Brain patterns of pace – but not rhythm – are associated with vascular disease in older adults

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ABSTRACT

Background: Distinct domains of gait such as pace and rhythm are linked to an increased risk for cognitive decline, falls, and dementia in aging. The brain substrates supporting these domains and underlying diseases, however, remain relatively unknown. The current study aimed to identify patterns of gray matter volume (GMV) associated with pace and rhythm, and whether these patterns vary as a function of vascular and non-vascular comorbidities.

Methods: A cross-sectional sample of 297 older adults (M Age = 72.5 years ± 7.2 years, 43% women) without dementia was drawn from the Tasmanian Study of Cognition and Gait (TASCOG). Factor analyses were used to reduce eight quantitative gait variables into two domains. The “pace” domain was primarily composed of gait speed, stride length, and double support time. The “rhythm” domain was composed of swing time, stance time, and cadence. Multivariate covariance-based analyses adjusted for age, sex, education, total intracranial volume, and presence of mild cognitive impairment identified gray matter volume (GMV) patterns associated with pace and rhythm, as well as participant-specific expression (or factor) scores for each pattern.

Results: Pace was positively associated with GMV in the right superior temporal sulcus, bilateral supplementary motor areas (SMA), and bilateral cerebellar regions. Rhythm was positively associated with GMV in bilateral SMA, prefrontal, cingulate, and paracingulate cortices. The GMV pattern associated with pace was less expressed in participants with any vascular disease; this association was also found independently with hypertension, diabetes, and myocardial infarction.

Conclusion: Both pace and rhythm domains of gait were associated with the volume of brain structures that have been linked to controlled and automatic aspects of gait control, as well as with structures involved in multisensory integration. Only the brain structures associated with pace, however, were associated with vascular disease.

1. Introduction

Clinical gait abnormalities occur in up to 35% of community-dwelling older adults, and reduced capacity to ambulate freely is predictive of falls, institutionalization, cognitive decline, vascular and non-vascular dementia, morbidity, and mortality [1–3]. Gait performance is sub-served by a broad and complex pattern of cortical and subcortical brain regions, their attendant white matter pathways, and peripheral sensorimotor afferent and efferent systems. Subtle radiographic features, such as white matter hyperintensities, while not necessarily associated with overt clinical events, are still associated with disrupted gait performance [4]. Interestingly, the neuroimaging correlates of vascular disease are associated with sensorimotor and multisensory integration [5–7], as well as with decline in cognitive and executive function [5,6]. Somewhat overlapping neuroimaging correlates (total and focal loss of gray matter volume, GMV) have also been described for
gait decline in older adults [8–14].

Gait performance is quantified in several different ways. While individuals gait variables – such as gait speed, stride length and cadence – provide unique data for the quantitative analysis of gait, these variables also exhibit some covariance. This interdependence of quantitative gait variables can be expressed through principal components derived from factor analyses of quantitative gait variables. Principal components, or domains, of quantitative gait are independently associated with cognitive decline and dementia [15–18]. As conceptualized by Verghese et al., pace (factor loadings include gait speed, stride length, and double support time) and rhythm (loading on cadence, swing time, and stance time) are two domains of quantitative gait that account for a significant proportion of the variance in several quantitative measures of gait [15, 16, 19, 20]. Worse performance in pace predicts vascular dementia and executive dysfunction, while worse performance in rhythm predicts all-cause dementia and memory impairments [19]. Yet, the brain substrates of these gait domains remain unknown because most studies investigate structural correlates of individual quantitative gait measures, such as gait speed, in isolation. This implies that research may have missed neural signatures of gait performance represented through broader constructs, such as gait domains including “pace” and “rhythm.” Consequently, this study aims to identify patterns or patterns of gray matter volume (GMV) associated with pace and rhythm using voxel-based morphometry and multivariate covariance-based analyses. Additionally, we investigate the modulation of pattern expression with various vascular and non-vascular comorbidities [21], to contextualize the impact that these diseases have on the expression of these patterns. Vascular diseases and their risk factors have a documented impact upon vascular structures [22–27]. If pattern expression is associated with vascular diseases, then gait domain performance and expression of associated GMV patterns would also serve as proxy measures for the brain’s structural integrity in older adults with these comorbidities. Given this information and the broad distribution of modalities likely sub-serving gait performance in older adults without dementia, we hypothesized that the GMV covariance patterns associated with pace and rhythm would include various brain structures involved in the controlled (or consciously directed) and motoric (or automatic) aspects of gait [28–30].

