Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

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

Susmit Tripathi [a], Joe Verghese [b,c], Michele Callisaya [d,e], Jeannette R. Mahoney [c], Velandai Srikanth [d,e], Helena M. Blumen [b,c,*]

[a] Department of Neurology, Weill Cornell Medicine, New York, NY 10065, USA
[b] Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[c] Department of Neurology, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[d] Peninsula Clinical School, Central Clinical School, Monash University, Victoria, Australia
[e] Menzies Institute for Medical Research, University of Tasmania, Tasmania, Australia

ARTICLE INFO

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 neural 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 (0.99)	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 (0.013)	0.02 (0.0173)	0.019 (0.0083)	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 (76)	65.7 (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 [36].

** 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 mm^3) 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

Multivariate 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 or 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

(52%), and stroke (15.5%) were the most frequently recorded comorbidities in this group. Vascular disease was present in 62.9% of all participants (59.4% of females and 65.7% of males). 4.4% of all participants were diagnosed with one or two pre-dementia syndromes: MCI (3%) or MCR (2%). Further details in Table 1.

3.2. Factor analysis and domains of gait

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.

3.3. GMV covariance pattern associated with Pace

The GMV covariance pattern associated with Pace was composed of eleven principal components with an $R^2 = 0.42$ ($p < 0.0001$). 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) with 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/VIIb/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.

Table 2
Factor analyses results showing loading (correlation, r) of constituent quantitative gait variables with the principal components of gait.

Quantitative Gait Variable	Pace (loading, r)	Rhythm (loading, r)
Gait speed	**0.889**	-0.352
Stride length	**0.949**	0.084
Double support time	**-0.731**	0.466
Cadence	0.374	**-0.908**
Swing time	0.047	**0.931**
Stance time	-0.563	**0.737**
Stride length variability	-0.120	0.051
Swing time variability	-0.511	0.366
% of Variance	38.0	35.0

3.4. GMV covariance pattern associated with rhythm

The GMV covariance pattern associated with rhythm was composed of four principal components with an $R^2 = 0.24$ ($p < 0.0001$). 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 ($p < 0.0001$).

4. 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.

4.1. 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 (PFC), 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
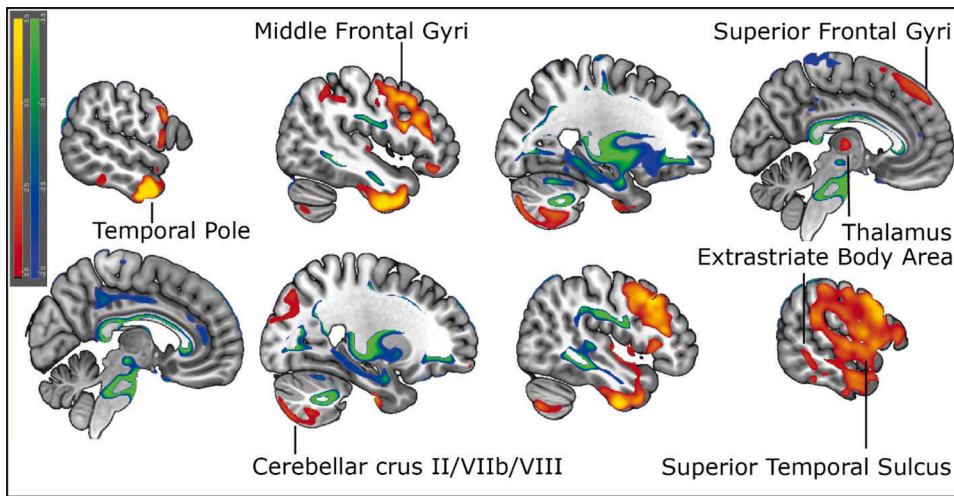
Fig. 1. GMV covariance pattern associated with pace includes regions involved in multi-sensory information processing as well as the control (consciously directed) and motoric (automatic) pathways of gait. Vascular disease is associated with reduced expression of this pattern. Positively (red-yellow; z-value≥ 1.96) and negatively (blue-green; z-value≤ -1.96) weighted areas correspond with relatively higher and lower GMV as a function of pace performance. Color bar indicates z-score ranges within clusters, with positive maximum and negative minimum represented by yellow and green, respectively.

Table 3

Expression (factor) scores for pace and rhythm patterns as a function of vascular disease and osteoarthritis (OA).

