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Theoretical Article

Do Alzheimer's and Lewy body disease have discrete pathological signatures of gait?

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Abstract

Objective: We aimed to refine the hypothesis that dementia has a unique signature of gait impairment reflective of underlying pathology by considering two dementia subtypes, Alzheimer's disease (AD) and Lewy body disease (LBD), and exploring the role of cognition in disease-specific gait impairments.
Background: Accurately differentiating AD and LBD is important for treatment and disease management. Early evidence suggests gait could be a marker of dementia due to associations between discrete gait characteristics and cognitive domains.
Updated Hypothesis: We hypothesize that AD and LBD have unique signatures of gait, reflecting disease-specific cognitive profiles and underlying pathologies. An exploratory study included individuals with mild cognitive impairment or dementia due to LBD (n = 45) and AD (n = 36) and 29 older adult controls. An instrumented walkway quantified 16 gait characteristics reflecting five independent domains of locomotion (pace, rhythm, variability, asymmetry, and postural control). The LBD group demonstrated greater impairments in asymmetry and variability compared with AD; both groups were more impaired in pace and variability domains than controls. Executive dysfunction explained 11% of variance for gait variability in LBD, whereas global cognitive impairment explained 13.5% of variance in AD; therefore, gait impairments may reflect disease-specific cognitive profiles. With a refined hypothesis that AD- and LBD-specific signatures of gait reflect discrete pathologies, future studies must examine the relationship between a validated model of gait with neural networks, using recognized biomarkers and postmortem follow-up.
Major Challenges for Hypothesis: Differential diagnosis of AD and LBD used appropriate criteria and required consensus from an expert diagnostic panel to improve diagnostic accuracy. Future work should follow the framework set out in Parkinson's disease to establish unique signatures of gait as proxy measures of disease-specific pathology; that is, use a validated gait model to explore the progressive relationship between gait, cognition, and pathology.
Linkage to Other Major Theories: These exploratory findings support the theory of interacting cognitive-motor networks, as the gait-cognition relationship may reflect cognitive control over motor networks. Unique signatures of gait may reflect different temporal patterns of pathological burden in neural areas related to cognitive and motor function.
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Keywords: Alzheimer's disease; Lewy body disease; Differential diagnosis; Gait analysis; Cognition

1. Objective

The objective of this article is to refine the current proposal that people with dementia may have a unique signature of gait impairment reflective of underlying

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neurodegenerative pathology. The present draft aims to investigate if gait analysis can distinguish cognitive impairments due to Alzheimer's disease (AD) and Lewy body disease (LBD) from each other and controls and if discrete gait impairments are explained by different cognitive impairments, which reflect AD's and LBD's cognitive profiles and underlying neuropathologies. This effort aims to provide initial evidence that gait could be a proxy measure for disease-specific pathology and provide recommendations for the design of future studies, such as key gait characteristics to assess information required for future power calculations.

2. Introduction

Early accurate diagnosis of dementia is important to allow individuals to understand their condition, make plans for their care, and to appropriately manage and treat the disease [1]. Gait impairments, such as slower pace and greater gait variability (i.e., step-to-step fluctuations such as changes in step length or time), occur in prodromal stages of dementia [2] and may predict dementia diagnosis [3]. As gait is a complex cognitive task requiring coordination between widespread brain regions [4–6], gait impairments may reflect neurodegeneration due to dementia even in mild stages of the disease. Therefore, gait analysis may be a useful prescreening tool to distinguish mild stages of dementia from normal aging.

In addition to indicating the presence of dementia, gait analysis may have potential to distinguish disease subtypes [7]. This may be useful for differentiating AD and LBD, which includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Due to underrecognition and inconsistent application of diagnostic criteria, LBD is underdiagnosed and may be mistaken for AD [8,9]. Accurate diagnosis is important for treatment and disease management, as people with LBD have a high sensitivity to antipsychotics, along with greater carer burden and frequency of hospital admission, lower quality of life, faster cognitive decline, and mortality [10,11].

There is growing evidence of an association between discrete gait and cognitive impairments [12]. For example, an individual with executive and attentional dysfunction may walk slower with greater variability of gait. Different profiles of cognitive impairment are found in dementia subtypes in mild disease stages [13], such as prominent memory impairment in AD, and attentional fluctuations and executive dysfunction in LBD. These cognitive impairments may reflect disease pathology in specific neural networks and regions. Gait impairments can differentiate amnestic and nonamnestic mild cognitive impairment (MCI) groups [14]; however, there is limited evidence in clinically defined AD and LBD groups as most studies only measure gait speed, which is not specific to subtype, and report inadequate clinical and cognitive measures [7].

3. Updated hypothesis

As such, we hypothesize that AD and LBD have unique signatures of gait impairment, which reflect their distinct cognitive profiles and underlying disease pathology. This refinement of the gait-dementia hypothesis requires further exploration in AD and LBD cohorts with well-defined gait and cognitive profiles. Gait impairments should be compared between older adult controls and aforementioned disease groups to account for age-related gait impairments, while examining if the role of cognition in gait may act as proxy for neuropathology. This research will lay a foundation to consider the association of gait with markers of pathology, such as imaging, cerebrospinal fluid (CSF), and genetics, and assess the utility of gait analysis as a clinical tool for dementia diagnosis. We present early evidence for unique pathological signatures of gait in AD and LBD from our exploratory study.