2. Materials and methods

2.1. Ethics statement

The Southern Tasmanian Human Research Ethics Committee and the Monash University Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants. The study was conducted according to the principles expressed in the Declaration of Helsinki. The current analysis was also approved by the Institutional Review Board at Albert Einstein College of Medicine.

2.2. Participants

We examined GMV covariance patterns associated with two domains of gait in 297 older adults (M Age = 72.5 years ± 7.2 years, 43% women) from the Tasmanian Study of Cognition and Gait (TASCOG) in Australia who received quantitative gait assessments. Study details have been previously published [31]. Briefly, older adults aged 60-85 were randomly selected from the Southern Tasmanian electoral roll; participants were excluded based on inability to walk unaided, standard contraindications to Magnetic Resonance Imaging (MRI), diagnosis of dementia (using the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders and a consensus procedure), or residence in an aged care facility [32]. While data from 330 TASCOG participants were originally available for analyses, 33 participants were excluded based on poor quality MRIs (following manual inspection of each image prior to processing, with particular emphasis on detecting motion/ring-like artefacts), and/or missing MRI, quantitative gait, or demographic data. Participants completed comprehensive neuropsychological and mobility assessments at baseline, as well as at biannual visits. Mild cognitive impairment [33–35] and MCR syndrome [3,36] were also determined based on clinical consensus procedure using established criteria previously applied to this cohort [12]. In short, our MCI criteria were a score of 1.5 SD below the mean in any of the following cognitive domains: (1) Executive Function: Victoria Stroop test [37], the word and category fluency tests from the Controlled Oral Word Association Test [38,39], and the Rey complex figure copy test [40] (2) Memory: Hopkins Verbal learning test [41] and the Rey complex figure delayed recall, (3) Attention: digit span, digit symbol coding and symbol search test from the Wechsler Adult Intelligence Scale–Revised Edition [42]. Our MCR criteria were gait speed more than 1 SD below age, sex cohort-specific means assess with a 20 feet GAITRite instrumented walkway (GAITRite System © Clifton, NJ) and subjective cognitive complaint on the Geriatric Depression Scale [37] and/or Instrumental Activities of Daily Living [43]. Demographics, gait characteristics, and comorbidities of all eligible participants are summarized in Table 1.

2.3. Gait measures

The quantitative measures of gait, including gait speed (cm/s), stride length (cm), double support time (s), cadence (steps/min), swing time

