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Hippocampal volume, early cognitive decline and gait variability: Which association?

Olivier Beauchet [a,*], Cyrille P. Launay [a], Cédric Annweiler [a,b], Gilles Allali [c,d]

[a] Department of Neuroscience, Division of Geriatric Medicine, Angers University Hospital, University Memory Clinic of Angers, UPRES EA 4638, University of Angers, UNAM, Angers, France
[b] Center for Functional Metabolic Mapping, Robarts Research Institute, Department of Medical Biophysics, Schulich School of Medicine and Dentistry, the University of Western Ontario, London, Ontario, Canada
[c] Department of Neurology, Geneva University Hospital and University of Geneva, Switzerland
[d] Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

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ABSTRACT

Background: In contrast to its prominent function in cognition, the involvement of the hippocampus in gait control is still a matter of debate. The present study aimed to examine the association of the hippocampal volume with mean values and coefficients of variation (CoV) of spatio-temporal gait parameters among cognitively healthy individuals (CHI) and patients with mild cognitive impairment (MCI).
Methods: A total of 90 individuals (47 CHI with a mean age of 69.7 ± 3.6 years and 48.9% women, and 43 MCI individuals with a mean age of 70.2 ± 3.7 years and 62.8% women) were included in this cross-sectional study. The hippocampal volume was quantified from a three-dimensional T_1-weighted MRI using semi-automated software. Mean values and CoV of stride time, swing time and stride width were measured at self-selected pace with a 10 m electronic portable walkway (GAITRite®). Age, gender, body mass index, number of drugs daily taken, Mini-Mental State Examination (MMSE) score, history of falls, walking speed and white matter signal-intensity abnormality scoring with Manolio scale were used as covariates.
Results: Patients with MCI had a lower MMSE score ($P < 0.001$), a higher CoV of stride time ($P = 0.013$) and a lower hippocampal volume ($P = 0.007$) compared with CHI. Multiple linear regression models showed that CoV of stride time was specifically associated with higher hippocampal volume among CHI ($P < 0.05$) but not among patients with MCI ($P > 0.650$).
Conclusions: Our findings revealed a positive association between a greater (i.e., better morphological structure) hippocampal volume and a greater (i.e., worse performance) stride time variability among CHI, but not among MCI individuals.

1. Introduction

The hippocampus is a key human brain region involved in memorization and locomotion (Seidler et al., 2010; Scherder et al., 2007; Lithfous et al., 2013). Atrophy of the hippocampus has been related to memory disorders and diagnosis of mild cognitive impairment (MCI), which is a transitional state between normal cognitive functioning and dementia (Fellgiebel & Yakushev, 2011; Leal & Yassa, 2013; Albert et al., 2011). In Alzheimer's disease (AD), the hippocampus constitutes one of the first brain areas affected by neurodegenerative lesions, causing its atrophy, explaining why hippocampal abnormality is considered as a biomarker of Alzheimer (Albert et al., 2011; Dubois et al., 2014). In contrast to its prominent function in cognition, the involvement of the hippocampus in gait control, and thus in the maintenance of gait stability, is still a matter of debate. For instance and when considering the hippocampal volume, Zimmermann et al. reported a non-significant association between hippocampal volume and stride-to-stride variability, whereas other studies showed a significant negative association (Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014).

Divergence could be due to the studied population and/or the type of spatio-temporal gait parameters examined. Negative results have been found in the unique study that examined both cognitive healthy individuals (CHI) and patients with MCI, whereas all other studies focused on CHI (Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014). In terms of control of gait, gait variability has been identified as an appropriate biomarker for the measure of the cortical control of gait in normal aging and in patients with dementia (Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012). Furthermore, higher (i.e., worse) stride time variability (STV) was specifically associated with lower cognitive performance in episodic memory

* Corresponding author at: Department of Neuroscience, Division of Geriatric Medicine, Angers University Hospital, 49933 Angers Cedex 9, France.
E-mail address: olbeauchet@chu-angers.fr (O. Beauchet).

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and executive function among older community-dwellers without dementia (Beauchet et al., 2014). This finding was confirmed by a meta-analysis underscoring that higher STV was related to both MCI and dementia (Beauchet et al., 2014). In addition, in terms of gait instability, it has been underscored that the general assumption that variability and stability are negatively correlated cannot be a universal rule. Indeed, higher and lower variability have been reported in younger and older CHI with safe gait, this apparent discrepancy being related to the type of gait parameters examined (Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012). In particular, lower STV, intermediate swing time variability and higher stride width variability have been associated with safe gait in CHI (Beauchet et al., 2009a). These results were explained by the fact that these spatio-temporal gait parameters reflect different components of gait control (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013). STV is a marker of the control of rhythmic stepping mechanism, whereas stride width reflects the dynamic postural control, and swing time combines the two previous components of gait control (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013).

