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Research Article

A Gray Matter Volume Covariance Network Associated with the Motoric Cognitive Risk Syndrome: A Multicohort MRI Study

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Abstract

Background: Motoric cognitive risk (MCR) syndrome is a predementia syndrome characterized by slow gait and cognitive complaint that predicts both Alzheimer's disease and vascular dementia. Yet, we know very little about the brain structures and brain pathologies associated with MCR. The aim of this study was to identify gray matter (GM) networks associated with MCR.
Methods: We used voxel-based morphometry and multivariate covariance-based statistics to identify GM networks associated with MCR in a pooled sample of 267 older adults without dementia from three different cohorts—two North American cohorts and one French cohort.
Results: The mean age of participants was 75.63 years, 50.56% identified as female, 57.68% had ≥13 years of education, and 5.99% had a prior history of stroke. A total of 14.23% participants met criteria for MCR. We identified a significant GM volume covariance pattern that was associated with MCR—even after adjusting for age, sex, education, mild cognitive impairment, stroke, total intracranial volume, and cohort status. This GM volume covariance network was primarily composed of supplementary motor, insular, and prefrontal cortex regions.
Conclusions: These findings suggest that MCR is primarily associated with GM atrophy in brain regions previously linked to the control aspects of gait such as motor planning and modulation rather than the motor aspects of gait such as gait initiation and maintenance.

Keywords: Motor cognitive risk, Slow gait, Cognitive complaint, Gray matter networks.

The motoric cognitive risk (MCR) syndrome is a predementia syndrome that is characterized by slow gait and cognitive complaint and reliably predicts both Alzheimer's disease and vascular dementia (1). Multicountry epidemiological studies suggest that the prevalence and incidence of MCR in older adults are 9.7% and 65.2/1000 person-years, respectively (2,3). The MCR syndrome is also a reliable predictor of mortality (4), and risk factors include increasing age, low education, diabetes, depressive symptoms, self-reported physical inactivity, and prior history of falls and stroke (2,5,6). The clinical utility of MCR is remarkable because, unlike other predementia syndromes such as mild cognitive impairment (MCI), it can be quickly diagnosed in most clinical settings without specialized equipment or personnel.

The brain structures and brain pathologies associated with the MCR syndrome are not well understood. One study links MCR to gray matter (GM) atrophy in premotor and prefrontal—particularly dorsolateral or opercular prefrontal cortex regions (7). Another study suggests that frontal lacunar infarcts are associated with MCR (8). A couple of studies, however, suggest that white matter (WM) hyperintensities are not associated with MCR (8,9). These studies provide initial evidence for both neurodegenerative and some (but not all) vascular brain pathologies, particularly in frontal and prefrontal cortex regions, contribute to MCR.

We have identified three key challenges associated with determining the brain structures and brain pathologies associated with the

MCR syndrome. First, structural and pathological brain measures are influenced by a number of different factors. Both GM atrophy and lacunar infarcts, for example, occur in cognitively healthy older adults (10,11), MCI (12), and Alzheimer's disease (13,14). Second, structural and pathological brain measures are not independent. WM hyperintensities, for example, contribute to GM atrophy in both healthy aging and Alzheimer's disease (15). Third, given a multicountry MCR prevalence of 9.7% (3), large samples and sensitive statistics are needed to identify the brain structures and brain pathologies associated with MCR.

One straightforward solution to these challenges is to collect more data. A less costly and time-consuming solution, however, is to pool already collected data from different cohorts and adjust for major confounders—but at the same time not over-adjusting, or adjusting for variables with a shared causal pathway. Hence, the current study examined GM volume covariance networks (or patterns) associated with MCR in a pooled sample of 267 older adults without dementia from three different cohorts after adjusting for key confounders, including age, sex, education, stroke, total intracranial volume, MCI, and cohort status. Microbleeds may also contribute to MCR and GM volume, but the prevalence of microbleeds is typically low and reliable detection of microbleeds demand nontraditional imaging sequences (susceptibility-weighted imaging)—which were not available in all three cohorts and therefore was not adjusted for in this study (16). We also have some prior evidence that microbleeds, like WM hyperintensities, are not associated with MCR (8). Finally, the current study employed multivariate covariance-based statistics to examine this issue because they largely avoid the multiple comparison problem of traditional univariate analyses and because they are resistant to between-subject variability and collinearity between the volume of different brain regions in general, and neighboring brain regions in particular (17,18).

