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Associations between gait speed and brain structure in amnesic mild cognitive impairment: a quantitative neuroimaging study

Pauline Ali^{1,2,3} · Matthieu Labriffe^{1,4} · Paul Paisant³ · Marc Antoine Custaud^{5,6} · Cédric Annweiler^{7,8} · Mickaël Dinomais^{1,2,3}

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Abstract

Background Patients with amnesic mild cognitive impairment (aMCI) present gait disturbances including slower speed and higher variability when compared to cognitively healthy individuals (CHI). Brain neuroimaging could explore higher levels of motor control. Our purpose was to look for an association between morphometrics and gait parameters in each group. We hypothesized that the relation between morphological cerebral alteration and gait speed are different following the group.

Methods Fifty-three participants (30 with aMCI and 23 CHI) were recruited in this French cross-sectional study (mean 72 ± 5 years, 38% female). Gait speed and gait variability (coefficients of variation of stride time (STV) and stride length (SLV)) were measured using GAITrite® system. CAT12 software was used to analyse volume and surface morphometry like gray matter volume (GMV) and cortical thickness (CT). Age, gender and education level were used as potential cofounders.

Results aMCI had slower gait speed and higher STV when compared to CHI. In aMCI the full adjusted linear regression model showed that lower gait speed was associated with decreased GMV and lower CT in bilateral superior temporal gyri ($p < 0.36$). In CHI, no association was found between gait speed and brain structure. Higher SLV was correlated with reduced GMV in spread regions ($p < 0.05$) and thinner cortex in the middle right frontal gyrus ($p = 0.001$) in aMCI. In CHI, higher SLV was associated with reduced GMV in 1 cluster: the left lingual ($p = 0.041$).

Conclusions These findings indicate that lower gait speed is associated with specific brain structural changes as reduced GMV and CT during aMCI.

Keywords Mild cognitive impairment · Brain imaging · Gait disorders · Statistical parametric mapping

Background

There is growing evidence that decline in cognitive performance results in gait deterioration. Even at early stage of dementia, including the prodromal stage of mild cognitive impairment (MCI), gait disturbances are observed when

compared to the gait of cognitively healthy individuals (CHI) (Verghese et al., 2008a). Some authors suggest that the decline in cognitive performance has a motor phenotype, which could be used to improve dementia's prediction (Beauchet et al., 2014; Verghese et al., 2013).

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Two main gait parameters have been related to the severity of the decline in cognitive performance (from CHI to patients with dementia): gait speed (propulsion component) and gait variability (stability component). High stride time (STV) and high stride length variability (SLV) have separately been identified as fall predictors whereas low variability in both these parameters have been associated with a safe gait. Gait variability represents the reliability of lower limb movements depending on cortical control (Beauchet et al., 2009).

Morphological brain volume changes associated with gait impairment in patients with cognitive decline are poorly studied (Allali et al., 2019a). The brain volume loss associated with reduced gait speed in normal aging is also not fully established (Beauchet et al., 2019). Neuroimaging studies analysing morphometry characteristics such as gray matter volume (GMV) or cortical thickness (CT) have been proved to be valuable measurements of brain atrophy. The newly CAT12 toolbox has been used for various populations such as elderly, MCI and Alzheimer disease subjects (Ali et al., 2020). It appears to be a robust method delivering accurate CT estimation (Seiger et al., 2018). Some studies have shown sizable associations between surface measures and cognitive performance in healthy aging, as well as in patients with MCI (Alzheimer's Disease Neuroimaging Initiative (ADNI) et al., 2012; Hirjak et al., 2017; Tomadesso et al., 2015). Few VBM studies have investigated a morphological pattern of brain regions associated with gait parameters in patients with MCI: in aMCI participants, Allali and associates have shown that faster normal gait speed was correlated with increased GMV in the left frontal cortex (Allali et al., 2019b). Doi and al. have described in MCI subjects that increased dual-task gait speed was associated with a GM pattern of increased volume in the medial frontal gyrus, superior frontal gyrus, anterior cingulate, cingulate, precuneus, fusiform gyrus, middle occipital gyrus, inferior temporal gyrus and middle temporal gyrus (Doi et al., 2017). Beauchet and associates found a positive association in patients with MCI between gait speed and striatum's GMV (left putamen and bilateral caudate nuclei) (Beauchet et al., 2019) and that hippocampal regions were distinctly correlated with stride time variability (Beauchet et al., 2015). One study has shown association between gait variability (stride time), neurochemistry and volume of primary motor cortex in patients with MCI (Annweiler et al., 2013a, b).

