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ORIGINAL RESEARCH

Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study

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Abstract

Accelerated gait decline in aging is associated with many adverse outcomes, including an increased risk for falls, cognitive decline, and dementia. Yet, the brain structures associated with gait speed, and how they relate to specific cognitive domains, are not well-understood. We examined structural brain correlates of gait speed, and how they relate to processing speed, executive function, and episodic memory in three non-demented and community-dwelling older adult cohorts (Overall $N = 352$), using voxel-based morphometry and multivariate covariance-based statistics. In all three cohorts, we identified gray matter volume covariance patterns associated with gait speed that included brain stem, precuneus, fusiform, motor, supplementary motor, and prefrontal (particularly ventrolateral prefrontal) cortex regions. Greater expression of these gray matter volume covariance patterns linked to gait speed were associated with better processing speed in all three cohorts, and with better executive function in one cohort. These gray matter covariance patterns linked to gait speed were not associated with episodic memory in any of the cohorts. These findings suggest that gait speed, processing speed (and to some extent executive functions) rely on shared neural systems that are subject to age-related and dementia-related change. The implications of these findings are discussed within the context of the development of interventions to compensate for age-related gait and cognitive decline.

Keywords Gait · Cognition · Magnetic resonance imaging · Gray matter · Multivariate analyses

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Introduction

Accelerated gait decline in aging is associated with many adverse physical and cognitive outcomes. It is associated with an increased risk for falls, hospitalization, disability, morbidity and mortality (Newman et al. 2006; Verghese et al. 2009). It is common in dementia and mild cognitive impairment (Verghese et al. 2002, 2007, 2008), and in cognitively-healthy older adults it is associated with an increased risk for future cognitive decline and dementia (Marquis et al. 2002; Verghese et al. 2007; Waite et al. 2005; Wang et al. 2006). The typical interpretation of such associations is that gait and cognition share common neural substrates that are subject to age-related and dementia-related change; for reviews see (Holtzer et al. 2014a; Rosso et al. 2013; Srikanth et al. 2010). The neural substrates of human locomotion, and how they relate to different cognitive domains, however, are not well-understood.

Gait speed (cm/s) is a relatively simple, yet useful, measure of human locomotion (Verghese et al. 2009). It can be assessed in the laboratory and most clinical settings, with an instrumented walkway or with a walk over a fixed distance timed with a stopwatch. Gait speed reliably predicts both adverse physical (Abellan van Kan et al. 2009) and cognitive outcomes (Buracchio et al. 2010; Mielke et al. 2013; Verghese et al. 2007). In fact, monitoring gait speed is a recommended strategy for identifying older adults at increased risk for a number of adverse health outcomes, including falls, frailty, and disability (Cummings et al. 2014; Panel on Prevention of Falls in Older Persons and British Geriatrics 2011; Society et al. 2001; Turner and Clegg 2014). Yet, the brain correlates of gait speed in older adults are not well-studied. The *functional* brain correlates of gait, for example, are not well-understood because conventional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) cannot image the brain during locomotion.

A select number of studies have examined the *structural* brain correlates of gait speed in older adults (Callisaya et al. 2013, 2014; Dumurgier et al. 2012; Nadkarni et al. 2014; Rosano et al. 2012), and results have been mixed. One study suggests that reduced cerebellar gray matter volume is associated with slow gait (Nadkarni et al. 2014), while another study of a similar, non-demented U.S. cohort suggests that reduced prefrontal cortex volume is associated with slow gait (Rosano et al. 2012). A French population-based study further suggests that the volume of the caudate nucleus (in the basal ganglia) is associated with gait speed in non-demented older adults (Dumurgier et al. 2012). A couple of studies of an Australian, non-demented older adult cohort, however, suggest that gait speed is associated with a more distributed network of brain regions, including cerebellar, occipital, basal ganglia, parietal, temporal, frontal and prefrontal regions (Callisaya et al. 2014), but that gait speed decline is specifically associated with hippocampal atrophy (Callisaya et al. 2013).

The discrepancy between the results of the studies reviewed above may be accounted for by methodological differences. The studies that linked a single brain region with gait speed or gait speed decline (Callisaya et al. 2013; Dumurgier et al. 2012; Nadkarni et al. 2014; Rosano et al. 2012) computed gray matter volume associated with particular brain regions, lobes, or cortices (e.g., hippocampal, occipital, or prefrontal) that were then correlated with gait speed or gait speed decline. The study that linked a more distributed network of brain regions to gait speed (Callisaya et al. 2014), however, correlated gray matter volume and gait speed across the whole-brain on a voxel-by-voxel basis – and therefore was able to identify regions of the occipital cortex, for example, that was associated with gait speed, even if the occipital cortex as a whole was not associated with gait speed. Additional studies of the structural brain correlates of gait speed are needed, yet attributing gait speed to a distributed network of brain regions would also be more consistent with the results of fMRI studies of imagined or motor imagery of gait (Allali et al. 2014; Blumen et al. 2014; la Fougere et al. 2010; van der Meulen et al. 2012; Zwergal et al. 2012), and a flourodeoxy-glucose positron emission tomography study of actual gait (la Fougere et al. 2010). In addition, the relationship between this distributed network of brain regions associated with gait and specific cognitive domains remain unexplored.

Cross-sectional and longitudinal studies have linked gait speed to several cognitive domains, including executive function, episodic memory, and processing speed. There is considerable evidence to suggest that executive function is a cognitive domain that is associated with gait speed and gait speed decline in older adults without dementia (Atkinson et al. 2007; Callisaya et al. 2015; Doi et al. 2014; Holtzer et al. 2014b, 2006, 2012; Watson et al. 2010). Yet, there is also some evidence to suggest that episodic memory (Holtzer et al. 2006, 2012) and processing speed are associated with gait speed in non-demented older adults (Nadkarni et al. 2014; Rosano et al. 2012). Executive function is an umbrella term for higher-order cognitive processes including planning, reasoning, selection and inhibition of appropriate responses, and monitoring and maintaining information in working memory (Norman and Shallice 1980). Executive function is typically attributed to prefrontal cortex regions (Alvarez and Emory 2006; Elderkin-Thompson et al. 2008; Koechlin et al. 2003; Miller and Cohen 2001). Episodic memory is memory for specific episodes or events, and the temporal and spatial relationship between episodes and events (Tulving 1972, 1985). It has been linked to a number of brain regions in the medial-temporal, posterior, and prefrontal cortices (Habeck et al. 2016; Lee et al. 2016; Shallice et al. 1994; Spaniol et al. 2009; Stern et al. 2014). Finally, processing speed is the general ability to process information efficiently to perform a

number of cognitive tasks, including memory, reasoning, and spatial tasks (Kail and Salthouse 1994; Salthouse 1996). Processing speed has also been linked to a number of different brain regions including cerebellar, somatosensory, parietal, basal ganglia, insular, and prefrontal cortex regions (Habeck et al. 2016; Lee et al. 2016; Nadkarni et al. 2014; Rosano et al. 2012; Rypma et al. 2006; Stern et al. 2014).