| Table 1 |
| --- |
| Summary statistics for participants overall and as a function of sex. |
| Variable | Full (n=297) | Female (n=128) | Male (n=169) | p |
| Age, years, mean (SD) | 72.5 (7.2) | 72.3 (7.1) | 72.7 (7.2) | 0.59 |
| Education, years, mean (SD) | 11.1 (3.7) | 10.8 (3.1) | 11.3 (4.0) | 0.25 |
| Global Cognition z-score mean (SD) | 0.056 | 0.143 (1.02) | -0.011 (0.96) | 0.19 |
| Gait speed (cm/s) | 115 (22.2) | 111.28 (24.54) | 117.8 (19.92) | 0.012 |
| Stride length (cm) | 124.2 (19.2) | 115.39 (18.53) | 130.9 (16.84) | <0.001 |
| Cadence (steps/min) | 110.8 (10.9) | 114.66 (11.78) | 107.8 (9.25) | <0.001 |
| Swing time (s) | 0.42 (0.04) | 0.405 (0.034) | 0.43 (0.038) | <0.001 |
| Stance time (s) | 0.67 (0.09) | 0.655 (0.118) | 0.69 (0.069) | 0.004 |
| Double support time (s) | 0.25 (0.08) | 0.254 (0.102) | 0.25 (0.049) | 0.968 |
| Stride length variability | 3.89 (1.44) | 3.95 (1.63) | 3.85 (1.27) | 0.541 |
| Swing time variability | 0.019 | 0.02 (0.013) | 0.019 (0.0073) | 0.422 |
| Depression, % (n) | 0 (0) | 0 (0) | 0 (0) | - |
| Diabetes, % (n) | 11.0 (33) | 9.4 (12) | 12.4 (21) | 0.41 |
| CHF, % (n) | 12.0 (36) | 11.9 (15) | 12.4 (21) | 0.88 |
| Hypertension, % (n) | 52.0 (155) | 53.9 (69) | 50.9 (86) | 0.61 |
| Angina, % (n) | 13.5 (40) | 11.7 (15) | 14.9 (25) | 0.43 |
| Myocardial Infarction, % (n) | 12.5 (37) | 8.6 (11) | 15.4 (26) | 0.08 |
| Stroke, % (n)** | 15.5 (46) | 14.8 (19) | 16.0 (27) | 0.79 |
| TIA, % (n)*** | 4.0 (13) | 4.7 (6) | 4.1 (7) | 0.99 |
| Parkinson’s Disease, % (n) | 0.7 (2) | 0 (0) | 1.2 (2) | 0.51 |
| Osteoarthritis, % (n) | 56 (167) | 64.8 (83) | 49.7 (84) | 0.009 |
| Vascular Disease****, % (n) | 62.9 (187) | 59.4 (70) | 67.5 (111) | 0.27 |
| MCR, % (n) | 2.0 (6) | 1.6 (2) | 2.4 (4) | 0.70 |
| MCI, % (n) | 3.0 (9) | 3.1 (4) | 3.0 (5) | 0.99 |
| Any MCI or MCR, % (n) | 4.4 (13) | 4.7 (6) | 4.1 (7) | 0.99 |

** Global cognition z-score generated from standardized performance on category fluency, digit span, and Hopkins Verbal Learning tests – derived for and reported in previous publication [35]. As expected, only a proportion of those with a history of stroke (19.56 %) showed overt signs of brain infarct on MRI [80].

*** Any one of hypertension, angina, myocardial stroke, TIA, or diabetes.
(s), and stance time (s), were measured over six trials using an instrumented walkway (609.60 cm/20 ft; GAITRite System® Clifton, NJ). Participants were instructed to walk at normal pace (without any assistive devices) over this instrumented walkway; participants started walking 2 m before the mat and stopped walking 2 m after the mat ended to allow for initial acceleration and terminal deceleration phases [44].

2.4. Factor analyses of gait measures

Principal component analysis (PCA) of quantitative gait measures was conducted with varimax rotation to derive orthogonal factor scores. Minimum eigenvalue for extraction was set to 1; factor, item, and cross-loadings along with scree plots were examined. Variable loadings greater than 0.5 were considered relevant [15,16].

