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ORIGINAL ARTICLE

Synergistic associations of cognitive and motor impairments with functional outcome in covert cerebral small vessel disease

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Abstract

Background: Cognitive and motor impairments are the key clinical manifestations of cerebral small vessel disease (SVD), but their combined effects on functional outcome have not been elucidated. This study investigated the interactions and mediating effects of cognitive and motor functions on instrumental activities of daily living (IADL) and quality of life in older individuals with various degrees of white matter hyperintensities (WMH).

Methods: Participants of the Helsinki Small Vessel Disease Study (n = 152) were assessed according to an extensive clinical, physical, neuropsychological and MRI protocol. Volumes of WMH and gray matter (GM) were obtained with automated segmentation.

Results: Cognitive (global cognition, executive functions, processing speed, memory) and motor functions (gait speed, single-leg stance, timed up-and-go) had strong interrelations with each other, and they were significantly associated with IADL, quality of life as well as WMH and GM volumes. A consistent pattern on significant interactions between cognitive and motor functions was found on informant-evaluated IADL, but not on self-evaluated quality of life. The association of WMH volume with IADL was mediated by global cognition, whereas the association of GM volume with IADL was mediated by global cognition and timed up-and-go performance.

Conclusion: The results highlight the complex interplay and synergism between motor and cognitive abilities on functional outcome in SVD. The combined effect of motor

and cognitive disturbances on IADL is likely to be greater than their individual effects. Patients with both impairments are at disproportionate risk for poor outcome. WMH and brain atrophy contribute to disability through cognitive and motor impairment.

KEYWORDS
cognition, instrumental activities of daily living, motor functions, neuropsychology, quality of life, small vessel disease, vascular cognitive impairment, vascular dementia

INTRODUCTION

Cognitive and motor impairments become increasingly prevalent with aging and pose a major public health concern in older people. Cognitive abilities are considered to play a key role in regulating complex motor functions such as gait and balance [1–3]. Cognitive impairment, executive dysfunction in particular, has been associated with risk of falls in community-dwelling older individuals [4].

Cerebral small vessel disease (SVD) is the leading cause of vascular cognitive impairment and a major contributor to functional disability [5,6]. It is characterized by insidious onset, gradually accumulating brain changes and progressive clinical symptoms [6,7]. Among the characteristic neuroimaging findings of SVD, white matter hyperintensities (WMH) and lacunes of presumed vascular origin, and brain atrophy have been the strongest determinants of cognitive decline [8–10]. Executive functions and processing speed have been regarded as the core domains of cognitive impairment in SVD [11–13]. With progressing brain changes the deterioration becomes more global and affects a wide range of cognitive functions [14,15].

Along with cognitive impairment, decline in motor functions is another important adverse outcome of SVD. The extent of WMH has been associated with impaired gait and balance as well as history of falls [16-20], whereas measures of gray matter (GM) atrophy have been related to gait performance [20,21]. Previously, the cognitive and motor symptoms of SVD have been explored in isolation, and therefore, little is known about their interrelations and cumulative effect on functional outcome.

This study investigated the associations and functional significance of cognitive and motor abilities in older individuals with different degrees of WMH by using standard physical and neuropsychological assessments and quantitative evaluation of brain changes on MRI. Specifically, our objectives were to

a. confirm the relationship of domain-specific cognitive functions (global cognition, executive functions, processing speed and memory) and motor performances (gait speed, balance and functional mobility) with WMH and GM volumes
b. investigate the reciprocal relationships between different motor and cognitive functions
c. show the associations and interactions of cognitive and motor functions on instrumental activities in daily living (IADL) and quality of life, and
d. explore the extent to which cognitive and motor functions mediate the effect of WMH and GM volumes on functional outcome.

METHODS

Participants

In total, 152 subjects with WMH were enrolled in the Helsinki Small Vessel Disease Study, a prospective cohort study investigating the imaging, clinical and cognitive characteristics of cerebral SVD. Subjects who had recently undergone brain scanning for one reason or another (listed in Table 1) were recruited from the imaging registry of the Helsinki University Hospital, Finland in 2016–2020 [22].

At study entry, all subjects underwent clinical, physical and neuropsychological examinations and a subsequent brain MRI within approximately 1 month. Detailed data of social background, medical history and lifestyle was collected with a structured interview and review of available medical records.

