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Cognitive heterogeneity among community-dwelling older adults with cerebral small vessel disease

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ABSTRACT

Some degree of ischemic injury to white matter tracts occurs naturally with age and is visible on magnetic resonance imaging as focal or confluent white matter hyperintensities. Its relationship to cognition, however, remains unclear. To explore this, community-dwelling adults between the ages 55 and 80 years completed structural imaging, neuropsychological testing, and questionnaires to provide objective measures and subjective experience of executive functioning. Volumetric lesion burden derived from structural MRI identified those with significant white matter hyperintensity burden ($\sim 10\ cm^3$). Half of those recruited met this criterion and were designated as the cerebral small vessel disease (CSVD) group. Subjective cognitive complaints but not objective test scores differentiated adults with and without CSVD. Hierarchical clustering revealed 2 CSVD subgroups that differentiated those with impaired versus preserved executive function relative to controls. Overall these results provide some explanation for behavioral heterogeneity often observed in studies of age-related white matter changes. They also support the use of questionnaires to assess subjective cognitive complaints that may point to subtle effects of vascular pathology not evident on standardized cognitive scores.

1. Introduction

First described by Binswanger (1894), ischemic white matter lesions and small subcortical infarcts are commonly reported in older adults as incidental findings on MRI (Longstreth et al., 2002). Despite much research into the pathological mechanisms surrounding these lesions (Gouw et al., 2011; Rincon and Wright, 2014; Wardlaw et al., 2013a), little is known about their clinical significance and impact on function in the absence of vascular dementia. Even in the absence of trauma, autoimmune disease, or cortical strokes, some degree of white matter damage occurs naturally with age—starting as early as the fifth decade of life (Wen et al., 2009). This is likely due to vascular pathology involving the deep penetrating end arteries of the brain that supply subcortical gray matter structures and white matter tracts, so called cerebral small vessel disease (CSVD) (Wardlaw et al., 2013b). These white matter lesions appear as hyperintensities on T2-weighted magnetic resonance imaging and hence are often referred to as white matter hyperintensities (WMHs). The rate at which WMHs accumulate in older adults is accelerated in those with vascular risk factors (e.g., hypertension, smoking, dyslipidemia [Khan et al., 2007; van Dijk et al., 2008]). While extensive WMHs are associated with vascular dementia (Jellinger, 2013), the relationship between mild to moderate white matter lesion burden and cognition is much less clear. For example, Burns et al. (2005) reported an association between deep and periventricular white matter lesion burden and reduced global cognition (including measures of visual memory, processing speed [PS], and executive function [EF]) in those with dementia, but not in nondemented aging. Nevertheless, a recent meta-analysis has shown that individuals with CSVD without dementia, compared with healthy controls, demonstrate impairment predominantly in the domain of PS and to a slightly lesser extent EF, as measured through neuropsychological testing (Vasquez and Zakzanis, 2015).

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This relatively weaker relationship with EF is surprising as executive dysfunction has long been considered a hallmark feature of vascular cognitive impairment (Prins et al., 2005; Sachdev et al., 2014). One possibility is that the weak relationship between WMH and behavior may reflect considerable heterogeneity within the population wherein some individuals are better able to compensate others, but at the expense of PS. This trade-off between accuracy and speed/efficiency is consistent with the temporal hypothesis for compensation (Martins et al., 2015) and the scaffolding theory of aging and cognition (Reuter-Lorenz and Park, 2014). Both theories posit a role for subjective cognitive complaints (SC) that may provide complementary information regarding cognition beyond what can be captured by traditional laboratory neuropsychological tests. For example, a mismatch between objective and subjective measures (e.g., high SC despite preserved performance) could suggest that performance is being boosted by compensatory processes at the cost of speed.

Another issue is that many studies exploring cognitive impairment in CSVD use a composite measure of EF that linearly combines scores (with equal weight) from a collection of diverse neuropsychological tests that were originally designed to assess different components of EF (Lawrence et al., 2015). This is problematic because EF is an umbrella term used to refer to a large collection of complex processes (Miyake et al., 2000)—abilities that may not be equally affected by WMHs.

While addressing the limitations aforementioned, this investigation has 2 major aims. The first is to study the relationship between WMH burden and objective and subjective measures of executive functioning in a sample of older, community-dwelling adults with multiple vascular risk factors. The second aim is to identify the pattern of cognitive changes, whether observable or experienced, associated with CSVD. We hypothesize that in older, community-dwelling adults, there will be a significant negative relationship between PS (and to a lesser extent EF) and WMH burden as well as a significant positive relationship between WMH burden and SC. Consistent with a compensation hypothesis (Martins et al., 2015), we predict that behavioral subgroups will emerge within the CSVD population, differentiating those with preserved EF (relative to age-matched controls) but slower PS, and those with reduced executive functioning.

2. Method

2.1. Inclusion/exclusion criteria

Inclusion criteria consisted of age between 55 and 80 years with at least one vascular risk factor from the following list: hypertension, hyperlipidemia, diabetes mellitus type 2, sleep apnea, active or history of cigarette smoking, history of transient ischemic attack, significant first-degree family history of cerebrovascular disease, or advanced age equal to or greater than 70 years. Risk factor information was recorded during screening and assessed based on self-report and/or prescription drug use (Dey et al., 2015). All participants were required to be fluent in written and spoken English. Aside from presence of CSVD-related lesions (WMHs and lacunes) on imaging, participants were otherwise healthy with no significant history of head trauma including concussion, cortical stroke, and/or other neurological/psychiatric conditions that may unduly affect cognitive performance. As this study focuses on mild-moderate CSVD, any participants with a clinical diagnosis of dementia or meeting criteria for dementia were excluded regardless of WMH burden. Dementia was identified by self/other report of a pre-existing diagnosis and reported impaired activities of daily living. Other exclusion criteria included MRI contraindications, significant speech or language impairment (aphasia), and/or any significant motor or sensory deficits (e.g., uncorrected visual impairment) that may interfere with their ability to take part in the study. Pharmacological history was reviewed for each participant, 2 participants reported taking low-dose antidepressants (duloxetine and amitriptyline), and one participant reported a history of taking low-dose clonazepam as needed for sleep (not taken during the period of this study).

