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RESEARCH ARTICLE

Discovering subtypes with imaging signatures in the Motoric Cognitive Risk Syndrome Consortium using weakly supervised clustering

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ABSTRACT

INTRODUCTION: Understanding the heterogeneity of brain structure in individuals with the Motoric Cognitive Risk Syndrome (MCR) may improve the current risk assessments of dementia.

METHODS: We used data from six cohorts from the *MCR consortium* ($N = 1987$). A weakly-supervised clustering algorithm called HYDRA (Heterogeneity through Discriminative Analysis) was applied to volumetric magnetic resonance imaging (MRI) measures to identify distinct subgroups in the population with gait speeds lower than one standard deviation (1SD) above mean.

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RESULTS: Three subgroups (Groups A, B, and C) were identified through MRI-based clustering with significant differences in regional brain volumes, gait speeds, and performance on Trail Making (Part-B) and Free and Cued Selective Reminding Tests.

DISCUSSION: Based on structural MRI, our results reflect heterogeneity in the population with moderate and slow gait, including those with MCR. Such a data-driven approach could help pave new pathways toward dementia at-risk stratification and have implications for precision health for patients.

KEYWORDS
cognitive complaints, dementia, gait, machine learning, MCR, volumetric imaging, weakly-supervised clustering

Highlights

- Different patterns of brain atrophy were observed among the people with moderate and slow gait speeds
- Slower gait speeds were associated with substantial cortical atrophy, higher rates of Motoric Cognitive Risk Syndrome (MCR), and worse cognitive performance
- This approach can aid patient stratification at early asymptomatic stages and have implications for precision health.

1 | INTRODUCTION

Dementia is marked by a progressive cognitive and functional decline. Accessible and informative clinical indicators for identifying individuals at risk of incident dementia could enable targeted, earlier and more effective interventions. Like mild cognitive impairment (MCI), Motoric Cognitive Risk Syndrome (MCR) is a pre-dementia state characterized by subjective cognitive complaints and objectively measured impairment.[1] While MCI is characterized by reduced performance on objective cognitive tests, MCR is characterized by slow gait speed and subjective cognitive impairment.[2] Studies show that MCR is a significant risk factor for dementia in older adults.[3] Compared to MCI, MCR does not require neuropsychological assessments, which are time-consuming. This makes MCR a more efficient and accessible solution for dementia risk stratification in community-dwelling adults and across various settings, from primary care to specialized neurology clinics [4]. Both components of MCR, slow gait and subjective cognitive impairment are independently predictive of future cognitive decline and incident dementia – but the MCR phenotype has higher predictive validity for dementia than either component alone.[5,6]

In older adults, slow gait speed can stem from various factors such as neurological issues, muscle-related conditions, arthritis, or a combination of these factors. Neurodegeneration caused by various dementia etiologies, such as Alzheimer's disease (AD) is considered one of the primary reasons behind declines in both gait speed and cognitive function.[7] The brain regions known to mediate executive functions (EFs), such as the frontal and prefrontal-lobe networks also control gait ability.[8,9] These brain regions are involved in integrating information from many cortical sensory systems, and producing goal-directed actions and behavior.[10] Atrophy in these regions causes both cognitive and gait decline concurrently with the aging process.[11,12] Preliminary intervention trials using cognitive training or brain stimulation to enhance EF have also shown improvements in gait velocity.[13] MCR, despite these shared neuroanatomical pathways, describes people who are still cognitively intact but with cognitive complaints and slowing of gait. The precise neuroanatomical signatures that correspond to the clinical manifestations in MCR, however are unknown. To study the biological underpinnings of MCR, an MCR-neuroimaging consortium was established across seven cohorts across five different countries and three continents, collecting structural MRIs, gait speeds, cognitive assessments, and other clinical symptoms. This consortium provides a valuable opportunity to study neurodegeneration patterns as identified through structural MRIs and to connect these findings with MCR, its components, and other clinical symptoms.

There is substantial neuroanatomical heterogeneity in preclinical stages of dementia.[14] Several studies have linked MCR to specific patterns of brain atrophy, specifically in prefrontal, supplementary motor, insular and motor cortices.[12,15] However, very few data-driven studies have explored the variability of neuroanatomical patterns in MCR and its components.[12] Therefore, in this study, we adopted a data-driven machine learning (ML) approach to investigate structural brain differences among participants in the MCR consortium using volumetric imaging. We employed a novel semi-supervised clustering approach called HYDRA (Heterogeneity through Discriminative Analysis)[16] to identify subgroups with distinct structural brain patterns within the MCR Consortium. Several other approaches were

previously proposed to reveal the inherent disease heterogeneity. But most of these methods either relied on predefined clinical subgroups, ignoring multivariate relationships in the data,[17,18] or applied clustering directly to brain anatomies, risking the identification of normal inter-individual variability which could be due to confounding factors like sex and age rather than disease-specific heterogeneity.[19] The HYDRA method enables us to mitigate these challenges and disentangles the heterogeneity in a population, using another reference population. This was achieved by leveraging data from a reference group composed of individuals with faster gait speeds (population FG, those with gait speed faster than 1 standard deviation (SD) above the population mean within each cohort). Identifying subgroups with homogenous neuroanatomical patterns in a cohort population with gait variability has a potential to further our understanding of biological underpinnings of MCR and in developing interventions for dementia.

