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Gait Variability as a Potential Digital Biomarker for Cognitive Decline: the wearable devices opportunity

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Gait Variability as a Potential Digital Biomarker for Cognitive Decline: the wearable devices opportunity

by

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Abstract

Gait Variability as a Potential Digital Biomarker for Cognitive Decline: the wearable devices opportunity

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Background and Objectives: Large public health burden of dementia and the absence of a cure highlight the need for early identification of those at risk for cognitive decline or dementia to prevent and/or delay the onset of dementia. Emerging evidence indicates gait variability, the fluctuation of a gait measure from one step to the next, strongly relate to the risk of cognitive decline, MCI and dementia. Gait variability obtain via wearable sensor is a promising digital biomarker for predicting risk of cognitive impairment due to its favorable practical advantages of being able to obtain measurements over a longer period of time under unsupervised real-world conditions at lower cost. In my thesis, I examine the possibility that gait variability measured by a single body-worn tri-axial accelerometer (TAA) can be used as a digital biomarker to predict future risk of cognitive decline. In the first study, I examined whether gait variability obtained by the body-worn TAA could predict future risk of cognitive

decline in older people with normal cognition (NC). In the second study, I then identify neural substrates that theoretically support the potential of gait variability as a digital biomarker in older adults with larger sample size and broader range of cognitive function. Additionally, I hypothesized higher gait variability would be related to lower cortical thickness, especially in regions important for cognitive function and memory, and that these regions would represent a shared neural substrate for gait control and cognitive impairment.

Methods: In the study I, we conducted 4-year prospective cohort study on 358 community-dwelling cognitively normal elderly individuals without cerebral ischemic burden or Parkinsonism. We evaluated gait speed and step time variability using a TAA placed on the center of body mass, and diagnosed mild cognitive impairment (MCI) according to the International Working Group on MCI. We performed Kaplan-Meier analysis with consecutive log-rank testing for MCI-free survival by cohort-specific quintiles of gait variability; hazard ratios (HR) of incident MCI were estimated using Cox proportional hazards regression analysis adjusted for age, sex, education level, Cumulative Illness Rating Scale score, GDS score, and presence of the apolipoprotein E ε4 allele.

In the study II, we cross-sectionally investigated the cortical and subcortical neural structures associated with gait variability, and the shared neural substrates of gait variability and cognitive function in 207 non-demented older adults. We obtained the cortical thickness and subcortical volumes from the magnetic resonance images, and examined associations between gait variability, cognitive function, and cortical thickness and subcortical volumes. Finally, we analyzed the mediation effect of the cluster cortical thickness and subcortical volume which had a significant association with both gait variability and cognitive function on the association between gait variability and cognition.

Results: In the study I, subjects with high gait variability showed about 2-fold higher

risk of MCI (HR = 2.12, 95% CI = 1.05–4.31) than those with 1st-to-4th quintiles of variability. However, those with slow gait speed showed comparable MCI risk to those with 2nd-to-5th quintiles of speed (HR = 1.06, 95% CI = 0.49– 2.30). We additionally found that no sex differences were found when assessing the ability of high gait variability to predict future cognitive decline. When we computed gait variability and gait speed as continuous variables to explore whether there are any threshold effects, the risk of incident cognitive decline increased 1.16 times per 10% increment of gait variability, whereas it did not change significantly with changes of gait speed.

In the study II, higher gait variability was associated with lower cognitive functions. We found the widespread decrease in cortical thickness with increasing gait variability while there was no significant association with the volume of subcortical structures. Among the clusters that showed significant correlation with the gait variability, a cluster that included the inferior temporal, entorhinal, parahippocampal, fusiform, and lingual in left hemisphere was also associated with global cognitive function, and verbal memory function. Cortical thickness of the cluster explained 17% of the total effect of gait variability on global cognitive function measured by CERAD-TS.

Interpretation: Gait variability measured by a single body-worn TAA could be a novel digital biomarker of risk of cognitive decline that could be used repeatedly and frequently and at low cost to test risk of individuals without clinical evidence of cognitive impairments.

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I Introduction

1. Study Background

Dementia is a major global health problem, affecting 46.8 million people worldwide, with prevalence predicted to increase exponentially to 131.5 million in 2050. The total global societal cost of dementia was estimated to exceed USD 818 billion in 2015, equivalent to 1.1% of global gross domestic product (GDP), to exceed USD 1 trillion in 2018 and forecast to double by 2030 and continues to rise. (Patterson 2018, FLEMING, ZEISE et al. 2020) This large public health burden and the absence of a cure highlight the need for early identification of those at risk for cognitive decline or dementia to prevent and/or delay the onset of dementia. The search for useful biomarkers in the early stages of cognitive impairment has important implications for initiating intervention and monitoring disease progression. Substantial progress has been made in the early diagnosis and identification of individuals at risk for cognitive impairment using cerebrospinal fluid, structural MRI imaging, and PET molecular imaging. However, their high cost, invasive nature, or low accessibility limit their widespread use as early biomarkers. Biomarkers based on MRI and PET imaging are available in specialty clinic settings in some countries, but the highest increase in prevalence and incidence of dementia in the coming years will be observed in low- and intermediate-income countries, where the accessibility to expensive biomarkers is limited. (de Jager, Msemburi et al. 2017) Blood-based biomarkers have been actively studied in recent years as a cost-effective and less invasive early screening biomarker of cognitive impairment. (O'Bryant, Mielke et al. 2017) However, studies have shown considerable variability owing to inconsistencies in clinical cohort, and problems with standardization of the samples, and pre- analytical and analytical differences. Assay reliability and robust replication and validation of initial results remain key issues for blood-based biomarker, and blood collection and processing procedures in studies are not applicable to standard clinical lab practice, which will cause substantial barriers to clinical application. (Hampel, O'Bryant et al. 2018)

Therefore, more studies are needed for biomarkers in the earliest stages of the cognitive impairments.

There has been a growing interest in examining gait function as a marker of early cognitive impairment. A simple but useful measure of human locomotion, gait speed is known to correlate with dementia; slow gait was associated with the accelerated cognitive decline and the risks of mild cognitive impairment (MCI) and dementia. (Camicioli, Howieson et al. 1998, Verghese, Lipton et al. 2002, Mielke, Roberts et al. 2013) Building on these findings, Verghese and colleagues defined motoric cognitive risk (MCR) syndrome as having cognitive complaint and slow gait speed, and proposed the MCR syndrome as a novel high-risk condition of dementia. (Verghese, Wang et al. 2013) The large study (17 countries with 22 cohorts resulting in 26,802 individuals) showed MCR was associated with increased cognitive impairment. However, MCR had increased risk of dementia and strongly predicted vascular dementia (VaD), but not predicted Alzheimer's dementia (AD) in the study. Moreover, in a multi-cohort MRI study, gray matter covariance patterns linked to gait speed were associated with processing speed but not with episodic memory. (Lo, Halko et al. 2017, Blumen, Brown et al. 2019) Slow processing speed and episodic memory loss are well-known symptoms that appear in the early stages of vascular dementia and Alzheimer's dementia, respectively. Considering such findings, gait speed may not be suitable as a predictive marker of cognitive decline due to neurodegenerative diseases, which accounts for the majority of dementia.

However, the gait of older adults can be characterized not only by the pace domain represented by speed, but also by the rhythm, variability, asymmetry, and postural control domains. (Lord, Galna et al. 2013) Gait parameters belonging to the rhythm, variability, asymmetry, and postural control cannot be easily measured with stop-watch and tapeline only, unlike gait speed, have been measured with computerized gait analysis via 3D gait analysis laboratory, electronic forceplate, and

inertial measurement unit sensors. (FRIGO 1992) More recently, the proliferation of wearable digital technologies in healthcare has provided new opportunities to assess gait performance outside of a gait laboratory, including detailed gait metrics. (Zhou, Al-Ali et al. 2018, Kang, Zhou et al. 2020) Among the detailed gait metrics, a decrease in stride length and gait symmetry, and an increase in gait variability were observed in subjects with MCI, a transition state between normal aging and dementia. (Verghese, Robbins et al. 2008) Specifically, subjects with amnestic MCI, a precursor state to Alzheimer's disease, in the study had worse variability scores while subjects with non-amnestic MCI had poor performance on the pace factor. Emerging evidence indicates gait variability, the fluctuation of a gait measure from one step to the next, strongly relate to the risk of cognitive decline, MCI and dementia. (Dodge, Mattek et al. 2012, Beauchet, Allali et al. 2013, Gillain, Dramé et al. 2016) In a recent Canadian multisite cross-sectional study with older adults across neurodegenerative conditions, high gait variability, but not other gait domains such as rhythm, pace, and postural control, was associated with lower cognitive performance and accurately discriminated AD from other neurodegenerative and cognitive conditions. (Pieruccini-Faria, Black et al. 2021) Gait variability has been associated with areas important for sensorimotor integration and coordination and relies on higher cortical brain control. (Tian, Chastan et al. 2017) Higher gait variability has been associated with structural and functional differences in gray matter regions; specifically, with lower levels of neuronal metabolism in hippocampus and structural degeneration in hippocampus, primary sensorimotor cortex, anterior cingulate cortex, basal ganglia in older adults. (Zimmerman, Lipton et al. 2009, Beauchet, Annweiler et al. 2014, Rosso, Hunt et al. 2014) The findings from cross-sectional and longitudinal studies on risk of cognitive impairment and from studies on the neural substrates related to gait variability suggest that gait variability could be a predictive biomarker for cognitive decline, particularly those due to Alzheimer's disease, which accounts for most of degenerative dementia.

However, the evaluation of detailed gait metrics is currently limited to research applications due to the need for institutional visits, the large space required for the institution, and the high cost. For instance, test-retest reliability of step time variability estimated using the GAITRite with an active area length of 3.65 m was very low in my previous study. (Byun, Han et al. 2016) The reliability of gait variability estimated using the GAITRite is reported to vary depending on the length of the active area on the walkway used for measuring the gait. The European GAITRite network group recommends the highest number of gait cycles possible from a practical standpoint, with a minimum of 6 consecutive gait cycles (i.e., a total of 12 consecutive steps) to evaluate stride time variability. A laboratory with a length of 15 m or more is required for this purpose. These limitations preclude repeated and frequent use to test an individual and specifically in the early pre-symptomatic stage of the neurodegenerative diseases. Recently, advancing mobile and wearable digital technology have the potential to overcome these limitations, and their application to the development of digital biomarkers for future cognitive decline has become an area of increased interest. (Kourtis, Regele et al. 2019) Furthermore, a recent meeting of the Alzheimer's Association Research Roundtable discussed how wearables and their digital biomarkers can be used in the dementia clinical trial space. Topics of discussion included how wearables can improve screening, engagement and compliance with treatment, while providing new insights towards personalized medicine. (Gold, Amatniek et al. 2018, Godfrey, Brodie et al. 2019) In our previous study, step time variability can be validly measured using a single tri-axial accelerometer (hereafter, TAA) placed over the center of body mass in older adults. (Hsu, Chung et al. 2014, Byun, Han et al. 2016, Del Din, Godfrey et al. 2016) Recent prospective longitudinal study has already shown the potential for step time variability and asymmetry measured by a wearable TAA to be potential prodromal markers for Parkinson disease (PD), the second common neurodegenerative disease. (Del Din, Elshehabi et al. 2019) Wearable sensor-based gait measurement has the

advantage of being able to obtain measurements over a longer period of time under unsupervised real-world conditions at lower cost. With these regards, the gait variability measured by TAA is a promising digital biomarker for predicting risk of cognitive impairment in the pre-clinical stages.

To summarize, identifying those at risk of cognitive impairment at the earliest stages of the disease is crucial for timely intervention and effective treatment. For this, gait variability obtain via wearable sensor is a promising digital biomarker due to its favorable practical advantages. To date, no prospective studies have investigated the association of gait variability and future cognitive decline using the body-worn TAA, and there have been only two prospective studies using conventional gait assessment tools. One study suggested that high gait variability may be associated with the future risk of Alzheimer's disease (AD) in those with MCI (Gillain, Drame et al. 2016). The other study suggested high variability factor scores were associated with future risk of dementia in non-demented old people (Verghese, Wang et al. 2007). In addition to being based on conventional gait assessment tools, the previous studies were subject to certain methodological limitations. The former study (Gillain, Drame et al. 2016) included only 13 subjects; the latter (Verghese, Wang et al. 2007) evaluated gait variability using a short electronic walkway, resulting in unreliable measurements (Kressig and Beauchet 2006). Furthermore, there was no study investigating whether a combination of gait speed and variability can better predict the risk of cognitive decline than either factor alone. Finally, these studies could not show whether the changes in gait variability preceded or merely accompanied mild cognitive impairment or dementia, because their samples included people with mild cognitive impairment at baseline.