2.2. Participants and recruitment

Between 2013 and 2017, older adults from the community meeting inclusion criteria were invited to participate in this prospective, population-based cohort study. Using previously reported mean effect sizes for EF and PS in adults with vascular cognitive impairment relative to healthy controls (Vasquez and Zakzanis, 2015), we calculated an a priori target sample size of 10–21 per group for a 2-tailed hypothesis to achieve at least 80% statistical power (based on the range of reported effect sizes). Participants were recruited through advertisements placed in the local newspaper, Rotman Research Institute's research participant database, and through individuals who had volunteered for research at Cogniciti.com, a cognitive testing website affiliated with Baycrest. A total of 193 adults were screened for inclusion/exclusion criteria, of which 61 (31.6%) were deemed eligible and invited to participate. Major reasons for exclusion included lack of vascular risk factors (23), not meeting age cutoff (17), MRI contraindication (21), history of large vessel stroke (9), other neurological comorbidity (13), and significant history of recent or active psychiatric illness (9). Vascular risk factors were cross-checked against medications (Dey et al., 2015). Of those deemed eligible, 54 completed both cognitive assessment and structural imaging. After excluding individuals with incidental findings ($n = 7$) and those with missing more than 10% of data fields for technical reasons or failure to complete the test battery, the final sample size was 46. Demographic and imaging characteristics of the population are described in Table 1. The mean age and years of education of our sample population were 70.13 ($SD = 5.08$) and 16.78 ($SD = 3.31$), respectively. Participants reported 2.85 ($SD = 1.49$) vascular risk factors on average. Relative to healthy controls (i.e. Non-CSVD) those with CSVD were more likely to report experiencing subjective cognitive complaints (yes/no) ($\chi^2=7.263$, $p = 0.007$). Aside from this, the groups only differed with respect to variables relating to lesion burden that were used to determine group membership. That is, the 2 groups were similar with respect to demographic and physiologic variables such as age, education, number of vascular risk factors, handedness, and brain volume. Notably, the mean and median white matter hyperintensity volumes (adjusted for intracranial volume) in the CSVD group were 12.03 cm^3 and 8.92 cm^3, respectively. This falls within the range of "mild to moderate severity" identified in prior larger population studies (Rost et al., 2014; Zheng et al., 2012). Each participant gave informed consent to the protocol, which was approved by 2 separate Research Ethics Boards at Baycrest Hospital and Sunnybrook Health Sciences. Participants were not informed of the results of their neuroimaging assessment at the time of testing. Therefore, any effects on subjective or objective measures cannot be accounted for by demand characteristics related to participants' knowledge of their imaging results. All testing and scans were completed at Baycrest hospital. See Fig. 1 for an overview of recruitment and study protocol.

2.3. Imaging parameters

Imaging parameters were selected in accordance with the proposed acquisition standard for neuroimaging of small vessel disease described in the STRIVE working group position paper (Wardlaw

Table 1
Summary of demographic and imaging characteristics across participants

Demographic/Imaging variable	CSVD (n = 23)	Non-CSVD (n = 23)	
	Mean (SD), ratio or count (%)	Mean (SD), ratio or count (%)	Sig. (2-tailed)
Age	71 (5.5)	69.33 (4.64)	0.359
Years of education	16.45 (3.57)	17.08 (3.11)	0.661
Number of vascular risk factors	2.5 (1.65)	2.17 (1.58)	0.281
Hypertension	13 (56.5%)	14 (60.9%)	
Diabetes mellitus	6 (26.1%)	2 (8.7%)	
Dyslipidemia	13 (56.5%)	9 (39.1%)	
Cigarette smoking (current/past)	10 (43.5%)	9 (39.1%)	
Sleep apnea	3 (13.0%)	1 (4.35%)	
Family history of cerebrovascular disease	5 (21.7%)	9 (39.1%)	
Prior transient ischemic attack(s)	6 (26.1%)	5 (21.7%)	
Sex (M: F)	10:12	10:14	0.79[c]
Handedness (R: L)	18:4	21:3	0.59[c]
Subject cognitive complaints (Yes: No)	18:5	9:14	0.007[c]
Supratentorial total intracranial volume (cm^3)	1249 (145)	1203 (141)	0.291
Gray matter volume (cm^3)	565.1 (45.7)	545.6 (53.3)	0.193
White matter volume (cm^3)	414.1 (59.2)	399 (66.9)	0.432
Sulcal cerebrospinal fluid (cm^3)	220.8 (44.1)	226.1 (45.1)	0.698
Ventricular cerebrospinal fluid (cm^3)	44.9 (22.5)	32.5 (14.1)	0.378
White matter hyperintensities (cm^3)[a]	11.267 (9.232)	1.838 (1.573)	<0.001[a]
Total periventricular WMHs (cm^3)[a]	9.591 (8.830)	1.630 (1.358)	<0.001[a]
Total deep WMHs (cm^3)[a]	1.675 (1.447)	0.225 (0.271)	<0.001[a]
Lacune volume (cm^3)[a]	0.297 (0.363)	0.0174 (0.019)	<0.001[a]
Lacune count[a]	2.87 (1.89)	0.45 (0.596)	<0.001
Adjusted white matter hyperintensities (cm^3)[a,b]	12.031 (9.48)	1.932 (1.515)	<0.001[a]
Percentage of white matter affected by white matter hyperintensity (%)	2.861 (2.43)	0.45 (0.34)	<0.001[a]
Percentage of supratentorial intracranial volume affected by white matter hyperintensity (%)[a]	0.918 (0.73)	0.149 (0.12)	<0.001[a]
Percentage of supratentorial intracranial volume affected by lacunar volume (%)[a]	2×10^{-4} (3×10^{-4})	1.4×10^{-5} (2×10^{-5})	<0.001[a]

Key: CSVD, cerebral small vessel disease; SD, standard deviation; WMH, white matter hyperintensity.
[a] Differences remain significant at $p < 0.001$ after natural log transformation to adjust for skewness.
[b] White matter hyperintensity volume corrected for total supratentorial intracranial volume.
[c] Non-parametric tests used.

et al., 2013b). Participants were scanned with a 3 Tesla magnetic resonance (MR) system (Siemens Magnetom Tim Trio system, Syngo MR 2006 VB17; Siemens, Germany) with a 12-channel matrix head coil. Anatomical scans were acquired via a T1-weighted 3-dimension (3D) magnetization-prepared rapid gradient-echo sequence (inversion time [TI]/repetition time [TR]/echo time [TE] = 1100/2000/2.63 ms, 160 slices, field of view [FOV] = 256 mm × 192 mm, voxel size = 1 × 1 × 1 mm^3, flip angle = 9°, oblique axial slice orientation, 256 × 256 acquisition matrix, scan time = 6:26). Proton density and T2-weighted images with a slice

