The Impact of Covert Lacunar Infarcts and White Matter Hyperintensities on Cognitive and Motor Outcomes After Stroke

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Background and Aims: In addition to overt stroke lesions, co-occurring covert lesions, including white matter hyperintensities (WMH) and covert lacunar infarcts (CLI), contribute to poststroke outcome. The purpose of this study was to examine the relationship between covert lesions, and motor and cognitive outcomes in individuals with chronic stroke. *Methods:* Volumetric quantification of clinically overt strokes, covert lesions (periventricular and deep: pWMH, dWMH, pCLI, dCLI), ventricular and sulcal CSF (vCSF, sCSF), and normal appearing white (NAWM) and gray matter (NAGM) was performed using structural magnetic resonance imaging. We assessed motor impairment and function, and global cognition, memory, and other cognitive domains. When correlation analysis identified more than one MR parameter relating to stroke outcomes, we used regression modeling to identify which factor had the strongest impact. *Results:* Neuropsychological and brain imaging data were collected from 30 participants at least 6 months following a clinically diagnosed stroke. Memory performance related to vCSF ($r = -0.52$, $P = .004$). The strongest predictor of nonmemory domains was pCLI ($r^2 = 0.28$, $P = .004$). Motor impairment and function were most strongly predicted by the volume of stroke and NAWM ($r^2 = 0.36$; $P = .001$), and dWMH ($r^2 = 0.39$; $P = .001$) respectively. *Conclusions:* Covert lesion type and location have important consequences for post-stroke cognitive and motor outcome. Limiting the progression of covert lesions in aging populations may enhance the degree of recovery post-stroke.
Key Words: Cerebral ventricle−cerebral small vessel disease−outcome−magnetic resonance imaging−white matter−upper-limb function and impairment

Background and Aims

Better interventions are critically needed to help the rising number of stroke survivors living with residual motor and cognitive disabilities. To do so, we need to expand our understanding of how neuroimaging biomarkers may predict stroke recovery/outcome.[1] Accurate prediction would enable appropriate allocation of

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resources, setting of realistic goals, and help improve the quality of rehabilitation trials by controlling for potential confounding difference. Previous work sought to establish a link between stroke size, location, and outcome.[2,3] Yet, these relationships are weak or lacking, particularly for cognitive outcomes.[2,3] suggesting that measures of lesion volume and location are inadequate to predict outcome after stroke. Advances in brain imaging and analysis techniques have improved volumetric analysis of brain tissue compartments and lesions.[4] Cerebral small vessel disease is highly prevalent especially in people with stroke, and results in covert lesions, including white matter hyperintensities (WMH) and covert lacunar infarcts (CLI).[5] WMH impact the recovery process after stroke[6] and their presence predicts poorer outcome.[2,7-9] Though studies in healthy elders demonstrate that collectively WMH and CLI impact cognitive and motor performance, and increase the risk of dementia,[10,11] little is known about the combined impact of WMH and CLI on stroke outcome.[12,13] Both cognitive and motor outcomes significantly contribute to poststroke quality of life;[14] however, many studies assessing the impact of covert lesions fail to adequately address the influence of each of these factors on poststroke outcome.[9,15,16]

Volumetric measures, including size of the primary stroke and covert lesions, normal appearing white/gray matter, and cerebrospinal fluid (CSF) must be considered to determine whether they are effective indicators of poststroke outcome. Past work has failed to comprehensively consider both cognitive and motor assessments in the same study, as such we do not understand the differential effects of covert lesions on these two important aspects of stroke outcome. Therefore, the aim of the current study was to measure global brain parenchymal volume (defined as normal appearing white and gray matter; NAWM, NAGM), ventricular and sulcal CSF (vCSF/sCSF), together with lesion volumes (stroke, CLI, and WMH) to identify the MR parameters that relate to chronic stroke cognitive and motor outcomes. We hypothesize that MR measures reflective of covert lesion load will be the best predictors of cognitive and motor outcomes.