3.1. Early experimental data—Methods

3.1.1. Participants

Participants with probable MCI and probable dementia due to AD and LBD (including DLB and PDD) were recruited. Two clinicians (A.T. and P.D.) reviewed patients' clinical notes and study assessments to verify the diagnosis for the study. A third clinician (J.P.T.) reviewed disagreements regarding diagnosis to reach a consensus. Standard research diagnostic criteria for dementia were applied [15–20]: Supporting biomarkers were included in the diagnosis where available. All participants had mental capacity to consent to the study. Control participants of a similar age were recruited to account for effects of aging on gait.

All participants had to be aged over 60 years and be able to walk for two minutes, as ascertained by self-report. Participants were excluded if they had drug-induced or vascular parkinsonism, any coexisting neurological conditions or movement disorders, severe mental illness (major depression, bipolar disorder, schizophrenia), evidence of stroke affecting motor function, or poor command of the English language. Controls must have had no signs of cognitive impairment (Mini–Mental State Examination [MMSE] $\geq$ 25), be functionally independent, no diagnosis of dementia, no diagnosis of Parkinson's disease (PD), and not on treatment for dementia (e.g., memantine, rivastigmine, donepezil, galantamine) or PD medication.

3.1.2. Ethical considerations

The NHS Local Research Ethics Committee, Newcastle and North Tyneside 1, approved this study, Reference: 16/NE/005, IRAS project ID: 192941.

3.1.3. Clinical assessment

Age, sex, height, weight, and faller status (if participants had fallen in the last 12 months) were recorded. The National

Adult Reading Test, Cumulative Illness Rating Scale–Geriatrics, Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III [21], Clinical Dementia Rating Scale, and Bristol Activities of Daily Living Scale were also assessed.

3.1.4. Cognitive assessment

Global cognition was measured using the standardized MMSE and Addenbrooke's Cognitive Examination III (ACE-III). The ACE-III subscales measured attention, memory, language, fluency, and visuospatial function. Trail Making Task A (TMT-A) measured information processing speed. Trail Making Task B (TMT-B) measured executive function; however, 33% of participants failed to complete or refused to do the assessment, and as such, it was excluded from analysis. The FAS verbal phonemic fluency test measured verbal fluency and executive function. The simple reaction time computerized test measured attention.

3.1.5. Gait assessment

Participants performed six 10-meter walks at their comfortable pace, across a 7 meter × 0.6 meter (length × width) instrumented walkway (GAITRite, version 4.5; CIR Systems Inc., USA). Sixteen gait characteristics representing pace, variability, rhythm (i.e., timing characteristics of gait such as step or stance time), asymmetry (i.e., the absolute difference between left and right steps), and postural control domains of gait (see Supplementary Table 1 for definitions) were measured. These were derived from Lord et al.'s [22] model of gait, developed in older adults and validated in PD. This model was chosen as a framework to inform selection of gait characteristics, allow results to be compared with previous work in PD [23–26], and aid interpretation and communication of findings.

3.1.6. Data analysis

Data were assessed for normality by inspection of histograms, boxplots, and Shapiro-Wilk tests. Gait variables that did not fit normal distribution were transformed using logarithmic or square root transformations. χ^2 tests were used to determine differences between groups for sex and faller status (participants with and without falls during the previous year). One-way analysis of variance and Kruskal-Wallis tests were used to examine differences between groups for all other variables; Fischer's Least Significant Difference post-hoc and Mann Whitney U tests established where differences lay between dementia subtypes and controls. Student's t-test was used to assess differences in gait characteristics between AD and LBD. A conservative threshold of $P \leq .01$ was applied to account for multiple comparisons. Stepwise analysis of covariance assessed group differences for gait outcomes while controlling for effects of age, height, and sex on gait outcomes.

Effect sizes (eta squared; η^2) were calculated for gait characteristics that distinguished LBD from AD, with η^2: 0.01–0.06 = small, 0.06–0.14 = medium and >0.14 = large [27]. Receiver operating characteristics and area under the curve (AUC) determined overall accuracy of selected gait characteristics, with AUC: 0.5 = test due to chance, 0.5–0.7 = low accuracy, 0.7–0.9 = moderate accuracy, 0.9–1 = high accuracy, and 1 = the perfect test [28,29]. Backward logistic regression identified the strongest combination of significant gait predictors for identifying LBD, and AUC was calculated from probability scores.

Univariate regressions were used to establish significant relationships between discrete gait impairments with demographics (age, sex, height), motor disease, and cognition (standardized MMSE, ACE-III visuospatial subscore, TMT-A, FAS, Simple Reaction Time task). Significant variables reported by univariate regressions were placed into the backward stepwise regression model to identify which factors made the strongest contribution to gait. Adjusted R^2 values were used as explanatory outcomes, demonstrating the amount of variance the predictors explained of the dependent gait variable.

3.2. Early experimental data—Results

3.2.1. Study participants and demographics

A total of 125 participants were recruited to this study. Fifteen participants were excluded from this analysis because of withdrawal from the study (n = 2), clinical diagnosis other than AD or LBD (n = 11), requirement of a walking stick (n = 1), and problems processing the data due to festination (episodic gait interruption) during assessment (n = 1). This left 110 participants (29 controls, 36 AD, and 45 LBD [30 DLB and 15 PDD]). Participants in the AD and LBD groups ranged from MCI to moderate dementia, but groups were primarily composed of mild dementia cases (see Table 1 for all clinical and demographic information). There were no significant differences for any gait characteristics between the MCI and dementia groups within each subtype; therefore, it was deemed feasible to include both stages of disease in each group (see Supplementary Table 2).

