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

Courtney Berezuk[a-c], Joel Ramirez[a-c], Alicia A. McNeely[a-c], Fuqiang Gao[a-c], Christopher J.M. Scott[a-c], Sandra E. Black[a-d]

[a] LC Campbell Cognitive Neurology Research Unit, Sunnybrook Heath Sciences Centre, Toronto, Canada, [b] Heart & Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, Canada, [c] Brain Sciences Research Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada, [d] Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Canada

BACKGROUND

- Virchow-Robin spaces (VRS) are fluid-filled spaces surrounding the brain's vasculature and play an important role in the clearance of interstitial fluids.[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 with ageing and in 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 to examine the differential relationships between regional VRS volumes (BG and WM) in males and females and in Alzheimer's disease (AD) and normal elderly controls (NC).

Hypothesis: Regional VRS volumes will moderate the relationship between males and females and AD and NC. We predict that males and AD patients will have higher VRS volumes than females and NCs.

SUBJECTS

All subjects were taken from the Sunnybrook Dementia Study:
- 203 AD patients (72.7 years ± 8.8)
- 94 NC (69.5 years ± 7.8)

METHODS

A modified version of Lesion Explorer (LE) was used to automatically segment cerebrospinal fluid (CSF) intense regions within the WM and subcortical grey matter using T2 and T1-weighted 1.5T MRI.[5] An expert then removed false positives from the mask.

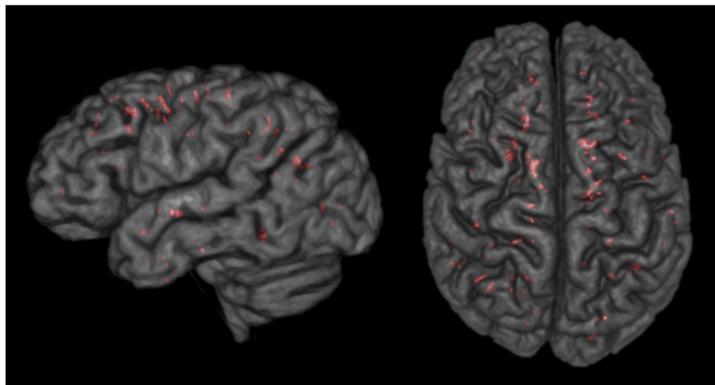The VRS segmentation was parcellated into BG and WM regions using the SABRE pipeline.[6]

Figure 1: Virchow-Robin space segmentation (red) within a 3D eroded brain of an AD patient

ANALYSIS

Non-parametric data were log-transformed (base 2). MANCOVAs were performed to analyse the effects of sex and disease state on VRS volumes. VRS volumes were converted into equal quartiles and further analyses were conducted on subjects with moderate to severe VRS volumes to account for a floor effect. A paired samples t-test was used to compare regionalized VRS volumes.

RESULTS

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

Demographics [a]	AD	NC	p	Cohen's d
n	203	94		
Age, y	72.7 (8.8)	69.5 (7.8)	**	0.4
Sex, n (%) female	108 (53.2)	53 (56.4)	-	-
Education, y	13.8 (3.9)	15.6 (3.0)	***	0.5
MMSE/30[a]	23.6 (3.8)	29.0 (1.2)	***	2.2
Volumetrics [b]				
WMH	4688.2 (9260.7)	2335.2 (3189.8)	**	0.4
Lacunes	29.2 (128.9)	12.0 (37.8)	***	0.6
Total VRS	42.5 (68.7)	38.8 (54.6)	n.s.	-
WM-VRS	31.7 (48.4)	21.7 (31.8)	**	0.3
BG-VRS	10.6 (17.7)	15.7 (20.13)	n.s.	-
Severe Cases [c]				
Total VRS	89.5 (82.0)	76.8 (75.4)	**	0.3
WM-VRS	51.6 (59.4)	43.8 (46.6)	***	0.6
BG-VRS	22.2 (29.2)	26.4 (29.6)	n.s.	-