Meanwhile, some studies have investigated the neural correlates of association between gait variability and the risk of cognitive decline. Higher gait variability indicates lower gray matter integrity and neuronal metabolism of hippocampus,

lower gray matter integrity of anterior cingulate gyrus, and decreased parietal gray matter volume.(Zimmerman, Lipton et al. 2009, Beauchet, Annweiler et al. 2014, Rosso, Hunt et al. 2014) Many of these areas that have been associated with gait variability are also related to Alzheimer's disease. (Jack, Petersen et al. 1998, Burgmans, Van Boxtel et al. 2009, Kawakami, Hasegawa et al. 2014) It appears plausible that gait variability and cognitive function would share neural substrates, and understanding the shared neural substrates between gait variability-cognitive function may provide a neurological explanation for a higher gait variability being associated with an increased risk of cognitive decline. However, such shared neural substrates have not been examined: there have been some studies of gait variability-neural substrates or gait variability-cognitive decline, respectively. And even studies that only reported the neural substrates associated with gait variability have limitations; most have focused on only a few pre-specified regions of interest, and cortical thickness has rarely been studied although cortical thickness methods have been shown to be more sensitive in detecting alterations in cortical morphology than the former volumetric approach, and a short-length forceplate was used to measure gait variability with insufficient consecutive steps. (Hutton, Draganski et al. 2009, Sakurai, Bartha et al. 2019, Jayakody, Breslin et al. 2020)

2. Purpose of Research

In my research, I examine the possibility that gait variability measured by a single body-worn TAA can be used as a digital biomarker to predict future risk of cognitive decline. To this end, I conducted two studies.

In the first study, I first examined whether gait variability obtained by the body-worn TAA could predict future risk of cognitive decline in older people with normal cognition (NC). To investigate whether the changes in gait variability precede MCI, we conducted a 4-year prospective study of elderly with NC who had no

evidence of cognitive impairment in well-characterized cohort of community dwelling older adults.

In the second study, I then identify neural substrates that theoretically support the potential of gait variability as a digital biomarker in older adults with larger sample size and broader range of cognitive function. I cross-sectionally investigated the cortical and subcortical neural structures associated with gait variability, and the shared neural substrates of gait variability and cognitive function in non-demented older adults. I anticipated that higher gait variability would be associated with reduced cortical thickness in regions implicated in sensorimotor control of gait in non-demented older adults, even though not associated with decreased subcortical volume. Additionally, I hypothesized higher gait variability would be related to lower cortical thickness, especially in regions important for cognitive function and memory, and that these regions would represent a shared neural substrate for gait control and cognitive impairment. Gait variability in the present study was quantified by step time variability since temporal gait variability measures such as step time variability and stride time variability are the most widely reported factors that predict cognitive decline, and the use of steps instead of strides to calculate gait variability has been suggested in previous studies. (Moe-Nilssen, Aaslund et al. 2010, Galna, Lord et al. 2013).

Altogether, I hypothesized that step time variability measured by a single body-worn TAA could be a novel digital biomarker of risk of cognitive decline that could be used repeatedly and frequently and at low cost to test risk of individuals without clinical evidence of cognitive impairments.

II Methods

1. Study 1: Can gait variability predict the risk of cognitive decline in cognitively normal elderly?

1.1. Study population

We undertook the current study as a prospective cohort study nested within the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD). The KLOSCAD is a population-based prospective multi-center cohort study on cognitive aging and dementia in elderly Koreans (age 60 years and over) who have been followed up every 2 years since 2010 (Kim, Park et al. 2013). Among the KLOSCAD participants who completed baseline assessment from January 2011 to December 2018 at Seoul National University Bundang Hospital, 506 volunteers who were eligible for inclusion criteria and exclusion criteria as follows completed gait assessment. They were non-demented, free from psychiatric, neurologic and serious medical disorders, any history of cerebrovascular accidents or operations on musculoskeletal system, or any painful condition or sensory impairment that may influence their gait. The level of visual function was operationally defined according to the following five levels: 0 Normal, 1 Diminished but able to see the newspaper or television without glasses or lenses., 2 Diminished and need to wear glasses or lenses to see the newspaper or television, 3 Difficult to see newspapers or television with glasses or lenses because of reduced vision 4 Not able to see anymore. We excluded people with a score of 3 or more through the interview with trained research nurses and excluded those who had diplopia, visual field defects, or other sensory deficits through neurological evaluation performed by geriatric psychiatrists. Out of 506 subjects who underwent gait evaluation, except for 148 subjects (10 subjects who were diagnosed with MCI through the neuropsychological test,120 subjects who did not meet the condition of Unified Parkinson's Disease Rating Scale Part III (UPDRS) (P. Martinez-Martin and tF. Bermejo 1994) motor score of 0 or a gait

subscale of Tinetti gait and balance assessment(Tinetti-gait) (Tinetti 1986) score of 12, and 18 with missing values in one of the covariates), a total of 358 subjects were included in this baseline sub-cohort. This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital. All subjects provided written informed consent themselves or via their legal guardians.

1.2. Clinical assessments

Geriatric psychiatrists administered a standardized diagnostic interview including a detailed medical history, physical and neurological examinations, and laboratory tests including APOE genotyping to each subject using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery (CERAD-K-C) (LEE, LEE et al. 2004), the Mini International Neuropsychiatric Interview (MINI) (Yoo, Kim et al. 2006), and the Cumulative Illness Rating Scale (CIRS) (Miller, Paradis et al. 1992). We determined the global severity of dementia using the Clinical Dementia Rating (CDR) (Morris 1993). We evaluated parkinsonian symptoms and gait disturbances using the UPDRS (range 0-108 with higher scores indicating more severe parkinsonian motor symptoms) and the gait subscale of Tinetti gait and balance assessment. The Tinetti instrument consists of three scales: a Gait Scale, a Balance Scale and then and overall Gait and Balance score. The maximum score for gait is 12. The higher the score, the better the performance. The Modified Hachinski Ischemic Score (MHIS) was employed for assessing vascular burden (Rosen, Terry et al. 1980). Trained neuropsychologists or research nurses administered neuropsychological assessments including the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-K-N) (Lee, Lee et al. 2002), the Korean version of the Frontal Assessment Battery (Kim, Huh et al. 2010) and the forward and backward Digit Span Test (D. 1987), and asked the participants to self-administer the Korean version of Geriatric Depression Scale

(GDS) (Kim, Park et al. 2008).

We determined the diagnosis and CDR of each subject through consensus diagnostic conferences in which three or more research geriatric psychiatrists participated. We diagnosed mild cognitive impairment (MCI) according to the diagnostic criteria for MCI proposed by the International Working Group on MCI (Winblad, Palmer et al. 2004) and dementia according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision) criteria (Association 2000). We diagnosed the presence of objective cognitive impairment if a subject scored worse than -1.0 standard deviation (SD) on the age-, gender-, and education-adjusted norms for Korean elders in any of the 11 neuropsychological tests other than the Mini-Mental State Examination (MMSE). We defined the subjects as cognitively normal whose CDR was 0 and neuropsychological performance was above -1.0 SD in all neuropsychological tests.

1.3. Gait Assessments

Gait analysis using a tri-axial accelerometer placed over the center of body mass (COM) was found to validly measure gait parameters including cadence, step time, step length, speed, and gait variability in older adults (Hartmann, Murer et al. 2009, Byun, Han et al. 2016). We measured the gait of each subject using the GAITRite and the tri-axial accelerometry-based gait analysis (TAAGA) that we reported in our previous work. (Byun, Han et al. 2016) The TAAGA showed excellent test-retest reliability in measuring cadence, step time, step length, step time variability, and step time asymmetry in cognitively normal older adults.

We obtained gait speed from the GAITRite. According to our previous work, we measured the step time variability of each participant using a TAA (FITMETER® [FitLife Inc., Suwon, Korea] or ActiGraph® [SMD solution, Seoul, Korea]) placed over the center of body mass (CoM). The IMUs were hexahedrons (35 × 35 × 13 mm [14 g]/30 × 40 × 10 mm [17 g]) with smooth edges and a digital tri-axial accelerometer (BMA255, BOSCH, Germany) and gyroscope (BMX055, BOSCH, Germany). They could measure tri-axial acceleration up to ± 8 g (with a resolution of 0.004 g/0.00024 g) and tri-axial angular velocity up to ±1,000°/s (with a resolution of 0.03°/s) at 250 Hz. We fixed an IMU to each participant at the 3^{rd} – 4^{th} lumbar vertebrae using Hypafix. We asked each participant to walk back and forth three times on a 14 m (or 20 m) flat straight walkway at a comfortable self-selected pace, and to start turning after passing the 14 m (or 20 m) line. We placed the GAITRite electronic mat in the middle of the walkway. To measure steady-state walking, we analyzed the data of the central 10 m-walk of the 14m-walk (or 15m-walk of the 20m-walk) after eliminating the 2 m-walks prior to the start and each turn. We calculated step time variability from vertical acceleration data using the method described by Zijlstra and Hof [i.e., % coefficient of variation (% CV) of step time = (standard deviation of step time/mean step time) × 100] (Zijlstra and Hof 2003). In

the present study, we used the natural log transformation of % CV of step time as gait variability since % CV of step time was not normally distributed. The detailed methods of signal processing and gait variability calculation are described elsewhere. (Byun, Han et al. 2016) In summary, we read acceleration data as comma separated value (CSV) files using FITMETER and ActiGraph manager software and loaded the CSV file into MATLAB (The MathWorks Inc., Natick, MA). We applied a low-pass filter (4th order zero-lag Butterworth filter at 2 Hz) to the acceleration data from three axes. After that, we took troughs of the processed data on vertical axis as the instant of a left or right foot contact for each walk. We calculated step times using the duration between acceleration troughs.

1.4. Statistical analysies

On the basis of sex, we classified each subject's gait variability as being in the 1st, 2nd, 3^{rd}, 4^{th}, 5^{th} quintiles, and the subjects' gait speed was also classified into the quintiles. We compared the demographic, clinical, and gait characteristics between the quintile groups using one-way analysis of variance (ANOVA) for continuous variables and chi square test or Fisher's exact probability test for categorical variables (Table 1).

Incidence of MCI over the 4-year follow-up was a primary outcome. We performed Kaplan–Meier analysis with consecutive log-rank testing for MCI free survival by cohort-specific quintiles of gait speed and variability to estimate the association between gait parameters and MCI risk.

We performed cox proportional hazard regression analyses to estimate multivariate-adjusted estimates of the hazard ratio (HR) of MCI according to gait speed and variability. We dichotomized the subjects by gait variability into a highest quintile group and a control group in conducting multivariate analysis. Similarly, gait

speed was entered into the multivariate model as a variable dichotomized into a control group and a lowest quintile group because slow gait, not normal or fast gait, had been a well-known predictor of cognitive decline (Mielke, Roberts et al. 2013, Verghese, Wang et al. 2013, Gale, Allerhand et al. 2014, Ojagbemi, D'Este et al. 2015), and the high gait speed group had no incidence of MCI. We constructed three models and adjusted age, sex, level of education, CIRS score, GDS score, and the presence of the apolipoprotein E (APOE) ε4 allele as covariates in all models, with gait speed included in Model A, gait variability in Model B, and both in Model C. We compared the predictive ability of these cox regression models using the likelihood ratio-test and C-statistic. Gait speed and variability status were entered into the Cox model as both continuous and dichotomized variables to test if there is a threshold effect. Natural logarithmic transformation was applied to the gait variability variable to achieve normality. Time to event was from enrolment to interview at which MCI was diagnosed or to final study contact. We tested the proportional hazards assumption using the methods based on scaled Schoenfeld residuals. In an additional analysis, we assessed the robustness of our analyses to potential reverse causation (that would occur if incipient cognitive impairment at baseline led to high gait variability and/or low gait speed status) by additionally adjusting the models for baseline cognitive performance measured by MMSE. Based on the Youden's J statistic (Youden 1950), the optimal cut-off value for gait measure that best predicts the incidence of cognitive decline 4 years after the baseline assessment was selected for men and women, respectively. All analyses were performed using SPSS version 20 (IBM Corp., New York, NY) and R version 3.3.2 (R Foundation for Statistical Computing).

2. Study 2: Shared Neural Substrates between Gait Variability-Cognitive Function

2.1. Study population

This study is embedded in the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), a population-based prospective multicenter cohort study on cognitive aging and dementia in elderly Koreans (age 60 years and over) who have been followed up every 2 years since 2010 (Kim, Park et al. 2013). This study is embedded in the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), a population-based prospective multicenter cohort study on randomly sampled elderly Koreans aged 60 years old and over. The KLOSCAD was launched in 2009 and have been followed up every 2 years until 2020 (Kim, Park et al. 2013). Among 232 individuals who completed the gait evaluation and brain MRI simultaneously in the KLOSCAD cohort, we included 207 participants in the final analysis after excluding following conditions: 1) dementia or major psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision) criteria; 2) major neurologic disorders including Parkinson's disease, brain tumor or stroke; 3) having a history of traumatic brain injury; 4) having the Tinetti Performance Oriented Mobility Assessment - Gait subscale (POMA-G) score of ≤ 10 (Tinetti 1986); 5) having one or more cardinal signs (bradykinesia, tremor, rigidity) or two or more non-cardinal signs in the Parkinsonism on the Unified Parkinson's Disease Rating Scale Part III (UPDRS) (P. Martinez-Martin and tF. Bermejo 1994).

