Gray Matter Patterns Associated with Quantitative Gait Factors in Older Adults

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Mobility Disability and Gait Decline in Older Adults

- Major public health issue
- The most common form of disability in older US adults (Wang et al., 2006)
- The prevalence of clinical gait abnormalities in community-dwelling older adults is 35% (Verghese et al., 2005)
- Accelerated gait decline in aging is associated with many adverse outcomes:
  - Morbidity
  - Hospitalization
  - Mortality
  - Falls
  - Future cognitive decline and dementia

Quantitative Gait Assessments

- Gait decline can be characterized in many different ways – not just gait speed/velocity (cm/s)
- Quantitative gait assessments include cadence, stride length, swing, double support, stride length variability, and swing time variability – typically assessed with a portable walkway gait analysis system.
- Quantitative gait assessments shown to be independently associated with adverse outcomes such as falls (Verghese et al, 2009)

Current understanding of Structural Brain Systems of Gait in Healthy Older Adults is Quite Limited

- **Accelerated gait decline:** linked to total and focal gray matter volume and gray matter changes, ventriculomegaly, white matter hyper-intensities (Holtzer, Epstein, Mahoney, Izzetoglu, & Blumen, 2014; Taki et al., 2011)
- **Declining balance:** linked to gray matter volume right putamen, right posterior superior parietal cortex, and bilateral cerebellum (Rosano, Aizenstein, Studenski, & Newman, 2007)
- **Bradykinesia:** linked to gray matter volume in left cerebellum, caudate nucleus, left prefrontal cortex, and sensorimotor areas (Chen, Novak, & Manor, 2014; Dumurgier et al., 2012)
- **Disturbances in other parameters of gait, including stride length, posture, gait speed, tremor, etc.:** medial temporal areas that do not overlap with the bradykinesia-associated pre- and post-central gyri (Rosano et al., 2012).

Gait Measure	Brain Structure
Gait Disturbance (stride length, posture, gait speed, tremor)	Medial temporal lobe
	Motor cortex
	Middle cingulate
	Anterior insula
	Right Caudate
	Anterior lobe of the cerebellum
Balance	Right Putamen
	Right Posterior Superior Cortex
	Parietal cortex
	Bilateral cerebellum
Bradykinesia	Left cerebellum
	Caudate nucleus
	Left prefrontal cortex
	Sensorimotor areas
	Medial Temporal Areas

Key limitations of previous studies:

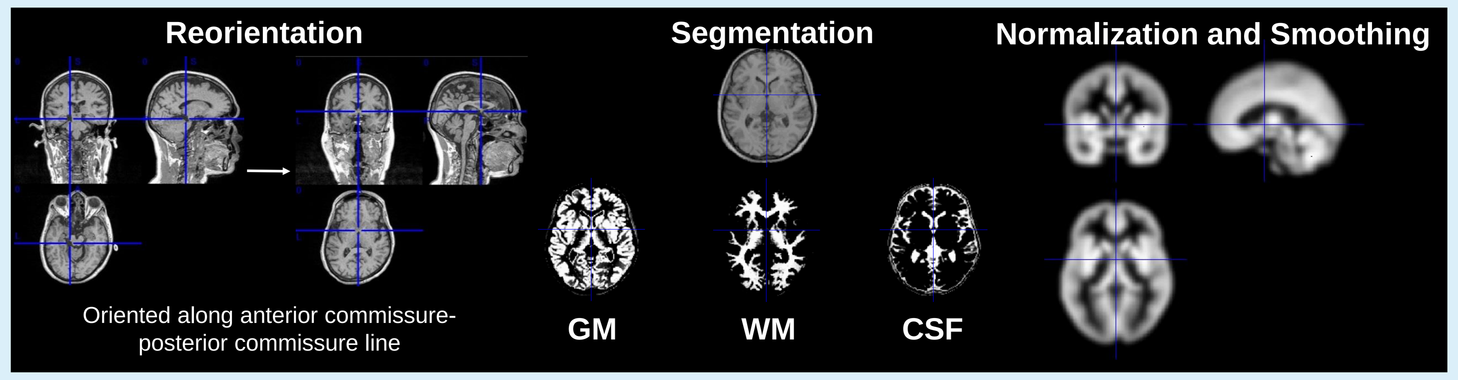
- Structural changes in the brain have been selectively linked to quantitative parameters, without considering the interplay among them.
- Focus on region-specific analysis, instead of broad patterns or "networks" of brain structures, and their relationship with different quantitative gait parameters.

Current study: Aimed to identify **gray matter networks** associated with three different aspects of gait: **pace, rhythm and variability,** in three different **non-demented** elderly cohorts from three different countries (France, Australia and India).

Procedure:

I. Factor Analysis of quantitative parameters of gait in Australian, French, and Indian cohorts to determine the cohort-specific weights of different quantitative gait measures of Pace, Rhythm, and Variability.
II. Pre-process MRI data from all three cohorts and implement DARTEL to generate template MRIs in preparation for multivariate analysis.
III. Multivariate analysis to identify gray matter covariance patterns associated with Pace, Rhythm, and Variability in each cohort.
IV. Localization of clusters correlated strongly and weakly with maintaining patterns of change in principal components of gait.