However, no studies have explored the relationship between gait disorders such as gait speed or gait variability and structural whole-brain changes in CHI and MCI populations via surface analysis. Understanding the factors contributing to impaired gait is essential for maintaining motor function and preventing adverse health events during the course of dementia. Structural brain changes may contribute directly to gait parameters modifications since gait depends

on cognitive abilities for locomotion and navigation (Annweiler et al., 2013a, b; Montero-Odasso et al., 2012b).

Using CAT12 algorithm, the objective of the present study is to evaluate the relationship between morphological changes across the whole-brain assessed by voxel-based and surface-based morphometry techniques as well as gait performance during aMCI disease and in non-dement older adults. We hypothesized that the relation between morphological cerebral alteration and gait parameters are different in MCI and CHI subjects.

Methods

Participants

We studied 53 participants from the IRMarche study enrolled between 2015 and 2017 (Labriffe et al., 2017): 30 participants with aMCI from the memory clinic of Angers University Hospital and 23 CHI over 60 years old recruited from our local clinical research centre in Angers Hospital. Inclusion criteria were an age over 60 years old, the absence of: clinical dementia, depression, neurological and orthopaedic disorders. We excluded participants with contraindication to MRI. The diagnosis of aMCI was based on the Dubois criteria which included memory complaints from the patient or relatives, objective memory impairment (assessed using a complete battery of neuropsychological tests designed to examine a full range of cognitive functions), preserved general intellectual function, no or minimal impairment of daily life activities and the absence of clinical dementia (according to NINCDS-ADRDA criteria). All participants included in the present analysis received a full medical examination, a neuropsychological assessment and a 3.0 Tesla magnetic resonance imaging (MRI) scan of the brain.

Ethics statement

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The entire study protocol was approved by the Angers Ethical Review Committee (Comité de protection des personnes, CPP ouest II, Angers, France, n° A.C D 2014-A01593-44, n° CPP: 2014/32). Written informed consent was obtained at enrolment.

Gait assessment

Gait parameters were measured using an electronic portable walkway called GAITRite® System, with embedded pressure sensor connected to a computer (GAITRite® Gold walkway, 9.72 m long, active electronic surface area

7.92 × 6.10 m, total 29,952 pressure sensors, scanning frequency 60 Hz, CIR System, Havertown, PA).

The GAITRite® system is commonly used in clinical and research settings including older adults and has excellent validity and reliability. According to the guidelines describe by the European GAITRite® society, all subjects received standardized walking instructions from a trained evaluator (European GAITRite® Network Group et al., 2006). Participants walked in a quiet and well-lit room, towards the same direction, with a single-task condition, wearing comfortable and usual footwear. Principal measures of interest were gait speed (comfortable in m/s), stride time and step length variability. For short distance gait tests, the least significant change is 0.05 m/s showing a small change and 0.1 m/s indicating a detectable clinically change (Beaudart et al., 2019; Perera et al., 2006). The GAITRite® software automatically calculated mean values and coefficient of variation ($CoV = ([SD/mean] \times 100)$). Stride time variability (STV) is the time elapsed between the first contact of 2 consecutive footfalls of the same foot expressed in milliseconds. Stride length (SLV) is the distance between 2 consecutive footfalls of the same foot expressed in metres. For these two parameters, variability was defined as the standard deviation from the individual steps from two passes.

MRI data acquisition

MRI data were acquired on the same 3.0 Tesla MRI scanner (MAGNETOM Trio Tim system, Siemens, Erlangen, Germany) at the University Hospital of Angers, using a standard MRI protocol. Acquisition parameters for sequences including a high-resolution 3D T1-weighted volume using a magnetization-prepared rapid acquisition gradient-echo sequence, covering the whole brain (cerebellum included) were: 176 slices, repetition time (TR) = 2300 ms, echo time (TE) = 4.18 ms, slice thickness = 1 mm, field of view (FOV) = 256 × 256, flip angle = 9, voxel size: 1 × 1 × 1 mm³.

Image pre-processing

All T1 images were converted from DICOM to NIFTI format using the MRICron software (<https://people.cas.sc.edu/roden/mricron/index.html>).

Voxel and surface-based morphometry across the entire brain were conducted with the CAT12 toolbox (<http://www.neuro.unijena.de/cat>) implemented in the SPM12 software (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) using a 2017a Matlab platform (The MathWorks, Natick, MA, USA), following the standard procedure.

Default options of the CAT12 manual were used. For basic VBM analysis: first 3D T1 volumes were segmented

in native-space to obtain 3 tissues classes: grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) with and without modulation (Ashburner & Friston, 2000). Then, non-linear modulation GM and WM volumes were aligned using the default DARTEL (diffeomorphic anatomical registration using exponential Lie algebra) template and were spatially normalized into the Montreal Neurological Institute space (ICBM) (Ashburner, 2007). Finally, images were smoothed by an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM). For SBM analysis we used a fully automated method using surface central reconstruction and thickness estimation (CT), performed in one step and based on the projection based thickness (PBT) method (Dahnke et al., 2013). We used the same MRI preprocessing as our previous work (Ali et al., 2020). Surfaces parameters were smoothed with a value of 15 mm as recommended. All data were inspected and visually checked after the automated procedure by PA and MD.