The inclusion criteria were: age 65–75 years; place of residence within the Helsinki and Uusimaa Hospital District; occurrence of not more than minor, temporary and local neurological symptoms (manifested 3–12 months before the enrolment) or no neurological symptoms at all; no more than slight disability in basic daily activities defined by the modified Ranking Scale score 0–2; and sufficient vision and hearing, and language skills to complete the full assessment protocol.

The exclusion criteria were: significant neurological disease (e.g. symptomatic stroke, multiple sclerosis or treatment resistant epilepsy); severe psychiatric disorder; current substance abuse; severe other medical condition preventing participation; traumatic brain injury that has required hospitalization; severe intellectual disability; and inability or refusal to undergo brain MRI. Additional exclusion criteria based on MRI findings were: cortical infarct; subcortical infarct larger than 15 mm (20 mm on diffusion-weighted images); hemorrhage larger than microbleed (>10 mm); brain tumor; and contusion, traumatic hemorrhage or diffuse axonal injury, as evaluated by an experienced neuroradiologist.

The study was approved by the Ethics Committee of the Helsinki University Hospital and informed written consent was received from each subject.

TABLE 1 Characteristics of the subjects in the Helsinki Small Vessel Disease Study ($n = 152$)

	All subjects
Demographics	
Age, mean (SD)	70.6 (2.9)
Men/women, *n*	57/95
Education, y, mean (SD)	13.0 (4.5)
Reasons for referral to initial brain imaging	
Transient ischemic attack, *n* (%)	40 (26)
Dizziness, *n* (%)	28 (18)
Headache or migraine, *n* (%)	15 (10)
Subjective cognitive complaints, *n* (%)	6 (4)
Visual symptoms, *n* (%)	17 (11)
Fall, *n* (%)	11 (7)
Syncope, *n* (%)	4 (3)
Other, *n* (%)	31 (20)
Clinical characteristics	
Hypertension, *n* (%)	105 (70)
Diabetes, *n* (%)	33 (22)
Hypercholesterolemia, *n* (%)	118 (78)
Atrial fibrillation, *n* (%)	17 (11)
Current smoking, *n* (%)	10 (7)
Subjective walking difficulties, *n* (%)	42 (28)
Falls during the last 12 months, *n* (%)	33 (22)
SPPB score ≤10, *n* (%)	42 (29)
MoCA score ≤25, *n* (%)	45 (30)
MRI findings	
WMH Fazekas score, no/mild/moderate/severe, *n*	14/76/42/20
Chronic small infarct, *n* (%)	11 (7%)
WMH volume, ml[a], mean, SD	10.5 (13.8)
Gray matter volume, ml[a], mean, SD	538.5 (30.0)

Abbreviations: MoCA, Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery; WMH, white matter hyperintensities.
[a]Normalized for intracranial volume.

Neuroimaging

The subjects were scanned using a 3T MRI scanner with 32-channel head coil (Siemens Magnetom Skyra/Verio). The protocol included the following sequences: a fast T1 gradient echo localizer in three orthogonal directions (0.9 × 0.8 mm in-plane resolution, 8 mm slice thickness, TR 9 ms, TE 4 ms, FA 20 degrees), sagittal 3D FLAIR SPACE (1.1 × 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices, TR 6000 ms, TE 389, ms, TI 2100 ms), sagittal 3D T2 SPACE (1.0 × 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices TR 3200 ms, TE 416 ms), and sagittal 3D T1 MPRAGE (1.1 × 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices, TR 1900 ms, TE 2.47 ms, FA 9 degrees).

WMH of presumed vascular origin were defined as hyperintense areas in the white matter without cavitation on FLAIR sequences according to the STRIVE neuroimaging guidelines [7]. WMH were first evaluated visually with the modified Fazekas scale by an experienced neuroradiologist [23]. Chronic small infarcts (other than defined in the exclusion criteria) were evaluated by number and location.

Volumes of brain structures and WMH were measured using the fully-automated cNeuro image quantification tool (www.cneuro.com/cmri/Combinostics, Finland) [24]. The tool segments the T1 images into 133 brain regions with a multi-atlas method based on 79 manually segmented atlases [25]. The segmentation of WMH was carried out on FLAIR images according to a multi-stage method based on the Expectation-Maximization algorithm [26]. All volumes were normalized for intracranial volume [27]. For the present analyses, the total volumes of WMH and cerebral GM were included. WMH volume was log transformed due to skewed distribution.

