



## Brain health imaging markers, post-stroke aphasia and Cognition: A scoping review

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### ABSTRACT

For the past decade, brain health has been an emerging line of scientific inquiry assessing the impact of age-related neurostructural changes on cognitive decline and recovery from brain injury. Typically, compromised brain health is attributed to the presence of small vessel disease (SVD) and brain tissue atrophy, which are represented by various neuroimaging features. However, to date, the relationship between brain health markers and chronic aphasia severity remains unclear. Thus, the goal of this scoping review was to assess the current body of evidence regarding the relationship between SVD-related brain health biomarkers and post-stroke aphasia and cognition. In all, 187 articles were identified from 3 databases, of which 16 articles met the criteria for inclusion. Among these studies, 11 focused on cognition rather than aphasia, while 2 investigated both. Of the 10 studies that used white matter hyperintensities (WMHs) as an indicator of SVD severity, 8 studies (80%) demonstrated a relationship between WMH load and worse cognition in stroke patients. Interestingly, among the studies that specifically investigated aphasia, all 5 studies (100%) demonstrated a relationship between SVD and worse language performance. They also indicated that factors other than brain health (e.g., lesion, age, time post onset) played an important role in determining aphasia severity at a single timepoint. These findings suggest that brain health is likely a crucial factor in the context of aphasia recovery, possibly indicating the necessity of cognitive reserve thresholds for the multimodal cognitive demands associated with language recovery. While SVD and structural brain health are not commonly considered as predictors of aphasia severity, more comprehensive models incorporating brain health have the potential to improve prognosis of post-stroke cognitive and language deficits. Given the variability in the existing literature, a uniform grading system for overall SVD would be beneficial for future research on the mechanisms related to brain networks and neuroplasticity, and their translational impact.

### 1. Introduction<sup>1</sup>

For the past decade, brain health has been an emerging line of scientific inquiry because of its close relationship with age-related functional decline and potential impact on recovery after brain injury. Per

PubMed (“brain health” - Search Results - PubMed., 2022), the number of annual publications on “brain health” increased by 1500% from 65 publications in 2011 to 1889 in 2021. Structurally, brain health is recognized as the integrity of brain tissue and typically relates to small vessel diseases (SVD). Markers of small vessel disease (SVD) are common

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<sup>1</sup> **Non-standard Abbreviations and Acronyms:** ACE-R: Addenbrooke’s Cognitive Examination – Revised; CAA: cerebral amyloid angiopathy; CMB: cerebral microbleed; cSS: cortical superficial siderosis; DTI: diffusion tensor imaging; DWMH: deep white matter hyperintensity; EPVS: enlarged perivascular spaces; FLAIR: fluid-attenuated inversion recovery; HTNA: hypertensive arteriopathy; ICH: intracerebral hemorrhage; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PVH: periventricular white matter hyperintensity; SVD: small vessel disease; TICS-m: Modified Telephone Interview for Cognitive Status; WAB-AQ: Western Aphasia Battery Aphasia Quotient; WAB-R: Western Aphasia Battery – Revised; WMH: white matter hyperintensity.

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in stroke survivors and are the leading cause of vascular cognitive impairment, with vascular dementia comprising 15–20% of dementia cases in North America (Zanon Zotin et al., 2021; Wolters and Arfan, 2019). While the imaging correlates of SVD have been defined, their relationships with cognition and stroke recovery are not well understood.

The STAndards for ReportIng Vascular changes in nEuroimaging (STRIVE) guidelines identify markers associated with SVD in the aging brain (Wardlaw et al., 2013). These markers include white matter hyperintensities (WMHs) as well as lacunes, enlarged perivascular spaces (EPVS), cerebral microbleeds (CMBs), small subcortical infarcts, and atrophy. WMHs, also referred to as white matter lesions or leukoaraiosis, tend to appear bilaterally and symmetrically as hyperintense regions on T2-weighted and T2-FLAIR (fluid-attenuated inversion recovery) MRI scans (Wardlaw et al., 2013). They can be categorized into deep and periventricular white matter hyperintensities (DWMH and PVH, respectively) based on location. The underlying pathogenesis of WMHs is not well understood. Lacunes are round or ovoid, subcortical, fluid-filled cavities approximately 3–15 mm in diameter. If the cavity is >15 mm, it may be classified as a small subcortical infarct (Wardlaw et al., 2013). EPVS, most commonly seen in the basal ganglia, are small, fluid-filled spaces that follow the course of a vessel through grey or white matter (Wardlaw et al., 2013). CMBs are small (2–5 mm in diameter), hypointense lesions that are well-defined on susceptibility-weighted and T2\*-weighted gradient recalled echo (GRE) sequences but are typically not visible on CT or other MRI sequences (Wardlaw et al., 2013). In SVD, brain atrophy, or cerebral atrophy, is most simply defined as a loss in brain volume over time not related to a discrete focal injury (e.g., trauma, stroke) (Wardlaw et al., 2013).

To date, most of the research in this area has focused on SVD markers and cognition (Guevarra et al., 2020; Bolandzadeh et al., 2012; Zhi et al., 2021), particularly the development of neurocognitive disorders such as vascular dementia and Alzheimer's disease (Hu et al., 2021). This focus may reflect that the severity of SVD markers typically increases with age, and the presence of SVD may explain some of the variability in cognitive dysfunction in older age. Similarly, SVD severity in individuals with stroke is also a pertinent avenue of research, particularly as stroke survivors tend to have more cardiovascular risk factors which may contribute to the progression of SVD (Zanon Zotin et al., 2021; Cipolla et al., 2018). Recovery from a stroke depends on the integrity of the remaining tissue (Bonilha et al., 2016); therefore, SVD may be an important determinant of recovery trajectories.

Many left hemisphere stroke survivors experience aphasia, a language disorder that substantially affects a person's quality of life by disrupting verbal communicative processes and/or comprehension of language. Aphasia is not a deficit of cognition per se, meaning that findings from studies of cognition in non-aphasic stroke patients cannot be generalized to language deficits. Nonetheless, aphasia severity and recovery are determined by the ability to recover from neurological injury and to regain function due to neuroplasticity. Aphasic symptoms are strongly determined by the size and the location of the stroke lesion, but also by the recovery-related engagement of associative multi-domain brain regions and networks (Kiran et al., 2019). As such, factors that reduce cognition may have a significant impact in chronic aphasic symptoms, which is why we sought to investigate the link between SVD and aphasia specifically.

Within the current literature, there is no clear consensus about how to quantify SVD and which markers of SVD are associated with language impairment following a stroke. Thus, we sought to determine the status and prevalence of existing literature on the relationship between SVD-related brain health markers and behavioral measures (specifically language) in patients with a history of stroke to determine areas where additional research is necessary to clarify purported connections. Due to the nature of the research question, and the more general focus on reported changes and relationships rather than the effects of a specific intervention, we chose to perform a scoping review in accordance with

the PRISMA guidelines for scoping reviews (Tricco et al., 2018). The following research question was formulated: What is known from the literature about the relationship between SVD-related brain health biomarkers and post-stroke aphasia and cognition?

## 2. Methods

### 2.1. Eligibility criteria

We performed a scoping review following the PRISMA Statement Guidelines (Tricco et al., 2018) to examine available evidence from original research studies regarding the association of post-stroke aphasia with brain health related to cerebral SVD. In this context, “brain health” was defined as the structural integrity of the intact brain tissue (i.e., non-lesioned by the stroke) as assessed by structural MR imaging. The STRIVE criteria provided a guide for neuroanatomic markers of compromised brain health related to SVD, particularly in the aging adult human brain. According to these criteria, imaging features of SVD include white matter hyperintensities, lacunes, enlarged perivascular spaces, cerebral microbleeds, small subcortical infarcts, and brain atrophy (Wardlaw et al., 2013) (Fig. 1). No stroke etiology, starting year, or language restrictions were applied to our search. The databases were last searched in December 2022.

### 2.2. Information sources/search strategy

The databases PubMed, CINAHL, and Scopus were searched for peer-reviewed journal papers using pre-defined search syntaxes (Table S1). The syntaxes were designed to search for articles that addressed brain health in combination with aphasia, stroke, and imaging-based signs of SVD.