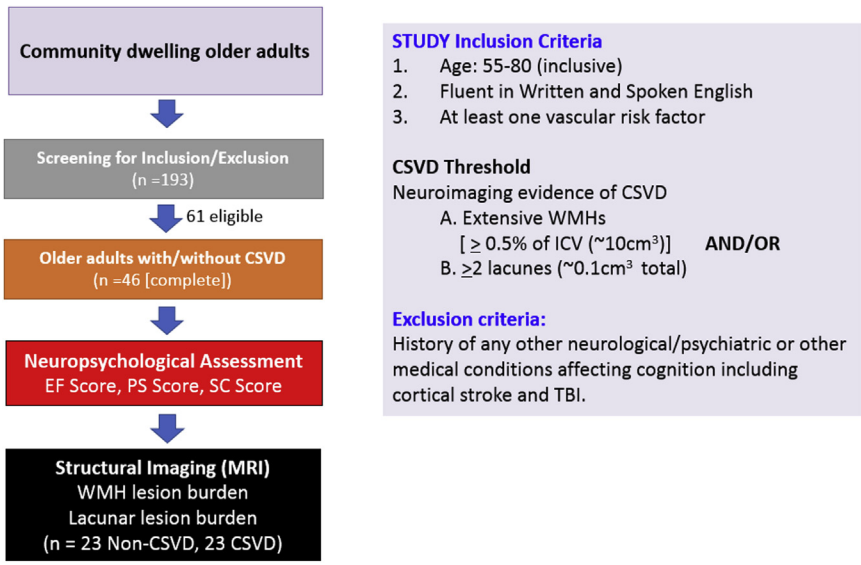

Fig. 1. Overview of recruitment and testing protocol. 193 older adults expressed interest in participating in the study. After screening for inclusion/exclusion criteria (age 55–80 years, English fluency, and at least one vascular risk factor), 61 were invited to participate in the study. 54 completed both cognitive assessment and structural imaging. However, 8 were subsequently excluded due to incidental findings and missing data, leaving a final sample size of 46. Ultimately, the participants were split equally among those with (n = 23) and without CSVD (n = 23) based on neuroimaging evidence of significant white matter lesion burden and/or the presence of 2 or more lacunes.

thickness of 3 mm were obtained using an interleaved axial multislice dual-turbo spin echo sequence (TE1/TE2/TR = 19/93/2900 ms, 48 slices, FOV = 224 × 185.5 mm, 256 × 256 acquisition matrix, flip angle = 180°, scan time = 6:24). For assessment of white matter lesion burden, a fluid-attenuated inversion recovery (FLAIR) sequence was obtained (TI/TR/TE = 2200/9000/108 ms, 48 contiguous slices at 3 mm thickness, FOV = 224 × 185.5 mm, 256 × 256 acquisition matrix, flip angle = 165°, oblique axial slice orientation, scan time 7:41). This T2 sequence has the benefit of suppressing the hyperintense cerebrospinal fluid signal, allowing for visualization of lesions close to the ventricles. Total scan time for each participant was 56:06 minutes summed across all sequences, including diffusion scans, not discussed here.

2.4. Volumetric quantification of lesion burden

All scans were processed through a pipeline developed at Sunnybrook Health Sciences Centre (http://sabre.brainlab.ca/docs/processing/index.html). See Fig. 2 for a visual summary of the processing pipeline. Image processing and tissue segmentation were performed using ITK-SNAP version 3.6 (Yushkevich et al., 2006). The first step was the coregistration of the PD and T2 images to T1 space. The next step (referred to as "Brain-Sizer") is described in detail in Ramirez et al. (2011) involved removing nonbrain voxels. In this step, a brain-extraction algorithm (Kovacevic et al., 2002) was run on the PD/T2 images, which were further manually edited on the T1 images. Then, after image alignment, using the T1 images, the brain was segmented into 4 tissue classes: gray matter, white matter, sulcal, and ventricular cerebrospinal fluid (CSF). Segmentation was performed using a local and global histogram-based automatic segmentation tool (Kovacevic et al., 2002). Designation of the ventricles and removal of the cerebellum was then carried out manually on the T1 image. The next step was lesion segmentation, which was accomplished with a C-means algorithm called fuzzy lesion extractor that was run on the FLAIR images (Gibson et al., 2010). All lesion segmented images were then further manually edited by reassigning false-negative and false-positive voxels. An automated 3D connectivity operation further classified all subcortical hyperintensities into either periventricular or deep white matter hyperintensities. All voxel clusters that were connected in 3D to the ventricles were classified as periventricular WMHs, and the remaining WMH voxels were classified as deep white WMHs. WMHs were also classified as lacunar or nonlacunar (aka "white matter hyperintensity"). This classification was performed by comparing how each identified WMH was classified on the T1-image: WMH voxels that were classified as CSF during the T1 tissue segmentation were classified as lacunar, whereas those classified as white matter were classified as nonlacunar. For counts, only lacunas with diameters between 3 and 15 mm were included. The diameter was measured by counting the voxels as the scan resolution was 1 × 1 × 1 mm. The segmented and processed image was processed using the Semi-Automated Brain Region Extraction (SABRE 2.0) method (Dade et al., 2004; Ramirez et al., 2011), which yields 26 regions customized to each participants' brain anatomy using 7 brain landmarks and coordinates and 6 sulcal tracings manually identified on each scan. The final output was a comprehensive volumetric profile of an individual's brain tissue volumes with regionalized segmentation data for gray matter, white matter, ventricular CSF, sulcal CSF, lacunar and nonlacunar periventricular WMH, lacunar and nonlacunar deep WMH in each of the 26 SABRE regions. In each participant, total supratentorial (i.e., cerebrum above the tentorium cerebelli) intracranial volume (ST-TIV) was calculated as the sum of all segmentation values while total WMH burden was calculated by summing periventricular WMH and deep WMH across the brain. To correct for head size, both total WMH burden and total lacunar volume measures were expressed as a percentage of ST-TIV. Percentage of white matter affected by WMH was calculated by