Evaluation of motor functions

The evaluation of motor functions included the Short Physical Performance Battery (SPPB), timed up-and-go (TUG) test and additional measurements of gait speed and balance. The SPPB is an assessment tool of lower extremity function and mobility comprising of subtests for standing, 4-meter walking and repeated chair stands [28]. The SPPB composite score ranges from 0 to 12, and score ≤10 was considered impaired. The TUG test is a measure of functional mobility, in which the subject is asked to stand up from an armchair, walk 3 meters, turn, walk back and sit down again [29]. The variable was the time taken in seconds to complete the test. Gait speed was measured from subjects walking an 8-meter course at one's usual pace. The faster of two trials was recorded (meters/second) [16]. Single-leg stance time was measured by asking the subject to balance on one leg with hands on the hips. The best time of four trials with a maximum of 60 s was used for the analyses [16]. In addition, subjective walking difficulties as reported by the patient or informant (yes/no) and the occurrence of falls within the last 12 months were recorded.

Neuropsychological assessment

Neuropsychological examination included an extensive battery of standard tests to evaluate all key domains of cognitive functions. The tests, variables and references are listed in Table S1. Briefly, processing speed was evaluated with Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding, Stroop test colour-congruent part and Flexible Attention Test (FAT) Numbers (computerized modification similar to Trail Making A). Executive functions were assessed with the Stroop colour-incongruent part, Hayling Sentence Completion Test, Brixton Spatial Anticipation Test, verbal fluency and FAT Number-Letter

(computerized modification similar to Trail Making B). Working memory was evaluated with Wechsler Memory Scale-III (WMS-III) Letter-Number Sequencing and Digit Span, and FAT Visuospatial Span. Memory was assessed with WMS-III Word Lists and Logical memory, and Rey Complex Figure Test (recall). Visuospatial perception was evaluated with WAIS-IV Block Design and Rey Complex Figure Test (copy), and verbal reasoning with WAIS-IV Similarities.

The distribution of each raw score was checked for non-normality and square root or log transformation was applied where appropriate. Missing values were few and were not replaced. To construct clinically relevant domain scores, the raw scores were first converted into z scores using the distributions of the present sample. The scales were inverted, if necessary, so that higher values represented better performance in all variables. The domain scores were calculated by averaging the z scores within each domain taking into account all available data. A global cognition score was defined as the mean of all 6 standardized domain scores. For the present analysis, we included global cognition, executive functions, processing speed and memory scores as the main cognitive composite measures. In addition, Montreal Cognitive Assessment was used as a measure of general cognitive status for descriptive purposes (Table 1) [30].

Evaluation of quality of life and functional abilities

Quality of life was assessed with self-evaluation using the EUROHIS-Qol index, a shortened version of the World Health Organization Quality of Life Instrument WHOQOL-BREF, consisting of eight questions (overall quality of life, health, energy, finances, daily activities, esteem, relationships and living conditions) [31]. The responses are given on a 5-point Likert scale and the total score is calculated by dividing the sum of all responses by the number of valid responses (≥7 required).

Abilities in everyday activities were evaluated by the subject's informant with the short version of the Amsterdam Instrumental Activities of Daily Living (A-IADL) questionnaire [32]. The questionnaire has undergone comprehensive construct validation and has demonstrated to provide valuable measurement across different countries [33]. The short A-IADL questionnaire includes 30 items assessing difficulty with a wide range of activities (household, appliances, handling finances, work, computer, leisure activities). Items are scored on a range from 0 (no difficulty) to 4 (unable to perform the activity), in which current performance is compared to past performance. Total scores are calculated based on item response theory and higher scores indicate better functioning.

Statistical analyses

Data were analyzed using SPSS 25 and Jamovi 1.6.23. Cognitive scores, gait speed, TUG, single-leg stance, EUROHIS-Qol, A-IADL questionnaire, WMH volume and GM volume were analyzed as continuous variables, whereas SPPB, recent falls and subjective walking difficulties were analyzed as dichotomous variables. Complete data for each subject was available for all cognitive composite scores, MRI measures, falls and subjective walking difficulties, while there were a few sporadic missing observations in SPPB ($n = 2$), TUG ($n = 2$), single-leg stance ($n = 4$), gait speed ($n = 2$) and EUROHIS-Qol ($n = 4$). Data of the proxy-based A-IADL questionnaire was available for 132 patients, who as a group did not differ from those with missing data ($n = 20$) in age, education, or WMH and GM volumes ($p > 0.05$), but they were more often men (Pearson $\chi^2 = 5.0$, $p = 0.026$). No imputation of missing data was done (available-case analysis).

