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Research Article

Brain Changes and Fast Cognitive and Motor Decline in Older Adults

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Abstract

Background: To identify brain magnetic resonance imaging (MRI) signatures characterizing people with different patterns of decline in cognition and motor function.

Methods: In the Swedish National Study on Aging and Care in Kungsholmen, Stockholm, 385 participants had available repeated brain MRI examinations, where markers of brain volumes and white matter integrity were assessed. The speed of cognitive and motor decline was estimated as the rate of a Mini-Mental State Examination and gait speed decline over 12 years (linear mixed models), and further dichotomized into the upper (25% fastest rate of decline) versus the lower quartiles. Participants were grouped in slow/no decliners (reference), isolated motor decliners, isolated cognitive decliners, and cognitive and motor decliners. We estimated the associations between changes in brain markers (linear mixed models) and baseline diffusion tensor imaging measures (linear regression model) and the 4 decline patterns.

Results: Individuals with concurrent cognitive and motor decline ($n = 51$) experienced the greatest loss in the total brain (β: −12.3; 95% confidence interval [CI]: −18.2; −6.38) and hippocampal (β: −0.25; 95% CI: −0.34; −0.16) volumes, the steepest accumulation of white matter hyperintensities (β: 1.61; 95% CI: 0.54; 2.68), and the greatest ventricular enlargement (β: 2.07; 95% CI: 0.67; 3.47). Compared to the reference, those only experiencing cognitive decline presented with steeper hippocampal volume loss, whereas those exhibiting only motor decline displayed a greater white matter hyperintensities burden. Lower microstructural white matter integrity was associated with concurrent cognitive and motor decline.

Conclusion: Concurrent cognitive and motor decline is accompanied by rapidly evolving and complex brain pathology involving both gray and white matter. Isolated cognitive and motor declines seem to exhibit brain damage with different qualitative features.

Keywords: Brain lesions, Cognitive decline, Gait speed decline, Population-based study

Dementia in old age is a multifactorial disorder where cognitive and motor domains closely interact (1,2). It is well-established that a mild impairment in cognition is an *at-risk* condition for dementia development (3). Interestingly, accumulating evidence has also shown that measures of motor function, like gait speed, are good indicators of impending dementia (4). Slow gait speed is regarded as one of the best, easy to administer motor test to capture future dementia (5). Notably, we have previously reported that including gait speed in the diagnostic workup of cognitively impaired persons might advance the early detection of dementia (6).

Even more important than impairment in either cognitive and/or motor domains, recent studies have pointed out that longitudinal changes better capture the intraindividual dynamics that characterize the aging process (7). A previous study including 154 community-dwelling

participants, part of the Gait and Brain study, showed that a concurrent decline in gait speed and cognitive function was associated with the highest hazard for dementia after 5 years (8). A meta-analysis across Europe and the United States showed that individuals who experienced a fast and dual decline in memory and gait speed had a 6 times higher risk of developing dementia compared to those without any decline (9). However, whether individuals experiencing a fast and concurrent decline in cognition and motor function progress to dementia through specific pathophysiological mechanisms different from others is unknown. Only one recent study has investigated the brain magnetic resonance imaging (MRI) longitudinal changes of individuals with a parallel decline in memory and gait speed and found that specific brain areas (superior frontal gyrus, precuneus, and thalamus) were damaged (8). However, it is still unknown whether other areas implicated in more Alzheimer's disease-like pathology (hippocampus) and/or global atrophy and/or white-matter lesions are at place. The nature of brain changes may provide insights into the mechanisms underlying a faster progression to dementia in dual decliners compared to others.

We hypothesize that a parallel and rapid decline in both cognitive and motor function would be accompanied by a greater degree of loss of brain integrity, both in gray and white matter.

Therefore, we aimed to detect the pathological brain changes over 6 years in relation to different patterns of decline in cognitive and motor function, using a population-based study with 12-year longitudinal clinical assessment and 6 years of repeated brain MRI.

