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Short report

Default mode network and the timed up and go in MCI: A structural covariance analysis

Gilles Allali[a,b,*], Maxime Montembeault[c,d], Alessandra Griffa[a,e], Olivier Beauchet[f,g,h,i]

[a] Department of Neurology, Geneva University Hospital, University of Geneva, Switzerland
[b] Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA
[c] Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Montréal H3W 1W5, Quebec, Canada
[d] Département de psychologie, Université de Montréal, Montréal H3C 3J7, Quebec, Canada
[e] Institute of Bioengineering, Center for Neuroprosthetics, Ecole Polytechnique Fédéerale de Lausanne (EPFL), Lausanne, Switzerland
[f] Department of Medicine, Division of Geriatric Medicine, Sir Mortimer B. Davis - Jewish General Hospital, Lady Davis Institute for Medical Research, McGill University, Montreal, Quebec, Canada
[g] Dr. Joseph Kaufmann Chair in Geriatric Medicine, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
[h] Centre of Excellence on Longevity of McGill integrated University Health Network, Quebec, Canada
[i] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

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ABSTRACT

Background: The timed up and go (TUG) is a test used to assess mobility in older adults and patients with neurological conditions. This study aims to compare brain gray matter (GM) correlates and structural covariance networks associated with the TUG time in cognitively healthy individuals (CHI) and in patients with mild cognitive impairment (MCI).

Methods: The TUG time was measured in 326 non-demented older community-dwellers (age 71.3 ± 4.5; 42% female) – 156 CHI and 170 MCI. GM covariance networks were computed using voxel-based morphometry with the main neural correlates of TUG for each group as seed regions.

Results: Increased TUG time (i.e., poor performance) was associated with distinct brain volume reductions between CHI and MCI. The covariance analysis showed cortical regions involving the default mode network in CHI and bilateral cerebellar regions in MCI.

Conclusions: GM networks associated with the TUG vary between CHI and MCI, suggesting distinct brain control for locomotion between CHI and MCI patients.

1. Introduction

Motor and cognitive impairments are reported in older adults at the onset of neurodegenerative or vascular brain diseases. The time to perform the timed up and go (TUG) test – a clinical test used in daily practice to assess mobility by measuring the time needed for standing up, walking 3 m, turning, walking back and sitting down (Podsiadlo and Richardson, 1991) – has been related with both cognitive and motor abilities in older adults with and without dementia (Herman et al., 2011; Mirelman et al., 2014). Regarding its easy use and its sensitivity for predicting fall, national organizations, such as the American Geriatrics Society and the British Geriatrics Society, recommend the TUG for initial screening test for falling in older adults (*J. Am. Geriatr. Soc.*, 2001). Brain volume reduction in total gray matter (GM) and specific brain regions, such as right and left hippocampus, have been associated with the TUG among non-demented older adults (Allali et al., 2016). Various neuroimaging methods have studied the brain correlates of locomotion in aging (Holtzer et al., 2014) and in patients with neurological conditions (Allali et al., 2018a). However, the use of GM volume covariance – a method measuring the topographical brain organization – has been poorly studied in the field of age-related changes in locomotion. In a previous study using this methodological approach, we demonstrated that gait speed covaried with a distributed network including the prefrontal cortex and the hippocampus among a cohort of non-demented older adults that combined cognitively healthy individuals (CHI) and patients with mild cognitive impairment (MCI) (Allali et al., 2018b).

In this study, we aim to compare regional GM volume reductions and the related structural covariance networks associated with the TUG

Abbreviations: CHI, cognitively healthy individuals; GM, gray matter; MCI, mild cognitive impairment; ROI, region of interest; TUG, timed up and go

* Corresponding author at: Department of Neurology, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland.
E-mail address: gilles.allali@hcuge.ch (G. Allali).

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time between CHI and patients with MCI. Establishing the GM volume covariance associated with the TUG in CHI and MCI will improve our understanding of the brain networks sustaining the TUG in older adults with early signs of pathological aging.