RESEARCH IN CONTEXT

1. **Systematic review:** A comprehensive literature review using traditional sources (like PubMed) was conducted. It has been shown that abnormal gait has been shown to be a reliable predictor of non-Alzheimer dementia. The brain regions that are known to control gait ability are also involved in mediating executive function. Cohort-based population studies of the Motoric Cognitive Risk Syndrome (MCR), which is characterized both slow gait speed and subjective cognitive complaints, highlight neuroanatomical heterogeneity in older adults.
2. **Interpretation:** Our results indicated that different gait speeds can be associated with distinct neuroanatomical patterns and that there could be a negative association between gait speed and impairment in executive function and global cognition.
3. **Future directions:** Our results describe the distinct neuroanatomical patterns in a cross-sectional cohort data. These results should be further validated and explored in longitudinal data to understand the patterns of neurodegeneration over time. The analyses must be further developed considering a more detailed account of comorbidities.

2 | METHODS

2.1 | Participants

Data from 2007 older adults in the MCR consortium was examined. The data were obtained from seven different cohorts and five different countries. The cohorts were:(i) the Central Control of Mobility in Aging Study (CCMA)[7,20] in the United States, (ii) the LonGenity study[21] in the United States, (iii) the Einstein Aging Study (EAS)[2] in the United States, (iv) the Tasmanian Study of Cognition and Gait (TASCOG)[22,23] in Australia, (v) the National Center for Geriatrics and Gerontology–Study of Geriatric Syndromes (NCGG-SGS)[24,25] in Japan, (vi) the Kerala-Einstein Study (KES)[26] in India, and (vii) the Gait and Alzheimer's Interactions Tracking study (GAIT)[9] in France. All procedures were approved by the local institutional review boards. All cohorts excluded individuals with prevalent dementia.

Data from all cohorts were used in the analyses. We reserved a subset of population from each cohort as the reference population for the clustering model, that had faster gait speeds (FG).

This analysis was approved by the institutional review board of the Albert Einstein College of Medicine (Bronx, NY). All participating cohorts have received approval from their local ethics committees.

2.2 | Study measures

Data from all cohorts included population demographics. To harmonize these data and address cohort variability, we followed a standardized process for the preparation of each data modality.

2.2.1 | Gait speeds

Gait speed (cm/s) was available in all studies. In all cohorts, except NCGG-SGS, it was quantified over 609.6 cm with GAITRite instrumented walkways (GAITRite System ® Clifton, NJ). In NCGG-SGS, it was quantified over 240 cm with the WalkWay MW-1000 instrumented walkway (Anima Co., Tokyo, Japan). Details of gait speed measurements and quantification were presented in previous studies.[5,27] After normalizing gait speed within each study, individuals with the normalized gait speed greater than 1 SD above the mean were labeled as FG, as 1SD provides clear separation from the "normal to slower gait" study population and a balanced sample size. The study population included the remaining individuals with gait speeds less than 1 SD above population mean (normal and slower gait speeds). The FG participants from all the studies were used as the reference population for the HYDRA clustering algorithm.

2.2.2 | Volumetric MRI

Magnetic resonance imaging (MRI) measures were collected at the respective study sites and harmonized at a single site using the Free Surfer pipeline version 6.0. Details on the specific scanner at each site are provided in Supporting Information. Images were harmonized for the volumetric measures, using the standard parcellation and correction methods, as described in our previous work.[15] For this study, we used the volumetric measures of 41 brain regions (Table S1), and total intracranial volume (tICV). To account for the individual differences in tICV, within each cohort the volume of each region (VR) was normalized

according to the mean tICV of the population within that cohort. The adjusted volume (VRa) of a brain region of an individual was calculated as

$$VRa = (VR/tICV) * mean(tICV)$$

2.2.3 | Neuropsychological evaluations

For the post-hoc analyses of objective cognitive scores of different subgroups obtained in our analyses, we used available neuropsychological scores from different studies, normalized per study wherever applicable. The following were the neuropsychological tests that were used: Trail Making Test, Part B (TMT-B),[28] Stroop Color Word test,[29] and Free and Cued Selective Reminding Test (FCSRT).[30] The details of each test and specific versions are reported in Supporting Information.

2.2.4 | Diagnosis of MCR

MCR is characterized by slow gait and cognitive complaints. Slow gait was defined as gait speed lesser than 1 SD below the age and sex-specific means in each cohort [31] (see Supporting Information). For our study, subjective cognitive complaint was determined using the memory item from Geriatric Depression Scale (GDS) uniformly in all cohorts[32] or the instrumental activities of daily living (I-ADL),[33] where available in cohorts CCMA and KES.

2.3 | Analytic approach

Figure 1 depicts the study s analytic pipeline. There were 41 brain region volumes available from structural MRI preprocessing using the Free Surfer pipeline. We used factor analyses (FA) to reduce the number of input variables to the clustering model, since some of the brain region volumes are highly correlated and using all of them together in a clustering model may skew and bias the results. FA was performed on the entire study cohort (the combined population of FG and the remaining study population) to ensure that the identified latent factors and their representative regions captured the overall structural variance present across all participants included in the analysis.