Materials and Methods

Study Population

The Swedish National study on Aging and Care in Kungsholmen (SNAC-K) brain magnetic resonance imaging study (SNAC-K-MRI) is embedded within the larger SNAC-K study. SNAC-K is an ongoing population-based longitudinal study with a response rate of 73%, as described elsewhere (10). The SNAC-K-MRI study includes a subsample of 555 noninstitutionalized, nondisabled, older adults without dementia who agreed to undergo structural brain MRI scans. Of these older adults, 260 also had diffusion tensor imaging (DTI) data available for the baseline assessment. Individuals less than 78 years (younger cohort) repeated the MRI scan after 6 years, whereas those aged 78 and older (older cohort) repeated the assessment after 3 and 6 years. The clinical assessments were available up to 12 years of follow-up.

For this study, at baseline, we excluded participants with suboptimal MRI quality (n = 53) and neurological or neuropsychiatric conditions (including brain infarcts, tumors, and aneurysms; n = 37). Reasons for suboptimal MRI quality were: excessive head motion artifacts and/or technical issues during the scanning. We further excluded participants with a baseline gait speed ≤ 0.6 m/s (n = 27) (9,11), and one participant with a Mini-Mental State Examination (MMSE) score < 24 at baseline. In addition, we excluded participants lacking a follow-up assessment (n = 52). Thus, our final sample included 385 participants, of which 193 had DTI data. At baseline 272 individuals were part of the young cohort and 75% (N = 204) repeated the MRI scan after 6 years, while 113 belonged to the older cohort and, of them, 78 (68%) repeated the MRI scan after 3 years and 52 of those who underwent the scan at 3 years (67%) also after 6 years. Reasons for missing data on MRI were not fulfilling the inclusion criteria, death, or refusal. Supplementary Figure S1 depicts the flow chart of the study.

Participants excluded at baseline were older (difference: +5.18 years; 95% confidence interval [CI]: 3.59; 6.77) and more likely to have: a lower level of education (elementary or high school level: 67% vs 56%; p: .016); a greater number of chronic diseases (difference: +1.08; 95% CI: 0.74–1.42), a lower mean MMSE score (difference: −0.75; 95% CI: −0.48; −1.03) and a slower gait speed (difference: −0.31; 95% CI: −0.25; −0.37) than those included in the analyses. The samples did not significantly differ by sex.

All participants provided written informed consent. The Regional Ethical Review Board in Stockholm, Sweden, approved the protocols of the SNAC-K study. The results of this study are reported following the STROBE recommendations.

Data Collection

Data were collected at our research center in accordance with standard procedures. Home visits were offered for those who agreed to participate but were unable to travel to the research center. Trained staff performed face-to-face interviews as well as clinical and laboratory examinations.

Data on age, sex, and education were obtained through a personal interview, conducted by nurses. Education was measured as the participant's highest level of formal education and categorized as elementary, high school, or university and above. Information on country of birth was collected during the nurse interview and categorized as Sweden or other countries. We used the MMSE as a measure of global cognition (12). Gait speed was reported in meters per second (m/s) and assessed by asking the participant to walk at their usual speed over 6, or 2.4 meters if the participant reported walking quite slowly or the evaluation was conducted at the participant's home, and space was restricted (13). Previous reports have shown that the use of different distances in the assessment of gait speed is highly comparable (13). In this study sample, 383 participants were assessed at the research center and only 2 at home. Comprehensive interviews and examinations conducted by physicians, laboratory test results, medication use, and records from the Swedish National Patient Register were used to define chronic diseases, in accordance with the International Classification of Diseases, 10th edition (ICD-10) (14). Medical conditions here considered included hypertension, heart diseases (atrial fibrillation, ischemic heart disease, and heart failure), and cerebrovascular diseases. Dementia and depression were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Parkinson's disease (PD) and parkinsonism were diagnosed according to a set of information retrieved during the physician interview, including clinical history, general and neurological examination, medication use, and records from the Swedish National Patient Register. None of the 385 individuals included in the present study suffered from PD nor parkinsonism. Participants' vital status was determined using death certificates from the Swedish Cause of Death Registry as well as medical records from the time of hospital discharge. DNA was extracted from peripheral blood samples, and the Apolipoprotein E (*APOE*) alleles were genotyped. Participants were categorized as ε4-carriers and ε4-noncarriers.