2.5. MRI data acquisition

MRI was obtained using a 1.5-Tesla machine (LX Horizon, General Electric, Milwaukee, WI) with the following sequences: high-resolution T1-weighted spoiled gradient echo (repetition time [TR] 35 ms, echo time [TE] 7 ms, flip angle 35°, field of view 24 mm; voxel size 1 mm³) comprising 120 contiguous slices, T2-weighted fast spin echo (TR 4300 ms, TE 120 ms, one excitation, turbo factor 48; voxel size 0.90 × 0.90 × 3 mm); fluid-attenuated inversion recovery (TR 8,802 ms, TE 130 ms, time interval 2,200 ms; voxel size 0.50 × 0.50 × 3 mm), gradient echo (GRE) (TR 800 ms, TE 15 ms, flip angle 30°; voxel size 0.93 × 0.93 × 7 mm) [45]. T1-weighted images were manually re-oriented to the anterior commissure – posterior commissure line and examined for brain infarcts for later comparison to self-reported history of stroke (see Table 1). Each T1-weighted image was then pre-processed in the same manner using SPM12 (Wellcome Department of Cognitive Neurology) implemented with MATLAB R2018b (Mathworks, Natick, MA). Each structural MRI image was analyzed using Voxel-Based Morphometry (VBM) and segmented into Gray Matter (GM), White Matter (WM), and Cerebrospinal Fluid (CSF), using a unified segmentation procedure and Diffeomorphic Anatomical Registration Through Exponentiated Line Algebra (DARTEL) [46]. DARTEL-VBM improves inter-subject alignment by modeling the shape of the brain using three parameters for each voxel. GM and WM are simultaneously aligned to produce a study-specific and increasingly crisp template to which the data are iteratively aligned. For each participant, a GM map, a WM map and a CSF map is produced in the same space as the original T1-weighted image, where each voxel is assigned a probability value. These probability maps were manually examined to ensure proper segmentation, and then spatially normalized [47] into Montreal Neurologic Institute (MNI) space. Finally, these probability maps were spatially smoothed with an isotropic Gaussian kernel, full-width-at-half-maximum = 8 mm. Only GM probability maps were used in subsequent analyses.

2.6. Factor analyses of gray matter volume

Multivariatve factor analyses were performed to identify GMV covariance patterns associated with Pace and Rhythm, separately. All analyses were adjusted by age, sex, education, total intracranial volume, and presence of any mild cognitive impairment (MCI) or motoric cognitive risk syndrome (MCR). MCI and MCR are pre-dementia syndromes; pre-existing lesions in participants with these syndromes would impact our findings, especially given that some neural structures comprising GMV patterns associated with MCI and MCR co-localize in areas we previously hypothesized as having roles in pace and rhythm [48,49]. Note also that our group-level covariance-based analyses involves dimensionality reduction, and thereby circumvents the multiple comparisons problem inherent in traditional univariate (voxel-based) neuroimaging analyses – while also being fairly resistant to between-subject variability and collinearity [30,50]. In other words, while univariate approaches typically perform a t-test (or equivalent) at each voxel, only two covariance-based models were performed here, one for Pace and one for Rhythm. There is also evidence that the diagnostic performance (for classifying dementia) and the replicability of multivariate factor analyses of MRI data is better than traditional univariate approaches [28,30,51].

Analyses were implemented with the PCA suite, http://www.nitrc.org/projects/gcva_pca [29,52]. A gray matter mask supplied by SPM12 was applied onto the GM probability maps to only include voxels with > 20% probability of being gray matter. PCA was then performed after participant means were subtracted from each voxel, to generate a set of principal components and their associated participant-specific (or pattern) expression scores. Participant-specific expression scores reflect the degree to which a participant displays a particular component or pattern. The GMV covariance patterns associated with pace and rhythm were then computed by regressing the participant-specific factor scores from the best linear combination of principal components (PCs), using the lowest Akaike information criteria score [53]. The stability of the voxels in each GMV covariance pattern associated with both measures were then tested using 1000 bootstrap resamples [54]. Voxels with bootstrap samples of |Z| > 1.96 and p < 0.05 were considered significant. Multivariate covariance-based analysis assigns positive and negative weightings (or loadings) to each voxel (or variable) included in the model [28]. In the current study, positively weighted regions are regions (or a cluster of voxels) that have relatively more GMV with higher factor scores in pace or rhythm, while negatively weighted regions have relatively less GMV with higher factor scores in pace or rhythm. Note, however, that both positively and negatively weighted regions are part of the particular GMV covariance pattern associated with pace and rhythm, and therefore cannot simply be interpreted as positively and negatively associated regions [28,55,56].

2.7. Localization of clusters comprising gray matter volume covariance patterns

Clusters contributing to GMV covariance patterns were visualized through MRICRON and MRICROGL using a threshold of |z| >1.96 (p < 0.05), https://www.nitrc.org/projects/mricron. The brain regions of peak voxels in clusters with |z| >1.96 and a size >50 voxels are listed in Tables 4 and 5. For each identified peak, the brain regions and the x, y, z MNI coordinates of the peak of each cluster are listed, identified manually and then cross-referenced using an automated labeling system [57].

