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Brain atrophy in cerebral small vessel diseases: Extent, consequences, technical limitations and perspectives: The HARNESS initiative

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Abstract

Brain atrophy is increasingly evaluated in cerebral small vessel diseases. We aim at systematically reviewing the available data regarding its extent, correlates and cognitive consequences. Given that in this context, brain atrophy measures might be biased, the first part of the review focuses on technical aspects. Thereafter, data from the literature are analyzed in light of these potential limitations, to better understand the relationships between brain atrophy and other MRI markers of cerebral small vessel diseases. In the last part, we review the links between brain atrophy and cognitive alterations in patients with cerebral small vessel diseases.

Keywords

Cerebral small vessel disease, brain atrophy, brain volume, segmentation, white matter hyperintensities, lacunes, cognitive performances, cognitive alterations

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Introduction

Cerebral small vessel diseases (SVD) are among the most frequent brain disorders. They are responsible for at least 20% of all strokes and are the second contributor to dementia after Alzheimer's disease (AD).[1] The clinico-radiological spectrum of SVD is wide. Clinical manifestations range from acute, such as stroke, to chronic, e.g. in the form of slow deterioration of cognitive functions.[2] On brain magnetic resonance imaging (MRI), SVD manifests with various loads of white matter hyperintensities (WMH), lacunes, dilated perivascular spaces (dPVS), and microbleeds (MB).[2]

Brain atrophy represents a final common pathway for pathological processes and is now recognized as a key MRI marker in SVD. As such, brain atrophy was part of the recent consensus criteria in SVD,[3] although little is known about its extent, correlates and consequences.[4]

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In the context of the HARNESS initiative (Harmonizing brain imaging methods for vascular contributions to neurodegeneration),[5] we were solicited as a group of experts to reach a consensus regarding the measure of brain atrophy in SVD.

Given the numerous potential methodological issues associated with the measurement of brain atrophy in the context of SVD-related brain lesions, the first part of this review is dedicated to methodological aspects. Subsequently, data from the literature are reported and analyzed according to these known limitations. We hope that this summary of current knowledge will encourage more research on SVDs and brain atrophy.

Material and methods

This systematic review follows the PRISMA statements (http://www.prisma-statement.org). Articles were retrieved from a PubMed search last conducted on 1 February 2019 with the following search terms: (((((((("cerebral atrophy" OR "brain atrophy" OR "atrophy" OR siena OR BSI)) AND ("small vessel disease" OR "small vessel diseases" OR microangiopathy OR lacunar OR lacunae OR "silent brain infarcts" OR "white matter hyperintensities" OR leukoaraiosis OR "white matter lesions" OR "subcortical ischaemic dementia" OR "ischemic dementia" OR "vascular dementia of the subcortical type")) AND english [Language])) NOT review[Publication Type]))) AND ("2000"[Date – Publication]: "2020"[Date – Publication]). Articles from the authors' personal databases were added to the search strategy. Articles not written in English, and review articles were excluded.

Two experienced readers (FDG and EJ) excluded irrelevant papers based on title and abstract reading. Full texts of remaining articles were further analyzed. Exclusion criteria were (1) subjects without SVD or MRI markers of SVD, (2) use of a qualitative (visual rating) atrophy scale, (3) computation of a quantitative but local measure of atrophy (i.e. studies reporting only regional measurements with voxel-based morphometry, regional volumetry or regional cortical thickness).

Only studies that described methods to quantify brain atrophy and to measure MRI markers of SVD were considered. Selected articles were reviewed in three parts: (1) comparison of atrophy measurements between a group of patients with clinically defined SVD and a control group; (2) relationship between brain atrophy and other MRI markers of SVD; (3) association between atrophy and cognitive outcomes. We recorded any effort to adjust the study findings for confounding effects of SVD lesions. Given the major confounding effect of AD which can lead to brain atrophy years before clinical symptoms,[6] only patients with a clinical or radiological diagnosis of SVD, or samples with a clear enrichment with SVD MRI markers were considered in the latter part.

Throughout this review, the term brain atrophy refers to the generic process of brain tissue loss with age or pathological processes. Regarding imaging measures, we refer to brain volume when measured cross-sectionally, and to brain atrophy when measured longitudinally as brain volume change (with at least two time points).

Results

The initial PubMed search yielded 1132 articles. Seven hundred and sixty-seven were excluded after title reading and 233 articles after abstract reading, leaving 132 articles for full text analysis.

Part I: Quantification of brain atrophy: Methods and technical limitations

Age-related brain atrophy is minimal, usually below 0.2% a year in middle-aged adults and below 1% a year in healthy elders.[4] Pathological states, particularly AD, increase brain atrophy rates in the late stages but rarely beyond 2% a year.[7] This led to the development of automated methods able to detect small differences in cross-sectional studies and even smaller variations in longitudinal studies.[8–11] Most cross-sectional and longitudinal algorithms tended to use as input three-dimensional T1 (3DT1) sequences, and occasionally used several sequences. High-resolution images, with voxels size approaching 1 mm^3, are currently the acquisitions of choice.