Methods

Participants

Participants at least 6 months following a clinically diagnosed stroke, ischemic or hemorrhagic, were recruited from the community. Exclusion criteria were: (1) age <40 or >80, (2) contraindications to magnetic resonance imaging (MRI) scanning, (3) altered communication skills that might interfere with study participation, (4) any other diagnosed neurological or psychiatric disease. The University of British Columbia research ethics board approved all aspects of this study; informed consent was obtained from all participants.

Motor Impairment and Function Assessment

All motor assessments were conducted by a licensed physical therapist (SP). The upper-extremity motor portion of the Fugl-Meyer assessment (FM) was used to index impairment of the hemiparetic arm (max score 66[17]). Motor function of the upper extremity was assessed with the Wolf Motor Function Test, which measures the time to complete 15 tasks.[18] Times for each individual task were used to calculate a mean rate per minute of task performance (Task rate = 60 seconds/performance time [sec]) with the average task rate used for subsequent analysis.[19] The FM and Wolf Motor Function Test are valid and sensitive measures of upper extremity motor impairment and function in individuals with stroke.[17,18]

Neuropsychological Testing of Cognitive Function

Memory function was assessed with: California Verbal Learning Test (immediate, delayed, and recognition),[20] and WMS Visual reproduction (short delay, long delay, and recognition).[21] Nonmemory functions were assessed with: Blocks,[22] Symbol Search[22] Word Association,[23] Backwards Digit Span,[22] Forward Digit Span,[22] and Trails Making A&B.[24] Raw scores were converted into standardized scores controlled for age and level of education with reference to published normative data,[20-24] and an average Z-score was calculated for memory and nonmemory cognitive performance.

Image acquisition Protocol

MRI was acquired at the University of British Columbia MRI Research Center on a Philips Achieva 3.0 Tesla whole body MRI Scanner (Phillips Healthcare, Andover, MD) using an 8-channel sensitivity encoding head coil. A T1-weighted (axial 3D SPGR: 3.1 ms TE, 6.8 ms TR, 1 NEX, 9° flip angle, 22 × 16.5 cm FOV, 0.859 × 0.859 mm in-plane resolution, 1 mm slice thickness), an interleaved proton density and T2-weighted (interleaved axial dual-echo spin echo: 30 and 80 ms TEs, 3 s TR, 0.5 NEX, 90° flip angle, 20 × 20 cm FOV, 0.781 × 0.781 mm in-plane resolution, 3 mm slice thickness), and fluid-attenuated inversion recovery (FLAIR: 90 ms TE, 9 s TR, 90° flip angle, 24 × 24 cm FOV, 3 mm slice thickness) were acquired from each participant.

Image Processing

All strokes were confirmed by imaging and were manually traced by an experienced rater (AA) on T1, confirmed with comparison to T2 and FLAIR, and verified by a research radiologist (FQG). Using a multifeature segmentation (T1, T2, proton density, and FLAIR), a previously validated semiautomatic image processing pipeline, Lesion Explorer,[4] was used to segment the brain into NAGM/NAWM, vCSF/sCSF, covert lacunar infarcts (CLI), and WMH. Covert lesions were further subdivided

into periventricular (pCLI, pWMH) and deep (dCLI, dWMH) by classifying all CLI/WMH connected in 3D to the ventricles as periventricular, with the remaining volumes classified as deep. An experienced technician (AA) confirmed all segmented lesions using appearance, size, and location. All brain volumes were corrected for head-size by expressing the tissue volumes as a percentage of the supratentorial total intracranial volume (TIV; TIV = NAGM + NAWM + vCSF + sCSF + stroke + CLI + WMH).

Statistical Analysis

Normality of the data was examined using Q-Q plots and the Shapiro-Wilk test. Non-normally distributed variables (pWMH, dWMH, pCLI, dCLI, stroke volume) were log transformed to create a normal distribution for parametric analysis. Quantitative variables were expressed as mean ± SD.

The relationship between motor impairment and cognitive outcome was assessed with planned Pearson's correlations analysis between cognitive outcomes (nonmemory, memory) and FM scores.