To find additional evidence, backward and forward reference searching were performed for a subset of search results (Varkanitsa et al., 2020; Wright et al., 2018; Basilakos et al., 2019; Wilmskoetter et al., 2019) that included human stroke patients with aphasia for whom brain health had been assessed from brain imaging data and who had completed language and/or cognitive testing. Backward reference searching was conducted by screening reference lists for non-duplicate articles that met the inclusion criteria; forward reference searching was conducted using the “Cited By” tool on PubMed.

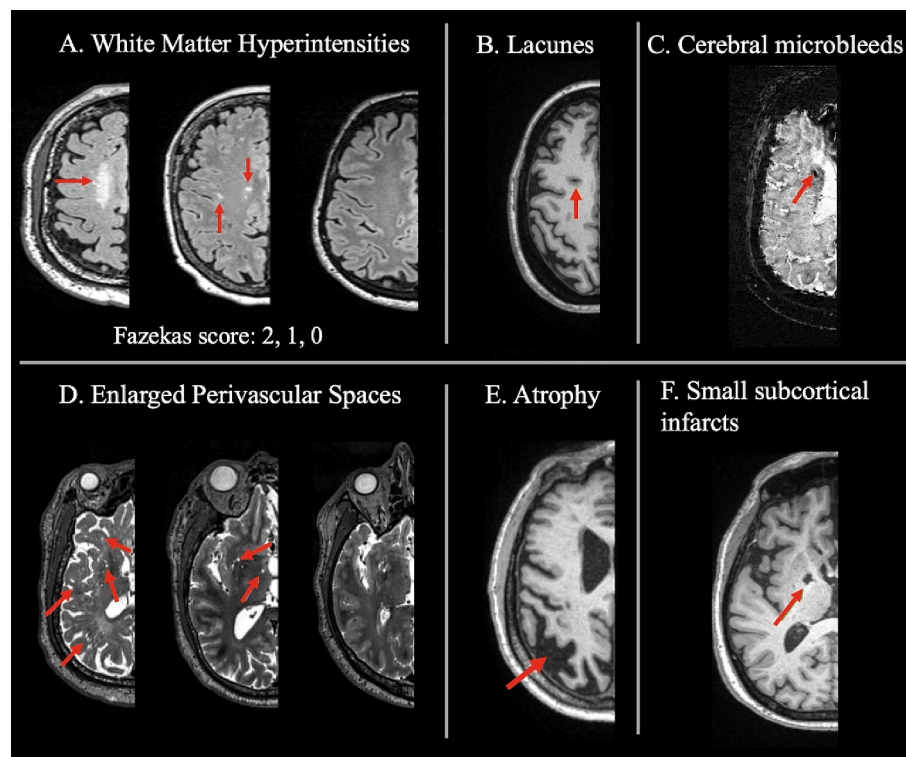
### 2.3. Selection process

Research articles were selected for inclusion if: (1) participants included human stroke patients for whom data were reported independently from stroke-free participants, (2) brain imaging data were available and included assessment of brain health, and (3) language and/or cognitive assessments were administered. Of particular interest were studies in which participants' MRIs were assessed according to the STRIVE criteria and in which participants' Western Aphasia Battery Aphasia Quotients (WAB-AQ) were used as an outcome variable. The WAB is a standard assessment of aphasia severity consisting of a series of tasks assessing naming, repetition, fluency, auditory verbal comprehension, and information content (Clark et al., 2020). The subtest scores are then used to derive a person's WAB-AQ, an overall aphasia severity score.

Studies for which participants' brain MRI data were available but which did not include assessment for at least one brain health biomarker (i.e., WMHs, CMBs, EPVS, atrophy) were excluded. Articles were not excluded based on whether patients received specific stroke interventions or speech language therapy, or whether they cited the STRIVE guidelines when identifying brain health biomarkers.

### 2.4. Data charting

For included articles, the following information was recorded:



**Fig. 1.** Examples of STRIVE markers of SVD on MRI in patients with left hemisphere stroke; only the uninjured right hemisphere is displayed. A. shows examples of WMHs, including Fazekas ratings of 0, 1, 2, highlighted with red arrows. B. shows a lacune. C. is an example of a cerebral microbleed. D. shows examples of differing severity of EPVS: none (right), mild (middle) and severe (left). E. is an example of atrophy. F. shows a small subcortical infarct (>15 mm).

objective, brain health measure(s), brain imaging technique(s), behavioral measure(s) for assessment of cognition and/or aphasia, key findings, and stroke type and time post-stroke of study population (if available).

Participant characteristics, time since stroke, and imaging methods are summarized in [Table S2](#). STRIVE markers assessed, language and/or cognitive measures used, and relevant findings of each study are summarized in [Table S3](#).

### 3. Results

A total of 187 publications were retrieved, including 152 from the three databases and 35 from reference searching (“Other Sources”); after duplicate results were removed, the number of results decreased to 128. Of these, 50 were excluded because they were not original research studies; 47 were excluded because they did not include human participants with stroke or did not report data from these participants as a separate group; 6 were excluded because they did not include assessment of brain health from neuroimaging data; and 9 were excluded because the participants did not undergo language and/or cognitive testing. After applying the eligibility and exclusion criteria, 16 studies were selected for inclusion in the review. See [Fig. 2](#) for further details.

#### 3.1. Results of individual sources of evidence

Of the 16 studies selected for inclusion, only five specifically assessed aphasia ([Wright et al., 2018](#); [Basilakos et al., 2019](#); [Wilmskoetter et al., 2019](#)). The WAB-R was used to diagnose or confirm aphasia in four studies; it was not clearly stated how aphasia was defined for Wright et al. The former utilized the WAB-AQ as a primary outcome measure for aphasia severity. In Wright et al., WAB-AQ was used but was not available for all participants; for reasons of objectivity and availability, performance on naming tasks was selected as the primary outcome with word fluency as the secondary outcome ([Wright et al., 2018](#)). The level,

type, and duration of speech and language treatment received varied among subjects and among studies. Among the included articles, the most assessed brain health indicator was WMH severity.

#### 3.2. Results synthesis

With two exceptions ([Taylor-Rowan et al., 2022](#)), all studies used MR imaging to examine brain health markers, although a variety of sequences were employed ([Table S2](#)). [Appleton et al. \(2020\)](#) rated SVD features primarily from CT, but their findings regarding associations between SVD features and patient outcomes were consistent with MRI-based studies. Taylor-Rowan et al. worked exclusively with CT imaging and applied three distinct visual ratings scales to assess white matter changes and atrophy.

Study population sizes varied greatly, from 30 to 4,011 participants. Those focusing on aphasia had the smallest populations, ranging from 30 to 106 participants (mean = 52.2, median = 42). Stroke etiology also varied, with two studies – from the same research group and describing the same cohort – including only participants with intracerebral hemorrhage ([Keins et al., 2021](#); [Pasi et al., 2021](#)), and six including only ischemic stroke survivors ([Wright et al., 2018](#); [Bahrainwala et al., 2014](#); [Kang et al., 2013](#); [Zhang et al., 2017](#); [Werden et al., 2017](#)).

In addition, the length of time after stroke when cognitive and/or language data were collected varied considerably among, and sometimes within, the selected studies. In those that assessed cognition but not language, assessment was typically performed once or twice (including one follow-up assessment). Two studies included extended follow-up periods of approximately four years, with multiple reassessments of cognition ([Keins et al., 2021](#); [Pasi et al., 2021](#)). In contrast, due to the nature of chronic aphasia, studies that assessed language reported longer average time post-stroke for participants, with more variability ([Wright et al., 2018](#); [Basilakos et al., 2019](#); [Wilmskoetter et al., 2019](#)).