2.8. Medical history

Self-reported medical history, including prior physician diagnoses of hypertension (HTN), angina, myocardial infarction (MI), diabetes mellitus (DM), transient ischemic attack (TIA), stroke, and osteoarthritis (OA) was obtained from a standardized questionnaire. The composite measure “vascular disease” was defined as presence of any one of HTN, DM, angina, MI, TIA, or stroke.

2.9. Student t-test analyses of pattern expression and gait measures

Participant-specific expression scores were compared in participants with and without these comorbidities using t-tests corrected for multiple comparisons and considered significant at p < 0.05. Normality and equality of variance assumptions were assessed graphically and statistically, respectively.

3. Results

3.1. Baseline characteristics

The average age of participants was 72.5 years (SD 7.2 years), and 43% participants were female. Osteoarthritis (56%, OA), hypertension
Factor analysis with varimax rotation revealed two orthogonal factors accounting for 73% of the variance in quantitative gait measures (Table 2). The factor accounting for the most variance was primarily composed of gait speed, stride length, and double support time; this was termed the “pace” factor, consistent with previous reports in other cohorts [19]. The second factor was primarily composed of cadence, swing time, and stance time, and this was termed the “rhythm” factor. Individual factor scores are interpreted based on the variables each factor correlates with – described sometimes as the variables “loading into” the factor. A positive (high) factor score in pace, for example, would indicate higher gait speed and stride length, along with shorter double support times. A negative (low) factor score points to slower gait speed, shorter stride length, and longer double support times.

GMV covariance pattern associated with Pace

The GMV covariance pattern associated with pace was composed of eleven principal components with an R² = 0.42 (p < 0.0001). This pattern was derived after adjusting for age, sex, education, total intracranial volume, and presence of MCI and/or MCR. Greater expression of the GMV pattern for pace, represented by a higher individual expression score (a factor score), was associated with relatively higher GMV in the positively weighted regions; meanwhile, negatively weighted regions have relatively lower GMV with greater expression of this pattern. As such, a higher factor score indicates both 1) relatively greater GMV in positively weighted regions and b) relatively lower GMV in negatively weighted regions. The GMV covariance pattern associated with pace (Fig. 1) extended into several regions with multiple clusters significant at |z| > 1.96 (p < 0.05) and with k>50 voxels (Table 4). The largest positively-weighted clusters (k>100 voxels) peaks of |z| > 1.96 (p < 0.05) were found to extend into the middle and superior frontal gyri (BA 6, 8, 46, all L>R), visual cortical areas (BA 19), extrastriate body area, superior temporal cortex (including superior temporal sulcus and superior temporal gyrus, both R>L), inferior temporal cortex, frontal orbital cortices (R>L), medial dorsal nucleus of the left thalamus, and bilateral cerebellar crus II/VII/VIII. The largest negatively-weighted clusters in this pattern covered several areas including the cingula, paracingula, precentral gyri, postcentral gyri, supplementary motor area, ventral basal ganglia, and the hippocampus.

Both males and females expressed this GMV pattern at approximately equal levels (p > .05). Expression of the GMV pattern associated with pace was significantly lower in participants with any vascular disease (p = 0.0008), HTN (p < 0.0001), OA (p < 0.0001), DM (p = 0.02), and MI (p = 0.04). Please refer to Table 3 for complete results.

