Research Article

Association of Motoric Cognitive Risk Syndrome With Brain Volumes: Results From the GAIT Study

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Abstract

Background: The “motoric cognitive risk” (MCR) syndrome is a newly reported predementia syndrome combining cognitive complaint and slow gait speed. We hypothesized that individuals with MCR syndrome would have lower brain volumes compared with non-MCR individuals. This study aims (i) to compare the cognitive profile of nondemented older community-dwellers with and without MCR syndrome and (ii) to examine association of global and regional brain volumes with MCR syndrome.

Methods: A total of 171 individuals (28 MCR and 143 non-MCR) were included in this cross-sectional study. Total white matter abnormalities, total white matter, total cortical and subcortical gray matters, hippocampus, motor cortex, premotor cortex, and prefrontal cortex were examined. Brain volumes were quantified from a three-dimensional T1-weighted magnetic resonance imaging using semi-automated software. Age, gender, education level, number of drugs taken daily, use of psychoactive drugs, and cognitive profile were also measured.

Results: The distribution of cognitively healthy individuals and those with mild cognitive impairment was not different in participants with and without MCR. Multiple logistic regression models showed that smaller volumes of total gray matter (p = .016), total cortical gray matter (p = .010), premotor cortex (p = .018), prefrontal cortex (p = .026), and dorsolateral segment of prefrontal cortex (p = .032) were associated with MCR status. The premotor cortex presented the highest mean difference for brain regional volume between MCR and non-MCR participants (p = .03).

Conclusions: The findings revealed similar cognitive profile in MCR and non-MCR participants, and MCR-related smaller global and regional gray matter volumes involving premotor and prefrontal cortices, suggesting that the MCR syndrome may predict cortical neurodegenerative dementia more than subcortical dementia.

Keywords: Gait disorders—Motor control—Cognitive disorders—MRI

Cognition and locomotion are two human abilities controlled by the brain (1). Their declines are highly prevalent with physiological and pathological aging, and exceed the simple sum of their respective prevalences, suggesting a complex age-related interplay between cognition and locomotion (1,2).

The “motoric cognitive risk” (MCR) syndrome is a newly reported predementia syndrome combining cognitive complaints with slow gait speed (3). MCR prevalence and incidence are high 9.7% and 65.2/1,000 person-years, respectively (4,5). MCR syndrome, which is a transitional state between normal aging and dementia, predicts the incident onset of dementia (3,4). The uniqueness of MCR syndrome, compared with the other clinical characteristics like cognitive performance on neuropsychological scales and biomarkers of blood or of cerebrospinal fluid used to predict dementia, is that it is...
a clinical syndrome easy to access in large older populations because it does not rely on complex and expensive evaluations (2–5). This latter clinical aspect of MCR syndrome assessment opens up new perspectives in the field of secondary prevention of dementia, which is a key to developing public health-related policies to counter the impressive growth of dementia (6).

There is little information on the cognitive profile among individuals with MCR syndrome (3–5). Furthermore, the clinical subtype of future dementia detected by MCR syndrome is still a matter of debate. Indeed, MCR syndrome was associated with increased risk of both Alzheimer’s disease (AD) and vascular dementia in recent studies (4,5). To better understand the complex relationship between the cognitive decline, the neural substrate (ie, neurodegenerative, vascular, or both) of MCR syndrome and its potential to detect specific subtypes of dementia, there is a need to explore the association between MCR syndrome and brain structures characteristics.

Neuroimaging studies support a common brain substrate for cognition and gait. Three brain regions have emerged as key regions for this close association, namely: the motor cortex, the hippocampus, and the prefrontal cortex (2,7–10). The volume of the motor cortex correlated positively with gait speed (11). Lower hippocampal volume has been related to both memory and gait disorders (2,7–9). Executive functions localized in the prefrontal cortex are also involved in gait control and gait disorders (2,7,9). When exploring the association between MCR syndrome and brain structures, it is important to take into consideration the presence of white matter abnormalities (WMA). WMA is defined as small scattered foci of magnetic resonance imaging (MRI) signal abnormalities (T2 hyperintensities, T1 hypointensities, or increased FLAIR signal) in the cerebral white matter (10). It has been reported that WMA are associated with decline in gait performance in older adults (12–14).