Some studies took a comprehensive approach to analyzing brain health markers, including the use of overall SVD scores and analysis of

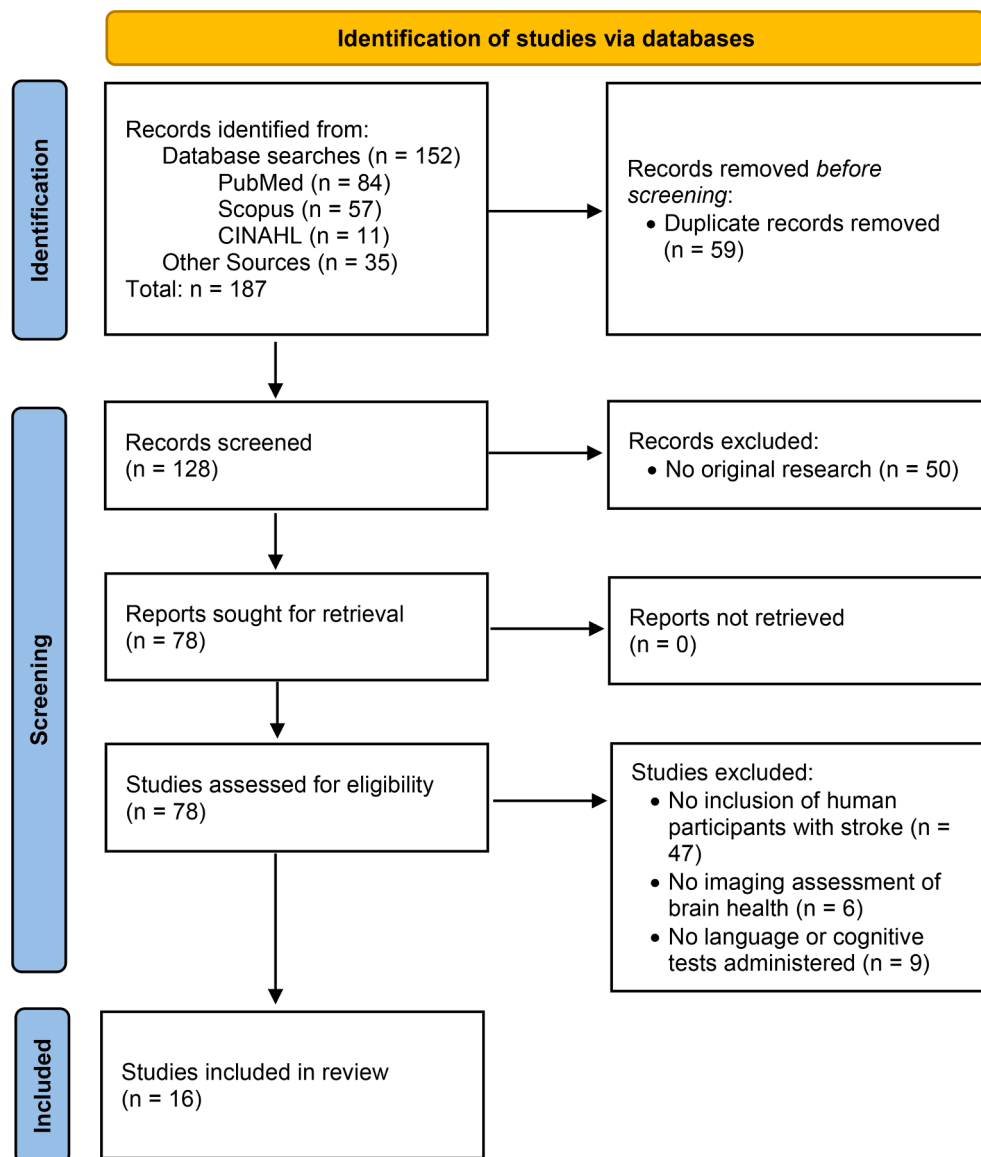


Fig. 2. Selection of sources of evidence according to PRISMA statement guidelines (Tricco et al., 2018).

multiple markers, while others focused primarily on a single measure – typically WMH severity (Varkanitsa et al., 2020; Wright et al., 2018; Basilakos et al., 2019; Wilmskoetter et al., 2019; Bahrainwala et al., 2014; Kang et al., 2013; Zhang et al., 2017). While the Fazekas scale, employed in 11 (69%) of the studies (Basilakos et al., 2019; Johnson et al., 2022; Kang et al., 2013; Keins et al., 2021; Lawrence et al., 2013, 2014; Pasi et al., 2021; Taylor-Rowan et al., 2022; Varkanitsa et al., 2020; Wilmskoetter et al., 2019; Zhang et al., 2017), was the tool most commonly used to assess WMH severity, other scales including the Cardiovascular Health Study scale and volume-based assessment were used in 8 (50%) of studies (Appleton et al., 2020; Bahrainwala et al., 2014; Dickie et al., 2018; Lawrence et al., 2013, 2014; Taylor-Rowan et al., 2022; Werden et al., 2017; Wright et al., 2018). All studies addressed WMH to some extent, whether as a distinct variable, an indicator of SVD for inclusion criteria purposes, or a component of a comprehensive SVD score.

Four studies employed an overall SVD score. The criteria for the 0–3 scale (Arba et al., 2017) used by Appleton et al. is describe in Table 1; the authors also used a three-point SVD score without atrophy and a four-point brain frailty scale that allotted points apiece for WMH, cerebral atrophy, and old infarcts. The van Swieten score rates white matter

lesions in two regions, the anterior horns of the lateral ventricles and the posterior region of the centrum semiovale and cella media. The CT version of this scale assesses severity based on whether the abnormality exists only in the region near the vesicles (score = 1) or extends to the cortex (score = 2) (van Swieten et al., 1990).

Dickie et al. used a previously validated (Klarenbeek et al., 2013; Staals et al., 2014; Lau et al., 2017) five-point SVD score; see Table 1 for scoring criteria. Both Pasi et al. and Keins et al. chose a modified version of the score used by Dickie et al. (Lau et al., 2017) (Table 1). This modified scale, ranging from 0 to 6 points and consisting of refinements proposed in a 2017 study (Lau et al., 2017), allocates one point for presence of: a) >1 lacunes; b) 1–4 CMBs; c) moderate to severe basal ganglia EPVS (>20); d) moderate WMH, (total Fazekas score 3–4). Two points were given for presence of: a) ≥5 CMBs; and b) severe WMH (total Fazekas score 5–6). (Keins et al., 2021; Lau et al., 2017) Pasi et al. also used cerebral amyloid angiopathy-specific (0–6 points) and hypertensive arteriopathy-specific (0–4 points) SVD scores (Table 2).

While assessment of cognition was similarly diverse, with over 15 different cognitive tests used across the 13 studies in which cognitive performance was an outcome of interest, assessment of aphasia was notably less so: all five studies utilized the WAB-AQ to gauge aphasia



**Table 1**  
SVD score criteria used in each study.

Study	Factor	Severity/count	Point (s)
Appleton et al. (max score=3)	WMH	van Swieten score 2 anteriorly or posteriorly	1
	lacunes	≥1	1
	atrophy	Severe (score of 2 cortically and/or centrally)	1
Dickie et al. (max score=4)	Lacunes	≥1	1
	Deep CMBs	≥1	1
	Basal ganglia	≥10	1
	EPVS		
	WMH	early confluent DWMH (Fazekas score 2–3) OR irregular PVH extending into the deep white matter (Fazekas score 3)	1
Pasi et al. and Keins et al. (max score=6)	Lacunes	≥1	1
	CMBs	1 to 4	1
		≥5	2
	Basal ganglia	>20	1
	EPVS		
	WMH	total Fazekas score 3–4	1
		total Fazekas score 5–6	2

**Table 2**  
Criteria for cerebral amyloid angiopathy (CAA)-specific and hypertensive arteriopathy (HTNA)-specific SVD scores.