2.3.1 | FA and weakly-supervised clustering

For the FA, we used maximum likelihood estimation and varimax rotation with the 41 regions available as input variables to obtain fewer latent factors relying on a matrix of weights or factor loadings. We choose one variable within each factor that had the highest loading to make the feature set ($Regions_{Factor}$) for the subsequent clustering model. Though other methods exist using representative loadings from each factor, using one high factor loading (e.g., |0.4| or higher) indicates that a variable strongly represents the underlying factor[34] simplifying inputs to the downstream model and balancing dimensionality reduction with anatomical interpretability. We used a variant of clustering model, a weakly-supervised algorithm called HYDRA, that also considers the characteristics of the FG group with faster gait speeds as reference, such that the population to be clustered can be simultaneously separated from the controls FG while quantifying the heterogeneity within the population through their association to the sub-classifiers that separate them from the reference group.[16] Age and sex were added as covariates in HYDRA, due to their well-established influence on both brain structure and gait speed.[35] More details are reported under Supporting Information.

2.3.2 | Statistical analyses

We examined the descriptive features of the entire population, each cohort, and subgroups resulted from clustering. The demographic variables such as age, sex, education, and ethnicity were included in the descriptive characteristics (see Supporting Information for details).

All the data preprocessing, FA, and HYDRA clustering were performed using Python with scikit-learn library for FA and mlni package for HYDRA clustering.[16] Statistical analyses used R statistical software, version 4.2.2 for MacOS.

3 | RESULTS

3.1 | Population characteristics

A total of 1987 participants were included in the final clustering model after excluding those with missing volumetric MRI data or outliers (mean age [MA], 71.73 ± 6.87 years; 47.7% female). There were 294 participants in the reference FG group (MA, 69.30 ± 5.52 years; 47.3% female) and 1693 participants in the remaining study population (MA, 72.15 ± 6.99 years; 47.8% female). The FG group had younger population compared to the study population ($p < 0.001$, effect size of -0.52). Both groups differed in the mean years of education of the population ($p = 0.03$, effect size of 0.14). There was no sex differences found between the groups. Both groups did not significantly differ in cohort membership. The reference group FG differed from the study population in the proportion of participants with MCR diagnosis as defined by 'slow gait', depending on threshold specific to the cohort, and subjective cognitive complaint as determined by either GDS or ADL (3.3% in the FG group, 13.3% in the study population, $p < 0.001$) (see Table 1).

3.2 | Factor analyses

We found 8 factors and conducted FA with them. Table S1 summarizes the factor loadings of each variable for all eight factors. For simplicity, we presented only those variables which had loadings of at least 0.4 in any factor. We chose one variable (region) from each factor that had the highest loading as the input for clustering model. The eight regions