Correlation between MRI tissue volumes and cognitive and motor outcomes

Planned Pearson's correlations between MR volumes (NAWM, NAGM, pWMH, dWMH, pCLI, dCLI, vCSF, sCSF, stroke) and cognitive (nonmemory, and memory performance) and motor (impairment, and function) outcomes were completed to identify significant relationships. Bonferroni corrections were used for a significant cutoff ($P \leq 0.05/9 = 0.005$) because of the 9 MR volumes that were assessed. For significant correlations, further partial correlations were completed controlling for the potential contribution of stroke volume, age, and time-post stroke. Education was added as an additional control variable for the cognitive outcomes. Because of the selective number of partial correlations completed, $P < .05$ was considered significant.

Linear regression analyses

For outcome measures that had multiple significant relationships with MR parameters ($P \leq .005$), multivariate linear regression with stepwise elimination was used to determine the most informative variables in predicting outcomes. Outcome scores (nonmemory, motor impairment, and motor function) were entered as the dependent variable and the imaging parameters that significantly correlated with each outcome measure were entered into the model. We assessed the variance inflation factors (all ≤ 1.37) ensuring that we could use each independent variable directly. Regression models were considered significant at $P < .05$. SPSS version 20.0.0 was used for all statistical analyses.

Results

Participant Demographics and Motor and Cognitive Outcomes

Brain imaging and neuropsychological data were collected from 30 participants, who had their last diagnosed stroke at least 6 months before participation in the study. Individual participant demographics and cognitive test results are provided in Supplementary Table 1.

Overt Stroke and Covert Lesion Findings

Overt strokes ranged from 0.16 to 250.45 cc (Fig 1). All participants (30 of 30) had both periventricular and deep WMHs. The majority of participants also had pCLIs 26 of 30, and 19 of 30 had dCLI; only 2 of 30 participants did not show either deep or periventricular CLI. Individual participant lesion volumes are provided in Supplementary Table 1.

Correlations Between Motor Impairment and Cognitive Performance

Motor impairment related to nonmemory cognitive performance (r = 0.38, $P = .04$), and subsequent partial correlations between MRI parameters of interest and nonmemory outcomes were controlled for level of motor impairment (ie, FM score). There was no relationship between motor impairment and memory performance (r = 0.20, $P = .28$).

Correlations Between MR Measures

Several MRI parameters related to each other (Supplementary Tables 2 and 3). No imaging parameters related to NAGM other than NAWM (r = 0.65, $P < .001$). Whereas, NAWM related to vCSF (r = −0.51, $P = .004$), pWMH (r = −0.56, $P = .001$), and dWMH (r = −0.57, $P = .001$), vCSF, in addition to relating to NAWM, also related to pWMH volume (r = 0.51, $P = .004$).

Correlational Analysis Between MR Measures and Cognitive Outcomes

Memory performance related to the vCSF volume (r = 0.53, $P = .003$). Nonmemory performance related to NAWM (r = 0.51, $P = .0004$), pCLI (r = −0.55, $P = .004$), and pWMH (r = −0.53; $P = .003$). All relationships between MR parameters and outcome measures were confirmed with partial correlation analyses (Table 1; Fig 2).

Correlational Analysis Between MR Measures and Motor Outcomes

Motor impairment and function respectively correlated with stroke volume (r = −0.54; r = −0.57), NAWM (r = 0.50; r = 0.54), and dWMH (r = −0.50, r = −0.64, $P \leq .005$; Table 1; Fig 3). Partial correlation found that