Scale	Factor	Severity/count	Point (s)
Cerebral amyloid angiopathy (CAA)-specific SVD score criteria (maximum score: 6)	Lobar CMBs	1 to 4	1
		≥5	2
	CSO EPVS	>20	1
	WMH	Fazekas score ≥2 for DWMH or >3* for PVMH	1
	cSS	focal	1
		disseminated	2
Hypertensive arteriopathy (HTNA)-specific SVD score criteria (maximum score: 4)	Lacunes	≥1	1
	WMH	Fazekas score ≥2 for DWMH or 3 for PVMH	1
	Deep CMBs	≥1	1
	Basal ganglia	>10	1
	EPVS		

\*The authors state in their article a cutoff of “>3” for periventricular WMHs; however, because the Fazekas scale has a maximum PVH score of 3, we assume the authors intended to write “≥2”.

severity. Only two studies assessed both aphasia and cognition; both focused on non-verbal executive function. Johnson et al. chose the Matrices subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997), while Varkanitsa et al. used the symbol trails, mazes, and design generation subtests of the Cognitive-Linguistic Quick Test (CLQT) (Helm-Estabrooks, 2001). The latter was the only study to use language tests other than the WAB assessments (the Boston Naming (Kaplan et al., 2001) and Pyramids and Palm Trees (Howard and Patterson, 1992) tests, Figure 3).

While the Werden et al. study satisfied the inclusion criteria, the authors did not investigate associations between the brain health markers and cognitive measures assessed therein, minimizing its relevance for this review. In a similar vein, the objective of Taylor-Rowan and colleagues was to compare the ability of two informant questionnaires to assess pre-stroke cognitive status. As such, they investigated the relationship between the questionnaires, brain health markers,

clinical diagnosis, and pre-stroke cognition, rather than post-stroke cognition, in their analyses. In addition, Bahrainwala et al. focused almost exclusively on hemispatial neglect in right-hemisphere stroke patients. While attentional deficits can be considered an example of cognitive decline, this nearly exclusive focus on neglect in right-hemisphere stroke survivors limits the generalizability of the results. Similarly, it is difficult to compare empathy-specific findings to results from more general cognitive testing described in the majority of the other cognition-focused studies.

### 3.2.1. WMH

Of the studies that individually examined WMH severity in relation to cognitive performance after stroke, 8 of 10 found a significant negative association (Varkanitsa et al., 2020; Johnson et al., 2022; Bahrainwala et al., 2014; Kang et al., 2013; Zhang et al., 2017), which in one case was not significant after controlling for network global efficiency (Lawrence et al., 2014). Dickie et al. used semi-automatically quantified WMH volumes, rather than employing a categorical visual scale, to gauge WMH severity, and failed to find a significant association between WMH volume and cognitive performance on ACE-R (Mioshi et al., 2006) ( $p > 0.05$ ) (Dickie et al., 2018). Lawrence et al. also failed to find an association between WMH and executive function or, after correction, processing speed. In this study, white matter lesion load was used to assess the severity of WMHs, and the authors observed that DTI measures (including axial and radial diffusivity) exhibited more sensitivity to white matter damage than white matter lesion load (Lawrence et al., 2013).

Whereas eight studies did find significant associations, the threshold of WMH severity and type of WMH (deep or periventricular) at which significant changes in cognitive ability were found varied among these studies. The assessment of cognition also differed. For example, cognition was assessed at a single time point post-stroke in five studies (Varkanitsa et al., 2020; Johnson et al., 2022; Bahrainwala et al., 2014; Lawrence et al., 2014; Appleton et al., 2020), at two or three time points in two more studies (Kang et al., 2013; Zhang et al., 2017), and multiple times with an extended follow-up in the remaining study (Pasi et al., 2021). The latter was most interested in rates of cognitive decline, as well as the incidence of dementia in stroke populations, and performed follow-up telephone assessments over a median period of 46.3 months.

Appleton et al. found that higher WMH severity and brain frailty scores were associated with worse performance on two telephone-based cognitive tests, the t-MMSE and TICS-m, but not on a verbal fluency assessment intended to assess executive function. Meanwhile, SVD score was associated with verbal fluency but not with other cognitive measures. Pasi et al. found that DWMH (Fazekas score 2–3), but not PVH, were associated with higher rates of cognitive decline. In comparison, Kang et al. categorized hyperintensities as mild/severe DWMH, mild/severe PVH, and found that both severe DWMH and severe PVH (Fazekas score 2–3) were associated with lower MMSE scores, and there was significant interaction between them. In the Zhang et al. study, individuals in the “severe” leukoaraiosis (total Fazekas score 3–6) group were compared with those in the “none-to-mild” (total Fazekas score 0–2) group. The none-to-mild leukoaraiosis group improved their MMSE scores in the 30 days between baseline and follow-up, while the severe group did not improve.

Regarding aphasia, all five of the articles in this review that specifically assessed aphasia investigated associations between WMH and aphasia severity (Wright et al., 2018; Basilakos et al., 2019; Wilmskoetter et al., 2019). Wilmskoetter and colleagues assessed this at a single timepoint and found a significant indirect effect of PVH severity on aphasia severity (WAB-AQ), mediated by the number of short- and long-range fibers. Similarly, Johnson et al. found a statistically significant effect of total Fazekas score on WAB-AQ ( $p = 0.0004$ ), and developed a model based on health factors (Fazekas score, BMI, exercise rate, and presence of diabetes) which explained 11% of the variance in aphasia severity unexplained by lesion factors. Wright et al. also

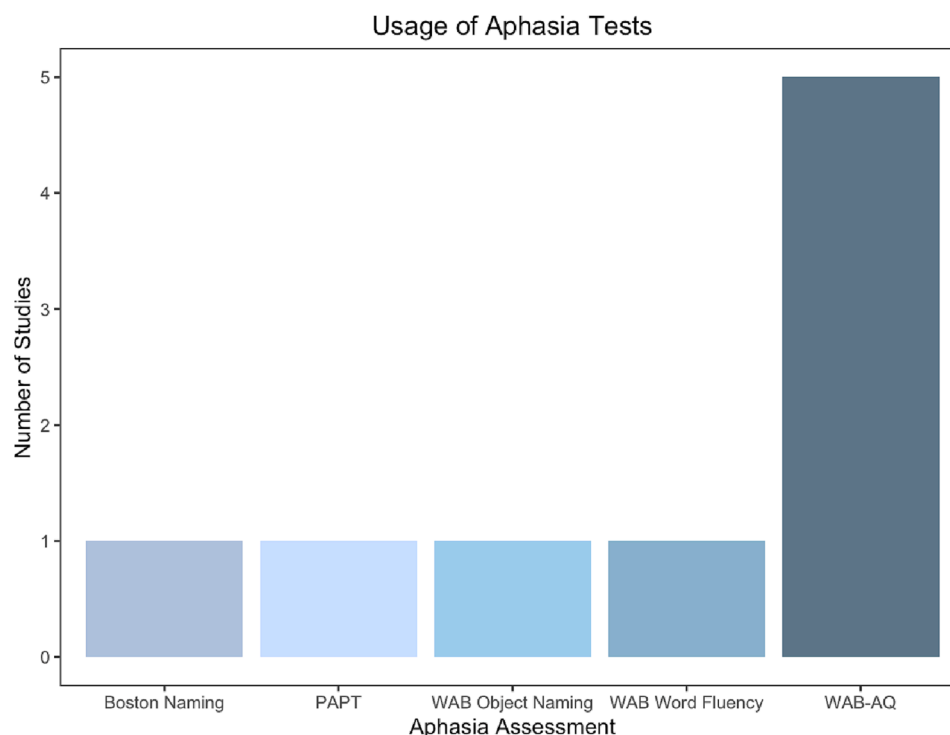


Fig. 3. Frequency of use of each language assessment employed in studies that considered aphasia.

investigated a single timepoint and demonstrated an independent association between right hemisphere WMH severity at stroke onset and object naming and word fluency outcomes. As all participants in this study had experienced a left-hemisphere stroke, the non-infarcted hemisphere was used for assessment of WMH severity. The other two studies focused on multiple timepoints, and Varkanitsa et al. found a significant effect of WMH score on language treatment outcome in people with aphasia that was particularly evident for DWMH. In the comparable study by Basilakos and colleagues, which enrolled a similar patient population to Wright et al. (but later after stroke), outcomes were measured as change in WAB-AQ at follow-up. As in the Wright study, severity of WMH was found to significantly predict decline in language abilities, with more severe WMH being associated with a 4.3 odds increase of decline. This correlation remained significant after controlling for time post-stroke.