	Pace, expression score (SD)			Rhythm, expression score (SD)		
	Not present	Present	p	Not present	Present	p
Diabetes	55 (9.8)	51 (12.0)	0.02	14 (14.3)	17 (13.7)	0.26
CHF	55 (10.1)	54 (10.2)	0.61	14.7 (13.9)	11.1 (15.6)	0.15
Hypertension	58 (9.1)	53 (10.4)	<0.0001	13.3 (13.8)	15.3 (14.7)	0.24
Angina	56 (10.2)	54 (9.3)	0.30	15.1 (14.4)	10.3 (12.6)	0.049
Myocardial Infarction	56 (10.0)	52 (10.0)	0.04	14.6 (14.2)	12.5 (14.5)	0.41
Stroke	56 (10.0)	53 (1.5)	0.073	14.5 (14)	13.4 (16)	0.63
TIA	55 (10.1)	52 (10.6)	0.20	14.2 (14)	18.5 (20)	0.28
Vascular Disease*	58 (9.4)	54 (10.2)	0.0008	14.5 (14)	14.3 (14.4)	0.91
Osteoarthritis	58 (9.6)	53 (10.0)	0.0001	12.5 (14.2)	15.8 (14.1)	0.049

* Any one of hypertension, angina, myocardial, stroke, TIA, or diabetes.

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 bilateral SMA, 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 diseases 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

Table 4

The gray matter volume covariance pattern associated with pace after adjusting for age, sex, education, total intracranial volume, and predementia syndromes (any mild cognitive impairment or motoric cognitive risk syndrome). All clusters with |z|>1.96 and k>50 voxels are presented. Clusters with Z>1.96 have greater GMV as a function of pace, while clusters with Z<1.96 have lower GMV.

x	y	z	k	Z_{peak}	Location of Z_{peak}
-56	0	-34	13534	4.26	Superior Temporal Gyrus, anterior division
51	30	25	66375	4.07	Middle Frontal Gyrus
-44	17	40	10787	3.50	Middle Frontal Gyrus
-10	35	53	3800	3.36	Superior Frontal Gyrus
-49	35	-14	534	2.82	Frontal Orbital Cortex
20	26	59	462	2.77	Superior Frontal Gyrus
-21	-88	-38	9450	2.75	Cerebellum (Crus II, VIIb, VIII)
45	-70	-46	5382	2.66	Cerebellum (Crus II, VIIb, VIII)
50	37	-15	236	2.50	Frontal Pole
20	-95	24	2702	2.48	Occipital Pole
12	-61	-60	562	2.48	Cerebellum VIII
18	65	-15	202	2.44	Frontal Pole
-51	-38	52	1296	2.38	Supramarginal Gyrus, anterior division
50	43	8	137	2.33	Frontal Pole
-5	-15	6	403	2.33	Thalamus
-60	-41	-24	340	2.28	Inferior Temporal Gyrus, posterior division
-1	60	-22	97	2.28	Frontal Pole
19	4	70	214	2.23	Superior Frontal Gyrus
-45	-17	1	61	2.18	Heschl's Gyrus (includes H1 and H2)
-55	-14	47	474	2.14	Postcentral Gyrus
40	-22	13	92	2.13	Heschl's Gyrus (includes H1 and H2)
18	-37	36	225206	-5.76	Cingulate Gyrus
-60	-68	25	3350	-4.35	Lateral Occipital Cortex, superior division
57	15	41	429	-4.21	Middle Frontal Gyrus
67	4	2	289	-3.75	Superior Temporal Gyrus, anterior division
20	-25	79	463	-3.50	Precentral Gyrus
-14	16	42	418	-3.46	Paracingulate Gyrus
-57	16	-5	207	-3.45	Temporal Pole
59	-5	50	61	-3.08	Precentral Gyrus
-19	51	20	693	-2.64	Frontal Pole
-7	45	13	206	-2.18	Paracingulate Gyrus
-29	-32	65	72	-2.09	Postcentral Gyrus