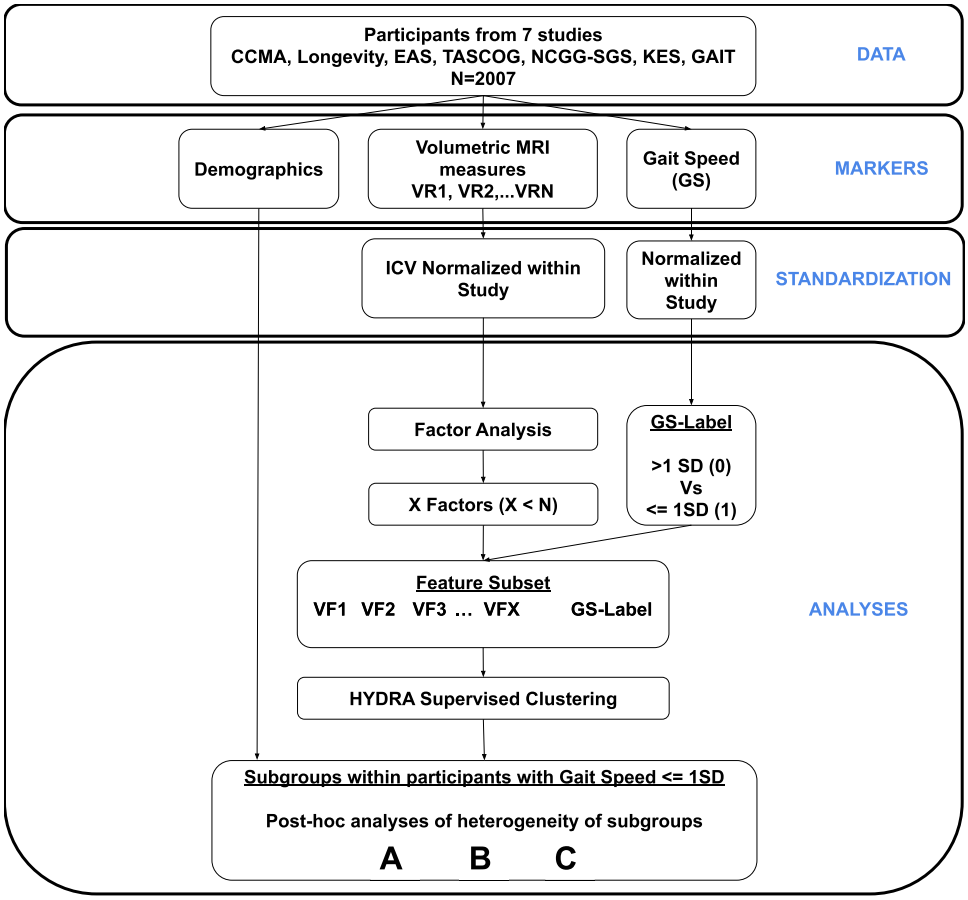

FIGURE 1 Plan of our study. CCMA, Central Control of Mobility in Aging Study in the United States; the LonGenity study in the United States; EAS, Einstein Aging Study in the United States; TASCOG, Tasmanian Study of Cognition and Gait in Australia; NCGG-SGS, the National Center for Geriatrics and Gerontology–Study of Geriatric Syndromes in Japan; KES, Kerala-Einstein Study in India; and GAIT, the Gait and Alzheimer's Interactions Tracking study; ICV, intracranial volume; MRI, magnetic resonance imaging; SD, standard deviation.

TABLE 1 Study characteristics.

Parameter	All participants	FG	Group A	Group B	Group C	*p*-Value
N	1987	294	585	455	653	
Age, mean (SD), y	71.73(± 6.87)	69.30(± 5.52)	72.07(± 6.80)	70.94(± 6.77)	73.06(± 7.18)	<0.001
Sex, female (%)	948(47.7%)	139(47.3%)	277(47.4%)	229(50.3%)	303(46.4%)	0.625
Education, mean (SD), y[#]	12.30(± 3.50)	12.73(± 3.70)	12.27(± 3.51)	12.39(± 3.22)	12.08(± 3.56)	0.08
Race/ethnicity, N(%)						0.016
Asian	1146(57.7%)	176(59.9%)	329(56.2%)	282(62.0%)	359(55.0%)	
White	769(38.7%)	112(38.1%)	225(38.5%)	160(35.2%)	272(41.7%)	
Other*	59(3.6%)	2(2.0%)	27(5.3%)	9(2.8%)	21(3.3%)	
Gait speed, cm/s	108.42(± 22.85)	141.21(± 11.52)	104.91(± 17.05)	103.79(± 18.28)	100.04(± 21.34)	<0.001
MCR, Positive**, N(%)	117(6.6%,N = 1778)	–	38(7.4%,N = 515)	26(6.4%,N = 405)	53(9%,N = 588)	<0.001

Abbreviations: FG, fast gait, a subgroup of participants with gait speed greater than 1 standard deviation above mean; Groups A,B, and C, gait speed lower than 1 SD above cohort specific mean; Subgroups obtained by the clustering model. *p*-Values reported for significant differences between FG and Subgroups

[#]Education was not available for the GAIT cohort.

*Other in race/ethnicity included primarily Black (3.0% of total population), Hispanic Black, Hispanic White and others.

**MCR positive is defined as slow gait (as defined by a cohort specific threshold) and any cognitive complaint in Geriatric Depression Scale (GDS) or activities of daily living (ADL) questionnaire.