The aim of the current study was to examine the structural brain correlates of gait speed – and how they relate to executive function, episodic memory, and processing speed – in three non-demented, community-dwelling older adult cohorts (Overall $N = 352$). To our knowledge, this is the first multi-cohort examination of the neural substrates of gait speed – and it is the neuroimaging extension of recent efforts to compare and pool gait and cognitive data from different cohorts in order to advance our understanding of the relationship between gait and cognition, and its clinical applications (Allali et al. 2015; Beauchet et al. 2016b, 2016c; Verghese et al. 2014a, b). Examining the structural brain correlates of gait speed in three different cohorts allowed us to examine both cohort-specific and cohort-general effects, to determine the reliability of brain, gait, and cognition relationships, and to establish appropriate methods for examining such relationships in future studies of these and other cohorts. Voxel-based morphometry methods and multivariate covariance-based statistics were used to identify gray matter covariance patterns or 'networks' associated with gait speed in each cohort. Multivariate covariance-based statistical approaches largely avoids the multiple comparison problem associated with traditional univariate neuroimaging analyses, and are particularly sensitive to detecting effects in the presence of between-subjects variability and collinearity – issues that are particularly important when analyzing neuroimaging data in general, and from older adult populations in particular (Ashby 2011; Habeck et al. 2005a; Habeck and Stern 2010). The expressions of these gray matter networks linked to gait speed were then correlated with analogous neuropsychological assessments of executive function, episodic memory, and processing speed.

Materials and methods

Participants

We examined gray matter covariance patterns or networks linked to gait speed, and their associations with specific cognitive domains, in three non-demented, community-dwelling older adult cohorts: 89 older adults (M Age = 76.07) from the Central Control of Mobility in Aging Study (CCMA) in the US [for additional details see (Blumen et al. 2014; Holtzer et al. 2014c), 93 older adults (M Age = 79.86) from the Einstein Aging Study (EAS) in the US [for additional details see (Katz et al. 2012)], and 170 older adults (M Age = 70.65) from the Gait and Alzheimer and Interactions Study (GAIT) in France [for additional study details see (Beauchet et al. 2013)]. These data was the MRI subset of larger behavioral data sets from these cohorts that has been described in previous publications (Verghese et al. 2014a, b)]. Note that the CCMA and EAS cohorts were recruited directly from the community, while the GAIT cohort was recruited within the context of a memory clinic. The demographic, cognitive, and gait characteristics of each cohort are summarized in Table 1. Persons with dementia were excluded based on clinical case conferences and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (Association 2000).

Gait and cognitive measures and covariates

Gait speed (cm/s) in all cohorts was measured quantitatively using instrumented walkways from the same manufacturer (GAITRite System ® Clifton, NJ) over a fixed distance (609.60 cm/20 ft). A *global cognition* measure was obtained from all three cohorts: the Repeatable Battery for the Assessment of Neuropsychological Status from the CCMA cohort (RBANS (Randolph et al. 1998)), the short Blessed (Katzman et al. 1983; Morris et al. 1989) from the EAS cohort, and the Mini Mental Status Exam (MMSE (Folstein et al. 1975)) from the GAIT cohort. Analogous assessments of *executive function* [The Trail Making Test: Time to complete Part B minus Part A; TMT:B-A (Reitan 1978)], *episodic memory* [free recall on the Free and Cued Selective Reminding Test; FCSRT (Buschke 1973)] and *processing speed* [Trail Making Test: Time to completed Part A (TMT:A)] were also obtained from all three cohorts. Clinical assessments of the presence and absence of non-neurological (e.g. arthritis or cardiac disease) and neurological gait disorders (e.g. cerebellar or neuropathic gait) were obtained from two (CCMA and EAS) of the three cohorts. Finally, the presence of mild cognitive impairment; MCI (Petersen 2004; Petersen et al. 1999, 2009) and past history of stroke was obtained from all cohorts, via a consensus procedure and self-report and/or manual inspection of MRI images, respectively.

MRI data acquisition

Images were first acquired at the Gruss Magnetic Resonance Research Center in Bronx (CCMA and EAS cohorts) or University of Angers Hospital in Angers (GAIT cohort), and then sent to Albert Einstein College of Medicine (Bronx, NY, USA) for pre-processing and group-level covariance analyses. The French images were acquired with a Magnetom Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) and the American images were acquired with a Philips 3 T MRI scanner (Achieva Quasar TX; Philips

Table 1 Participant characteristics for each study cohort

	CCMA-US (*N* = 89)	EAS-US (N = 93)	GAIT-FRANCE (N = 170)
Age (Mean ± SD, years)	76.07 ± 5.79	79.86 ± 5.15	70.65 ± 4.37
% Female	52.81	63.44	38.24
Education			
% ≤ 4 years	00	1.08	1.76
% 5–8 years	3.33	5.38	40.00
% 9–12 years	22.22	31.18	34.12
% ≥13 years	74.44	62.37	24.12
Stroke, %	4.49	10.75	4.12
MCI % (N)	7.87	12.90	15.88
TIV (mean ± SD, liters)	1.46 ± .12	1.10 ± .10	1.54 ± .13
Gait Speed (mean ± SD)	105.17 ± 23.68	95.03 ± 20.37	109.38 ± 20.21
Global Cognition (mean ± SD)	93.62 ± 13.29 (RBANS-TOTAL;0–128)	2.18 ± 2.26 (Blessed 0–28)	27.77 ± 1.95 (MMSE; 0–30)
Episodic Memory (mean ± SD)	29.94 ± 8.78 (FCSRT, 0–48)	32.67 ± 6.02 (FCSRT, 0–48)	15.92 ± 3.96 (FCSRT, 0–48)
Executive Function (mean ± SD)	76.03 ± 54.98 (TMT: B-A, secs.)	74.67 ± 46.20 (TMT: B-A, secs.)	74.80 ± 51.68 (TMT: B-A, secs.)
Processing Speed (mean ± SD)	46.76 ± 23.48 (TMT: A, secs.)	52.00 ± 20.25 (TMT: A, secs.)	52.58 ± 20.18 (TMT; A, secs.)