3.2.2. Differences in gait impairments between AD and LBD

Participants with DLB and PDD had no significant differences in any gait characteristics ($P \geq .05$; see Fig. 1 and Supplementary Table 2), and the groups were combined to form a LBD group, increasing statistical power.

In an adjusted model controlling for age, sex, and height, people with LBD walked slower ($P = .016$; $\eta^2 = 0.061$) with shorter steps ($P = .011$; $\eta^2 = 0.066$); greater step ($P \leq .001$; $\eta^2 = 0.151$), swing ($P = .020$; $\eta^2 = 0.057$), stance time ($P = .015$; $\eta^2 = 0.069$), and step length variability ($P \leq .001$; $\eta^2 = 0.126$); and greater

Table 1
Demographic, clinical, and cognitive information for controls and dementia disease subtypes

s	Controls	AD	LBD	F/χ^2	*P*
N	29	36	45		
MCI/dementia	N/A	15/21	20/25	0.003	.570
Age	74 ± 9	77 ± 6	77 ± 6	1.7	.180
Sex (% F)	59^{D,P}	58^{D,P}	16	21	**≤.001**
CDR Scale (0–3)	0 ± 0^{A,D,P}	0.8 ± 0.3^{C}	0.9 ± 0.4	120.7	**≤.001**
Dementia treatment (% Yes)	0^{A,L}	53^{C}	71^{C}	36.9	**≤.001**
Antipsychotics (%Yes)	0	0	0		
DAT scan (%Completed)	0^{L}	0^{L}	42.2^{C,A}	33.2	**≤.001**
DAT scan positive/negative	N/A	N/A	15/4		
NART	123 (114–126)^{A,D,P}	117 (101–125)	116 (101–124)	25	**≤.001**
% Faller	19^{A,D,P}	44^{C}	64	14.4	**.002**
Height (m)	1.67 ± .096	1.66 ± .105	1.69 ± .09	0.8	.500
BMI	26 (21–35)	26 (18–42)	26 (18–43)	2.2	.535
CIRS-G (0–56)	4 (0–11)^{A,D,P}	8 (3–19)^{C}	10 (3–18)	30.7	**≤.001**
UPDRS III	1 (0–11)^{A,D,P}	7 (0–19)^{C,D,P}	31(0–78)	67	**≤.001**
GDS (0–15)	1 (0–5)^{A,D,P}	4 (0–10)^{C}	5 (0–13)	38.2	**≤.001**
ESS (0–24)	4 ± 3^{D,P}	6 ± 4^{D,P}	10 ± 4	14.7	**≤.001**
ABC (0–100)	94 (52–100)^{A,D,P}	89 (37–100)^{C,P}	78 (21–100)	26.9	**≤.001**
BADLS (0–60)	0 (0–1)^{A,D,P}	6 (0–31)^{C,D}	13 (1–31)	55.8	**≤.001**
Cognitive assessments					
MMSE (0–30)	30 (25–30)^{A,L}	23 (14–29)^{C}	24 (12–30)^{C}	53.2	**≤.001**
ACE-III Attention (0–18)	18 (17–18)^{A,L}	14 (6–18)^{C}	15 (7–18)^{C}	46.7	**≤.001**
ACE-III Memory (0–26)	25 (19–26)^{A,L}	13 (3–23)^{C,L}	20 (0–26)^{C,A}	54.3	**≤.001**
ACE-III Fluency (0–14)	13 (5–14)^{A,L}	9 (0–13)^{C}	8 (2–13)^{C}	45.2	**≤.001**
ACE-III Language (0–26)	26 (24–26)^{A,L}	23 (11–26)^{C}	24 (0–26)^{C}	37.5	**≤.001**
ACE-III Visuospatial (0–16)	16 (13–16)^{A,L}	14 (6–16)^{C,L}	12 (0–16)^{C,A}	33.1	**≤.001**
ACE-III Total (0–100)	97 (87–100)^{A,L}	74 (29–90)^{C}	77 (15–95)^{C}	59.9	**≤.001**
TMT-A (secs)	31 (19–65)^{A,L}	049 (29–306)^{C,L}	105 (24–955)^{C,A}	47.6	**≤.001**
FAS	48 ± 12^{A,L}	35 ± 15^{C,L}	28 ± 14^{C,A}	18.1	**≤.001**
Simple RT (ms)	373 (291–493)^{A,L}	415 (287–773)^{C,L}	455 (287–3792)^{C,A}	17.9	**≤.001**

NOTE. Data displayed as mean ± standard deviation were assessed using one-way ANOVAs and Students t-tests, whereas data displayed as median (minimum-maximum) were assessed using Kruskal-Wallis and Mann Whitney U tests. Bold values highlight significant differences.

C, different to controls; A, different to AD; D, different to DLB; P, different to PDD; L, different to LBD.

