

# Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? A pilot study

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Received: 4 February 2015 / Accepted: 22 May 2015  
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## Abstract

**Background** Previous literature demonstrates the interest of gait analysis to predict cognitive decline in old people. **Aims** This pilot study aims to determine if gait speed or gait variability is a marker able to early identify, among mild cognitive impairment (MCI) subjects, those at risk to develop Alzheimer's disease (AD) in the future.

**Methods** 13 MCI subjects were included in 2007. Their gait parameters (walking speed, stride length and gait frequency, regularity and symmetry) were measured in 2007 and 2008 in simple task (ST) and in dual task (DT) using a triaxial accelerometer (Locometrix<sup>®</sup>). Among the 13 MCI subjects included in 2007, 10 were assessed in 2008. So, 23 (13 in 2007 + 10 in 2008) gait tests were collected. In 2011, MCI people were considered as "MCI+" when they developed AD (between baseline and 2011) and as "MCI-" if they did not. Among the 23 gait tests, 15 were from MCI+ (9 gait tests in 2007 and 6 in 2008) and 8 from MCI- (4 gait tests in 2007 and 4 gait tests in 2008). Mann-

Whitney non-parametric *U* test was used to compare gait parameters of MCI+ and MCI-.

**Results** Gait speed, symmetry and regularity were lower in MCI+ than in MCI-.

**Discussion** Despite the small sample size, the results presented in this original pilot study are in line as the infrequent previous literature related to this topic. The authors discuss lacks and strengths of this work.

**Conclusions** These results suggest that both gait speed and gait variability could be markers to early identify MCI at risk to develop AD.

**Keywords** Variability · Regularity · Gait speed · MCI · Alzheimer disease

## Abbreviations

AD	Alzheimer disease
CIRS	Cumulative Illness Rating Scale
DT	Dual task
GDS-15	Geriatric Depression Scale—15 items
MNA	Mini Nutritional Assessment
MCI	Mild Cognitive Impairment
MCI+	MCI who will develop AD
MCI-	MCI who will not develop AD
MCR	Motor cognitive risk
MMSE	Mini Mental State Evaluation
ST	Simple task

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## Introduction

Since the last 20 years, the number of studies including instrumental gait analysis are growing, especially those concerning the relationships between gait performances

and cognitive functions [1, 2], the relationships between the gait performance and the brain modifications related to neurodegenerative process [3, 4], and the relationship between gait performance and vascular burden [5, 6].

In this context, gait speed [7, 8] and variability of the gait seem to be potential parameters predicting cognitive decline and dementia in seniors [9, 10]. Performances in these two parameters could be influenced by several confounders as the age [11, 12], the gait speed [12], history of falls [13], cognitive functioning [10, 14], frail status [15] and the walking conditions [16]. A recent study tries to identify between these two parameters which one is the most associated with specific cognitive functions among MCI people [17]. But actually it remains unclear which parameters (gait speed, gait variability or both) are most useful to predict cognitive decline.

The goals of this prospective and exploratory study were first, to analyze gait performance of a group of MCI presenting at least a possible confounder; second, after a 3-year follow-up, to identify into this group, the MCI patients who will develop AD and those who will not; third, to compare gait performance obtained at baseline. The authors hypothesize that the gait speed and the parameters showing the variability of the gait could help the clinician to discern earlier MCI at risk to develop AD.

## Population, materials and method

### Population

The MCI patients were recruited among those attending Liège University Hospital's Memory Centre. Memory disorders were diagnosed by standard medical imaging and neuropsychological evaluation methods. According to Petersen criteria [18], the diagnostic of MCI was established when patients present a confirmed, isolated cognitive disorder without important impact on their activities of daily living and undergo neurological, neuropsychological and neuro-imaging diagnostic evaluations with a clinical dementia rating score (CDR) below 0.5 [19]. Other exclusion criteria included mental retardation, less than four regular years of education, cranial trauma, epilepsy, cancer, depression, drugs abuse or any other acute organic disease. At inclusion, none of the patients was taking any medication likely to influence their cognitive performance. Their score in the Mini Mental State Examination (MMSE) [20] had to be 24/30 or more. In 2011, after a 4-year follow-up, MCI considered as "MCI+" were diagnosed as having probable AD according to the criteria defined by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) [21]. All subjects attending this study were assessed by a complete

neurological and neuropsychological evaluation, and with a FDG-PET scan to provide the diagnosis.