Statistics

Clinic and demographic differences between groups were investigated using median or frequencies and percentages through the Chi-square test or the Mann–Whitney U test, as appropriate. Statistical analyses were performed using Tanagra 2.0 software (<http://eric.univ-lyon2.fr/~ricco/tanagra/fr/tanagra.html>), Excel (Microsoft office Professional Plus 2013), SPM12 and CAT12.

For neuroimaging, smoothed, modulated and normalized data were used. With CAT12, we correlated with a linear regression model gait assessment and morphometric data in the two group: aMCI and CHI subjects.

We used threshold-free cluster enhancement (TFCE) for a combined non parametric analysis about height and size of the effects and applied FWE (family wise error) corrected threshold of $p < 0,05$ (<http://www.neuro.uni-jena.de/tfce>). Minimum cluster size was set at 10 contiguous voxels. Wfu-pickatlas (https://www.nitrc.org/projects/wfu_pickatlas/) and CAT12 software were used for anatomical localisation defined by the Desikan-Killiany atlas (DK40) (Desikan et al., 2006).

Covariates

Age, gender, education level and total intracranial volume (TIV) (the latter parameter was used only for VBM analysis) were included as potential confounders for the analysis. Education level was evaluated using standardized questionnaires. Higher education level was defined as an education level (whether undergraduate or post-graduate) following the completion of a school providing a secondary education.

Results

Participant characteristics

As summarized in Table 1, aMCI subjects were significant older (75 ± 4 years) than CHI (68 ± 4 years). The two groups were no different in term of gender, laterality and education level distribution.

CHI were faster than aMCI (1.31 ± 17 m/s versus 1.17 ± 21 m/s) during comfortable gait speed, ($p=0.00673$).

Stride time variability (STV) was higher (worse, 2.9%) in aMCI group than CHI group (2.1%) ($p=0.0109$).

Step length variability (SLV) did not show any difference between groups ($p=0.0503$).

Association with gait parameters

In CHI group

Gait speed No significant association were found between gait speed and GMV nor CT in this group.

STV STV was negatively associated with GMV in 1 cluster: left caudate ($[-17\ 23\ 0]$, TFCE = 1983) (Table 2 Fig. 1).

No significant association between STV and CT.

SLV SLV was negatively associated with GMV in 1 cluster: left lingual ($[-20\ -44\ -5]$, TFCE = 1953) (Table 2 Fig. 1).

No significant association between SLV and CT.

In aMCI group

Gait speed Gait speed was significantly positively associated with increased GMV in 2 clusters located in the right superior temporal gyrus ($[68\ -36\ 6]$, TFCE = 2192) and the left superior temporal pole ($[-48\ 9\ -6]$, TFCE = 1725). In other terms: the lower was the GMV, the slower were the participants (Table 3 Fig. 2A).

Regarding the correlation between CT and gait speed, we found a positive one, in 2 significant clusters located in the left superior temporal gyrus ($[-66\ -23\ 3]$, TFCE = 21,050) and the right superior temporal gyrus ($[41\ 12\ 7]$, TFCE = 19,734) (Table 3 Fig. 2B).

STV No significant association was found between stride time variability and GMV or CT.

SLV There was a negative association between the GMV and SLV in many clusters (19) ($p < 0.05$): reduced GMV in the right middle temporal gyrus, right middle, superior and inferior frontal gyri, right precentral gyrus, left supplementary motor cortex (SMC), precuneus, fusiform, putamen, lingual, parahippocampal gyri and left cerebellum. 6 regions were associated with higher SLV (Table 3 Fig. 3A). In other terms: the lower was the GMV, the higher were the SLV.

CT was negatively associated with SLV in 2 clusters: in the right middle frontal caudal and rostral gyri (Table 3 Fig. 3B).