Variable	Kerala Einstein Study	French GAIT	Tasmanian TASCOG
N	50	170	376
Age (years	66.8 (5.44)	70.14(4.38)	72.66 (7.07)
Sex (% female)	20	37	43
Non-amnestic Mild Cognitive Impairment	16/50	26/170	9/376
Amnestic Mild Cognitive Impairment	1/50	72/170	5/376



MRI pre-processing workflow

- MRI data from all three cohorts was analyzed independently.
- MRI reoriented manually along anterior commissure-posterior commissure line.
- Reorientation, segmentation, normalization, and smoothing all carried out in preparation for comparison relative to cohort-specific templates generated via DARTEL.

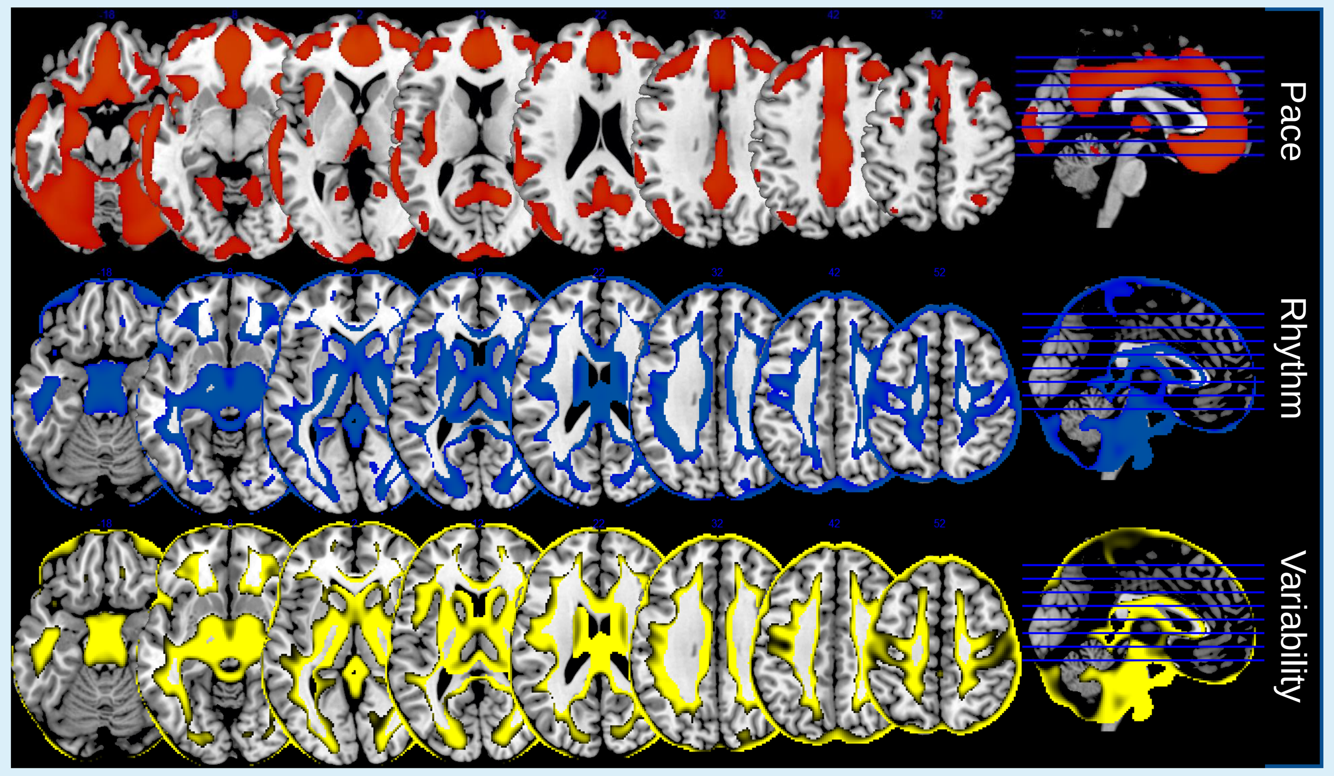
Factor analysis of quantitative gait measures

- Quantitative gait measures: *gait speed*, *stride length*, *cadence*, *double support time*, *swing time*, *stance time*, *stride length variability*, and *swing time variability*.
- Factor analysis determines the individual weightage of each parameter as they inform the principal components of gait: Pace, Rhythm, and Variability.
- **Pace** is influenced most closely by *gait speed*, *stride length*, and *double support time*.
- **Rhythm** is governed largely by *cadence*, *swing time*, and *stance time*. The Indian KES data also includes *swing time variability* as a factor of rhythm.
- **Variability** is influenced largely by *stride length variability* with added weighting of *swing time variability* in the French GAIT and Australian TASCOG cohorts.

Factor Loading of Quantitative Gait Variables on Three Independent Gait Factors Rotated and Extracted by Factor Analysis for Indian KES, French GAIT, and Australian TASCOG cohorts.