The relationships between MRI measures, motor performances and cognitive scores were analyzed with separate logistic regression models for the dichotomous dependent variables and with linear regression models for the continuous variables. Further analyses focused on the continuous variables only. Interaction terms were added to the linear regression models to examine the combined effects of motor and cognitive functions on quality of life and IADL. Finally, mediation analyses were carried out with the PROCESS 3.5 for SPSS to examine the extent to which cognitive and motor functions explain the association between WMH and functional outcome [34]. All models were adjusted for age, sex and years of education. Statistical significance was set at 0.05 and false discovery rate (FDR) method was used as the multiplicity correction within sets of linear regression analyses (cognitive and motor variables in Tables 2–4).

RESULTS

Characteristics of the subjects

Demographic and clinical characteristics and MRI findings of the subjects are described in Table 1. Subject's age (65–75 years) correlated significantly with GM volume (Pearson $r = 0.19$, $p = 0.018$), but not with WMH volume ($r = 0.16$, $p = 0.057$).

Associations between MRI volumetrics, motor functions and cognitive performance

After adjusting for age, sex and education, WMH volume was associated with subjective walking difficulties (OR 2.5, CI 95% 1.0–6.3, $p = 0.047$) and impaired SPPB score ≤10 (OR 3.0, CI 95% 1.2–7.8, $p = 0.024$), but not with recent falls. GM volume was inversely associated with impaired SPPB (OR 0.99, CI 95% 0.972–0.998, $p = 0.029$), but not with walking difficulties or recent falls.

The associations between WMH and GM volumes and the continuous motor and cognitive measures were all significant (FDR-adjusted), except for the relationship between GM and single-leg stance (Table 2).

As shown in Table 3, cognitive functions were significantly associated with most of the motor performances (FDR-adjusted). The strongest relationships were observed between global cognition and

TABLE 2 Associations of the total volumes of cerebral white matter hyperintensities (WMH) and gray matter (GM) with motor and cognitive functions

	WMH volume		GM volume	
	Stand. β (CI 95%)	p (p^{FDR})	Stand. β (CI 95%)	p (p^{FDR})
Motor functions				
Gait speed	−0.25 (−0.41−−0.9)	0.002 (0.003)	0.21 (0.05–0.37)	0.011 (0.015)
Single-leg stance	−0.32 (−0.47−−0.18)	<0.001 (<0.001)	0.15 (−0.01–0.31)	0.059 (0.059)
Timed up and go	0.29 (0.14–0.44)	<0.001 (<0.001)	−0.32 (−0.48−−0.17)	<0.001 (<0.001)
Cognitive functions				
Global cognition	−0.26 (−0.40−−0.12)	<0.001 (<0.001)	0.25 (0.11–0.39)	<0.001 (0.002)
Executive functions	−0.27 (−0.42−−0.13)	<0.001 (<0.001)	0.21 (0.06–0.36)	0.005 (0.009)
Processing speed	−0.26 (−0.41−−0.11)	<0.001 (0.001)	0.19 (0.03–0.34)	0.019 (0.022)
Memory	−0.18 (−0.33−−0.04)	0.015 (0.015)	0.25 (0.11–0.40)	<0.001 (0.002)

Note: Standardized β coefficients (CI 95%) and p values (p^{FDR}, false discovery rate adjusted p values) from linear regression analyses with white matter hyperintensities (WMH) and gray matter (GM) volumes as independent variables and cognitive/motor functions as dependent variables. The associations were examined in separate models adjusted for age, sex and years of education.

TABLE 3 Relationships between motor and cognitive performances

	Gait speed		Single-leg stance		Timed up and go	
	Stand. β (CI 95%)	p (p^{FDR})	Stand. β (CI 95%)	p (p^{FDR})	Stand. β (CI 95%)	p (p^{FDR})
Global cognition	0.38 (0.21–0.56)	<0.001 (<0.001)	0.35 (0.18–0.51)	<0.001 (<0.001)	−0.40 (−0.57−−0.24)	<0.001 (<0.001)
Executive functions	0.38 (0.21–0.55)	<0.001 (<0.001)	0.43 (0.27–0.58)	<0.001 (<0.001)	−0.34 (−0.50−−0.17)	<0.001 (<0.001)
Processing speed	0.33 (0.17–0.50)	<0.001 (<0.001)	0.26 (0.10–0.42)	0.001 (0.002)	−0.37 (−0.52−−0.21)	<0.001 (<0.001)
Memory	0.26 (0.09–0.44)	0.003 (0.003)	0.14 (−0.03–0.30)	0.113 (0.113)	−0.30 (−0.47−−0.14)	<0.001 (<0.001)

Note: Standardized β coefficients (CI 95%) and p values (p^{FDR}, false discovery rate adjusted p values) from linear regression analyses with cognitive functions as independent variables and motor functions as dependent variables in separate models. All analyses were adjusted for age, sex and years of education.