Table 1 Characteristics and comparison of the participants, separated into two groups according to the cognitive status

	Total cohort	CHI	aMCI	P-value*
Demographics and clinical features:				
N =	53	23	30	
Age (years) [SD]	71.7 [5]	68.2 [4]	75.3 [4]	< 0.001
Female gender (%)	20 (38%)	12 (52%)	8 (26%)	0.0576
Number of righter n (%)	50 (94.3%)	22 (96.6%)	28 (93.3%)	0.717
High education level † n (%)	29 (54.7%)	14 (60.8%)	15 (50.0%)	0.431
Gait performances:				
Normal gait speed (m/s) [SD]	1.23 [20]	1.31 [17]	1.17 [21]	0.00673
Maximal gait speed (m/s)	1.80 [29]	1.96 [23]	1.68 [26]	< 0.001
Stride time variability (%)	2.6 [1]	2.1 [1]	2.9 [1]	0.0109
Step length variability (%)	3.1 [2]	3.1 [1]	3.0 [2]	0.503

* Comparisons of cognitively healthy controls with participants with amnesic Mild Cognitive Impairment (a-MCI) based on the Chi-square test or Mann–Whitney U test, as appropriate

† Secondary school and higher education

P significant (i.e. < 0.05) indicated in bold

Table 2 Detailed results of of the association between morphometric changes and gait parameters in CHI group (TFCE, $p < 0.05$, FWE-corrected)

k	Localization	Hemisphere	x	y	z {mm}	TFCE	P-value*
GMV and STV (negative)							
72	Caudate	Left	-17	23	0	1983.18	0.033
GMV and SLV (negative)							
32	Lingual	Left	-20	-44	-5	1953.39	0.041

Discussion

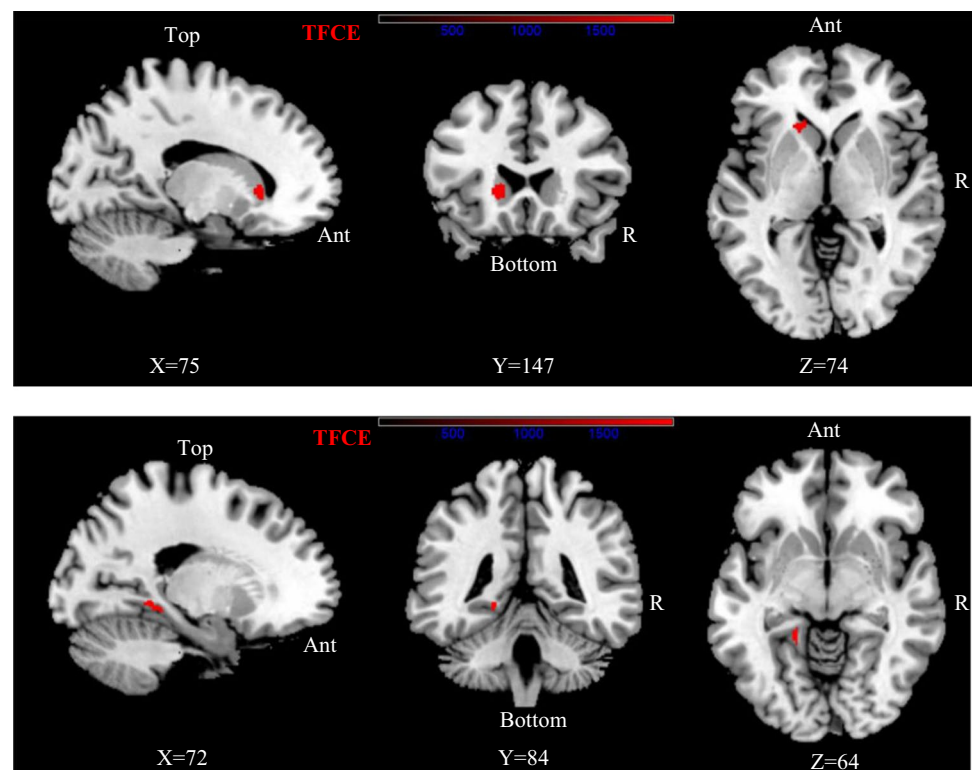
This is the first study that combines gait variability parameters (in addition to the gait speed) and brain changes analysed by SBM in the whole brain. We confirm that there are some differences in gait parameters in aMCI patients when comparing to the control group: slower gait speed and higher STV. Modified gait speed in aMCI is involved with brain structural changes. In this group, we demonstrated that slower gait speed was significantly associated with volume reduction and cortical thickness alterations in brain regions identified as bilateral superior temporal gyri. Higher stride length variability (SLV) was negatively associated with GMV and CT in aMCI group in the right middle frontal gyrus. In CHI, no morphological alteration was associated with gait speed. CHI and aMCI have two different patterns of brain changes related to gait parameters.