In cross-sectional studies, brain volume can still be estimated from 2D scans, but results will be affected by substantial partial volume effects due to large slice thickness. To take into account interindividual differences, it is mandatory to normalize brain volumes to intracranial cavity volume as an indication of the individual's original brain size.[12–15]

Longitudinal analyses do not require such normalization (the subject is its own control), although it should be considered when feasible since rates of decline may be influenced by initial brain size. Longitudinal changes measured over short periods of time (typically a few years) are so small that it becomes crucial to minimize the variability of each measurement. When brain volumes are measured separately in different follow-up MRI scans and then subtracted, the variability of each measurement adds up.[16] Alternative methods relying on the joint processing of several images simultaneously are thought to be preferable. The most popular suites are SIENA,[14] the Boundary Shift Integral (BSI),[17] FreeSurfer[18] and derived algorithms, although caution is required when assessing brains with established SVD

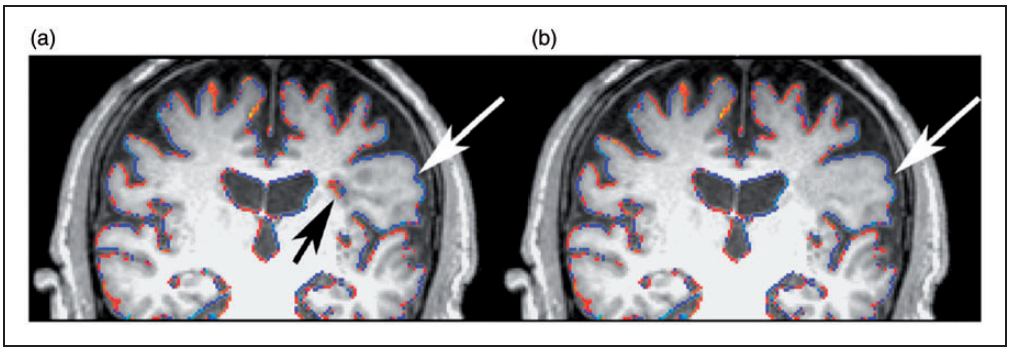

Figure 1. Comparison between SIENA with default settings (a) and SIENA with lesion filling (b). Hot colors indicate areas of growth and cold colors areas of atrophy. The region of surface atrophy (white arrows) near the infarct is fairly consistent between methods, but lesion filling removes an area of apparent change within the infarct (black arrow). Courtesy of Yassi et al.[21] Reprinted by permission from Springer © 2015.

since all the above suites can be influenced by signal variance due to SVD lesions (see below). Within-center reproducibility of quantitative image-processing methods for atrophy assessment has been shown to be relatively high in several studies.[8]

In patients with SVD, none of the above-mentioned cross-sectional or longitudinal methods has, however, been specifically validated, and it is important to understand that these methods are usually developed upon normal brain anatomy in young subjects. Several factors may strongly influence their reliability in the context of SVD. For instance, severe WMH often appear hypointense on 3DT1 images with a signal close to that of the cerebral cortex or of cerebrospinal fluid (CSF). Thus, they may be at least partly classified as CSF. Few studies have so far addressed these aspects.[19,20] The behavior or the different algorithms with lacunes may also be erratic, as they may be unpredictably considered as brain parenchyma or as CSF (Figure 1).[21] Cortical infarcts, not caused by SVD are also detected in up to 3% of healthy elders. The impact of their presence on brain segmentation is unpredictable. Given their proximity with the outer brain, they are more likely to be segmented as CSF unless they are mainly malacic in which case they may be mistaken for WMH. By contrast, cortical microinfarcts, given their size inferior to 1 to a few millimeters, do not influence the segmentation. In addition, the space occupied by acute ischemic or hemorrhagic lesions, which will disappear on follow-up images, will probably be considered by automated methods as brain atrophy.[24] Finally, the contrast between gray and white matter may be altered, particularly in severe SVD.[22,23]

Thus, in severe SVD, careful visual inspection of the different post-processing steps is needed. This approach is difficult to set up in large datasets, but one must keep in mind that up to 5% of healthy elders might present extensive and confluent WMH.[25] Visual inspection of a randomly selected subsample with systematic oversampling of individuals with the largest WMH volumes may be a trade-off. Regarding focal lesions, few approaches have been developed. The simplest is to mask lesions manually, which is time consuming and may be difficult to do when they are common (Figure 2). Some authors have proposed to "hide" the lesions visible on 3DT1 scans with WMH masks obtained from FLAIR sequences before segmentation.[26] Finally, given that the identification of the border between gray and white matter depends on gray to white contrast which may be altered in SVD, the interpretation of separate measures for gray and white matter should be made with particular caution. Main recommendations of the study group are gathered by domain in Table 1.

Part II: Quantification of brain atrophy: Results

Brain atrophy in SVD patients compared to controls (Table 2)

We found only two studies in sporadic SVD[27,28] (from the same group) and two in CADASIL (based on the same small cohort) that compared brain volumes in patients with SVD to age- and sex-matched controls (Table 1).[29,30] Patients with sporadic SVD were included if they had a clinical lacunar stroke syndrome with a corresponding subcortical ischemic lesion on MRI as well as confluent WMH.[27,28] Both cross-sectional and longitudinal measures were reported in one study.[28] CADASIL patients were included if they were not cognitively impaired. High-resolution 3DT1 acquisitions were used in all studies, with normalization to intracranial cavity volume and careful visual checking of segmentations in all cases. In three out of four studies, lesion filling was used to avoid misclassification of severe WMH into CSF.[27,29,30] For instance, WMH