All the participants had provided written informed consent themselves or via their legal guardians. This study had been approved by the Institutional Review Board of the Seoul National University Bundang Hospital.

2.2. Assessments of cognition and medical conditions

Geriatric psychiatrists administered a standardized diagnostic interview including a

detailed medical history, physical and neurological examinations, and laboratory tests to each subject using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery (CERAD-K-C) (LEE, LEE et al. 2004) and the Mini International Neuropsychiatric Interview (MINI) (Yoo, Kim et al. 2006). They evaluated the burden of comorbidities using the Cumulative Illness Rating Scale (CIRS) (Miller, Paradis et al. 1992) and the vascular burden using the Modified Hachinski Ischemic Score (MHIS) (Rosen, Terry et al. 1980), and identified the presence of degenerative arthritis of spine and/or lower extremities through the musculoskeletal category of the CIRS [34]. They evaluated Parkinsonian symptoms and gait disturbances using the UPDRS and the POMA-G. The maximum score of the UPDRS is 108 and the higher score indicates more severe Parkinsonian motor symptoms. The maximum score of the POMA-G is 12 and the higher the score indicates the better gait performance.

Trained neuropsychologists or research nurses administered neuropsychological assessments including the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-K-N) (LEE, LEE et al. 2004), the Korean version of the Frontal Assessment Battery (Kim, Huh et al. 2010) and the Digit Span Test (D. 1987).

The CERAD-K-N consists of nine neuropsychological tests, including the Categorical Fluency Test (CFT), the Modified Boston Naming Test (mBNT), the Mini Mental Status Examination (MMSE), the Word List Memory Test (WLMT), the Constructional Praxis Test (CPT), the Word List Recall Test (WLRT), the Word List Recognition Test (WLRcT), the Constructional Recall Test (CRT), and the Trail Making Test A (TMT-A). We calculated the CERAD-K total scores (CERAD-TS) by summing the scores of CFT, mBNT, WLMT, WLRT, WLRcT, and CPT (Seo, Lee et al. 2010). We defined the Verbal Memory Score (VMS) as the weighted average of the scores of WLMT, WLRT, and WLRcT. The CERAD-TS and VMS range from 0

to 100 and 0 to 30, respectively, and higher scores represent better cognitive function.

Research nurses asked the participants to self-administer the Korean version of Geriatric Depression Scale (GDS) (Kim, Park et al. 2008) to evaluate the severity of depressive symptoms.

2.3. Gait assessments

We measured the temporal gait variability because temporal parameters were more affected dementia-related gait parameters than spatial parameters and temporal, but not the spatial gait parameter, were associated with AD pathology (Wennberg, Savica et al. 2017, Chiaramonte and Cioni 2021). In measuring the temporal gait variability, we used the steps instead of strides because gait variability from left and right steps combined was more reliable that using strides (Moe-Nilssen, Aaslund et al. 2010, Galna, Lord et al. 2013).

According to our previous work (Hartmann, Murer et al. 2009, Byun, Han et al. 2016), we measured the step time variability of each participant using a TAA (FITMETER® [FitLife Inc., Suwon, Korea] or ActiGraph® [SMD solution, Seoul, Korea]) placed over the center of body mass (CoM). The IMUs were hexahedrons (35 × 35 × 13 mm [14 g]/30 × 40 × 10 mm [17 g]) with smooth edges and a digital tri-axial accelerometer (BMA255, BOSCH, Germany) and gyroscope (BMX055, BOSCH, Germany). They could measure tri-axial acceleration up to ± 8 g (with a resolution of 0.004 g/0.00024 g) and tri-axial angular velocity up to ±1,000°/s (with a resolution of 0.03°/s) at 250 Hz. We fixed an IMU to each participant at the 3^{rd} – 4^{th} lumbar vertebrae using Hypafix. We asked each participant to walk back and forth three times on a 14 m (or 20 m) flat straight walkway at a comfortable self-selected pace, and to start turning after passing the 14 m (or 20 m) line. To measure steady-state walking, we analyzed the data of the central 10 m-walk of the 14m-walk (or

15m-walk of the 20m-walk) after eliminating the 2 m-walks prior to the start and each turn. We calculated step time variability from vertical acceleration data using the method described by Zijlstra and Hof [i.e., % coefficient of variation (% CV) of step time = (standard deviation of step time/mean step time) × 100] (Zijlstra and Hof 2003). In the present study, we used the natural log transformation of % CV of step time as gait variability since % CV of step time was not normally distributed. The detailed methods of signal processing and gait variability calculation are described elsewhere. (Byun, Han et al. 2016)

We also measured the leg length which was the distance between the anterior superior iliac spine (ASIS) and the lateral malleolus, as a covariate, because leg length is associated with spatiotemporal gait parameters. (Ko, Gunter et al. 2007)

2.4. Magnetic resonance imaging (MRI) acquisition and preprocessing

We obtained three-dimensional structural T1-weighted spoiled gradient echo magnetic resonance (MR) images of the participants within a year from their clinical and neuropsychological assessments using a 3.0 Tesla GE SIGNA Scanner (GE Healthcare; Milwaukee, WI) in Digital Imaging and Communications in Medicine format with the following parameters: acquired voxel size = 1.0 × 0.5 × 0.5 mm3, 1.0 mm sagittal slices with no inter-slice gap, echo time = 3.68 ms, repetition time = 25.0 ms, number of excitations = 1, flip angle = 90°, field of view = 240 × 240 mm, and 175 × 240 × 240 matrix in the x-, y-, and z- dimensions. We bias-corrected the T1 images to remove intensity inhomogeneity artifacts using Statistical Parametric Mapping software (version 8, SPM8; Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl. ac.uk/spm). We then resliced the bias-corrected T1 images into isotropic voxels (1.0 × 1.0 × 1.0 mm3).

We performed cortical reconstruction and volumetric segmentation with the

FreeSurfer v6.0 (http://surfer.nmr.mgh.harvard.edu/). We smoothed thickness maps with a 10 mm full-width half-maximum (FWHM) Gaussian kernel prior to statistical analysis. Based on gyral and sulcal anatomy, we segmented the cortex into 34 different gyral regions per hemisphere (13 frontal, 9 temporal, 4 occipital, 7 parietal, and insula), using the Desikan–Killiany Atlas (Desikan, Ségonne et al. 2006)

2.5. Statistical analyses

To examine the association of gait variability with cognitive function measures (CERAD-TS and VMS), we performed a multivariate general linear model (GLM) adjusted for age, sex, education, GDS, CIRS, leg length and the presence of arthritis using the linear model function of the Stats package in R version 3.3.2 (R Foundation for Statistical Computing).

To examine the association of gait variability with cortical thickness, we performed vertex-wise analyses using the FreeSurfer QDEC module (Query, Design, Estimate, Contrast [http://surfer.nmr.mgh.harvard.edu]), which allows users to perform inter-subject/group averaging and inference using the general linear model on the morphometric data produced by the FreeSurfer processing stream. We applied correction for multiple comparisons using the built-in Monte Carlo simulation at a threshold set at a p value, 0.05, a cluster-wise correction that controls for the rate of false positive clusters. In QDEC, we used a GLM with each gait parameters as the continuous predictor, and age, estimated total intracranial volume (eTIV) as nuisance variables within the different offset, different slope design matrix. Because of limitations in the number of covariates in QDEC, we exported cortical thickness for each participant for the identified clusters into R to assess whether the associations withstood correction for confounding factors. To do so, we created a region of interest (ROI) for each cluster that was significantly associated with gait variability. We mapped back this normalized ROI to each participant (using deformation tools in

FreeSurfer) to generate a mean thickness value for that ROI for each participant. We performed further linear model analyses using the mean cortical thickness of ROIs as dependent variables and gait variability as an independent variable and corrected for age, sex, education level, GDS, CIRS, leg length, the presence of arthritis, and eTIV.

To examine the association of gait variability with volumes of subcortical grey matter structures (caudate, putamen, globus pallidus, thalamus, and nucleus accumbens), amygdala, hippocampus, and cerebellum, we also performed a multivariate GLM adjusted for age, sex, education, GDS, CIRS, leg length, the presence of arthritis and eTIV. False discovery rate correction was applied to correct for multiple comparisons. Eight ROIs from each hemisphere were selected a priori based on their known associations with gait control.

To examine the association of cognitive function measures with the cortical thickness and subcortical volume of the structures that were found to be associated with the gait variability, we performed a multivariate GLM that adjusted for age, sex, education, GDS, CIRS and eTIV.

Finally, we performed mediation analysis using the PROCESS macro developed for SPSS (Hayes 2017). Through mediation analysis, we quantify the extent to which the association between gait variability and cognitive function (VMS, CERAD-TS) could be explained by the cluster cortical thickness or subcortical volume which had a significant association with both gait variability and cognitive function. We performed the parallel mediation analyses separately for each cognitive assessment using 5,000 bootstrapped samples. In these analyses, we adjusted for sex, age, education, GDS, CIRS, and eTIV. Path a represents the effect of gait variability on the neuroimaging measures, and path b represents the effect of neuroimaging measures on cognition. Path c indicates the total effect of gait variability on cognition and path c’ indicates the direct effect of gait variability on cognition. The indirect

effect (path a × b) measures the effect of gait variability on cognition via the cluster cortical thickness or subcortical volume. 95% confidence intervals that do not include the value of 0 indicate a significant indirect effect.

III Results

1. Study 1: Can gait variability predict the risk of cognitive decline in cognitively normal elderly?

At baseline assessment, the mean age of the 358 subjects was 70.6±5.40 years and the mean level of education was 13.6±3.68 years. The MHIS scores of the subjects were 0 or 1, which indicates a very low cerebral ischemic burden. Demographic and clinical characteristics of the subjects were comparable between the gait variability quintile groups at baseline assessment. Subjects in the lowest quintile of gait speed were older, and had a greater burden of physical comorbidities than those in the 3rd, 4th, and 5th quintiles. At the baseline assessment, MMSE scores were within the normal range of age-, sex- and education-adjusted norms in all gait speed and variability quintile groups, and comparable between groups. The highest gait variability group showed worse WLMT score compared with the 3rd quintile, FAB score compared with the 1st, 2nd, and 3rd quintiles, TMT-A score compared with the 3rd, and 4th quintiles, and CFT compared with the 1st quintile. The lowest gait speed group showed worse DSB score compared with the 4th quintile (Table 1)

1.1. Association of gait variability and gait speed status with the risk of MCI

Out of the 358 participants in the baseline assessment, 318 who completed one or more 2-year follow-up assessments were included in the multivariate survival analysis. Median duration of follow-up was 45.3 months (interquartile range=28.9–50.3). During the follow-up period, 43 (13.5%) developed MCI (with 10 cases of amnestic multiple domain MCI, 16 cases of amnestic single domain MCI, 14 cases of non-amnestic single domain MCI, and 3 cases of non-amnestic multiple domain MCI).

The Kaplan-Meier curves for unadjusted rates of incident MCI show evident differences in risk by gait variability group (Figure 1A). The mean MCI-free survival of participants in the high variability group was 10.4% shorter than that of the group of other quintiles (48.94±1.29 [SD] vs. 54.64±1.21 months; $\chi 2$=4.56, p=0.033, log-rank test), whereas there was no group difference dependent on gait speed (51.96±1.22 vs. 55.18±1.39 months; $\chi 2$=0.086, p=0.770) (Figure 1B).