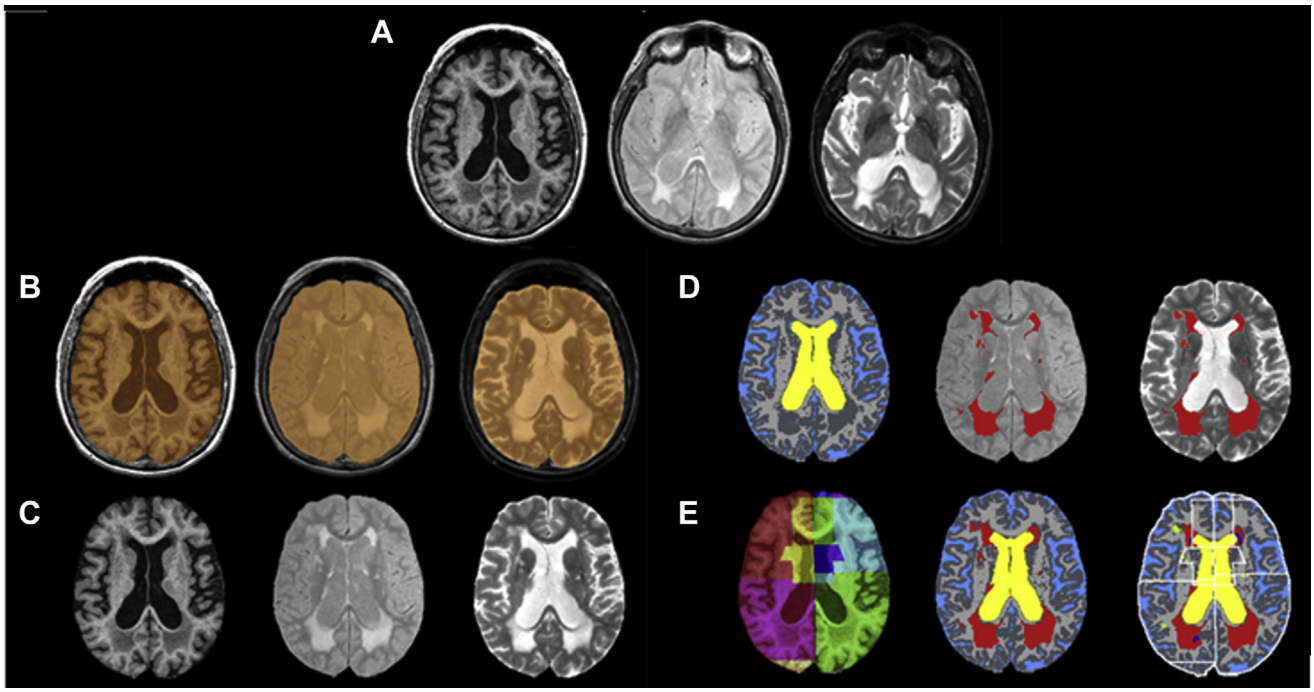

Fig. 2. Processing pipeline for quantification of lesion burden. (A) T1, PD, T2, and FLAIR MRI (not shown). (B) Coregistration of PD, T2, and FLAIR to T1 space, with binary mask overlaid for brain extraction. (C) Extraction of brain and subdural CSF for tissue segmentation preparation. (D) T1-segmentation (cerebrospinal fluid = blue, white matter = light gray, gray matter = dark gray) and lesion segmentation using the fuzzy lesion extractor pipeline (red overlay on PD-T2 image). (E) T1 segmentation corrected for subcortical hyperintensities and separated into SABRE regional compartments (colors present different regions). This figure has been reproduced and modified with permission from Ramirez et al. (2011). Details available at www.sabre.brainlab.ca.

dividing WMH burden by total intracranial white matter volume (i.e., deep WMH + periventricular WMH + normal appearing white matter). Because the positive tail of the distributions for WMH burden and lacunar burden were skewed, both variables were natural log transformed before statistical analysis.

2.5. Threshold for cerebral small vessel disease

While there is no widely held consensus on a precise diagnostic threshold of lesion burden for CSVD from quantified images, DeCarli et al. (1995) found that WMH burden exceeding 0.5% of intracranial volume (~10 cm^3) to be associated with larger ventricular volume, reduced brain volume and frontal glucose metabolism, and reduced EF scores in a sample of healthy older adults. This approximates a score of 1–2 on the Fazekas scale (a widely used categorical measure for visual rating of WMH; (Fazekas et al., 1987) (Svärd et al., 2017; White et al., 2013). That said, we classified those with white matter hyperintensity volume exceeding 0.5% of intracranial volume (~10 cm^3) as having CSVD. A CSVD diagnosis was also assigned to participants with 2 or more small subcortical infarcts/lacunes (Wardlaw et al., 2013b) and/or one strategically placed subcortical infarct/lacune (within the thalamus, basal ganglia, or internal capsule) as assessed by a neurologist or neuroradiologist. Lacunes were defined as focal hyperintensities on T2-weighted images, 3 mm–15 mm in diameter, and with a corresponding prominent hypointensity on T1-weighted images (Wardlaw et al., 2013b). Distribution of lesion burden across groups is described in the scatterplot in Fig. 3. Five participants were identified as meeting criteria for CSVD based on lacune count (≥2) despite having subthreshold levels of white-matter hyperintensity volume. No individuals were identified as having CSVD solely on the basis of a strategic lesion.

2.6. Cognitive assessment

All participants also completed a 2-hour battery of neurocognitive tests and functional questionnaires specifically designed to assess attention and EF. These tests include the Symbol-Digit Modalities Test (Smith, 1978), the Self-Ordered Pointing Test (Petrides and Milner, 1982), and Digit Span. In addition, neuropsychological tests from the Delis-Kaplan Executive Function System were used, namely: the Trail-Making Test, the Tower Test, the Colour-Word Inference Test, and tests of Verbal/Design/Category Fluency (Delis et al., 2001; Spreen and Strauss, 1998). To increase sensitivity of behavioral assessment, functional-behavioral measures such as the Hotel task (Manly et al., 2002) (a task designed to assess an individual's ability to manage multiple goals and tasks) and the Test of Everyday Attention (visual elevator subtest) (Robertson et al., 1996) were included.

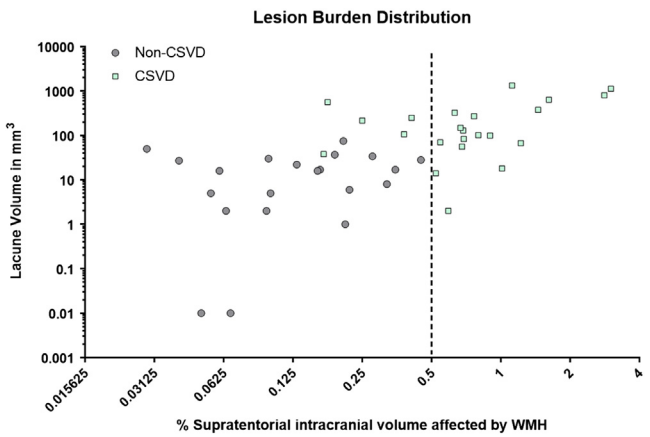

Fig. 3. Distribution of lesion burden across sample. This scatterplot displays the distribution of lesion burden across the sample, with CSVD represented as aqua squares and non-CSVD controls represented by gray circles. White matter hyperintensity expressed as a percentage of supratentorial intracranial volume is plotted on the X axis, while lacune volume (mm^3) is plotted on the Y axis. Scales were adjusted to accommodate skewness of the lesion burden measures (log 10). The dotted line represents the thresholds used to identify the groups. Five individuals met criteria for CSVD based on number of lacunes alone (≥2).

Subjective cognitive complaints (SC) were assessed through self-ratings and close-other ratings on the Cognitive Failures Questionnaire (CFQ) (Broadbent et al., 1982), and the Dysexecutive Questionnaire (Wilson et al., 1996)—validated questionnaires designed to measure behavioral problems associated executive dysfunction in daily life such as poor attentiveness, memory failures, and disinhibition. On the CFQ, participants were asked to answer 25 questions and rate their responses on a 5-point scale from "never" to "very often", with higher scores suggesting poor attentiveness and greater memory failures. Sample questions from the CFQ include "do you fail to notice signposts on the road?" and "do you start doing one thing at home and get distracted into doing something else (unintentionally)?" The Dysexecutive Questionnaire contains 20 questions rated on a 5-point scale concerning inhibition, affect, planning, and memory. For example, "I have difficulty realizing the extent of my problems and am unrealistic about the future". The scores from these questionnaires were combined into a composite score for SC. SC were associated with neither EF ($r = -0.12$, $p = 0.432$) nor PS ($r = -0.23$, $p = 0.124$). This is consistent with the notion that these questionnaires reflect performance on unstructured daily life tasks that do not necessarily overlap with performance on structured neuropsychological tests (Burgess et al., 2006). It is also possible that a decline in EF may hinder insight into one's deficits (Brookes et al., 2014).

Finally, the Hopkins Verbal Learning Test–Revised (Benedict et al., 1998) was included in the battery to identify any individuals with significant impairments in learning and/or memory. While not an exclusion criterion, none of the participants included in the final sample were found to be impaired on the HVLT based on their normalized T-score.