Methods

Participants

We examined GM covariance networks associated with MCR in a pooled sample of 267 community-dwelling older adults without dementia from three different cohorts: 89 from the Central Control of Mobility in Aging Study (CCMA) in the United States (for additional details see (19)), 89 from the Einstein Aging Study (EAS) in the United States (for additional details see (20)), and 89 from the Gait and Alzheimer and Interactions Study (GAIT) in France (for additional details see (21)). Although we had access to a total of 362 (89 in CCMA, 93 in EAS, and 170 in GAIT) participants, we wanted to reduce potential cohort effects and therefore included all 89 CCMA participants and a random sample of 89 older adults from the EAS and GAIT cohorts in our analyses (Supplementary Material). The CCMA and EAS cohorts were recruited from the community. The GAIT cohort was recruited within the context of a memory clinic. Demographic characteristics of this pooled cohort are summarized in Table 1. Persons with dementia, diagnosed using the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria at consensus clinical case conferences, were excluded from analyses (22).

Motor Cognitive Risk and Other Covariates

The MCR syndrome is characterized by slow gait and cognitive complaint in older individuals without dementia or mobility disability. Gait speed (cm/s) in all cohorts was quantified over a fixed distance (609.60 cm/20 feet) using instrumented walkways (GAITRite System, Clifton, NJ). Slow gait was defined as gait speed one standard deviation or more below age and sex-specific means in each cohort. These cohort-specific slow gait cuts were obtained from a larger number of older adults from the same cohorts (CCMA N = 326; EAS N = 813; GAIT = 354 (2,3)), not only those that had undergone MRI and were included in the current study. Subjective cognitive complaint was obtained from the Geriatric Depression Scale (23) or the Ascertain Dementia 8-item Informant Questionnaire (24) in the CCMA cohort, from a health self-assessment form in the EAS cohort and from a self-report cognitive questionnaire in the GAIT cohort. A strength of the MCR construct is that slow gait is objectively defined and independent of clinical gait evaluations that likely vary across examiners and researcher sites. Moreover, while slow gait is multifactorial, previous research suggests that slow gait is associated with cognitive decline regardless of etiology (25,26). The predictive ability of MCR is also greater than its individual components, even after accounting for overlap with MCI syndrome (3). The presence of MCI, past history of stroke, falls (past 12 months), diabetes, hypertension, and depression were obtained from all cohorts, via a consensus procedure and self-report and/or manual inspection of MRI images in the case of stroke. Stroke was included as a covariate because it likely interferes with GM volume and is associated with MCR (8). A uniform measure of global cognition was not available across cohorts, but the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS (27)) was obtained from the CCMA cohort, the short Blessed (28) from the EAS cohort, and the Mini-Mental Status Exam (MMSE (29)) from the GAIT cohort. Sample characteristics as a function of MCR and cohort status were compared using Student's t-tests or Mann–Whitney tests for continuous variables and Fisher exact test or Pearson χ^2 tests for categorical variables, using STATA version 14.1 (StataCorp LP, College Station, TX). P values < .05 were considered statistically significant.

MRI Data Acquisition

Images were acquired at the Gruss Magnetic Resonance Research Center in the Bronx (CCMA and EAS) or University of Angers Hospital in Angers (GAIT) and transferred to Albert Einstein College of Medicine in the Bronx for processing and analyses. American images were acquired with a Philips 3T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, Netherlands), and French images were acquired with a Magnetom Avanto 1.5T MRI scanner (Siemens Medical Solutions, Erlangen, Germany). Standard three-dimensional T1-weighted images were obtained from all cohorts: (a) CCMA: TR/TE of 9.9/4.6 ms., 240 mm^2 FOV, 240 × 240 × 240 matrix and 1 mm voxel size (for additional details see (19)), (b) EAS: TR/TE of 9.9/4.6 ms., 240 mm^2 FOV, 240 × 240 × 220 matrix and 1 mm voxel size (for additional details see (30)), and (c) GAIT: TR/TE 2170/4.07 ms., 240 mm^2 mm FOV, 256 × 256 × 144 matrix and 1 mm voxel size (for additional details see (7)).