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
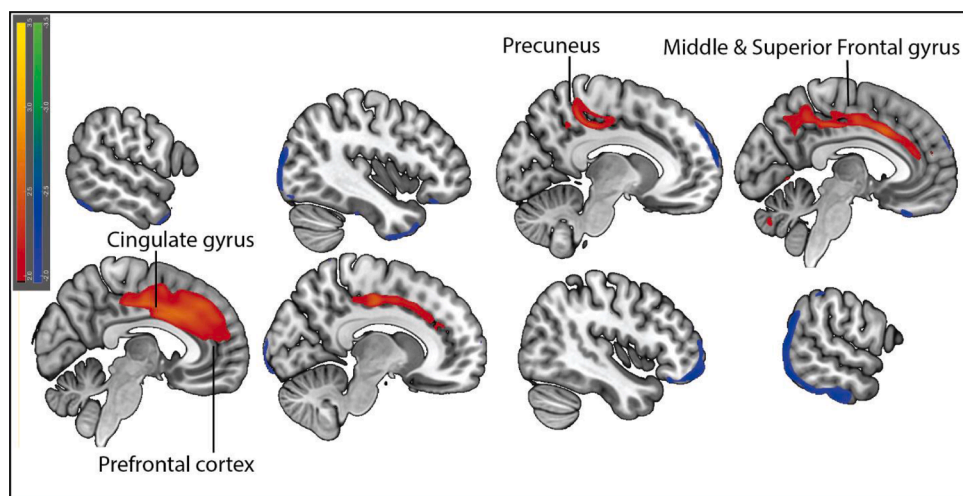
Fig. 2. GMV covariance pattern associated with rhythm (all participants) is composed of medially located clusters extending into prefrontal, frontal, cingulate, and paracingulate cortices, as well as the precuneus and cerebellum. Positively (red-yellow; z-value≥ 1.96) and negatively (blue-green; z-value≤ -1.96) weighted areas correspond with relatively higher and lower GMV as a function of rhythm performance. Color bar indicates z-score ranges within clusters, with positive maximum and negative minimum represented by yellow and green, respectively.

Table 5

Rhythm is associated with a gray matter volume covariance pattern associated with Rhythm, after adjusting for age, sex, education, total intracranial volume, and predementia syndromes (any mild cognitive impairment or motoric cognitive risk syndrome). All clusters with |z|>1.96 and k>50 voxels are presented. Clusters with Z>1.96 have relatively greater GMV as a function of rhythm, while clusters with Z<1.96 have relatively lower GMV.

Rhythm, all participants					
x	y	z	k	Z_{peak}	Location of Z_{peak}
3	8	32	30600	2.69	Cingulate Gyrus, anterior division
26	35	41	795	2.23	Middle Frontal Gyrus
-5	-79	-36	105	2.13	Cerebellum Crus II
-25	44	32	298	2.11	Frontal Pole
-49	16	-39	1794	-2.20	Temporal Pole
-28	2	-48	63	-2.02	Temporal Fusiform Cortex, anterior division
40	20	-41	301	-2.09	Temporal Pole
66	-51	26	14663	-2.59	Angular Gyrus
-4	30	-30	196	-2.18	Frontal Medial Cortex
-55	-64	-19	487	-2.33	Lateral Occipital Cortex, inferior division
-17	30	-23	134	-2.08	Frontal Orbital Cortex
44	46	-19	3829	-2.42	Frontal Pole
-46	31	-20	481	-2.34	Frontal Pole
20	-98	5	2822	-2.20	Occipital Pole
-42	-90	15	2527	-2.42	Lateral Occipital Cortex, superior division
-11	68	18	1011	-2.33	Frontal Pole
68	-12	30	635	-2.25	Postcentral Gyrus

slower gait speed (loads into pace), diminished cadence (loads into rhythm), and shorter step length (loads into pace) [73]; these associations were found to be even more pronounced with greater age. Our study provides further structural evidence supporting the negative association between the pace domain of gait and even less clinically overt cerebrovascular disease.

We found that pace is associated with a distributed GMV pattern, which would be more sensitive to globally occurring lesions and cerebral small vessel disease (CSVD) causing diffusely decreased GMV or atrophy. This may explain why expression of the focal and medially localized rhythm pattern is not associated with most vascular diseases. Vascular diseases and their risk factors are known to reduce total and focal GMV in regions serving decision-making, impulse-control, sensory processing, and motor function [22–27,74–78]. Elevated hypertensive and sub-hypertensive blood pressures correlate with lower GMV in several brain regions, including frontal, temporal, parietal, and subcortical structures, as shown in younger [74] and older adults [25–27]. Early-life reductions in GMV indicate that hypertension may cause accelerated brain atrophy in selected regions far earlier than expected and that this cannot be attributable to strokes alone. DM, through

hyperglycemia-mediated metabolic derangements and cellular dysfunction, is associated with reduced global GMV [75], and its specific impact on focal GMV is also documented. A meta-analysis of seven studies found that reduced GMV in middle and superior temporal gyri, medial superior frontal gyrus, insula, median cingulate cortex, precuneus cortex, and the left lentiform nucleus [24] correlated with co-morbid 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 gyrus, precentral gyrus, precuneus, posterior cingulate, postcentral gyrus, inferior parietal lobule, cingulate gyrus, insula and superior temporal gyrus [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 [30,50,52]. 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.