### 3.2.2. SVD score(s)

Among the studies that used an SVD score, findings regarding associations with cognition were mixed. Appleton et al., reported an association between SVD score and verbal fluency, but not with performance on the t-MMSE or TICS-M 90 days after stroke. Likewise, Dickie et al. failed to find a significant association between total SVD score and cognitive performance on ACE-R. However, Pasi et al. found significant associations between cognitive decline and all three SVD scores used in the study (global, CAA-specific, and HTNA-specific). Keins et al. similarly reported a significant association between SVD severity (particularly the CAA type) and cognitive decline, manifesting as late-onset dementia. The two studies that reported significant findings used the same scale, which was a modified version of the SVD scale used in the study by Dickie et al. that did not find a significant association with cognition.

Appleton et al. found that overall SVD score along with brain frailty was associated with verbal fluency. Pasi et al. investigated a large set of STRIVE markers, and found lacunes, EPVS in the basal ganglia, deep and lobar cerebral microbleeds, deep WMH, disseminated cSS, cerebral atrophy, and three SVD scores (global, CAA-specific, and HTNA-specific) to be significantly associated with rate of cognitive decline ( $p < 0.05$

for all).

### 3.2.3. Other brain health markers

Other markers of SVD were also individually investigated in relation to post-stroke cognitive and language-related performance. As with WMH, methods of assessment differed, and the consistency of findings varied by marker. In linear mixed model analyses, Pasi et al. investigated a large set of STRIVE markers and found lacunes, EPVS in the basal ganglia, deep ( $\geq 1$ ) and lobar ( $\geq 2$ ) CMBs, DWMH, disseminated cSS, cerebral atrophy, and three SVD scores (global, CAA-specific, and HTNA-specific) to be significantly associated with rate of cognitive decline ( $p < 0.05$  for all). Associations for focal cSS or centrum semiovale EPVS did not reach statistical significance. Likewise, Lawrence and colleagues reported associations of lacunes with cognition and found that the number of lacunar infarcts predicted processing speed and executive function. They did not, however, find such an association for CMBs but did find that network disruption was correlated with both SVD severity and cognition.

For atrophy, results indicated a consensus that decreased brain volume is associated with worse cognitive performance. While Lawrence et al. used normalized brain volume (NBV) as a measure of atrophy (Lawrence et al., 2013; Lawrence et al., 2014), Appleton et al. used a three-point cerebral atrophy score to rate atrophy in cortical and central regions (Appleton et al., 2020). Pasi et al. summed regional atrophy ratings (0–4) based on the size of gyri and sulci in all four lobes and the insular region to give an overall score out of 15 (Pasi et al., 2021). In the study by Taylor-Rowan et al., the Scheltens scale was used to assess medial temporal lobe atrophy (Taylor-Rowan et al., 2022). In the sole aphasia study to look at atrophy, Wright et al. estimated atrophy in the right hemisphere by calculating the ratio of brain volume to cerebrospinal fluid volume. Despite finding a mild correlation between atrophy and WMH severity, the authors failed to find an independent association with naming and word fluency outcomes. Ultimately, six studies found associations between atrophy and cognitive performance. In both studies by Lawrence and colleagues, atrophy was associated with cognition and predicted processing speed, respectively, while Pasi, Appleton, and Taylor-Rowan found associations between higher

cerebral atrophy scores and worse cognitive performance.

Using a four-point scale to evaluate brain frailty, Appleton et al. found that higher scores were associated with worse cognitive performance on the t-MMSE, TICS-M, and verbal fluency assessments. Brain frailty score – based on presence of WMH, cerebral atrophy, and old vascular lesions – was the only metric significantly associated with performance on all three cognitive measures in this study. Measured on very a similar scale, in the study from Taylor-Rowan et al., brain frailty was significantly associated with scores on two informant-based cognitive screening tests (Informant Questionnaire for Cognitive Decline in the Elderly Short Form and Ascertain Dementia 8).

#### 4. Discussion

The purpose of this scoping review was to identify and compare all published, peer-reviewed studies investigating the association between imaging-based markers of brain health and behavioral outcomes (cognition and aphasia) in stroke patients. A total of 16 articles met the inclusion criteria, with 5 including assessment of aphasia and the remaining 11 investigating associations with cognition.

Of note, all studies meeting the inclusion criteria were published between 2013 and present, indicating increased attention in the field of brain health in recent years. The majority focused on the relationship between markers of brain health and cognition in stroke patients, highlighting the emphasis on cognition rather than aphasia within the stroke population. A variety of factors may contribute to this disparity, including the comparative difficulty of assessing language rather than cognition, particularly in outpatient settings. Three of the cognition-focused studies relied upon telephone-based assessments of cognition, which present a barrier for patients with language difficulties. In using the MMSE, Zhang et al. and Kang et al., chose to exclude patients with severe aphasia in addition to those with pre-stroke severe dementia. (Kang et al., 2013; Zhang et al., 2017) While aphasia, as a language disorder, does not necessarily involve impairment of cognitive function, nonverbal cognitive testing is considered most appropriate for this population to avoid confounding effects brought on by failure of participants to comprehend instructions or aphasia-affected performance on verbal tasks.

##### 4.1. WMH and aphasia

Among the five publications directly addressing the relationship between WMH severity and aphasia severity, there was not a clear consensus on the association between initial aphasia severity and WMH. Wright et al. found that WMH severity at stroke onset was significantly associated with naming ability at a single later timepoint ( $\geq 3$  months post-stroke). Similarly, Johnson and colleagues found a strong correlation between total Fazekas score and WAB-AQ, as assessed  $\geq 6$  months post-stroke (Johnson et al., 2022). However, both Basilakos et al. and Varkanitsa et al. failed to find an association between WMH severity and initial (pre-treatment) aphasia severity. This may reflect differences in the behavioral test used, where Wright et al. focused on object naming and word fluency outcomes, whereas Basilakos et al. and Varkanitsa et al. used WAB-AQ, which is a composite score of spontaneous speech, auditory verbal comprehension, repetition, and naming and wordfinding. However, Basilakos et al. did report a significant association between WMH severity and aphasia severity at follow-up after adjusting for time post-stroke (Basilakos et al., 2019). This might suggest that other factors (e.g., the lesion) may contribute to initial aphasia severity, but the status of the remaining brain tissue (e.g., severity of WMHs) are important for recovery. Similarly, in Varkanitsa et al., language was assessed pre-and post-treatment with a semantic feature analysis protocol. Post-treatment, overall WMH severity and DWMH severity predicted language treatment outcomes, providing further support to the theory that WMH severity is an important factor for treatment outcomes following stroke. Given that the health and integrity of the residual brain

tissue is likely important for recovery after stroke, it follows that WMHs, a marker of overall brain health, may influence the variability in treatment response. In the fourth study, Wilmskoetter et al. found a significant indirect effect of WMHs, moderated by the number of long- and short-range white matter fibers, as well as a total effect of PVH severity on single-timepoint aphasia severity in people with aphasia at least one year post stroke. This effect was not found for DWMH (Wilmskoetter et al., 2019). These results are particularly interesting, as they begin to explore the mechanism by which WMHs affect aphasia severity. Taken together, this evidence suggests that factors other than brain health (e.g., lesion volume, age, time post onset, network connectivity) may play a larger role in determining aphasia severity at a single timepoint in the chronic stage, but that brain health can have a long-term effect on a patient's potential for recovery. Further research is necessary to disentangle the effects of deep and periventricular white matter hyperintensities on language recovery.

While frequently grouped together, the behavioral and clinical correlates of DWMH and PVH differ (Griffanti et al., 2018). The visual difference between the two classes of hyperintensities is more readily defined than the functional and etiological distinctions. Present evidence points to differential effects of DWMH and PVH on cognition, mood, and neural network structure. For instance, PVH are characterized by gliosis, demyelination, and loosening of white matter fibers, while DWMH are more strongly associated with axonal loss, arteriosclerosis, and vacuolization (Griffanti et al., 2018). In some studies, PVH but not DWMH, have been associated with cognitive function, (Bolandzadeh et al., 2012; Taylor-Rowan et al., 2022; Kim et al., 2008); however, other studies (e.g., Pasi et al., 2021) have reported the opposite. While inconclusive, these findings underscore the value of separately analyzing the effects of DWMH and PVH by supporting the idea that each type may represent distinct microstructural changes and thus affect behavior by unique mechanisms.