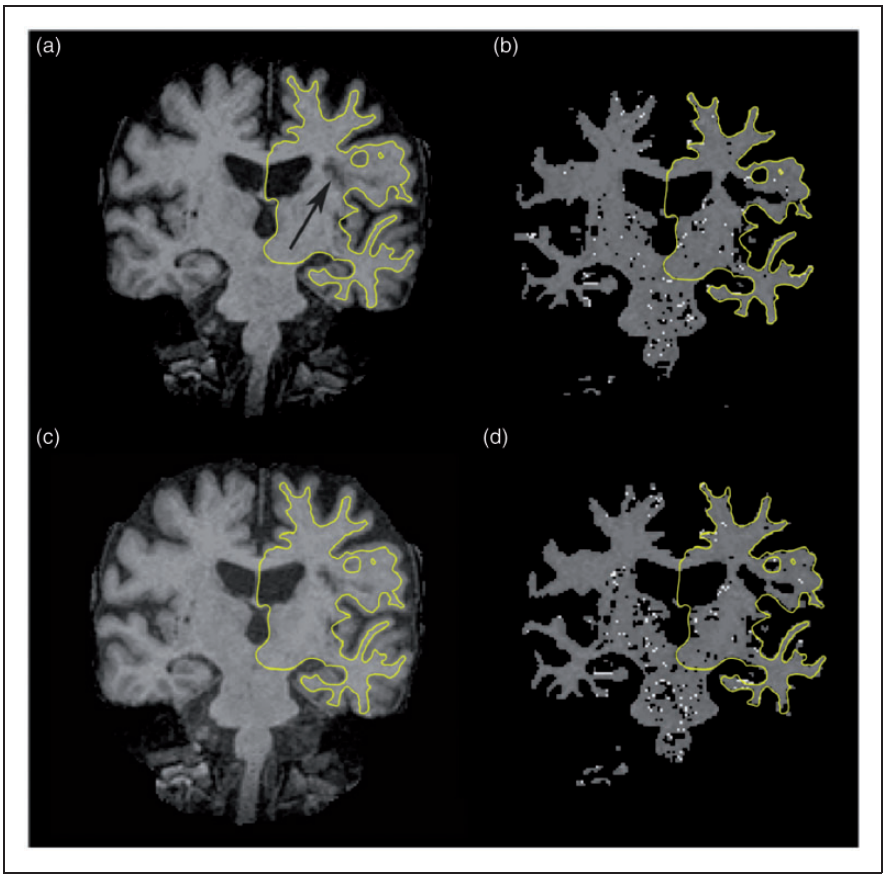

Figure 2. FreeSurfer segmentation of one-month MPRAGE post-stroke (a) with lesion arrowed. FreeSurfer handling of white-matter segmentation and volumetric results in lesion voxels being excluded from segmentation (b). Three-month MPRAGE post-stroke (c) and FreeSurfer white-matter segmentation (d). In this example, brain volumes at one and three months cannot be compared due to inconsistent brain segmentations induced by the lesion. Courtesy of Yassi et al.[21] Reprinted by permission from Springer © 2015.

masks determined on FLAIR images were pasted with the signal of normal white matter over 3DT1 images before segmentation in two studies.[29,30]

Cross-sectional studies reported lower brain volumes (of about 3%, $p < 0.005$ and $p = 0.02$) in the sporadic SVD group.[27,28] In addition, the unique longitudinal study also showed higher brain atrophy in 26 sporadic SVD patients (0.91% per year vs. 0.5%, $p = 0.02$).[28] Importantly, while the mean age of patients was 70 or above, no method was used to exclude potentially associated AD.

In contrast, the two studies in CADASIL patients did not find lower brain volumes compared to controls.[29,30] To note, in this cohort, patients were younger (mean age 53) and were free of cognitive impairment.

Links between brain atrophy and other MRI markers of SVD

WMH (Table 3). WMH is the earliest conventional MRI to appear in SVD with the largest burden. It has been long considered that they result from chronic hypoperfusion, but recently a number of alternative hypotheses arose,[31] in particular from animal models. In CADASIL, WMH have also been associated with tissue edema.[29] In addition, WMH often coexist with lacunes that may also be associated with brain volume and brain atrophy. Thus, the nature of the links between brain volume (or brain atrophy) and WMH remain uncertain.

Cross-sectional data

We found few studies evaluating the relationships between brain volume and WMH. Two were population based,[32,33] one (SMART-MR) included patients with symptomatic atherosclerotic disease affecting the heart, peripheral arteries or the brain (patients with infarcts related to large vessel disease were excluded),[34] and another subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.[35] Patients with lacunar stroke and confluent WMH were included in a previously mentioned study.[28] Four additional

Table 1. Technical recommendations for studying brain volume and brain atrophy in SVD.