Acknowledgment

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100154.

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, N. Engl. J. Med. 347 (2002) 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.1532-5415.2012.04209.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. Heshmatollah, S.K.L. Darweesh, L.J. Dommershuijsen, P.J. Koudstaal, M.A. Ikram, M.K. Ikram, Quantitative gait impairments in patients with stroke or transient ischemic attack: a population-based approach, Stroke 51 (2020) 2464–2471, https://doi.org/10.1161/STROKEAHA.120.029829.

[5] K.F. De Laat, A.G.W. Van Norden, R.A.R. Gons, L.J.B. Van Oudheusden, I.W.M. Van Uden, B.R. Bloem, M.P. Zwiers, F.E. De Leeuw, Gait in elderly with cerebral small vessel disease, Stroke 41 (2010) 1652–1658, https://doi.org/10.1161/STROKEAHA.110.583229.

[6] 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.

[7] 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.

[8] R. Holtzer, N. Epstein, J.R. Mahoney, M. Izzetoglu, H.M. Blumen, Neuroimaging of mobility in aging: a targeted review, J. Gerontol. A Biol. Sci. Med. Sci. 69 (2014) 1375–1388, https://doi.org/10.1093/gerona/glu052.

[9] Y. Taki, S. Kinomura, K. Sato, R. Goto, K. Wu, R. Kawashima, H. Fukuda, Correlation between gray/white matter volume and cognition in healthy elderly people, Brain Cogn. 75 (2011) 170–176, https://doi.org/10.1016/j.bandc.2010.11.008.

[10] A. Ezzati, M.J. Katz, M.L. Lipton, R.B. Lipton, J. Verghese, The association of brain structure with gait velocity in older adults: a quantitative volumetric analysis of brain MRI, Neuroradiology 57 (2015) 851–861, https://doi.org/10.1007/s00234-015-1536-2.

[11] N.K. Nadkarni, E. Mawji, W.E. McIlroy, S.E. Black, Spatial and temporal gait parameters in Alzheimer's disease and aging, Gait Posture 30 (2009) 452–454, https://doi.org/10.1016/j.gaitpost.2009.07.003.

[12] H.M. Blumen, L.L. Brown, C. Habeck, G. Allali, E. Ayers, O. Beauchet, M. Callisaya, R.B. Lipton, P.S. Mathuranath, T.G. Phan, V.G. Pradeep Kumar, V. Srikanth, J. Verghese, Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study, Brain Imaging Behav. 12 (2018) 1–15, https://doi.org/10.1007/s11682-018-9871-7.

[13] M.L. Callisaya, R. Beare, T.G. Phan, J. Chen, V.K. Srikanth, Global and regional associations of smaller cerebral gray and white matter volumes with gait in older people, PLoS One 9 (2014) e84909, https://doi.org/10.1371/journal.pone.0084909.

[14] C. Rosano, H.J. Aizenstein, S. Studenski, A.B. Newman, A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults, J. Gerontol. A Biol. Sci. Med. Sci. 62 (2007) 1048–1055.

[15] J. Verghese, M. Robbins, R. Holtzer, M. Zimmerman, C. Wang, X. Xue, R.B. Lipton, Gait dysfunction in mild cognitive impairment syndromes, J. Am. Geriatr. Soc. 56 (2008) 1244–1251, https://doi.org/10.1111/j.1532-5415.2008.01758.x.

[16] S. Lord, B. Galna, J. Verghese, S. Coleman, D. Burn, L. Rochester, Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach, J. Gerontol. A Biol. Sci. Med. Sci. 68 (2013) 820–827, https://doi.org/10.1093/gerona/gls255.

[17] J.H. Hollman, E.M. McDade, R.C. Petersen, Normative spatiotemporal gait parameters in older adults, Gait Posture 34 (2011) 111–118, https://doi.org/10.1016/J.GAITPOST.2011.03.024.