To reduce the test data according to its underlying structure, subjective and objective measures were separately entered into a principal component analysis with varimax rotation and Kaiser normalization. This was performed using the dimension reduction feature of SPSS version 24.0. Before entry into the principal component analysis, all timed variables were inversed and any scores that were significantly skewed were natural log transformed. From the principal component analysis, only components with eigenvalues more than 1 were selected. Among objective measures, 2 orthogonal components scores representing executive function/working memory (EF) and PS were identified, accounting for 40.9% of the total variance. Among subjective measures, only one component (SC) was identified, accounting for 65.6% of the total variance. Factor weights for the component scores are reported in the Supplemental Materials. In addition, information regarding self-reported vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, family history of cerebrovascular disease, sleep apnea, and history of transient ischemic attacks) and depressive symptoms as measured by the 30 question geriatric depression scale (GDS) (Yesavage et al., 1982) were also collected.

2.7. Statistical analysis

All data analysis was performed with SPSS Statistics 24, and R Studio (version 1.0.143) was used primarily for visualization. Descriptive statistics for the data (e.g., quantitative imaging

measures, cognitive measures, and demographic information) across the entire sample as well as between clinical groups (non-CSVD vs. CSVD) are described in Table 1. For continuous variables, independent samples *t*-tests were used to assess group differences. Data for skewed variables such as lesion burden were natural log transformed before analysis. For categorical variables, χ^2 test for independence (with Yates continuity correction) was used to compare group differences.

To address the first aim of this study, multiple regression was used to assess the ability of lesion burden measures (white matter hyperintensity volume and lacunar volume) to predict cognition (EF, PS, and SC score) in older adults across our entire sample after accounting for variance attributable to age and education. Separate regression models were run for each dependent cognitive measure. Both lesion burden measures were entered as a percentage of total supratentorial intracranial volume to correct for head size and natural log transformed to correct for skewness. Age and education were also added to the model. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity. Pearson correlations between the dependent and independent variables were also explored. Concerning the second aim of this study, to explore patterns of cognitive change associated with CSVD, a one-way multivariate between-groups analysis of covariance (MANCOVA) was run to compare the cognitive profile of older adults with and without CSVD across the 3 cognitive measures (EF, PS, and SC). The clinical group was the sole fixed factor independent variable, whereas EF, PS, and SC scores were dependent variables. Age and education were also entered as covariates in this analysis. Distribution of the dependent variables in both the groups was visualized using a kernel density plot. Finally, to investigate behavioral subgroups within the CSVD sample, hierarchical clustering was used to identify data clusters with EF, PS, and SC scores as inputs. Ward's method was selected as the clustering method and squared Euclidean distance as the unit of measure. This analysis identified 2 data clusters within the CSVD population which primarily differed with respect to their EF component score. Accordingly, these data clusters were labeled as CSVD-High performing (CSVD-H) and CSVD-Low performing (CSVD-L). Non-CSVD controls were not included in the cluster analysis as we were interested in exploring how these subgroups compare with healthy controls. That said, to assess between-cluster differences in demographic and quantitative imaging measures, a one-way ANOVA was performed, considering participant cluster as the independent variable and demographic/lesion burden measures (age, years of education, number of vascular risk factors, WMH burden, lacune burden) as dependent variables. A one-way MANCOVA was run to explore if differences between the CSVD clusters and controls across cognitive measures persist after adjusting for covariates. In this final analysis, simplified group/cluster membership (Non-CSVD vs. CSVD-H vs. CSVD-L) was entered as the independent variable, and the cognitive measures of EF, PS, and SC scores were entered as dependent variables. Age, education, sex, and WMH lesion burden were also entered as covariates. Pairwise comparisons with Bonferroni correction were then performed to explore the relative performance between age-matched controls the 2 CSVD subgroups.

3. Results

3.1. Relationship between lesion burden and cognition

Multiple regression was used to assess the ability of WMH and lacunar lesion burden to predict cognition (PS, EF, and SC) while controlling for the influence of age, education, and sex. Findings are summarized in Table 2. While none of the regressions models met criteria for significance, there was a significant positive correlation between SC and WMH burden ($r = 0.295$, $p = 0.023$). WMH lesion burden, overall, was a relatively strong predictor of cognition across all the models. Although this should be interpreted with caution, this finding is consistent with larger studies (Molad et al., 2017; Uiterwijk et al., 2016).

3.2. Cerebral small vessel disease and cognition

Between-groups MANCOVA revealed group differences across cognitive measures while adjusting for covariates (age and education). SC ($F[1,42] = 7.865$, $p = 0.008$, partial eta squared = 0.1580) but not PS ($F[1,42] = 1.29$, $p = 0.263$) or EF ($F[1,42] = 0.35$, $p = 0.557$) significantly distinguished older adults with and without CSVD. An independent-samples *t*-test showed no significant differences in subjective scores between males and females; $t(44) = 0.691$, $p = 0.493$. The 2 groups were also indistinguishable with respect to memory performance as assessed by the Hopkins Verbal Learning Test delayed recall ($F[1,42] = 2.374$, $p = 0.131$) and recognition subtests ($F[1,42] = 0.048$, $p = 0.828$). The groups, however, differed with respect to reporting of depressive symptoms as assessed by the GDS, with the CSVD group reporting greater depressive symptoms ($F[1,42] = 5.063$, $p = 0.030$, partial eta squared = 0.118). None of the participants met criteria for clinical major depression, and 39/46 (85%) had GDS scores <10. These

Table 2
Multiple regression analysis—predictors of cognitive function

Dependent variable	Model	R square	Model sig.	Beta	Sig.	Pearson correlation	Sig.
PS score	Age	0.128	$F(5,40) = 1.174$, $p = 0.339$	−0.131	0.402	−0.197	0.095
	Years of education			0.054	0.730	0.144	0.235
	Sex			−0.185	0.246	−0.230	0.062
	WMH lesion burden[b]			−0.253	0.224	−0.230	0.062
	Lacunar lesion burden[b]			0.081	0.694	−0.058	0.351
EF score	Age	0.092	$F(5,40) = 0.808$, $p = 0.551$	−0.108	0.498	−0.137	0.183
	Years of education			0.049	0.757	0.025	0.436
	Sex			0.172	0.292	0.122	0.209
	WMH lesion burden[b]			−0.294	0.168	−0.227	0.064
	Lacunar lesion burden[b]			0.138	0.511	−0.087	0.284
SC score	Age	0.171	$F(5,40) = 1.655$, $p = 0.168$	−0.252	0.101	−0.181	0.114
	Years of education			−0.097	0.525	−0.178	0.119
	Sex			0.104	0.501	0.104	0.247
	WMH lesion burden[b]			0.355	0.083	0.295	[a]0.023
	Lacunar lesion burden[b]			−0.039	0.847	0.185	0.109

Key: PS, processing speed; EF, executive function; SC, subjective cognitive complaints; WMH, white matter hyperintensity.
[a] Significant at $p < 0.05$.
[b] Expressed as % of supratentorial intracranial volume and natural log transformed.