After adjustment for age, sex, level of education, CIRS score, GDS score, and the presence of APOE ε4, multivariable Cox proportional hazard analysis showed that low gait speed had no significant association with MCI risk (HR=1.06, 95% CI=0.49–2.30, Covariates + Gait Speed, Model A; see Table 2). When gait variability status was included in the multivariate model instead of gait speed, gait variability was a significant and independent predictor of MCI. Over the follow-up period, the high gait variability group showed about 2-fold risk of incident MCI (HR=2.12, 95% CI=1.05–4.31, covariates + gait variability; Model B). The C-statistic and likelihood ratio test showed that the model including gait variability had significantly higher predictive ability (Model B; C-statistic 0.687, likelihood ratio test p=0.048) compared to the model including gait speed (Model A; C-statistic 0.661). Furthermore, when both gait parameters were included in the prediction model, gait

variability remained as a significant predictor of MCI (HR=2.13, 95% CI=1.04–4.34), whereas gait speed was not associated with incident MCI risk (HR=0.98, 95% CI=0.44–2.14). The C-statistic and likelihood ratio test showed that adding gait speed to the previous model did not significantly increase predictive ability (covariates + gait speed + gait variability; C-statistic 0.688, likelihood ratio test p=0.954; see Table 2). We also analyzed sex differences on association between gait variability and cognitive decline by adding interaction term between gait variability group and sex to Model B and C, there were no sex difference that high gait variability predicted future cognitive decline. (gait variability × sex added to model B: p=0.425; gait variability × sex added to model C: p=0.398). In a supplementary analysis, high gait variability showed a trend toward higher risk for incident cognitive decline but without statistical significance when the baseline MMSE score was adjusted in addition (HR=2.00, 95% CI=0.98–4.10, p=0.058). When we computed gait variability and gait speed as continuous variables, the risk of incident MCI increased 1.16 times per 10% increment of gait variability (HR=1.16, 95% CI=1.02–1.32), whereas it did not change significantly with changes of gait speed (HR=0.93, 95% CI=0.87–1.34). The optimal cut-off values for gait variability to predict the incidence of cognitive decline after 4 years were 3.24 %CV for women and 2.7 %CV for men. (sensitivity = 0.384, specificity = 0.931 in women, sensitivity = 0.736, specificity = 0.775 in men).

2. Study 2: Shared Neural Substrates between Gait Variability-Cognitive Function

As summarized in Table 3, men were more educated (mean difference = 3.58, t = 6.82, $p < 0.001$), had longer leg length (mean difference = 5.36, t = 6.43, $p < 0.001$) and showed higher CERAD-TS cognitive function scores (mean difference = 3.11, t = 2.00, p = 0.047) than women. Although both men and women did not have a

depressive disorder, men showed the lower GDS score than women (mean difference = 3.16, t = 4.09, $p < 0.001$). Degenerative arthritis of spine or lower limbs were less prevalent in men than in women ($\chi 2 = 23.50$, $p < 0.001$).

The higher gait variability was associated with the lower CERAD-TS (t = -3.56, $p < 0.001$) and VMS (t = -3.44, $p < 0.001$) in multivariate GLM adjusted for age, sex, education, GDS, CIRS, leg length and existence of arthritis ($R^2 = 0.260$, $F_{6,200} = 11.73$, $p < 0.001$ for CERAD-TS; $R^2 = 0.022$, $F_{6,200} = 9.16$, $p < 0.001$ for VMS).

As summarized in Table 4 and Figure 2, the higher gait variability was associated with the lower cortical thickness of five regions (2 clusters in left hemisphere and 3 clusters in right hemisphere) in the vertex-wise analysis. However, there were no clusters where their volume was associated with gait variability. In the left hemisphere, one cluster (LH1) included the inferior temporal cortex, covering portions of the middle, and superior temporal cortices. This cluster extended medially to include the entorhinal, and para-hippocampal cortices, as well as posteriorly to include fusiform gyrus, and lingual cortex ($p = 0.0001$). The other cluster (LH2) included superior frontal gyrus, which contains supplementary motor area, medial frontal gyrus, and covered a part of the paracentral lobule ($p = 0.0001$). In the right hemisphere, one cluster (RH1) included superior frontal gyrus, which is mostly the supplementary motor area, medial frontal gyrus, and paracentral lobule. This cluster extended laterally to the part of caudal- and rostral middle frontal gyri ($p = 0.0001$). Another cluster (RH2) included the precentral gyrus and extended to anteriorly include a part of the caudal middle frontal cortex anteriorly and inferiorly to the parsopercularis. ($p = 0.0004$). The other cluster (RH3) included the fusiform gyrus, and lateral occipital cortex ($p = 0.0001$). As shown in Table 5, all these associations were also significant when sex, education level, GDS, CIRS, leg length and the existence of arthritis were adjusted.

Cortical thinning of the LH1 was associated with the lower CERAD-TS and VMS. This was the case when age, sex, education level, GDS, CIRS, leg length, the presence of arthritis and eTIV were adjusted. However, cortical thickness of other clusters was not associated with CERAD-TS and VMS (Table 6). In the mediation analyses, the cortical thickness of LH1 mediated the association of gait variability with CERAD-TS (indirect effect = -1.65, SE = 0.79, bias-corrected 95% confidence interval = [-3.38, -0.23]; Figure 3A) and explained 17% of the total effect of gait variability on CERAD-TS. However, the mediating role of the cortical thickness of LH1 in the association of the gait variability with VMS was not statistically significant (indirect effect = -0.49, SE = 0.31, bias-corrected 95% confidence interval = [-1.14, 0.08]; Figure 3B).

IV Discussion

1. Summary

In the current thesis, I investigated the feasibility of gait variability as a novel digital biomarker of cognitive decline. Ultimately, I aimed to identify a marker that is not only practical (non-invasive and widely accessible) but can also sensitively predict cognitive decline in early stages. This was motivated by the need for earlier diagnoses which would lead to more efficient treatments and alleviate the projected socioeconomic burden of dementia in the coming years.

In the first part of my research, I focused on exploring the predictive potential of gait variability, and comparing it with that of gait speed. As a result, we found that gait variability can predict the risk of cognitive decline in cognitively normal older people and better than gait speed, the most widely studied gait parameter as a predictive marker of cognitive decline. We additionally found that no sex differences were found when assessing the ability of high gait variability to predict future cognitive decline. When we computed gait variability and gait speed as continuous variables to explore whether there are any threshold effects, the risk of incident cognitive decline increased 1.5 times per 10% increment of gait variability, whereas it did not change significantly with changes of gait speed.

In the second part of my research, I investigated which degenerative structural changes in the brain may underlie the observed predictive power of gait variability and focused on the shared neural substrates for gait variability and cognitive function. I found the widespread decrease in cortical thickness with increasing gait variability while there was no significant association with the volume of subcortical structures. Among the clusters that showed significant correlation with the gait variability, a cluster that included the inferior temporal, entorhinal, parahippocampal, fusiform, and lingual in left hemisphere was also associated with global cognitive function, and verbal memory function. In mediation analysis, I reaffirmed that cortical thickness of the cluster played a significant mediating role in the association

of gait variability with cognitive function.

2. Gait variability and incident cognitive decline

In the first study, we explored the predictive potential of gait variability through 4-year prospective cohort study on community-dwelling cognitively normal elderly individuals. We demonstrated that high gait variability showed about 2-fold higher risk of MCI than those in other quintiles. However, gait speed could not predict the future risk of MCI in this cognitively normal elderly population. To our knowledge, this is the first prospective cohort study directly showing that gait variability, but not gait speed, may precede cognitive decline and thus be a predictive biomarker of MCI in the cognitively normal elderly population. Our observation is in line with previous longitudinal observations showing that high gait variability factor scores were associated with future risk of dementia in non-demented elderly individuals and high gait variability predicted future risk of AD in people with MCI (Gillain, Drame et al. 2016).

In contrast to our observation, previous longitudinal studies reported that slow gait speed often precedes cognitive impairment and predicts faster cognitive decline (Camicioli, Howieson et al. 1998, Deshpande, Metter et al. 2009, Taniguchi, Yoshida et al. 2012). A longitudinal study from Japan showed that cognitively intact older adults in the low tertiles of gait speed were 2.06 times more likely to develop cognitive decline, defined as a decrease of three points or more on the MMSE, during a 4-year period (Taniguchi, Yoshida et al. 2012). Other prospective studies from the United States found that cognitively normal elderly individuals with slow gait speed were more likely to develop cognitive decline (Camicioli, Howieson et al. 1998). Unlike these studies, ours found that gait speed failed to predict significant cognitive decline. These conflicting results may be attributable to several methodological

differences between the current study and previous studies. First, previous studies employed different thresholds for categorizing gait speed than the current study. For example, the threshold of the lowest tertile in a study from Japan was ≤1.19 m/s for men and ≤1.11 m/s for women (Taniguchi, Yoshida et al. 2012), and that of the lowest quartile in a study from United States was 1.08 m/s without sex stratification (Deshpande, Metter et al. 2009): the threshold values in the Japanese study are slightly higher than ours, and those in the American study are close to ours. (<1.10 m/s for men; <1.08 m/s for women). However, in our population, slow gait speed was also not associated with MCI risk when we employed the same cutoffs as the cited studies (data not shown). Thus, the conflicting results on the association of slow gait speed with MCI risk may be better explained by differences in the characteristics of the study samples or the definition of cognitive decline across studies.

In this study, we rigorously excluded participants maintaining normal cognition despite subclinical neurologic conditions that may impair gait by using UPDRS, POMA, and MHIS. These neurologic conditions may impair cognition as well as gait. In a recent systematic review demonstrating associations between functional and structural cerebral changes and AD-related gait disorders, slower gait speed was associated with white matter lesions mainly in the medial frontal lobes and basal ganglia, whereas higher gait variability was associated with lower hippocampal volume and function (Annweiler, Beauchet et al. 2012). In the present study, even though elderly in highest quintile of gait variability had normal range of MMSE scores at baseline, they showed poorer performance on verbal memory and executive function already at the baseline than those in other quintiles. The result is consistent with previous findings that gait variability is associated with not only hippocampal but also fronto-executive function. (Sheridan, Solomont et al. 2003, Allali, Kressig et al. 2007) Those functions have been known as firstly affected cognitive domains in the course of neurodegenerative disease. Taken together with our observations, gait

variability may predict future cognitive decline early in the course of neurodegenerative disease, and may predict better than gait speed especially in cognitively normal elderly individuals without cerebral ischemic burdens and Parkinsonism. In addition to the differences in the characteristics of study samples between studies, differences in the definition of cognitive decline might also have contributed to the conflicting results on the association of gait speed and the risk of cognitive decline in the current and previous studies. In this study, we defined cognitive decline as incident MCI according to the diagnostic criteria proposed by the International Working Group on MCI (Winblad, Palmer et al. 2004). However, in previous studies, cognitive decline was defined as a decline of 3 points or more on MMSE (Deshpande, Metter et al. 2009) or a decline of 0.5 or more on CDR (Camicioli, Howieson et al. 1998).

To the best of our knowledge, this is the first prospective cohort study directly showing that increased gait variability may precede cognitive decline and thus be a predictive biomarker of incident cognitive decline in the NC population. In addition, the present study used wearable sensor-based gait analysis as a tool to predict cognitive decline for the first time. Another strength of this study is that we comprehensively measured the participant's cognitive function to determine whether it is possible to predict future cognitive decline even in NC conditions that do not meet the diagnostic criteria of MCI. However, this study had several limitations. First, the sample size was small and the follow-up duration relatively short. Second, our subjects were relatively young, cognitively normal, and free from cerebrovascular diseases and Parkinsonism. Therefore, our observations cannot be generalized to the complete cognitively normal elderly population. Given the youth and uniqueness of our population, further study is warranted to generalize these interesting findings. Third, a single gait assessment may not reflect typical daily gait speed or variability. Further research on neural substrates that may explain this

relationship between gait variability measured with TAA and cognitive decline is warranted.

3. Shared neural substrates between gait variability-cognitive function

In the second study, I investigated which degenerative structural changes in the brain may underlie the observed predictive power of gait variability and focused on the shared neural substrates for gait variability and cognitive function. This study found that the higher gait variability was associated with the lower global cognition and verbal memory in non-demented older adults, which is in line with our previous work on cognitively normal older adults (Byun, Han et al. 2018). This study also found that the cortical thinning of the clusters including the inferior temporal, entorhinal, parahippocampal, fusiform, and lingual in left hemisphere mediated the association between the higher gait variability and the lower cognitive function.

The current study found that the higher step time variability was associated with the thinner GM of prefrontal, supplementary motor, and paracentral lobule in both hemispheres and superior temporal, middle temporal, and inferior temporal in the left hemisphere. Motor cortex is one of the regions to show significantly reduced cortical thickness with increased temporal gait variability in the present study, which is consistent with previous studies (Annweiler, Beauchet et al. 2013, Jayakody, Breslin et al. 2020). More specifically, we identified cortical thinning of paracentral lobule, the medial continuation of primary motor and sensory gyri, which controls lower limb movement. We also found that the thinning of the medial frontal gyri including the supplementary and pre-supplementary motor areas was associated with high temporal gait variability. The findings suggest that not only the primary motor cortex involved in execution phase (i.e. converting motor programs into movements) but also other frontal areas involved in planning and programming may influence the

temporal gait variability. In addition, other non-frontal regions such as both fusiform gyrus, left parahippocampal, inferior temporal and lingual gyri, and right lateral occipital cortex that play important roles in the visual network also influenced the temporal gait variability. Theses regions are known to be involved in visual processing (Weiner and Zilles 2016), visual perception (Koenraadt, Roelofsen et al. 2014), and spatial orientation and navigation (Buckner, Andrews-Hanna et al. 2008). Dynamic instability may be better explained by cerebral cortical misprocessing than abnormal subcortical gait control (Annweiler, Beauchet et al. 2012).