[18] V.J.A. Verlinden, J.N. Van Der Geest, A. Hofman, M.A. Ikram, Cognition and gait show a distinct pattern of association in the general population, Alzheimer's and Dementia. 10 (2014) 328–335. 10.1016/j.jalz.2013.03.009.

[19] J. Verghese, C. Wang, R.B. Lipton, R. Holtzer, X. Xue, Quantitative gait dysfunction and risk of cognitive decline and dementia, J. Neurol. Neurosurg. Psychiatry 78 (2007) 929–935, https://doi.org/10.1136/jnnp.2006.106914.

[20] E.I. Ayers, A.C. Tow, R. Holtzer, J. Verghese, Walking while talking and falls in aging, Gerontology 60 (2014) 108–113, https://doi.org/10.1159/000355119.

[21] J. Verghese, A. LeValley, C.B. Hall, M.J. Katz, A.F. Ambrose, R.B. Lipton, Epidemiology of gait disorders in community-residing older adults, J. Am. Geriatr. Soc. 54 (2006) 255–261, https://doi.org/10.1111/j.1532-5415.2005.00580.x.

[22] S. Debette, S. Seshadri, A. Beiser, R. Au, J.J. Himali, C. Palumbo, P.A. Wolf, C. DeCarli, Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline, Neurology 77 (2011) 461–468, https://doi.org/10.1212/WNL.0b013e318227b227.

[23] E. Kotkowski, L.R. Price, C. Franklin, M. Salazar, M. Woolsey, R.A. DeFronzo, J. Blangero, D.C. Glahn, P.T. Fox, A neural signature of metabolic syndrome, Hum. Brain Mapp. (2019), https://doi.org/10.1002/hbm.24617 hbm.24617.

[24] J. Liu, T. Liu, W. Wang, L. Ma, X. Ma, S. Shi, Q. Gong, M. Wang, Reduced gray matter volume in patients with type 2 diabetes mellitus, Front. Aging Neurosci. 9 (2017) 161, https://doi.org/10.3389/fnagi.2017.00161.

[25] T. den Heijer, L.J. Launer, N.D. Prins, E.J. van Dijk, S.E. Vermeer, A. Hofman, P.J. Koudstaal, M.M.B. Breteler, Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe, Neurology 64 (2005) 263–267, https://doi.org/10.1212/01.WNL.0000149641.55751.2E.

[26] E.C. Leritz, D.H. Salat, V.J. Williams, D.M. Schnyer, J.L. Rudolph, L. Lipsitz, B. Fischl, R.E. McGlinchey, W.P. Milberg, Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults, Neuroimage 54 (2011) 2659–2671, https://doi.org/10.1016/j.neuroimage.2010.10.050.

[27] O. Beauchet, S. Celle, F. Roche, R. Bartha, M. Montero-Odasso, G. Allali, C. Annweiler, Blood pressure levels and brain volume reduction, J. Hypertens. 31 (2013) 1502–1516, https://doi.org/10.1097/HJH.0b013e32836184b5.

[28] C. Habeck, 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) 1503–1515, https://doi.org/10.1016/j.neuroimage.2008.01.056.

[29] A.M. Brickman, C. Habeck, E. Zarahn, 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.

[30] C. Habeck, Y. Stern, the A.D.N. Alzheimer's disease neuroimaging initiative, multivariate data analysis for neuroimaging data: overview and application to Alzheimer's disease, Cell Biochem. Biophys. 58 (2010) 53–67, https://doi.org/10.1007/s12013-010-9093-0.

[31] P. Choi, M. Ren, T.G. Phan, M. Callisaya, J.V. Ly, R. Beare, W. Chong, V. Srikanth, Silent infarcts and 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.

[32] 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/10.1016/B978-0-12-809324-5.05530-9.

[33] R.C. Petersen, R.O. Roberts, D.S. Knopman, B.F. Boeve, Y.E. Geda, R.J. Ivnik, G.E. Smith, C.R. Jack, Mild cognitive impairment: ten years later, Arch. Neurol. 66 (2009) 1447–1455, https://doi.org/10.1001/archneurol.2009.266.

[34] R.C. Petersen, Mild cognitive impairment as a diagnostic entity, J. Intern. Med. (2004) 183–194, https://doi.org/10.1111/j.1365-2796.2004.01388.x.

[35] R.C. Petersen, G.E. Smith, S.C. Waring, R.J. Ivnik, E.G. Tangalos, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch. Neurol. 56 (1999) 303–308, https://doi.org/10.1001/archneur.56.3.303.