Medical Systems, Best, Netherlands). Standard three-dimensional T1-weighted images were obtained from all three cohorts: 1) CCMA: TR/TE of 9.9/4.6 ms., 240 mm^2 FOV, 240 × 240 × 240 matrix and 1 mm voxel size [for additional acquisition details see (Blumen et al. 2014)], 2) EAS: TR/TE of 9.9/4.6 ms., 240 mm^2 FOV, 240 × 240 × 220 matrix and 1 mm voxel size [for additional acquisition details see (Ezzati et al. 2015)], and 3) GAIT: TR/TE 2170/4.07 ms., 240 mm^2 mm FOV, 256 × 256 × 144 matrix and 1 mm voxel size [for additional acquisition details see (Beauchet et al. 2016a)].

MRI pre-processing

T1-weighted images from all cohorts were first manually re-oriented to the anterior commissure – posterior commissure line, and then pre-processed in the same manner using SPM8 (Wellcome Department of Cognitive Neurology) implemented with MATLAB R2016b (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 the unified segmentation procedure, Diffeomorphic Anatomical Registration Through Exponentiated Line Algebra (DARTEL; (Ashburner 2007; Ashburner and Friston 2005)). DARTEL is a VBM technique that ensures proper inter-subject alignment by modeling the shape of the brain using three parameters for each voxel. DARTEL simultaneously aligns gray matter and white matter to produce a study-specific and increasingly crisp template to which the data are iteratively aligned. For each participant, DARTEL produces a GM map, a WM map and a CSF map in the same space as the original T1-weighted image, where each voxel is assigned a probability. These probability maps were first manually examined to ensure proper segmentation, and then spatially normalized (Friston et al. 1995) 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 the upcoming analyses.

Group-level covariance analyses

Multivariate analyses were performed to identify gray matter covariance patterns or 'networks' associated with gait speed in each cohort separately. All analyses were adjusted by age, sex, education. MCI status, total intracranial volume, and past history of stroke (see Table 1). Analyses were implemented with the principal components analysis (PCA) suite, http://www.nitrc.org/projects/gcva_pca (Habeck et al. 2005b; Habeck and Stern 2007). Gray matter probability maps were first masked with a gray matter mask supplied by SPM8 to only include voxels with >20% probability of being gray matter. A principal components analysis (PCA) was then performed after participant means were subtracted from each voxel, in order to generate a set of principal components and their associated participant-specific (or pattern) expression scores that

could be grouped. Participant-specific expression scores reflect the degree to which a participant displays a particular component or pattern. The gray matter volume covariance patterns associated with gait speed were then computed by regressing the participant-specific factor scores from the best linear combination of principal components (PCs) – selected using the Akaike information criteria (Burnham and Anderson 2002) – against gait speed. The stability of the voxels in each GM volume covariance pattern associated with gait speed were then tested using 1000 bootstrap resamples (Efron and Tibshirani 1994). Voxels with bootstrap samples of $[Z] > +1.96$ or < -1.96, $p < .05$ (.025 in each tail) were considered significant. These group-level covariance analyses allowed us to identify key 'nodes' in the gray matter volume covariance 'networks' (Habeck et al. 2005a; Habeck and Stern 2007; Steffener et al. 2013) associated with gait speed. Note that covariance patterns obtained from any multivariate analysis assigns positive and negative weightings (or loadings) to each voxel included in the analysis (Habeck et al. 2008). In the current study, voxels or brain regions with positive loadings show relatively *more* gray matter volume with increasing gait speed, and brain regions with negative loadings show relatively *less* gray matter volume with increasing gait speed. In other words, gray matter volume increases with increasing gait speed in brain regions with positive loadings, while gray matter volume decreases with increasing gait speed in brain regions with negative loadings. It is important to remember, however, that both positively and negatively weighted regions contribute to the derived gray matter covariance patterns that are associated with gait speed (Habeck et al. 2008; Spetsieris and Eidelberg 2011; Steffener et al. 2013).

Results

The mean age in years was 76.06 ($SD = 5.79$) in the CCMA cohort, 76.86 ($SD = 5.15$) in the EAS cohort and 70.65 ($SD = 4.37$) in the GAIT cohort (see Table 1). Measures of global cognition were indicative of normal cognition in the CCMA (RBANS Total: $M = 93.62$, $SD = 13.29$), EAS (Short Blessed: $M = 2.18$, $SD = 2.11$) and GAIT (MMSE: $M = 27.89$, $SD = 1.95$) cohorts. The percentage of non-neurological gait disorders were 12.36% and 24.73% in the CCMA and EAS cohort, respectively. The percentage of neurological or both non-neurological gait disorders were 20.22% and 9.68% in the CCMA and EAS cohort, respectively. Clinical gait assessments were not available for the GAIT cohort. Our multivariate analyses revealed a gray matter volume covariance pattern whose expression varied as a function of gait speed in all three cohorts. The gray matter volume covariance patterns associated with gait speed in each cohort were composed of both shared and distinct brain regions (see Table 2, Fig. 1 Panel A-C, and Fig. 2). We also found that greater expression of the gray matter pattern associated with gait speed was associated with better processing speed in all three cohorts, and with better executive function in one of the cohorts (the CCMA cohort). We describe these results in more detail below.

