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Association between gait, cognition and grey matter volumes in Mild Cognitive Impairment and healthy controls

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Key words: gait speed; cadence; stride length; MCI; cognitive functioning; memory; dementia.

Abstract

Aims: To assess the correlation between cognitive functioning and three gait parameters (gait speed, cadence and stride length) in persons with Mild Cognitive Impairment (MCI) and cognitively healthy controls and investigate linear correlations between gait and GM volumes.

Methods: Participants were recruited at IRCCS San Camillo Hospital, Venice, Italy (MCI=43; age-matched controls=43). Participants underwent comprehensive neuropsychological assessment. Gait speed, cadence, and stride length, were assessed with the BTS FREEMG 300 device. Three-dimensional (3D) T1-weighted MR images were acquired using a 1.5 T Philips Achieva MRI system with a Turbo Field Echo sequence.

Results: In MCI there was a positive correlation between gait speed and memory tests ($p<0.05$). In controls all three gait parameters correlated with executive functioning ($p<0.01$). Temporal and limbic areas (i.e. superior temporal gyrus, thalamus and parahippocampal gyrus) were associated with gait parameters in MCI whereas in controls the associations were with frontal areas (i.e. middle, inferior and superior frontal gyrus) and in the cerebellum (anterior and posterior lobe).

Conclusions: Our results highlight a distinct pattern of association between GM volume and gait parameters in MCI patients and controls (temporal areas in MCI and frontal areas in healthy elderly), suggesting a relationship between dementia-related pathology and gait dysfunction.

1. Introduction

Mild cognitive impairment (MCI) is a syndrome characterized by significant cognitive deficits in persons without dementia[1,21-2], and is associated with an increased rate of progression to dementia disorders such as Alzheimer's disease (AD). However, MCI is a heterogeneous syndrome - a large percentage of patients progress to a full dementia state within five years, but a substantial proportion of persons remain stable or improve in cognitive functioning[3]. This raises the importance of identifying factors that predict cognitive decline in these patients. Several factors have been shown to increase progression to dementia in MCI patients, including psychiatric factors[4], vascular factors[5] , instrumental functioning deficits[6], carotid atherosclerosis[7], CSF and neuroimaging biomarkers[8]. Recently, research has focused on motor functioning, including gait control, as a potential clinical marker in persons in the prodromal phase of dementia.

Gait control is a complex process involving various parameters, including walking speed, stride length, and cadence. A review suggested that several gait parameters should be examined in order to identify persons at risk of cognitive decline[9], including gait variability and gait speed. In cognitively healthy persons, gait control is bilateral, and involves the hippocampus, prefrontal cortex, and parietal lobe[10]. Executive functioning is associated with balance control[11] and gait control, particularly in persons with MCI and AD[10,11]. Other cognitive domains such as processing speed and memory are also associated with gait speed and other gait parameters in healthy persons and those with cognitive impairment[12,13].

Gait performance is often impaired in persons with AD, and gait-related problems such as falls are more common in dementia patients than in cognitively healthy older persons[14,15]. Gait and balance are associated with cognitive decline[16,17] and progression to AD in patients with MCI[16,17]. Further, research suggests that specific MCI subtypes have different motor signatures[18], with amnestic-MCI patients exhibiting slower gait performance during dual tasking[10,19]. A systematic review showed that slow walking speed combined with subjective cognitive impairment, a syndrome termed "motoric cognitive risk syndrome", is associated with more than a twofold risk of incidence dementia[20].

The above evidence suggests that gait is often impaired in MCI, is associated with an increased risk of dementia, and is associated with cognitive functioning in specific domains. This raises the question of whether there are specific brain structures that are related to gait performance in MCI patients, which may

indicate an ongoing neurodegenerative process. One study investigated the association between hippocampal volumes and gait performance in MCI patients and cognitively healthy controls[21]. Although they identified a positive association between greater hippocampal volumes and poorer stride performance in cognitively healthy persons, they found no association for MCI patients in any gait parameters. In contrast, another study demonstrated that poorer gait performance was associated with lower total white and grey matter (GM) and lower hippocampal volume in non-amnestic MCI patients[21]. Interestingly, the pattern of brain volume reduction was different for MCI patients compared to cognitively healthy controls.