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; PDD, LBD, Lewy body dementia; Parkinson's disease dementia; CDR, Clinical Dementia Rating; NART, National Adult Reading Test; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale–Geriatric; UPDRS-III, Unified Parkinson's Disease Rating Scale III; MMSE, Mini–Mental State Examination; ACE-III, Addenbrookes Cognitive Examination III; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; ABC, Activities Balance Confidence Scale; BADLS, Bristol's Activities of Daily Living; TMT-A, Trail Making Test Part A; FAS, FAS test; Simple RT, Simple Reaction Time Test Mean Time; ANOVA, analysis of variance.

step ($P \leq .001$; $\eta^2 = 0.151$) and swing time asymmetry ($P \leq .001$; $\eta^2 = 0.145$) compared with AD (see Fig. 1 and Table 2). When considering the more stringent $P \leq .01$, only step time and step length variability, and step and stance time asymmetry remained significantly different between groups. Fig. 2 depicts these characteristics in receiver operating characteristics plots.

The AUC was highest for step length variability (AUC: 0.68). All characteristics showed modest accuracy (0.6-0.7) for distinguishing LBD from AD (see Fig. 2). Backward logistic regression revealed both step length variability and step time asymmetry were significant predictors of LBD with a sensitivity of 73% and specificity of 40% (AUC = 0.739; $P \leq .001$).

3.2.3. Gait impairments in dementia subtypes compared with controls

In an adjusted model controlling for age, sex, and height, both AD and LBD demonstrated with shorter steps; longer stance; and greater stance, step, swing time, step velocity, and step length variability than controls ($P \leq .01$). Participants with LBD also walked slower, with longer step times; greater step, swing, and stance time asymmetry; and wider steps than controls ($P \leq .01$).

3.2.4. Explanatory variables of discrete gait impairments in dementia subtypes

Table 1 reports significant differences between groups for cognitive assessments. The relationship between gait variables that significantly differed between disease groups and normal aging with the cognitive variables that significantly differed between AD and LBD (memory, visuospatial, attention, and executive function) were examined. The relationship between motor disease severity and discrete gait characteristics was also assessed.

In AD, greater step velocity variability was significantly explained by greater global cognitive impairment,

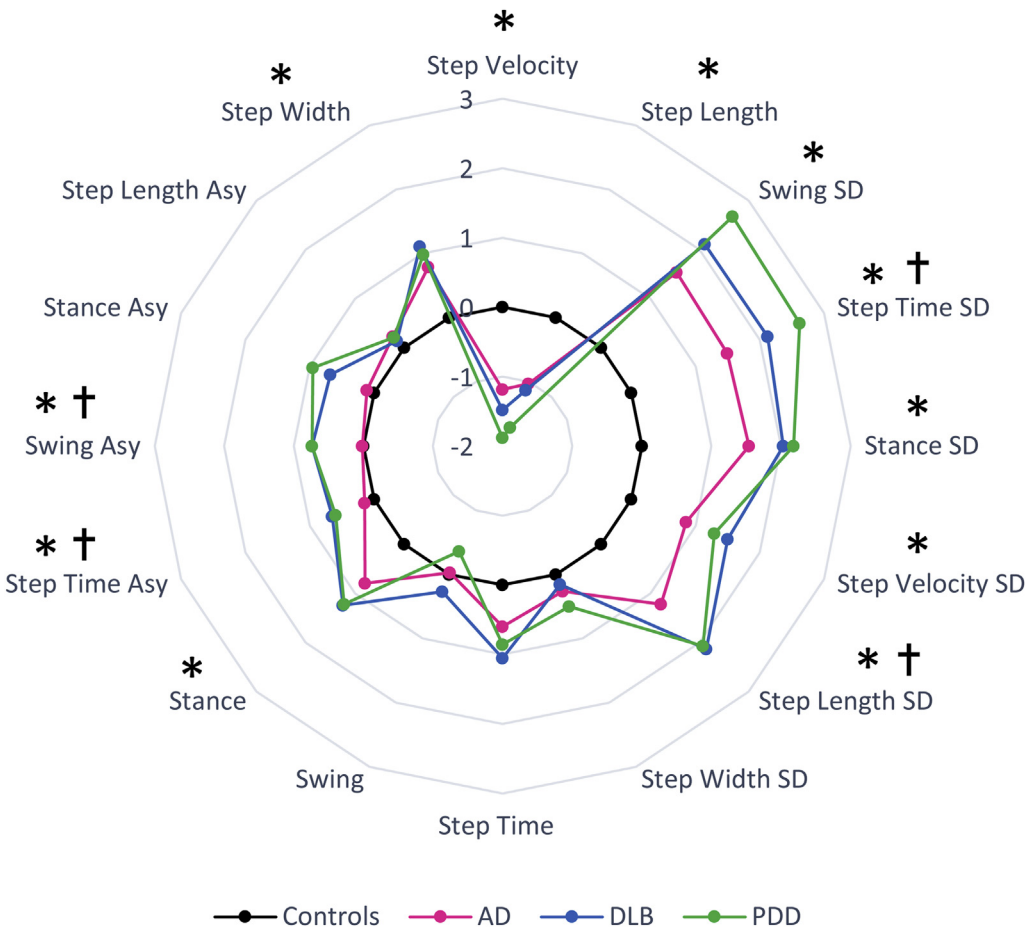

Fig. 1. Radar plots illustrating patterns of gait impairment in disease subtypes. The central black line represents control data, and the lines representing AD, DLB, and PDD demonstrate how many standard deviations from zero (z scores based on control means and standard deviations). Abbreviations: SD, variability; asy, asymmetry; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; LBD, Lewy body dementia. * = differences between controls and disease groups, † = differences between AD and LBD.

accounting for 13.5% of the variance. Slower step velocity, shorter steps, greater step, and stance time variability were significantly explained by greater motor disease severity, accounting for 11%–20% of the variance (see Table 3 for significant explanatory models, and Supplementary Table 3 for all univariate regressions).

