 ± 0.75–2.03, .40	40 (37%)	1.40 ± 0.86–2.26, .17
Disinhibition	74 (16.2%)	25 (19.2%)	1.50 ± 0.86–2.58, .15	11 (22.4%)	2.53 ± 1.13–5.35, .018*	17 (16.8%)	1.09 ± 0.56–2.01, .79	12 (11.1%)	0.66 ± 0.33–1.27, .24
Motor disturbance	47 (10.3%)	15 (11.5%)	1.22 ± 0.56–2.50, .60	4 (8.2%)	1.49 ± 0.42–4.21, .49	14 (13.9%)	1.42 ± 0.67–2.87, .34	19 (17.6%)	1.92 ± 0.98–3.64, .050*
Nighttime behaviors	74 (16.2%)	31 (23.8%)	1.46 ± 0.86–2.44, .15	16 (32.7%)	**3.49 ± 1.68–7.10, <.001****	28 (27.7%)	1.90 ± 1.09–3.25, 0.020*	35 (32.4%)	**2.38 ± 1.43–3.90, <.001****
Appetite/eating problems	83 (18.1%)	21 (16.2%)	1.21 ± 0.67–2.11, 0.52	10 (20.4%)	2.01 ± 0.88–4.33, 0.084	25 (24.8%)	1.90 ± 1.07–3.31, 0.025*	34 (31.5%)	1.95 ± 1.16–3.25, .011*

Table 4. Rates of comorbid dementia pathologies in AD participants with and without motor dysfunction in early AD. Frontotemporal Lobar degeneration includes patients with Tau pathology. *$p < .05$.

	Motor dysfunction group (*N* = 398)	No motor dysfunction group (*N* = 458)	OR ± 95% CI	*P*-value
Frontotemporal lobar degeneration	56 (14.1%)	53 (11.6%)	1.10 ± 0.71–1.69	.69
Lewy body disease	152 (38.2%)	148 (32.3%)	1.41 ± 1.03 – 1.93*	.035

Impact of motor dysfunction on non-AD neuropathology

Participants with motor dysfunction in early AD had significantly higher odds of having comorbid Lewy Body disease pathology on autopsy. Rates of Frontotemporal Lobar degeneration with Tau pathology did not differ significantly between AD participants with and without early motor dysfunction (see Table 4 for OR and 95% CI).

Discussion

The results of this study support our primary study hypothesis that AD patients who present with motor dysfunction preceding clinically meaningful cognitive decline have higher rates of distinct non-cognitive NPS than patients who do not present with motor dysfunction (although not in the specific domains of agitation and disinhibition, more on this below). Moreover, in line with our hypotheses, our data suggests that these associations may be at least partially explained by comorbid Lewy Body disease pathology.

The NPI-Q includes an 'Aberrant Motor Behavior' domain which comprises repetitive motor behaviors such as punding and pacing, but these are likely only a subset of motor symptoms in AD. In this study, associations between a different set of motor symptoms (gait disorder, falls, tremor, and slowness) were associated with non-cognitive NPS in AD. Some of the strongest associations between motor dysfunction and NPS were in the specific NPI-Q domains of apathy/indifference and depression/dysphoria, contrary to our hypothesis that NPS such as agitation and disinhibition would be most elevated in these patients. A potential explanation for this pattern of results is that a well-established motor-related clinical feature of depressive syndromes is psychomotor slowing, a visually apparent slowing of gait, movement, reaction time, and/or speech (Bennabi et al., 2013). Similarly, apathy/indifference, related to the classic depressive symptom of anhedonia, may also cause a decrease in

overall motor activity by decreasing the ability or drive to initiate activity. Patients with motor dysfunction also had higher rates of nighttime behaviors (such as excessive daytime naps, early wakening, and disrupted sleep). This finding could additionally be connected to depressive syndromes as these specific forms of sleep disruption are common in major depressive disorder.

The etiology of depression in AD is thought to be very heterogeneous (Lee and Lyketsos, 2003), and other than agitation, apathy and depression are some of the most common NPS that present in patients with AD, with an approximate prevalence of about 70% and 30–50%, respectively (Lyketsos & Olin, 2002; Mega et al., 1996). Since motor symptoms may be more likely than apathy and depression to prompt patients to visit their care providers and are more easily identified at routine clinical visits than NPS, their identification may provide clinicians a more objective method of identifying early AD patients at high risk of severe clinical and neuropathological outcomes.

