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Development and initial evaluation of a semi-automatic approach to assess perivascular spaces on conventional magnetic resonance images

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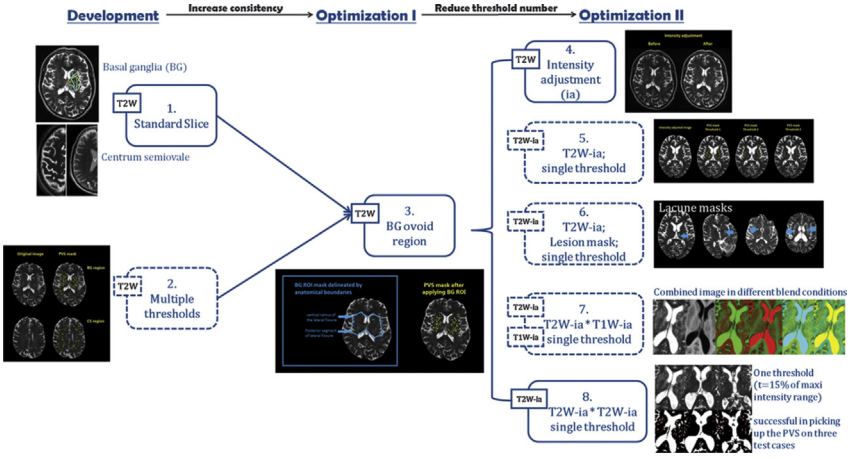
HIGHLIGHTS

- User-friendly semi-automatic perivascular spaces segmentation method is efficient in quantifying PVS from conventional T2-weighted MRI.
- Semi-automatically determined perivascular spaces count and volume agree with visual ratings.
- Semi-automatic perivascular spaces assessment proves useful for clinical studies and MRI protocols.
- Rigorous statistical analysis evaluating the new method on a longitudinal stroke sample.
- Potential for use in studies of cerebral small vessel disease and in a range of other neurological diseases.

GRAPHICAL ABSTRACT



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ABSTRACT

Purpose: Perivascular spaces (PVS) are associated with ageing, cerebral small vessel disease, inflammation and increased blood brain barrier permeability. Most studies to date use visual rating scales to assess PVS, but these are prone to observer variation.
Methods: We developed a semi-automatic computational method that extracts PVS on bilateral ovoid basal ganglia (BG) regions on intensity-normalised T2-weighted magnetic resonance images. It uses Analyze™10.0 and was applied to 100 mild stroke patients' datasets. We used linear regression to test association between BGPVS count, volume and visual rating scores; and between BGPVS count & volume, white matter hyperintensity (WMH) rating scores (periventricular: PVH; deep: DWMH) & volume, atrophy rating scores and brain volume.

Abbreviations: WMH, white matter hyperintensities; PVS, perivascular spaces; BG, basal ganglia; CS, centrum semiovale; T1W, T1-weighted MRI sequence; T2W, T2-weighted MRI sequence; PVH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; SVD, small vessel disease.

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Results: In the 100 patients WMH ranged from 0.4 to 119 ml, and total brain tissue volume from 0.65 to 1.45 l. BGPVS volume increased with BGPVS count (67.27, 95%CI [57.93 to 76.60], $p < 0.001$). BGPVS count was positively associated with WMH visual rating (PVH: 2.20, 95%CI [1.22 to 3.18], $p < 0.001$; DWMH: 1.92, 95%CI [0.99 to 2.85], $p < 0.001$), WMH volume (0.065, 95%CI [0.034 to 0.096], $p < 0.001$), and whole brain atrophy visual rating (1.01, 95%CI [0.49 to 1.53], $p < 0.001$). BGPVS count increased as brain volume (as % of ICV) decreased (−0.33, 95%CI [−0.53 to −0.13], $p = 0.002$).
Comparison with existing method: BGPVS count and volume increased with the overall increase of BGPVS visual scores (2.11, 95%CI [1.36 to 2.86] for count and 0.022, 95%CI [0.012 to 0.031] for volume, $p < 0.001$). Distributions for PVS count and visual scores were also similar.
Conclusions: This semi-automatic method is applicable to clinical protocols and offers quantitative surrogates for PVS load. It shows good agreement with a visual rating scale and confirmed that BGPVS are associated with WMH and atrophy measurements.