In LBD, greater step and stance time variability were significantly explained by greater impairments in verbal fluency, accounting for 11% of the variance (see Table 4 for significant explanatory models and Supplementary Table 4 for all univariate regressions). Slower step velocity was significantly explained by greater motor disease severity with trends indicating verbal fluency contributed, accounting for 17.5% of the variance. Shorter steps were also explained by greater motor disease severity and shorter height, accounting for 37.6% of the variance.

3.3. Future experiments and validation studies

The objective of this article was to consider if AD and LBD have unique signatures of gait impairment that reflect underlying disease pathology. This pilot study provides initial evidence of discrete pathological signatures of gait in AD and LBD, and for the differential role of cognition in gait in each subtype, acting as a proxy for underlying pathology. In addition, it suggested four key characteristics of gait (step time variability, step length variability, step time asymmetry, and swing time asymmetry) could distinguish LBD and AD with modest accuracy for single characteristics and large effect sizes. This is the largest study of its kind and the results expand and refine the findings by Fritz et al. [30], the only other study to look at AD and LBD. In addition, no significant differences were found between MCI and dementia groups within each subtype, contradicting previous literature [7,31,32]. This reflected the mild nature of participants with dementia, as they were required to have capacity to consent and the ability to engage in sustained testing of >2 hours per session. The finding that people with MCI had gait impairments that mirrored those with established dementia supports the use of gait analysis as an early clinical marker for identification of cognitive

Table 2
Comparison of gait characteristics between controls and dementia disease subtypes

Gait characteristics	Controls	AD	LBD	Unadjusted model F	Unadjusted model *P*	Adjusted model F	Adjusted model *P*
Pace							
Step velocity (m/s)	1.26 ± 0.19^{A,L}	1.03 ± 0.24^{C}	0.95 ± 0.24^{C}	16.5	**≤.001**	16	**≤.001**
Step length (m)	0.70 ± 0.09^{A,L}	0.57 ± 0.11^{C}	0.55 ± 0.12^{C}	11.5	**≤.001**	15.9	**≤.001**
Swing SD (ms)^{ln}	14 (7–21)^{A,L}	20 (9–45)^{C}	25 (11–87)^{C}	24.1	**≤.001**	18	**≤.001**
Step time SD (ms)^{ln}	15 (9–23)^{A,L}	21 (9–48)^{C,L}	29 (13–80)^{C,A}	25.1	**≤.001**	20.7	**≤.001**
Stance SD (ms)^{ln}	17 (12–31)^{A,L}	29 (12–69)^{C}	35 (14–118)^{C}	22.5	**≤.001**	19.8	**≤.001**
Variability (SD)							
Step velocity SD (m/s)^{ln}	0.052 (0.04–0.11)^{A,L}	0.066 (0.03–0.11)^{C}	0.073 (0.05–0.15)^{C}	12.1	**≤.001**	8.7	**≤.001**
Step length SD (m)^{ln}	0.021 (0.01–0.04)^{A,L}	0.030 (0.01–0.04)^{C,L}	0.035 (0.02–0.08)^{C,A}	32.4	**≤.001**	22.8	**≤.001**
Step width SD (m)^{ln}	0.021 (0.01–0.03)	0.022 (0.01–0.04)	0.022 (0.01–0.05)	0.6	.536	0.2	.812
Rhythm							
Step time (ms)	536 ± 48^{L}	565 ± 57	584 ± 70^{C}	5.3	**.006**	3.9	.024
Swing (ms)	391 ± 32	391 ± 37	393 ± 52	0.04	.961	0.6	.537
Stance (ms)^{ln}	681 (571–787)^{A,L}	722 (615–902)^{C}	777 (599–1029)^{C}	9.2	**≤.001**	7.5	**≤.001**
Asymmetry							
Step time asymmetry (ms)^{sqrt}	9 (0.31–43)^{A,L}	12 (0.44–34)^{C,L}	16 (2–65)^{C,A}	4.8	.011	7.8	**≤.001**
Swing asymmetry (ms)^{sqrt}	6 (2–24)^{A,L}	6 (0.34–31)^{C,L}	14 (0.57–44)^{C,A}	4.9	**.010**	7.3	**≤.001**
Stance asymmetry (ms)^{sqrt}	7 (0.58–24)	8 (0.20–33)	14 (0.13–47)	4.4	.014	4.3	.017
Postural control							
Step length asymmetry (m)^{sqrt}	0.018 (0–0.06)	0.019 (0–0.13)	0.02 (0–0.07)	0.3	.741	0.9	.400
Step width (m)	.081 ± .023^{L}	.099 ± .029	.105 ± .024^{C}	8.1	**≤.001**	6.2	**.003**

NOTE. Normally distributed data displayed as mean ± standard deviation. Data for transformed variables are displayed as median (minimum-maximum) and refer to the nontransformed values. Significant values refer to differences between controls, AD, and LBD in the adjusted model controlling for age, sex, and height. Bold values highlight significant differences.

C, different to controls; A, different to AD; L, different to LBD.