GMV covariance pattern associated with Rhythm

The GMV covariance pattern associated with rhythm was composed of four principal components with an R² = 0.24 (p < 0.0001). As with pace, this pattern was adjusted for age, sex, education, total intracranial volume, and presence of MCI and/or MCR. Greater expression of the GMV pattern for rhythm, represented by a higher absolute individual factor score, was associated with relatively higher GMV in clusters with higher positive Z-scores. The GMV covariance pattern associated with rhythm extended into several regions with multiple clusters significant at |z| > 1.96 (p < 0.05) and with k>50 voxels (Fig. 2, Table 5). The largest positively-weighted clusters (k>100 voxels) were found largely in the medial brain, with peaks of |z| > 1.96 (p < 0.05) localizing in the cerebellar crus II, cingulate, paracingulate, middle frontal, and superior frontal gyrus (including orbitofrontal cortex, prefrontal cortex, supplementary motor area, primary motor cortex). Negatively-weighted clusters in this pattern were distributed broadly and extended into supramarginal, fusiform, orbital, superior frontal, middle frontal, and the middle and inferior occipital gyri. Expression of the GMV pattern for rhythm was lower in participants with comorbid angina (p = 0.049) but increased with OA (p = 0.049). Expression of GMV pattern for rhythm was not associated with other vascular diseases (Table 3). On average, female participants had higher expression scores than males (p < 0.0001).

Discussion

This study derived GMV covariance patterns associated with gait pace and rhythm in an ambulatory sample of community-dwelling older adults without dementia, while adjusting for critical covariates. To our knowledge, only one prior study has examined brain structures associated with different gait domains [58]. In that study, pace was positively associated with cortical thickness in left cingulate while rhythm was associated with paracentral, inferior parietal and pericalcarine thickness. As shown in other cross-sectional, region-of-interest VBM analyses, slow gait speed is associated with reduced GMV in various parts of the cerebellum, caudate nucleus, left prefrontal cortex, pre- and post-central gyri, cingula, and sensorimotor areas [13,59–62]. Another cross-sectional study employing VBM and multivariate covariance analysis identified a gait speed GMV pattern comprising brain stem, precuneus, fusiform, motor, supplementary motor, and prefrontal cortices, adding to and corroborating the distributed neural signature of gait speed shown through ROI analyses [12]. We found that GMV patterns associated with pace and rhythm include neural structures previously associated with gait speed, as well as novel brain regions that have unclear implications on gait performance, such as those involved in multisensory integration and cognition. Furthermore, we found that vascular diseases, independently and as a composite measure, are associated with reduced expression of the GMV pattern associated with pace, but not with rhythm.

GMV patterns of pace and rhythm and controlled and automatic regulation of gait

Conscious and automatic gait performance are supported by two broad yet interacting neural pathways. The control and motoric pathways represent the cognitively directed and automatic aspects of gait, respectively [63–65]. The control pathway supports motor planning and dynamic modulation; it originates in the supplementary motor area (SMA) and prefrontal cortex (PPC), relaying with the brain stem and cerebellum through the ventral basal ganglia. The motoric (automatic) pathway supports gait initiation and maintenance, originating in the brain stem and relaying with the motor cortex and dorsal basal ganglia. Representations of the conscious and automatic pathways have been reported previously in GMV patterns associated with gait speed [12,66], but not with the broader gait domains, as we have shown here. The GMV...
pattern for pace included elements of the control pathway in bilateral SMA, cerebellar crus II/VIIb/VIII, and to a lesser degree, in the bilateral ventral basal ganglia, prefrontal, cingulate, and paracingulate cortices. The rhythm pattern also included regions in the control pathway such as ventral basal ganglia, prefrontal, cingulate, and paracingulate cortices. Prior studies investigating GMV patterns associated with gait speed showed separate, positively-weighted clusters corresponding with the control pathway and less so with the automatic pathway [12,66].