CCMA-US cohort

The gray matter volume covariance pattern associated with gait speed in the CCMA cohort was composed of three principal components (PCs) and had an R^2 of .23. Recall that positive and negative weightings are assigned to each voxel in the analysis, that both positive and negative weights contribute to the gray matter volume covariance patterns associated with gait speed, and that brain regions with positive loadings show relatively *more* gray matter volume with increasing gait speed while brain regions with negative loadings show relatively *less* gray matter volume with increasing gait speed. Positively-weighted regions included bilateral cerebellar (Crus II), fusiform, and ventrolateral prefrontal cortex regions. Negatively-weighted regions included brain stem (reticular formation and peduncolopontine nucleus (PPN)), right precuneus regions, right supplementary motor, left cingulate, and dorsolateral prefrontal cortex regions. This gray matter pattern was associated with processing speed (TMT A: $r = -.29$, $p < .0052$) and executive function (TMT: B-A, $r - .25$, $p = .02$), but was not associated with episodic memory (FCSRT; $r = .12$, $p = .26$). In other words, greater expression of the gray matter pattern associated with gait speed was associated with better (faster) processing speed and better executive function in the CCMA cohort.

EAS-US cohort

The gray matter volume covariance pattern associated with gait speed in the EAS cohort was composed of two principal components (PCs) and had an R^2 of .24. Positively weighted regions included bilateral fusiform and left posterior parietal/precuneus regions. Negatively weighted regions included brainstem (medulla, pons, reticular formation and PPN), bilateral thalamic, bilateral putamen, right globus pallidus, left precuneus, bilateral anterior cingulate, bilateral motor, bilateral supplementary motor, and left ventrolateral prefrontal regions. This gray matter volume covariance pattern was associated with processing speed (TMT: A, $r = -.24$, $p = .02$), but not with executive function (TMT: B-A, $r = -.10$, $p = .34$) or with episodic memory (FCSRT, $r = -.14$, $p = .18$). In other words, like in the CCMA cohort greater expression of the gray matter pattern associated with gait speed was associated with better (faster) processing speed, but was not associated with episodic memory, in the EAS cohort. Unlike the CCMA cohort, however, greater expression of the gray matter pattern associated with gait speed was not associated with executive function.

Table 2 Brain regions associated with positive and negative pattern weights in each cohort. Threshold z = ± 1.96, $p < .05<$, k > 10 voxels

Brain Region(s)	X	Y	Z	z-value	k
CCMA-US					
Positive					
Inferior Frontal Gyrus (Ventrolateral Prefrontal)	−53	23	18	2.2255	63
Inferior Frontal Gyrus (Ventrolateral Prefrontal)	56	20	13	2.1634	68
Inferior Temporal Gyrus	49	−3	−41	2.1557	75
Inferior Frontal Gyrus (Ventrolateral Prefrontal)	−52	34	0	2.1329	222
Fusiform Gyrus	27	13	−45	2.0805	167
Fusiform Gyrus	−24	6	−45	2.0691	241
Superior Temporal Gyrus	58	−21	8	2.0583	153
Cerebellum (Crus II)	−20	−90	−37	2.0557	92
Temporal Pole	49	20	−25	2.0457	49
Middle Occipital Gyrus	−40	−89	−1	2.0419	62
Somatosensory	−64	−27	23	2.0413	32
Superior Temporal Gyrus	−63	−38	16	2.0357	18
Superior Temporal Gyrus	62	−2	−2	2.0331	29
Middle Frontal Gyrus (Orbitofrontal)	25	35	−19	2.0263	18
Cerebellum (Crus II)	22	−91	−35	2.0208	39
Fusiform Gyrus	−33	−14	−37	2.0068	11
Inferior Temporal Gyrus	45	11	−42	2.0059	15
Negative					
Medial Frontal Gyrus (Supplementary Motor)	−6	33	39	−2.2301	380
Brain Stem (Reticular Formation)	8	−25	−26	−2.1306	378
Middle Frontal Gyrus (Dorsolateral Prefrontal Cortex)	−23	42	32	−2.1072	189
Middle Cingulum	−4	7	38	−2.1018	176
Parietal/White Matter	19	−41	42	−2.2711	56
Supplementary Motor/White Matter	17	−3	49	−2.1340	53
Calcarine Sulcus	20	−75	16	−2.1520	37
Medial Frontal Gyrus (Supplementary Motor)	6	40	43	−2.0646	35
Mid Occipital/White Matter	37	−62	−1	−2.0961	32
Precuneus	4	−33	43	−2.0061	27
Middle Frontal Gyrus/White Matter	30	24	28	−2.0608	17
EAS-US					
Positive					
Fusiform gyrus	−43	−76	−16	2.1584	2165
Precuneus	0	−61	17	2.0758	3207
Fusiform gyrus (Inferotemporal gyrus)	43	−71	−18	2.0598	267
Lingual gyrus (fusiform gyrus)	−16	−48	−6	1.9743	16
Fusiform gyrus	27	−38	−18	1.9711	32
Negative					
Superior Frontal Gyrus (Motor. Supplementary Motor)	18	45	25	−2.2778	45,995
Superior Frontal Gyrus (Motor, Supplementary Motor)	−14	5	54	−2.2372	16,432
Inferior Occipital Gyrus	35	−76	−2	−2.1076	492
Superior Parietal Gyrus (Precuneus)	30	−74	54	−2.1016	4443
Parietal (Visuomotor)	−26	−56	36	−2.0950	431
Brain Stem(medulla, pons, retricular formation, pendunculopontine nuclues)	7	−38	−39	−2.0825	13,856
Parietal (Somatosensory)	−43	−42	33	−2.0775	360
Inferior Parietal Gyrus (Somatosensory)	−48	−45	59	−2.0769	535
Middle Temporal Gyrus	−48	−51	−2	−2.0720	429

Table 2 (continued)