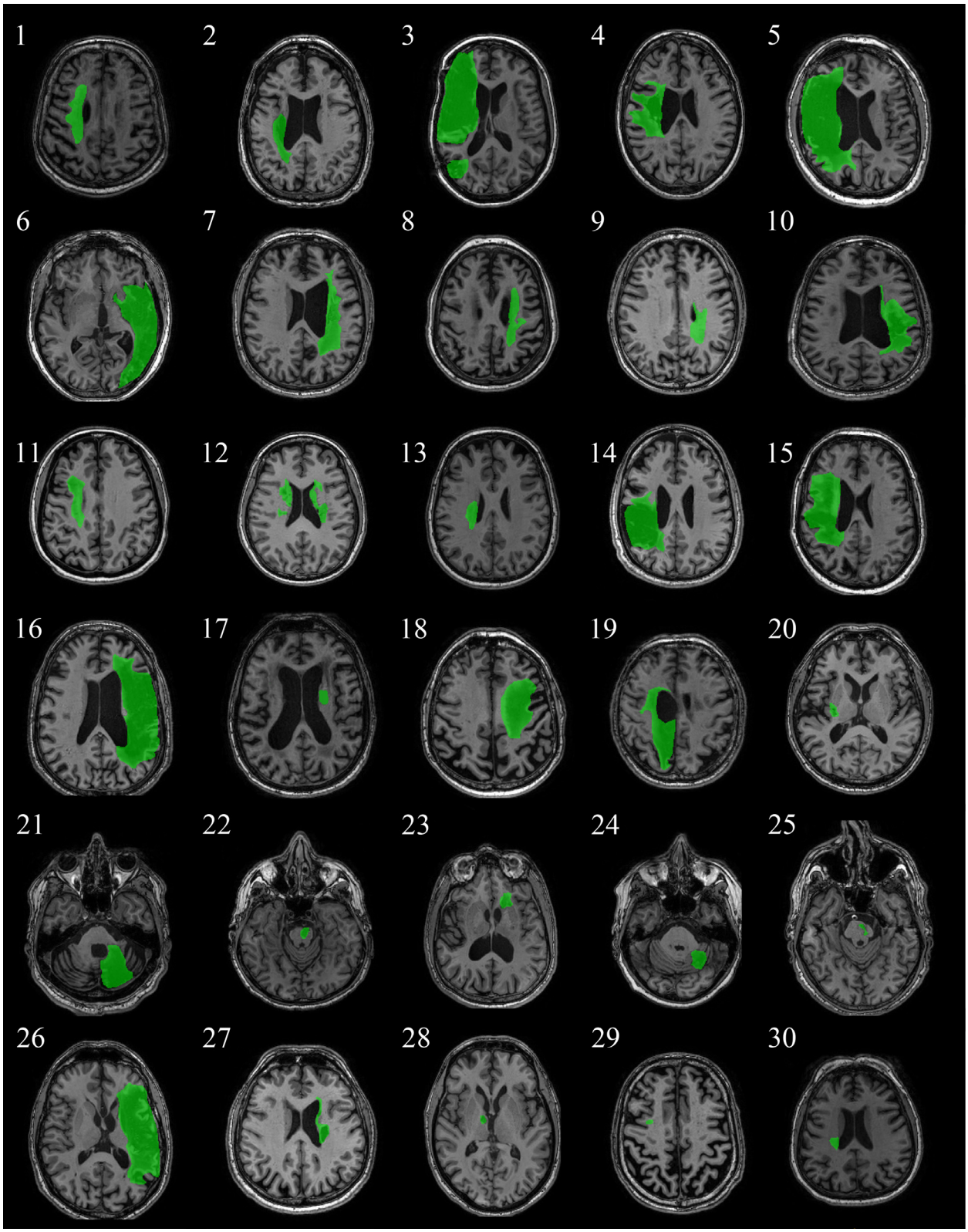

Figure 1. *Stroke profiles of each participant. Each axial T1 image is taken from the site of maximal injury. Stroke lesion is identified in green. Images correspond to the demographic information in Supplementary Table 1.*

Table 1. *Pearson's correlation coefficients between cognitive measures, motor impairment, motor function and MRI parameters*