##### 4.2. WMH and cognition

Ten studies specifically investigated the relationship between WMH and cognition, with eight finding a significantly negative association. In five of the ten studies, cognition was assessed at two or more follow-up timepoints, allowing for the investigation of changes in cognitive performance over time after stroke (Keins et al., 2021; Pasi et al., 2021; Kang et al., 2013; Zhang et al., 2017; Dickie et al., 2018).

Both studies by Lawrence et al. used data from the same group of participants. In the 2014 study, the association between WMH severity and cognition in stroke patients with SVD ceased to be independently significant when the authors controlled for network global efficiency. Otherwise stated, network efficiency has a mediating effect on the relationship between WMH and cognitive performance (Lawrence et al., 2014). In this study, network global efficiency was used to describe the integration of the whole brain network, and was estimated by averaging the efficiency of node pairs which were extracted from diffusion tensor imaging (DTI) (Lawrence et al., 2014). Network global efficiency was adjusted for in a multiple linear regression model. The same study provides evidence of broad disruption of network connectivity in SVD patients, similar to the findings of Wilmskoetter et al. Together, these findings suggest a possible mechanism by which WMHs affect behavior. Further research into the mechanism by which WMHs disrupt network efficiency, and the effect of this relationship on cognitive outcomes in stroke patients, may prove useful in predicting cognitive decline in this population.

Methodological differences in the assessment of WMH severity may have contributed to the mixed results among studies that investigated associations between cognition and WMH severity. The two studies (Lawrence et al., 2013; Dickie et al., 2018), that failed to find a significant association used semi-automatically quantified WMH and white matter lesion load, respectively, while the studies that found significant associations used visual rating scales (primarily the Fazekas scale).

Notably, visual ratings were made by observers that were masked to the behavioral measures. Automatic and semiautomatic quantification of WMH volumes, both of which require manual editing, provide contextual information such as the specific location of WMHs and can be used to track volume changes over time. In addition, this type of assessment is not hampered by ceiling effects, unlike visual scales (e.g., Fazekas). However, the volumetric quantification method used by Dickie et al. does not differentiate between PVH and DWMH (Valdés Hernández et al., 2010). As previously mentioned, by equivocating these types of WMH, a difference in effect between DWMH and PVH may have been ignored. If PVH and DWMH differentially affect cognition, this may explain why the studies that used a visual rating scale that separately rated DWMH and PVH in addition to overall WMH severity found more significant relationships between WMH and behavior. Additionally, participants in Dickie et al. were primarily milder stroke patients, and the cognitive exam used (ACE-R) was not used in any other study included in this review. However, this scale has been shown to be comparable to the MoCA and in fact incorporates the MMSE (Pendlebury et al., 2012). Limiting study eligibility to patients who had experienced a mild (NIHSS <7) or nondisabling stroke may have reduced the number of eligible participants with more severe SVD, taking into consideration that PVH severity may be associated with NIHSS (National Institutes of Health Stroke Scale) score (Kang et al., 2013). It is also possible that the effect of WMH is not continuous (and thus not detected by associations with continuous measures), but that there is a “threshold effect.” That is, the effect on language/cognitive outcomes is almost nil until some threshold of severity is reached.

Three cognitive studies evaluated the effects of PVH and DWMH individually (Pasi et al., 2021; Kang et al., 2013). Among these, Kang et al. found significant interaction between the subtypes, which were associated with lower MMSE scores at both the initial assessment (two weeks post stroke) and one-year follow up. PVH were also significantly associated with greater stroke severity and worse functional outcomes at both timepoints (Kang et al., 2013). DWMH of Fazekas grade 2 or 3 were demonstrated by Pasi et al. to be associated with the rate of cognitive decline, while PVH were not (Pasi et al., 2021). In contrast, Taylor-Rowan et al. reported stronger and more significant correlations for PVH than for DWMH with two informant-based assessments of pre-stroke cognitive function (Taylor-Rowan et al., 2022).

#### 4.3. Other markers of brain health

While WMH were the most frequently investigated marker of brain health, other STRIVE measures were associated with cognitive performance in stroke survivors. Most notably, composite SVD scores provide an interpretation of overall brain health based on three or more visible markers. The heterogeneity of these scales, which are continually being refined, makes comparison among rating systems more difficult; four studies included in this review reported use of five different SVD scoring systems, and consequently, the results were mixed.

An SVD score adapted for CT imaging (Table 1) was used by Appleton et al., as most of their participants had CT scans rather than MRI, although it should be noted that certain STRIVE markers (EPVS, CMBs) are not visible on CT. The scale incorporated lacunes, brain atrophy, and WMH rated according to the CT version of the van Swieten scale (van Swieten et al., 1990), and found an association between verbal fluency and both presence of lacunes and brain atrophy.

Three SVD scales were used by Pasi et al. (Tables 1 and 2). Higher scores on all scales were associated with rate of cognitive decline and predicted post-stroke dementia, with the global summary score being the strongest predictor. The global score considered presence of lacunes, >20 EPVS in the basal ganglia, and differentiated between higher and lower CMB counts and moderate and severe total WMH burden according to Fazekas scores. Similarly, Keins et al. found that higher global SVD scores on the same scale independently predicted late-onset depression and dementia.

There has been a recent trend towards using automated methods to detect and quantify markers of SVD. For example, Dickie et al. used the Brain Health Index, an automated combined measure of brain atrophy, ischemia and SVD burden. They found that this measure of SVD was more strongly associated with cognitive performance on ACE-R in individuals with mild stroke than an SVD score that incorporated presence of lacunes and CMBs, basal ganglia EPVS, and WMH (Dickie et al., 2018). The SVD score used did moderately correlate with the Brain Health Index (Dickie et al., 2018). Increased use of automated measures such as the Brain Health Index may facilitate easier comparisons across studies and patient populations in future research. While the STRIVE guidelines provide useful definitions of brain health markers, the next step should be the development of a comprehensive consensus scale for the assessment of SVD in order to compare the effects of SVD across studies and populations.

As well as combining measures into an overall SVD score, some markers of SVD have also been investigated separately across these studies. Individually, cerebral atrophy (Taylor-Rowan et al., 2021; Pasi et al., 2021; Appleton et al., 2020), brain frailty (Taylor-Rowan et al., 2021; Appleton et al., 2020), lacunes (Pasi et al., 2021; Lawrence et al., 2013; Lawrence et al., 2014), EPVS in the basal ganglia (Pasi et al., 2021), CMBs (Pasi et al., 2021), and disseminated cSS (Pasi et al., 2021) were each associated with poorer cognitive performance in one or more studies, although this was not consistent across all studies (see Wright et al.). While rating multiple markers across a single set of scans is time-consuming, it is important to consider the independent effects of these individual markers to determine which meaningfully contribute to behavioral changes. This may streamline the development of a comprehensive SVD score for use in behavioral studies. Additionally, the effects of different SVD markers could vary depending on their etiology and location in the brain, which justifies efforts to isolate their respective effects on language, cognition, structural connectivity, and beyond.

#### 4.4. Limitations

We restricted our search to the databases PubMed, Scopus, and CINAHL, so studies meeting the inclusion criteria, but which appear only on other databases were not considered in this review. The databases were last searched in December 2022; studies published after that time were not included. Forward and reverse searching of references was conducted only for the subset of studies that specifically investigated aphasia. Further, we focused on SVD as the primary marker for brain health. Future reviews may address other biomarkers for brain health.

### 5. Conclusions

The evidence reviewed herein supports a relationship between more severe SVD and worse cognitive and language performance after stroke. In patients with aphasia, the available literature consistently indicates that WMH severity, an indicator of SVD, plays a role in the extent of language recovery in the chronic phase of aphasia. Further study is needed to determine whether this effect exists in the acute stage of aphasia. In terms of cognition, greater SVD severity is associated with cognitive decline and poorer performance on a variety of cognitive assessments, including those assessing language, recall, and executive function, although this relationship is less clear than that between WMH and aphasia. Analysis of brain imaging in accordance with the STRIVE guidelines for features of SVD may give further understanding into the prognosis of an individual's post-stroke cognitive and language, but this potential will be hindered while researchers and clinicians lack a uniform grading system for a summary score of brain health in SVD. Whereas a standardized SVD score has not been agreed upon, there appears to be value in investigating the effects of multiple markers of brain health to best predict behavioral outcomes. With the information obtained from brain imaging, a patient's brain health assessment can serve as a tool in creating treatment plans that best suit their individual



needs and goals.