Brain Region(s)	X	Y	Z	z-value	k
Parietal (Visuomotor)	27	−56	36	−2.0512	168
Superior Parietal Gyrus	21	−54	76	−2.0483	53
Middle Frontal Gyrus (Mid-Prefrontal Cortex)/White Matter	32	38	14	−2.0402	71
Inferior Temporal Gyrus	44	−51	−6	−2.0317	316
Precuneus	−15	−56	45	−2.0219	424
Precuneus/white matter	18	−42	36	−2.0203	269
Superior Temporal Gyrus	70	−9	12	−2.0182	197
Superior Temporal Gyrus	68	−3	−12	−2.0132	33
Precentral Gyrus (Motor)	−32	−20	74	−2.0036	229
Parietal/White Matter	37	−50	32	−2.0029	27
Parietal/White Matter	36	−61	21	−1.9971	16
Precuneus	6	−55	75	−1.9952	14
Angular Gyrus	43	−44	27	−1.9887	33
Precuneus	5	−61	71	−1.9867	14
Somatosensory	−23	−42	50	−1.9848	69
Middle Cingulum	10	−1	35	−1.9841	73
Posterior Caudate/White matter	20	−21	24	−1.9815	29
Middle Temporal Gyrus	52	−36	−12	−1.9812	11
Thalamus, ventral anterior n. region	−13	−7	6	−1.9810	300
Precentral Gyrus (Motor)	−12	−24	54	−1.9788	26
Caudate	−5	15	9	−1.9786	348
Inferior Frontal Gyrus (Orbitofrontal)	54	35	−15	−1.9770	11
Postcentral Gyrus (Somatosensory)	−41	−43	67	−1.9763	12
Supramarginal Gyrus	70	−23	24	−1.9730	23
Middle Temporal Gyrus	49	−45	−3	−1.9695	39
Globus Pallidus	18	3	5	−1.9695	37
Thalamus	16	−12	6	−1.9671	69
Thalamus, ventroposterolateral (VPL)	12	−21	−6	−1.9627	18
GAIT-FRANCE					
Positive					
Inferior Frontal Gyrus (Ventrolateral Prefrontal)	54	26	21	2.9785	9892
Inferior Frontal Gyrus (Ventrolateral Prefrontal)	−50	24	21	2.9523	12,768
Supplementary Motor	10	18	70	2.9508	12,930
Middle Frontal Gyrus (Dorsolateral Prefrontal)	39	26	52	2.8093	425
Middle Frontal gyrus	−36	14	62	2.6962	549
Middle Frontal Gyrus (Dorsolateral Prefrontal)	−24	36	44	2.6902	406
Precentral Gyrus (Motor)	−51	0	52	2.6042	147
Posterior Cingulum	−12	−51	30	2.5139	158
Supplementary Motor	8	−12	57	2.4390	87
Middle Frontal Gyrus (Dorsolateral Prefrontal, Supplementary Motor)	−39	15	39	2.4100	69
Supplementary Motor	−10	0	78	2.3294	36
Middle Frontal Gyrus	28	48	33	2.3278	50
Superior Frontal Gyrus (Dorsolateral Prefrontal Cortex)	26	44	45	2.2486	19
Cuneus	−15	−72	32	2.2153	49
Postcentral Gyrus (Somatosensory)	−42	−36	64	2.2010	27
Cerebellum (VIIIA)	−34	−62	−51	2.1582	274
Middle Frontal Gyrus (Dorsolateral Prefrontal)	39	8	62	2.1504	13
Middle Frontal Gyrus	−28	−9	51	2.1438	41
Postcentral Gyrus (Somatosensory)	34	−45	72	2.1057	10

Table 2 (continued)

Brain Region(s)	X	Y	Z	z-value	k
Superior Frontal Gyrus (Orbitofrontal)	−12	54	−14	2.0502	15
Superior Frontal Gyrus (Ventrolateral prefrontal)	21	70	3	2.0351	15
Middle Frontal Gyrus (medial)	−12	45	−12	2.0213	12
Middle Frontal Gyrus (medial)	−4	56	0	2.0178	25
Negative					
Postcentral Gyrus (Somatosensory)	12	−33	78	−2.3757	393
Middle Temporal Gyrus	60	−38	−4	−2.3465	95
Middle Temporal Gyrus	46	−46	−3	−2.3007	55
Temporal pole	18	8	−32	−2.2945	81
Middle Occipital Cortex	−18	−94	−3	−2.2789	37
Cerebellum (Vermis)	−2	−68	−14	−2.2614	22
Cerebellum (Crus II)	−54	−50	−42	−2.2227	114
Precentral Gyrus (Motor)	−33	−21	58	−2.1917	74
Superior Occipital Cortex	26	−84	33	−2.1506	64
Inferior Occipital Cortex	−34	−81	−3	−2.1390	10
Superior Parietal Cortex	−24	−56	50	−2.0973	39
Superior Occipital Cortex	−33	−76	22	−2.0342	10
Precentral Gyrus (Motor)	27	−21	69	−2.0273	11
Cuneus	0	−94	20	−2.0067	15
Superior Parietal Cortex	15	−48	58	−2.0042	10
Angular Gyrus	38	−54	52	−1.9978	14

France-GAIT cohort

The gray matter volume covariance pattern associated with gait speed in the French cohort was composed of five PCs and had an R^2 of .21. Positively weighted regions included left cerebellar (VIII), bilateral putamen, left posterior parietal/precuneus, bilateral somatosensory, left motor, left posterior cingulate, bilateral supplementary motor, right medial prefrontal, and bilateral dorsolateral prefrontal and ventrolateral prefrontal cortex regions. Negatively weighted regions included bilateral cerebellar (VIIII, X, Vermis, Crus II), bilateral occipital, right thalamic, left angular gyrus, left motor, bilateral somatosensory cortex regions. This gray matter covariance pattern was associated with processing speed (TMT: A; $r = -.26$, $p < .01$), but not with episodic memory (FCSRT; $r = -.11$, $p = 18$), or executive function (TMT: B-A; $r = .04$, $p > .05$). In other words, like in the CCMA and EAS cohorts, greater expression of the gray matter pattern associated with gait speed was associated with better processing speed in the French cohort.

Cross-cohort comparisons

To examine the similarity between the gray matter volume covariance patterns associated with gait speed in the different cohorts, we computed inter-pattern correlations within each cohort (i.e. we forward-applied and correlated each pattern score with the other pattern scores in each cohort). We also explored the topographic similarity between the patterns generated in each cohort. These analyses showed that the gray matter volume covariance pattern scores associated with gait speed in the CCMA and EAS cohorts were more strongly associated and topographically similar than the French pattern. More specifically, the CCMA and the EAS pattern scores were significantly associated with each other in the CCMA cohort ($r = .50$, $p < .0001$), the EAS cohort ($r = .53$, $p < .0001$), and the French-GAIT cohort ($r = .46$, $p < .0001$). The EAS and the French pattern scores were not significantly associated with each other in the CCMA cohort ($r = .11$, $p > .05$), but was significantly associated with each other in the EAS cohort ($r = .22$, $p < .05$) and the French cohort ($r = .16$, $p < .05$). Finally, the CCMA and the French pattern scores were not significantly associated in the CCMA cohort ($r = .10$, $p > .05$) or the EAS cohort ($r = .03$, $p > .05$), but was significantly associated in the French cohort ($r = .19$, $p < .05$). The topographic correlation coefficient between the gray matter volume covariance patterns associated with gait speed in the CCMA cohort and the EAS cohort was .24, in the CCMA and French cohort .07, and in the EAS and French cohort was .05. Taken together, these cross-cohort comparisons suggest that the gray matter volume covariance patterns associated with gait speed in the CCMA and EAS cohorts are more associated and more topographically similar than the French cohort.