TUG test, and between executive functions and single-leg stance time (Cohen's f^2 0.14–0.17) roughly corresponding to medium effect sizes after adjustment for confounders [35].

MRI, cognitive and motor predictors of quality of life and disability

Both WMH and GM volumes were significantly related to informant-evaluated IADL (standardized β −0.28 and 0.24, respectively, $p < 0.01$), but not with self-evaluated quality of life. Nearly all motor and cognitive measures were associated with quality of life and IADL (FDR-adjusted) (Table 4). Quality of life was most strongly predicted by the TUG test (Cohen's f^2 0.19), whereas IADL was most strongly predicted by global cognition and the TUG test (Cohen's f^2 0.12 and 0.11, respectively).

We further examined the combined effects of motor and cognitive functions on quality of life and IADL by adding the centered predictor variables and their interaction terms in the models adjusted for the demographic factors. We found significant interactions between several cognitive and motor functions on IADL suggesting synergistic effects between these two factors on functional outcome, but only one (memory × gait speed) on quality of life, which did not survive the FDR correction (Table 4). Specifically, low cognitive scores together with poorer performance in the TUG test and gait speed were strongly related to impaired IADL. As seen in Figure 1, subjects with low performance in both cognitive and motor assessments had disproportionally low scores in IADL, while either impairment alone had little impact.

Mediation analysis

Finally, we tested whether the cognitive and motor performances with the strongest relationships with IADL (global cognition and TUG) mediated the relationship of WMH or GM volume with IADL by using multivariable linear regression and the PROCESS macro for SPSS to estimate bootstrapped confidence intervals for the indirect

TABLE 4 Associations and interactions of motor and cognitive functions on quality of life and instrumental activities of daily living (IADL)

	Quality of life		IADL	
	Stand. β (CI 95%)	p (p^{FDR})	Stand. β (CI 95%)	p (p^{FDR})
Motor functions				
Gait speed	0.29 (0.13–0.45)	<0.001 (0.002)	0.26 (0.08–0.44)	0.004 (0.008)
Single-leg stance	0.19 (0.01–0.36)	0.041 (0.048)	0.23 (0.04–0.42)	0.016 (0.016)
TUG	−0.42 (−0.59–−0.27)	<0.001 (<0.001)	−0.35 (−0.53–−0.17)	<0.001 (<0.001)
Cognitive functions				
Global cognition	0.25 (0.07–0.44)	0.007 (0.017)	0.37 (0.19–0.56)	<0.001 (<0.001)
Executive functions	0.24 (0.06–0.42)	0.008 (0.014)	0.24 (0.06–0.43)	0.011 (0.013)
Processing speed	0.16 (−0.01–0.34)	0.067 (0.067)	0.31 (0.13–0.49)	<0.001 (0.002)
Memory	0.19 (0.01–0.37)	0.035 (0.049)	0.27 (0.08–0.46)	0.006 (0.008)
Interactions				
Global cognition × gait speed	−0.12 (−0.28–0.05)	0.159 (0.382)	−0.27 (−0.43–−0.11)	0.001 (0.002)
Global cognition × single-leg stance	−0.10 (−0.26–0.07)	0.264 (0.395)	−0.11 (−0.028–0.06)	0.200 (0.200)
Global cognition × TUG	0.15 (−0.01–0.32)	0.068 (0.405)	0.27 (0.11–0.43)	0.001 (0.002)
Executive × gait speed	−0.09 (−0.26–0.08)	0.286 (0.344)	−0.25 (−0.42–−0.08)	0.004 (0.007)
Executive × single-leg stance	−0.08 (−0.25–0.09)	0.363 (0.363)	−0.14 (−0.31–0.03)	0.108 (0.117)
Executive × TUG	0.09 (−0.08–0.26)	0.274 (0.366)	0.19 (0.02–0.37)	0.028 (0.042)
Processing speed × gait speed	−0.08 (−0.25–0.08)	0.311 (0.339)	−0.29 (−0.45–−0.13)	<0.001 (0.001)
Processing speed × single-leg stance	−0.11 (−0.28–0.05)	0.184 (0.369)	−0.18 (−0.35–−0.02)	0.031 (0.037)
Processing speed × TUG	0.14 (−0.03–0.30)	0.110 (0.330)	0.34 (0.18–0.49)	<0.001 (<0.001)
Memory × gait speed	−0.19 (−0.35–−0.03)	0.019 (0.228)	−0.31 (−0.47–−0.15)	<0.001 (<0.001)
Memory × single-leg stance	−0.10 (−0.27–0.06)	0.221 (0.380)	−0.19 (−0.36–−0.02)	0.028 (0.037)
Memory × TUG	0.14 (−0.02–0.29)	0.088 (0.351)	0.33 (0.17–0.49)	<0.001 (<0.001)