MRI Preprocessing

All T1-weighted images were manually reoriented to the anterior commissure-posterior commissure line and preprocessed using SPM8 (Wellcome Department of Cognitive Neurology) and implemented with MATLAB R2016b (Mathworks, Natick, MA). Voxel-based morphometry was used to segment each image into GM, WM, and cerebrospinal fluid, using the unified segmentation procedure, Diffeomorphic Anatomical Registration Through Exponentiated Line Algebra (DARTEL (31,32)). DARTEL ensures proper inter-subject alignment by modeling the shape of the brain using three

Table 1. Demographic Characteristics and Bivariate Statistics of a Pooled Sample of 267 Older Adults From Three Different Cohorts Overall and as a Function of MCR and Cohort Status

	All (*N* = 267)	MCR (*N* = 38)	Non-MCR (*N* = 229)	*p* value
Age, mean (SD) years	75.63 (6.36)	74.74 (6.56)	75.78 (6.33)	.27
Female, % (*N*)	50.56 (135)	39.47 (15)	52.40 (120)	.14
Education				<.01
≤4 years, % (*N*)	1.12 (3)	0 (0)	1.31 (3)	
5–8 years, % (*N*)	11.61 (31)	31.58 (12)	8.30 (19)	
9–12 years, % (*N*)	29.96 (80)	26.32 (10)	30.57 (70)	
≥13 years, % (*N*)	57.68 (154)	42.11 (16)	59.83 (137)	
Stroke, % (*N*)	5.99 (16)	7.89 (3)	5.68 (13)	.59
Diabetes, % (*N*)	11.24 (30)	5.26 (2)	12.23 (28)	.27
Hypertension, % (*N*)	37.08 (99)	42.11 (16)	36.24 (83)	.49
Depression, % (*N*)	7.12 (19)	13.16 (5)	6.11 (14)	.12
Gait speed, mean (SD) cm/s	102.26 (22.59)	82.07 (22.92)	105.61 (20.77)	<.0001
Falls history, % (*N*)	25.09 (67)	25.76 (8)	21.05 (59)	.54
MCR, % (*N*)	14.23 (38)	N/A	N/A	—
MCI, % (*N*)	12.36 (33)	15.79 (6)	11.79 (27)	.49
	CCMA (*N* = 89)	EAS (*N* = 89)	GAIT (*N* = 89)	*p* value
Age, mean (SD) years	76.07 (5.79)	80.14 (5.04)	70.69 (4.22)	<.001
Female, % (*N*)	52.81 (47)	60.67 (54)	38.20 (34)	<.05
Education				<.001
≤4 years, % (*N*)	0 (0)	2.24 (2)	1.12 (1)	
5–8 years, % (*N*)	2.24 (2)	4.49 (4)	28.09 (25)	
9–12 years, % (*N*)	22.47 (20)	31.46 (28)	35.96 (32)	
≥13 years, % (*N*)	75.28 (67)	71.80 (55)	34.86 (31)	
Stroke, % (*N*)	4.49 (4)	11.24 (10)	2.25 (2)	<.05
Diabetes, % (*N*)	20.22 (18)	10.11 (9)	3.37 (3)	<.05
Hypertension, % (*N*)	39.33 (35)	38.20 (34)	33.71 (30)	.71
Depression, % (*N*)	7.87 (7)	2.25 (2)	11.24 (10)	.06
Gait speed, mean (SD) cm/s	105.17 (23.68)	95.37 (20.89)	106.24 (21.77)	<.001
Falls history, % (*N*)	26.97 (24)	22.47 (20)	25.85 (23)	.77
Global cognition	93.62 (13.29) (RBANS-TOTAL; 40–160)	2.11 (2.32) (Blessed; 0–28)	27.89 (2.01) (MMSE; 0–30)	N/A
MCR, % (*N*)	6.74 (6)	10.11 (9)	25.84 (23)	<.001
MCI, % (*N*)	7.87 (7)	12.36 (11)	16.85 (15)	.19

CCMA = Central Control of Mobility in Aging Study; EAS = Einstein Aging Study; GAIT = Gait and Alzheimer and Interactions Study; MCI = mild cognitive impairment; MCR = motoric cognitive risk; MMSE = Mini-Mental Status Exam; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

parameters for each voxel and simultaneously align GM and WM to produce a study-specific, and increasingly crisp, template to which the data are iteratively aligned. DARTEL produces GM, WM, and cerebrospinal fluid probability maps in the same space as the original T1-weighted images, which were then spatially normalized into Montreal Neurologic Institute space and spatially smoothed with an isotropic Gaussian kernel, full-width at half-maximum = 8 mm. Only GM maps were used in the upcoming analyses.