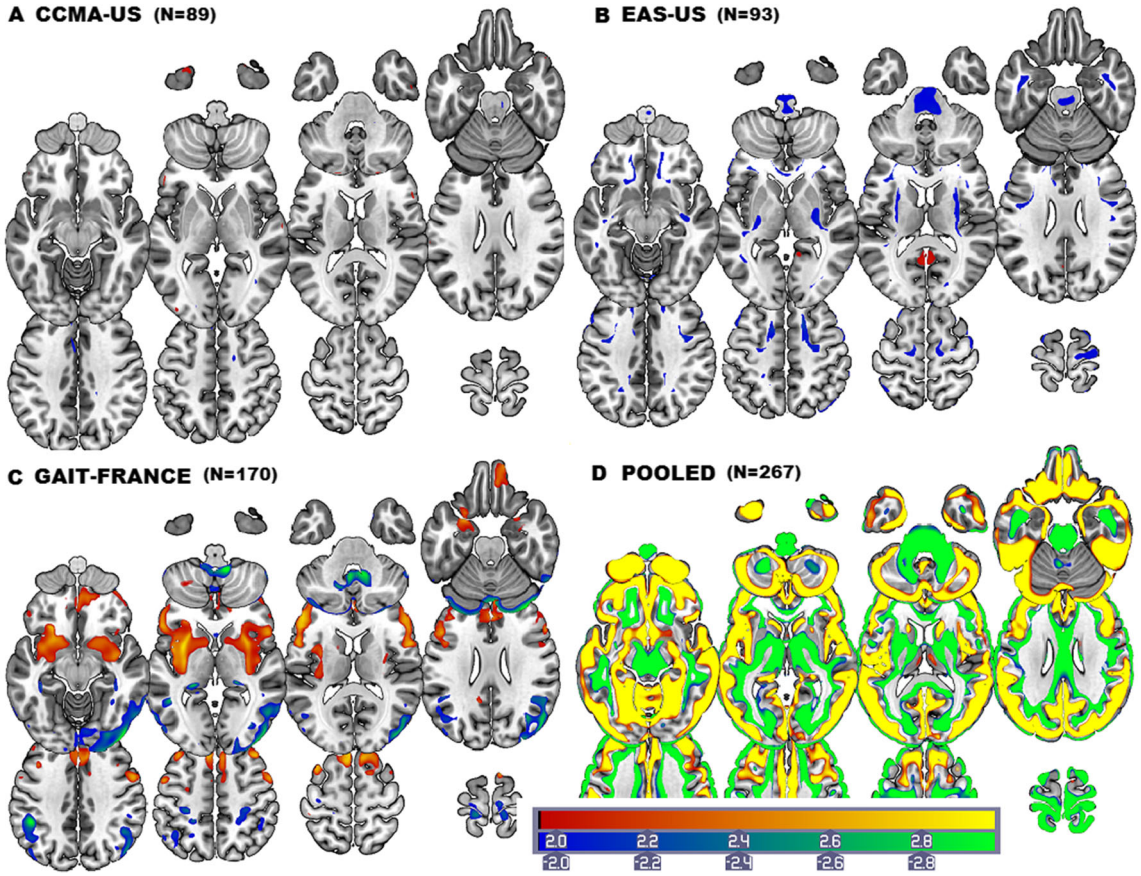

Fig. 1 Gray matter covariance networks associated with gait speed in three cohorts of older adults without dementia, and in a pooled cohort. Threshold [Z] > + 1.96 or < −1.96, $p < .05$ (.025 in each tail)

Discussion

This study examined gray matter volume correlates of gait speed – and how they relate to executive function, episodic memory, and processing speed – in three non-demented older adult cohorts. In all three cohorts we identified distributed gray matter volume covariance networks associated with gait speed, which were composed of both shared and distinct brain regions (see Table 2, Figs. 1 and 2). In all three cohorts, greater expression of these gray matter covariance networks linked to

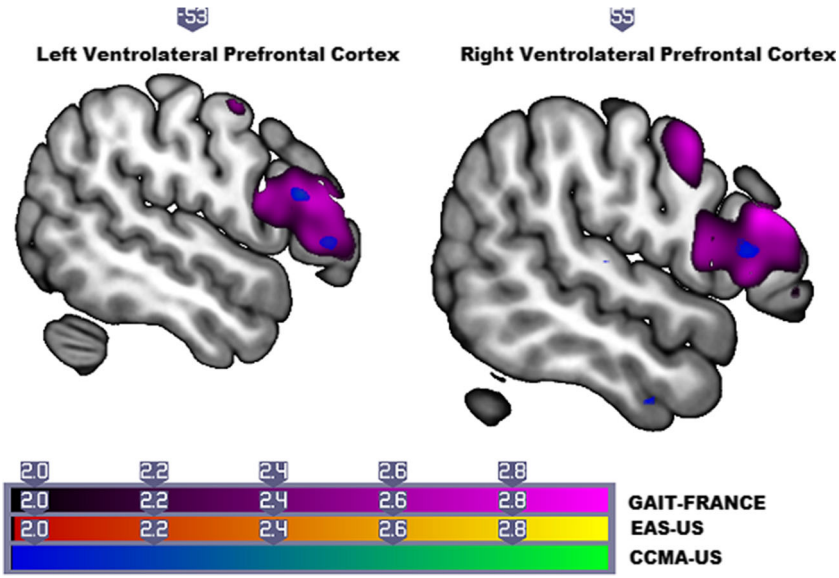

Fig. 2 Shared regions in the gray matter covariance networks associated with gait speed in three cohorts of older adults without dementia. Threshold [Z] > + 1.96

gait speed was associated with better processing speed, and in one cohort with better executive function. In addition, we found that the gray matter volume covariance pattern associated with gait speed in the CCMA and EAS cohorts were more strongly associated and topographically similar than the French pattern associated with gait speed. We discuss these results in more detail next.