[a] Values reported are mean (SD), mm³.
[b] Values reported are median (IQR).
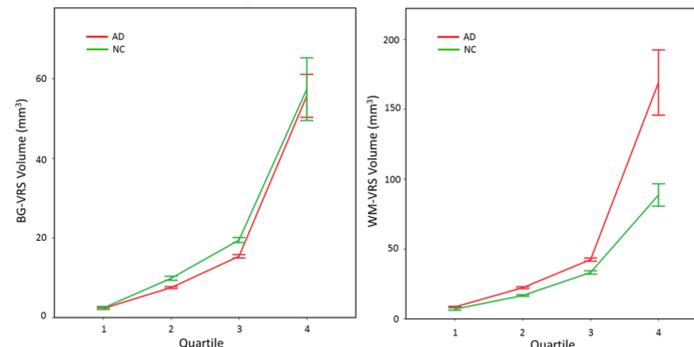[c] Comprised of the top 2 quartiles in each group: 103 AD and 48 NC.

Figure 2: VRS mean volumes in the basal ganglia and white matter for AD (red) and NC (green) split into 4 quartiles. Error bars represent ± 1 SE.

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

	Male	Female	p-value	Cohen's d
AD				
n	95	108		
WMH	4400.1 (8655.3)	4877.4 (10147.1)	n.s.	-
Lacunes	23.9 (116.8)	30.8 (137.2)	n.s.	-
Total VRS	44.1 (69.5)	41.5 (64.6)	*	0.3
WM-VRS	35.1 (49.63)	27.3 (42.3)	**	0.4
BG-VRS	10.3 (21.6)	11.1 (17.0)	n.s.	-
NC				
n	41	53		
WMH	2705.2 (5489.5)	1967.7 (2754.5)	n.s.	-
Lacunes	13.4 (68.5)	10.6 (27.21)	n.s.	-
Total VRS	64.2 (87.0)	32.0 (31.76)	***	0.8
WM-VRS	41.3 (60.5)	14.5 (23.8)	***	1
BG-VRS	17.6 (28.9)	12.4 (16.0)	n.s.	-

Data are presented as raw volumes and as median (IQR) (mm³)
Age at scan, years of education and disease state were entered as covariates
*p<0.05, **p<0.01, ***p<0.001

A paired samples t-test revealed significantly greater WM-VRS volumes compared to BG-VRS in AD (t(202)=-12.7, p<0.001) and NC (t(93)=-4.6, p<0.001) (See Figure 3).

COMPLEMENTARY STROKE STUDY

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In a separate study of 26 subjects (60 years ± 17.1; 11 males) taken from a stroke prevention clinic, VRS were segmented using a 3D T1-based approach. A Wilcoxon-signed rank test was used due to non-normality. In this sample, BG-VRS volumes were significantly greater compared to WM-VRS with Z(25)=-3.5, p=0.001 (See Figure 3).
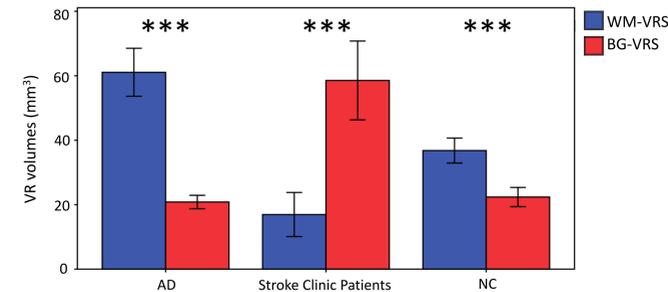