The use of a variety of cognitive measures also appears to be a strength when looking collectively at the body of literature on WMH and cognitive performance. While this may contribute to differences in results among studies, the findings described here displayed considerable uniformity despite the variety of assessments. Given this, the use of alternative or supplementary language measures in addition to the WAB may provide a more thorough knowledge base and allow for more nuance in comparing different language tasks in individuals with post-stroke aphasia. Conversely, the contrast between the uniformity of the aphasia findings and the variability in the cognition findings highlights the relevance of brain health and cognitive reserve thresholds for the multimodal demands associated with language recovery.

Understanding the implications of patients' SVD status may not be essential for all aspects of stroke recovery or "cognition" in general, but it is important for language. Given this, brain health markers should be part of the models for personalized prediction in patients with stroke: while these markers may not be relevant for all patients, they are likely crucial for those with aphasia.

### 5.1. Recommendations for Future Studies

Studies of novel treatment paradigms may wish to consider variation in SVD severity among participants, in addition to criteria such as lesion size, as a potential moderator of treatment effectiveness in chronic aphasia. Given the emphasis on cognition rather than aphasia throughout the literature, we recommend that future studies include more assessments focused on aphasia severity and recovery from aphasia when considering the role of SVD in a stroke aphasia population. Similarly, if testing general cognition, investigators should consider the type of test used and the manner of its use (i.e., moving away from telephone assessments and towards non-verbal ways of assessing behavior) to try to separate the effects of the aphasia from general cognition. In addition, when investigating the relationship between SVD and aphasia severity, we recommend that such studies include a more varied battery of assessments, rather than relying solely on the WAB, to assess the interaction between brain health and language recovery more comprehensively.

This review highlights that other factors may play a larger role in determining aphasia severity at a single timepoint, but brain health may have a more striking impact on an individual's potential for recovery, therefore studies investigating treatment approaches or changes in behavior over time should include measures of SVD. Likewise, when clinicians are deciding on potential treatment approaches, SVD severity (i.e., intact tissue health) and intact networks should be considered to best prescribe a treatment that matches the individual's recovery potential.

Finally, when exploring the role of SVD, there is a need for consistent scanning types (i.e., use of FLAIR scans rather than CT scans) and a consistent way to investigate SVD severity. Currently, although the most-studied marker of SVD, WMH severity is not measured consistently throughout the literature, with some studies using visual scales such as the Fazekas scale and others using volumetric measures, and some using a combined DWMH and PVH score while others use separate measures. Similarly, many studies disregard other markers of SVD. When all are considered, there is no consistent way to summarize these scores into one total measure of SVD severity. It is imperative that consistent scores are used across studies to adequately test and compare the impact of SVD on cognition and aphasia.

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### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data availability

No data was used for the research described in the article.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2023.103480>.

### References

- "brain health" - Search Results - PubMed. Accessed July 10, 2022. <https://pubmed.ncbi.nlm.nih.gov/?term=%22brain+health%22>.
- Appleton, J.P., Woodhouse, L.J., Adami, A., Becker, J.L., Berge, E., Cala, L.A., Casado, A. M., Caso, V., Christensen, H.K., Dineen, R.A., Gommans, J., Koumellis, P., Szatmari, S., Sprigg, N., Bath, P.M., Wardlaw, J.M., 2020. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 94 (5), e439–e452.
- Arba, F., Inzitari, D., Ali, M., Warach, S.J., Ruby, M., Lees, K.R., 2017. Small vessel disease and clinical outcomes after IV rt-PA treatment. *Acta Neurol. Scand.* 136 (1), 72–77.
- Bahrainwala, Z.S., Hillis, A.E., Dearborn, J., Gottesman, R.F., 2014. Neglect performance in acute stroke is related to severity of white matter hyperintensities. *Cerebrovasc. Dis.* 37 (3), 223–230. <https://doi.org/10.1159/000357661>.
- Basilakos, A., Stark, B.C., Johnson, L., Rorden, C., Yourganov, G., Bonilha, L., Fridriksson, J., 2019. Leukoaraiosis Is Associated With a Decline in Language Abilities in Chronic Aphasia. *Neurorehabil. Neural Repair* 33 (9), 718–729.
- Bolandzadeh, N., Davis, J.C., Tam, R., Handy, T.C., Liu-Ambrose, T., 2012. The association between cognitive function and white matter lesion location in older adults: A systematic review. *BMC Neurol.* 12 (1), 1–10. <https://doi.org/10.1186/1471-2377-12-126/TABLES/6>.
- Bonilha, L., Gleichgerricht, E., Nesland, T., Rorden, C., Fridriksson, J., 2016. Success of anomia treatment in aphasia is associated with preserved architecture of global and left temporal lobe structural networks. *Neurorehabil. Neural Repair* 30 (3), 266–279. <https://doi.org/10.1177/1545968315593808>.
- Cipolla, M.J., Liebeskind, D.S., Chan, S.L., 2018. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *J. Cereb. Blood Flow Metab.* 38 (12), 2129. <https://doi.org/10.1177/0271678X18800589>.
- Clark, H.M., Utianski, R.L., Duffy, J.R., Strand, E.A., Botha, H., Josephs, K.A., Whitwell, J.L., 2020. Western Aphasia Battery-Revised Profiles in Primary Progressive Aphasia and Primary Progressive Apraxia of Speech. *Am. J. Speech Lang. Pathol.* 29 (1S), 498–510.
- Dickie, D.A., Valdés Hernández, M.D.C., Makin, S.D., Staals, J., Wiseman, S.J., Bastin, M. E., Wardlaw, J.M., 2018. The brain health index: Towards a combined measure of neurovascular and neurodegenerative structural brain injury. *Int. J. Stroke* 13 (8), 849–856.
- Griffanti, L., Jenkinson, M., Suri, S., Zsoldos, E., Mahmood, A., Filippini, N., Sexton, C.E., Topiwala, A., Allan, C., Kivimäki, M., Singh-Manoux, A., Ebmeier, K.P., Mackay, C. E., Zamboni, G., 2018. Classification and characterization of periventricular and deep white matter hyperintensities on MRI: A study in older adults. *Neuroimage* 170, 174–181.
- Guevarra, A.C., Ng, S.C., Saffari, S.E., Wong, B.Y.X., Chander, R.J., Ng, K.P., Kandiah, N., Pase, M., 2020. Age Moderates Associations of Hypertension, White Matter Hyperintensities, and Cognition. *J. Alzheimers Dis.* 75 (4), 1351–1360.
- Helm-Estabrooks, N., 2001. *Cognitive Linguistic Quick Test: Examiner's Manual*. Psychological Corporation.
- Howard, D., Patterson, K., 1992. *The Pyramids and Palm Trees Test*. Thames Valley Test Company.
- Hu, H.-Y., Ou, Y.-N., Shen, X.-N., Qu, Y.-i., Ma, Y.-H., Wang, Z.-T., Dong, Q., Tan, L., Yu, J.-T., 2021. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. *Neuroscience and Biobehavioral Reviews* 120, 16–27.
- Johnson, L., Nemati, S., Bonilha, L., Rorden, C., Busby, N., Basilakos, A., Newman-Norlund, R., Hillis, A.E., Hickok, G., Fridriksson, J., 2022. Predictors beyond the lesion: Health and demographic factors associated with aphasia severity. *Cortex* 154, 375–389.
- Kang, H.-J., Stewart, R., Park, M.-S., Bae, K.-Y., Kim, S.-W., Kim, J.-M., Shin, I.-S., Cho, K.-H., Yoon, J.-S., 2013. White matter hyperintensities and functional outcomes at 2 weeks and 1 year after stroke. *Cerebrovasc. Dis.* 35 (2), 138–145.
- Kaplan, E., Goodglass, H., Weintraub, S., 2001. *The Revised Boston Naming Test*. Lea & Febiger.
- Keins, S., Abramson, J.R., Castello, J.P., Pasi, M., Charidimou, A., Kourkoulis, C., DiPucchio, Z., Schwab, K., Anderson, C.D., Gurol, M.E., Greenberg, S.M., Rosand, J., Viswanathan, A., Biffi, A., 2021. Latent profile analysis of cognitive decline and