Because MCR syndrome combines both cognitive and gait criteria (3–5) and because the motor cortex, the hippocampus, and the prefrontal cortex are three brain structures associated with both cognition and gait, and that their lower volumes are associated with either lower cognition and/or gait performance (2,7–9,15,16), we hypothesized that older individuals with MCR would have lower brain volumes in these three regions compared with non-MCR individuals. This study aims (i) to compare the cognitive profile in nondemented older community-dwellers with and without MCR syndrome and (ii) to examine the associations of global and regional brain volumes with MCR syndrome.

Methods
Participants
A total of 171 individuals (28 with MCR syndrome and 143 with non-MCR syndrome) were recruited in the “Gait and Alzheimer Interactions Tracking” (GAIT) study, which is an ongoing cross-sectional study conducted in France. This subset of individuals was included between November 2009 and July 2014 and consented to perform a brain MRI. The study design and assessments have been previously described in detail (17). All eligible participants were referred to the memory clinic of Angers University Hospital, France, for an evaluation of cognitive complaints. The GAIT eligibility criteria were aged 65 years and older, community-dwellers, and an adequate understanding of French. Exclusion criteria included acute medical illness in the past month, extrapyramidal rigidity of the upper limbs, neurological and psychiatric diseases other than cognitive impairment, and severe medical conditions affecting gait with an inability to walk 15 minutes unassisted. For the present analysis, we excluded participants with dementia and those with contraindications to MRI. The diagnosis of dementia was made during multidisciplinary meetings involving geriatricians, neurologists, and neuropsychologists of Angers University Memory Clinic and was based on review of all available neuropsychological tests, physical examination findings, blood test results, and applying the NINCDS/ADRDA criteria (18).

Study Assessments
A full-standardized medical examination, neuropsychological evaluation, quantitative gait assessment, and MRI of the brain were performed in all participants. Cognitive complaint was recorded using a standardized questionnaire exploring memory, attention, and executive complaints expressed by the participants and/or by their relatives who accompanied them to the memory clinic. Age, gender, educational level evaluated with the number of years of schooling and categorized by high school level (ie, yes or not), the number of drugs taken daily, which is an objective accessible and inexpensive strategy to assess the morbidity burden among older adults (19), and use of psychoactive drugs (ie, benzodiazepines, antidepressants, or neuroleptics) were recorded. High blood pressure, dyslipidemia, and diabetes were considered to be present if participants took drugs for these chronic diseases on a daily basis and were coded as binary variables (yes vs no). Drugs were recorded during the medical interview. Diabetes was considered to be present if use of oral antidiabetic drugs or insulin were reported. Antihypertensive drugs use was defined by the use of at least one of the following drugs: renin–angiotensin inhibitor agents, beta-blocking agents, diuretics, calcium channel blockers, and/or central antihypertensive agents. The use of any antihypertensive drugs was collapsed into a single “Yes” versus “No” category. Dyslipidemia was defined by the use of lipid-lowering drugs.

Gait speed was measured with 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). A face-to-face neuropsychological assessment was performed with each participant by a neuropsychologist. The following standard-ardized tests were used to probe several aspects of cognitive function: Mini-Mental State Examination (MMSE) (20), Frontal Assessment Battery (FAB) (21), French version of the Free and Cued Selective Reminding Test–Total Recall (FCSRT-TR) (22), the direct (ie, forward) Digit Span (23), Trail Making Test (TMT) parts A and B (24), Stroop (25) and Instrumental Activities of Daily Living scale (IADL) (26). Significant depressive symptoms were defined as a score ≥1 on the 4-item geriatric depression scale (GDS) (27).

MCR Syndrome Diagnosis
The diagnosis of MCR syndrome was made following Verghese and colleagues criteria (3–5): a combination of cognitive complaint with the presence of slow gait and the absence of dementia or mobility disability. As cognitive complaint was the reason for referral to the memory clinic of Angers University Hospital, France, all participants met this criterion. Slow gait speed was defined as gait speed 1 SD or more below age- and sex-appropriate mean values established in the present cohort like in previous studies (3–5). Because dementia was an exclusion criterion for MCR, no included participants were demented.

Although a clinical strength of the MCR concept is that it does not require cognitive tests for diagnosis, participants had a comprehensive neuropsychological assessment that permitted a
classification in cognitively healthy individuals (CHI), amnestic and nonamnestic mild cognitive impairment (aMCI and naMCI). CHI presented normal cognitive function with all cognitive scores at 1.5 SDs or above the age-appropriate means. Participants with aMCI and naMCI were diagnosed when they reported spontaneous cognitive complaints and presented an objective impairment, respectively, in the memory or the nonmemory domains (ie, defined as a score 1.5 SDs or more below the age-appropriate mean), without impairment into the activities of daily living (28).