As expected, this study confirmed that aMCI subjects have got modified gait parameters when compared to CHI: they were slower in gait speed and they had a higher STV

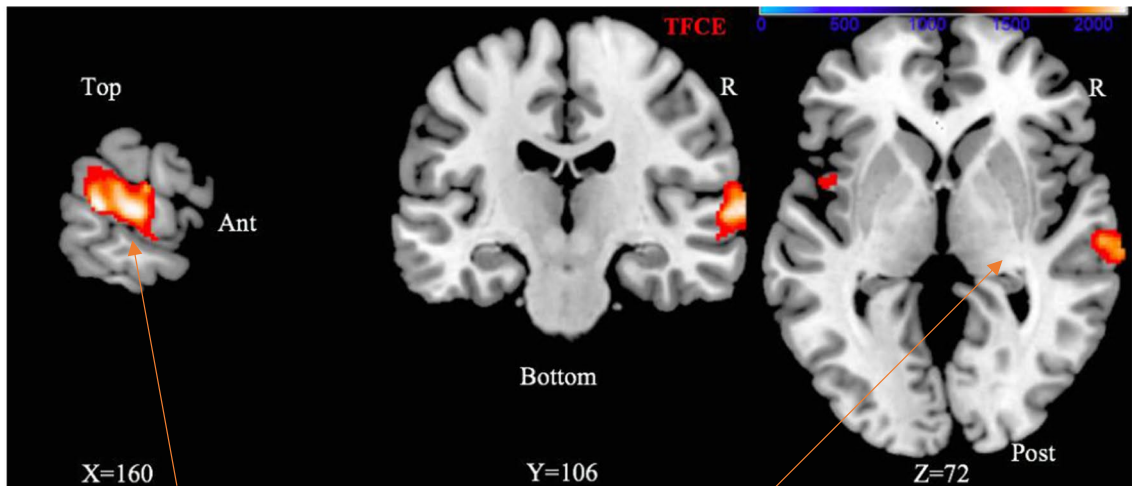
than healthy controls in accordance with the literature (Beauchet et al., 2013; Castrillo et al., 2016; Verghese et al., 2008b). Furthermore, this difference in comfortable gait speed (0.14 m/s in the study) appears to be a clinically detectable change by the standard described in the literature (greater than 0.05 m/s) (Beaudart et al., 2019; Perera et al., 2006). Verghese and al. mention the “motoric cognitive risk syndrome” to characterise the close link between gait and cognition (Verghese et al., 2013). We did not found any difference between the groups regarding the SLV. It could be explained by the fact that gait disorders in MCI patients are more sensitive during dual-task which has not been evaluated in our cohort (Montero-Odasso et al., 2009). In line with previous authors, we have chosen to separate participants based on their cognitive status (Beauchet et al., 2019).

In a MCI, relevant positive association was found between increased GMV, higher CT and faster gait speed in bilateral temporal superior gyri. Temporal superior gyri is often mentioned as an altered zone during MCI when

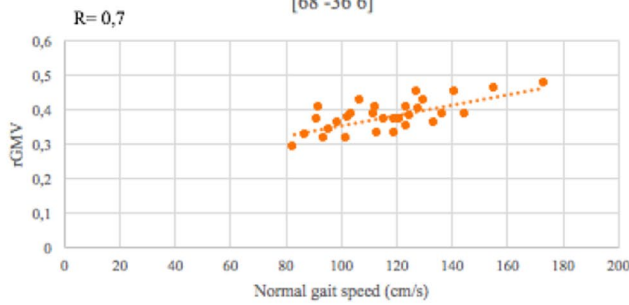
Fig. 1 Negative association between GMV and STV in caudate left gyrus (A) and GMV and SLV in lingual left gyrus (B) in CHI participants:



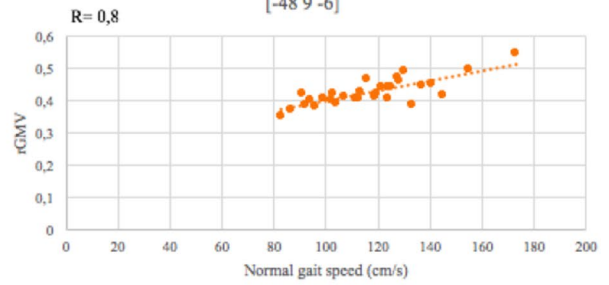
A



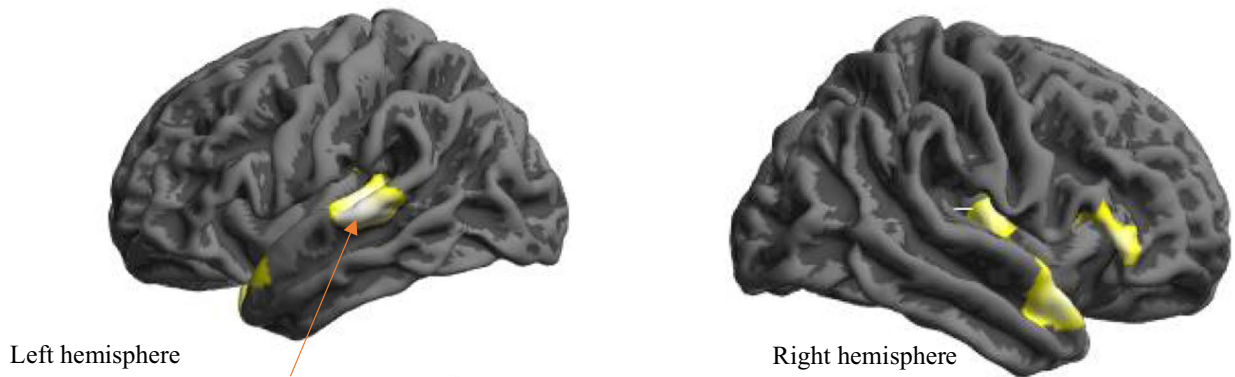
Cluster 1 correlation: right superior temporal gyrus [68 -36 6]



Cluster 2 correlation: superior temporal pole [-48 9 -6]



B



Left hemisphere

Right hemisphere

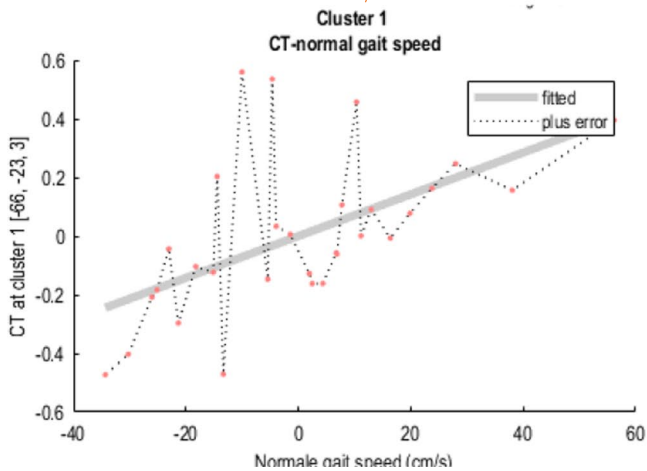


Fig. 2 GM volume (A) and CT (B) showing a positive correlation with normal gait speed in aMCI group: The statistical map is coregistered and superimposed on 3DT1-weighted sagittal, coronal and axial (MNI coordinates (x y z) [160 106 72] (MNI T1-weighted template available on MRICRON software), results are showed with a significance of $p < 0.05$, TFCE, FWE-corrected):

compared to CHI, (Bell-McGinty et al., 2005; Karas et al., 2004; Liu et al., 2013; Pennanen et al., 2005). The association between this region and the gait speed could play a key role in the locomotion high-level control in this population. This area is mostly involved in sounds recognition. During gait process, people need sensorial stimuli to help their external guidance. For older adults, hearing impairment is predictive of slower maximal gait speed (Viljanen