Brain MRI data acquisition and processing

The MRI acquisition protocol and details of the imaging processing are described in the Supplementary Material. In brief, T1-weighted images were segmented into gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume (CSFV) volumes using SPM12 in Matlab 10. Total brain tissue volume (TBV) was calculated by summing the GMV and WMV. Total intracranial volume (TIV) was obtained by summing GMV, WMV, and CSFV. FreeSurfer automated segmentation was used to extract the hippocampal volume (HV) (15).

The lateral ventricles were segmented automatically in the ALVIN toolbox, and their volumes were calculated (16). A neuroimaging expert (G.K.) visually inspected each of the segmentations and manually drew the white matter hyperintensities volume (WMHV) on FLAIR images (17). All MRI measurements were adjusted by TIV, and the adjusted volumes were used in data analyses (18).

Concerning the DTI measures, the images were preprocessed using an iterative optimization algorithm for the diffusion tensor calculation. Fractional anisotropy (FA) and mean diffusivity (MD) measures were, then, derived on a voxel-by-voxel basis. Further processing of the FA data were conducted using the tract-based spatial statistics (TBSS) tool of the FMRIB Software Library Analysis Group (FMRIB, Oxford, UK). Fourteen masks, one for each tract of interest in both hemispheres, were created and used to extract the FA and MD values of each participant, as previously described (19). For both FA and MD, all tracts were included in the global model, and the mean values were used in the current analyses.

Operationalization of patterns of decline

To estimate the rate of cognitive and motor decline for each individual, we implemented linear mixed models, where MMSE and gait speed were the dependent variables, and the intercept and follow-up time provided the fixed and random effect. The rates of decline were examined by quartile. Based on the rates of decline quartiles in MMSE and gait speed, the participants were grouped into 4 mutually exclusive groups: (a) Slow/no decliners ($n = 238$): participants who belonged to the lower 3 quartiles of decline in both MMSE score and gait speed (reference group); (b) Fast cognitive decliners ($n = 46$): participants who belonged to the upper quartile of decline only in MMSE score; (c) Fast motor decliners ($n = 50$): participants who belonged to the upper quartile of decline only in gait speed; and (d) Fast decliners in both cognition and motor function ($n = 51$): participants who belonged to the upper quartile of decline in both MMSE score and gait speed.

Statistical Analyses

We used linear mixed models to estimate the rate of decline in MMSE score and gait speed, prior to death or end of follow-up of 12 years.

Linear mixed models were used to estimate the association between the rate of change in brain MRI volumes and white-matter lesions with the patterns of decline in cognitive and motor function. We used linear regression models to test the association between baseline DTI measures and patterns of decline. Potential confounders were chosen a priori based on a literature review, and included sex, age, education, heart diseases (ie, heart failure, ischemic heart disease, and atrial fibrillation), cerebrovascular diseases, hypertension, depression, and the *APOE* genotype. Analyses on DTI measures were adjusted for age, sex, education, and the presence of WMHs.

Two-sided $p < .05$ indicated statistical significance. All statistical analyses were performed with Stata, version 15 (StataCorp, College Station, TX).

Sensitivity analyses

To account for the possibility of death being a competing outcome, we repeated the analyses by computing the linear mixed models to estimate the pattern of MMSE and gait speed decline by adjusting for survival status during follow-up.

Results

Over the follow-up (mean: 10.0 ± 2.61 years), of the 385 study participants, 122 died ($n = 43$ among the younger cohort; $n = 79$ among the older one) and 44 ($n = 29$ among the younger cohort; $n = 15$ among the older one) dropped out. Supplementary Figure S1 depicts the study participation flow chart over time.

At study entry, the mean (standard deviation [*SD*]) age of the participants was 69.6 (±8.6) years, 227 (59%) were female, and 41 (11%) had an education level of elementary or below. Baseline characteristics by the pattern of decline are reported in Table 1. Overall, 51 (13%) participants belonged to the highest 25th percentile of decline in both cognition and motor function. People who declined both in cognitive and motor function were more likely to be older, female, less educated, and suffered from a greater number of chronic diseases compared to those in the reference group. Overall, 45% ($n = 22$) of those with both cognitive and motor function decline developed dementia over 12 years.