Table 3
Cognition in older adults with and without CSVD

Cognitive measure	Non-CSVD mean (95% CI)	CSVD mean (95% CI)	*p*-value[a]	Partial eta squared
Neuropsych component 1 (PS)	0.168 (−0.252 to 0.588)	−0.168 (−0.588 to 0.252)	0.263	0.03
Neuropsych component 2 (EF)	0.090 (−0.342 to 0.522)	−0.090 (−0.522 to 0.342)	0.557	0.008
Subjective cognitive complaints (SC)	−0.386 (−0.776 to 0.004)	0.386 (−0.004 to 0.776)	0.008[a]	0.158
HVLT delayed recall	10.373 (9.602–11.145)	9.540 (8.768–10.311)	0.131	0.053
HVLT recognition	11.103 (10.653–11.554)	11.027 (10.576–11.478)	0.828	0.001
Geriatric Depression Scale	3.438 (1.303–5.572)	6.856 (4.918–8.794)	0.030[a]	0.118

MANCOVA—values adjusted for covariates of age and education.
Key: HVLT, Hopkins Verbal Learning Test—Revised; PS, processing speed; EF, executive function; SC, subjective cognitive complaints.
[a] Significant at $p < 0.05$.

results are summarized in Table 3 with group differences in cognitive measures visualized in the dot plot in Fig. 4A. Density plots highlighting the distribution of the data across groups are shown in Fig. 4B.

3.3. Behavioral subgroups

Using EF, PS, and SC component scores as inputs, hierarchical clustering identified 2 data clusters across the CSVD sample. The 2 CSVD subgroups were named CSVD-H (green) and CSVD-L (blue). "H" and "L" here represent high and low EF components scores, respectively. As summarized in Table 4, despite behavioral differences, one-way ANOVA found no statistically significant differences between the 2 clusters with respect to age, years of education, number of vascular risk factors, WMH lesion burden, and number of lacunes. One notable difference is that females represent a larger proportion of those in the higher performance CSVD-H subgroup ($\chi^2 = 5.239$, $p = 0.022$). The behavioral profile of these 2 subgroups was plotted alongside non-CSVD controls (Fig. 5). A one-way between-groups MANCOVA was performed to investigate group differences in objective and subjective measures of cognition. Three dependent variables were used: EF score, PS score, and SC score. The independent variable was group membership. Age, education, and WMH lesion burden were also entered as covariates. The MANCOVA revealed group differences with respect to EF ($F[2,39] = 9.296$, $p < 0.001$, partial eta squared = 0.323), PS ($F[2,39] = 4.374$, $p = 0.019$, partial eta squared = 0.183) and SC ($F[2,39] = 4.453$, $p = 0.018$, partial eta squared = 0.186). Notably, results were largely unchanged if WMH burden was dropped as a covariate. Pairwise comparisons between healthy controls and the CSVD subgroups across the 3 cognitive measures (with Bonferroni correction) revealed that compared with healthy (non-CSVD) controls, those within the CSVD-H subgroup scored significantly lower on PS ($p = 0.045$, Cohen's $d = 0.87$) and reported greater SC ($p = 0.016$, Cohen's $d = 1.28$) despite no statistically significant difference in EF. By contrast, the CSVD-L scored significantly worse than controls on EF

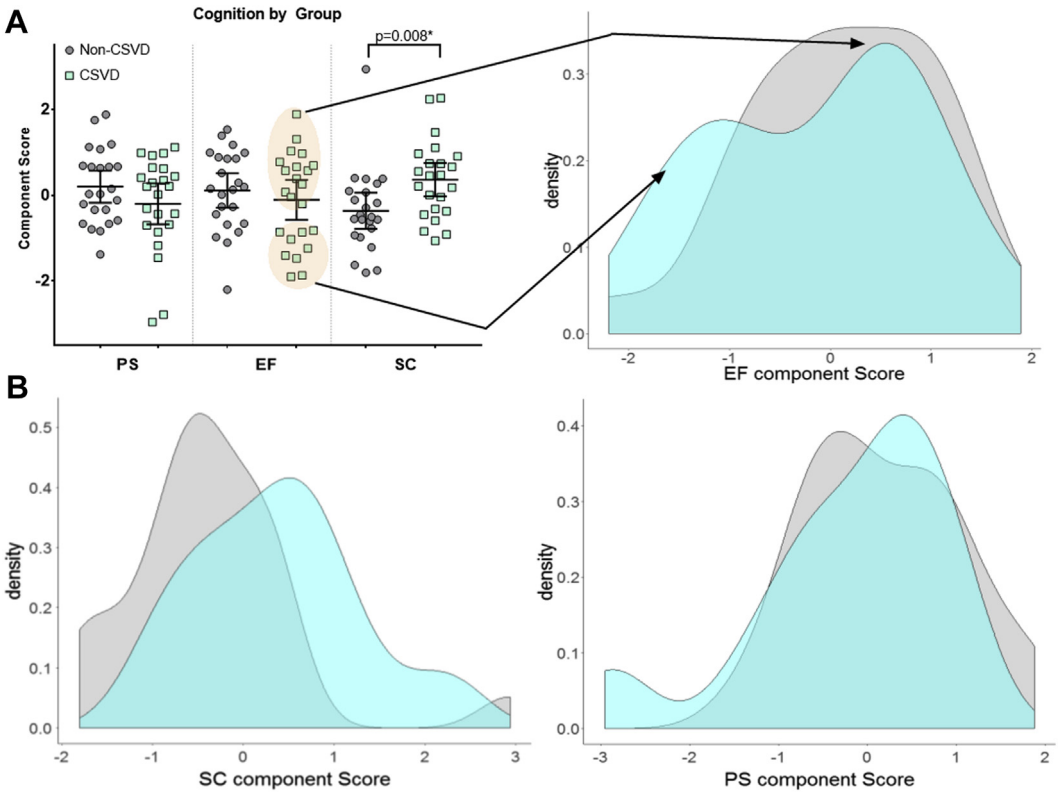

Fig. 4. Density plots of cognition in older adults with and without CSVD. (A) Dot plot showing group differences across component scores derived from the neuropsychological assessment battery and questionnaires. The error bars represent 95% confidence intervals. From left to right; processing speed (PS), executive function (EF), and subjective cognitive complaints (SC). Of the measures, only SC significantly distinguished the 2 groups, with more complaints reported among those with CSVD ($p = 0.008$). (B) Density plots show the spread of data, with signs of a possible bimodal distribution visible on the plot for executive function (EF). Non-CSVD controls are represented in gray, whereas the CSVD group is represented in light blue.