	Nonmemory Pearson corr (*P* value)	Memory Pearson corr (*P* value)	Fugl-Meyer Pearson corr (*P* value)	WMFT Mean Rate Pearson corr (*P* value)
Stroke	−0.361 (.05)	−0.088 (.64)	**−0.543 (.002*)**	**−0.569 (.001*)**
NAGM	0.456 (.01)	0.258 (.17)	0.151 (.43)	0.149 (.43)
NAWM	**0.508 (.004*)**	0.385 (.04)	**0.498 (.005*)**	**0.536 (.002*)**
sCSF	−0.093 (.62)	−0.210 (.27)	−0.047 (.81)	−0.101 (.60)
vCSF	−0.299 (.11)	**−0.515 (.004*)**	−0.144 (.45)	−0.165 (.38)
pCLI	**−0.551 (.004*)**	−0.306 (.13)	−0.352 (.08)	−0.406 (.04)
pWMH	**−0.525 (.003*)**	−0.423 (.02)	−0.381 (.04)	−0.377 (.04)
dCLI	−0.143 (.56)	−0.006 (098)	−0.386 (.10)	−0.401 (.09)
dWMH	−0.349 (.06)	−0.320 (.09)	**−0.502 (.005*)**	**−0.639 (<.001*)**
Partial correlations controlling for volume of stroke, TPS, and age for all significant correlations identified above.				
NAWM	0.508 (.004†)		0.390 (.04†)	0.436 (.02†)
vCSF		−0.527 (.003†)		
pCLI	−0.577 (.003†)			
pWMH	−0.499 (.007†)			
dWMH			−0.307 (.11)	−0.488 (.007†)

nonmemory comparisons controlled for level of impairment. NAGM/NAWM, normal appearing gray/white matter; pCLI/dCLI, periventricular/deep covert lacunar infarcts; pWMH/dWMH; periventricular/deep white matter hyperintensities; sCSF/vCSF, sulcal/ventricular CSF; WMFT, Wolf Motor Functional Test.

*Correlation is significant at a corrected level $P \leq .005$.

†Correlation is significant at an uncorrected level $P < .05$.

motor impairment significantly related to NAWM (r = 0.39, $P = .04$) but not dWMH (r = −0.31, $P = .11$); and motor function related to NAWM (r = 0.44, $P = .02$) and dWMH (r = −0.49; $P = .01$).

Regression Results Between Cognitive and Motor Outcomes and Tissue Volumes

For regression Model 1, nonmemory performance was the dependent variable, with NAWM, pCLI, and pWMH as independent variables. pCLI was identified as the only significant factor, accounting for 28% of the variance ($P = .004$; Table 2). For regression Models 2 and 3, with motor impairment and function as the dependent variables respectively, the independent variables entered were stroke volume, NAWM, and dWMH. Both stroke volume and NAWM related to motor impairment, accounting for 36% of the variance ($P = .001$). For motor function, dWMH was the only significant predictor, accounting for 39% of the variance ($P < .001$).

Conclusions

In participants with chronic stroke, impaired cognitive performance is associated with greater covert lesion volume. Contrarily, higher levels of motor impairment relate to larger stroke volume. Motor function, evaluated as a timed performance of complex motor output, relates more strongly to covert than overt stroke volume. Our volumetric assessment of multiple MR parameters supports the important link between white matter and motor outcome following stroke, whereby volumes of NAWM, but not NAGM, related to motor impairment and function. Our findings suggest that one reason for this relationship is that NAWM correlates with covert lesion volume whereas NAGM does not, indicating that NAWM may be the stronger indicator of structural brain reserve than NAGM.

Poststroke Cognitive Performance is Associated with Covert Lesion Volume

Periventricular lacunes significantly contribute to global and nonmemory cognitive outcomes after stroke, and do so independently of stroke volume. Our findings are in line with previous research assessing the impact of covert lesions on poststroke cognition. In a study that assessed both CLI and WMH, stroke participants with executive dysfunction had more CLIs and a greater prevalence of WMH classified as moderate-to-severe than stroke participants without executive dysfunction.[13] These results together with our current findings support the conclusion that covert lesions are detrimental to poststroke cognition, and must be considered when relating cognitive deficits to brain damage and outcome.