Figure 1 shows the trajectories of brain MRI volumes over time according to the patterns of decline, after controlling for potential confounders. At baseline, individuals who declined both in MMSE and gait speed presented a smaller TBTV (average difference: −26.3; 95% CI: −45.2; −7.51) and larger ventricles volumes (average difference: 10.7; 95% CI: 5.5; 16.0), compared with the reference group (slow/no decliners). Similarly, they had a smaller HV (average difference: −0.27; 95% CI: −0.51; −0.04) and a larger volume of WMHs (average difference: +4.43; 95% CI: 1.42; 7.44) than those in the reference group. Participants presenting with both motor and cognitive decline over 12 years experienced the most rapid loss of TBTV (average change: −12.3; 95% CI: −18.2; −6.38) during the first 6 years of follow-up, and, in parallel, the greatest enlargement of ventricles volume (average change: 2.07; 95% CI: 0.67; 3.47). These participants also demonstrated the greatest HV loss (average change: −0.25; 95% CI: −0.34; −0.16), followed by those who declined only in cognition (average change: −0.17; 95% CI: −0.25; −0.08), and finally by those who declined only in motor function (average change: −0.09; 95% CI: −0.17; −0.02). Accumulation of WMHs was also the largest in those who declined in both motor function and cognition (average change: 1.61; 95% CI: 0.54; 2.68), but in this case, followed first by those who declined only in motor function, and then by those who experienced a decline in cognitive function, although not statistically significant (average change: 0.73; 95% CI: −0.20; 1.67 and 0.69; 95% CI: −0.32; 1.70, respectively).

Supplementary Figure S2 shows the association between the baseline DTI measures (MD in panel A; FA in panel B) and patterns of decline. People who declined in both cognition and motor function had worse baseline MD (average difference: 2.17; 95% CI: 0.78; 3.54) values compared with the reference group. Similar coefficients for FA were observed in those who declined in both cognition and motor function (average difference: −0.96; 95% CI: −1.79; −0.11), as well as those who declined only in cognition (average difference: −1.03; 95% CI: −1.90; −0.22).

Sensitivity Analyses

When we repeated the analyses by computing the mixed models to estimate the decliners profile adjusted for death we obtained similar results (see Supplementary Table S1)

Discussion

According to our findings, individuals who were free from dementia, cognitive impairment, and disability at baseline who rapidly declined in both cognitive and motor functions experienced the steepest loss in total brain tissue and HV, the greatest ventricular

Table 1. Sample Baseline Characteristics by Patterns of Decline in the SNAC-K MRI Study

	Patterns of Decline				
	Slow/No Decliners *N* = 238	Isolated Motor Decliners *N* = 46	Isolated Cognitive Decliners *N* = 50	Cognitive and Motor Decliners *N* = 51	*p* Value
Female	146 (61.3)	27 (58.7)	18 (36.0)	36 (70.6)	.003
Age (mean ± *SD*)	65.7 ± 6.3	73.9 ± 7.3	74.8 ± 9.3	79.0 ± 6.0	.001
Education					
Elementary school	11 (4.6)	5 (10.9)	14 (28.0)	11 (21.6)	<.001
High school	104 (43.7)	20 (43.5)	20 (40.0)	28 (54.9)	
University	123 (51.7)	21 (45.7)	16 (32.0)	12 (23.5)	
Country of birth					.644
Sweden	212 (92.9)	45 (91.8)	53 (88.3)	43 (89.6)	
Other*	16 (7.1)	4 (8.2)	7 (11.7)	5 (10.4)	
MMSE (mean ± *SD*)	29.4 ± 0.8	29.3 ± 0.7	28.8 ± 1.2	28.5 ± 1.2	<.001
Gait speed (mean ± *SD*)	1.3 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	.540
Clinical assessment					
No. of chronic diseases (mean ± *SD*)	1.5 (1.5)	2.8 (2.2)	2.2 (1.6)	2.7 (1.6)	.007
Hypertension	144 (60.5)	39 (84.8)	38 (76.0)	42 (82.4)	.001
Heart diseases†	20 (8.4)	7 (15.2)	11 (22.0)	13 (25.5)	.002
Atrial fibrillation	7 (2.9)	3 (6.5)	2 (4.0)	4 (7.8)	.352
Ischemic heart disease	11 (4.6)	3 (6.5)	9 (18.0)	7 (13.7)	.004
Heart failure	4 (1.7)	2 (4.4)	4 (8.0)	7 (13.7)	.001
Cerebrovascular diseases	2 (0.8)	2 (4.4)	1 (2.0)	1 (2.0)	.355
Depression and mood disorders	12 (5.0)	5 (10.9)	3 (6.0)	7 (13.7)	.108
APOE genotype (at least 1 ε4 allele)	64 (27)	8 (18)	15 (31)	14 (28)	.516