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; PDD, LBD, Lewy body dementia; Parkinson's disease dementia; SD, variability; ln, log transformed; sqrt, square root transformed.

impairment. Therefore, we refine our hypothesis to predict that characteristics of gait variability and asymmetry reflect underlying disease pathology and could be useful for differentiating AD and LBD in early stages of disease.

A larger replication study with well-defined AD and LBD groups is required in the future to establish gait as a proxy marker for underlying neuropathology and therefore its potential as a diagnostic tool. This pilot study included a well-characterized dementia cohort, diagnosed using relevant criteria and requiring consensus from multiple clinicians. However, lack of diagnostic certainty is a limitation for all studies using clinical diagnosis. A definite diagnosis of dementia subtype can only be ascertained postmortem, and even this can be complicated by the presence of multiple pathologies such as AD and LBD. Postmortem follow-up was not within the scope of this study but will provide valuable insight in future research. Where information about imaging or recognized biomarkers were available, they were considered. However, this was not possible in all cases and limited our analysis from considering imaging and biomarkers in statistical models.

The participants included in each disease groups represented a spectrum of cognitive impairment. This allowed greater recruitment within a small catchment area, and only 4% of participants were considered to have moderate dementia based on the Clinical Dementia Rating Scale; leaving 96% with a rating of MCI or mild dementia. Combining these groups allowed greater power for statistical analysis and was considered appropriate for a pilot study. In addition, disease-specific MCI criteria were applied for this study, a newly emerging concept. Previously, MCI was considered either amnestic or nonamnestic. There is now a movement to define people with MCI by their LBD symptoms, based on the diagnostic criteria for DLB [15], along with biomarkers such as positive dopamine transporter single photon emission computerized tomography imaging techniques, also known as DAT scans [16]. The criteria has good face validity for the diagnosis of MCI due to LBD [33]; however, it has not yet been validated using pathological findings postmortem—this is an area of ongoing investigation. Future studies can address this issue through longitudinal follow-up assessments—this may give insight into the utility of gait to predict progression from MCI to dementia.

Another limitation of this study was the absence of information regarding comorbidities affecting gait, such as arthritis or presence of cerebrovascular lesions. Owing to the small sample size, we chose to be conservative in the variables included in our adjusted models. As such

Table 3
Significant explanatory variables of laboratory-based gait impairment in Alzheimer's disease

Gait characteristics	β	SE	t	*P*	F	R	R^2	Adjust R^2	95% CI lower bound	95% CI upper bound
Step velocity										
UPDRS-III	−0.019	0.000	−2.8	**.009**	7.8	0.436	0.190	0.166	−0.031	−0.005
Step length (m)										
UPDRS-III	−0.007	0.003	−2.3	**.029**	5.2	0.369	0.136	0.110	−0.013	−0.001
Step time SD										
UPDRS-III	0.630	0.230	2.7	**.010**	7.5	0.430	0.185	0.160	0.162	1.098
Stance time SD										
UPDRS-III	0.987	0.317	3.1	**.004**	9.7	0.477	0.228	0.204	0.343	1.631
Step velocity SD										
MMSE	−0.002	0.001	−2.5	**.016**	6.5	0.400	0.160	0.135	−0.003	0.000
Stance time asymmetry										
Age	0.598	0.233	2.6	**.015**	6.6	0.403	0.163	0.138	0.125	1.071

NOTE. Bold values highlight significant differences.
Abbreviations: MMSE, Mini–Mental State Examination; UPDRS-III, Unified Parkinson's disease rating scale III; SD, variability.

it was not feasible to control for comorbidities or dementia medication, and this may have impacted our results as they are known covariates of gait and may have improved or hindered gait performance [4,34–37]. Future studies require larger age- and gender-matched disease cohorts to conduct more robust statistical analysis and consider potential confounders. These cohorts should be characterized through recognized biomarkers and followed up at autopsy to provide clearer results and consider explanatory variables of gait impairment. Improved accuracy of discrete gait characteristics for correctly identifying LBD from AD may also be found with a better characterized cohort.

Although this exploratory study is the largest of its kind to date, sample sizes were small because of a limited catchment area; future studies require collaborative multicenter initiatives to recruit sufficiently large cohorts. Power calculations for sample sizes can be derived from these results, allowing future research greater generalizability of results and ability to conduct more complex analysis, such as machine-learning techniques and validation of gait as a clinical prescreening tool for differential diagnosis.

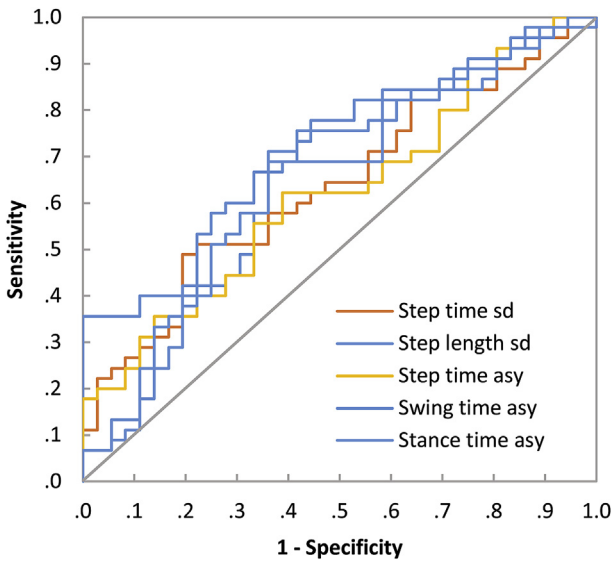

Fig. 2. Receiver operating characteristic plot for gait characteristics that distinguish disease subtypes. Abbreviations: SD, variability, asy, asymmetry.