Note: The main effects were analyzed by separate linear regression models with cognitive/motor functions as independent variables and quality of life/IADL as dependent variables. Interaction terms were added in a second set of models. All analyses were adjusted for age, sex and years of education. Values are standardized β coefficients (CI 95%) and p values (p^{FDR}, false discovery rate adjusted p values). TUG, Timed up and go test.

effects [34]. The direct effects between the variables are presented in Tables 2 and 4 and the significant indirect effects in Figure 2. Controlling for age, sex and education, the relationship between WMH and IADL was mediated by global cognition, which reduced the strength and thereby explained 28% of the association (standardized β for WMH decreased from −0.284 to −0.206). Global cognition also mediated the relationship between GM volume and IADL by 38% (standardized β for GM decreased from 0.239 to 0.149). Both indirect effects were significant: β −0.913, CI 95% −2.317–−0.065 and β 0.014, CI 95% 0.001–0.033, respectively ($p < 0.05$). Performance in the TUG test significantly mediated the relationship between GM volume and IADL explaining 46% of the association (standardized β for GM decreased from 0.240 to 0.130; indirect effect β 0.016, CI 95% 0.004–0.033). However, the indirect effect of TUG on the association between WMH and IADL did not reach significance.

DISCUSSION

This study elaborated the complex relationship and clinical importance of cognitive and motor disturbances in older individuals with different degrees of SVD-related brain changes. We first confirmed the significance of WMH and GM volumes as predictors of motor, cognitive and functional impairments. We then showed that various aspects of motor and cognitive functions were strongly related to each other, and that combinations of motor and cognitive deficits had synergistic effects on functional impairment in IADL. Moreover, we demonstrated that the associations of WMH and GM with IADL were largely explained by related cognitive and motor deficits.

The association of WMH with reduced mobility in the elderly has been well established. The severity of WMH has been related to falls [17,36] and disturbances in gait, balance and functional mobility [16,19,37]. In addition, brain atrophy as indicated by GM volume or cortical thinning has correlated with gait disturbances [20,21]. In this study, both WMH and GM volumes were significantly associated with various manifestations of motor disturbances such as impaired SPPB score, gait speed, balance and TUG performance, but not with self-reported recent falls. The associations of WMH and brain atrophy with cognitive decline in SVD has also been established in numerous studies [8,10,38,39]. Expectedly, in the present sample, both findings were strongly linked with impairment in global cognition and in specific domains.