Notes: Unless otherwise specified, figures show number (%). *p* Values were obtained through chi-squared test for categorical and ANOVA for continuous variables. *SD* = standard deviation; *APOE* ε4 = apolipoprotein epsilon 4 (at least 1 allele); MMSE = Mini-Mental State Examination; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; MRI = magnetic resonance imaging.

Data on *APOE* available for 380 individuals.

*Of them, 16 born in other Nordic countries (ie, Denmark, Norway, and Finland).

†Heart failure, ischemic heart disease, and atrial fibrillation.

enlargement, and the largest accumulation of white matter lesions. The subanalyses, including DTI measures, further supported these findings by showing lower microstructural white matter integrity in people with co-occurring cognitive and motor decline, beyond the presence of macrostructural white matter lesions. Finally, although these results need to be interpreted with caution due to unprecise estimates and nonstatistically significant between-group differences, some qualitative differences arose in terms of brain lesion burden when isolated decline in cognition or motor function was considered. In particular, compared to slow/no decliners, individuals with isolated cognitive decline experienced a steeper HV loss, whereas those with isolated motor decline presented with a greater white matter hyperintensity accumulation.

Our longitudinal findings add weight to an existing body of literature on brain MRI markers and cognitive and motor decline studied as separate entities, and cross-sectional studies on brain correlates of the motoric cognitive risk syndrome (MRC) where slow gait speed coexists with subjective cognitive decline (20). Notably, our findings also advance recent results from a study using the Baltimore Longitudinal Study of Aging, including 391 individuals with longitudinal brain MRI data (8). In that study, individuals with a dual memory and gait speed decline presented more gray matter loss in specific brain areas such as the superior frontal gyrus, precuneus, and thalamus that play critical roles in both memory and motor control as well as sensorimotor integration. We here found that individuals with concurrent cognitive and motor decline present also a steeper loss in HV and a greater accumulation of white matter hyperintensities. These results, taken as a whole, advance our knowledge of the pathophysiological pathways at a place when a dual decline occur and shed some light on the possible mechanisms eventually leading to future dementia.

The pathological processes at play in the development of dementia are known to be complex, beginning years, if not decades, before a diagnosis is made (21). The prodromal phase of dementia is frequently featured by subtle cognitive, behavioral, and neurological changes. Notably, noncognitive manifestations have also been found to be related to future dementia and mild cognitive impairment (MCI) (5,22,23). Among others, motor slowing appears as early as 12 years before the onset of MCI (24). It is associated with a worse clinical progression in Alzheimer's disease (AD) (25,26), and with a higher AD-like neuropathological burden at autopsy (27). Postmortem studies have associated indices of AD with a steeper decline in gait speed prior to death, suggesting that AD pathology might account for a substantial proportion of not only cognitive, but also motor, decline (28). Cognitive and physical functions are closely linked and play a major role in the development of dementia.