Besides depressive symptoms, one of the strongest associations found between motor dysfunction and NPS was in the domain of psychotic symptoms (delusions and hallucinations). These findings may be explained at least partially by neuroimaging findings linking the salience network to both psychotic and motor symptoms, by way of its role in assisting targeted brain regions in the generation of appropriate behavioral responses to salient stimuli (Balthazar et al., 2014). Other theories postulate that the disruption of dopamine function in the basal ganglia that leads to parkinsonian motor symptoms may similarly be associated with the misattribution of salience to stimuli, resulting in hallucinations (Cho et al., 2014; Macpherson & Hikida, 2019). Finally, given past research that psychotic symptoms were most strongly related to cognitive dysfunction in AD when compared to other NPS, it is worth considering that motor dysfunction and hallucinations/delusions are linked not in a system of pathology, but rather are independent markers of poor prognosis (Fuller et al., 2019).

By contrast, NPS such as agitation, elation, and disinhibition, which may be related to heightened energy states, were not higher in AD patients with motor dysfunction. These findings may be explained by the fact that the motor symptoms that these participants were exhibiting (gait disorder, falls, tremor, and slowness) are not uniformly characterized by heightened energy states, as opposed to repetitive motor behaviors such as punding and pacing that are measured by the NPI-Q Aberrant Motor Behavior domain. Another explanation may be related to the caregiver-rated nature of the NPI-Q, with consequent reporting bias. One study found that certain NPS such as depression, hallucinations, aberrant motor behavior, and delusions were more highly associated with caregiver burden than other NPS including elation and agitation (Iravani et al., 2022). It is possible that caregivers may be less likely to report less burdensome symptoms, accounting for the lack of observed association with motor symptoms.

The presence of motor dysfunction in this sample of NACC participants was not associated with significantly higher odds of motor disturbance positivity on the NPI-Q, however, as described above, motor disturbance as operationalized by the NPI-Q measures a different motor phenomenon than the NACC variable used in this analysis. NPI-Q motor disturbance specifically assesses for repetitive motor activities (punding and pacing), while the NACC variable DECCLMOT assesses for the general presence or absence of a different set of motor symptoms (gait disorder, falls, tremor, and slowness) that may be more typically thought of as features of parkinsonism. For this reason, we performed post-hoc analyses to determine whether these motor symptoms were reflective of co-occurring Parkinson's Disease. However, clinical diagnoses of Parkinson's Disease (NACC variable: PARK) in the motor dysfunction group at the index visit were low, with only 6.3% of participants receiving this diagnosis, suggesting that these motor symptoms measured by the NACC are indeed unique features of AD.

According to our secondary neuropathology analyses, the found association between motor dysfunction in early AD and a higher number/severity of NPS may be at least partially explained by comorbid Lewy Body disease pathology. The presence of motor dysfunction was found to be significantly associated with Lewy Body disease pathology in the limbic system and neocortex. This finding is unsurprising given that several of the strongest associations observed between motor dysfunction and NPS, including hallucinations, delusions, and nighttime behaviors, are core features of the clinical disease course of Lewy Body Dementia and have been observed previously to be highly associated with post-mortem Lewy Body pathology (Shaw et al., 2024). Moreover, motor dysfunction itself is a core feature of Lewy Body Dementia and may be the first presenting symptom in some patients (Haider et al., 2024). This subset of patients with early motor dysfunction in AD may be a particularly high-risk group that may be susceptible to developing multiple patterns of neuropathologic decline. Conversely, early

motor dysfunction in AD was not associated with higher odds of having NPS commonly observed in Frontotemporal Lobar Dementia, such as disinhibition (Khan & De Jesus, 2024; Olney et al., 2017), which may explain the lack of association observed between motor dysfunction and neuropathological Frontotemporal Lobar degeneration. This lack of association also suggests that higher rates of co-occurring NPS may also represent a manifestation of more severe AD, which aligns with existing evidence that the presence and severity of NPS in patients with AD portends worse clinical outcomes (Shaw et al., 2024).