1. Introduction

Perivascular spaces (PVS), or Virchow–Robin spaces, have been defined as fluid-containing spaces that surround the walls of arteries, arterioles, veins and venules as they course from the subarachnoid space into the brain parenchyma (Etemadifar et al., 2011; Kwee and Kwee, 2007). PVS are round or linear delineated structures seen on MRI with intensities close to cerebrospinal fluid (CSF) and less than 3 mm (Kwee and Kwee, 2007) diameter in cross section (Wardlaw et al., 2013). PVS may function as drainage and fluid circulation pathways for soluble and insoluble material through the central nervous system (Rennels et al., 1985). They may provide imaging evidence of vascular and inflammatory changes in the brain. PVS are specific sites for immune cell accumulation, reaction and transmigration into the brain parenchyma (e.g., leukocytes, dendritic cells, T-cells, B-cells and macrophages (Polledo et al., 2012; Sagar et al., 2012; Wuerfel et al., 2008)). More PVS visible on MRI are associated with increasing age, cognitive impairment, cerebral small vessel disease (SVD) lacunar stroke and white matter hyperintensities, (WMH), multiple sclerosis, and may be related to altered blood brain barrier permeability (Doubal et al., 2010; MacLullich et al., 2004; Potter, 2011; Potter et al., 2013; Wardlaw, 2010; Zhu et al., 2010).

PVS on MRI are commonly assessed using visual rating scales, several of which have been proposed (MacLullich et al., 2004; Potter, 2011; Potter et al., 2013; Zhu et al., 2010; Chen et al., 2011; Patankar et al., 2005; Rouhl et al., 2008). These differ in how they score the anatomical location or range of PVS, as summarised in (Potter, 2011). Potter and colleagues (Potter, 2011) reviewed and evaluated the ambiguities and advantages in the existing PVS visual rating scales and combined their strengths to develop a more comprehensive visual rating scale (available at http://www.sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf). This new scale used standard T2-weighted (T2W) structural brain MRI to assess the severity of the PVS located in three major anatomical regions (midbrain, basal ganglia (BG) and centrum semiovale (CS)).

Potential confounds in PVS visual ratings have been previously discussed (Potter, 2011): differences in PVS visibility, presence of WMH, varying number of PVS on different slices, 'double counting' of linear PVS, poor scan quality including movement, asymmetry in background brain appearances, asymmetry in PVS, presence of focally dilated PVS that could be mistaken for lacunes, and differences between most severe categories and variations in lesion load between cohorts. Therefore, all existing rating scales share similar limitations: intra- and inter-observer differences and ceiling and floor effects caused by the few categories into which PVS are condensed. These limitations could be overcome by the use of computational methods, which, if they can avoid observer bias and provide a quantitative rather than qualitative PVS measure, may provide more precise estimates of PVS severity and also allow their size & volume to be measured. Such methods could be useful to detect more subtle differences in PVS between subjects, for example calculating the percentage of PVS volume in the total brain volume and investigating an association between PVS volume and WMH volume.

To our knowledge, few studies have described any computational methods suitable for PVS quantification (Wuerfel et al., 2008; Descombes et al., 2004; Uchiyama et al., 2008). A systematic review found 6 studies that used computational methods to assess PVS and 4 studies that presented approaches with potential for quantifying PVS (Valdes Hernandez et al., 2013). Though these computational methods were promising, they have not been widely used in the target population of patients with small vessel disease, and required to be validated on scans acquired with different protocols.

In this paper, we present a user-friendly computational method for counting the number and measuring the volume of PVS in relevant regions-of-interest (ROI) as a surrogate for PVS load to be used in large clinical research studies. We present the development of the method, results from calculating the intra- and inter-observer agreement in a small number of representative test cases, describe thresholds that work in most cases, and describe the methods for assessing difficult cases. Then we evaluate the method's performance in 100 patients by comparing the PVS computational counts and volumes with the validated visual rating scale scores. Finally, we investigated the associations between BG PVS count & volume, and WMH rating scores (periventricular hyperintensities: PVH; deep white matter hyperintensities: DWMH) and volume, atrophy rating scores and brain volume.

2. Materials and methods

2.1. Sample selection

For developing and testing the computational approach, the imaging datasets for 16 subjects were chosen from a sample of older subjects: The Lothian Birth Cohort 1936 Study (http://www.lothianbirthcohort.ed.ac.uk/) (LBC1936) to represent a full range of PVS, WMH, lacunes, and brain atrophy based on previous analyses (Potter, 2011; Deary et al., 2007, 2012). The MRI protocol has been previously published (Wardlaw et al., 2011).

For evaluation, we applied the method to 100 patients with clinical features of a lacunar or mild cortical stroke recruited in a study of stroke mechanisms: 100 had full baseline imaging assessments and 46 returned for follow-up imaging after a median of 39 months (IQR 30–45 months). Full study details have been published previously (Wardlaw et al., 2009).

2.2. Brain MRI acquisition

All MRI acquisition was conducted in the Brain Research Imaging Centre, University of Edinburgh (http://www.bric.ed.ac.uk). A GE Signa Horizon HDx 1.5T clinical scanner (General Electric,