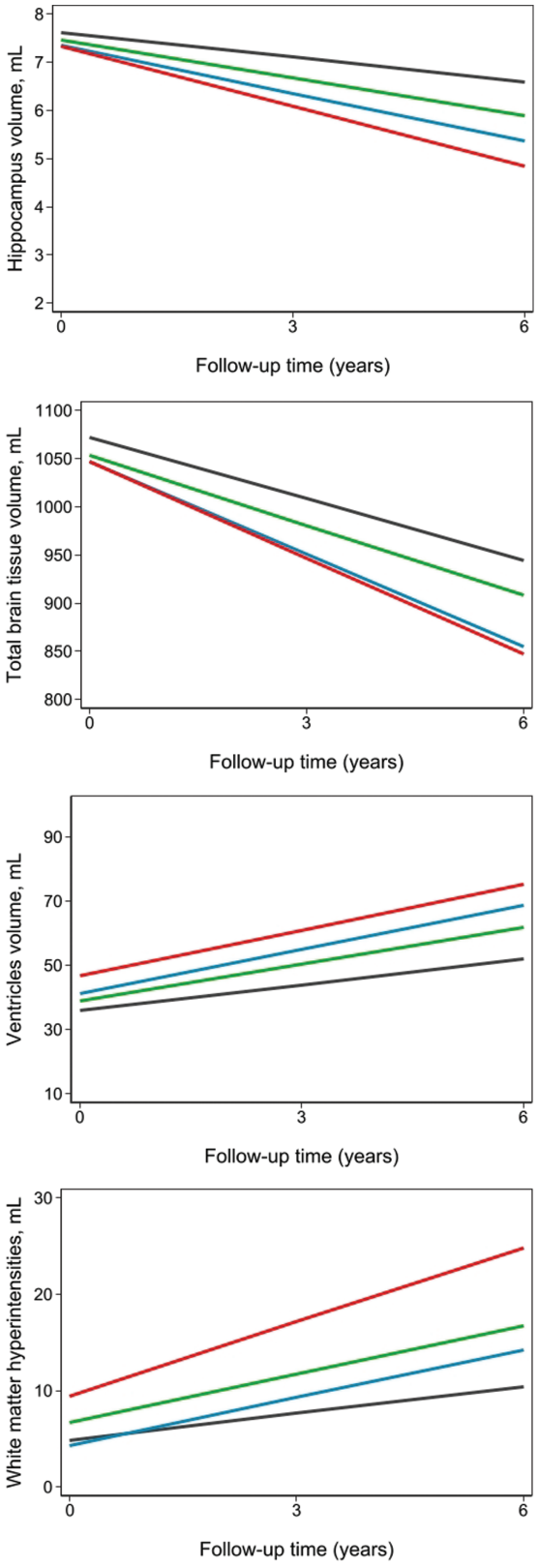

Figure 1. Brain magnetic resonance imaging (MRI) changes by patterns of cognitive and motor decline. Models are adjusted for age, sex, education, cardiovascular diseases (intended as atrial fibrillation, heart failure, ischemic heart disease, and cerebrovascular diseases), depression, and *APOE* genotype. Brain volumes (mL) were adjusted for intracranial volume. Slow/no decliners-black line, isolated motor decliners-green line, isolated cognitive decliners-blue line, and cognitive and motor decliners-red line.

Individuals with a concomitant decline in both cognition and physical function have the highest probability of developing dementia (6,9). In addition, adding a measure of physical function to the cognitive battery improves the diagnostic accuracy of detecting impending dementia, suggesting that gait speed might capture a complementary dimension of dementia development (6). Although the identification of individuals experiencing cognitive and motor decline in parallel has provided useful clinical insights, the biological substrate of this observation remains unclear.

Our results indicate that those who rapidly decline in both cognition and motor function present several deleterious neuroimaging correlates: low total brain tissue and HVs, ventricle enlargement, high WMH burden, and compromised microstructural white matter integrity. These findings support the hypothesis that when the decline occurs in both functions, there is an underlying rapidly evolving and mixed (ie, gray and white matter) neuropathology in place.