Distributed patterns of gray matter volume are associated with gait speed

Fairly distributed patterns of gray matter volume were associated with gait speed in all three cohorts – and shared regions among the cohorts included brain stem (reticular formation and peduncolopontine nucleus) precuneus, fusiform, motor, supplementary motor, and prefrontal (particularly ventrolateral prefrontal) cortex regions. Gray matter volume in the fusiform gyrus, for instance, increased with increasing gait speed in the CCMA and EAS cohorts, while the volume of the peduncolopontine nucleus decreased with increasing gait speed in these cohorts. Although cross-cohort comparisons suggested that the gray matter volume covariance patterns in the CCMA and EAS cohorts were more strongly associated and topographically similar than the French cohort, overlapping 'nodes' between the French and the CCMA patterns and the French and the EAS patterns associated with gait speed were also evident, particularly in ventrolateral prefrontal cortex and the primary motor cortex, respectively. More specifically, gray matter volume in the ventrolateral prefrontal cortex increased with increasing gait speed in the French and CCMA cohorts (see Fig. 2), while gray matter volume in the motor cortex decreased with increasing gait speed in the French and EAS cohorts. A positive relationship between gray matter volume and gait speed in a particular brain region implies that this region is particularly important for maintaining gait speed in older adults. A negative relationship between gray matter volume and gait speed in a particular brain region implies that this region is relatively less important for maintaining gait speed in older adults.

The gray matter covariance pattern associated with gait speed in the French cohort were also more distributed than in the CCMA and EAS cohorts (See Fig. 1, Panel A-C), and this finding may be attributed to that this cohort had a larger sample size ($N = 170$) than the other cohorts ($N = 89$ and $N = 93$). To more formally explore this issue, we also ran a pooled analysis of 267 older adults without dementia from the three different cohorts. Although we had access to a total of 362 older adult participants from the different cohorts, we wanted to reduce potential cohort effects, and therefore included all 89 CCMA participants in our analyses, and then obtained a random sample of 89 older adults from the EAS and 89 older adults from the French cohorts (See Table 1). In addition to adjusting for age, sex, education. MCI status, total intracranial volume, and past history of stroke, we adjusted for cohort status in this pooled analysis. As is evident from Fig. 1 (Panel D), an even more distributed gray matter volume covariance pattern – including considerable cortical and subcortical regions – was associated with gait speed in this pooled analysis. Thus, the mixed results of previous studies examining the structural brain correlates of gait may be related to sample size as well as statistical methodology. Attributing gait speed to a distributed gray matter volume covariance pattern is consistent with that gait has been linked to numerous adverse physical and cognitive outcomes. Attributing gait speed to a distributed gray matter volume covariance pattern is also consistent with what is known about the functional neural substrates of actual and imagined locomotion in healthy younger and older adults (Allali et al. 2014; Blumen et al. 2014; Iseki et al. 2008; la Fougere et al. 2010; van der Meulen et al. 2012; Zwergal et al. 2012), and a previous study that linked gait speed in 305 older adults to gray matter volume in precuneus, cingulate, supplementary motor, and ventrolateral prefrontal cortex regions, as well as cerebellar, basal ganglia, motor, insular, and orbitofrontal regions (Callisaya et al. 2014).

Gray matter volume covariance networks of gait speed and neural pathways of human locomotion

Human locomotion can be broadly considered to involve two different, yet interacting, neural pathways: a motoric pathway and a cognitive (or control) pathway (la Fougere et al. 2010; Leisman et al. 2016; Zwergal et al. 2012). The motoric pathway is primarily engaged during gait initiation and maintenance, and originates in the brain stem, which activates central pattern generators in the spinal cord that in turn relay this information to the motor cortex via the dorsal basal ganglia. The cognitive pathway is primarily engaged during motor planning and modulation, and originates in supplementary motor and other prefrontal cortex regions, which are then relayed to the brain stem via the ventral basal ganglia where they are integrated with signals from the cerebellum. Clearly, the connections, functions, and the interactions of these pathways are more complicated and extensive than outlined above (Haber 2016; Marinelli et al. 2017), and the distinction between the motor and cognitive pathways (or aspects of gait) not clear-cut – yet this distinction is helpful for interpreting the gray matter covariance patterns associated with gait speed in the current study of non-demented older adults, and how they relate to different cognitive functions (Leisman et al. 2016).

A positive relationship between gray matter volume and gait speed in the non-demented older adult cohorts examined in this study, was primarily observed in brain regions that are believed to be important for the cognitive aspects of gait, while a negative relationship between gray matter volume and gait speed was primarily observed in brain regions that

are believed to be important for the motoric aspects of gait. The positive relationship observed between gait speed and ventrolateral prefrontal cortex volume, and the negative relationship between gait speed and motor cortex volume, in two of the three cohorts are consistent with this suggestion. Functional neuroimaging studies have also specifically linked the ventrolateral prefrontal cortex to motor inhibition – the inhibition or stopping of motor actions – a modulatory aspect of gait (see (Levy and Wagner 2011) for a meta-analysis).

A positive relationship between gait speed and fusiform gyrus volume, however, was also observed in two of the three cohorts. The fusiform gyrus is not a key component of the cognitive or the motor pathway of human locomotion, but has been linked to motor planning – more specifically, motor imagery of walking in younger adults (Jahn et al. 2004) and motor imagery of stepping over obstacles in older adults with Parkinson's disease (Wai et al. 2012). Finally, a negative relationship between gait speed and peduncolopontine volume was observed in two of the three cohorts. The peduncolopontine nucleus is traditionally known to support gait initiation by activating central pattern generators in the spinal cord, and relaying this information to the basal ganglia (Garcia-Rill 1991). A more recent extracellular single-unit recording study, however, suggests that distinct networks within the peduncolopontine nucleus are activated during motor planning (imagined gait) and gait initiation (Tattersall et al. 2014). Taken together, the current study suggest that brain regions primarily, but not exclusively, linked to the cognitive aspects of gait are particularly important for maintaining gait speed in older adults without dementia.