Figure 3. Raw volumes of regionalized VRS volumes for AD, stroke clinic patients, and NC samples. ***p<0.001
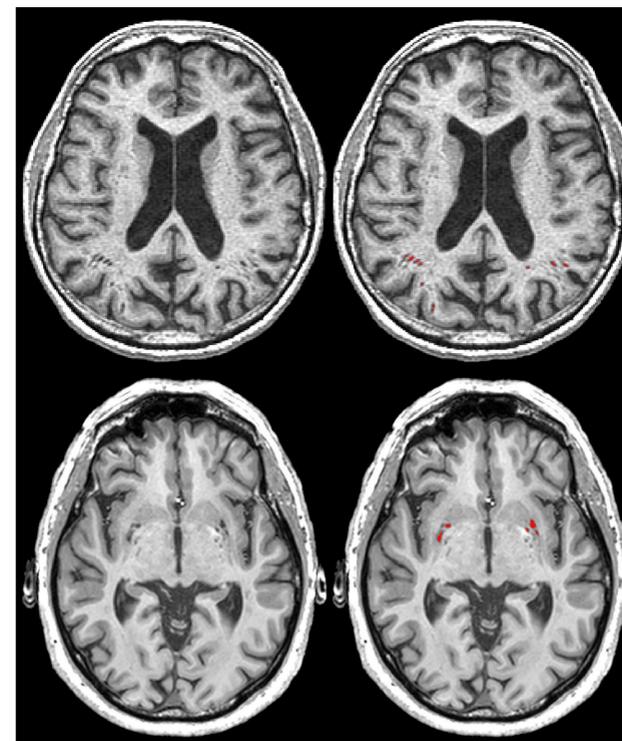

Figure 4. Axial T1 MRI with out VRS segmentation (left) and with VRS segmentation overlaid in red (right) for an AD (top) and stroke clinic (bottom) patients.

DISCUSSION

This study suggests that there is a significant difference between WM-VRS and BG-VRS, both in terms of sex and disease state. Compared to NC, AD patients had significantly greater volumes of WMH, lacunes, WM-VRS, but not BG-VRS (see Table 1).

Although AD patients generally present with more WM-VRS than NC, this difference was most prominent in severe cases. However, this difference was not seen in the basal ganglia, suggesting that VRS in the white matter may be indicative of AD pathology (see Figure 2).

Additionally, males had significantly higher VRS volumes compared to females in both the AD and NC sample. This relationship was not found with BG-VRS volumes. (see Table 2).

Finally, in both AD and NC, WM-VRS volumes were significantly greater than BG-VRS with the relationship being stronger in AD. Comparing these findings to a complementary study, a sample taken from a stroke clinic revealed a reverse relationship where BG-VRS volumes were significantly greater than WM-VRS (See Figures 3 and 4).

In conclusion, VRS in the WM may reflect different pathological processes compared to those in the BG, a relationship which may be exacerbated by AD and cerebrovascular disease (CVD). 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 further light on these questions.

ACKNOWLEDGEMENTS

REFERENCES

1. Abbott NJ (2004) Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. Neurochem Int 45:545-552
2. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H (2010) Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. Stroke 41:2483-2490
3. Chen W, Song X, Zhang Y (2011) Assessment of the Virchow-Robin Spaces in Alzheimer disease, mild cognitive impairment, and normal aging, using high-field MR imaging. AJNR Am J Neuroradiol 32:1490-1495
4. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ (2004) Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. J Neurol Neurosurg Psychiatry 75:1519-1523
5. Ramirez J, Gibson E, Quddus A, Lobaugh NJ, Feinstein A, Levine B, Scott CJ, Levy-Cooperman N, Gao FQ, Black SE (2011) Lesion Explorer: A comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. Neuroimage 54:963-973
6. Dade, L.A., Gao, F.Q., Kovacevic, N., Roy, P., Rockel, C., O'Toole, C.M., Lobaugh, N.J., Feinstein, A., Levine, B., Black, S.E.(2004). Semiautomatic brain region extraction: a method of parcellating brain regions from structural magnetic resonance images. NeuroImage, 22, 1492-1502.
7. Charidimou A, Meegahage R, Fox Z, Peeters A, Vandermeeren Y, Laloux P, Baron JC, Jager HR, Werring DJ (2013) Enlarged perivascular spaces as a marker of underlying arteriopathy in intracerebral haemorrhage: a multicentre MRI cohort study. J Neurol Neurosurg Psychiatry 84, 624-629.

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