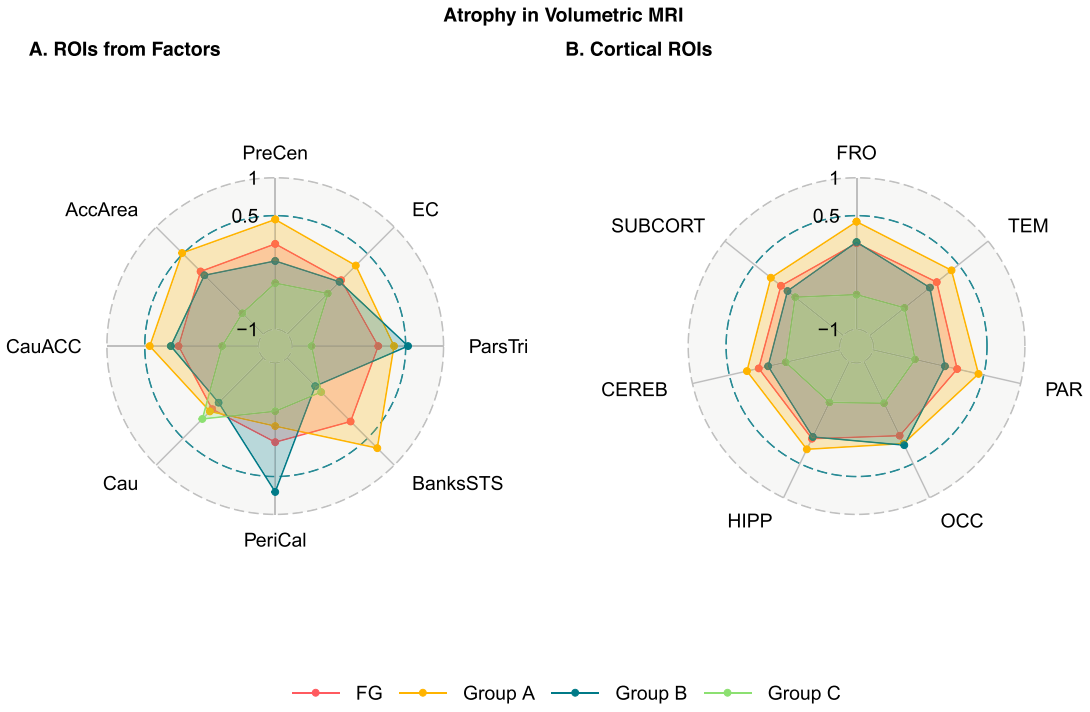

FIGURE 2 Subgroup differences in MRI volumes by regions: group differences in MRI volumes. PreCen, precentral gyrus; EC, entorhinal cortex; ParsTri, pars triangularis; BanksSTS, banks of superior temporal sulcus; PeriCal, pericalcarine; Cau, caudate nucleus; CauACC, caudal anterior cingulate; AccArea, nucleus accumbens; FRO, frontal cortex; PAR, parietal cortex; TEM, temporal lobe; OCC, occipital lobe; HIPP, hippocampus; CEREB, cerebellar cortex; SUBCORT, subcortical regions (basal ganglia nuclei, amygdala, thalamus.

that were chosen to be the input features for the clustering model, $Regions_{Factor}$ were the following: accumbens area, caudate, banks of the superior temporal sulcus (banksSTS), caudal anterior cingulate, entorhinal cortex, pars triangularis, pericalcarine, and precentral gyrus.

3.3 | HYDRA clustering analyses

We obtained three subgroups within the study population from HYDRA, with an adjusted Rand index (ARI) of 0.1. We performed statistical analyses to assess the differences across the three subgroups, Group A, Group B, and Group C, between each of them as well as with respect to the FG group. Table 1 summarizes population characteristics in each subgroup. Of the 1693 individuals, 585 were grouped under Group A (mean age, 72.07 ± 6.80 years; 47.4% female), 455 were grouped under Group B (mean age ± SD, 70.94 ± 6.77 years; 50.3% female), and 653 under Group C (mean age, 73.06 ± 7.18 years; 46.4% female). The mean gait speed (± SD) in Group A was 104.91(± 17.05), 103.79(± 18.28) in Group B and 100.04(± 21.34) in Group C.

3.4 | Heterogeneity in brain patterns in the MCR Consortium participants

Post-hoc pairwise group comparisons revealed significant differences across the subgroups for most of the regions (Table S2 and Figure S2, Factors). Among all the subgroups, Group A had the highest volumes of accumbens area (mean *z*-score of 0.481 ± 0.140), followed by group FG (0.434 ± 0.126), Group B (0.425 ± 0.106) and Group C (0.329 ± 0.106). Group A had the highest volumes of caudal anterior cingulate (mean *z*-score of 0.513 ± 0.117), followed by Group B (0.478 ± 0.113), FG (0.465 ± 0.126), and Group C (0.392 ± 0.118). Except Groups FG and B, all the pairs of groups differed significantly in their volumes of accumbens area and caudal anterior cingulate ($p < 0.0001$). All the pairs of subgroups differed significantly in their volumes of banksSTS, parstriangularis, pericalcarine, and precentral gyrus. While Group A had the highest volume of banksSTS and precentral gyrus, Group B had the highest volume of parstriangularis and pericalcarine. Group B and FG did not differ significantly in their precentral gyrus volumes.

Next, we combined the brain region volumes into respective cortical, subcortical, and other regions that were generally implied in MCR and dementia, that is, cortical/subcortical (C/S) regions of interest (ROIs) are frontal, temporal, parietal, occipital, hippocampus, cerebellum, and subcortical (basal ganglia nuclei, amygdala, and thalamus). We repeated the analysis of covariance (ANCOVA) analyses and post-hoc pairwise comparisons to examine the differences across the subgroups. Differences in the C/S ROIs between the subgroups are reported in Table S3; Figure S2, Cortical). Group B did not show any significant differences in the volumes of C/S ROIs compared to FG, except in the occipital lobe. Group A showed significant differences in all the C/S ROI volumes compared to Group B, except in the occipital lobe. Group A had the highest volumes across all the C/S ROIs while Group

TABLE 2 Pairwise subgroup differences in gait speed and cognition.

Measure	FG	Group A	Group B	Group C	P-value	Group A—FG	Group B—FG	Group C—FG	Group A—group B	Group C—Group A	Group C—group B
Gait speed (Z-score)	1.531 (± 0.466)	−0.192 (± 0.739)	−0.223 (± 0.793)	−0.364 (± 0.864)	***	***	***	***	0.58	0.003**	0.22
Cognition											
TMT-B	−0.354 (± 0.892)	−0.044 (± 0.905)	−0.066 (± 0.906)	0.174 (± 1.153)	***	0.05*	0.03*	***	0.98	0.02*	0.09
FR96	0.599 (± 0.716)	=	0.148 (± 0.871)	−0.125 (± 1.136)	0.005**	0.95	0.23	0.02*	0.31	0.01*	0.61
Stroop-INT	−0.025 (± 0.918)	0.069 (± 1.175)	0.061 (± 0.923)	0.076 (± 1.122)	0.99	–	–	–	–	–	–