	Indian KES			French GAIT			Australian TASCOG		
	Pace	Rhythm	Variability	Pace	Rhythm	Variability	Pace	Rhythm	Variability
Velocity	.945	-.249	.020	.891	-.392	-.044	.889	-.352	-.133
Stride Length	.924	.123	.057	.950	.200	-.015	.949	.084	-.160
Cadence	.570	-.712	-.047	.343	-.930	-.053	.374	-.908	-.123
Double support time	-.831	.406	.133	-.773	.534	.075	-.731	.466	.218
Swing Time	-.131	.944	-.129	.175	.910	.160	.047	.931	.057
Stance Time	-.706	.636	.095	-.572	.794	.000	-.563	.737	.234
Stride Length SD	-.018	.059	.990	.036	.045	.948	-.120	.051	.958
Swing Time SD	-.038	.684	.175	-.110	.108	.937	-.511	.366	.599

Results: Australian-TASCOG Cohort

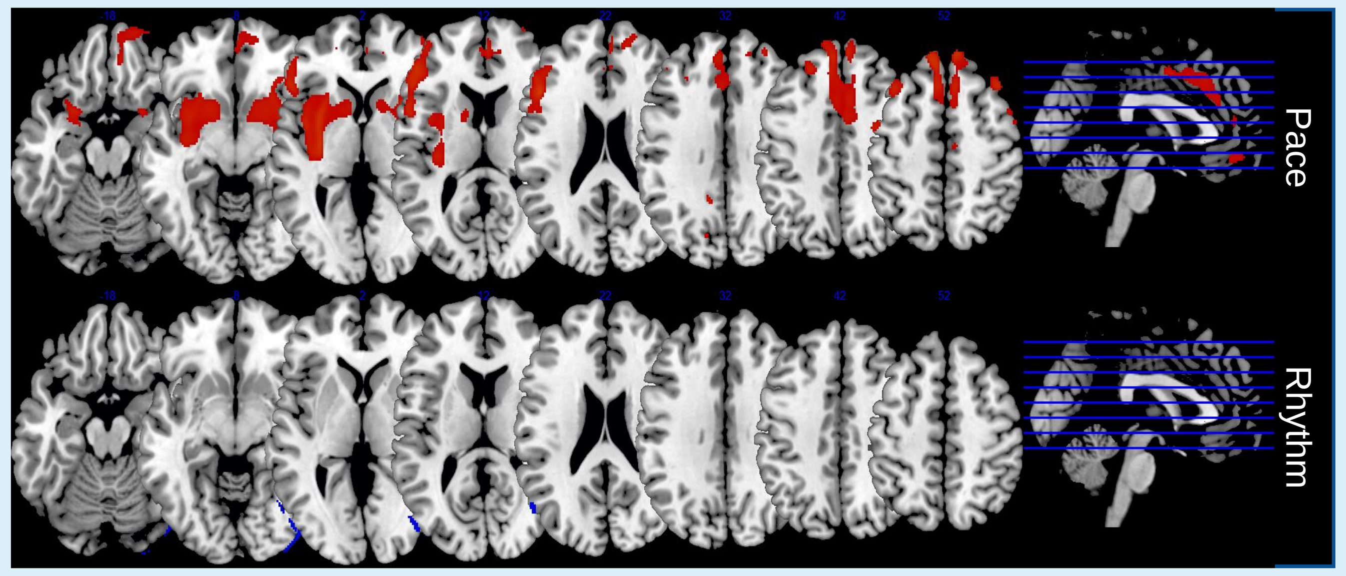


Pace was associated with a network of gray matter volume primarily composed of cingulate, prefrontal and cerebellar regions. Additional involvement of lateral occipital gyrus, middle frontal gyrus, and supramarginal gyrus noted.

Rhythm was associated with a network of gray matter volume primarily composed of middle frontal gyrus**.**

Variability was associated with a network of gray matter volume primarily composed of the frontal pole.

Results: French GAIT cohort



Pace was associated with a network of gray matter volume primarily composed of cingulate, inferior frontal, insular, precentral gyrus, and frontal pole.

Rhythm was associated with significant, but small clusters in the lateral occipital cortex.

Discussion

- Gray matter volume changes in cerebellar, cingulate and prefrontal cortex regions were associated with pace in TASCOG and GAIT cohorts.
- Gray matter volume changes in sensorimotor, basal ganglia, thalamic, and cerebellar regions were associated with rhythm and variability, as observed largely in the TASCOG cohort.
- These results are consistent with previous studies linking gray matter volume to gait speed and balance.
- The quantitative gait parameters informing Pace, Rhythm, and Variability are largely conserved across three demographically distinct cohorts.
- Gait analysis in this multi-factorial manner provides a more precise view of gait decline, thereby increasing the predictive value of this widely used tool.
- By expanding current understanding of which structural changes are correlated with observed changes in the principal components of gait, we are providing a first look at a network-level vision into the neural structures subserving gait.
- If successful, our efforts could create a foundation for pairing neuroimaging with gait testing for earlier diagnosis of pathological gait decline, thereby also allowing for earlier prognostic ability of this test to predict dementia.

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