To the best of our knowledge, this is the first study to directly demonstrate the gait-cognition relationship through a shared neural network in an older non-demented population. We combined exploratory mapping and a priori ROI-based measurement techniques, first by performing an exploratory analysis of cortical thickness across the entire cortical mantle to map the "cortical signature" of regional thinning correlated with gait variability and then by using this map to generate ROIs to find out, in an a priori fashion, the regional cortical thinning correlated with poorer cognitive functions simultaneously. We identified that cortical thinning of the cluster including the entorhinal, parahippocampal, fusiform, lingual, and inferior temporal in left hemisphere linked to gait variability was also correlated with lower VMS and CERAD-TS. Medial temporal cortex, including entorhinal and parahippocampal cortex, has been widely studied to be related to episodic memory, and is one of the first regions to exhibit neurodegeneration in AD (Jack, Petersen et al. 1997). Also, the network coves entorhinal, parahippocampal, and fusiform areas is known to be involved in visuospatial navigation and the imagination of the visual environment, which is needed for locomotion (Ekstrom, Kahana et al. 2003, Jahn, Deutschländer et al. 2004). Through mediation analysis, we confirmed that the cortical thickness of the cluster including the entorhinal, parahippocampal, fusiform, lingual, and inferior temporal in left hemisphere mediates the association of CERAD-TS with gait

variability. That accounted for 17% of the total effect of gait variability on CERAD-TS. Together, our findings suggest that gait variability and cognitive function rely on shared neural systems that are firstly affected by pathological aging such as AD. In a recent multisite cross-sectional study with older adults across neurodegenerative conditions, high gait variability discriminated AD from other neurodegenerative and cognitive conditions. Taking a step further from the results, the present study showed that neurodegenerative changes in widespread cerebral regions, measured by cortical thinning, may manifest as increased gait variability at an earlier stage than can be detected by clinical diagnosis of dementia. Also, our results suggest that the gait variability obtained from a body-worn TAA may be a potential digital biomarker of neurodegenerative diseases such as AD. Its properties of being free from time and space constraints and low cost makes it potentially usable in the clinical setting or clinical trials, especially in non-face-to-face environments. Our results also highlight the importance of examining comprehensive metrics of gait beyond simple gait speed measurement.

The current study also found that the cortical thickness of entorhinal and parahippocampal cortices but not the volume of hippocampus was associated with the gait variability in non-demented older adults. A large-scale neuroimaging study proposed that the better option to assess neurodegeneration in regions characteristic of Alzheimer's disease is to use thickness measurements rather than volumes, because thickness is sufficiently uncorrelated with TIV (Schwarz, Gunter et al. 2016). In addition, in detecting MCR, cortical thickness was better than cortical volume or surface area. (Blumen, Schwartz et al. 2021). Consistent with these results, cortical regions that were associated with gait variability disappeared, when the GM thickness was changed to the volume in the present study. The studies on the association between the regional cortical volume and the temporal gait variability in the older adults without neurological diseases were limited and their results were

inconsistent. Beauchet et al. reported that the higher temporal gait variability was associated with the larger hippocampus (Beauchet, Launay et al. 2015) while other studies could not find the association of temporal gait variability with hippocampal volume. (Manor, Newton et al. 2012, Beauchet, Annweiler et al. 2014, Sakurai, Bartha et al. 2018) Sakurai et al. reported that smaller entorhinal cortex but not hippocampus was associated with the slower dual task gait speed in older adults with MCI, (Sakurai, Bartha et al. 2018) which is in line with the results of the current study. Growing body of literature indicates that entorhinal cortex atrophy precedes hippocampal atrophy in pathological aging (Killiany, Hyman et al. 2002, deToledo-Morrell, Stoub et al. 2004, Stoub, Bulgakova et al. 2005).

This study has several limitations. First, the cross-sectional nature of the current study does not allow for causal interpretation between cortical thinning and higher gait variability. Future longitudinal studies are needed to examine changes in cortical thickness over time and how they relate to gait variability. Second, the gait variability obtained from one-time assessment may not properly reflect one's gait variability. The shared neural substrates between gait variability and cognitive function needs to be replicated using the gait features obtained for longer period using a wearable inertia sensor.

4. Conclusion and perspectives

Overall, gait variability measured by a TAA demonstrates potential as a low-cost digital biomarker for prediction of cognitive decline years before clinical diagnosis. Gait variability can predict the risk of cognitive decline over 4 years in NC older people and better than gait speed. Medial temporal cortex, one of the first regions to exhibit neurodegeneration in Alzheimer's disease, was the shared neural substrates for gait variability and cognitive function. Degenerative structural changes in the areas may underlie the observed predictive power of gait variability for cognitive

decline.

Evaluation of detailed gait metrics is currently limited to research applications due to the cost and nature of their visits to institutions. Furthermore, assessments performed under observation and use of instrumented walkways are limited, snapshot evaluations in unnatural environments. These limitations preclude repeated and frequent use to test an individual and specifically in the early pre-symptomatic stage of the neurodegenerative diseases. Wearable sensor-based measurements do not require visits to the clinic or laboratory-based assessment, therefore natural gait in real world environments can be evaluated over longer periods of time and at a lower cost. These strengths also have raised the possibility that wearable sensor-based biomarkers can be used as new patient-focused outcomes in real-life scenarios in clinical trials. Elsewhere, a difference in wearable physical activity counts for those within a heart failure intervention compared to a placebo was identified, but not by the traditional regulatory-accepted patient-reported biomarker. (Redfield, Anstrom et al. 2015) Although gait variability is more difficult and expensive to measure than gait speed in research and clinical settings, body-worn activity sensors may be a better option to introduce gait variability as a window into brain functioning for neurological conditions in various settings than a pressure-sensor walkway or 3D video gait analysis because they are cost-efficient, easy to apply, sensitive, and reliable (Byun, Han et al. 2016, Del Din, Godfrey et al. 2016).

A growing body of evidence indicates that cognitive, sensory changes, as well as motor changes, may precede clinical manifestations of AD by several years. Many digital markers through various wearable devices have been proposed for Alzheimer's disease: camera-measured eye movements, gaze, pupil reflexes, and facial expression traits, photoplethysmography based beat-by-beat heart rate measurement, heart rate variability, and oxygen saturation (SpO2), body temperature measured with a thermometer on a ring, patch or watch, smart-phone based

monitoring of social network activity, and more. Combination of gait variability and such digital markers has the potential to further enhance the predictive power of cognitive decline, and studies on them also need to be conducted actively in the future.

Acknowledgment

Potential Conflicts of Interest

Nothing to report.

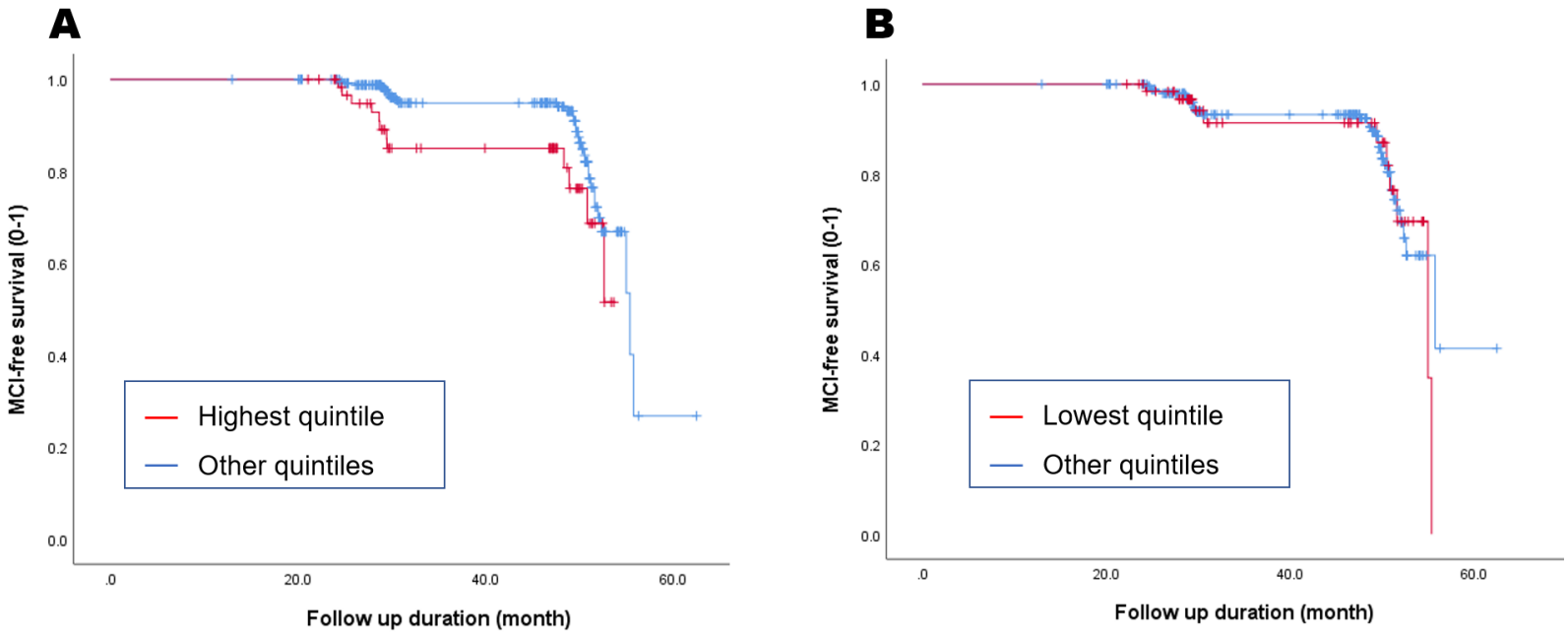

Figure 1. Risk of incident mild cognitive impairment (MCI) over 4 years stratified by variability ($\chi 2 = 4.56$ and $p = 0.033$ by log-rank test) (a) and gait speed ($\chi 2 = 0.086$ and $p = 0.770$ by log-rank test) (b). The mean MCI free survival of participants in the high variability group was 10% shorter than that of the other quintiles group (a), whereas there was no group difference according to gait speed (b).