[36] J. Verghese, C. Annweiler, E. Ayers, N. Barzilai, O. Beauchet, D. a Bennett, S.A. Bridenbaugh, A.S. Buchman, M.L. Callisaya, R. Camicioli, B. Capistrant, S. Chatterji, A.M. de Cock, 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. Wang, Motoric cognitive risk syndrome: multicountry prevalence and dementia risk, Neurology (2014), https://doi.org/10.1212/WNL.0000000000000717. WNL.0000000000000717-.

[37] J.A. Yesavage, T.L. Brink, T.L. Rose, O. Lum, V. Huang, M. Adey, V.O. Leirer, 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)90033-4.

[38] K.D. Benton, L, A, Hamsher, Multilingual Aphasia Examination, SpringerReference, 2012, https://doi.org/10.1007/springerreference_183669.

[39] M.D. Lezak, Neuropsychological assessment, (1995) 1026.

[40] J.E. Meyers, K.R. Meyers, Rey complex figure test under four different administration procedures, Clin. Neuropsychol. 9 (1995) 63–67, https://doi.org/10.1080/13854049508402059.

[41] J. Brandt, The hopkins verbal learning test: development of a new memory test with six equivalent forms, Clin. Neuropsychol. 5 (1991) 125–142, https://doi.org/10.1080/13854049108403297.

[42] J.J. Ryan, S.J. Lopez, Wechsler adult intelligence scale-III. Understanding Psychological Assessment, Springer, Boston, MA, 2001, pp. 19–42, https://doi.org/10.1007/978-1-4615-1185-4_2.

[43] C. Graf, The lawton instrumental activities of daily living scale, Am. J. Nurs. 108 (2008) 52–62, https://doi.org/10.1097/01.NAJ.0000314810.46029.74.

[44] M.L. Callisaya, L. Blizzard, M.D. Schmidt, K.L. Martin, J.L. Mcginley, L.M. Sanders, V.K. Srikanth, Gait, gait variability and the risk of multiple incident falls in older people: a population-based study, Age Ageing 40 (2011) 481–487, https://doi.org/10.1093/ageing/afr055.

[45] T.P. Siejka, V.K. Srikanth, R.E. Hubbard, C. Moran, R. Beare, A. Wood, T. Phan, M.L. Callisaya, Frailty and cerebral small vessel disease: a cross-sectional analysis of the tasmanian study of cognition and gait (TASCOG), J. Gerontol. Ser. A 73 (2018) 255–260, https://doi.org/10.1093/gerona/glx145.

[46] J. Ashburner, A fast diffeomorphic image registration algorithm, Neuroimage 38 (2007) 95–113, https://doi.org/10.1016/j.neuroimage.2007.07.007.

[47] I.C. Wright, P.K. McGuire, J.B. Poline, J.M. Travere, R.M. Murray, C.D. Frith, R.S. Frackowiak, K.J. Friston, A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia, Neuroimage 2 (1995) 244–252, https://doi.org/10.1006/nimg.1995.1032.

[48] H.M. Blumen, G. Allali, O. Beauchet, R.B. Lipton, J. Verghese, A gray matter volume covariance network associated with the motoric cognitive risk syndrome: a multi-cohort MRI study, J. Gerontol. Ser. A (2018), https://doi.org/10.1093/gerona/gly158.

[49] T. Doi, H.M. Blumen, J. Verghese, H. Shimada, H. Makizako, K. Tsutsumimoto, R. Hotta, S. Nakakubo, T. Suzuki, Gray matter volume and dual-task gait performance in mild cognitive impairment, Brain Imaging Behav. 11 (2017) 887–898, https://doi.org/10.1007/s11682-016-9562-1.

[50] F. Ashby, Statistical analysis of fMRI data, 2011.

[51] C. Habeck, Y. Stern, Neural network approaches and their reproducibility in the study of verbal working memory and Alzheimer's disease, Clin. Neurosci. Res. 6 (2007) 381–390, https://doi.org/10.1016/J.CNR.2007.05.004.

[52] C. Habeck, J.W. Krakauer, C. Ghez, H.A. Sackeim, D. Eidelberg, Y. Stern, J.R. Moeller, A new approach to spatial covariance modeling of functional brain imaging data: ordinal trend analysis, Neural Comput. 17 (2005) 1602–1645, https://doi.org/10.1162/0899766053723023.