MRI acquisitions	• Use volumetric sequences with T1 contrast (MPRAGE...) or multi-contrast including T1 • Rely on voxels with isotropic dimensions (similar in all three directions), close to or inferior to 1 mm
Image segmentation	• Prefer commonly used suites (FSL, FreeSurfer, SPM...) to locally developed software unless specific needs • Set up systematic procedures for checking segmentation results, particularly in patients with large loads of lesions/markers • Interpret with caution the gray-white border which can be altered in SVD
Normalization	• Normalize to intracranial cavity in cross-sectional studies (either by using normalized brain volumes or by including intracranial cavity volume as covariate in statistical analyses) • Normalization is optional in longitudinal studies (depending on the study question)
Longitudinal studies	• Prefer the use of dedicated methods with joint processing of different acquisitions rather than repeating measures
Identify brain tissue lesions and MRI markers that may interfere with measures	• Consider grading (or ideally quantifying volume) of WMH for driving segmentation and validation procedures • Consider masking WMH for improving result segmentation in subjects with large WMH burden • Search systematically for chronic (lacunes, cortical infarcts, hemorrhagic scars) and acute (positive diffusion lesions, macroscopic hemorrhages) lesions/markers given that they may interfere with the measure of brain volume and of brain atrophy • Consider excluding subjects or filling lesions/markers depending on lesion type and prevalence
Scanner and sequence upgrades	• Consider the effect of sequence and scanner upgrade for longitudinal studies and in large cross-sectional studies when acquisitions span several years
Exclusion of concomitant AD	• In exposed samples, try to exclude or minimize the role of concomitant primary neurodegeneration (particularly AD)

SVD: small vessel disease; WMH: white matter hyperintensities; MRI: magnetic resonance imaging; AD: Alzheimer's disease.

studies included CADASIL patients, among which three were based on the same CADASIL cohort at different stages of recruitment (respectively, 129, 143 and 278 patients).[36–38] Only two studies relied on low-resolution acquisitions: 4 mm thick slices were used in SMART-MR[34] and 5 mm thick slices in the German CADASIL sample.[39] Normalization to intracranial cavity volume was performed in all but the ADNI study. Segmentations were specifically checked in one study in population-based elders[33] and in three CADASIL studies.[39] Associated AD was not excluded, even in the ADNI sample where controls were defined on clinical data alone.

Lower brain volumes were associated with larger WMH in five studies. However, significant associations only appeared when patients with the upper quartile of WMH were compared to the others in SMART-MR. In the ADNI study, the association only tended towards significance in controls. The confounding effect of lacunes was not considered, but the presence of lacunar infarcts (hyperintense T2/FLAIR lesions with hypointense T1 signal) was controlled for in SMART-MR. Results were adjusted for age, sex and cardiovascular risk factors in all but one[35] studies.

By contrast, no relationship was found, either before or after adjustment for cardiovascular risk factors or other MRI markers, between brain volume and WMH in CADASIL samples.[36–39] In the study evaluating the largest number of CADASIL patients (278), those with smaller brain volumes had larger volumes of WMH in univariate analyses, but after adjustment for age and the volume of lacunes, patients with larger brain volumes actually had larger WMH.[38]

Longitudinal data

We found seven studies evaluating the links between brain atrophy and WMH,[35,39–44] three of which corresponded to the longitudinal analyses of studies presented in the preceding paragraph. Brain atrophy was measured from 4- or 5-mm slice thickness acquisitions in three studies.[39,40,42] Two studies used the same methodology to process data from ADNI and obtained identical results.[35,41] Results of the segmentations were not specifically checked.

Four studies (including both on ADNI) reported larger brain atrophy in patients with larger baseline WMH.[35,41,42,44] The confounding effect of baseline or incident lacunes was not evaluated nor was that of cardiovascular risk factors. In one study, brain atrophy was more important in patients with larger progression of WMH, but analyses were not adjusted for

Table 2. Comparisons between patients with cerebral small vessel disease and controls.

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/markers	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Nitkunan et al.[28]	SPGR T1 $1 \times 1 \times 1.5$ mm^3	SIENAX	Not detailed	SIENAX		WMH	No	No	WMH	Lower brain volumes in patients (did not persist after adjustment for WMH)
Lawrence et al.[27]	SPGR T1 $1 \times 1 \times 1.1$ mm^3	SIENAX	Manual	SIENAX		Lacunes[a], no detail about cortical lesions, WMH, MB	Yes	No	Lacunes, MB, diffusion, WMH	Lower brain volumes in patients
De Guio et al.[29]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		Lacunes, no detail about cortical lesions, WMH, MB	Yes	No	No	No group difference
Delorme et al.[30]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		Lacunes, no detail about cortical lesions, WMH, MB	Yes	No	No	No group difference
Nitkunan et al.[28]	SPGR T1 $1 \times 1 \times 1.5$ mm^3	SIENA	Not detailed		SIENA	WMH	No	No	WMH (baseline)	Larger brain atrophy in patients (did not persist after adjustment for baseline WMH)

Note: Shaded cells represent cases not following the present recommendations.
ICCV: intracranial cavity volume; SE: spin-echo; SPGR: spoiled gradient echo; MPRAGE: magnetization prepared rapid gradient echo; HASTE: half Fourier acquisition single shot turbo spin echo; GRE: gradient echo; WMH: white matter hyperintensities; MB: brain microbleeds; MRI: magnetic resonance imaging.
[a]Described in the manuscript as "lacunar infarcts" but with the definition of lacunes according to STRIVE criteria.

Table 3. Links between brain volume or brain atrophy and white matter hyperintensities.