As the difference in GM volume involved in gait in MCI and cognitively unimpaired persons is still unclear, we aimed to investigate these parameters in a clinical sample of MCI patients compared to age-matched healthy controls in a motor-neurorehabilitation hospital in Venice, Italy. The specific objectives of the current study were to: 1) assess the correlation between domain-specific cognitive functioning and three gait parameters (gait speed, cadence and stride length) in persons with MCI and cognitively healthy controls; 2) identify differences in the correlation between cognitive functioning and the three gait parameters in persons with MCI compared to cognitively healthy controls and; 3) investigate linear correlations between GM volumes and the three gait parameters in MCI and healthy controls, and compare whether the associated structures differ between the two groups.

2. Material and methods

2.1 Participants.

Forty-three MCI patients (mean age 74.7, SD 6.9; mean education 10.3, SD 4.2; females n=26, 60.5%) diagnosed according to Petersen et al's criteria[1,2] and 43 age-matched healthy controls (mean age 72.2, SD 6.1; mean education 11.9, SD 4.1; females n=25, 58.1%) took part in the VPH-DARE@IT project, an FP7 Project supported by the European Union. All participants were recruited at IRCCS San Camillo Hospital in Venice, Italy. Only those able to walk independently without a gait aid (e.g. cane or walking stick) were included in the study. All participants underwent a complete neuropsychological assessment as well as an experimental gait protocol. The patient and control group did not differ in terms of demographics, however significant differences were found in gait speed, stride length and cadence (see Results).

2.2 Ethics.

The study was approved by the joint ethics committee of the Health Authority Venice 12 and the IRCCS San Camillo (Protocol number 2014.08). All participants gave written informed consent prior to participation in the study.

2.3 Neuropsychological assessment.

Cognitive functioning was evaluated with a comprehensive neuropsychological assessment. The following standardized tests were used to evaluate several cognitive functions: the Mini-Mental State Examination (MMSE)[22] to assess global cognition; Digit Span Forward and Backwards[23], Prose Memory Test and the Paired Associates Test[24,25] as measures of episodic memory, verbal short-term memory and working memory; Corsi Test[23], Corsi Supra Span[26], Rey-Osterrieth complex figure[27] to measure visuospatial memory and visuoconstructive skills. Phonologic and semantic fluency were tested with the Letter Fluency Test[24] and the Category Fluency Test[24]. The Digit Cancellation Test[26] was used as a measure of visual search and speed of processing; a component of executive functioning was assessed with the short version of the Stroop Test[27]. The Token Test[26] was chosen as a measure of comprehension and receptive language; the Similarities Test from the Wechsler Adult Intelligence Scale-Revised battery[28] and the Raven Progressive Matrices[29] were chosen as verbal and non-verbal measures of abstract reasoning respectively. Raw scores on tests were corrected for age and level of education for clinical purposes, using various sources of normative data except for the Digit Span Backwards for which no normative data exist for the relevant population.

2.4 Gait assessment

Participants were asked to walk a fixed distance (10 m) along a delimited indoor walkway, at their usual self-selected walking speed in a quiet room. Spatial-temporal gait parameters, including gait speed, cadence (number of steps per minute) and stride length (distance walked from the heel-down time to the next heel-down time of the same foot), were recorded using a specific tool – BTS FREEMG 300 – that provides integration of kinematics, dynamics, and surface electromyography all in one device. Ten meters of space was calibrated for collection of gait data in the system.