[53] K.P. Burnham, D.R. Anderson, Model Selection and Multimodel Inference, Springer, New York, New York, NY, 2004, https://doi.org/10.1007/b97636.

[54] B. Efron, R.J. Tibshirani, An introduction to the bootstrap, J. Am. Stat. Assoc. 89 (1993) 436.

[55] J. Steffener, A.M. Brickman, C.G. Habeck, T.A. Salthouse, Y. Stern, Cerebral blood flow and gray matter volume covariance patterns of cognition in aging, Hum. Brain Mapp. 34 (2013) 3267–3279, https://doi.org/10.1002/hbm.22142.

[56] P.G. Spetsieris, D. Eidelberg, Scaled subprofile modeling of resting state imaging data in Parkinson's disease: methodological issues, Neuroimage 54 (2011) 2899–2914, https://doi.org/10.1016/j.neuroimage.2010.10.025.

[57] R.J. Killiany, A.M. Dale, F. Ségonne, R.S. Desikan, D. Blacker, R.L. Buckner, R.P. Maguire, B. Fischl, B.C. Dickerson, M.S. Albert, B.T. Hyman, B.T. Quinn, An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Neuroimage 31 (2006) 968–980, https://doi.org/10.1016/j.neuroimage.2006.01.021.

[58] I. Maidan, A. Mirelman, J.M. Hausdorff, Y. Stern, C.G. Habeck, Distinct cortical thickness patterns link disparate cerebral cortex regions to select mobility domains, Sci. Rep. 2021 (2021) 1–11, https://doi.org/10.1038/s41598-021-85058-z, 11:1.11.

[59] I.H. Chen, V. Novak, B. Manor, Infarct hemisphere and noninfarcted brain volumes affect locomotor performance following stroke, Neurology 82 (2014) 828–834, https://doi.org/10.1212/WNL.0000000000000186.

[60] J. Dumurgier, F. Crivello, B. Mazoyer, I. Ahmed, B. Tavernier, D. Grabli, C. François, N. Tzourio-Mazoyer, C. Tzourio, A. Elbaz, MRI atrophy of the caudate nucleus and slower walking speed in the elderly, Neuroimage 60 (2012) 871–878, https://doi.org/10.1016/j.neuroimage.2012.01.102.

[61] C. Rosano, D.A. Bennett, A.B. Newman, V. Venkatraman, K. Yaffe, T. Harris, S. Kritchevsky, H.J. Aizenstein, Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults, J. Gerontol. A Biol. Sci. Med. Sci. 67 (2012) 957–962, https://doi.org/10.1093/gerona/glr262.

[62] C. Rosano, S.A. Studenski, H.J. Aizenstein, R.M. Boudreau, W.T. Longstreth, A.B. Newman, Slower gait, slower information processing and smaller prefrontal area in older adults, Age Ageing 41 (2012) 58–64, https://doi.org/10.1093/ageing/afr113.

[63] A. Zwergal, J. Linn, G. Xiong, T. Brandt, M. Strupp, K. Jahn, Aging of human supraspinal locomotor and postural control in fMRI, Neurobiol. Aging 33 (2012) 1073–1084, https://doi.org/10.1016/j.neurobiolaging.2010.09.022.

[64] G. Leisman, A. Moustafa, T. Shafir, Thinking, walking, talking: integratory motor and cognitive brain function, Front. Public Health 4 (2016) 94, https://doi.org/10.3389/fpubh.2016.00094.

[65] C. la Fougère, A. Zwergal, A. Rominger, S. Förster, G. Fesl, M. Dieterich, T. Brandt, M. Strupp, P. Bartenstein, K. Jahn, Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison, Neuroimage 50 (2010) 1589–1598, https://doi.org/10.1016/j.neuroimage.2009.12.060.

[66] S. Tripathi, J. Verghese, H.M. Blumen, Gray matter volume covariance networks associated with dual-task cost during walking-while-talking, Hum. Brain Mapp. (2019), https://doi.org/10.1002/hbm.24520.

[67] K.F. de Laat, H.A.C. van den, A.G.W. Berg, R.A.R. van Norden, M.G.M. Gons, F.E.D.L. Olde Rikkert, Microbleeds are independently related to gait disturbances in elderly individuals with cerebral small vessel disease, Stroke 42 (2011) 494–497, https://doi.org/10.1161/STROKEAHA.110.596122.