Multivariate Covariance-Based Analyses

The principal components analysis suite, http://www.nitrc.org/projects/gcva_pca (33) was used to identify GM covariance patterns associated with MCR. These multivariate analyses were adjusted for age, sex, education, total intracranial volume, past history of stroke, MCI, and cohort status (Table 1). First, GM maps were masked with a mask supplied by SPM8 to only include voxels with >20% probability of being GM. After overall participant means were subtracted from each voxel (ie, *Z*-transformed), a principal components analysis was performed, to generate a set of principal components and their associated participant-specific (or pattern) expression scores. A principal component is a set of GM voxels that covary. Participant-specific expression scores reflect the degree to which a participant displays a particular component or pattern. A GM covariance pattern associated with MCR was then computed by regressing participant-specific factor scores from the best linear combination of principal components, selected using the Akaike information criteria, against MCR. The stability of the voxels in this GM covariance pattern was then tested using 1000 bootstrap resamples. Voxels with bootstrap samples of $[Z] > +1.96$ or < -1.96, $p < .05$ (.025 in each tail) were considered significant. Within the context of the current analyses, significant voxels are key "nodes" in the GM volume covariance "networks" associated with MCR (33). A voxel with a positive weighting (*Z* value) has a relatively greater value within the respective network, while a voxel with a negative weighting (*Z* value) has a relatively lower value within the respective network. Within the context of the current analyses, positively weighted regions show relatively *more volume* (*less atrophy*) while negatively weighted regions show relatively *less volume* (*more atrophy*) as a function of MCR.

Results

Overall sample characteristic and as a function of MCR and cohort status are summarized in Table 1. The prevalence of MCR in the pooled sample was 14.23% (*N* = 38), including 6.74% (*N* = 6) from the CCMA cohort, 10.11 % (*N* = 9) from the EAS cohort, and 25.84 % (*N* = 23) in the GAIT cohort. The mean age was 75.63 years, 50.56% identified as female, 57.68% had ≥13 years of education, and 6.0% had a prior history of stroke. Measures of global cognition were indicative of normal cognition in the CCMA (RBANS total:

M = 93.62, *SD* = 13.29), EAS (short blessed: *M* = 2.11, *SD* = 2.32), and GAIT (MMSE: *M* = 27.77, *SD* = 1.95) cohorts. Although age, sex, education, past history of stroke, diabetes, and MCR status (but not MCI status, falls, or depression) differed between cohorts, participants with and without MCR in the pooled sample were comparable in terms of age, sex, past history of stroke, falls, diabetes, hypertension, depression, and MCI status. Participants with MCR, however, had lower levels of education than participants without

Table 2. Gray Matter Volume Covariance Network Associated With Mild Cognitive Risk (MCR) in a Pooled Sample of 267 Older Adults From Three Different Cohorts—After Adjusting for Age, Sex, Education, Total Intracranial Volume, Past History of Stroke, Mild Cognitive Impairment (MCI), and Cohort Status