2. Methods

2.1. Participants

We selected 326 participants (age: 71.3 ± 4.5; 42% female) – 156 CHI and 170 MCI - enrolled in the "Gait and Alzheimer Interactions Tracking" (GAIT) study (Allali et al., 2016), with a measure of the TUG and a brain T1-weighted MRI. The participants were referred to the memory clinic (Angers, France) for a cognitive complaint. Exclusion criteria were an acute medical illness in the past month, neurological and psychiatric diseases other than cognitive impairment, and medical conditions affecting gait, extrapyramidal rigidity of the upper limbs, inability to walk 15 min without any walking aid, dementia, morphological or vascular abnormalities on the MRI. Cognitive status (i.e., MCI and CHI) was defined by the international standard criteria (Winblad et al., 2004), following a comprehensive medical and neuropsychological assessment, at a multidisciplinary meeting. The diagnosis of MCI was established following the Winblad consensus criteria (Winblad et al., 2004). Both amnestic and non-amnestic MCI were combined in the MCI group. The instructions for completing the TUG was standardized and given by a trained evaluator. The participants completed the TUG task once, without any specific training. The TUG was measured at self-selected speed, while the participants have to turn on their preferred side. Fall status was self-reported (retrospectively) and fear of falling was assessed by a single yes/no question: Are you afraid of falling? The Review Board of Angers University Hospital approved the study.

2.2. Neuroimaging protocol and analysis

Imaging was performed with a 1.5 and 3 Tesla MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) following a scanning protocol previously described (Allali et al., 2018b). The structural images were processed using voxel-based morphometry (VBM) implemented in SPM12. First, we investigated the neuroanatomical correlates of TUG in CHI and MCI: TUG was entered as a covariate of interest in two separate multiple regression models (one for CHI and one for MCI) - assuming that increased TUG would be associated with locally decreased GM volumes. Statistical threshold of P-value < 0.05 cluster-corrected was used. Each model was adjusted by age, sex, intracranial volume, white matter abnormalities, and scanner field strength (1.5 T versus 3 T). Then, we investigated the GM structural covariance networks associated with the key anatomical correlates of TUG in each group separately: the peak voxel (highest T value) correlating with TUG for each group in the first analysis was used as region of interest (ROI) to seed GM structural covariance networks in each group separately. Two separate correlation analyses were performed by entering the extracted GM volumes from each ROI as a covariate of interest, as well as the same nuisance covariates as in the first analysis. For each ROI, specific contrasts were set to identify voxels that expressed a positive correlation with the GM volume in the ROI in each group of subjects (controlling for nuisance variables). Correlation maps were thresholded at P-value ≤ 0.05, cluster corrected.

3. Results

The clinical characteristics of MCI and CHI are compared in Table 1.

MCI were slightly older, and slightly less educated than CHI. Gender repartition was similar between both groups. Both groups took similar number of drugs (total number and psychoactive). MCI included less fallers than CHI (faller status was retrospectively reported), while both groups presented similar recurrent fallers. Fear of falling was similarly reported in both groups. MCI performed poorer in term of global cognitive performance, as well as in executive functions in comparison to CHI. The TUG was performed slower in MCI than in CHI (10.4 ± 3.1 s versus 9.5 ± 1.8 s, respectively, P = 0.004).

Table 1
Clinical characteristics of participants (n = 326).

	Individuals		P-value*
	CHI (n = 156)	MCI (n = 170)	
Age (years), mean ± SD	70.4 ± 3.7	72.0 ± 5.1	**0.001**
Female, n (%)	74 (47.4)	63 (37.1)	0.072
Education (1-3)	2.1 ± 0.8	1.8 ± 0.8	< **0.001**
Number of therapeutic classes per day, mean ± SD	2.8 ± 2.6	3.1 ± 3.1	0.301
Number of psychoactive drugs per day, mean ± SD	0.1 ± 0.0.3	0.2 ± 0.4	0.354
Previous fall, n (%)	52 (33.3)	38 (22.4)	**0.035**
Recurrent falls, n (%)	10 (6.4)	5 (2.9)	0.187
Fear of falling, n (%)	17 (10.9)	26 (15.3)	0.256
MMSE score (/30), mean ± SD	28.6 ± 1.4	27.1 ± 1.9	< **0.001**
FAB score (/18), mean ± SD	16.7 ± 1.2	15.5 ± 1.9	< **0.001**

MCI: mild cognitive impairment; CHI: cognitively healthy individuals; SD: Standard deviation; MMSE: Mini mental state examination; FAB: Frontal battery assessment; Education: 1: elementary school, 2: secondary school, 3: university; Previous and recurrent falls: yes/no question (retrospectively); Fear of falling: yes/no question.