The following medical conditions were exclusion criteria: vascular stroke with motor or sensory disorder; Parkinson's disease; non-compensated diabetes; non-compensated arterial hyper- or hypotension; any cardiac or respiratory disease which could cause gait-limiting weakness or dyspnea; a hip or knee prosthesis; arthritis or another invalidating bone/joint disease.

The use of benzodiazepine, antidepressant or small doses of neuroleptics (without motor repercussions) was accepted. Patients needing glasses and/or hearing aid were eligible but the subjects had to be completely satisfied with the performance of these sensory aids. A medical evaluation including an interview (to establish the subject's full personal medical history), and a comprehensive clinical and functional examination was performed for all patients to check for the absence of exclusion criteria and to ensure that the gait test results and the neuropsychological assessment would not be influenced by any organic, affective or functional factors. Then, medical and functional assessment included sex, age, body mass index (BMI in  $\text{kg}/\text{m}^2$ ), Mini Nutritional Assessment (MNA) [22], comorbidities according to the Cumulative Illness Rating Scale (CIRS) [23], pain evaluation using pain horizontal analogue visual scale [24, 25], mood evaluation using the 15-items Geriatric Depression Scale (GDS-15) [26] and an evaluation of autonomy for basic and instrumental daily living activities using Katz scale (ADL) [27] and Lawton scale (IADL) [28], respectively. The scores considered for the GDS and the Lawton scale were the sum of the score obtained divided by the number of items applied (an item were not applied if the activity never has been done by the subject; e.g. men never doing housework).

After this assessment, 13 MCI persons are eligible and accept the follow-up. They were informed about the experimental procedure and provided written informed consent. The study was approved by the local ethics committee of the University Medical Centrum of Liège (Belgium).

## Material

### Gait analysis system

The gait analysis system used (Locometrix<sup>®</sup>) is an accelerometric method comprising an acceleration sensor, a recording device and a computer program for processing the acceleration signal. The sensor is composed of two accelerometers placed perpendicularly to each other in a plastic box as previously explained [29, 30]. The sensor's box is incorporated in an elastic abdominal belt, behind the back over the L3–L4 intervertebral lumbar space (the third

lumbar vertebra level) using an elastic, abdominal belt. The first accelerometer is aligned to the mediolateral axis of the body; the second is aligned to the cranio-caudal axis. Acquisition frequency of the signal was of 50 Hz. The system can record continuously for 10 min. The recorded signals are transferred to a laptop computer using a transfer program operated under windows 98, formatted in files and analyzed by software developed in the MATLAB 5 environment. The data are transferred to a computer for statistical spreadsheet analysis.

### Gait analysis

As explained previously [31, 32], during the test, the subject walks up and back along a straight 40 m corridor, free of obstacles or visual/auditory distractions, at a freely chosen pace and cadence, and using their usual walking shoes avoiding high heels. Two timing lines are located 5 m after the starting line and 5 m before the 40 m line, respectively, allowing the time measurement on 30 m walk. First, subjects were asked to walk in simple task at preferred walking speed. The same day, subjects were asked to walk in dual task condition, again at preferred walking speed and without prioritization instructions. According to Professor O. Beauchet, we choose a count-down from 50 as cognitive task during dual task because this is the additional cognitive task that perturbs most of the gait parameters in a dual-task paradigm [33].