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/ markers other than WMH	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Peters et al.[39]	SE T1 $1 \times 1 \times 5$ mm^3	SIENAX	Manual	SIENAX		None	No	No	No	NS
Jouvent et al.[36]	SPGR T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		Lacunes, no detail about cortical infarcts, MB	No	No	Lacunes, MB, diffusion metrics	NS
O'Sullivan et al.[37]	SPGR T1 $1 \times 1 \times 1$ mm^3	SIENAX, BRAINVISA, SPM	Manual	Brain volume/ ICCV		Lacunes, cortical infarcts systematically evaluated, MB	No	No	No	NS
Ikram et al.[46]	HASTE $1 \times 1 \times 1.3$ mm^3	In house	Manual	Brain volume/ ICCV		Lacunar infarcts, cortical infarcts, MB	No	Yes	No	Lower BV with larger WMH
Appelman et al.[34]	GRE T1 $1 \times 1 \times 4$ mm^3	In house	Manual	Brain volume/ ICCV		Lacunar infarcts (patients with large infarcts excluded), MB	No	No	Lacunar infarcts	Lower BV in upper quartile WMH
Nitkunan et al.[28]	SPGR T1 $1 \times 1 \times 1.5$ mm^3	SIENAX	Not detailed	SIENAX		None	No	No	No	Lower BV with larger WMH
Yao et al.[38]	SPGR T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		Lacunes, MB	No	No	Lacunes, MB	Larger BV with larger WMH
Aribisala et al.[33]	SPGR T1 $1 \times 1 \times 1.3$ mm^3	In house	Manual	Adjustment for TIV		None	No	No	No	Lower BV with larger WMH
Fiford et al.[35]	MPRAGE T1 $1 \times 1 \times 1.5$ mm^3	In house	Not detailed	Adjustment for TIV		None	No	No	No	Lower BV with larger WMH in AD and MCI
Schmidt et al.[42]	SE T1, T2, PD $1 \times 2 \times 5$ mm^3	SIENA	Not detailed		SIENA	None	No	No	No	Larger brain atrophy with larger baseline WMH
Peters et al.[39]	SE T1 $1 \times 1 \times 5$ mm^3	SIENA	Manual		SIENA	None	No	No	No	NS
Firbank et al.[43]	SPGR T1 $1 \times 1 \times 1.7$ mm^3	In house	Manual		BSI	None	No	No	No	NS
Kloppenborg et al.[40]	GRE T1 $1 \times 1.4 \times 4$ mm^3	In house	Manual		Individual processing	Lacunar infarcts, MB	No	No	Lacunar infarcts	NS
Barnes et al.[41]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	SPM	Not detailed		BSI	None	No	No	No	Larger brain atrophy with larger baseline WMH in the control group

(continued)

Table 3. Continued.

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/ markers other than WMH	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Fifford et al.[35]	MPRAGE T1 $1 \times 1 \times 1.5$ mm^3	SPM	Not detailed	Adjustment for TIV	BSI	None	No	No	No	Larger brain atrophy with larger baseline WMH in the control group
Van Leijsen et al.[44]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	SPM	Manual		Individual processing	Lacunes, MB	Yes	No	No	Larger brain atrophy with larger baseline WMH and more incident WMH

Note: Shaded cells represent cases not following the present recommendations.
ICCV: intracranial cavity volume; SE: spin-echo; SPGR: spoiled gradient echo; MPRAGE: magnetization prepared rapid gradient echo; HASTE: half Fourier acquisition single shot turbo spin echo; GRE: gradient echo; MRI: magnetic resonance imaging; BV: brain volume; AD: Alzheimer's disease; WMH: white matter hyperintensities.

cardiovascular risk factors nor for other MRI markers of SVD.[44]

By contrast, three studies did not find a significant association between brain atrophy and baseline volume of WMH. Baseline or incident lacunes were not considered in one study,[43] and adjustment for baseline or incident lacunar infarcts (not lacunes) did not alter the results in another.[40] In the study on German CADASIL patients, brain atrophy was not associated with baseline or progression of WMH, and lacunes were not taken into account.[39] The confounding effect of AD was not considered in any of these studies.

Lacunes (Table 4). Since the STRIVE criteria in 2013, the term lacune is reserved for cavitated lesions appearing with the signal of the CSF on all MRI sequences.[3] They must be distinguished from lacunar lesions which were often defined as focal hyperintense lesions on T2 together with hypointense aspect on T1. Given the very low burden of lacunes compared to that of WMH and often close to the reliability of brain volume and atrophy measures, whether links between the two parameters can be identified is uncertain.[45]

Cross-sectional data

We found only two studies by the same group on the same CADASIL cohort in which were evaluated the links between brain volume and lacunes[36,37] and two studies in other settings in which were evaluated the links between brain volume and lacunar infarcts.[34,46] One was population based (Rotterdam scan study), the other was SMART-MR. Only SMART-MR relied on low resolution acquisition. Studies in CADASIL included a careful checking of segmentations but not the two others. Lacunes were evaluated by their volume, while lacunar infarcts were evaluated by their presence,[46] or their grade.[34]

Lower brain volumes were observed in patients with larger volumes of lacunes in the two CADASIL studies. In one, the association was not adjusted for WMH nor for cardiovascular risk factors,[37] while in the other, the association persisted after adjustment for both.[36] In line, lower brain volumes were associated with the presence and larger grades of lacunar infarcts, even after adjustment for cardiovascular risk factors.[34,46] The association also persisted after adjustment for the presence of WMH in one.[34] The effect of AD was not controlled in these studies.

Longitudinal data

We found only one study in which the longitudinal links between brain atrophy and lacunar infarcts were tested.[40] In SMART-MR, patients with lacunar

Table 4. Links between brain volume or brain atrophy and lacunes or lacunar infarcts.