* Comparisons based on unpaired t-test or Chi-square test, as appropriate; P-value significant (i.e.; < 0.05) indicated in bold.

A negative correlation between TUG time and GM volume was found in the right inferior frontal gyrus (pars triangularis) in CHI; while the TUG was negatively correlated with the bilateral cerebellum (lobule 8), and the left middle cingulate cortex in MCI (Supplementary Table e-1). The right inferior frontal gyrus (MNI coordinates: 53, 32, 0) selected as ROI for CHI covaried with an extended bilateral fronto-temporo-parietal network including the bilateral precuneus, the cingulate cortex, hippocampus, and the middle temporal gyrus, which are parts of the default mode network (Greicius et al., 2003; Raichle, 2015) (Fig. 1A – Supplementary Table e-2). The left cerebellum (MNI coordinates: −30, −45, −51) selected as ROI for MCI covaried with bilateral cerebellar regions, right middle cingulate cortex, left middle frontal gyrus, right thalamus and precuneus (Fig. 1B – Supplementary Table e-3).

Structural covariance networks obtained by using the right inferior frontal gyrus (pars triangularis) ROI as seed for cognitively healthy individuals (Fig. 1A) and the left cerebellum (Lobe 8) as seed for MCI participants (Fig. 1B).

4. Discussion

This study reveals that increased TUG time (i.e., poor performance) was associated with regional brain volume reductions, which differed between CHI and patients with MCI. GM volume covariance analysis showed pure cortical regions involving the majority of the default mode network in CHI and mainly bilateral cerebellar regions in MCI.

These findings suggest that MCI status is associated with a modification of the brain control of a complex motor task requiring elaborated movement. In CHI, the brain regions associated with the TUG not surprisingly involved the default mode network that has been associated with mobility and cognitive control (Cavanna and Trimble, 2006; Hsu et al., 2014) – in our sample, both cognitive and motor performances were reduced in MCI in comparison to CHI. In patients with MCI, we observed a network comprising cerebellar regions. Changes in the default mode network have been previously observed in patients