Abbreviation FG, population with fast gait, gait speed greater than 1SD above population-mean; Groups A, B, and C, result of HYDRA Clustering of the remaining population (gait speed slower than 1 SD above population-mean); *p*-value, significance Pr(> F) in ANCOVA corrected for age and sex; Pairwise comparisons: Multiple Comparisons of Means with Tukey Contrasts. TMT-B: Trail Making Test, Part B, log-transformed, z-score normalized, available in CCMA, LonGenity, EAS, NCGG-SGS, Kes and GAIT, Stroop-INT:Stroop Color Word test, consisting of subtests measuring time required to name the colors seen (COLOR), read the given words (WORD) and name the color of the printed word (COLOR_WORD); Stroop-INTthe difference between the third subtask and the first task (COLOR_WORD—COLOR), available in EAS, TASCOG, and GAIT; FR96, Free and Cued Selective Reminding Test (FCSRT), a recall test that uses either words or images. Scores include the sum of free recall (FR) alone (range 0-48) and combined with cued recall as total recall (TR); FR96, the sum of FR and TR (range 0-96); available in CCMA, EAS, and LonGenity.
***p-values < 0.0001.
**p-values < 0.001.
*p-values < 0.01

C had the least. Group C showed significant differences in all the C/S ROI volumes compared to FG, except in the subcortical regions. Group C showed significant differences in the all the C/S ROI volumes compared to Group B, except in the cerebellum and subcortical regions. Finally, Group C and Group A differed across all the C/S ROI volumes.

3.5 | Heterogeneity in gait speeds and cognition in the MCR Consortium participants

Analysis of Covariance (ANCOVA) analyses showed that the subgroups differed in their gait speeds. A post-hoc analysis was performed to evaluate subgroups differences. While Group B did not show a significant difference with either Group A or Group C, the mean gait speed of Group A was higher than that of Group C (−0.192 ± 0.739 vs. −0.364 ± 0.864, $p = 0.003$). In the ANCOVA analyses with each cognitive score as the outcome, all subgroups differed in their TMT-B and FR96 scores but not in their Stroop-INT scores. For TMT-B, the FG group had better scores (mean ± SD: −0.354 ± 0.892) compared to Group B (−0.066 ± 0.906, $p = 0.03$), Group A (−0.044 ± 0.905, $p = 0.05$), and Group C (0.174 ± 1.153, $p < 0.001$). Within the subgroups, only Groups A and C showed a significant difference ($p = 0.02$). Regarding FR96 scores, the FG group had higher scores (0.599 ± 0.716) compared to Group C (−0.125 ± 1.136, $p = 0.02$). Group A also had higher scores (0.389 ± 0.778) compared to Group C ($p = 0.01$). The groups did not show significant differences in their Stroop-Int scores. Table 2 and Figure 3 summarize the ANCOVA and post-hoc pairwise comparison results for gait speed and cognitive scores across the subgroups.

4 | DISCUSSION

The MCR Consortium includes over 2000 MRIs from older adults without dementia from multiple locations worldwide. It provides a valuable repository of neuroimaging and other measures for understanding MCR as a crucial risk factor for dementia. Using a novel data-driven ML approach, we explored the heterogeneity among those with fast and normative gait speeds (slower than 1 SD above the population mean), while accounting for the distinct neuroanatomical patterns that separate each subgroup from the population with fast gait speeds. Among the participants without dementia and gait speeds in the normal to slow range, we found three subgroups which significantly differed in the patterns of brain regional volumes, gait speeds, and cognitive performance (Table 3). Group A had slower gait speeds compared to the reference FG group and largest volumes of cortical and subcortical regions. Group B had intermediate gait speeds and cortical volumes like the reference group. Group C had the slowest gait speeds, the smallest overall regional brain volumes in most brain regions and the highest prevalence of MCR. The subgroups also differed in their performance in TMT-B and FCSRT.

Abnormal gait has been shown to be a reliable predictor of non-Alzheimer's dementia.[36] Since slowing of gait speed precedes cognitive decline,[27] understanding the heterogeneity related to gait speed patterns can be very valuable in characterizing predementia syndromes such as MCR. MCR, which is characterized by slow gait and subjective cognitive impairment, depends on varying thresholds to determine slow gait ranging from 44.4 to101.9 cm/s among men and 36.9 to 97.4 cm/s among women as observed across different study locations.[5] In our analyses, instead of studying abnormal gait using fixed thresholds, we considered a broader group of older population