- depressive symptoms after intracerebral hemorrhage. *BMC Neurol.* 21 (1) <https://doi.org/10.1186/s12883-021-02508-x>.
- Kim, K.W., MacFall, J.R., Payne, M.E., 2008. Classification of White Matter Lesions on Magnetic Resonance Imaging in Elderly Persons. Published online 64 (4), 273–280.
- Kiran, S., Meier, E.L., Johnson, J.P., 2019. Neuroplasticity in Aphasia: A Proposed Framework of Language Recovery. *J. Speech Lang. Hear. Res.* 62 (11), 3973–3985. <https://doi.org/10.1044/2019.JSLHR-L-RSNP-19-0054>.
- Klarenbeek, P., van Oostenbrugge, R.J., Rouhl, R.P.W., Knottnerus, I.L.H., Staals, J., 2013. Ambulatory blood pressure in patients with lacunar stroke: Association with total MRI burden of cerebral small vessel disease. *Stroke* 44 (11), 2995–2999. <https://doi.org/10.1161/STROKEAHA.113.002545/FORMAT/EPUB>.
- Lau, K.K., Li, L., Schulz, U., Simoni, M., Chan, K.H., Ho, S.L., Cheung, R.T.F., Küker, W., Mak, H.K.F., Rothwell, P.M., 2017. Total small vessel disease score and risk of recurrent stroke: Validation in 2 large cohorts. *Neurology* 88 (24), 2260–2267.
- Lawrence, A.J., Patel, B., Morris, R.G., MacKinnon, A.D., Rich, P.M., Barrick, T.R., Markus, H.S., Baron, J.-C., 2013. Mechanisms of cognitive impairment in cerebral small vessel disease: multimodal MRI results from the St George's cognition and neuroimaging in stroke (SCANS) study. *PLoS One* 8 (4), e61014.
- Lawrence, A.J., Chung, A.W., Morris, R.G., Markus, H.S., Barrick, T.R., 2014. Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology* 83 (4), 304–311. <https://doi.org/10.1212/WNL.0000000000000612>.
- Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., Hodges, J.R., 2006. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int. J. Geriatr. Psychiatry* 21 (11), 1078–1085. <https://doi.org/10.1002/GPS.1610>.
- Pasi, M., Sugita, L., Xiong, L.i., Charidimou, A., Boulouis, G., Pongpitakmetha, T., Singh, S., Kourkoulis, C., Schwab, K., Greenberg, S.M., Anderson, C.D., Gurol, M.E., Rosand, J., Viswanathan, A., Biffi, A., 2021. Association of Cerebral Small Vessel Disease and Cognitive Decline After Intracerebral Hemorrhage. *Neurology* 96 (2), e182–e192.
- Pendlebury, S.T., Mariz, J., Bull, L., Mehta, Z., Rothwell, P.M., 2012. MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke. Published online 43 (2), 464–469.
- Staals, J., Makin, S.D.J., Doubal, F.N., Dennis, M.S., Wardlaw, J.M., 2014. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* 83 (14), 1228–1234.
- Taylor-Rowan, M., McGuire, L., Hafdi, M., Evans, J., Stott, D.J., Wetherall, K., Elliott, E., Drozdowska, B., Quinn, T.J., 2022. Comparative validity of informant tools for assessing pre-stroke cognitive impairment. *Int. J. Geriatr. Psychiatry* 37 (4). <https://doi.org/10.1002/GPS.5700>.
- Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D.J., Horsley, T., Weeks, L., Hempel, S., Akl, E.A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M.G., Garrity, C., Lewin, S., Godfrey, C.M., Macdonald, M.T., Langlois, E.V., Soares-Weiser, K., Moriarty, J.O., Clifford, T., Tunçalp, Ö., Straus, S.E., 2018. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* 169 (7), 467–473.
- Valdés Hernández, M.D.C., Ferguson, K.J., Chappell, F.M., Wardlaw, J.M., 2010. New multispectral MRI data fusion technique for white matter lesion segmentation: method and comparison with thresholding in FLAIR images. *Eur. Radiol.* 20 (7), 1684. <https://doi.org/10.1007/S00330-010-1718-6>.
- van Swieten, J.C., Hijdra, A., Koudstaal, P.J., van Gijn, J., Van, J.C., van Gijn, S.J., 1990. Grading white matter lesions on CT and MRI: a simple scale. *J. Neurol. Neurosurg. Psychiatry* 53, 1080–1083. <https://doi.org/10.1136/jnnp.53.12.1080>.
- van Swieten, J.C., Hijdra, A., Koudstaal, P.J., van Gijn, J., 1990. Grading white matter lesions on CT and MRI: a simple scale. *Neurosurgery, and Psychiatry.* 53, 1080–1083. <https://doi.org/10.1136/jnnp.53.12.1080>.
- Varkanitsa, M., Peñaloza, C., Charidimou, A., Caplan, D., Kiran, S., 2020. White Matter Hyperintensities Predict Response to Language Treatment in Poststroke Aphasia. *Neurorehabil. Neural Repair* 34 (10), 945–953. <https://doi.org/10.1177/1545968320952809>.
- Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., Black, S.E., Brayne, C., Breteler, M., Chabriat, H., DeCarli, C., de Leeuw, F.-E., Doubal, F., Duering, M., Fox, N.C., Greenberg, S., Hachinski, V., Kilimann, I., Mok, V., Oostenbrugge, R.V., Pantoni, L., Speck, O., Stephan, B.C.M., Teipel, S., Viswanathan, A., Werring, D., Chen, C., Smith, C., van Buchem, M., Norrving, B.o., Gorelick, P.B., Dichgans, M., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 12 (8), 822–838.
- Wechsler, D., 1997. Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). The Psychological Corporation.
- Werden, E., Cumming, T., Li, Q.i., Bird, L., Veldsman, M., Pardoe, H.R., Jackson, G., Donnan, G.A., Brodtmann, A., 2017. Structural MRI markers of brain aging early after ischemic stroke. *Neurology* 89 (2), 116–124.
- Wilmskoetter, J., Marebwa, B., Basilakos, A., et al., 2019. Long-range fibre damage in small vessel brain disease affects aphasia severity. *Brain.* 142 (10), 3190–3201. <https://doi.org/10.1093/BRAIN/AWZ251>.
- Wolters, F.J., Arfan, I.M., 2019. Epidemiology of Vascular Dementia: Nosology in a Time of Epiomics. *Arterioscler. Thromb. Vasc. Biol.* 39 (8), 1542–1549. <https://doi.org/10.1161/ATVBAHA.119.311908>.
- Wright, A., Tippett, D., Saxena, S., Sebastian, R., Breining, B., Faria, A., Hillis, A.E., 2018. Leukoaraiosis is independently associated with naming outcome in poststroke aphasia. *Neurology* 91 (6), e526–e532.
- Zanon Zotin, M.C., Sveikata, L., Viswanathan, A., Yilmaz, P., 2021. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. *Curr. Opin. Neurol.* 34 (2), 246–257. <https://doi.org/10.1097/WCO.0000000000000913>.
- Zhang, Z., Ren, W., Shao, B., Xu, H., Cheng, J., Wang, Q., Gu, Y., Zhu, B., He, J., 2017. Leukoaraiosis is Associated with Worse Short-Term Functional and Cognitive Recovery after Minor Stroke. *Neurologia Medico-Chirurgica (Tokyo)* 57 (3), 136–143.
- Zhi, N., Zhang, L., Wang, Y., Bai, S., Geng, J., Yu, L., Cao, W., Zhuang, L., Zhou, Y., Guan, Y., 2021. Modified cerebral small vessel disease score is associated with vascular cognitive impairment after lacunar stroke. *Aging (Albany NY)* 13 (7), 9510–9521.