Footswitches were used to define the contact points of deambulation. The BTS FREEEMG permits up to 8 basographic zones to be measured, usually subdivided into 4 zones per side (right and left). The footswitches consist of a resistive membrane, 18 mm in diameter and with thickness of less than 0.5 mm, expressly

designed for applications in the analysis of movement. Acceleration and deceleration effects were later corrected during the phase of statistical analysis.

2.5 MRI protocol and image processing.

Three-dimensional (3D) T1-weighted MR images were acquired using a 1.5 T Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1.1 x 1.1 x 0.6 mm (gap 0.6 mm) and the field of view was 250 mm with a matrix size of 256 x 256 x 124. A number of pre-processing steps were followed, using SPM12 (Welcome Centre for Human Neuroimaging, UCL, London, UK)[30], to obtain the GM and white matter (WM) segments from the 3D T1-weighted structural scan. This procedure included tissue-class segmentation and spatial smoothing, carried out with an 8mm Full-Width at Half Maximum Gaussian kernel. Smoothing was applied to reduce between participant variability and improve the normality of the distribution of the imaging data, both of which are important for statistical analysis. Global native –space volumes of GM, WM, and cerebrospinal fluid were extracted from all scans to compute total intracranial volume (TIV).

2.6 Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics 20 software. The Shapiro-Wilk test was used to explore the normality of data distribution; non-parametric statistics were then used for further analyses. Specifically, differences between groups in all gait parameters (e.g. gait speed, cadence, stride length) were investigated using the Mann-Whitney test. T-tests were used to test differences in cognitive test between healthy controls and MCI. Spearman rho correlations were computed to test the association between cognitive tests and gait parameters. A Bonforoni correction was applied to account for multiple cognitive tests (n=20), with significance set at <0.0025.

For the analysis of MRI, first, the reduction of GM volumes in the MCI group compared with the healthy control group was explored. Second, smoothed GM segments were entered into a voxel-based multiple regression analysis to investigate linear correlations between GM volumes and each gait parameter (gait speed, cadence and stride length) separately for each group (MCI and healthy controls). Age, years of education and total intracranial volume values were included as covariates in all multiple regression models.

Threshold was set at $p < .05$ for all MRI analyses. Significant MNI-space peak coordinates were converted into Talairach space using a non-linear transform[31] and interpreted using the Daemon client[32].

3. Results

The MCI and healthy control group did not differ significantly in demographic characteristics. There were differences in all gait parameters (i.e. gait speed, cadence, and stride length) between the two groups (Table 1). As expected, MCI patients had poorer performance in comparison to healthy controls in all cognitive domains (Table 1).Spearman's correlation analysis showed a significant relationship between gait parameters and some cognitive domains in controls (Table 2). There was a positive correlation between one gait parameter (i.e. gait speed) and the Stroop test, a test that measures executive functioning (ρ =-0.595, $p <$ .000). Stride length correlated with Digit Cancellation ($\rho = .477$, $p < .001$), Similarities ($\rho = -.499$, $p < .001$), Stroop error ($\rho = -.589$, $p < .000$), and Digit Span Backward ($\rho = .477$, $p < .001$).

When the MCI group was compared with the healthy controls, differences in GM volumes were detected (Table 3).

In the MRI analyses, a significant positive association in the healthy control group was found between average gait speed, cadence, stride length and GM volumes in frontal areas (i.e. middle, inferior and superior frontal gyrus) and in the cerebellum (anterior and posterior lobe) after adjustment for age, years of education and total intracranial volume values

In the MCI group, average gait speed and stride length showed significant associations with GM volumes in the temporal and limbic areas (i.e. superior temporal gyrus, thalamus and parahippocampal gyrus). The cadence parameter showed no significant association with GM volumes. Table 4 and Figure 1 show a summary of these findings.

4. Discussion

The main findings of our study are that there are distinct patterns of association between GM volume and gait parameters in healthy elderly and MCI patients. Temporal and limbic areas (i.e. superior temporal gyrus, thalamus and parahippocampal gyrus) are associated with gait parameters in MCI whereas in healthy elderly the associations are with frontal areas (i.e. middle, inferior and superior frontal gyrus) and in the cerebellum (anterior and posterior lobe).