Brain regions	*X*	*y*	*z*	*z* value	*k*
Positive					
Cerebellum (IV, V)	20	−51	−20	2.6477	17,703
Cerebellum (IV, V)	−14	−54	−19	2.5127	4,490
Inferior temporal gyrus	−51	−55	−9	2.4422	301
Inferior temporal gyrus	53	−48	−11	2.3274	291
Parahippocampal gyrus	18	−36	−4	2.3254	176
Temporal pole (middle)	23	8	−38	2.1451	121
Temporal pole (middle)	48	−56	0	2.0972	55
Precuneus	9	−64	45	2.0530	92
Cerebellum (Crus I)	−27	−78	−22	2.0486	192
Inferior frontal gyrus (orbital)	22	22	−18	2.0147	7
Middle temporal gyrus	−47	−63	1	1.9991	15
Middle cingulum	11	−35	43	1.9961	14
Middle occipital gyrus	−36	−62	34	1.9880	4
Middle occipital gyrus	37	−72	18	1.9764	8
Middle temporal gyrus	−47	−52	8	1.9708	4
Brain regions	x	y	z	z value	K
Negative					
Inferior frontal gyrus (orbital)	47	19	−9	−2.7458	3,893
Insula	−36	18	14	−2.7080	1,108
Inferior frontal gyrus (opercular)	41	13	13	−2.6935	1,194
Supplementary motor	−11	−4	52	−2.6096	495
Inferior temporal gyrus	−38	−15	−10	−2.5598	542
Superior frontal gyrus (medial)	0	62	7	−2.4682	1,489
Superior temporal gyrus	−46	6	−7	−2.4503	1,894
Inferior frontal gyrus (triangular)	39	29	9	−2.4239	238
Rolandic operculum	−47	−21	23	−2.3956	119
Precentral gyrus	−30	−12	59	−2.3794	715
Superior temporal gyrus	18	−5	−8	−2.3258	191
Supplementary motor	−8	−12	65	−2.3171	110
Superior frontal gyrus	33	−6	66	−2.3157	632
Supplementary motor	13	−3	51	−2.3003	45
Inferior frontal gyrus (orbital)	−3	30	−30	−2.2911	117
Middle frontal gyrus	−25	24	52	−2.2235	145
Superior frontal gyrus (medial)	−10	26	46	−2.2150	441
Inferior frontal gyrus (orbital)	−20	21	−8	−2.1686	52
Temporal pole (superior)	−44	25	−26	−2.1598	48
Middle frontal gyrus	49	52	3	−2.1265	114
Inferior frontal gyrus (triangular)	−49	25	30	−2.1252	105
Superior frontal gyrus	21	−3	57	−2.1136	163
Superior frontal gyrus	−17	20	53	−2.0758	34
Putamen	−22	11	14	−2.0710	40
Precentral gyrus	−49	11	42	−2.0706	20
Superior temporal gyrus	13	23	41	−2.0642	12
Middle frontal gyrus	29	41	43	−2.0413	28
Superior frontal gyrus	33	65	3	−2.0178	26
Postcentral gyrus	−48	−5	41	−2.0154	19
Inferior frontal gyrus (opercular)	54	18	28	−2.0125	35
Postcentral gyrus	−52	−9	23	−2.0026	8
Supplementary motor	15	4	−16	−1.9935	6
Temporal pole (superior)	−35	16	−24	−1.9904	7
Supplementary motor	14	10	58	−1.9853	9

Brain regions with positive (relatively less atrophied) and negative (relatively more atrophied) pattern weights as a function of MCR status are listed. Threshold $z = \pm 1.96$, $p < .05$, $k > 4$.

MCR ($p < .01$). Only 6 of the 38 participants (15.8 %) with an MCR classification also had an (amnestic or nonamnestic) MCI diagnosis.

The GM volume covariance pattern—that is, the best linear combination of principal components (ie, with the lowest Akaike information criteria) associated with MCR, after adjusting for age, sex, education, total intracranial volume, stroke, MCI, and cohort status—was composed of four principal components and accounted for 12% ($R^2 = .12$) of the variance. Positively weighted regions—or relatively less atrophied regions as a function of MCR—included cerebellar (IV, V, and Crus 1), inferior and middle temporal, parahippocampal, and precuneus regions (Table 2; Figure 1). Negatively weighted regions—or relatively more atrophied regions as a function of MCR—included precentral (motor), supplementary motor, insular, and superior (medial) and inferior (orbital, opercular, and triangular) prefrontal cortex regions (Table 2; Figure 1).

Discussion

This is the first study to evaluate GM volume covariance networks associated with MCR. In secondary analyses of a pooled sample of 267 older adults without dementia from three different cohorts, we identified a GM covariance network associated with MCR, which was primarily composed of cerebellar, inferior temporal, parahippocampal, motor, supplementary motor, insular, and (medial, orbital, opercular, and triangular) prefrontal cortex regions. Within this network, there was relatively more GM atrophy as a function of MCR in supplementary motor, insular, and prefrontal cortex regions, and relatively less GM atrophy in cerebellar, temporal, and parahippocampal regions. These findings are consistent with a previous study that linked MCR to GM atrophy in dorsolateral or opercular prefrontal cortex regions (7) using a traditional univariate statistical approach but also extend them by showing that GM volume in a more distributed network of brain regions is associated with MCR in older adults. Follow-up analyses aimed at identifying a GM covariance network associated with slow gait alone further suggest that the GM atrophy observed as a function of MCR status is similar, yet more specifically tied to supplementary motor, insular, and prefrontal cortex regions than the GM atrophy observed as a function of slow gait in general (see Supplementary Material). Finally, the GM covariance network associated with MCR observed in the current study was more restricted than the GM covariance network associated with gait speed that was recently observed in the same equally weighted pooled cohort of 267 older adults that included considerable cortical and subcortical regions (34).