Table 4
Characteristics of CSVD behavioral subclusters

Measure	Non-CSVD		CSVD-H		CSVD-L	
	Mean/count	SD	Mean/count	SD	Mean/count	SD
Sample size	23		12		11	
Age	69	5	70	6	72	4
Years of education	16.8	3.1	16.4	3.3	17.3	4
# of vascular risk factors	3	2	3	2	3	1
Gender (M: F)	9:14		3:9[a]		8:3	
WMH lesion burden (% ICV)	0.143	0.112	0.714	0.770	1.048	0.658
Lacune lesion burden (cm^3)	0.018	0.02	0.269	0.316	0.279	0.419
# of lacunes	0	1	2	2	3	2
Geriatric depression scale	3.00	2.74	7.83	6.79	5.73	4.0

Key: SD, standard deviation; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity.
[a] Binomial test significant at $p < 0.05$.

($p = 0.028$, Cohen's $d = 1.13$) with no significant differences with respect to SC or PS. Pairwise comparisons are summarized in Table 5. Pairwise comparisons between the CSVD subgroups are also reported for descriptive purposes and not discussed as these differences were used to define the groups by the cluster analysis.

4. Discussion

Half of the community-dwelling older adults with vascular risk factors recruited for this study were found to have significant white matter hyperintensities, consistent with CSVD. This highlights how common white matter hyperintensities are in the general population, particularly among those with vascular risk factors. We sought to investigate the relationship between WMH burden and objective and subjective measures of EF, and to identify the pattern of deficits that distinguish older adults with and without CSVD.

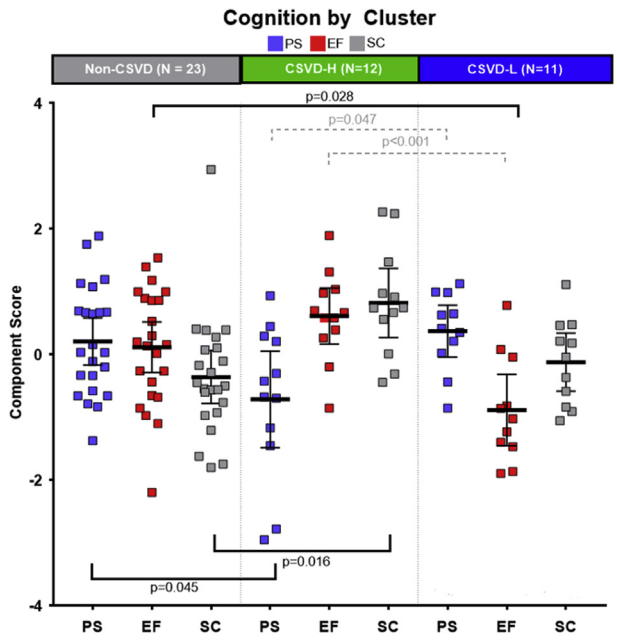

Fig. 5. CSVD-high performers versus CSVD-low performers. Dot plot comparing behavioral characteristics across all groups. Reported statistics represent Bonferroni adjusted pairwise comparisons between groups following adjustment for age, education, and WMH lesion burden. Along the horizontal axis are the primary cognitive measures; processing speed component score (PS, purple), executive function component score (EF, red), and subjective complaints component score (SC, gray). The horizontal axis is subdivided into 3 sections for the 3 groups; Non-CSVD (n = 23), CSVD-H (n = 12), and CSVD-L (n = 11). Relative to Non-CSVD controls, older adults in the CSVD-H subgroup were significantly slower (PS, $p = 0.045$) and reported greater subjective cognitive complaints (SC, $p = 0.016$) despite no statistically significant difference in executive function (EF). By contrast, the CSVD-L subgroup scored significantly worse than Non-CSVD controls on EF ($p = 0.028$) with no significant differences with respect to subjective cognitive complaints (SC) or processing speed (PS).

4.1. Subjective complaints differentiated older adults with and without CSVD

When older adults were divided into those with and without CSVD (WMH burden $> \sim 10\ cm^3$), SC, but not objective test findings, significantly distinguished the 2 groups after adjusting for age and education. One explanation for this finding is that neuropsychological tests may not be sufficiently sensitive to detect executive dysfunction in high-functioning older adults with only mild to moderate damage (Benedictus et al., 2015; Burgess et al., 2006). Impairments in executive functioning in such individuals may only become evident when performing complex real-world tasks as they may be able to compensate up to a certain level of difficulty by drawing on cognitive reserve and/or using compensatory strategies. In patients with cerebrovascular disease, greater self-report of cognitive difficulties at the baseline predicted poorer cognitive performance at 12-month follow-up (Haley et al., 2009). The value of tracking subjective cognitive decline in clinical populations was also recently highlighted by Vogel et al. (2017) who reported that among patients with β-amyloid pathology the rate of cognitive decline was most steep for those reporting the greatest subjective cognitive decline. In that study, subjective cognitive decline also predicted a faster decline in working memory independent of β-amyloid burden (see also Buckley et al. (2017)). Overall these findings support the notion that SC may provide clinicians and researchers additional information regarding the cognitive effects of white matter lesion burden that may be missed by traditional cognitive testing.

4.2. Interindividual variability in CSVD may relate to compensation

The fact that our objective test battery did not distinguish older adults with and without CSVD was remarkable given that it contained state-of-the-art clinical measures of EF, attention, working memory, and simulated real-life function. Although it was not sensitive to CSVD across all participants, we noted high heterogeneity within the CSVD population. Inspection of the density plots of neuropsychological test performance revealed a bimodal distribution with respect to EF. This was supported by hierarchical cluster analysis, which revealed 2 distinct behavioral subgroups within our CSVD sample that differed with respect to EF and PS, despite being similar with respect to age, education, and most importantly, WMH burden. This suggests that cognition in older adults with mild to moderate CSVD may be influenced by factors that cannot be readily captured by traditional clinical neuroimaging tools. That is, simply looking at total lesion burden may not provide an accurate

Table 5
Pairwise comparison between Non-CSVD and CSVD behavioral subgroups

	Processing speed			Executive function			Subjective complaints		
	Mean difference	Std. Error	Sig.	Mean difference	Std. Error	Sig.	Mean difference	Std. Error	Sig.
Non-CSVD									
CSVD-H	0.816	0.320	**0.045**[a]	−0.605	0.307	0.168	−0.934	0.318	**0.016**[a]
CSVD-L	−0.134	0.361	1	0.948	0.346	**0.028**[a]	−0.249	0.358	1
CSVD-L[b]									
CSVD-H	0.950	0.376	N/A	1.553	0.360	N/A	−0.684	0.373	N/A

Key: CSVD, cerebral small vessel disease; CSVD-H, CSVD-High performing; CSVD-L, CSVD-Low performing.
[a] Mean difference is significant at .05 level. Bonferroni correction for multiple comparisons applied.
[b] For descriptive purposes only. Differences between CSVD subgroups were used to create the groups.

reflection of cognitive status. One possibility is that interindividual variability in CSVD may relate to differences in cognitive reserve and ability to compensate in response to age-related white matter changes. This explaination also fits with previous findings of no significant relationship between EF and CSVD (Burns et al., 2005).