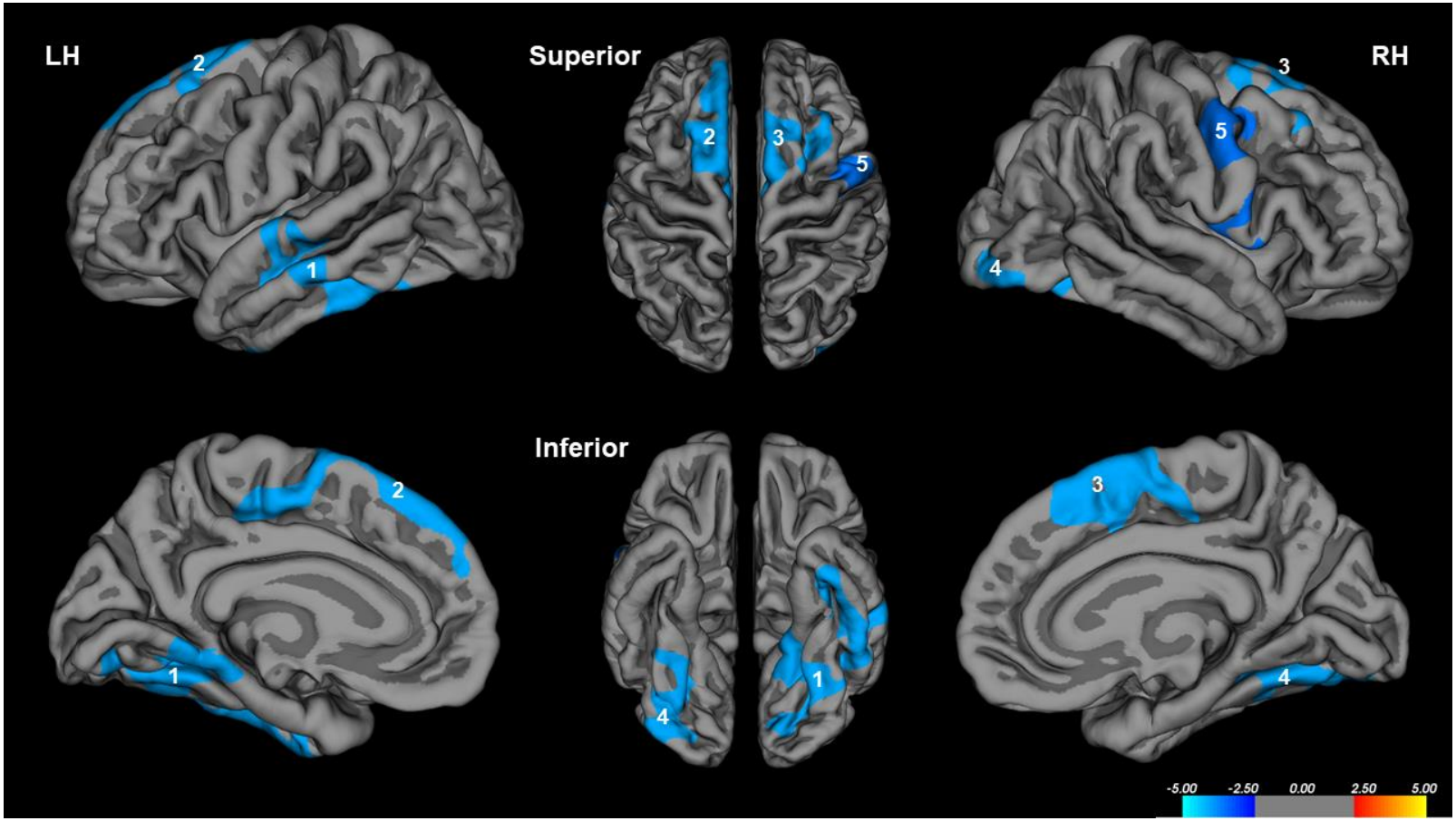

Figure 2. Cortical thickness and gait variability in non-demented older adults

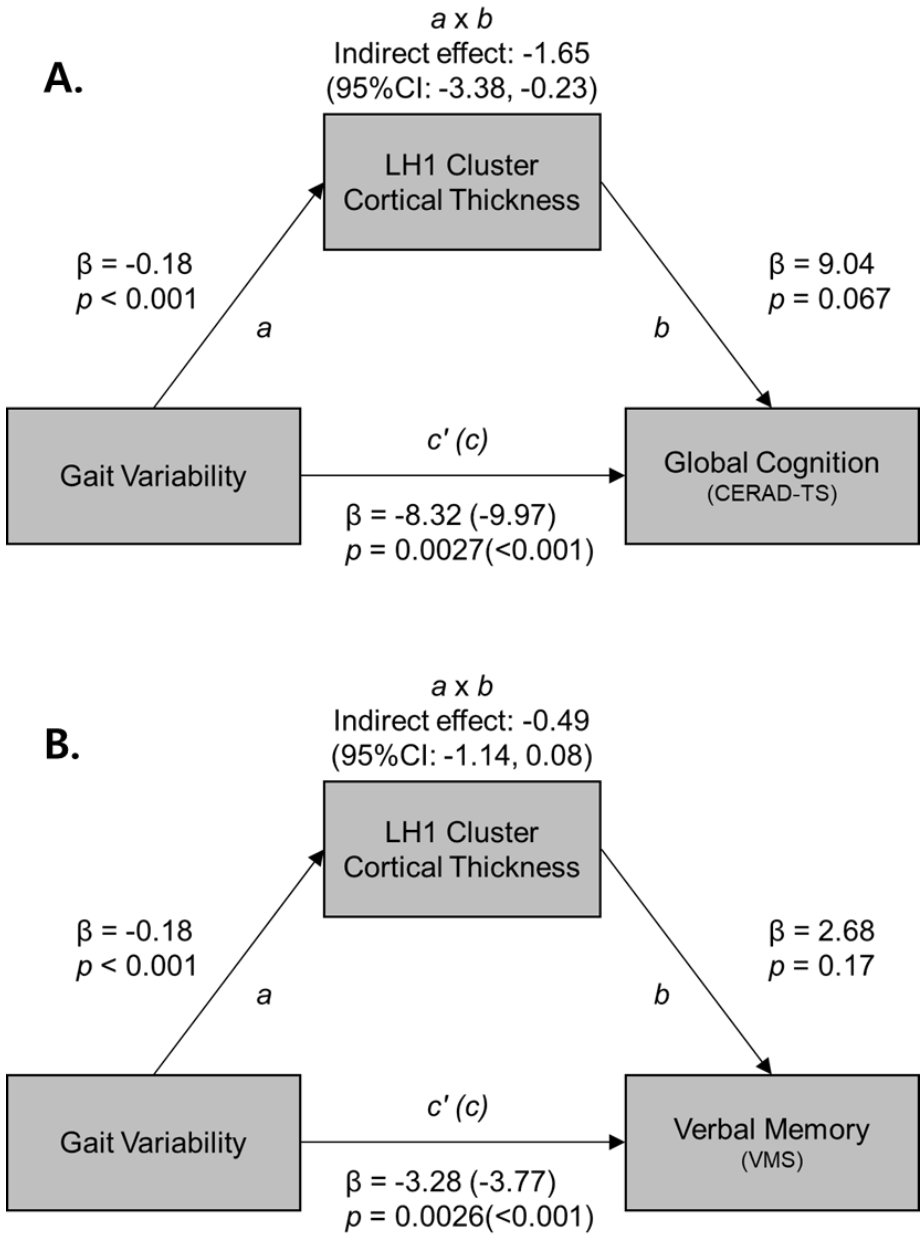

Figure 3. Cortical thickness of LH1 cluster mediates[a] effect of gait variability on (A) CERAD-TS and (B) VMS.
LH1 cluster: a cluster including part of temporal, fusiform, and lingual gyrus; VMS = Verbal Memory Score; CERAD-TS = Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery total score; GDS = Geriatric Depression Scale; CIRS = Cumulative Illness Rating Scale; eTIV = estimated total intracranial volume.
[a]Parallel mediation analyses, adjusted for sex, age, education, GDS, CIRS, and eTIV.

Table 1. Demographic, clinical, cognitive function, and gait characteristics of the subjects

	Gait variability						**Gait speed**					
	1^{st} (N = 73)	2^{nd} (N = 72)	3^{rd} (N = 71)	4^{th} (N = 71)	***5^{th}(Highest)*** (N = 71)	*P**	***1^{st}(Lowest)*** (N = 73)	2^{nd} (N = 72)	3^{rd} (N = 71)	4^{th} (N = 71)	5^{th} (N = 71)	*P**
Clinical parameters												
Age (years, mean ± SD)	70.4 ± 4.7	70.9 ± 5.4	70.1 ± 4.4	71.4 ± 5.9	70.1 ± 6.4	0.580	73.2 ± 5.7	71.2 ± 5.0	69.5 ± 4.9	70.6 ± 5.1	68.4 ± 5.1	**<0.001**
Sex (female, %)	49.3	48.6	49.3	49.3	49.3	1.000	49.3	48.6	49.3	49.3	49.3	1.000
Education (years, mean ± SD)	13.4 ± 3.6	13.8 ± 3.1	13.6 ± 3.8	13.9 ± 3.6	13.5 ± 4.3	0.913	14.3 ± 3.3	13.2 ± 4.5	13.1 ± 3.9	14.0 ± 3.3	13.5 ± 3.3	0.250
CIRS (points, mean ± SD)	6.5 ± 3.1	6.0 ± 2.8	6.1 ± 3.1	5.8 ± 3.0	5.9 ± 3.1	0.641	7.3 ± 3.0	6.2 ± 3.1	5.9 ± 2.8	5.9 ± 3.1	4.9 ± 2.5	**<0.001**
GDS (points, mean ± SD)	7.3 ± 5.0	6.4 ± 5.4	6.6 ± 4.6	6.6 ± 5.6	8.5 ± 6.0	0.106	7.4 ± 6.0	7.9 ± 6.2	6.9 ± 4.9	6.6 ± 5.1	6.6 ± 4.5	0.507
Presence of APOE ε4 allele (%)	19.2	11.1	25.4	26.8	21.1	0.154	28.8	8.3	19.7	19.7	26.8	**0.024**
Neuropsychological test scores												
MMSE	28.2 ± 1.5	28.0 ± 1.6	28.5 ± 1.4	28.4 ± 1.6	27.8 ± 2.5	0.098	28.0 ± 2.0	28.1 ± 2.3	28.0 ± 1.7	28.5 ± 1.5	28.4 ± 1.4	0.394
WLMT	20.2 ± 3.1	20.0 ± 3.8	21.1 ± 3.7	19.6 ± 3.6	19.1 ± 3.9	**0.026**	19.5 ± 4.0	20.2 ± 3.8	19.4 ± 3.2	20.7 ± 3.8	20.1 ± 3.6	0.217
WLRT	6.9 ± 1.7	6.8 ± 1.8	6.9 ± 1.8	6.9 ± 1.8	6.4 ± 1.9	0.417	6.9 ± 1.8	6.7 ± 1.7	6.6 ± 1.7	7.0 ± 1.8	6.8 ± 1.9	0.782
WLRcT	9.6 ± 0.7	9.5 ± 0.8	9.4 ± 0.9	9.5 ± 0.8	9.3 ± 1.1	0.505	9.5 ± 1.0	9.5 ± 0.9	9.3 ± 0.8	9.5 ± 0.9	9.5 ± 0.8	0.581
CRT	8.4 ± 2.3	8.6 ± 2.5	8.6 ± 2.1	8.2 ± 2.3	7.6 ± 2.4	0.104	8.2 ± 2.1	8.2 ± 2.5	8.5 ± 2.4	8.2 ± 2.4	8.4 ± 2.4	0.882
FAB	16.5 ± 1.2	16.5 ± 1.4	16.4 ± 1.5	16.2 ± 1.8	15.6 ± 2.1	**0.010**	16.3 ± 1.4	16.1 ± 1.9	16.0 ± 2.0	16.5 ± 1.3	16.3 ± 1.5	0.439
TMA-A	41.0 ± 14.6	40.9 ± 20.9	38.5 ± 12.7	40.3 ± 13.3	51.2 ± 42.2	**0.011**	42.3 ± 17.5	44.9 ± 41.1	42.6 ± 18.7	39.6 ± 15.7	42.4 ± 15.6	0.774
CFT	20.5 ± 5.4	19.2 ± 4.5	19.6 ± 4.7	19.5 ± 4.0	17.8 ± 5.2	**0.020**	18.6 ± 4.9	19.9 ± 5.3	18.9 ± 4.3	19.5 ± 4.8	19.8 ± 4.8	0.416
15-BNT	14.3 ± 0.9	14.3 ± 0.9	14.5 ± 0.8	14.2 ± 1.0	13.9 ± 1.5	0.060	14.1 ± 1.2	14.2 ± 1.4	14.4 ± 0.9	14.4 ± 0.9	14.2 ± 0.9	0.368
CPT	10.6 ± 0.6	10.6 ± 0.6	10.7 ± 0.6	10.6 ± 0.7	10.6 ± 0.9	0.949	10.7 ± 0.6	10.4 ± 1.0	10.7 ± 0.5	10.6 ± 0.6	10.7 ± 0.5	**0.004**

DSF	7.4 ± 2.3	7.8 ± 2.2	8.0 ± 2.3	8.1 ± 2.2	7.2 ± 2.3	0.111	7.8 ± 2.1	7.5 ± 2.4	7.8 ± 2.3	7.9 ± 2.5	7.4 ± 2.2	0.645
DSB	5.8 ± 1.9	5.9 ± 1.9	6.1 ± 2.1	5.7 ± 1.8	5.5 ± 1.8	0.461	5.4 ± 1.6	5.9 ± 2.1	5.7 ± 2.1	6.4 ± 1.7	5.7 ± 1.9	**0.024**
Gait parameters												
Variability (%CV, mean ± SD)†	1.8 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	2.7 ± 0.1	3.5 ± 0.6	<0.001	2.8 ± 0.7	2.5 ± 0.6	2.4 ± 0.6	2.4 ± 0.6	2.5 ± 0.6	0.005
Speed (m/s, mean ± SD)	1.2 ± 0.1	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.034	1.0 ± 0.1	1.1 ± 0.0	1.2 ± 0.0	1.3 ± 0.0	1.4 ± 0.1	<0.001

CIRS, Cumulative Illness Rating Scale; GDS, Geriatric Depression Scale; APOE, Apolipoprotein E; MHIS, Modified Hachinski Ischemic Score; MMSE = Mini Mental Status Examination; WLMT = Word List Memory Test; WLRT = Word List Recall Test; WLRcT = Word List Recognition Test; CRT = Constructional Recall Test; FAB = Frontal Assessment Battery; TMA-A = Trail Making Test A; CFT = Categorical Fluency Test; 15-BNT = 15 item Boston Naming Test; CPT = Constructional Praxis Test; DSF = Digit Span Forward; DSB = Digit Span Backward; CV, Coefficient of Variance

*Chi-square test or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables

†We used 79.89 ± 1.82 (mean ± standard deviation) steps for measuring of gait variability