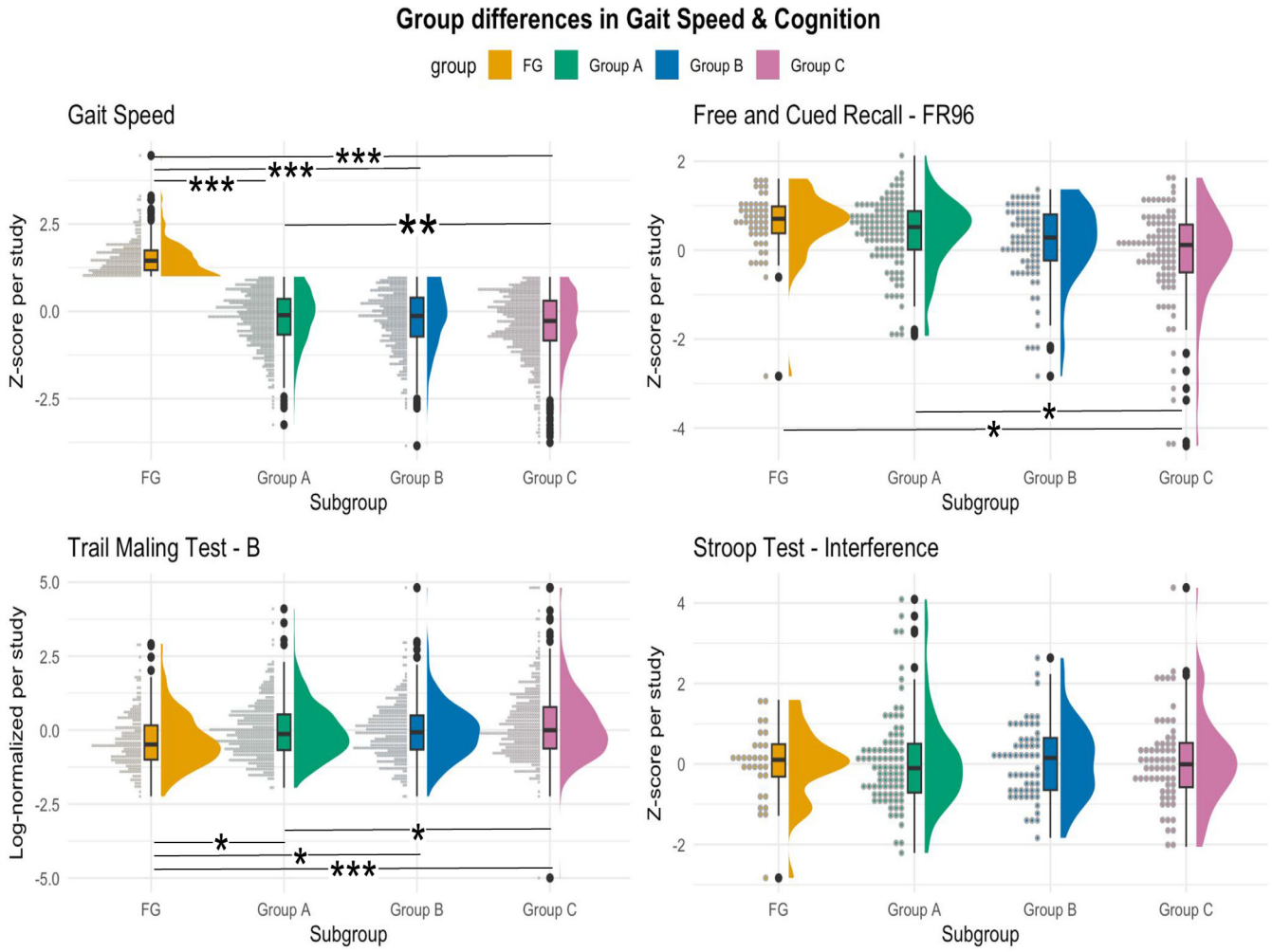

FIGURE 3 Subgroup differences in cognition by regions: group differences in gait speed and cognition. TMT-B, Trail Making Test, Part B; log-transformed, z-score normalized, available in CCMA, LonGenity, EAS, NCGG-SGS, KES, and GAIT; FR96, Free and Cued Selective Reminding Test (FCSRT), a recall test that uses either words or images. Scores include the sum of free recall (FR) alone (range 0-48) and combined with cued recall as total recall (TR). FR96: the sum of FR and TR (range 0-96); available in CCMA, EAS, and LonGenity; Stroop-INT, Stroop color word test, consisting of subtests measuring time required to name the colors seen (COLOR), read the given words (WORD), and name the color of the printed word (COLOR_WORD); Stroop-INT: the difference between the third subtask and the first task (COLOR_WORD—COLOR) available in EAS, TASCOG, and GAIT.

without dementia with gait speeds that are fast or normative (less than 1 SD above population mean). We were interested in studying neuroanatomical patterns within this population in relation to their gait speed and in exploring possible differences in their cognition. As hypothesized, we found homogenous subgroups that showed significant differences in their mean gait speeds accompanied by corresponding distinct neuroanatomical patterns as shown by differences in their brain region volumes. The subgroup with the slowest mean gait speed (Group C) had the least volumes across the prefrontal, temporal, and parietal cortex regions, hippocampus and cerebellar cortex than any other subgroups, resembling a pathological pattern of an MCR subtype accompanied by olfactory dysfunction that is more likely to be associated with Alzheimer and Lewy body dementias.[37] Our results were consistent with the previous MCR studies that showed higher association of lower cortical gray matter volumes and total hippocampal volumes with incident MCR.[8,9,15] Similar results were observed across the regions that were used in the clustering model, except for the caudate nucleus, for which no significant difference was found across any of the groups. Interestingly, Group A, which had a slower mean gait speed compared to the reference fast gait group had higher brain region volumes across prefrontal, hippocampal, temporal, parietal regions. We could not find a specific neuroanatomical pattern that could explain why Group A had slower gait speeds and greater brain region volumes than the reference group FG. This finding might be explainable by other comorbidities. However, due to the lack of detailed data on these comorbidities, we could not study them in the context of the current study.