We adopted this classification because MCI status presents with a variety of symptoms (29). Thus, when memory loss was the predominant deficit, patients were classified as aMCI, and when memory loss was not the predominant symptom and/or was combined with other cognitive dysfunctions, patients were classified as naMCI. This classification was used because aMCI is considered to be a prodromal stage of AD (28).

Brain Volumetry
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 (30) including 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) axial images (acquisition matrix = 256×256×144, FOV = 240×240×187 mm, TE/TR/TI = 4.07/2,170/1,100 ms), and fluid-attenuated inversion recovery (FLAIR) axial images (acquisition matrix = 256×192, FOV = 240×180 mm, slice thickness = 5 mm, slice gap = 0.5 mm, 30 slices, TE/TR/TI = 122/9,000/2,500 ms).

The volumetric 3D T1-weighted images were segmented using the FreeSurfer software package (version 5.1.0) to calculate the brain volumes. FreeSurfer is a set of tools that automatically segments and labels brain structures based on established processing steps as described previously (31). Briefly, this processing included removal of non-brain tissue using a hybrid watershed/surface deformation procedure (32), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter structures (33,34), tessellation of the gray matter/white matter boundary, automated topology correction (32,35), registration to a spherical atlas (36), parcellation of the cerebral cortex into units based on gyral and sulcal structures (33,37), surface inflation, and creation of surface-based data (38). The procedures for the measurement of brain volumes have been validated against histological analysis (39) and manual measurements (40,41). FreeSurfer morphometric procedures have demonstrated good test–retest reliability across scanner manufacturers and across field strengths (42,43). All volumes are expressed in cm³ and correspond to the sum of volumes of right and left brain regions. The following brain volumes were examined: total white matter abnormalities, total white matter, total gray matter, cortical gray matter, and subcortical gray matter. WMA were defined as small scattered foci of MRI signal abnormalities (T1 hypointensities) in the cerebral white matter. In our study, WMA was measured using FreeSurfer. The segmentation process, subsequently extended to label WMA, has been described in detail elsewhere (31). WMA calculated on T1 images with this methods has been shown to be highly correlated with manual and semi-manual measurements from T2/FLAIR (r > .93 when including extreme values; r > .72 when excluding extreme values) (44,45). Based on our a priori hypothesis, four specific regional brain volumes were also measured including hippocampus, motor cortex, premotor cortex, and prefrontal cortex (separated into dorsolateral, orbito, and ventromedial segments). We used bilaterally averaged cortical region analyzed because of the low number of participants in the group of MCR (n = 28) making it non-relevant to separated analyses of right and left sides.

Standard Protocol Approvals, Registrations, and Patient Consents
The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Participants in the study were included after obtaining written informed consent for research. The Angers local Ethical Committee approved the study protocol.

Statistics
The participants’ characteristics were summarized using means and SDs or frequencies and percentages, as appropriate. Participants were classified into MCR and non-MCR groups. Between-group comparisons were performed using unpaired t test, Mann–Whitney, or chi-square test, as appropriate. p Values less than .00179 were considered as statistically significant after adjustments for multiple comparisons (n = 28). Second, multiple logistic regression analyses were performed to examine the association between MCR syndrome (dependent variable) and the global or regional brain volumes (independent variables) adjusted on the total cranial volume (model 1), and on total cranial volume plus participants’ characteristics significantly different or with a tendency to be different (ie, p < .10; number of drugs taken daily, FAB score, ratio score TMT-B/TMT-A, and use of psychoactive drugs) between participants with and without MCR syndrome (model 2). p Values less than .05 were considered as statistically significant for this analysis. To give a better sense of the brain regions contribution to MCR syndrome, we graphed the “mean difference” of each brain regional volume significantly different between participants with and without MCR status. The mean difference is commonly used for meta-analysis of continuous data, which refers to data that can take any value in a specified range. In our study, we used the mean difference to compare the difference of brain volume between participants with and without MCR using fixed-effects meta-analysis strategy. This approach generates a summary measure of the mean difference (95% confidence interval) of brain volumes of MCR and non-MCR participants. Results are presented as forest plots. Heterogeneity between studies was assessed using Cochran’s chi-square test for homogeneity (I²), and the amount of variation due to heterogeneity was estimated by calculating the I². Statistical analyses were performed using the software programs Review Manager (RevMan) version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark). Statistics were also performed using SPSS (version 15.0; SPSS, Inc., Chicago, IL).