Table 2. Prediction of mild cognitive impairment in cognitively normal elderly individuals*

	Model A : Gait speed only			Model B : Gait variability only			Model C : Both gait speed and variability		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Gait speed									
Other quintiles	1.00						1.00		
Lowest quintile	1.06	0.49, 2.30	0.883				0.98	0.44, 2.14	0.950
Gait variability									
Highest quintile				1.00			1.00		
Other quintiles				2.12	1.05, 4.31	**0.037**	2.13	1.04, 4.34	**0.038**
Measures of fit									
-2 Log likelihood	378.2			374.3			374.3		
p value†				0.048†			0.954‡		
C-index	0.661			0.687			0.688		

HR, hazard ratio; CI, confidence interval

*Multivariable Cox proportional hazard analysis adjusting age, sex, education, Cumulative Illness Rating Scale score, Geriatric Depression Scale score, and presence of apolipoprotein E e4 allele as covariates

†Compared to Model A

‡Compared to Model B

Table 3. Characteristics of participants (N=207)

	All (N = 207)	Male (N = 113)	Female (N = 94)	p*
Age at MRI scan (years)	72.7 ± 6.7	73 ± 6.9	72.2 ± 6.5	0.375
Education (years)	13.0 ± 4.1	14.6 ± 3.7	11.0 ± 3.8	<0.001
Leg length (cm)	84.2 ± 6.7	86.7 ± 6.8	81.3 ± 5.2	<0.001
Gait variability (ln % CV)†	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.2	0.313
Gait speed (m/s)	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	0.603
GDS (points)	7.9 ± 5.7	6.5 ± 5.3	9.6 ± 5.7	<0.001
CIRS (points)	7.1 ± 3.3	7.2 ± 3.6	6.9 ± 2.8	0.575
MHIS (points)	0.8 ± 1.2	0.9 ± 1.4	0.7 ± 0.8	0.283
Existence of arthritis (%)	29.0	15.0	45.7	<0.001
CERAD-TS (points)	76.8 ± 10.9	78.2 ± 9.2	75.1 ± 12.5	0.047
VMS (points)	21.7 ± 4.1	21.8 ± 4	21.7 ± 4.3	0.859

Note. CV, Coefficient of Variance; GDS, Geriatric Depression Scale; CIRS, Cumulative Illness Rating Scale; MHIS, Modified Hachinski Ischemic Score; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery total score; VMS, Verbal Memory Score.

*Student's t test for continuous variables (presented as mean ± standard deviation) and Chi-square test for categorical variables (presented as %)

†Natural log transformation of % CV of step time was used as gait variability since % CV of step time was not normally distributed.

Table 4. Vertex-Wise Analyses of Gait Variability and Cortical Thickness (N=207)

Clusters	Cluster Size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices Within Cluster	p*
Left hemisphere				
Temporal/fusiform (LH1)	4460.81	-53.1, -24.0, -4.0	7678	0.0001
Superior frontal/paracentral (LH2)	1766.48	-6.6, 33.8, 49.8	3417	0.0001
Right hemisphere				
Superior frontal/paracentral (RH1)	2289.14	11.0, 14.6, 62.2	4455	0.0001
Fusiform/lingual (RH2)	1792.45	34.3, -73.5, -12.0	2823	0.0001
Precentral (RH3)	1723.35	40.2, -10.9, 42.6	3519	0.0004

*Analyses were corrected for multiple comparisons using the built-in Monte Carlo simulation at a threshold set at a p value <0.05, a cluster-wise correction that controls for the rate of false positive clusters.

Table 5. Regression Analyses of Gait Variability and Cortical Thickness

Clusters	B	SE	*t*	*p*[*]	β
Left hemisphere					
Temporal/fusiform (LH1)					
Unadjusted	-0.196	0.038	-5.168	<0.001	-0.329
Adjusted[*]	-0.177	0.038	-4.685	<0.001	-0.297
Superior frontal/paracentral (LH2)					
Unadjusted	-0.219	0.048	-4.543	<0.001	-0.302
Adjusted[*]	-0.209	0.049	-4.264	<0.001	-0.289
Right hemisphere					
Superior frontal/paracentral (RH1)					
Unadjusted	-0.225	0.045	-5.010	<0.001	-0.330
Adjusted[*]	-0.211	0.045	-4.668	<0.001	-0.309
Fusiform/lingual (RH2)					
Unadjusted	-0.222	0.046	-4.801	<0.001	-0.309
Adjusted[*]	-0.213	0.046	-4.578	<0.001	-0.296
Precentral (RH3)					
Unadjusted	-0.225	0.044	-5.065	<0.001	-0.333
Adjusted[*]	-0.214	0.044	-4.894	<0.001	-0.316

[*]Adjusted for age and total intracranial volume. Adjusted model additionally adjusted for sex, education level, GDS, CIRS, leg length, and the existence of arthritis.

Table 6. Associations between Cortical Regions related with Gait Variability and Cognitive Function (N=207) [a]

	CERAD-TS				VMS			
	B	SE	*t*	*p*[*]	B	SE	*t*	*p*
Left hemisphere								
Temporal/fusiform (LH1)	14.09	4.74	2.97	0.003	4.71	1.86	2.53	0.01
Superior frontal/paracentral (LH2)	3.62	3.80	0.95	0.34	1.62	1.48	1.09	0.28
Right hemisphere								
Superior frontal/paracentral (RH1)	3.35	4.10	0.82	0.42	1.60	1.60	1.00	0.31
Fusiform/lingual (RH2)	6.80	3.97	1.72	0.09	1.58	1.55	1.02	0.31
Precentral (RH3)	8.00	4.22	1.90	0.06	2.92	1.65	1.77	0.08

Note. CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery total score; VMS, Verbal Memory Score; SE, Standard Error; GDS, Geriatric Depression Scale; CIRS, Cumulative Illness Rating Scale; eTIV, estimated total intracranial volume.
[*]Adjusted for sex, age, education, GDS, CIRS, leg length, existence of arthritis, and eTIV.

Bibliography

Allali, G., et al. (2007). "Changes in gait while backward counting in demented older adults with frontal lobe dysfunction." Gait Posture **26**(4): 572-576.

Annweiler, C., et al. (2013). "Motor cortex and gait in mild cognitive impairment: a magnetic resonance spectroscopy and volumetric imaging study." Brain **136**(3): 859-871.

Annweiler, C., et al. (2012). "Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review." American Journal of Alzheimer's Disease & Other Dementias® **27**(6): 371-380.

Annweiler, C., et al. (2012). "Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review." **27**(6): 371-380.

Association, A. P. (2000). "DSM-IV-TR: Diagnostic and statistical manual of mental disorders, 4th ed., text revision." Washington, DC: American Psychiatric Association **75**.

Beauchet, O., et al. (2013). "Gait variability at fast-pace walking speed: a biomarker of mild cognitive impairment?" The journal of nutrition, health & aging **17**(3): 235-239.

Beauchet, O., et al. (2014). "Higher gait variability is associated with decreased parietal gray matter volume among healthy older adults." Brain Topogr **27**(2): 293-295.

Beauchet, O., et al. (2015). "Hippocampal volume, early cognitive decline and gait variability: which association?" Exp Gerontol **61**: 98-104.

Blumen, H. M., et al. (2019). "Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study." Brain Imaging and Behavior **13**(2): 446-460.

Blumen, H. M., et al. (2021). "Cortical Thickness, Volume, and Surface Area in the Motoric Cognitive Risk Syndrome." **81**(2): 651-665.

Buckner, R. L., et al. (2008). "The brain's default network: anatomy, function, and relevance to disease." **1124**(1): 1-38.

Burgmans, S., et al. (2009). "Prefrontal cortex atrophy predicts dementia over a six-year period." Neurobiology of aging **30**(9): 1413-1419.

Byun, S., et al. (2018). "Gait variability can predict the risk of cognitive decline in cognitively normal older people." Dementia and geriatric cognitive disorders **45**: 251-261.

Byun, S., et al. (2016). "Test-retest reliability and concurrent validity of a single tri-

axial accelerometer-based gait analysis in older adults with normal cognition." PloS one **11**(7): e0158956.

Camicioli, R., et al. (1998). "Motor slowing precedes cognitive impairment in the oldest old." Neurology **50**(5): 1496-1498.

Chiaramonte, R. and M. J. H. K. P. J. Cioni (2021). "Critical spatiotemporal gait parameters for individuals with dementia: A systematic review and meta-analysis." **41**(01): 1-14.

D., W. (1987). "Wechsler Memory Scale-Revised." The Psychological Corporation.

de Jager, C. A., et al. (2017). "Dementia prevalence in a rural region of South Africa: a cross-sectional community study." Journal of Alzheimer's Disease **60**(3): 1087-1096.

Del Din, S., et al. (2019). "Gait analysis with wearables predicts conversion to Parkinson disease." Annals of Neurology **86**(3): 357-367.

Del Din, S., et al. (2016). "Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length." Journal of neuroengineering and rehabilitation **13**(1): 1-12.

Del Din, S., et al. (2016). "Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: toward clinical and at home use." IEEE journal of biomedical and health informatics **20**(3): 838-847.

Deshpande, N., et al. (2009). "Gait speed under varied challenges and cognitive decline in older persons: a prospective study." Age and ageing **38**(5): 509-514.

Desikan, R. S., et al. (2006). "An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest." **31**(3): 968-980.

deToledo-Morrell, L., et al. (2004). "MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD." **25**(9): 1197-1203.

Dodge, H., et al. (2012). "In-home walking speeds and variability trajectories associated with mild cognitive impairment." Neurology **78**(24): 1946-1952.

Ekstrom, A. D., et al. (2003). "Cellular networks underlying human spatial navigation." Nature **425**(6954): 184-188.

FLEMING, R., et al. (2020). "World Alzheimer Report 2020: Design Dignity Dementia: dementia-related design and the built environment." Alzheimer's Disease International **1**.

FRIGO, C. (1992). "METHODS FOR GAIT ANALYSIS." Restoration of Walking for Paraplegics: Recent Advancements and Trends **11**: 95.

Gale, C. R., et al. (2014). "The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing." Age **36**(4): 9682.

Galna, B., et al. (2013). "Is gait variability reliable in older adults and Parkinson's disease? Towards an optimal testing protocol." Gait & posture **37**(4): 580-585.

Gillain, S., et al. (2016). "Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? A pilot study." Aging clinical and experimental research **28**(2): 249-255.

Godfrey, A., et al. (2019). "Inertial wearables as pragmatic tools in dementia." **127**: 12-17.

Gold, M., et al. (2018). "Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials." **4**: 234-242.

Hampel, H., et al. (2018). "Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic." Nat Rev Neurol **14**(11): 639-652.

Hartmann, A., et al. (2009). "Reproducibility of spatio-temporal gait parameters under different conditions in older adults using a trunk tri-axial accelerometer system." Gait & posture **30**(3): 351-355.

Hayes, A. F. (2017). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach, Guilford publications.

Hsu, Y., et al. (2014). "Gait and Balance Analysis for Patients With Alzheimer's Disease Using an Inertial-Sensor-Based Wearable Instrument." IEEE Journal of Biomedical and Health Informatics **18**(6): 1822-1830.

Hutton, C., et al. (2009). "A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging." Neuroimage **48**(2): 371-380.

Jack, C. R., et al. (1998). "Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease." Neurology **51**(4): 993-999.

Jack, C. R., et al. (1997). "Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease." Neurology **49**(3): 786-794.

Jahn, K., et al. (2004). "Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging." Neuroimage **22**(4): 1722-1731.

Jayakody, O., et al. (2020). "Regional Associations of Cortical Thickness With Gait Variability-The Tasmanian Study of Cognition and Gait." J Gerontol A Biol Sci Med Sci **75**(8): 1537-1544.

Kang, G. E., et al. (2020). "Characteristics of the gait initiation phase in older adults

with diabetic peripheral neuropathy compared to control older adults." Clinical Biomechanics **72**: 155-160.

Kawakami, I., et al. (2014). "Tau accumulation in the nucleus accumbens in tangle-predominant dementia." Acta neuropathologica communications **2**(1): 1-11.

Killiany, R., et al. (2002). "MRI measures of entorhinal cortex vs hippocampus in preclinical AD." **58**(8): 1188-1196.

Kim, J. Y., et al. (2008). "Standardization of the Korean version of the geriatric depression scale: reliability, validity, and factor structure." Psychiatry investigation **5**(4): 232-238.

Kim, T. H., et al. (2010). "Korean version of frontal assessment battery: psychometric properties and normative data." Dementia and geriatric cognitive disorders **29**(4): 363-370.

Kim, T. H., et al. (2013). "Overview of the Korean Longitudinal Study on Cognitive Aging and Dementia." Alzheimer's & Dementia **9**(4): P626-P627.