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/markers other than lacunes	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Jouvent et al.[36]	SPGR T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ICCV		WMH, no detail about cortical infarcts	No	No	WMH, MB, diffusion metrics	Lower BV with larger lacunes
O'Sullivan et al.[37]	SPGR T1 $1 \times 1 \times 1$ mm^3	SIENAX, BRAINVISA SPM	Manual	Brain volume/ICCV		WMH, cortical infarcts systematically evaluated	No	No	No	Lower BV with larger lacunes
Ikram et al.[46]	HASTE $1 \times 1 \times 1.3$ mm^3	In house	Manual	Brain volume/ICCV		WMH, no detail about cortical infarcts	No	Yes	No	Lower BV with more lacunar infarcts
Appelman et al.[34]	GRE T1 $1 \times 1 \times 4$ mm^3	In house	Manual	Brain volume/ICCV		WMH (patients with cortical infarcts excluded)	No	No	No	Lower BV with more lacunar infarcts
Kloppenborg et al.[40]	GRE T1 $1 \times 1.4 \times 4$ mm^3	In house	Manual		Individual processing	WMH, no detail about cortical infarcts	No	No	WMH	Larger brain atrophy with more lacunar infarcts

Note: Shaded cells represent cases not following the present recommendations.
ICCV: intracranial cavity volume; SE: spin-echo; SPGR: spoiled gradient echo; MPRAGE: magnetization prepared rapid gradient echo; HASTE: half Fourier acquisition single shot turbo spin echo; GRE: gradient echo; MRI: magnetic resonance imaging; WMH: white matter hyperintensities; BV: brain volume.

infarcts at baseline showed higher brain atrophy rates during a mean follow-up of 3.9 years, and patients with incident lacunar infarcts showed higher atrophy rates than patients without. The results persisted after adjustment for WMH and progression of WMH and cardiovascular risk factors. The effect of AD was not controlled for in this study.

Other MRI markers (supplementary Table 5). We found six studies in which links between brain volume or atrophy and various MRI markers were tested.[36,47–51] These markers comprise MB in two studies, diffusion tensor imaging metrics in one, perivascular spaces in one and cortical microinfarcts in two.

Cognitive correlates of brain volume or brain atrophy in patients with SVD (Table 5)

Cross-sectional data. We found 10 studies in patients with SVD in which the links between brain volume and cognitive performances were tested.[27,28,36,37,39,50,52–55] Two included patients with lacunar strokes, two were based on the same sample of individuals with radiological SVD independently of associated symptoms, one included non-demented patients with CAA, one included patients with a high burden of WMH, one was based on older community-dwelling individuals with hypertension and five included patients with CADASIL. One study compared four different groups, one of which consisted in relatively young subjects from the general population, and as such, was not considered in the present review.[55] Results from the previously mentioned SMART-MR were not considered given that links between brain volume, and cognitive performances were reported while not excluding patients with large vessel stroke lesions.

Among 10 studies, nine relied on 3DT1 high-resolution acquisitions. Normalization to intracranial cavity volume was performed in all cases. Lacunes or lacunar infarcts were measured in all but four studies. Only one of these studies used a specific protocol to overcome SVD-related issues for segmentation, while visual inspection and manual corrections were performed in three of five CADASIL studies. In four of 10 studies, the relationships between brain volume and cognitive performances were tested without considering the effect of other MRI markers. In one study, there was no adjustment for age and sex, while in four, the level of education was not considered as a confounder.

In all studies, whatever the underlying diagnosis, consistent relationships were reported between brain atrophy and global cognitive performances. The effect of concomitant AD was not considered in any of these studies.

Table 5. Links between brain volume (or brain atrophy) and cognitive outcomes (or cognitive worsening).

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/markers	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Peters et al.[39]	SE T1 $1 \times 1 \times 5$ mm^3	SIENAX	Manual	SIENAX		WMH	No	No	No	Lower global cognitive scores with lower BV
Jouvent et al.[36]	SPGR T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		WMH, lacunes (no detail about cortical infarcts), MB	No	No	Lacunes, MB, diffusion metrics	Lower global cognitive scores with lower BV
O'Sullivan et al.[37]	SPGR T1 $1 \times 1 \times 1$ mm^3	SIENAX, BRAINVISA SPM	Manual	Brain volume/ ICCV		WMH, lacunes, cortical infarcts systematically evaluated, MB	No	No	No	Lower global cognitive scores with lower BV
Viswanathan et al.[52]	SPGR T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual	Brain volume/ ICCV		WMH, lacunes (no detail about cortical infarcts), MB	No	No	Lacune, WMH, MB, diffusion metrics	Lower global cognitive scores with lower BV
Nitkunan et al.[28]	SPGR T1 $1 \times 1 \times 1.5$ mm^3	SIENAX	Not detailed	SIENAX		WMH	No	No	WMH	Lower global cognitive scores with lower BV
Lawrence et al.[27]	SPGR T1 $1 \times 1.1 \times 1$ mm^3	SIENAX	Manual	SIENAX		WMH, lacunes (no detail about cortical infarcts), MB	Yes	No	Lacunes, WMH, MB	Lower executive function and processing speed associated with lower BV
Xiong et al.[53]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	FreeSurfer	Not detailed	Brain volume/ ICCV		WMH, MB	No	No	No	Slower processing speed and worse performance on executive function with lower BV
Tuladhar et al.[54]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	SPM	Manual	Brain volume/ ICCV		WMH	No	No	No	Lower cognitive index and psychomotor speed with lower BV
Baykara et al.[55]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	SPM	Not detailed	Brain volume/ ICCV		WMH, lacunes, MB, diffusion metrics	Yes	No	Lacunes, WMH, MB, diffusion metrics	Lower cognitive scores with lower BV
Moonen et al.[50]	MPRAGE T1 $1.1 \times 1.2 \times 2$ mm^3	FSL	Manual	SIENAX		WMH, lacunes[a], MB	Yes	No	Lacunes, MB	Lower global cognitive scores with lower BV
Peters et al.[39]	SE T1 $1 \times 1 \times 5$ mm^3	SIENA	Manual		SIENA	WMH	No	No	No	Global cognitive worsening associated with larger brain atrophy
Liem et al.[56]	SE Details not provided	In house	Manual		Individual processing	WMH, lacunar infarcts, MB	No	No	No	NS
Jouvent et al.[58]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	In house	Manual		Joint processing (in house)	WMH, lacunes, MB	Yes	No	No	Global cognitive worsening associated with larger brain atrophy
Ling et al.[57]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	BRAINVISA	Manual		SIENA	WMH, lacunes, MB	Yes	No	No	Global cognitive worsening associated with larger brain atrophy