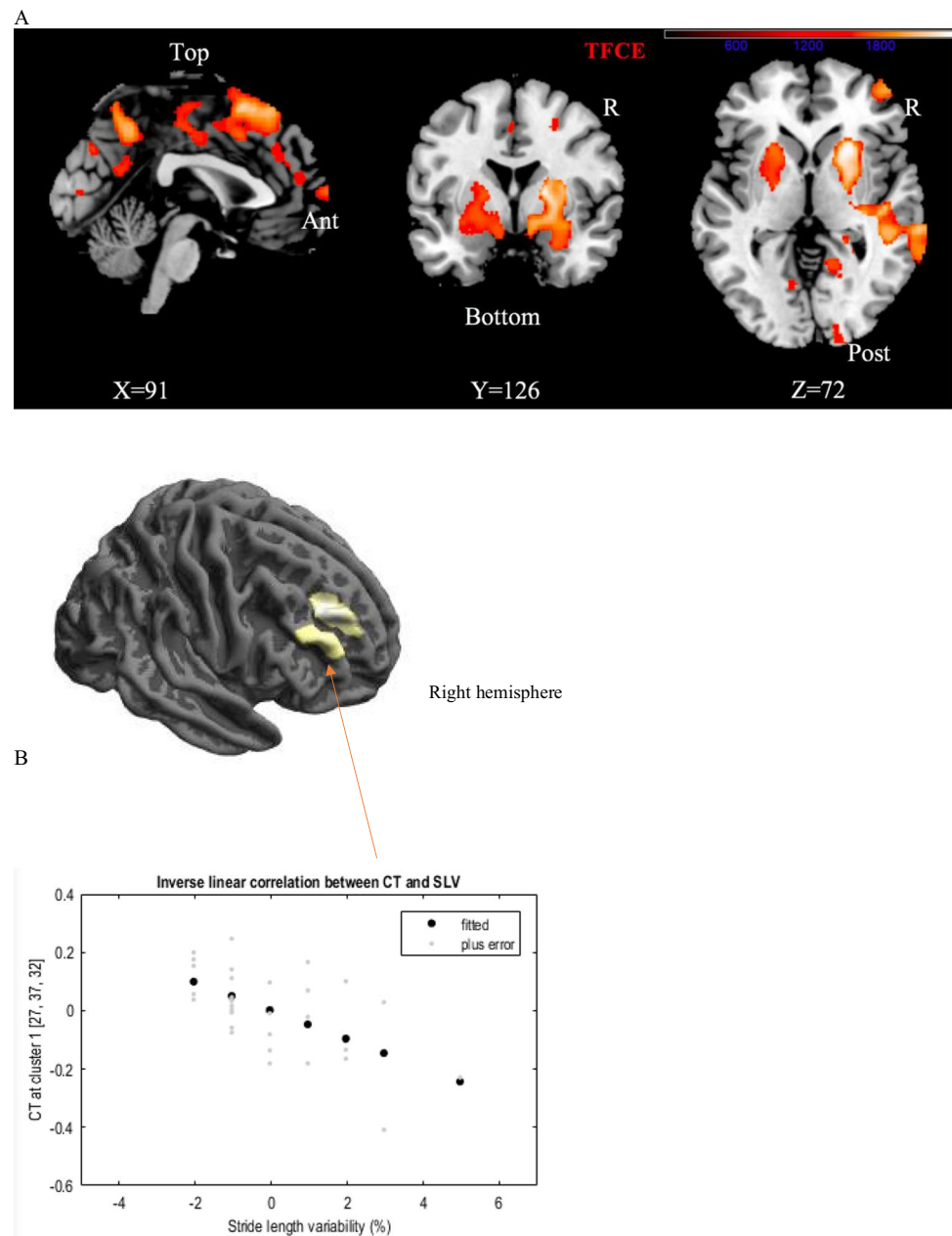
et al., 2009). This link between morphometrics changes and gait speed was not significant in CHI. Our result seems all the more powerful as it is found in volumetric and surface analyses. These results suggest that gait control is sustained by different brain regions with separate brain networks in CHI and MCI. Beauchet and al. also described in his study two different patterns of brain GMV association with gait speed: the frontal cortex for CHI and the striatum for MCI (Beauchet et al., 2019).

Stride time variability (STV) was not associated with topographical brain regions in our cohort of aMCI. This gait parameter may originate from an automated more than a cortical control in this population. In CHI, an association was noticed between GMV and a subcortical region: the left caudate nucleus. Some authors found no correlation between

Table 3 Detailed results of the association between morphometric changes and gait parameters in aMCI (TFCE, $p < 0.05$, FWE-corrected)

Cluster	k	Localization	Hemisphere	x	y	z {mm}	TFCE	P-value*
GMV and gait speed (positive)								
1	1490	Superiortemporal	Right	68	-36	6	2192.73	0.016*
Middle temporal	Right	71	-21	5	2179.70	0.017*		
Postcentral	Right	62	-33	11	2140.19	0.018*		
2	120	Temporal pole sup	Left	-48	9	-6	1725.89	0.035*
CT and gait speed (positive)								
1	978	Superiortemporal	Left	-66	-23	3	21,050.85	0.026*
Transv. temporal	Left	-45	-18	-6	18,542.32	0.035*		
Insula	Left	-36	-28	20	17,760.81	0.040*		
2	1299	Superiortemporal	Right	41	12	7	19,734.48	0.031*
Parstriangularis	Right	36	-9	11	19,196.80	0.033*		
GMV and SLV (negative)								
1	11,176	Mid. Temporal	Right	65	-35	-8	2398.97	0.008*
2	2612	Sup motor cortex	Left	-3	21	59	2302.96	0.010*
3	6239	Precuneus	Left	-9	-59	74	2249.24	0.011*
4	2274	Inf. frontal orbital	Right	51	45	-11	2034.93	0.017*
5	510	Sup frontal medial	Right	5	66	9	1875.30	0.023*
6	3248	Putamen	Left	-21	17	-3	1793.98	0.028*
7	1190	Precentral	Right	47	-14	57	1732.83	0.031*
8	1123	SMC	Left	-6	-12	65	1707.91	0.033*
9	372	Fusiform	Left	-23	-50	-17	1651.36	0.037*
10	158	Mid. frontal	Right	50	48	9	1605.82	0.040*
11	240	Mid. frontal	Right	29	20	53	1561.75	0.044*
12	273	Lingual	Left	-17	-65	-8	1560.83	0.044*
13	223	Sup frontal medial	Left	-2	36	33	1552.17	0.044*
14	91	Mid. frontal	Right	27	60	26	1543.83	0.044*
15	234	Sup. frontal	Right	20	9	57	1542.59	0.044*
16	67	Parahippocampal	Left	-23	-33	-12	1537.78	0.044*
17	146	Sup. frontal	Right	24	47	24	1522.20	0.047*
18	28	Cerebellum 6	Left	-38	-56	-26	1512.57	0.048*
19	29	Inf. frontal orbital	Right	33	27	-26	1505.08	0.049*
CT and SLV (negative)								
1	198	Caudal mid frontal	Right	27	37	32	18.226	0.004*
2	126	Rostral mid frontal	Right	40	42	26	16.917	0.004*