Although it largely consists of automatic movements and is considered to be a relatively simple act, human gait is, indeed, a complex task that relies on integrating several low- and high- level areas of the central nervous system (5,29). Neuroimaging studies using functional MRI have shown that motor control and cognitive processes share common neuronal substrates, particularly in the prefrontal, parietal, and temporal regions of the brain (30,31). In addition, a handful of cross-sectional studies have indicated that cerebral in vivo β-amyloid deposition—particularly in the putamen, occipital cortex, and anterior cingulate—is associated with slow gait speed in older adults without dementia (27,32,33). Rosso et al. showed that gait slowing was associated with an increased risk of cognitive impairment (MCI or dementia) up to 14 years later and that hippocampus was the only region associated with both slow gait speed and cognitive impairment (34). These findings support the hypothesis that the relation between slow gait speed and cognitive dysfunction is due to shared underlying neuropathology. Interestingly, we also observed smaller HVs when a dual decline was in place, while we did not observe smaller HVs when slow gait speed occurred in isolation. According to our findings, individuals with isolated motor function decline experienced a greater WMH accumulation compared to those with only cognitive decline. These findings should be interpreted with caution, as the paucity of observations might be responsible for less precise estimates and prevent us from detecting a statistically significant between-groups difference. The association between slow gait speed and greater WMH burden might allow for interesting interpretations. Slow gait speed might be the result of several clinical and subclinical dysfunctions, including, among others, the presence of several co-occurring diseases (including sensory and vestibular dysfunction), systemic inflammation, and hormonal and/or mitochondrial dysfunction (5). Slow gait speed might, in other words, reflect a systemic vulnerability that, in turn, affects vulnerable brain regions. In fact, white-matter lesions are frequently associated with clinical and subclinical heart and vascular diseases (as well as risk factors), and may disrupt the neural pathways involved in motor function, leading to gait slowing and impairment (35). This would translate in a more "vascular pathway" toward dementia rather than a more neurodegenerative one. However, our results concerning this perspective are preliminary, and open for new possible hypotheses, and future studies are needed to investigate this issue by including more specific markers of AD pathology, such as amyloid-β and tau deposition.

Regardless of the specific pathways behind cognitive and motor decline, it is plausible that established cognitive, and motor impairments are characterized by complex and mixed (white

and gray matter, including atrophy and vascular lesions) brain deterioration.

Strengths and Limitations

These findings are derived from a large, well-established population-based cohort, involving a long follow-up and extensive individual-level evaluations that include repeated brain MRI measurements. We were also able to account for several relevant confounders in our analyses. However, the following limitations must be mentioned. First, SNAC-K, especially SNAC-K-MRI, includes older adults living in central Stockholm who are healthy, fit, of high socioeconomic status, and mainly born in Sweden, which might limit the generalizability of our results to other countries or study populations. Furthermore, the MMSE is a reliable and easy to administer test, but it might not be sensitive enough to capture subtle cognitive changes. This lack of sensitivity might have led to an underestimation of our findings regarding cognitive decline. While gait speed is a sensitive tool to capture motor changes, MMSE does not properly and accurately capture a deterioration in example, executive function. Future studies should include tests that more comprehensively assess a broader spectrum of cognitive functions and relate them to the simultaneous motor slowing and brain correlates. Third, to estimate the rate of cognitive and motor decline, we implemented linear mixed models over 12 years, while the change in brain MRI measures was assessed during the first 6 years. This means that we here partly study a concurrent change between brain MRI measures and cognitive and motor function. However, structural brain MRI damages usually precede the clinical manifestation of a (cognitive/motor) impairment. Thus, even if cautiously, a direction in the observed association can be postulated. Finally, there are other neuroimaging markers (eg, microbleeds and amyloid deposition) that are worthy of further investigation in this context, but they are not available in our population-based data set. Future studies are needed to investigate these aspects and clarify whether some brain areas are more vulnerable and implicated in the progression of these profiles to dementia, as well as deepen our knowledge of the mechanisms (AD-like, vascular, and neuroinflammation) implicated in the brain damage.

Conclusion

Our findings demonstrate that cognitive and motor impairments tend to be characterized by complex, rapidly evolving, and mixed brain damage. Further research should examine the isolated decline in cognition and motor function, specifically investigating whether these types of decline follow specific pathophysiological pathways, as suggested by our findings. Identifying underlying mechanisms of cognitive and motor decline, occurring together or in isolation, might open new research avenues for the prevention and treatment of dementia.

Supplementary Material

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

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Role of the Funding Source

The founder had no role in study design, data collection, data analyses, data interpretation, or writing of the report. The corresponding and the last authors had full access to all the data in the study and have final responsibility for the decision to submit it for publication.

Conflict of Interest

None declared.

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Author Contributions

G.G., D.L.V., L.F., and D.R. contributed to the conception and design of the study. G.G. and D.R. conducted the statistical analyses. G.G. conducted the literature search. All the authors contributed to interpretation of the results. G.G. drafted the first version of the manuscript. All the authors critically revised the manuscript for important intellectual content. All the authors made a significant contribution to the research and the development of the manuscript and approved the final version for publication. SNAC-K personnel collected the data for the study.

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