### Data processing

As explain before [29, 30], two periods of steady state walking of 20.48 s was selected from each subject. The first one was concerning simple task (ST) conditions and the other one concerned dual task (DT) conditions. Each period (of 20.48 s) contained about 1024 acceleration measurements and provided an optimal calculation time. This period correspond to 19–21 gait cycles. Using the walking time and according to the software (using fast Fourier transformation), the following gait variables are available:

- Gait speed, measured using a timing line and expressed in meters/second.
- Stride frequency or number of cycles per second (Hz), calculated from the cranio-caudal acceleration following application of a Fourier transform.
- Stride length, deduced from the equation [speed = frequency  $\times$  stride length] and expressed in meters.
- Regularity, measured by the similarity (in terms of duration and amplitude) of the shape of cranio-caudal acceleration curves from steps and strides. This parameter is expressed in absolute value.

- Symmetry, defined as the similarity (in terms of duration and amplitude) of the shape of cranio-caudal acceleration curves when focusing on the right and left steps. This parameter is expressed in absolute value.

As explain before [29, 30], symmetry and regularity were calculated based on two different coefficients, C1 and C2. These coefficients are calculated based on the auto correlation of the vertical accelerating signal. C1 represents the correlation between the vertical accelerating signals considering one step to the following step (a step is a part of a stride and a stride includes a left step and a right step). In fact, each step is correlated to the following step (autocorrelation) and C1 shows the mean value of all these autocorrelations. C2 represents the correlation between the vertical accelerating signals considering all successive strides. The symmetry is calculated as  $C1/C2 \times 100$ . The regularity is calculated as  $(C1 + C2) \times 100$ .

All subjects walked first time in ST and after in DT.

From 2007 until 2011, all subjects were yearly assessed by neuropsychological testing as used in the memory clinic. Their cognitive status was classified according to the neurological and neuropsychological criteria previously detailed. In 2011, according to the neurological diagnosis, subjects were considered as “MCI+” when they developed AD between 2007 and 2011 and as “MCI–” if they did not. According to this distribution, 15 gait tests were coming from MCI+ patients and 8 gait tests were coming from MCI– patients. Among the 23 gait tests, 15 were from MCI+ (9 gait tests in 2007 and 6 in 2008) and 8 from MCI– (4 gait tests in 2007 and 4 gait tests in 2008). In the pilot study, we considered each gait testing as an individual gait test and not as a serial test on the same person. Then, we performed statistical analysis concerning 23 walking tests. We use the Mann–Whitney *U* test, a non-parametric statistical test to do the comparison between the mean gait performance of “MCI+” and “MCI–” patients. A *p* value  $<0.05$  was considered significant throughout and data normality was confirmed using the Lilliefors test.

### Results

Main medical characteristics, functional and neuropsychological performances from MCI subjects at inclusion are presented in the Table 1.

As shown in Table 2, MCI+ patients have a significant statistical difference with MCI– patients concerning the gait speed (in ST and DT) and concerning the symmetry in DT. Gait speed and symmetry are higher in MCI– patients than in MCI+ patients.

All MCI people show worse gait performances in DT compared to ST.

**Table 1** Main characteristics of MCI at inclusion

Medical and functional variables	MCI+, N = 9 (mean ± SD)	MCI-, N = 4 (mean ± SD)
Age	74.44 ± 4.16	70.00 ± 2.16
Sex	4 women	2 women
MNA	19.87 ± 7.00	23.25 ± 6.86
CIRS	5.00 ± 2.60	5.50 ± 3.42
Visual analog scale pain	0.89 ± 2.67	0.50 ± 1.00
GDS	0.13 ± 0.14	0.19 ± 0.02
ADL	6 ± 0.00	6 ± 0.00
IADL	0.26 ± 0.03	0.26 ± 0.00
MMSE	26.11 ± 1.45	27.25 ± 1.70
Mattis, total score	133.11 ± 5.67	137.50 ± 5.20
Mattis, attentional score	35.78 ± 1.09	36.00 ± 1.15
Mattis, initiation score	32.89 ± 3.56	36.00 ± 1.41
Mattis, construction score	5.78 ± 0.44	6.00 ± 00
Mattis, conception score	37.22 ± 1.48	37.25 ± 1.71
Mattis, memory score	21.44 ± 3.28	22.25 ± 2.28
GrB, free recall total score	15.77 ± 8.13	18.50 ± 8.70
GrB, cued free recall	35.11 ± 8.82	38.00 ± 9.83
GrB, delay free recall	4.33 ± 2.45	5.50 ± 4.36
GrB, delay cued free recall	12.00 ± 2.78	13.00 ± 3.46