Results
Clinical and morphological brain characteristics are presented in Table 1. Both groups (ie, MCR and non-MCR participants) were similar in terms of age, gender, and education level. MCR participants exhibited the same global cognitive function but had a trend for worse executive function (FAB: 15.9 ± 1.5 vs 16.4 ± 1.6, p = .046) compared with non-MCR participants. Furthermore, there was a trend for a higher number of drugs per day in MCR participants compared with non-MCR participants (p = .038). The distribution of CHI, aMCI, and naMCI in participants with and without MCR was similar. The 4-item GDS score was 0 in all participants. Volumes of total cortical gray matter (p = .033), motor cortex (p = .013), premotor cortex (p = .008), prefrontal cortex (p = .035), and dorsolateral segment of prefrontal cortex (p = .025) tended to be
Table 1. Clinical and Brain Structure Volumes of Participants According to MCR Status (n = 171)

<table>
<thead>
<tr>
<th></th>
<th>MCR</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 143)</td>
<td>Yes (n = 28)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD (y)</td>
<td>70.1 ± 4.0</td>
<td>70.6 ± 4.2</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>55 (38.5)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Education1, n (%)</td>
<td>57 (39.9)</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>Number of drugs taken daily, mean ± SD</td>
<td>2.4 ± 2.4</td>
<td>3.7 ± 3.5</td>
</tr>
<tr>
<td>Use psychoactive drugs2, n (%)</td>
<td>22 (15.4)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>High blood pressure3, n (%)</td>
<td>54 (37.8)</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>Dyslipidemia4, n (%)</td>
<td>17 (11.9)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Diabetes5, n (%)</td>
<td>4 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Walking speed (cm/s), mean ± SD</td>
<td>114.7 ± 15.4</td>
<td>80.2 ± 12.4</td>
</tr>
<tr>
<td><strong>Cognitive characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score (/30), mean ± SD</td>
<td>28.0 ± 1.8</td>
<td>27.5 ± 1.8</td>
</tr>
<tr>
<td>FAB score (/18), mean ± SD</td>
<td>16.4 ± 1.6</td>
<td>15.9 ± 1.5</td>
</tr>
<tr>
<td>FCSRT-TR score (/48), mean ± SD</td>
<td>44.4 ± 4.0</td>
<td>44.7 ± 3.4</td>
</tr>
<tr>
<td>Digit Span score6, mean ± SD</td>
<td>5.3 ± 1.0</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>Ratio score TMT-B/TMT-A7, mean ± SD</td>
<td>2.5 ± 1.0</td>
<td>2.2 ± 0.9</td>
</tr>
<tr>
<td>Ratio score Stroop Part III/Part I**, mean ± SD</td>
<td>2.7 ± 0.7</td>
<td>2.8 ± 0.9</td>
</tr>
<tr>
<td><strong>Diagnosis of cognitive status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHI5</td>
<td>68 (47.6)</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>aMCI</td>
<td>23 (16.1)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>naMCI</td>
<td>52 (36.4)</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td><strong>Brain structure volumes (cm³)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cranial volume</td>
<td>1533.3 ± 141.2</td>
<td>1520.7 ± 156.1</td>
</tr>
<tr>
<td>Total white matter abnormalities8†</td>
<td>2.9 ± 2.2</td>
<td>4.9 ± 7.4</td>
</tr>
<tr>
<td>Total white matter</td>
<td>465.4 ± 55.4</td>
<td>454.5 ± 52.4</td>
</tr>
<tr>
<td>Total gray matter</td>
<td>585.8 ± 50.0</td>
<td>560.3 ± 53.4</td>
</tr>
<tr>
<td>Total cortical gray matter</td>
<td>419.5 ± 38.7</td>
<td>397.8 ± 43.2</td>
</tr>
<tr>
<td>Total subcortical gray matter</td>
<td>108.0 ± 63.3</td>
<td>93.5 ± 60.4</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>7.5 ± 1.0</td>
<td>7.2 ± 1.1</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>8.3 ± 1.2</td>
<td>7.7 ± 1.1</td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>32.2 ± 4.5</td>
<td>29.5 ± 4.3</td>
</tr>
<tr>
<td>Prefrontal cortex9‡</td>
<td>61.9 ± 6.4</td>
<td>58.5 ± 6.9</td>
</tr>
<tr>
<td>Orbital segment</td>
<td>38.6 ± 4.7</td>
<td>36.2 ± 4.8</td>
</tr>
<tr>
<td>Ventromedial segment</td>
<td>13.7 ± 1.3</td>
<td>13.2 ± 1.5</td>
</tr>
</tbody>
</table>

Notes: aMCI = amnestic mild cognitive impairment; CHI = cognitively healthy individuals; FAB = Frontal Assessment Battery; FCSRT-TR = Free and Cued Selective Reminding Test-Total Recall; MCR = motoric cognitive risk syndrome; MMSE = Folstein Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment; TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B.