Gray matter volume covariance networks of gait speed, processing speed (executive function) and intervention

The gray matter volume patterns linked to gait speed in the current study were not associated episodic memory, but were associated with a measure of processing speed in all three cohorts, and with a measure of executive function in one cohort (the CCMA cohort). These findings provide convincing new evidence for the suggestion that gait and some, but not all cognitive domains, rely on shared neural systems that are affected by normal and pathological aging. These findings are consistent with a previous study, which showed that the association between prefrontal gray matter volume and gait speed is attenuated when controlling for processing speed (Rosano et al. 2012). More importantly, they extend previous findings by showing that greater expression of a distributed network of gray matter volume linked to gait speed is consistently associated with improved processing speed, and in one case executive function.

These findings are also consistent with what is known about the neural substrates of processing speed and executive function. Processing speed – the general ability to process information efficiently that is critical to most cognitive tasks – has also been linked to a distributed network of brain regions, including cerebellar, parietal/precuneus, basal ganglia, and prefrontal cortex regions (Habeck et al. 2016; Lee et al. 2016; Nadkarni et al. 2014; Rosano et al. 2012; Rypma et al. 2006; Stern et al. 2014). While executive function – the higher-order ability to plan, reason and select and inhibit responses – has primarily been linked to different prefrontal cortex regions (Alvarez and Emory 2006; Elderkin-Thompson et al. 2008; Koechlin et al. 2003; Miller and Cohen 2001).

A better understanding of when and how these shared neural systems break down in the course of normal and pathological aging is needed – yet, the findings of the current study suggest that interventions targeted at improving gait should be considered as potential avenues for improving cognitive functions, and vice versa. In other words, shared neural pathways of gait and cognitive functions implies that we should consider shared paths to intervention. A small pilot intervention, for example, has shown that cognitive remediation targeted to improving executive function, improves gait speed in sedentary older adults (Verghese et al. 2010). The results of the current study suggest that interventions targeted at improving gait speed may improve processing speed and executive function, and that interventions targeted at improving processing speed and executive function may improve gait speed. Given the distributed nature of the gray matter volume covariance patterns associated with gait speed in the current study, it is also possible that multi-modal interventions targeted at promoting overall brain health via physical, cognitive, and potentially social, activities may be most effective for preventing or reducing the risk for adverse physical and cognitive outcomes in aging.

Strengths, limitations, and recommendations for future research

Examining associations between gray matter volume and gait speed, and how they relate to different cognitive functions, in three non-demented elderly cohorts with a consistent, appropriate, and sensitive analytic approach are the main strengths of this study. This approach permitted us to examine both general and cohort-specific gray matter covariance networks associated with gait speed, and to determine the reliability of brain, gait speed, and cognition relationships.

Examining associations between gray matter volume, gait speed, and different cognitive domains in three different cohorts, however, also introduces variability that limits our interpretations of cohort-specific effects. Although great concern was afforded to: 1) control for standard covariates (e.g. age, sex, education and total intracranial volume) and other covariates that differed between the cohorts (e.g. MCI, past

history of stroke and cohort status), and 2) to process and analyze neuroimaging data similarly, and 3) use analogous measures of cognition across cohorts – it is difficult to attribute cohort-specific effects to a parsimonious set of explanatory factors. It would make sense, for example, to attribute the insular components of the gray matter volume covariance networks associated with gait speed in the GAIT cohort to the fact that the cohort was recruited from a memory clinic and displayed poorer episodic memory performance than the other two cohorts. Such a conclusion would make sense given that insular, particularly right insular, cortex volume has been linked to memory awareness and awareness of cognitive errors in general (Cosentino et al. 2015; Klein et al. 2007). However, this cohort-specific effect could also be attributed to differences in image acquisition specifics (differences between MRI strength, make, or acquisition parameters), or cognitive assessment administration. For these reasons, we chose to focus our discussion on the shared regions that were part of the gray matter volume covariance networks associated with gait speed in most cohorts, despite this variability between cohorts. Focusing on the shared components of the gray matter patterns associated with gait speed in most cohorts also served the ultimate goal of informing the development of high-impact interventions that can be used to compensate for age-related gait and cognitive decline.

Examining associations between gray matter volume and gait speed, and how they relate to different cognitive functions, in three cross-sectional samples of non-demented older adults also limits our interpretation of how the structural brain correlates of gait change during the course of normal and pathological aging, or as a function of socially, physically and cognitively active and inactive lifestyles. We know that gray matter volume is influenced by a number of different factors, including normal aging, MCI, Alzheimer's disease, small vessel disease – that was not examined in this study (Karas et al. 2004; Lambert et al. 2016; Raz 2000; Thompson et al. 2003; Verghese et al. 2006). Previous studies also suggest that gray matter volume can be influenced by participation in social (Mortimer et al. 2012), physical (Colcombe et al. 2006; Erickson et al. 2011) and cognitive (Ceccarelli et al. 2009; Kühn et al. 2014; Lambert et al. 2016; Takeuchi et al. 2011) interventions and activities. Slow gait can also be the result of non-neurological factors such as arthritis. In the current study, we had access to clinical assessments of gait in two of the three cohorts. The expression of the gray matter volume networks associated with gait speed in these cohorts, however, did not vary as a function of clinical gait status (none, non-neurological, neurological or both; data not shown). Nevertheless, future studies are needed to extend and delineate the boundaries of the shared neural systems of gait speed, processing speed and executive function to more diverse populations of older adults (including those with non-neurological and neurological gait abnormalities), to longitudinal samples of older adults, and within the context of socially, physically, and or cognitively active and inactive lifestyles.

Conclusions

Gait speed in non-demented older adults is associated with distributed patterns of gray matter volume, including brain stem, cerebellar, fusiform, motor, pre-motor, supplementary motor, ventromedial prefrontal and other prefrontal cortex regions – regions that have been previously linked to gait control, as well as processing speed and executive function. Greater expression of this gray matter pattern associated with gait speed is also associated with improved processing speed, and in some cases executive function. These findings suggest that gait speed, processing speed, and executive function rely on distributed and shared neural substrates, and that interventions that aim to train gait may be effective for improving processing speed and executive function, and vice versa.

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Compliance with ethical standards

Conflict of Interest All authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in these studies involving human subjects were in accordance with the ethical standards of the institutions, and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in each study.

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