Mechanistic understandings of the association between motor symptoms and non-cognitive NPS in AD are just beginning to be explored (Nowrangi et al., 2023). One recent systematic review elucidates some of the associations observed in this study by exploring the neural pathogenesis of NPS in AD (Balthazar et al., 2014). One explanation from the referenced review suggests that increased functional connectivity in the anterior cingulate cortex and right insula of the salience network may be common to NPS and motor symptoms, by way of assisting targeted brain regions in the generation of appropriate behavioral responses to salient stimuli. When this process goes awry (ineffective or enhanced detection of salient events), inappropriate behaviors, including irritability, hallucinations, delusions, and/or motor symptoms, may arise (Balthazar et al., 2014). However, these findings may be more relevant to the aberrant motor behaviors assessed by the NPI-Q, rather than the parkinsonian symptoms assessed by the NACC variable utilized for our study. Alternatively, PET studies have shown that motor symptoms may be associated with hypometabolism in the striatum, which is a cluster of interconnected nuclei forming part of the basal ganglia that is involved in decision making functions, such as motor control, emotion, and reward, and may help to explain the association between parkinsonian motor symptoms and NPS in early AD (Meguro et al., 1997). More specifically, apathy in AD, which our study found to be strongly associated with motor symptoms, has been linked to decreased metabolism in parts of the basal ganglia, which is strongly implicated in the neuropathology of parkinsonism (Dickson, 2018; Dolphin et al., 2023). Future research is needed to more precisely link neuropathological correlates common to both motor symptoms and non-cognitive NPS in early AD.

In efforts to understand more precisely the relationship between motor symptoms in early AD and non-cognitive NPS among our study sample, we performed an exploratory analysis to assess the relationship between each specific presenting motor symptom (gait disorder, falls, tremor, and slowness) and the presence of NPS. Although some overlap between specific motor symptoms and co-occurring non-cognitive NPS was observed (odds of hallucinations were elevated (OR > 2) across all motor symptoms), our results demonstrated that each presenting motor symptom may have distinct neuropsychiatric manifestations (Table 3). For example, patients who presented with falls were found to have higher odds of having depression and apathy (which remained significant in the domain of apathy after adjusting for multiple comparisons), while patients with gait disorder were found to have higher odds of having delusions. These findings may reflect the heterogeneity of brain networks that may be affected depending on the presenting motor symptom, in contrast to the notion that these parkinsonian symptoms reflect one overlapping entity. However, it is important to note that very few of these associations remained significant after adjusting for multiple comparisons, limiting the interpretability of these findings. Further study and replication of these findings is warranted to provide a better understanding of the shared neural network dysfunctions that may occur in these distinct motor symptoms.

Results of the present study should be interpreted within the context of its limitations. We relied on autopsy data rather than clinical data to define patients with diagnosed AD, which is considered the only method of definitively diagnosing AD (Scheltens & Rockwood, 2011) but may not always correlate with clinical findings. The fact that AD patients had relatively high rates of co-occurring non-AD pathologies further emphasizes the potential lack of clinical specificity of this autopsy diagnosis. We were unable to meaningfully assess the relationship between motor dysfunction and other common neuropathological subtypes of Frontotemporal Lobar degeneration, such as TDP-43, due to low rates (~1%) within our sample. Additionally, given that the NACC is a referral population, patients included in our analyses may be more symptomatic than the general population, and rates of NPS in these patients may be elevated. Finally, our sample was predominantly white and highly educated, limiting the generalizability of our findings. For this reason, the impact of race on the hypotheses of interest could not be meaningfully assessed.

The results of our analyses suggest that the presence of motor symptoms in early AD is associated with increased rates of distinct non-cognitive NPS, including delusions, hallucinations, depression, irritability, apathy, anxiety, motor disturbance, and

nighttime behaviors, which may be partially explained by comorbid Lewy Body disease pathology. Moreover, our findings suggest that distinct motor symptoms may be associated with distinct neuropsychiatric manifestations. These results emphasize the need for structured motor symptom examinations specific to AD populations who are early in their disease course. Future analyses should conduct a survival analysis to determine whether motor dysfunction in early AD is also associated with more abrupt subsequent clinical and functional decline.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and/or analyzed during the current study can be made available from the corresponding author on reasonable request.

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