* Comparison based on independent t test, Mann–Whitney test, or chi-square test, as appropriate.
† High school level.
‡ Use of benzodiazepines or antidepressants or neuroleptics.
§ Defined by daily taking on a daily basis an antihypertensive, lipid-lowering drugs, or antidiabetic drugs, respectively.
** Values less than .00179 considered as statistically significant (cutoff value corresponding to an adjustment on the number of comparisons performed [n = 28]).
†† Total number of digits that a participant can absorb and recall in correct forward serial orders after hearing them.
†‡ Times to “connect-the-dots” as quickly as possible of 25 consecutive targets on a sheet of paper; part A the targets are numbers, and part B alternated numbers and letters.
** Ratio score Stroop Color Word test Part III/Part I (Part I corresponding to time to name color, and Part III corresponding to time to name the color of incongruent color words).
‡‡ Defined as MRI signal abnormalities (T1 hypointensities) and measured using FreeSurfer.

smaller in MCR participants compared with non-MCR ones. There was no significant difference for the other characteristics.

Multiple logistic regression analyses showed that smaller volumes of total gray matter (p < .017), of total cortical gray matter (p < .011), of premotor cortex (p < .019), of prefrontal cortex (p < .027), and of dorsolateral segment of prefrontal cortex (p < .033) were significantly associated with MCR syndrome whatever the adjustment, except for motor cortex in which significant association was found with model 1 (p = .007) but only a trend was seen in model 2 (p = .080; Table 2). No other significant associations were reported.

Figure 1 shows that the highest mean difference for brain regional volume between MCR and non-MCR participants was with the premotor cortex (p = .03).
Discussion

Our findings show that MCR participants did not differ in terms of cognitive profile but had smaller cortical gray matter volume compared with non-MCR ones. The gray volume reduction specifically affected the premotor and prefrontal cortices, and more precisely its dorsolateral segment. A borderline association was seen with the motor cortex, which did not survive adjustments for covariates. In addition, there was a trend for a greater burden of morbidity (expressed here by the number of daily medications) in MCR participants compared with non-MCR ones.

The main finding of our study is that MCR syndrome was characterized by smaller gray matter volume with no significant white matter difference. As MCR is a newly proposed predementia syndrome, no other study has reported thus far its neural association, making comparisons with previous studies impossible. Nonetheless, these results could provide insights into the clinical subtypes of future dementia detected by this syndrome. Indeed, chronic white matter ischemia due to microvascular disease is reported to contribute to gait disorders (12–14). Finally, we observed that there was no significant difference in terms of cardiovascular risk factors in MCR and non-MCR participants, suggesting no specific exposure to these risk factors for MCR individuals.

On the other hand, the lack of significant hippocampal volume difference in MCR participants compared with controls does not support any specific relationship with AD. Indeed, hippocampal atrophy is usually considered as an early biomarker of AD (46,47). A caveat is that all our controls had cognitive complaints, which has been shown to increase the risk of dementia (41,48,49). Furthermore, it is important to consider that MCR is not solely related to memory disorders as it combines cognitive complaint and slow walking speed (3). The presence of these two components implicates in the pathogenesis of MCR a wider involvement of brain regions not limited to the hippocampus, which is a key brain region for memorization and spatial navigation processes (47–49).

At this point, the present finding supports that MCR syndrome may represent an early stage of cortical dementia that specifically affects the prefrontal cortex, like the frontal variant of AD or dementia with Lewy bodies. As vascular dementia and the frontal variant rationale for the low probability of the involvement of vascular, and in particular of ischemic lesions, in MCR syndrome. Indeed, chronic white matter ischemia due to microvascular disease is reported to contribute to gait disorders (12–14). Finally, we observed that there was no significant difference in terms of cardiovascular risk factors in MCR and non-MCR participants, suggesting no specific exposure to these risk factors for MCR individuals.