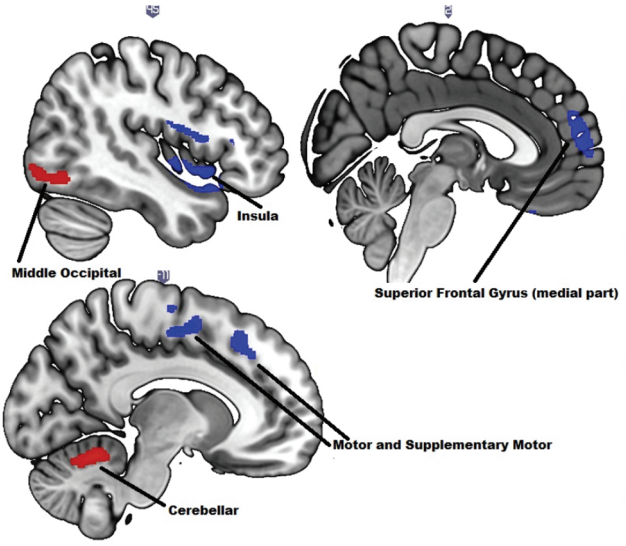

Figure 1. Gray matter volume covariance network associated with MCR in 267 older adults from three different cohorts. Positively weighted regions are displayed in red, implying relatively larger volumes (less atrophy) in the network associated with MCR. Negatively weighted regions are displayed in blue, implying relatively smaller volumes (more atrophy) in the networks associated with MCR. Threshold $Z = \pm 1.96$, $p < .05$.

Human locomotion can be broadly considered to engage two distinct, yet interacting, neural pathways (35–37). The motoric pathway— involved in the motoric aspects of gait such as *gait initiation* and *maintenance*—originates in the motor cortex and directly activates central pattern generators in the spinal cord, before relaying information back to the motor cortex via the brain stem, cerebellum, and basal ganglia. The control pathway—involved in the "cognitive" or control aspects of gait such as *motor planning* and *modulation*—originates in supplementary motor regions and relays information to the brain stem and spinal cord via the basal ganglia, where it is integrated with information from the cerebellum, and relayed back to supplementary motor regions. The novel finding that GM atrophy in MCR was most pronounced in supplementary motor, insular, and prefrontal cortex regions suggest that the control aspects of gait are more affected by MCR than the motoric aspects of gait. Note that the primary role of insular brain regions is limbic (eg, drives and emotions), yet more recent studies have shown that insular brain regions play an important role in cognitive control and attentional processes as well as memory awareness (38,39). Note also that although atrophy was most pronounced in the control pathway of human locomotion, regions typically attributed to the motor pathway such as cerebellar regions IV and V (40) were also components of the GM covariance networks associated with MCR, yet was associated with relatively less atrophy.

There are important strengths and weaknesses of the current study. Identifying GM volume covariance networks associated with MCR in a randomly created, and equally weighted, pooled sample of older adults without dementia from three different cohorts—with a consistent, appropriately adjusted, yet sensitive, multivariate statistical approach—are the key strengths of this study. This approach allowed us to identify a fairly distributed network of GM volume associated with MCR and explore regions within this network that were particularly affected by MCR. Secondary analyses to identify GM volume covariance networks associated with MCR in a pooled sample of older adults from different cohorts also introduces variability that is difficult to adjust for with any statistical approach—including variability in MRI acquisition specifics, sample characteristics, and the classification of MCR between different study sites. Identifying GM covariance networks associated with MCR in a cross-sectional sample of older adults also limits our interpretation of how this GM volume covariance network associated with MCR changes over time in older adults with and without MCR. Thus, future studies are needed to determine the reliability of this GM volume covariance network linked to MCR in different populations and to examine changes to this network as a function of MCR status.

Conclusion

This study suggests that the MCR syndrome is associated with relatively more GM atrophy in brain regions previously linked to the more "cognitive" or control aspects of gait such as motor planning and coordination—particularly supplementary motor, insular, and prefrontal cortex regions—than the motor aspects of gait such as gait initiation and maintenance.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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