We demonstrated a link between poststroke memory performance and ventricular CSF, and found that higher ventricular volume correlates with larger periventricular WMH volumes and lower NAWM. Together these findings suggest that ventricular CSF is sensitive to white matter health, and may be a biomarker for chronic poststroke memory function. These results are in accordance with previous findings in aging individuals showing: (1) a relationship between higher ventricular volume and impaired episodic memory,[25] and (2) longitudinal WMH growth related to increased ventricular volume and decreased memory performance.[26] Future studies will need to

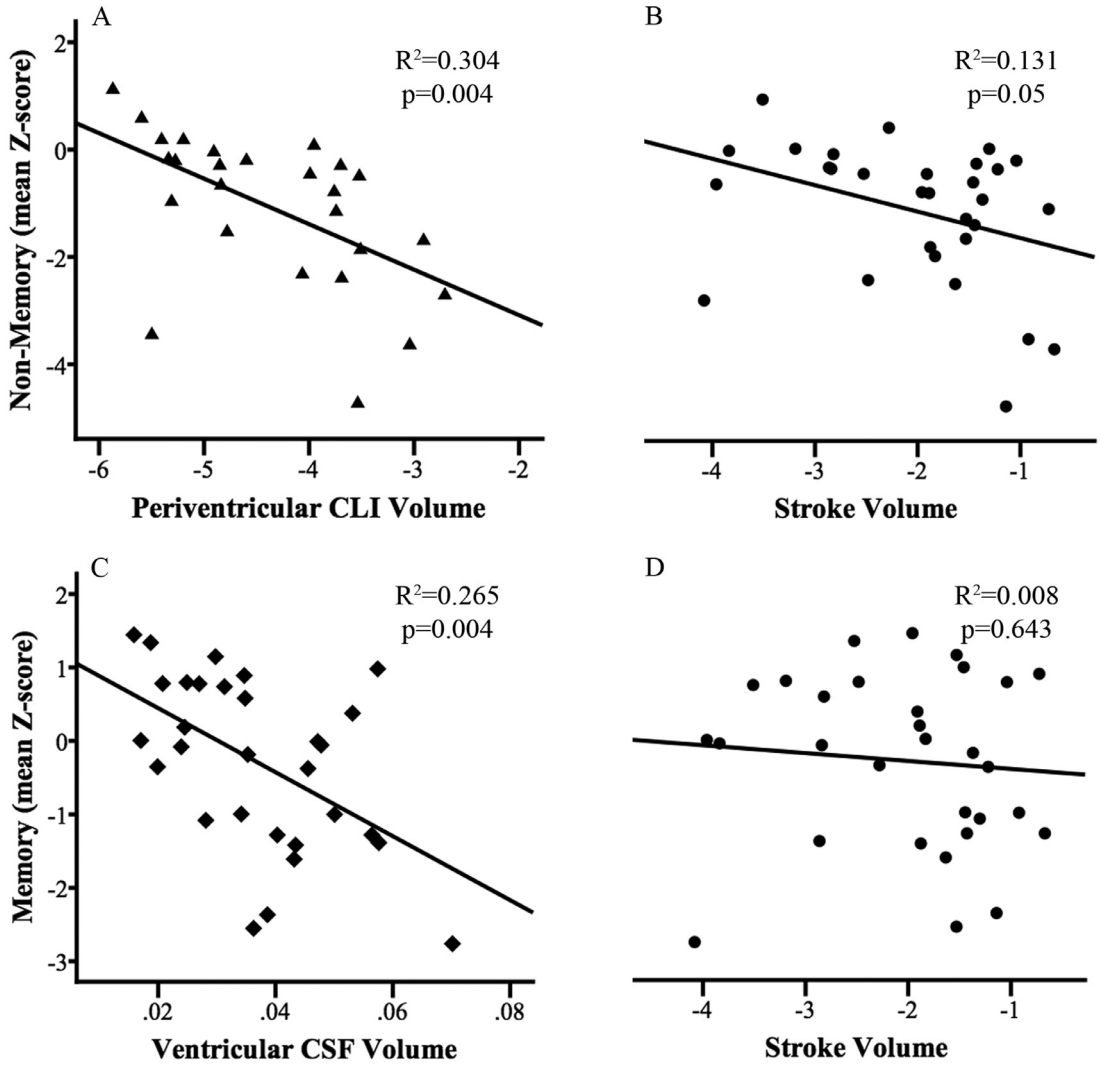

Figure 2. *Correlations between cognitive outcomes, periventricular covert lacunar infarcts (pCLI; A), stroke volume (B and D), and ventricular CSF (C).*

determine if baseline ventricular volume relates to poststroke memory performance, which could provide a valuable marker of brain health and reserve.