Fig. 3 GM volume (A), CT (B) showing a negative correlation with SLV in aMCI:



STV and hippocampal volume in their study among patients with MCI while they described some for CHI (Beauchet et al., 2015). In a previous study, STV was mainly sensitive to neural functions (in spectroscopy) rather than morphometric parameters and could explain the absence of difference here (Annweiler et al., 2013a, b).

We observed an inverse linear association between unstable gait through stride length variability (SLV) and morphometry in aMCI: increased SLV was correlated with reduced GMV. This atrophy is observed in the following regions: on the right hemisphere, in the superior and middle frontal, the precentral and the middle temporal gyri; on the left hemisphere, the supplementary motor cortex, the putamen,

the precuneus and the left cerebellum. Increased SLV was also associated with thinner thickness in the right frontal lobe. This associative cortical network is involved in the integration of auditory, somatosensory and visual information (Cavanna & Trimble, 2006). Morphometrics changes in these areas could alter sensory functions and be part of the reduced gait speed during aMCI process. We also found a negative correlation in aMCI group between GMV and SLV in the cerebellum. This structure coordinates voluntary movements such as posture, balance, coordination. An atrophy of this region could explain higher SLV, expressed clinically in greater instability. In CHI, only a small cluster in the lingual region was identified as associated with worse

SLV. This structure is involved in visual memory. A previous attempt to find a correlation between stride length variability and the hippocampus' volume was not successful in older adults (Zimmerman et al., 2009). Our study suggests that the groups have not the same brain morphological alteration's pattern. An inverse linear association between gait variability and structural brain changes was shown for the first time among older adults CHI and aMCI. Cerebral structure alteration appears to differ between the two groups. There were associated regions in both volume and surface analyses only in the MCI group. This association should be considered as the strongest combination. This new result reinforces the current thinking that gait variability may serve as a surrogate marker of the function and efficiency of higher-level motor control (Beauchet et al., 2013; Hausdorff, 2005).

The study's strengths were that we focused on a specific subtype of MCI, amnesic, with the primary endpoint of exploring the specific relationship between morphometrics changes and early gait disorders in subject during the prodromal stage of dementia. CAT12 was used as an innovative algorithm exploring a new folding measure such as CT in addition to the current GMV measure. These features may contain important data for a better understanding of the correlation between function and anatomy. More thorough investigation will be necessary in the future. Furthermore, the complete analysis of the "whole brain" brings power and the full automated analysis provides less manipulator bias. Additionally, gait performances were measured using a standardized and validated automated computerized gait analyse technique.

The present study has also several limitations. The cross-sectional design limits causal inferences, and we have studied a relatively small sample size. Longitudinal studies would be more suitable to evaluate causal associations between brain structural changes and gait performances (Doi et al., 2017). The aMCI group was older than CHI (we resolved it by adding this parameter as a covariate). There was no information about the occurrence of Alzheimer disease converters (no clinical follow-up) and no information about the beta amyloid and apoE4 profile of patients. For further studies, we should add a test in dual task conditions requiring an increased attention demand for MCI subjects (Beauchet et al., 2013; Montero-Odasso et al., 2012a).

In conclusion, this study provides new evidence in the exploration of structural brain changes and gait performance in older adults. In aMCI, decreased GMV and thinner cortex were associated with normal gait speed in the bilateral superior temporal gyri. Gait instability analysed through stride length variability was associated with brain atrophy (decreased GM) in spread regions and with thinner cortex in the right frontal lobe. It would therefore be interesting in future prospective and longitudinal studies to follow the evolution of anatomical surface parameters during the physical therapeutic actions.

Author contributions Conceptualization; Data curation; MD and CA. Methodology and writing: PA and MD. Supervision: PP, CA and MD.

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The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The entire study protocol was approved by the Angers Ethical Review Committee (Comité de protection des personnes, CPP ouest II, Angers, France, n° A.C D 2014-A01593-44, n° CPP: 2014/32). Written informed consent was obtained at enrolment.

Declarations

Conflict of interest C. Annweiler serves as an editor for *Maturitas*. All authors declare they do not have any other financial and personal conflicts of interest with this manuscript.

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