4.2. Vascular disease is negatively associated with Pace pattern expression

We found that lower expression of the pace pattern was seen with any vascular disease, and independently with self-reported hypertension, diabetes, and MI. Reduced pattern expression with vascular disease was not observed with rhythm, except for a small reduction in expression with angina. Subclinical cerebrovascular disease commonly presents as a mixture of white matter hyperintensities (WMH), silent infarctions (SI), and microbleeds (MBs). All three are separately associated with worse gait performance in older adults without dementia or overt cognitive decline [67–71]. Furthermore, this negative impact is summative, increasing with greater disease burden of WMHs, SIs, and MBs [31]. Worse gait performance, increased gait variability, and increased incidence of falls are all associated with more numerous and larger volume white matter lesions (WMHs) [72]. A longitudinal study among a subset of TASCOG participants, with mean follow-up of 30.6 months, found higher baseline white matter lesions were associated with...
Vascular diseases and their risk factors are known to reduce total and focal GMV [24, 25], and shorter step length (loads into pace) [73]; these associations were found to be even more pronounced with greater age. Our studies found that reduced GMV in middle and superior temporal gyri, insula, median cingulate cortex, precuneous cortex, and the left lentiform nucleus [24] correlated with comorbid DM as well as the duration of this diagnosis. Furthermore, presence of DM negatively influenced the relationship of multisensory integration with pace in a large sample of older adults [79]. As with DM and HTN, higher waist circumference (WC) and body mass index (BMI) were negatively associated with total and focal GMV in bilateral temporal lobes, thalamus, frontal gyri, precentral gyrus, precuneus, posterior cingulate, postcentral gyrus, inferior parietal lobule, cingulate gyrus, insula and superior temporal gyri [76]. Taken together, these studies and ours show that vascular diseases, including HTN and DM, and their risk factors, such as WC and BMI, are associated with reduced GMV in brain regions comprising the GMV pattern for Pace, but not as closely with regions comprising the pattern for Rhythm.

### 4.3. Strengths and limitations

This cross-sectional study’s strengths include its population-based design, large sample size, use of volumetric MRI analyses, and quantitative measurements of gait. GMV covariance analysis circumvents the multiple comparisons problem inherent in traditional univariate neuroimaging methods, while also being resistant to inter-subject variability and collinearity [30, 56, 52]. Furthermore, this methodology identified structures and patterns that may have been previously overlooked while studying the neural substrates of gait. Limitations of our study include limited generalizability to older adults with significant cognitive/motoric disabilities, self-report of comorbidities, and lack of clinical gait evaluations. Future studies may also evaluate the interrelationship between participation in physical activities, disease, and gait domains. Furthermore, the GMV patterns presented here would benefit from cross-validation in other cohorts and lifetime samples.

### 5. Conclusion

We examined the structural covariance patterns associated with pace and rhythm gait domains in a population-based cohort of community-dwelling older adults without dementia. With these patterns, we add to existing literature by documenting the widespread neural signature of controlled and automatic gait processes. We found that vascular disease is associated with reduced expression of the pace pattern, and that this relationship is not seen with expression of the rhythm pattern. Together,
these findings provide a broader view of the structural correlates of gait, as well as the relationship between expression of these neural signatures with vascular comorbidities.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cjb.2022.10154.