Poststroke Motor Impairment and Function are Associated with Stroke Volume and Covert Lesion Volume, Respectively

Three factors related to motor impairment and function are as follows: stroke, NAWM, and deep WMH volumes. However, after individual regression analyses, different primary predictors were identified. Less motor impairment was predicted by smaller stroke and greater NAWM volume, whereas, better motor function was most strongly predicted by smaller deep WMH volume. Motor impairment depends heavily on corticospinal tract output and has a strong association with structural damage after stroke.[3,27] We found that total cerebral volume of NAWM is more predictive of motor outcome than total NAGM. We also found that total white matter also relates to ventricular CSF, and periventricular and deep WMH volume. Suggesting, that total white matter is a more sensitive measure of poststroke structural reserve than total gray matter. Other findings from diffusion imaging studies confirm the importance of white matter in poststroke outcomes.[28] Additionally, integrity of white matter connections, calculated from overlaying lesion maps on previously identified white matter pathways, correlate more strongly with motor function than cognition after stroke,[3] supporting our finding that global NAWM relates to motor but not cognitive outcomes.

We found that dWMH volume correlated with both motor function and impairment but was the strongest predictor of motor function. Motor impairment was indicated by the ability to complete a movement,[17] whereas function was assessed as the time to complete movements (efficiency).[18] This illustrates that disruption of white matter pathways may affect speed of information processing and movement time. There is an established link between higher impairment on complex poststroke motor assessments, and