(continued)

Table 5. Continued.

Study	MRI acquisitions	Image segmentation	Systematic checking of segmentation	Normalization	Longitudinal studies	Identification of brain lesions/markers	Lesion masking	Use of gray/white contrast	Adjustment for other MRI markers	Results
Xiong et al.[51]	MPRAGE T1 $1 \times 1 \times 1$ mm^3	FSL	Manual		NA	WMH, cortical siderosis, cortical microinfarcts, MB (not details about lacune and cortical infarcts)	Yes	No	WMH, cortical siderosis, MB	More conversion to dementia with lower baseline brain volumes

Note: Shaded cells represent cases not following the present recommendations.
ICCV: intracranial cavity volume, SE: spin-echo, SPGR: spoiled gradient echo; MPRAGE: magnetization prepared rapid gradient echo; HASTE: half Fourier acquisition single shot turbo spin echo; GRE: gradient echo; MB: microbleeds; MRI: magnetic resonance imaging; BV: brain volume; WMH: white matter hyperintensities.
[a]Lacunar infarct in the manuscript, but definition in agreement with STRIVE criteria.

Longitudinal data. We found five studies that evaluated the relationships between brain atrophy and variations of cognitive performance with prospective longitudinal designs.[36,39,51,56,57] Among them, four evaluated the links between brain atrophy and cognitive worsening, while one evaluated the links between brain volume at baseline and subsequent conversion to dementia during follow-up. Four of the five studies included patients with CADASIL, two being based on the same cohort at different periods and one included non-demented CAA patients. The study on non-demented CAA patients and the two studies from the Paris group used 3DT1 high-resolution acquisitions. Masking of WMH on 3DT1 scans was used in two studies.[57,58] In the study in CAA, the brain volume was calculated by multiplying by 2 that of the non-hemorrhagic hemisphere.[51]

Three of the four studies in CADASIL reported significant associations between brain atrophy and cognitive worsening during follow-up. Surprisingly however, the fourth study reported a significant association between ventricular enlargement and cognitive worsening, which strongly questions the method to measure brain atrophy. In the study in non-demented CAA patients, brain volume at baseline predicted conversion to dementia during follow-up. Only two studies reported results corrected for the baseline volume of WMH, while in the others, no adjustment for other MRI marker was performed. Adjustment for cardiovascular risk factors was performed in two studies, while only one considered the level of education. Finally, none of these studies evaluated the possible confounding effect of concurrent AD.

Discussion

The results of the present systematic review strongly support that brain atrophy is a key MRI marker in SVD. Both brain volume and brain atrophy can be measured with high precision with automated methods and were repeatedly shown to be associated with cognitive performances (or their variation with time) in SVD patients. In statistical models, brain volume and brain atrophy regularly outperform other lesion-based MRI markers of SVD for predicting cognitive outcomes.

While this systematic review only considered automated measures and found no study before 2003, several methodological improvements can already be noted between the older and more recent studies. Imaging protocols are now getting harmonized. Thick slice acquisitions, particularly sensitive to partial volume effects, are less often used and have been abandoned for longitudinal studies, for which most protocols now rely on 3D high resolution T1 contrast