Prior studies link MCR syndrome to poorer performance in attention, memory, and global cognition with gait attributes like speed and stride length associated with specific cognitive domains adults.[38,39] In

TABLE 3 MCR Consortium participant subgroup characteristics.

Group	Gait speed, imaging, and cognition
Fast gait (FG)	Reference group, used by the clustering algorithm
Gait speed > mean+1SD	Best scores in FCSRT and TMT-B, No cortical or subcortical atrophy
Study Population Gait Speed < mean+1SD	
Group A	Fastest gait, largest volumes across almost all ROIs
Group B	Intermediate gait speed, similar cortical volumes as reference group
Group C	*Slowest gait, lowest cortical volumes, highest prevalence of MCR*

Abbreviation: FG, population with fast gait, gait speed greater than 1SD above population-mean; Groups A,B&C, result of HYDRA Clustering of the remaining population (gait speed slower than 1 SD above population-mean); *p*-value, significance Pr(> F) in ANCOVA corrected for age and sex; pairwise comparisons, multiple comparisons of means with Tukey contrasts; SD, standard deviation; TMT-B, Trail Making Test, Part B; log-transformed, z-score normalized, available in CCMA, LonGenity, EAS, NCGG-SGS, KES, and GAIT; FCSRT, Free and Cued Selective Reminding Test (FCSRT), a recall test that uses either words or images. Scores include the sum of free recall (FR) alone (range 0-48) and combined with cued recall as total recall (TR); FR96, the sum of FR and TR (range 0-96); available in CCMA, EAS, and LonGenity.

our analysis, all slow-gait subgroups performed worse than the faster gait group on TMT-B and FCSRT (FR96). TMT-B scores differed across most subgroups (except A vs. B), reinforcing the link between executive function and gait.[8,13] Only the slowest subgroup (C) showed significantly lower FR96 scores. No subgroup differences were observed in cued recall or Stroop-Interference likely due to the dementia-free baseline. This aligns with prior evidence linking slower gait to executive and global cognitive decline.[38,40,41]

There are few notable limitations in our study. We did not have consistent data across cohorts on musculoskeletal or peripheral contributors to gait slowing (e.g., joint pain, arthritis), limiting our ability to adjust for these potential confounders. Future studies should incorporate such measures to better isolate neuroanatomical contributions from peripheral ones. While the cross-sectional design limits causal inference, future longitudinal analyses could reveal whether neuroanatomic subgroups with distinct gait patterns follow different cognitive or motor trajectories. A future direction of study could be whether these subgroups that differ in their neuroanatomic and gait speed patterns, show different trajectories in their gait speed slowdown or cognitive decline. Although in the case of MCR it was shown that cortical thickness detected neurodegeneration easier than cortical volumes,[15] it was shown that cortical volume can be more sensitive to detecting changes in brain structure associated with aging and neurodegenerative processes[42] and numerous studies have successfully used cortical volumes in ML models for various neurological conditions.[43,44] The effects of using cortical thickness on the resulting subgroups should be further explored. While the novel approach combining factor analysis with weakly-supervised clustering is not tailored specifically for gait-neuroanatomy associations, it effectively addresses collinearity in brain volumes. However, the adding only one region from each factor as a feature to the HYDRA algorithm, while clinically interpretable may lose crucial information from the variance of regions not included. Finally, as the data used in our study is from various cohorts/study sites, within-study normalization of gait speeds does not account for differences in demographic and clinical characteristics across these study sites[45,46] (See Table S4 for differences in demographic, clinical characteristics, and gait speeds across study sites.) and therefore we accounted for age and sex differences in our model. Similarly, since the images were not collected particularly for our study focusing on MCR, harmonization, and standardization of acquisition protocols are needed to further address the challenges related to consistency of measurements. While this is indeed a well-recognized and complex challenge in multi-site neuroimaging studies,[47] the image processing pipeline used to obtain the volumetric data used in our study – Free Surfer 6.0 has been shown to be quite reliable across scans and centers.[48,49] In addition, cognitive performance comparisons across subgroups may lack generalizability due to variability in test types and availability across cohorts. Future work using harmonized, longitudinal cognitive data and other recent generative methods [50] could better characterize heterogeneity, subtypes, and disease progression in gait impairments and MCR.

Our work highlights the potential of uncovering hidden heterogeneity in individuals with slow gait, an at-risk group for MCR and dementia. By identifying distinct subgroups based on brain volume patterns and related biomarkers, we enhance the understanding of the underlying pathophysiology and support early, stratified intervention strategies. Our methodology effectively handles complex multi-site neuroimaging data, offering a robust framework for precision health in aging and dementia research. This contributes to more targeted approaches for early detection and prevention of cognitive decline.

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CONFLICTS OF INTEREST STATEMENT

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CONSENT STATEMENT

All human subjects across all the study locations provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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