SEMI-AUTOMATIC SEGMENTATION FOR OBTAINING REGIONAL VOLUMETRICS OF VIRCHOW-ROBIN SPACES IN ALZHEIMER'S AND ELDERLY POPULATIONS

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BACKGROUND

- Virchow-Robin spaces (VRS) are fluid-filled spaces surrounding the brain's vasculature and play an important role in clearance of interstitial fluid [1].
- Although their clinical significance is not well understood, MRI-based studies on ageing and dementia suggest that VRS in the basal ganglia (BG) and white matter (WM) are more common in ageing and males [2].
- VRS are believed to reflect some form of small vessel disease and are possibly associated with decreased cognitive functioning [3, 4].

PURPOSE & HYPOTHESIS

Purpose: To develop a semi-automated VRS segmentation and examine the differential relationships between regional VRS volumes (BG and WM), sex, age, and years of education in Alzheimer's disease (AD) and normal elderly control (NC) populations.

Hypothesis: Regional VRS volumes will moderate the relationship between males and females and AD patients and NCs. Based on existing research, we predict that males and AD patients will have higher VRS volumes than females and NCs, respectively.

METHODS

A modified version of Lesion Explorer (LE) [5] was used to automatically segment cerebrospinal fluid (CSF) intensity regions within the WM and subcortical grey matter (GM) using T2-weighted MRI. A trained user then removed false positive non-VRS voxels (e.g. lacunes, subcortical hyperintensity (SH), and ventricular/sulcal CSF) from the mask.

VRS were differentiated from lacunar infarcts based on the following criteria (in order of priority):

1. **Location**: Black holes on T1 (CSF intensity) located in the BG are probable VRS.
2. **Shape**: Lacunes tend to be spherical and have stationary cores on multiple slices. VRS are typically linear and follow parallel to the vasculature.
3. **Relative intensity**: Both lacunes and VRS are CSF intensity on T1 and T2, however, they are differentiated using the PD where lacunes tend to be hyperintense and VRS are isointense to CSF.
4. **Size**: Lacunes tend to be larger than 5 mm in diameter where VRS are usually less than 5 mm.

The VRS segmentation was parcellated into BG and WM regions using the SABRE pipeline [6].

An inter-rater reliability test was performed between two experts (ICC=0.99, SI=0.96).

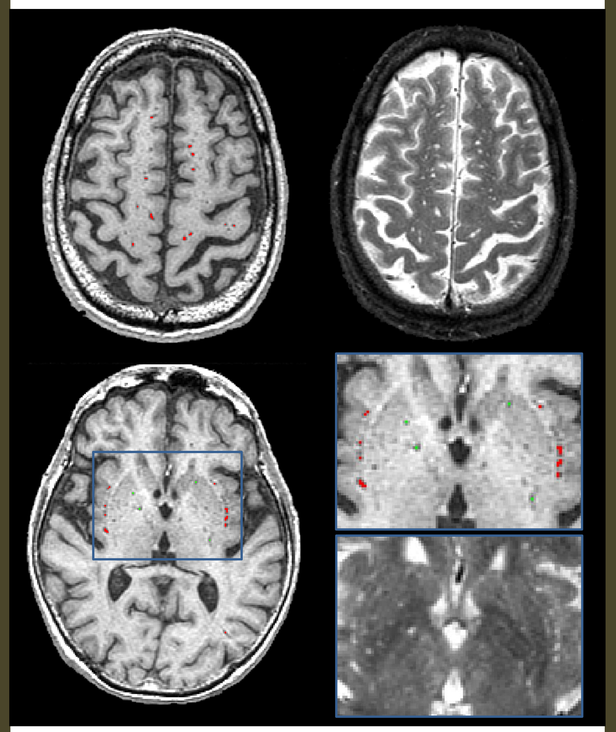

Figure 1: Virchow-Robin space segmentation (white matter VRS=red, basal ganglia VRS=green) overlaid on an axial T1 weighted MRI

SUBJECTS

All subjects were taken from the Sunnybrook Dementia Study and provided informed consent to participate. See Table 1 for demographic information.

ANALYSIS

- Non-parametric data were log-transformed (base 2) and then converted into z-scores to account for skewness.
- MANCOVAs were performed to analyze the effects of sex and disease state on head size corrected VRS volumes.
- VRS volumes were converted into equal tertiles and further analyses were conducted on subjects with moderate to severe VRS volumes to account for a floor effect.