**Table 2** Gait performances in simple task (ST) and dual task (DT) of MCI+ patients and MCI- patients and respective *p* value obtained using the *U* test of Mann–Whitney

Gait's parameters	Gait of MCI+ (N = 15), mean ± SD	Gait of MCI- (N = 8), mean ± SD	<i>p</i> value
Speed in ST (m/s)	1.15 ± 0.13	1.29 ± 0.10	<b>0.017</b>
Regularity in ST	286.20 ± 37.45	298.0 ± 22.46	0.196
Symmetry in ST	219.47 ± 36.92	269.13 ± 69.86	0.061
Speed in DT (m/s)	1.01 ± 0.18	1.18 ± 0.12	<b>0.036</b>
Regularity in DT	220.67 ± 254.88	254.88 ± 32.86	0.129
Symmetry in DT	220.60 ± 66.78	201.13 ± 28.03	<b>0.039</b>

Bold values indicate *p* < 0.05

Moreover, the regularity is lower in MCI+ than in MCI-, but the difference is not statistically significant.

## Discussion

The results of this pilot study highlight the interest of accelerometric measurements of gait to help the early detection of MCI at risk of developing AD, especially according to the gait speed and its symmetry. According to the recent literature, we would discuss the interest to study the gait speed, the use of a DT and the interest to consider the variability of gait.

Concerning the gait speed, in this study, MCI patients who develop AD have a lower gait speed (in ST and in DT) than those who do not. Our results are convenient with those obtained in different cohort included in prospective

study with dementia as clinical outcome [2, 7, 8]. Actually, these previous studies highlight the interest of gait speed essentially concerning the risk of vascular dementia. According to JM Hausdorff [34], imaging studies and pathology studies highlight the presence of vascular burden and AD lesions even in older people without clinical signs of dementia. According to Verghese [35], studying gait speed of an old person already presenting a mild cognitive decline could help to detect people at risk to develop dementia. The main idea of the concept of MCR is that the motor dysfunction and the cognitive decline are both sign of the same pathological process including diffuse lesions in the brain leading to dementia. This MCR concept has already shown its association with cognitive decline in a wider cohort [36]. Unfortunately and according to our knowledge, no published data shows a strong relation between slow gait speed and specific risk to specifically

develop AD. Then, a strict comparison of our results to previous literature is still limited.

Concerning the use of a DT, in this study, all MCI people show worse gait performances in DT comparing in ST. These results are similar to those found by Montero-Odasso and Muir using a GaitRite system, and showing the importance of executive function and working memory considering gait performances in DT [37, 38]. Concerning the variability of the gait, and as explained previously, the parameters available with the Locometrix<sup>®</sup> are the regularity showing the shape of cranio-caudal acceleration curves from steps and strides, and the symmetry showing the similarity (in terms of duration and amplitude) of the shape of cranio-caudal acceleration curves when comparing right and left steps. In the actual literature [11, 39], the terms used to translate the variability (or the less-regularity) of the gait are more often the “variability of the stride length” or the “variability of the stride time” or the “variability of the step width” as expressed in terms of the coefficients of variation for each term [CV or CoV calculated as  $(SD/mean) \times 100$ ]. According to Moe-Nilssen [40], step time variability seems to be correlated with vertical (cranio-caudal) interstep trunk variability.

Considering that Locometrix, regularity is calculated on cranio-caudal accelerations curves, and considering findings of Moe-Nilssen, the authors allow themselves that the regularity and the symmetry obtained by the Locometrix<sup>®</sup> could represent a translation of the “step time variability”.