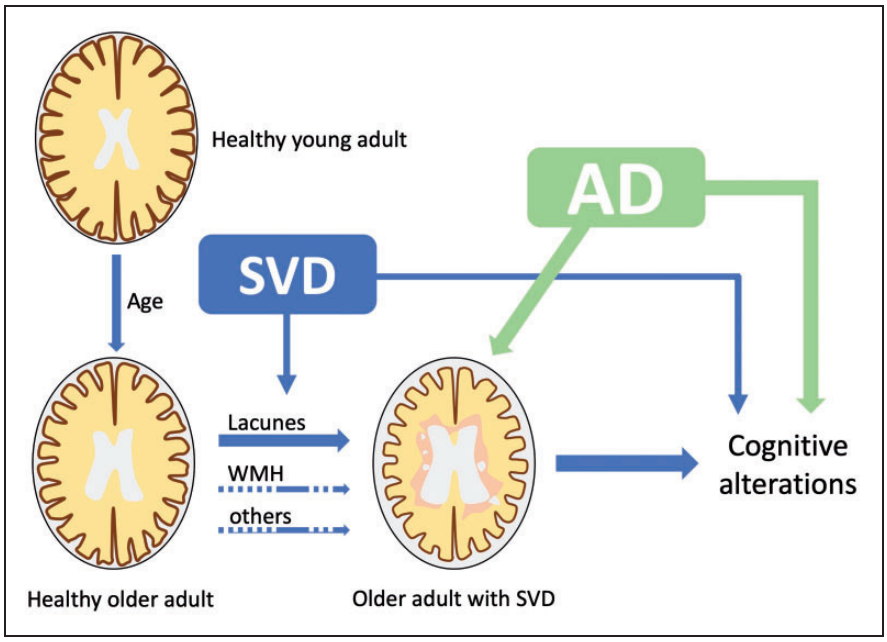

Figure 3. Brain volume is a key imaging marker of cognitive alterations, both in cerebral small vessel disease (SVD) and in Alzheimer's disease (AD). In SVD, lacunes are the MRI marker whose links with brain volume appear the most consistent. While AD is known to promote both cognitive impairment and brain atrophy, studies in sporadic SVD after exclusion of concomitant AD are lacking. WMH: white matter hyperintensities.

acquisitions. With time, the algorithms used to segment the brain tissue also tended to harmonize, and mostly rely nowadays on major suites such as FSL or FreeSurfer. Normalization to intracranial cavity volume is in general correctly performed. To note, even studies including hundreds of patients over periods of several years in general do not provide details regarding possible software or hardware updates, even though this might clearly impact the measures.[8] This potential issue is even stronger in longitudinal designs.

In addition, the behavior of the different algorithms can be erratic in the context of extensive WMH. While this might not have any major influence on volumetric measures in population-based studies where lesion loads are low, the consequences might be huge in patients with severe SVD. Unsurprisingly, the most elaborate procedures developed to deal with severe WMH or multiple lacunes were used in studies including patients with severe forms.[27] A simple approach may be to paste the registered binary mask of WMH on 3DT1 images with the expected intensity of the normal appearing white matter, which often improves the behavior of many algorithms.[26] Whether such approaches are of any interest in larger samples including subjects with mostly low lesion loads has to be determined.

Moreover, very few study protocols deal with acute lesions that may appear on systematic MRI scans such as recent small subcortical infarcts on diffusion-weighted imaging. While this might seem anecdotic, a simple calculus shows that such a lesion becoming a spherical lacune of 10 mm diameter without any other change occurring in the brain over a few months could lead to about 0.1% difference in brain volume which might not be negligible considering the typical observed rates of atrophy in healthy elders (1.0% or less). The effect of such misclassifications has been previously highlighted in a small population of patients with acute lacunar or small cortical strokes.[24]

Beyond methodological matters, numerous questions remain unanswered. We were surprised to find very few studies comparing SVD patients to age- and sex-matched controls, precluding a reliable estimation of the actual role of SVD in promoting brain atrophy. Not only the results of this limited number of studies showed some discrepancies, but the potential confounding effect of AD pathology has quite never been evaluated. Additional data are needed to disentangle the role of SVD from that of primary neurodegeneration, AD in particular, in promoting brain tissue loss.

Regarding the links between brain volume or brain atrophy and WMH, the results are intriguing. In cross-sectional analyses of the links between brain volume of WMH, there is a clear-cut discrepancy between the results in CADASIL, which were all negative, and that of all other samples, which all found significantly lower brain volumes in patients with the largest loads of WMH. By contrast, in longitudinal analyses, there

were a similar number of positive and negative studies, irrespective of the underlying SVD subtype. Variable adjustment for other MRI markers may be one reason for the different results. Some authors have shown that WMH may vanish in certain circumstances.[59] While this phenomenon has also been described for lacunes, it may be much less frequent.[44] By contrast, while the total number of studies was lower for the study of lacunes or lacunar infarcts, their impact on brain atrophy seems clear, whatever the sample and the study design.[60] Given the low burden of lacunes, often close to the reliability of brain tissue measures, this suggests that they promote more diffuse brain tissue loss through secondary degeneration,[45] or that they are associated with more diffuse destructive lesion such as microinfarcts.[61]

The results of the present review also show that brain volume and brain atrophy are strongly linked with cognitive alterations and cognitive worsening, respectively. However, despite the consistent results obtained in different settings with different approaches, various questions also remain. The number of SVD cohorts in which these associations were tested remains relatively low. The confounding effect of other MRI markers, particularly of lacunes that are also strongly associated with cognitive outcomes, has been assessed very rarely. Brain atrophy is likely the cumulative consequence of the effect of both SVD burden and other neurodegenerative processes and as such will likely show the closest relationships with cognitive alterations. Further studies will help determine whether the type, extent and/or location of MRI markers may improve the prediction of cognitive alterations based on brain quantitative metrics alone. Finally, we found no study that evaluated the links between brain atrophy and cognitive alterations in SVD while systematically controlling for AD, either with amyloid-PET or CSF biomarkers (Figure 3). While beyond the scope of this study, measures of regional brain volume or atrophy or intermediate metrics such as ventricle size and cortical sulci span may be of interest, particularly for disentangling the effect of primary neurodegeneration from that of SVD.

In summary, despite the number of unsolved questions regarding their exact extent, correlates and consequences, brain volume and brain atrophy already appear as valuable MRI markers in SVD. Whether their role will be limited to the late stages of SVD or can be extended as soon as the early stages are currently undetermined and will require further studies.

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Supplemental material

Supplemental material for this article is available online.

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