Ko, S.-U., et al. (2007). "Stride width discriminates gait of side-fallers compared to other-directed fallers during overground walking." **19**(2): 200-212.

Koenraadt, K. L., et al. (2014). "Cortical control of normal gait and precision stepping: an fNIRS study." **85**: 415-422.

Kourtis, L. C., et al. (2019). "Digital biomarkers for Alzheimer's disease: the mobile/ wearable devices opportunity." NPJ Digit Med **2**.

Kressig, R. W. and O. Beauchet (2006). "Guidelines for clinical applications of spatio-temporal gait analysis in older adults." Aging clinical and experimental research **18**(2): 174-176.

LEE, D. Y., et al. (2004). "A normative study of the CERAD neuropsychological assessment battery in the Korean elderly." Journal of the International Neuropsychological Society **10**(01): 72-81.

Lee, J. H., et al. (2002). "Development of the Korean Version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) Clinical and Neuropsychological Assessment Batteries." The Journals of Gerontology Series B: Psychological Sciences and Social Sciences **57**(1): P47-P53.

Lo, O.-Y., et al. (2017). "Gait Speed and Gait Variability Are Associated with Different Functional Brain Networks." Frontiers in aging neuroscience **9**: 390-390.

Lord, S., et al. (2013). "Moving forward on gait measurement: Toward a more refined approach." Movement Disorders **28**(11): 1534-1543.

Manor, B., et al. (2012). "The relationship between brain volume and walking outcomes in older adults with and without diabetic peripheral neuropathy." Diabetes care **35**(9): 1907-1912.

Mielke, M. M., et al. (2013). "Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging." J Gerontol A Biol Sci Med Sci **68**(8): 929-937.

Miller, M. D., et al. (1992). "Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale." Psychiatry research **41**(3): 237-248.

Moe-Nilssen, R., et al. (2010). "Gait variability measures may represent different constructs." Gait & posture **32**(1): 98-101.

Morris, J. C. (1993). "The Clinical Dementia Rating (CDR): current version and scoring rules." Neurology.

O'Bryant, S. E., et al. (2017). "Blood-based biomarkers in Alzheimer disease: current state of the science and a novel collaborative paradigm for advancing from discovery to clinic." Alzheimer's & Dementia **13**(1): 45-58.

Ojagbemi, A., et al. (2015). "Gait speed and cognitive decline over 2 years in the Ibadan study of aging." Gait & posture **41**(2): 736-740.

P. Martinez-Martin, A. G.-N., L. Morlfin Gracia, J. Balseiro GCimez, J. Martinez-SarriCs, and a. T. C. M. G. tF. Bermejo (1994). "Unified Parkinson's Disease Rating Scale Characteristics and Structure." Movement Disorders **9**(1): 76-83.

Patterson, C. (2018). World Alzheimer report 2018, Alzheimer’s Disease International.

Pieruccini-Faria, F., et al. (2021). "Gait variability across neurodegenerative and cognitive disorders: Results from the Canadian Consortium of Neurodegeneration in Aging (CCNA) and the Gait and Brain Study." Alzheimer's & Dementia.

Redfield, M. M., et al. (2015). "Isosorbide mononitrate in heart failure with preserved ejection fraction." **373**(24): 2314-2324.

Rosen, W. G., et al. (1980). "Pathological verification of ischemic score in differentiation of dementias." Annals of Neurology **7**(5): 486-488.

Rosso, A. L., et al. (2014). "Higher step length variability indicates lower gray matter integrity of selected regions in older adults." Gait & posture **40**(1): 225-230.

Sakurai, R., et al. (2018). "Entorhinal Cortex Volume Is Associated With Dual-Task Gait Cost Among Older Adults With MCI: Results From the Gait and Brain Study." The Journals of Gerontology: Series A **74**(5): 698-704.

Sakurai, R., et al. (2019). "Entorhinal cortex volume is associated with dual-task gait cost among older adults with MCI: results from the gait and brain study." The Journals of Gerontology: Series A **74**(5): 698-704.

Schwarz, C. G., et al. (2016). "A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity." **11**: 802-812.

Seo, E. H., et al. (2010). "Total scores of the CERAD neuropsychological assessment battery: validation for mild cognitive impairment and dementia patients with diverse etiologies." The American Journal of Geriatric Psychiatry **18**(9): 801-809.

Sheridan, P. L., et al. (2003). "Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease." J Am Geriatr Soc **51**(11): 1633-1637.

Stoub, T., et al. (2005). "MRI predictors of risk of incident Alzheimer disease: a longitudinal study." **64**(9): 1520-1524.

Taniguchi, Y., et al. (2012). "A prospective study of gait performance and subsequent cognitive decline in a general population of older Japanese." Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences **67**(7): 796-803.

Tian, Q., et al. (2017). "The brain map of gait variability in aging, cognitive impairment and dementia-A systematic review." Neuroscience and biobehavioral reviews **74**(Pt A): 149-162.

Tinetti, M. E. (1986). "Performance-oriented assessment of mobility problems in elderly patients." Journal of the American Geriatrics Society **34**(2): 119-126.

Verghese, J., et al. (2002). "Abnormality of gait as a predictor of non-Alzheimer's dementia." New England Journal of Medicine **347**(22): 1761-1768.

Verghese, J., et al. (2008). "Gait Dysfunction in Mild Cognitive Impairment Syndromes." Journal of the American Geriatrics Society **56**(7): 1244-1251.

Verghese, J., et al. (2013). "Motoric cognitive risk syndrome and the risk of dementia." Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences **68**(4): 412-418.

Verghese, J., et al. (2013). "Motoric cognitive risk syndrome and the risk of dementia." J Gerontol A Biol Sci Med Sci **68**(4): 412-418.

Verghese, J., et al. (2007). "Quantitative gait dysfunction and risk of cognitive decline and dementia." Journal of Neurology, Neurosurgery & Psychiatry **78**(9): 929-935.

Weiner, K. S. and K. J. N. Zilles (2016). "The anatomical and functional specialization of the fusiform gyrus." **83**: 48-62.

Wennberg, A. M., et al. (2017). "Cerebral amyloid deposition is associated with gait parameters in the mayo clinic study of aging." **65**(4): 792-799.

Winblad, B., et al. (2004). "Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment." Journal of internal medicine **256**(3): 240-246.

Yoo, S., et al. (2006). "Validity of Korean version of the Mini-International Neruopsychiatric Interview." Anxiety and Mood **2**(1): 50-55.

Youden, W. J. (1950). "Index for rating diagnostic tests." **3**(1): 32-35.

Zhou, H., et al. (2018). "Hemodialysis impact on motor function beyond aging and diabetes—objectively assessing gait and balance by wearable technology." Sensors **18**(11): 3939.

Zijlstra, W. and A. L. Hof (2003). "Assessment of spatio-temporal gait parameters from trunk accelerations during human walking." Gait & posture **18**(2): 1-10.

Zimmerman, M. E., et al. (2009). "MRI-and MRS-derived hippocampal correlates of quantitative locomotor function in older adults." Brain research **1291**: 73-81.

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초 록

배경 및 목적: 치매로 인한 공공보건 부담이 가중됨에도 만족스러운 치료법은 부재한 현 상황은 치매 발병을 예방하거나 진행을 지연시키기 위해 인지저하 또는 치매 위험이 있는 사람들을 조기에 식별해야 할 필요를 더욱 부각시킨다. 최근 연구들은 보행 시 한발-한발 사이 보행인자들의 변동성을 의미하는 보행변이성이 인지저하, 경도인지장애 및 치매의 위험과 밀접하게 관련되어 있다는 것을 보였다. 특히 웨어러블 센서를 통해 얻은 보행변이성은 감독이 없는 자연스러운 환경에서 더 오랜 기간 동안 측정값을 낮은 비용으로 얻을 수 있다는 실용적인 이점으로 인해 인지저하의 위험을 예측하는 유망한 디지털 바이오마커로 활용될 수 있다. 본 논문에서는, 신체에 부착한 단일 삼축가속계로 측정된 보행변이성이 미래의 인지저하 위험을 예측하는 디지털 바이오마커로 사용될 수 있을지에 대해 연구하였다. 첫 번째 연구에서는 신체부착 삼축가속계로 얻은 보행변이성이 정상인지를 가진 노인에서 미래 인지저하의 위험을 예측할 수 있는지를 조사했다. 두 번째 연구에서는 더 큰 표본 크기와 더 넓은 범위의 인지 기능을 가진 비치매 노인을 대상으로, 디지털 바이오마커로서 보행 변이성의 가능성을 이론적으로 뒷받침할 수 있는 신경기질에 대해 조사하였다. 또한, 높은 보행 변이성이 인지 기능 및 기억 기능에 관련된 것으로 밝혀진 뇌 영역에서의 얇아진 대뇌 피질 두께와 관련되어 있을 것이며, 그 영역이 보행-인지 사이의 연관성을 설명하는 공유 신경 기질에 해당할 것이라는 가설을 검증하였다.

방법: 연구 I에서 우리는 뇌허혈이나 파킨슨병이 없으면서, 지역사회에 거주하는, 인지적으로 정상인 노인 358명을 대상으로

4년 전향적 코호트 연구를 수행하였다. 체중심에 부착한 삼축가속계를 이용하여 보행변이성을 측정하였고, 경도인지장애에 관한 국제 워킹 그룹의 진단기준에 따라 경도인지 장애를 진단했다. 우리는 보행 변이성의 크기에 따라 연구대상자를 삼분위수로 분류하여, 보행변이성이 가장 큰 일분위 그룹과 나머지 그룹을 관찰하며 4년 동안의 경도인지장애의 발병을 추적하였다. 그룹간 경도인지장애 발병 위험 비교는 Log-rank test와 Kaplan-Meier 분석을 통해 수행했다. 경도인지장애 발병 위험비(Hazard Ratio, HR)는 연령, 성별, 교육수준, 누적질병평가척도 점수, GDS 점수, 아포지단백 E ε4 대립유전자 유무를 보정한 콕스 비례위험 회귀분석을 사용하여 추정하였다.

연구 II에서 우리는 207명의 치매가 없는 노인을 대상으로, 보행변이성과 연관된 뇌 피질 및 피질 하 신경 구조, 보행변이성-인지기능의 공유신경기질을 횡단적으로 연구하였다. 자기공명영상에서 뇌 피질의 두께와 피질 하 구조물 부피를 구하여 보행변이성, 인지기능, 피질 두께와 피질 하 구조물 부피와의 연관성을 각각 조사했다. 또한 보행변이성과 인지기능 양쪽에 모두 유의한 연관성을 보이는 뇌영역의 피질 두께 또는 피질 하 구조물 부피가 실제로 보행변이성과 인지기능 관계에 미치는 매개효과를 분석하였다.

결과: 연구 I에서 보행변이성이 일분위에 속하는 노인들은 나머지 노인들에 비해서 4년 간 경도인지장애 발병 위험이 약 2배 더 높았다. (HR = 2.12, 95% CI = 1.05-4.31). 그러나 느린 보행 속도를 가진 노인들은 나머지 노인들과 비슷한 경도인지장애 발병위험을 보였다. (HR = 1.06, 95% CI = 0.49- 2.30). 우리는 또한 보행변이성이 미래 인지저하를 예측하는 것에는 성별에 따른 차이가 유의하지 않다는

것을 밝혔다. 연구 대상자들을 보행변이성의 크기로 삼분위화 하는 과정에서의 역치효과 (threshold effect) 유무를 알아보기 위해, 보행변이성과 보행속도를 연속변수로 두고 분석하였을 때에도 보행변이성이 10% 증가할 때마다 인지저하의 위험이 1.16배 증가하는 반면 보행속도의 변화에 따라 인지감퇴 위험의 유의한 변화는 없었다.

연구 II에서 높은 보행변이성은 낮은 인지기능과 관련이 있었다. 우리는 높은 보행변이성이 광범위한 영역에서 대뇌피질 두께 감소와 연관이 있다는 것을 확인했다. 반면, 보행변이성은 피질 하 구조물의 부피와는 유의한 연관성을 보이지 않았다. 보행변이성과 유의한 상관관계를 보인 피질 클러스터 중 좌반구의 inferior temporal, entorhinal, parahippocampal, fusiform, and lingual을 포함하는 클러스터의 피질 두께는 전반적 인지기능 및 언어기억기능과 연관이 있었다.

결론 및 해석: 결론적으로 본 연구는, 신체부착 단일 삼축가속계로 측정한 보행변이성의 인지저하 위험 예측 디지털 바이오마커로서의 가능성에 근거를 제시하고 있다.

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- Byun, Seonjeong, et al. “Gait variability can predict the risk of cognitive decline in cognitively normal older people.” Dementia and geriatric cognitive disorders, 45(2018), 251-261.

주요어 : 보행, 디지털 바이오마커, 삼축가속계, 공유신경네트워크, 치매, 종단연구

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