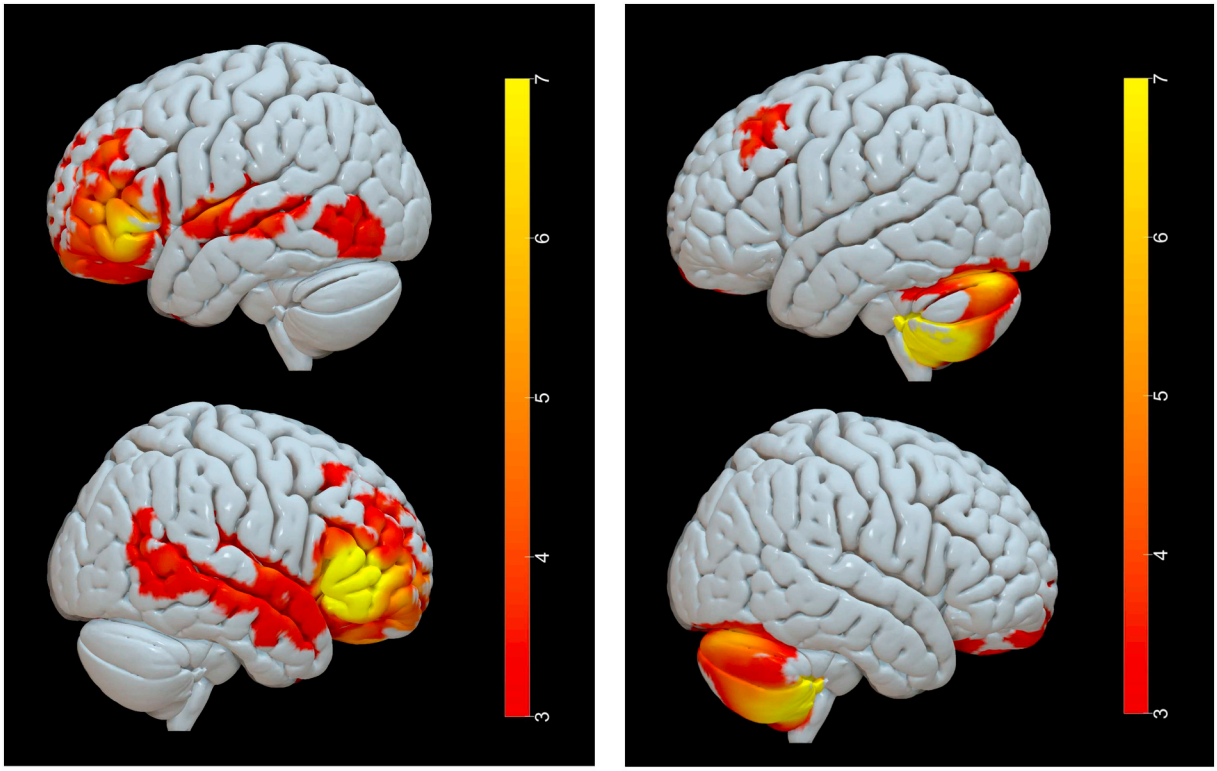

Fig. 1. Structural covariance networks between gray matter volume and timed up and go in cognitively healthy individuals (Panel A) and MCI participants (Panel B).

with MCI in functional studies and have been suggested as an early marker of Alzheimer's pathology (Rombouts et al., 2005). Related to this observation, our MCI patients are more likely to present an underlying Alzheimer's pathology, as they were recruited from a memory clinic. From the perspective of an underlying Alzheimer's pathology in MCI participants, motor disturbances in Alzheimer's disease have been related to degeneration of the cholinergic system (Schirinzi et al., 2018a). The cholinergic system also projects to the cerebellum (Zhang et al., 2016; Schafer et al., 1998); some authors have hypothesized a potential cerebellar cholinergic contribution to motor disturbances, such as dystonia (Schirinzi et al., 2018b). This putative mechanism may explain this cerebellar network associated with TUG performance in MCI participants.

Distinct brain regions are associated with TUG performance between CHI and MCI: a cortical network for CHI and a subcortical one for MCI. Studies conducted in aging or neurological conditions reported contrasting correlations between TUG and cognitive performances (Allali et al., 2012; Sukockien et al., 2019; Ramnath et al., 2018). Although the TUG may be affected by other factors than cognition (i.e. osteoarticular), brain changes associated with cerebrovascular or neurodegenerative processes, as found in patients with MCI, may explain for these contrasting correlations. Furthermore, we should highlight that the instructions for performing the TUG (i.e. self-selected versus fast speed) may affect the underlying brain correlates. Future studies should also include the brain correlates of TUG subtasks (i.e., sit-to-stand, walking, turning), as these subtasks refer to different motor and cognitive domains (Mirelman et al., 2014).

Assessing such a high number of participants while comparing CHI and MCI for a covariance structural analysis of the TUG represents the main strength of this study. However, some limitations need to be acknowledged: first, the generalization of the study findings should be limited to older adults with cognitive complaints; second, although we adjusted our analyses on age, sex, intracranial volume, and white matter abnormalities, some residual potential risk factors might still be present. Third, we also adjusted our analyses on scanner field strength, as we included brain imaging acquired with 1.5 and 3 T scanners. Furthermore, 1.5 and 3 T scanners reported similarities in detecting neurodegenerative changes (Ho et al., 2010); and the validity of automated methods for brain volume measurement between 1.5 versus 3 Tesla scanners has been studied in older subjects scanned the same day on both scanners (Heinen et al., 2016). Four, history of falls was self-reported: we cannot exclude a recall bias among MCI participants that may explain the highest proportion of fallers among MCI. Five, we should highlight that the MCI participants are slightly older than the CHI; however, each model was adjusted by age.

In conclusion, this study – using structural covariance analysis for identifying neuronal networks sustaining the TUG in non-demented older adults – reveals distinct brain regions between CHI and MCI. The default mode network was involved in CHI, while cerebellar network was involved in patients with MCI. These findings provide a rationale for clinical intervention targeting these regions and associated functions to improve locomotion in normal aging and in patients with MCI.

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Declaration of competing interest

None.

Author contribution

Gilles Allali, MD, PhD: Drafting the manuscript; Study concept or design; Analysis or interpretation of data; Obtaining funding. Maxime Montembeault, PhD: Revising the manuscript; Study concept or design; Analysis or interpretation of data; Statistical analysis. Alessandra Griffa, PhD: Revising the manuscript; Analysis or interpretation of data. Olivier Beauchet, MD, PhD: Revising the manuscript; Study concept or design; Acquisition of data; Analysis or interpretation of data; Obtaining funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2019.110748.

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