The Scaffolding Theory of Aging and Cognition (STAC) model (Reuter-Lorenz and Park, 2014) proposes that the adverse effects of neural decline may be attenuated through reorganizing/creating alternative neural circuits (compensatory scaffolds). These additional neural circuits provide the computational support needed to preserve cognitive function in the face of neurofunctional decline, albeit at the cost of efficiency. That is, there is a trade-off between performance and efficiency. Consistent with this idea, those in the higher performing CSVD group (CSVD-H) demonstrate preserved EF and lower speed of processing despite reporting greater SC (relative to controls). In this group, one can argue that there has been a compensatory trade-off between speed and accuracy resulting in preserved EF but slower speed of processing. These individuals however still report high SC as they are still able to perceive that they are not as fast as before. However, not all individuals with CSVD are able to adjust. The poorer performing CSVD group (CSVD-L) demonstrates preserved speed of processing (relative to controls) despite relatively low EF, suggesting failed/absence of compensation, with less subjective awareness of their deficits (Brookes et al., 2014).

4.3. Limitations

As the study is observational, conclusions regarding causality cannot be inferred. Despite a starting sample size of 46 and having equal numbers of older adults with and without CSVD, subgroup analysis of the CSVD sample yielded groups of only 12 and 11, which limits the generalizability of findings. In addition, as our power calculations were based on effect sizes taken from a meta-analysis reporting a very large effect size (Vasquez and Zakzanis, 2015), the power of our study is limited to the detection of effects beyond the range of what is conventionally considered to be a large effect. Furthermore, as large effects are often found in small samples due to overfitting, these findings would need to be replicated in an independent, preferably larger sample. Another potential limitation is the use of self-reported vascular risk factors, which tend to be under-reported in older adults (Dey et al., 2015). To mitigate this risk, we cross-checked their risk factors against participants' medications. Although participants were required to have at least one vascular risk factor to meet inclusion criteria, they reported an average of 2 more risk factors, suggesting that under-reporting was unlikely. Because recruitment was dependent on participants calling in response to ads or being registered within the Rotman Research Institute's participant directory, the study may be susceptible to recruitment bias which again limits the generalizability of findings. APOE 4 status was not screened for in this study. It is possible that some of the cognitive effects observed in this study may be partially related to the accumulation of beta-amyloid pathology (Vogel et al., 2017).

Those with CSVD reported more depressive symptoms relative to those without CSVD. The relationship between depression and cognitive deficits is well established (Rock et al., 2014) and could represent a possible confound to the extent that depressive symptoms could be associated with test scores. Although none of our participants met criteria for a diagnosis of depression, we examined the relationship of GDS scores to the component scores from our neuropsychological battery. There were no significant correlations between GDS scores and EF ($r = -0.042$, $p = 0.784$) or PS scores ($r = -0.146$, $p = 0.339$), nor did GDS scores significantly differ between the 2 CSVD subgroups. The only statistically significant relationship observed was between GDS scores and SC ($r = 0.62$, $n = 45$, $p < 0.001$), likely accounted for by overlapping questions within the GDS that pertain to memory and concentration (Adams et al., 2004; Hohman et al., 2011). It is possible that the presence of CSVD may predispose individuals to developing depressive symptoms (Van Sloten et al., 2015), possibly through disruption of brain structures involved in mood regulation (Taylor et al., 2013). Regardless, the presence of concurrent depressive symptoms does not invalidate our participants' subjective experience of cognitive decline. Indeed, participant self-report was corroborated by the collection of paired assessments from a close relative. With respect to sex-related differences, while there were no significant differences in EF [$(t44) = -0.816$, $p = 0.419$)], PS [$(t44) = 1.564$, $p = 0.125$)], or SC [$t(44) = 0.691$, $p = 0.493$] scores between males and females, females were over-represented in the CSVD-H group. These findings are contrary to what is typically reported in the acquired brain injury literature wherein functional outcomes and quality of life after a stroke or mild TBI are consistently poorer in women (Bazarian et al., 2010; Reeves et al., 2008). Further research into sex-differences in cognition and cognitive reserve in older adults with CSVD is recommended.

Another limitation in our study relates to the definition of CSVD used. At present there is no clear consensus in the literature with respect to what amount of lesion burden equates to clinically significant CSVD. For this study, we used a quantitative cutoff of lesion burden as reported by DeCarli et al. (1995) as this was the most objective and widely accepted definition we identified in the literature at the outset of our study that continues to be used (Chao et al., 2013; Svärd et al., 2017; White et al., 2013). More recently, several groups have started using an ordinal SVD score of 0–4, representing the total MRI load of CSVD by counting the presence of 4 MRI features (WMHs, lacunes, microbleeds, and enlarged perivascular spaces) (Staals et al., 2015). The problem with this score however is that it is overly reliant on visual scales that are troubled by issues such as poor sensitivity to group differences, high intersubject variability and significant ceiling/floor effects. These issues limit the utility of this measure. Indeed, Staals et al. (2015) found no

association between total SVD load and PS and memory. As such we have avoided such scales. With that said, a 0.5% WMH volumetric threshold roughly corresponds to a Fazekas score of 1, whereas volumes over 1% of intracranial volume correspond to Fazekas scores of 2 and above (Svärd et al., 2017).

Next, although as WMH volume was extracted from 3 mm FLAIR slices (as per current imaging guidelines), it is plausible that smaller WMH volumes may have been missed in our study. Any sub 3 mm lesions missed likely would have had little impact on the interpretation of our results.

Finally, in this study, a global measure of WMH burden was used, whereas regional differences in the distribution of lesion burden may have provided more information and may have shared a stronger relationship with measures of cognition. For example, lower cognitive speed and flexibility is associated with WMH burden in the superior corona radiata (Birdsill et al., 2014). That said, when we repeated our analyses using regional WMH volumes, no significant correlation with any of the cognitive measures was found. This may relate to the mild degree of severity in this community sample of individuals with risk factors (but not diagnosed CSVD), where regional effects may not be sufficient to account for variance relative to the diffuse effects of global lesion burden.

5. Conclusion

This study aimed to investigate the relationship between ischemic lesion burden and objective and subjective measures of cognitive function in a sample of older community-dwelling adults with vascular risk factors. Half of our recruited community sample were found to have neuroimaging evidence of CSVD, highlighting the commonality of such changes that should be considered when interpreting findings in older adults. We found distinct behavioral subgroups that were matched with respect to age, education, and WMH burden—separating those who could compensate (at the cost of reduced speed of processing) versus those who could not. This may provide some explanation for the large behavioral heterogeneity often observed in studies of age-related white matter changes. Finally, SC but not objective test scores differentiated those with and without CSVD, supporting the use of subjective measures of cognitive impairment. Such measures can supplement objective testing by detecting subtle effects of pathology that are difficult to reliably measure via laboratory testing and that may be masked by individual differences in cognitive reserve and compensation. These findings encourage future investigation into functional brain changes associated with white matter hyperintensities to provide insights into the contribution of brain reserve and compensation to individual differences in cognitive abilities as humans age. Ultimately, a better understanding of the mechanisms contributing to cognitive changes, whether objectively or subjectively measured, may have implications for guiding the development of novel and more targeted assessment and intervention strategies for older adults with mild to moderate CSVD.

Disclosure

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.12.011.

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