This study shows that MCI patients present a specific association between gait parameters and grey matter loss in mediotemporal structures, highlighting a relationship between dementia-related pathology and gait dysfunction. These findings are in line with those of other studies; poorer gait performance was associated with lower total white and grey matter and lower hippocampal volume in non-amnestic MCI patients[33] and these patterns were different for cognitively healthy persons where an association was only observed for the lower right hippocampal volume. It has also been reported that different patterns of brain volume reduction are associated with increased Timed Up and Go tests in MCI and cognitively healthy persons[21]. Another study reported an association between greater hippocampal volume and poorer gait performance in persons with subjective cognitive impairment[34].

It is interesting to note that gait in MCI is not associated with automatic motor areas such as the cerebellum, as was seen in the cognitively healthy controls, but instead was associated with the brain structures related to memory, including the temporal and limbic structures. A systematic review highlights that motoric cognitive risk syndrome is associated with low grey matter volume in the premotor and the prefrontal cortex[20]. These findings raise the question of whether gait changes from being an automatic function to being planned activity. A previous fMRI study demonstrated that activation patterns change with aging, as older persons have increased left hippocampal activation than younger persons during gait control, and a review concluded that poor mobility outcomes are associated with reduced grey and white matter volume[35].

Our study included age-matched controls with a mean age of 72.2 years, allowing us to differentiate between normal and pathological aging. In cognitively healthy older persons gait was associated with attention and executive functioning, and a recent meta-analysis concluded that interventions that combine physical and cognitive exercise with training of attention and executive functioning improve gait performance[36]. This highlights the importance of assessing gait control in all older individuals, not just those with MCI, as there

is a potential positive effect of interventions, which may in turn help the reduction of risk of falls and related negative outcomes.

The strengths of our study include the comprehensive neuropsychological assessment, extensive gait analysis, and thorough MRI analysis. We used a detailed diagnostic procedure for diagnosing MCI and included a matched control group. The fact that we included all types of MCI, not just amnestic-MCI can be viewed both as a strength and limitation. On one hand, it is good to include all types of MCI patients, but on the other hand, it may be clinically interesting to focus on amnestic forms of MCI that are more often associated with the preclinical stages of AD. Another limitation is that our sample was quite small, but considering the extensive MRI and gait analysis, and the fact that we were able to identify significant associations, it is unlikely that this is a major problem. Unfortunately, we only assessed three measures of gait, yet it is a complex process that can include others measurements such as stance time, swing time, and double support, which have shown to be affected in persons with cognitive impairment[18,37,38]. Further, we did not examine dual task gait, which may reveal interesting differences as dual-task gait performance significantly declines across the cognitive spectrum[39].

Our findings have important clinical relevance. Measures of gait might be useful proxies of cognitive decline in the early stage of AD-related neurodegeneration. Recent research suggest that cerebral Aβ deposition is associated with reduced gait speed in older adults with cognitive impairment[40]. Specific gait measures may be useful for predicting which patients will have a faster cognitive decline, and might be used as a marker of potential GM reduction in specific brain structures. As gait disturbances are symptoms that can be visually identified, and are relatively inexpensive to assess, it may be useful to screen for gait problems to identify persons in need of comprehensive neuropsychological testing. Importantly, clinical trials suggest that dual task performance can be improved with training in dementia patients[41], and interventions that combine strength and balance training can improve gait performance in persons with both dementia and MCI[42]. Gait parameters are useful predictors of falls, which can cause fall-related injuries that affect quality of life and increased healthcare costs, for example, persons with both MCI and slow gait have a twofold risk of falling[43]. Therefore, gait analysis may be an important measure to include in the standard assessment of geriatric patients and those at risk for cognitive impairment.