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At this point, the present finding supports that MCR syndrome may represent an early stage of cortical dementia that specifically affects the prefrontal cortex, like the frontal variant of AD or dementia with Lewy bodies. As vascular dementia and the frontal variant...
of AD could share similar neuropsychological profiles at disease onset (49), the changes in the prefrontal cortex in MCR syndrome could explain the discrepancies in dementia subtype prediction between the two previous MCR studies that examined the nature of incident dementia following MCR (3,4). Our findings also show MCR-related cortical brain structures association involving two categories of brain regions: those directly and specifically involved in locomotion control, and those involved both in cognition and locomotion control. First, smaller motor and premotor cortex volumes were reported in MCR participants compared with non-MCR ones. The main function of these two brain regions is motor control (2,7). As one of the two components of the MCR definition is slow gait, this association is not surprising (3–5). Second, reduction in prefrontal cortex volume, and more specifically in its dorsal-lateral segment, was reported in our study. This brain region has been identified as a key region supporting executive functions involved in memory process (1,2,7,10). Furthermore, converging reports suggested that executive functions also contribute closely to gait control (1,2). Thus, the combined abilities of prefrontal cortex—locomotion and cognitive function—are in concordance with this result as the two components of MCR are cognitive complaints and slow gait (3–5).

In terms of cognitive functioning, MCR and non-MCR participants exhibited similar cognitive performances, with a trend for a lower FAB score in participants with MCR syndrome compared with non-MCR participants, which is a global measure of executive functions (21). Using a quantitative approach measuring the association between total FAB score and brain perfusion assessed by SPECT, a previous report showed that the total FAB score was specifically associated with the dorsolateral segment of the prefrontal cortex (50). This result supports the findings of the present study that smaller volume of the dorsolateral segment of the prefrontal cortex was associated with the MCR group, in which the participants exhibited worse FAB score. Interestingly, in the initial validation study of the MCR syndrome (3), MCR and non-MCR individuals differed on the global cognitive functioning, assessed by the Blessed test (51), but also on the subtests of executive functions and memory. The discrepancy with the present study, in which only the total FAB score was different between the two groups, could be explained by the specific characteristics of the studied population: all included participants of the present study were referred for the assessment of a cognitive complaint to the memory clinic, whereas the participants enrolled in the validation study (3) were community-residing older adults with a broader array of cognitive status and complaints recruited in the Einstein Aging Study.

Finally, our findings show that there was a trend for a greater number of drugs taken per day in MCR compared with non-MCR participants. The number of drugs taken per day is considered as a surrogate measure of morbidity burden in older adults (19,52). Indeed, an association between the Cumulative Illness Rating Scale geriatric form (CIRS-G), which is a scale to use to score morbidity burden, and the number of drug classes daily taken has previously been reported; an increase of three drug classes corresponded to a one-point increase in the CIRS-G score (19). This result is in concordance with the fact that slow gait speed at usual pace, which is one component of MCR, has also been considered as a surrogate marker of health status and a predictor of multiple adverse outcomes in community-dwelling older people (1).

Measuring brain volumes in a large sample of participants to study the association between MCR syndrome and brain volume changes based on a robust a priori hypothesis represents the main strengths of this study.

Some limitations should be considered. First, although this study is the first to report an association between MCR syndrome and brain structure volumes, the cross-sectional design does not afford any causal inference. Only longitudinal designs will allow determination of whether MCR-related lower brain volumes predict the onset of neurodegenerative or vascular dementias. Second, although our single center sample could be considered representative of the patient populations seen in French memory disorders clinics, neural substrates also need to be investigated using neuroimaging methods in other populations and settings. Third, all participants in this study had a cognitive complaint. Thus, the non-MCR participants in this study cannot be considered as strictly cognitively intact. This may also explain lack of significant group differences in our other brain region of interest, such as the hippocampus. Fourth, the prevalence of women in our sample of participants was low (eg, under 40% in both groups) compared with men and also with the classical prevalence of women in population of older community-dwelling population as well as in older adults with cognitive decline (52). It has been reported that sex may influence the morbidity (53,54). Thus, this unusual low prevalence of women in our study that could reflect referral biases in our catchment area could have an impact on the findings.

Conclusion

This study found similar cognitive profile in MCR and non-MCR participants, and MCR-related smaller global and regional gray matter volume involving specific cortical brain areas; premotor and prefrontal cortices. These results suggest that MCR syndrome may be an early stage of neurodegenerative dementia of the cortical type.

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