References

[1] J. Verghese, R.B. Lipton, C.B. Hall, G. Kuslansky, M.J. Katz, H. Buschke, Abnormality of gait as a predictor of non-Alzheimer’s dementia, Neurology 47 (2001) 1761–1768.
[2] M. Montero-Odasso, J. Verghese, O. Beauchet, J.M. Hausdorff, Gait and cognition: a complementary approach to understanding brain function and the risk of falling, J. Am. Geriatr. Soc. 60 (2012) 2127–2136, https://doi.org/10.1111/j.1532-5415.2012.04299.x.
[3] J. Verghese, C. Wang, R.B. Lipton, R. Holtzer, Motoric cognitive risk syndrome and the risk of dementia, J. Gerontol. A. Biol. Sci. Med. Sci. 68 (2012) 412–418, https://doi.org/10.1093/gerona/gls191.
[4] A. Heshmatollahi, S.K.L. Darweesh, L.J. Dommershuisjui, P.J. Koudstaal, M. A. Ibrah, M.K. Ikram, Quantitative gait impairments in patients with stroke or transient ischemic attack: a population-based approach, Stroke 51 (2020) 2644–2647, https://doi.org/10.1161/STROKEAHA.120.029829.
[5] K.F. De Laat, A.G.W. Van Norden, T.G. Phan, V.G. Pradeep Kumar, V. Srikanth, T.G. Phan, J. Chen, R. Beare, J.M. Stapleton, D.C. Reutens, The location of white matter lesions and gait—a voxel-based study, Ann. Neurol. 67 (2010) 265–269, https://doi.org/10.1002/ana.21826.
[6] J.R. Mahoney, K. Cotton, J. Verghese, Multisensory integration predicts balance and falls in older adults, J. Gerontol. Ser. A (2018), https://doi.org/10.1093/gerona/gly245.
[7] R. Holtzer, N. Epstein, J.R. Mahoney, N.L. Foster, R. Perneczky, A. Kurz, P. Alexopoulos, R.A. Koeppe, A. Drzezga, Y. Stern, Multivariate and univariate neuroimaging biomarkers of Alzheimer’s disease, Neuroimage 40 (2008) 1903–1915, https://doi.org/10.1016/j.neuroimage.2008.01.056.
[8] A.M. Brickman, C. Habeck, E. Zarrahn, J. Flynn, Y. Stern, Structural MRI covariance patterns associated with normal aging and neuropsychological functioning, Neurobiol. Aging 28 (2007) 284–295, https://doi.org/10.1016/j.neurobiolaging.2005.12.016.
[9] C. Habeck, Y. Stern, the A.D.N. Alzheimer’s disease neuroimaging initiative, multivariate data analysis and neuroimaging data overview and application to Alzheimer’s disease, Cell Biochem. Biophys. 58 (2010) 53–67, https://doi.org/10.1007/s12013-010-0909-0.
[10] P. Choi, M. Ren, T.G. Phan, M. Callisaya, J.V. Ly, R. Beare, W. Chong, V. Srikanth, Silencing the infants of cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study, Stroke 43 (2012) 1505–1510, https://doi.org/10.1161/STROKEAHA.111.647271.
[11] V. Del Barrio, Diagnostic and statistical manual of mental disorders. The Curated Reference Collection in Neuroscience and Biobehavioral Psychology, American Psychiatric Association, 2016, p. 886, https://doi.org/10.1097/978-0-12-809244-5.05530-0.
[12] R.C. Petersen, R.O. Roberts, D.S. Knopman, B.F. Boeve, Y.E. Gedj, R.J. Ivnik, G. E. Smith, C.R. Jack, Mild cognitive impairment: mild memory impairment: mild cognitive impairment, Arch. Neurol. 66 (2009) 1447–1455, https://doi.org/10.1001/archneur.56.3.303.
[13] R.C. Petersen, Mild cognitive impairment as a diagnostic entity, J. Intern. Med. (2004) 183–194, https://doi.org/10.1111/j.1365-2796.2004.01988.x.
[14] R.C. Petersen, G.E. Smith, R.J. Ivnik, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch. Neurol. 56 (2009) 303–308, https://doi.org/10.1001/archneur.56.3.303.
[15] J. Verghese, C. Habeck, E. Ayers, N. Barasilii, O. Beauchet, J. Bennett, S. A. Brudnohaugh, A.S. Buchman, M.L. Callisaya, R. Camicioli, R. Capistrant, S. Chatterji, A.M. Deock, L. Ferrucci, N. Giladi, J.M. Guralnik, J.M. Hausdorff, R. Holtzer, K.W. Kim, P. Kowal, R.W. Kressig, J.Y. Lim, S. Lord, K. Meguro, M. Montero-Odasso, S.W. Muir-Hunter, M.L. Noone, L. Rochester, V. Srikanth, C. Habeck, Mild cognitive impairment: multidomain prevalence and dementia risk, Neurology (2014), https://doi.org/10.1212/WNL.00000000000000717.
[16] J.A. Vesayave, T.L. Brink, T.L. Rose, O. Lum, V. Huang, M. Adey, V.O. Deere, Development and validation of a geriatric depression screening scale: a preliminary report, J. Psychiatr. Res. 17 (1982) 37–49, https://doi.org/10.1016/0022-3956(82)90034-3.
[17] K.D. Branton, L. Hamar, Multilingual Aphasia Examination, SpringerReference, 2012, https://doi.org/10.1007/springerreference.183669.
[18] M.D. Lezak, Neuropsychological assessment, (1995) 1026.