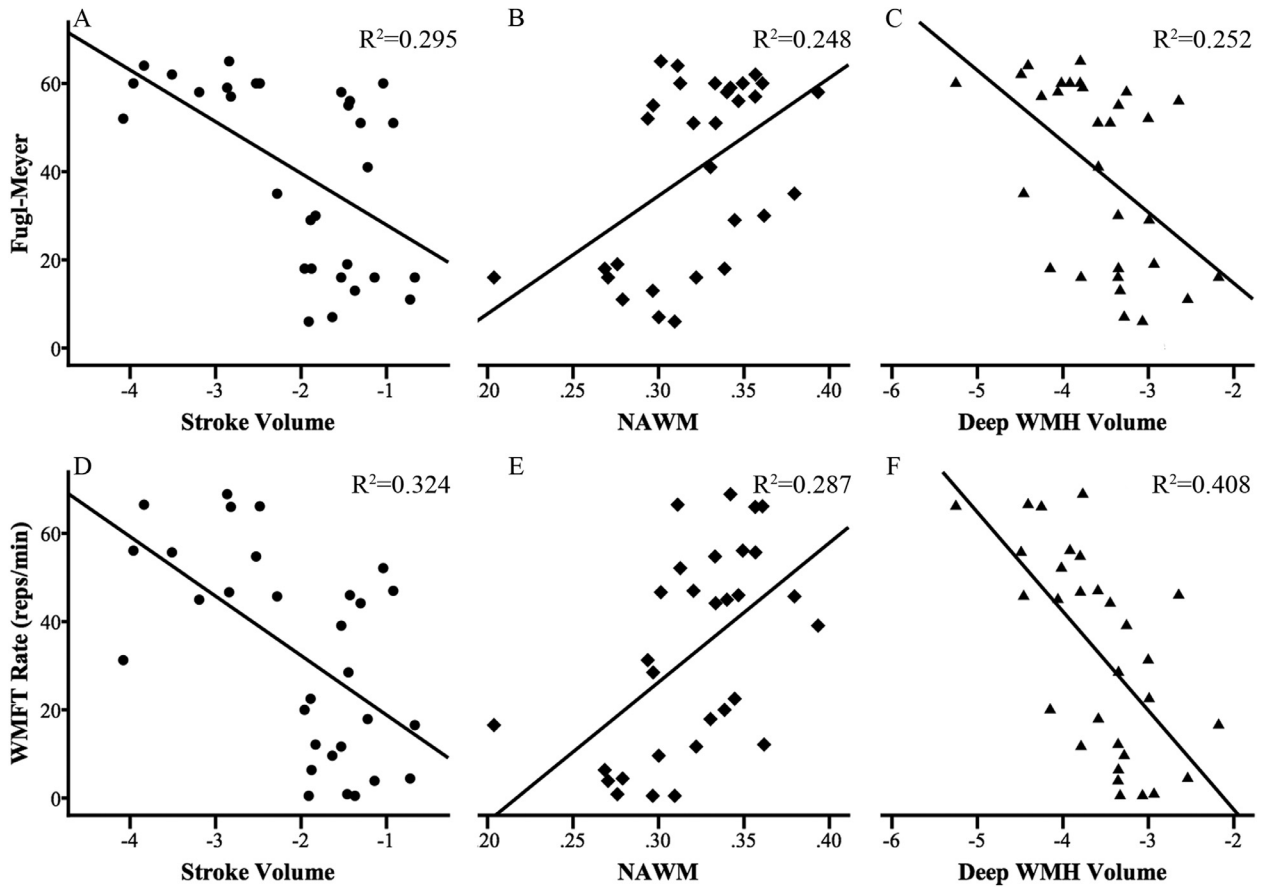

Figure 3. *Correlations between motor outcomes, Fugl-Meyer and Wolf motor functional Test (WMFT), and stroke volume (A, D), normal appearing white matter (NAWM; B, E), and deep white matter hyperintesities (WMH; C, F). All correlations are significant P ≤ .005.*

greater volume of covert lesions.[9,11] Our findings support those of previous researchers but also highlight the need to consider multiple measures of motor outcome to enhance the understanding of how covert lesions may have a greater impact on function than impairment.

Limitations

The current study is a cross-sectional assessment of chronic poststroke outcome, meaning that we could not determine when the covert lesions occurred relative to the overt stroke, or determine recovery profile. We were able to use our knowledge of the primary stroke symptoms to confirm which lesion was the primary stroke. However, it is possible that a primary stroke lesion was misidentified as a covert lesion. We selected a heterogeneous sample of participants, ranging from mild to severe impairment, which may have obscured more nuanced relationships between recovery and covert lesions for different severities and stroke types. Our selection criteria, requiring an MRI and cognitive assessment, limits broad generalizability to a larger stroke population due to the exclusion of individuals with communication difficulties or MRI contraindications.

Table 2. *Multivariate stepwise elimination linear regression models with 3 different dependent variables*

		Adjusted			
Dependent variable used	Independent variables remaining in model	R^2 (*P* value)	Standardized coefficient B	*P* value	95% CI for B
Non Memory	pCLI	0.275 (.004)	−0.551	.004	−1.39 to −0.31
Fugl-Meyer	Stroke		−0.42	.014	−16.08 to −2.01
	NAWM	0.358 (.001)	0.350	.037	12.68 to 363.13
WMFT	dWMH	0.387 (<.001)	−0.639	<.001	−32.95 to −11.98

Models include the MRI variables significantly correlated with dependent variable. CI, confidence interval; dWMH, deep white matter hyperintensity; NAWM, normal appearing white matter; pCLI, periventricular covert lacunar infarct; WMFT, Wolf Motor Functional Test.

Our study provides evidence that covert lesions adversely affect both motor and cognitive outcomes after stroke, and highlights the need to consider their burden on poststroke outcomes. Further studies, utilizing a longitudinal assessment of a representative sample, are needed to characterize the relationship between covert and overt lesions and the combined impact on cognitive and motor recovery.

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Supplementary Materials

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