To better understand the relationship between hippocampal volume, early cognitive decline and gait variability, there is a need to examine the association of hippocampal volume with specific gait parameters reflecting the different components of gait control such as stride time, swing time and stride width among CHI and patients with MCI. Because it has been shown that patients with MCI present independently a greater gait variability and a lower hippocampal volume compared to CHI (Albert et al., 2011; Dubois et al., 2014; Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014), we hypothesized that higher gait variability would be stronger associated with lower hippocampal volume in MCI individuals compared to CHI. We had the opportunity to test this hypothesis in the "Gait and Alzheimer Interactions Tracking" (GAIT) study, which is a cross-sectional study aiming to compare gait characteristics of CHI and patients with MCI and AD, and to examine the association between gait characteristics and brain morphology. The aim of the present study was to examine the association of the hippocampal volume with stride time, swing time and stride width variability among CHI and individuals with any form of MCI (i.e., amnestic or non-amnestic, and single or multiple domains).

2. Material and methods

2.1. Participants

Between November 2009 and July 2010, 90 individuals (47 CHI and 43 MCI individuals) were recruited in the GAIT study, which is an ongoing study. The study procedure has been previously described in detail (Beauchet et al., 2013). Briefly, all participants were referred for the evaluation of memory complaints at the memory clinic of Angers University Hospital, France. The eligibility criteria were: age 65 years and over, ambulatory, an adequate understanding of French, and no acute medical illness in the past month. For the present analysis, exclusion criteria were: dementia, extrapyramidal rigidity of the upper limbs, neurological and psychiatric diseases other than cognitive impairment, severe medical conditions affecting walking, inability to walk 15 min unassisted, or the presence of depressive symptoms defined by a 4-item Geriatric Depression Scale score above 1 (Shah et al., 1997). All participants received a full standardized medical examination, a neuropsychological and gait assessment, and MRI of the brain. The number of drugs taken daily, and the use of psychoactive drugs (i.e., benzodiazepines, antidepressants, or neuroleptics), antidiabetic drugs, antihypertensive drugs and lipid-lowering drugs were recorded. Antidiabetic, antihypertensive and lipid-lowering drugs were combined into a single category of cardiovascular drugs.

2.2. Neuropsychological assessment

A neuropsychological assessment was performed on each participant during a face-to-face examination by a neuropsychologist. The following standardized tests were used to probe several aspects of cognitive function: MMSE (Folstein et al., 1975), Frontal Assessment Battery (FAB) (Dubois et al., 2000), Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog) (Rosen et al., 1984), Trail Making Test (TMT) parts A and B (Brown et al., 1958), French version of the Free and Cued Selective Reminding Test (Grober et al., 1988; Van der Linden et al., 2004), and Instrumental Activities of Daily Living scale (IADL) (Pérès et al., 2006). The diagnosis of MCI was made during multidisciplinary meetings involving geriatricians, neurologists, and neuropsychologists of Angers University Memory Clinic, and was based on the aforementioned neuropsychological tests, physical examination findings, blood tests, and MRI of the brain. MCI was diagnosed according to the criteria detailed by Dubois et al. (2010). Participants with any form of MCI, amnesic or non-amnesic and affecting single or multiple domains, were included in this study. Participants who had normal neuropsychological and functional performances were considered as cognitively healthy.

2.3. Gait assessment

Spatio-temporal gait parameters including stride time, swing time and stride width were recorded at self-selected usual pace using a computerized walkway with embedded pressure sensors (GAITRite® Gold walkway, 972 cm long, active electronic surface area 792 × 610 cm, total 29,952 pressure sensors, scanning frequency 60 Hz, CIR System, Havertown, PA) according to the European guidelines for spatio-temporal gait analysis in older adults (Beauchet et al., 2011; Kressig & Beauchet, 2006). Briefly, the participants were asked to walk at their usual self-selected walking speed in a quiet, well-lit corridor wearing their own footwear. To avoid acceleration and deceleration effects, participants started walking 1 m before reaching the electronic walkway and completed their walk 1 m beyond it. For each parameter, mean value and coefficient of variation (CoV = (standard deviation/mean) × 100) were recorded.

2.4. Hippocampal volume

Imaging of the brain was performed with a 1.5-Tesla MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) using a standard MRI protocol (Dubois et al., 2009) including 3D T_1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) axial images (acquisition matrix = 256 × 256 × 144, FOV = 240 mm × 240 mm × 187 mm, TE/TR/TI = 4.07 ms/2170 ms/1100 ms), and fluid-attenuated inversion recovery (FLAIR) axial images (acquisition matrix = 256 × 192, FOV = 240 mm × 180 mm, slice thickness = 5 mm, slice gap = 0.5 mm, 30 slices, TE/TR/TI = 122 ms/9000 ms/2500 ms).

The volumetric 3D T_1-weighted images were segmented using the FreeSurfer software package (version 5.1.0; 33) to calculate the hippocampal volume. FreeSurfer is a set of tools that automatically segments and labels brain structures based on established processing steps; the technical specifications of these procedures have been described previously (Fischl et al., 2002). Briefly, this processing included removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Jovicich et al., 2006), automated Talairach transformation, segmentation of the sub-cortical white matter and deep gray matter structures (Segonne et al., 2004; Fischl et al., 2004), tessellation of the gray matter/white matter boundary, automated topology correction (Jovicich et al., 2006; Fischl et al., 2001), registration to a spherical atlas (Fischl et al., 1999a), parcellation of the cerebral cortex into units based on gyral and sulcal structures (Segonne et al., 2004; Fischl et al., 1999b), surface inflation and creation of surface-based data (Desikan