4. Major challenges for the hypothesis

When considering a discrete pathological signature of gait in dementia subtypes, we must address major challenges surrounding limitations in our understanding of age-related gait impairments, potential mixed pathology in participants, and the translational potential from research to clinical use.

Slowing of gait in older age is recognized, and the causes are likely multifactorial [38], such as age-related changes in physiological, cognitive, and neurological function. Therefore, it may be difficult to distinguish age-related and disease-specific gait impairments. This study addressed this challenge by recruiting older adult controls and controlling for age within the comparative analysis. Longitudinal studies are required to identify gait impairments more specific to aging than disease; this has been done in PD [39] but has yet to be considered in comparison to dementia subtypes.

As addressed in Section 3.3, mixed pathology is an ongoing challenge with diagnosis of AD and LBD. Within dementia subtypes, there is also the issue of phenotypes within the subtypes themselves. For example, posterior cortical atrophy is an atypical form of AD, which initially presents with visuospatial impairments [40], whereas those with logopenic aphasia, a variant of primary progressive aphasia, experience language difficulties as the core clinical feature [41]. Both atypical phenotypes are predominately associated with AD pathology and also demonstrate neuropathological lesions in other neural regions, such as the occipital and parietal lobe in posterior cortical atrophy and the left temporoparietal junction area in logopenic aphasia [42]. As it is hypothesized that underlying neuropathology is

Table 4
Significant explanatory variables of laboratory-based gait impairment in Lewy body disease

Gait characteristics	β	SE	t	*P*	F	R	R^2	Adjust R^2	95% CI lower bound	95% CI upper bound
Step velocity										
UPDRS-III	−0.005	0.002	−2.9	**.005**	8.7	0.410	0.168	0.149	−0.008	−0.002
FAS	0.005	0.003	2.1	**.040**	4.5	0.318	0.101	0.078	0.000	0.011
Total model				**.009**	5.4	0.464	0.215	0.175		
FAS	0.004	0.003	1.7	.097					−0.001	0.009
UPDRS-III	−0.004	0.002	−2.4	**.022**					−0.008	−0.001
Step length (m)										
Sex (male)	0.120	0.045	2.6	**.012**	7.0	0.373	0.139	0.119	0.028	0.211
Height (m)	0.667	0.169	4.0	**.000**	15.6	0.516	0.267	0.250	0.327	1.007
UPDRS-III	−0.003	0.001	−4.2	**.000**	17.4	0.537	0.288	0.272	−0.005	−0.002
FAS	0.003	0.001	2.4	**.020**	5.8	0.357	0.127	0.105	0.000	0.006
Total model				**.001**	13.3	0.637	0.406	0.376		
UPDRS-III	−0.003	0.001	−3.5	**.001**					−0.004	−0.001
Height (m)	0.543	0.167	3.3	**.002**					0.206	0.880
Step time SD										
FAS	−0.375	0.154	−2.4	**.019**	5.9	0.360	0.129	0.108	−0.686	−0.064
Stance time SD										
FAS	−0.533	0.214	−2.5	**.017**	6.2	0.366	0.134	0.113	−0.966	−0.100

NOTE. Variables that were selected for the backward regression models are detailed under each gait variable. Bold values highlight significant differences.
Abbreviations: FAS, FAS Test; UPDRS-III, Unified Parkinson's disease rating scale III; SD, variability.

associated with discrete gait characteristics, it is possible that different phenotypes will also have their own unique gait signature. This has yet to be explored in the literature, but research in the overarching subtypes of AD and LBD paves the road for narrowing the scope of these studies even further.

To validate gait as a useful tool for differential diagnosis, it should be considered with regard to current validated biomarkers, such as CSF and imaging biomarkers [15,17]. It was beyond the scope of this pilot study to address this; however, we identified discrete gait impairments between groups despite the potential influence of mixed pathology. This provides positive evidence that should this study be replicated in a cohort with established indirect measures of pathology, such as imaging, biomarkers, and CSF markers and followed up to postmortem, true cases of AD and LBD are likely to have a unique pathological signature of gait. In addition, the AD and LBD groups presented with the expected cognitive profiles, supporting the accuracy of clinical diagnosis and allowing inferences about the role of underlying pathology in gait, as discussed in Section 5. Future research should address this challenge by establishing neural correlates of gait and garnering a better understanding of the interaction about cognitive and motor neural pathways in the facilitation of gait.

There is growing interest in the potential of gait analysis as a diagnostic tool for dementia, with suggestions of instrumented walkways being implemented into doctor's offices and processed with a risk score algorithm [38]. However, this plan is limited by the high cost, large space requirements, restriction to spatiotemporal gait characteristics, and length of walk based on the mat's dimensions [43]. This study used characteristics derived from an instrumented walkway to demonstrate unique signatures of gait between dementia subtypes; however, to translate this research to clinic, a more user-friendly approach considering other instruments for gait analysis along with a cost-effectiveness analysis is required.