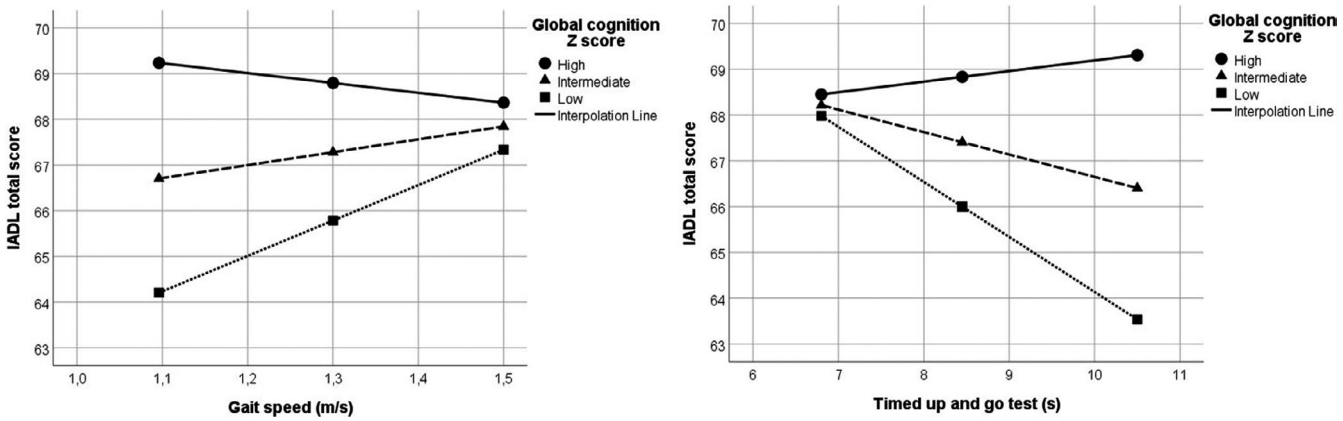

FIGURE 1 Combined associations of global cognitive and motor performances with instrumental activities on daily living (IADL) in subjects with WMH. Global cognition *z* score is depicted with interpolation lines according to 16th, 50th and 84th percentiles (low, intermediate and high performance, respectively) to show its potentiating effect on the associations between motor performances and IADL. Subjects with low performances in both cognitive and motor measures had the poorest outcome in IADL. The results of the interaction analyses are presented in Table 4

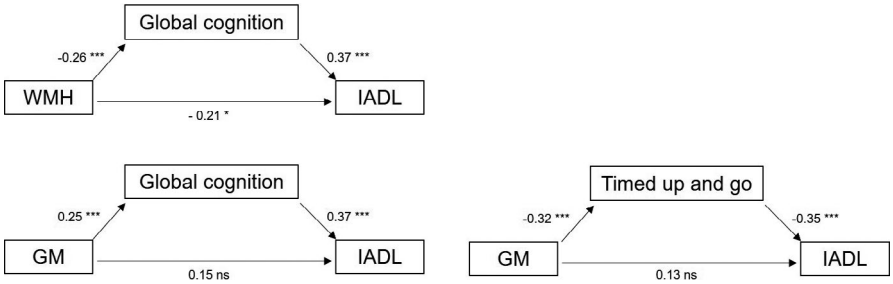

FIGURE 2 The relationship between white matter hyperintensities (WMH) and instrumental activities of daily living (IADL) was mediated by global cognition, whereas the relationship between gray matter (GM) volume and IADL was mediated by global cognition and timed up and go performance. Standardized β coefficients of linear regression analyses are presented adjacent to arrows (***$p < 0.001$; *$p < 0.05$; ns, non-significant). The indirect effects were significant adjusting for age, sex and education

Majority of previous studies have examined the cognitive and motor symptoms of SVD separately, so their mutual relationships have not been elucidated. To address this gap, we showed a consistent pattern of associations between various aspects of motor and cognitive functions independently of sociodemographic factors. Gait speed, balance and the TUG test reflecting functional mobility were prominently associated with global cognition, executive functions and processing speed, whereas memory had weaker relations with motor abilities. Meta-analyses of studies with healthy elderly have suggested a close link between cognitive performance and risk of falls as well as gait dysfunction [4,40]. Of cognitive domains, executive functions have been most commonly connected with mobility [1,4,41]. Very few studies have focused on the interrelations of cognition and mobility in patients with cerebrovascular disease. Recently, associations between measures of motor and cognitive abilities have been reported in older individuals with atrial fibrillation, although these relationships were not related to cerebral lesion burden [42]. In chronic cerebrovascular disease, executive functions, but not global cognition, has been associated with risk of falls, while balance had no correlations with neuropsychological measures [43].

The role of WMH in old-age disability in IADL has been well documented [6]. We observed both WMH and GM volumes to be associated with IADL as evaluated by the patient's close informant. There were no significant relationships between the volumes and self-rated quality of life reflecting overall satisfaction to personal health, daily activities and life conditions. Although SVD-related brain changes are shown to be critical to functional abilities, they seem not to have a prominent association with subjective well-being at preclinical stage. However, several measures of cognitive and motor functions were directly related to both IADL and quality of life, the most significant predictors being TUG and global cognition.

Of particular importance is that motor and cognitive deficits showed consistent synergistic interactions on IADL. Subjects with low scores in both cognitive and motor measures had remarkably poor IADL as compared to those with impairment in only one function. This over and above effect was apparent for all cognitive and motor measures, although the interactions with balance were somewhat weaker. To our knowledge, such findings have not been reported before in SVD. In a community sample, Rosano et al. have demonstrated an additive combined association of processing speed

and gait speed with disability in basic daily activities, but the interaction between these measures did not reach significance [44].