RESULTS

Table 1. Demographic and raw volume data for AD and NC

	AD	NC	p value	Cohen's d
Demographics				
N	207	95		
Age, y	72.2 (9.6)	69.2 (8.3)	*	0.34
Sex, n (%) female	110 (53)	53 (56)	n.s.	
Education, y	13.7 (3.9)	15.6 (3.0)	***	0.55
MMSE/30 [a]	23.7 (3.8)	28.9 (1.2)	***	2.08
Volumetrics (cc)				
ST-TIV	1215.9 (135.7)	1226.0 (113.8)	n.s.	
GM	516.7 (53.0)	560.9 (46.0)	***	0.89
WM	368.5 (54.3)	404.2 (57.2)	***	0.64
sCSF	270.6 (62.4)	221.8 (46.3)	***	0.90
vCSF	51.9 (26.9)	34.1 (16.0)	***	0.83
SH, Median (IQR)	4.4 (9.2)	2.3 (3.2)	**	0.34

[a] Available in 93 NC and 204 AD subjects

[b] Avaliable in 172 AD subjects

*p<0.05, **p<0.01, ***p<0.001

Table 2. MANCOVA comparing male and female regional VRS volumes for AD and NC

	AD			
	Males	Females	p-value	Cohen's d
n	97	110		
Total VRS (mm^3)	44.1 (69.5)	40.6 (65.0)	**	0.05
BG-VRS (mm^3)	10.3 (19.6)	11.5 (17.3)	n.s.	
WM-VRS (mm^3)	35.1 (50.6)	27.1 (41.9)	**	0.17
	NC			
n	42	53		
Total VRS (mm^3)	63.2 (83.9)	32.0 (31.8)	***	0.54
BG-VRS (mm^3)	17.9 (28.3)	12.4 (16.0)	n.s.	
WM-VRS (mm^3)	39.9 (60.2)	14.5 (23.8)	***	0.60

Data are presented as raw volumes and as median (IQR)
Age at scan, years of education and disease state were entered as covariates
*p<0.05, **p<0.01, ***p<0.001

Table 3. MANCOVA comparing total and regional VRS volumes between AD and NC

	AD	NC	p-value	Cohen's d
Total, n	207	95		
Total VRS (mm^3)	41.6 (68.7)	39.3 (54.4)	n.s.	
BG-VRS (mm^3)	10.6 (17.7)	16.0 (20.7)	n.s.	
WM-VRS (mm^3)	31.7 (48.4)	21.7 (31.7)	n.s.	
Moderate + Severe, n [a]	143	64		
Total VRS (mm^3)	66.5 (70.9)	56.6 (56.0)	n.s.	
BG-VRS (mm^3)	16.0 (29.5)	20.4 (24.4)	n.s.	
WM-VRS (mm^3)	44.3 (53.2)	36.2 (47.6)	**	0.16

All date are raw and represented in Median (IQR)
Age at scan, years of education and disease state were entered as covariates
[a] Excluding mild tertile

DISCUSSION

This study suggests that there is a significant difference in prevalence of WM VRS and BG VRS, both in terms of sex and disease state.

Firstly, males have significantly higher total and WM VRS volumes than females, irrespective of disease group. This finding was not shown with BG VRS volumes suggesting that the relationship between sex and VRS is driven primarily by VRS in the WM.

When further comparing VRS between AD and NC, there does not appear to be a significant difference, possibly due to a floor effect. Furthermore, when mild cases are excluded, the AD group shows significantly more WM VRS than NC. This may reflect a threshold effect where the relationship with disease state may only be significant when VRS are stratified.

VRS in the WM may reflect different pathological processes compared to those in the BG, a relationship which may be influenced by disease state. The etiology of VRS is debateable with some suggesting that WM VRS are related to cerebral amyloid angiopathy and BG VRS are more closely related to hypertensive arteriopathy [7]. Future VRS analyses looking at vascular risk factors and ApoE genotyping may shed light on these questions.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Canadian Institute of Health Research (MT#13129), Alzheimer Society of Canada, Alzheimer's Association (USA), The L. C. Campbell Foundation and The Heart and Stroke Foundation Centre for Stroke Recovery.

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