Research in PD is paving the way to validate gait as a clinical biomarker for neurodegeneration [26,39,44–46]. To consider gait as a potential biomarker for differential diagnosis of dementia, we must follow the examples set out in PD research. This suggests we use a validated model of gait to measure a comprehensive range of characteristics of gait [47], establish the relationship between discrete gait and cognitive impairments [12,26] and markers of pathology [39,45,46,48], and demonstrate the feasibility of inexpensive tools to measure gait, such as wearable technology [44].

This work has begun in dementia [4,7,14,49–52]; however, to translate this work for clinical use, we must move beyond gait speed to consider a range of gait characteristics, identify progressive gait impairments in prodromal dementia cohorts, and associate such progression with the sequence of cognitive and pathological changes within specific dementia subtypes. In addition, replication studies using inexpensive tools for measuring gait, such as wearable technology, are essential for clinical translation.

5. Linkage to major theories

5.1. Associations between discrete gait and cognitive impairments reflect neuropathological change

Supporting the current theory that discrete gait characteristics are associated with specific cognitive impairments,

executive function (mediated by the prefrontal cortex) explained greater gait variability in LBD but not AD. Previous research has also associated gait characteristics involved in pace, variability, rhythm, and postural control with cognitive performance in attention, executive function, information-processing, memory, and visuospatial abilities—functions mediated by the prefrontal cortex and associated networks [12,53,54]. These cognitive abilities are largely regarded as reliant on coordination of these neural networks to carry out behaviors [55]. The prefrontal cortex has connections with the brainstem, basal ganglia, limbic system, and thalamus, and integration of these areas is key to carrying out cognitive functions.

Gait may similarly require coordination of neural networks connected to the prefrontal cortex. There is a proposed reciprocal hierarchical relationship between these structures [55], suggesting that gait engages two distinct but interacting neural pathways: motor and cognitive [56,57]. For example, the prefrontal cortex and the motor cortex require two-way communication to carry out movements. Should dysfunction arise in either structure, gait impairment would occur. Pathological changes in discrete neurodegenerative disorders affect selective neural pathways during different disease stages. As such, unique patterns of gait impairment in different disease subtypes are expected, reflecting the underlying pathological process.

Pathology impacts associated networks of the prefrontal cortex early in LBD and later in AD, which may contribute to differing cognitive presentation, and in turn, the differing degree of gait impairment for cognitively mediated characteristics, for example, gait variability [58]. Speculatively, this may suggest that prominent gait impairments occur early in LBD due to the dysfunction in motor networks, such as the basal ganglia and associated networks [59,60]. As such, the cognitive network may take greater control of gait facilitation, transforming gait from an automatic motor function to a cognitive task. In contrast, AD pathology occurs in the temporal lobe early in the disease stages and does not spread to the basal ganglia until later in the disease [61]. Therefore, cognitive control of gait may diminish earlier in AD and result in greater reliance on the motor network to facilitate and modulate gait—hence why gait impairments are associated with greater motor disease severity in AD. This may be why the relationship between gait and prefrontally mediated cognitive functions, such as executive function, appears more prominently in LBD than AD.

5.2. Gait could act as proxy measure for neuropathology

It is theorized that gait impairments reflect underlying neurodegenerative pathology. For example, disturbed amyloid metabolism is implicated in greater impairments in gait variability as PD progresses [39], whereas cholinergic dysfunction contributes to impairments in pace in early PD [45]. The finding of greater asymmetry in LBD supports gait as a surrogate marker for brain function [62], as this may reflect the asymmetric origins of pathology in LBD. Asymmetrical neurodegeneration of the striata has been reported in PD, contributing to the unilateral onset of motor symptoms [63]. Asymmetrical uptake of dopamine has been similarly shown in the posterior putamen in PDD [64], and asymmetrical alterations of the basal ganglia and subcortical areas have been observed in DLB and PDD [65], supporting our suggestion. To our knowledge, this is the first study investigating gait asymmetry in AD and LBD. This work can be advanced by considering CSF, imaging, genetics, and postmortem findings in relation to discrete gait impairments in AD and LBD.

6. Conclusions and recommendations

In conclusion, early evidence suggests there are discrete pathological signatures of gait in very mild AD and LBD, and that this may be due to the disease-specific role of cognition in gait. We recommend this research is replicated with larger well-defined AD and LBD cohorts, taking into account proxy measures of pathology such as CSF and imaging analysis and followed up longitudinally until postmortem. This will allow greater confidence in findings, as well as furthering our knowledge of the interactions between discrete gait characteristics and neural networks. In addition, we recommend future research follow the framework set out in PD to describe the trajectory of change in gait during different disease stages and subtypes and consider the cognitive functions and pathology that underpins disease-specific signatures of gait.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.06.4953.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional academic databases (e.g., Scopus), published a structured review of the literature (Mc Ardle et al., 2016), and updated this search before this article. All relevant publications have been appropriately cited.
2. Interpretation: Our findings provide initial evidence that Alzheimer's disease and Lewy body disease have unique signatures of gait impairment, which reflect profiles of cognitive impairment. This supports the current theory that gait may act as a proxy for neuropathology, as gait-cognition relationships are different between subtypes, and more asymmetrical gait in Lewy body disease may reflect more asymmetrical neurodegeneration.
3. Future direction: This article recommends areas for future research based on these findings and limitations within this study. Examples include using well-established biomarkers to improve confidence in clinical diagnosis for future gait studies and considering the relationship between discrete gait characteristics and neuropathology.

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