[68] A. Soumaré, A. Elbaz, Y. Zhu, P. Maillard, F. Crivello, B. Tavernier, C. Dufouil, B. Mazoyer, C. Tzourio, White matter lesions volume and motor performances in the elderly, Ann. Neurol. 65 (2009) 706–715, https://doi.org/10.1002/ana.21674.

[69] C. Rosano, J. Brach, S. Studenski, W.T. Longstreth Jr., A.B. Newman, Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults, Neuroepidemiology 29 (2007) 193–200, https://doi.org/10.1159/000111582.

[70] K.F. de Laat, A.G.W. van Norden, R.A.R. Gons, L.J.B. van Oudheusden, I.W.M. van Uden, B.R. Bloem, M.P. Zwiers, F.E. de Leeuw, Gait in elderly with cerebral small vessel disease, Stroke 41 (2010) 1652–1658, https://doi.org/10.1161/STROKEAHA.110.583229.

[71] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (2010) 689–701, https://doi.org/10.1016/S1474-4422(10)70104-6.

[72] V. Srikanth, R. Beare, L. Blizzard, T. Phan, J. Stapleton, J. Chen, M. Callisaya, K. Martin, D. Reutens, Cerebral white matter lesions, gait, and the risk of incident falls, Stroke 40 (2009) 175–180, https://doi.org/10.1161/STROKEAHA.108.524355.

[73] M.L. Callisaya, R. Beare, T.G. Phan, L. Blizzard, A.G. Thrift, J. Chen, V.K. Srikanth, Brain structural change and gait decline: a longitudinal population-based study, J. Am. Geriatr. Soc. 61 (2013) 1074–1079, https://doi.org/10.1111/jgs.12331.

[74] H.L. Schaare, S. Kharabian Masouleh, F. Beyer, D. Kumral, M. Uhlig, J.D. Reinelt, A.M.F. Reiter, L. Lampe, A. Babayan, M. Erbey, J. Roebbig, M.L. Schroeter, H. Okon-Singer, K. Müller, N. Mendes, D.S. Margulies, A.V. Witte, M. Gaebler, A. Villringer, Association of peripheral blood pressure with gray matter volume in 19- to 40-year-old adults, Neurology 92 (2019) e758–e773, https://doi.org/10.1212/WNL.0000000000006947.

[75] C. Moran, R.J. Tapp, A.D. Hughes, C.G. Magnussen, L. Blizzard, T.G. Phan, R. Beare, N. Witt, A. Venn, G. Münch, B.C. Amaratunge, V. Srikanth, The Association of type 2 diabetes mellitus with cerebral gray matter volume is independent of retinal vascular architecture and retinopathy, J. Diabetes Res. 2016 (2016), 6328953, https://doi.org/10.1155/2016/6328953.

[76] Y.K. Hayakawa, H. Sasaki, H. Takao, T. Yoshikawa, N. Hayashi, H. Mori, A. Kunimatsu, S. Aoki, K. Ohtomo, The relationship of waist circumference and body mass index to grey matter volume in community dwelling adults with mild obesity, Obes. Sci. Pract. 4 (2018) 97–105, https://doi.org/10.1002/osp4.145.

[77] M. Hamer, G.D. Batty, Association of body mass index and waist-to-hip ratio with brain structure, Neurology 92 (2019) e594–e600, https://doi.org/10.1212/WNL.0000000000006879.

[78] Y. Dong, Q. Wang, H. Yao, Y. Xiao, J. Wei, P. Xie, J. Hu, W. Chen, Y. Tang, H. Zhou, J. Liu, A promising structural magnetic resonance imaging assessment in patients with preclinical cognitive decline and diabetes mellitus, J. Cell. Physiol. (2019), https://doi.org/10.1002/jcp.28359.

[79] JR M, J V, Does Cognitive Impairment Influence Visual-Somatosensory Integration and Mobility in Older Adults? J. Gerontol. A Biol. Sci. Med. Sci. 75 (2020) 581–588, https://doi.org/10.1093/GERONA/GLZ117.

[80] H.P. Aben, L. Luijten, B.P. Jansen, J.M. Visser-Meily, J.M. Spikman, G.J. Biessels, P.L. de Kort, Absence of an infarct on MRI is not uncommon after clinical diagnosis of ischemic stroke, J. Stroke Cerebrovasc. Dis. 29 (2020), https://doi.org/10.1016/J.JSTROKECEREBROVASDIS.2020.104979.