In this study, MCI+ group has a lower regularity than MCI- group. And overall, MCI+ group shows a decreasing regularity when walking in DT. Unfortunately, and even if this decreasing regularity in DT seems to be important, the difference between the two groups remains statistically non-significant, probably because of the sample size.

The second parameter showing the variability of the gait using this accelerometer is symmetry. In our study, MCI+ group presents in DT a symmetry significantly lower than MCI- group. This observation can be explained by the way used by the software to obtain the symmetry. Indeed, symmetry is calculated as  $C1/C2 \times 100$ . So the symmetry can increase in case of an increase of C1 or in case of a decreasing C2. This second possibility is probably the best explanation of this decrease of symmetry in DT.

Moreover, the fact that this decrease in C2 is more “numerically important” in terms of symmetry than in terms of regularity, is probably linked to the mean to obtain the regularity [ $(C1 + C2) \times 100$ ], decreasing the relative importance of a decrease of C2.

These results considering the regularity and the symmetry are in the same line that other studies showing an increasing variability of the gait in MCI people at risk to develop AD [2, 17].

This study has a number of limitations and our results have to be considered with caution.

First, the size of the sample is reduced because of the size of the only memory clinic attending, the number of exclusion criteria and the long time of the follow-up. The results presented have to be considered with caution.

Second, a comparison would be interesting between the four sub-types of MCI (anamnestic single domain MCI, amnestic multiple domain MCI, executive single domain MCI and executive multiple domain MCI) but unfortunately this cohort included mainly amnestic MCI whose usually does not present a high level of gait modification. However, considering the fact that FDG-PET scanner realized at inclusion confirmed the neurodegenerative process occurring in the brain and the high level of AD development in this cohort (9 MCI/13 in 3 years), we could consider these MCI particularly “at risk” to develop AD and probably presenting widespread brain lesions. This “at risk” status could probably explain the early gait modifications.

Third, we do not know the time of conversion from MCI to AD, because we do not consider when they develop AD. Finally, only MCI developing AD was considered. MCI developing other dementia, for example, vascular dementia or frontotemporal dementia were excluded.

The strengths of this pilot study include a population strictly selected. Exclusion criteria included a lot of potential confounders as orthopedic prosthesis, previous falls, depression, sedative medication, previous neurologic pathology, clinical neurologic disorders or abnormalities. All subjects attending this study were assessed by a complete neurological, neuropsychological and with a brain FDG-PET scan to confirm the MCI neurodegenerative syndrome. MCI patients included by this way were free of confounders usually met in older people and they were more prompt to develop AD.

Moreover, the length of the straight long corridor used (40 m) allows guaranteeing strong conditions to reliably assess the gait parameters. Indeed, we exclude more than the first 2.5 m of walking to be sure to achieve the steady state walking as recommended by Lindeman [41] and with the guidelines for clinical applications of spatio-temporal gait analysis in older adults from the European Gait Rite Network [42]. Regarding the assessment of gait variability, the same author recommends walking at least 20 gait cycles. In our study, the mean cadence was  $0.89 \pm 0.05$  for the MCI who will develop AD and the cadence of those who will not develop AD was  $0.95 \pm 0.04$ . So, by considering and analyzing period of 20, 48 s., all subjects walked at least 20 gait cycles as recommended [41].

Furthermore these results are really interesting regarding their statistical significance using a non-parametric statistical test.



Further research are needed to confirm these results in bigger sample, including not only amnesic MCI but also executive MCI, and not only considering AD as the only outcome but rather all the cognitive evolutions.

## Conclusion

In this prospective and exploratory study, MCI who will develop AD have lower gait speed, lower symmetry and lower regularity in DT than those who will not develop AD. According with previous literature, and even if this results have to be considered with caution, the gait speed and the parameters showing the variability of gait seem to be important, considering the risk of developing dementia among MCI people.

**Acknowledgments** The authors wish to acknowledge the Professor Olivier Beauchet, from the CHU of Angers in France, for his lecture and his precious advices in the preparation of this paper.

**Conflict of interest** None of the authors have a financial or personal relationship with people or organizations that could inappropriately influence this work.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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