Furthermore, our results indicated that the association between WMH volume and IADL was mediated and thereby partly explained by global cognitive dysfunction. The association between GM volume with IADL, in turn, was mediated by functional mobility (TUG) and global cognition. Although age-related WMH and brain atrophy as well as cognitive and motor deficits are known to co-occur, these indirect pathways have not been statistically proven before.

Taken together, the results support the view that deterioration of motor and cognitive functions are interrelated processes and should not be seen as separate coincidental problems. Gait and cognitive deficits coexist already in the early stages of aging and are important determinants of old-age disability [45]. The interplay between cognitive and motor disturbances may reflect compromised integrity in shared neuronal networks and watershed brain regions susceptible to vascular risk factors and microvascular damage. In particular, frontal atrophy and WMH may simultaneously cause dysfunction in motor and cognitive systems because of the proximity of frontal subcortical networks controlling for both functions [45].

Our study is limited by the cross-sectional design, which precludes interpretations of causal relationships. Instead of analyzing the full variety of SVD-related brain changes [15], we focused on WMH and GM volumes shown to have the strongest associations with clinical outcomes [8]. Since subjects with cortical and large subcortical infarcts were excluded, there were only a few cases with small chronic infarcts evident on MRI. The age range of this study (65–75 years) provides a time window in which SVD brain changes and preclinical cognitive decline are already present, but the likelihood of coexisting neurodegenerative disorders is low. However, the results may not fully represent older age groups or more severe stages of vascular cognitive impairment. Moreover, 13% of the subjects did not have an evaluation of IADL given by an informant. These subjects were otherwise comparable to the rests of the sample, but women were overrepresented, introducing possible selection bias.

The strengths of the study are the detailed evaluations of motor, cognitive and functional abilities with objective well-validated tests. Neuropsychological assessment included multiple psychometrically sound tests within each domain to achieve robust composite measures for relevant cognitive domains. As recommended based on recent meta-analysis, a comprehensive test battery is necessary to accurately assess the full extent of SVD-related cognitive impairments [15]. The raw scores were converted into comparable domain scores based on the present sample instead of normative data. In addition to age and sex, all our analyses were controlled for education, which is an important indicator of individual cognitive reserve [22].

In conclusion, this study highlights the combined effects of cognitive and motor impairments on functional outcome in covert SVD. Deficits in gait, balance and functional mobility had strong connections with global cognition, executive functions, processing speed and memory, and these dysfunctions together had synergistic detrimental associations with IADL. The findings also suggest that more severe WMH load and reduced GM volume contribute to disability in IADL through impaired global cognition and functional mobility. The results have profound clinical implications underlining the need for comprehensive approach in the assessment and management of SVD. Patients with both cognitive and motor impairments are at disproportionate risk for poor outcome and may benefit from multidomain interventions to promote functional independence.

CONFLICT OF INTEREST

S.A.M. Sikkes provided consultancy services for Boehringer and Toyama, and received license fees for the use of the Amsterdam IADL Questionnaire: all funds were paid to her institution. J. Koikkalainen is a shareholder at Combinostics Ltd. J. Lötjönen received lecture fees from Merck and Sanofi, and is a shareholder at Combinostics Ltd. The other authors report no disclosures relevant to the manuscript.

AUTHOR CONTRIBUTIONS

Hanna Jokinen: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (equal); Investigation (lead); Methodology (lead); Project administration (equal); Supervision (equal); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Hanna Maria Laakso:** Data curation (equal); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Matti Ahlström:** Data curation (equal); Investigation (equal); Writing-review & editing (equal). **Anne Arola:** Data curation (equal); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Juha Elias Lempiäinen:** Data curation (equal); Investigation (equal); Writing-review & editing (equal). **Johanna Pitkänen:** Data curation (equal); Formal analysis (equal); Investigation (equal); Writing-review & editing (equal). **Teemu Paajanen:** Methodology (equal); Software (equal); Writing-review & editing (equal). **Sietske Sikkes:** Methodology (equal); Software (equal); Writing-review & editing (equal). **Juha Koikkalainen:** Methodology (equal); Software (equal); Writing-review & editing (equal). **Jyrki Lötjönen:** Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Antti Korvenoja:** Conceptualization (equal); Methodology (equal); Writing-review & editing (equal). **Timo Erkinjuntti:** Conceptualization (lead); Funding acquisition (equal); Methodology (lead); Project administration (lead); Resources (lead); Supervision (equal); Writing-review & editing (equal). **Susanna Melkas:** Conceptualization (lead); Funding acquisition (lead); Methodology (lead); Project administration (lead); Resources (lead); Supervision (lead); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Tab S1

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