Future studies should focus on assessing dual task gait, which can provide additional valuable clinical information and it may have the potential to enhance diagnostic capabilities in MCI[36]. It is also relevant to

examine differences in MCI subtypes. For example, one study demonstrated that poorer gait performance was associated with lower total white and grey matter and lower hippocampal volume in non-amnestic MCI patients, but this association was not seen for amnestic-MCI patients[33]. Further, GM volume covariance associated with gait speed differs according to MCI subtype; it involves the frontal cortex in amnestic-MCI patients and subcortico-frontal regions in non-amnestic-MCI[44]. Also of interest would be to include imagined walking test assessment, such as a previous study[33], which found that left premotor cortex volumes were associated with poorer imagined gait performance in non-amnestic MCI patients.

In conclusion, our results highlight a distinct pattern of association between GM volume and gait parameters in healthy elderly and MCI patients (temporal areas in MCI and frontal areas in healthy elderly) and indicate that detection of gait abnormalities in a geriatric population has diagnostic valence and might flag individuals at greater risk of cognitive decline.

Figure Legend

Figure 1. Association between GM volumes and gait parameters in MCI and healthy controls

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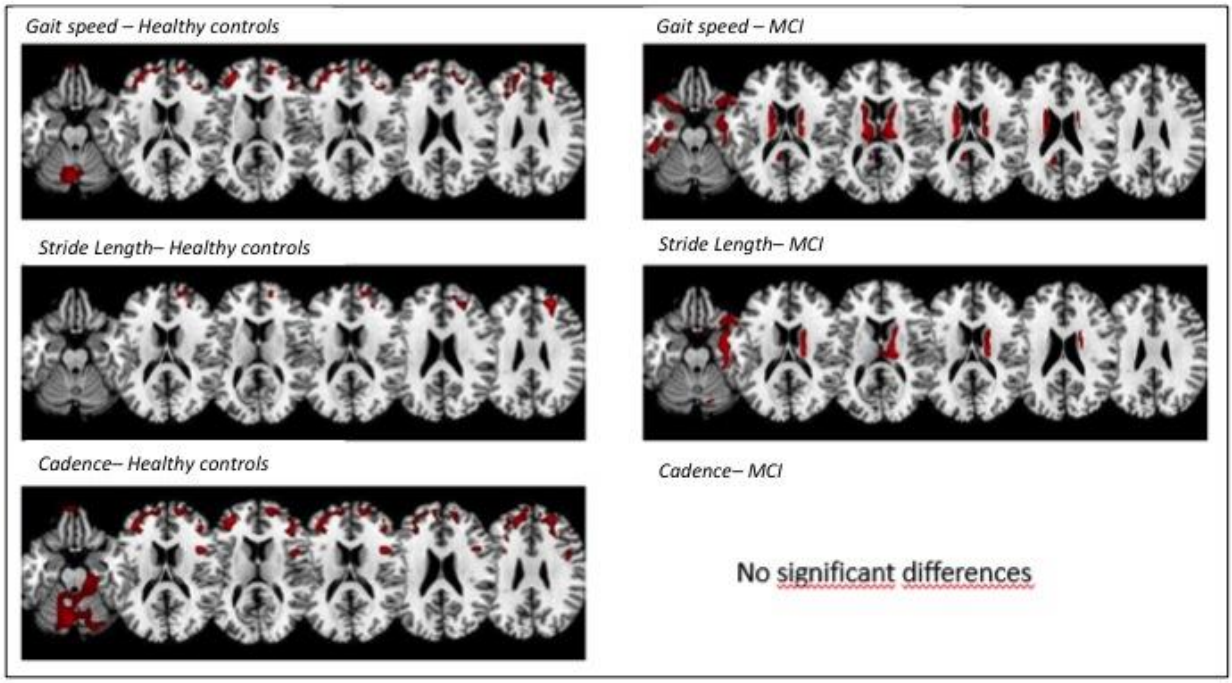

Figure 1. Association between GM volumes and gait parameters in MCI and healthy controls