LONGITUDINAL CHANGES OF VIRCHOW-ROBIN SPACE VOLUMES AND COGNITION IN ALZHEIMER'S DISEASE AND NORMAL ELDERLY COHORTS

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BACKGROUND

- Virchow-Robin spaces (VRS) are fluid filled cavities surrounding perforating arteries in the brain and have been linked to cerebral waste clearance[1].
- White matter (WM) VRS may indicate underlying amyloid angiopathy while basal ganglia (BG) VRS may reflect hypertensive arteriopathy[2].
- VRS severity increases with age[3], greater VRS load has been found in men[4] and VRS have been associated with cerebral small vessel disease and cognitive decline[5,6].
- Most VRS studies are cross-sectional and assess VRS load with semi-quantitative rating scales.

PURPOSE

To investigate longitudinal VRS volumetric changes in Alzheimer's disease (AD) and normal elderly (NC) subjects and link VRS with cognitive decline.

METHODS AND ANALYSIS

Study Participants:

- AD (n=61) and NC (n=39) participants with an inter-scan interval of 1-2 years (see Table 1).

VRS Definition[7]:

- Isointense to cerebrospinal fluid on all MRI sequences.
- Round or linear, usually <3mm in diameter.

Image Processing:

- VRS segmentation: Modified Lesion Explorer[8].
- VRS regional parcellation (BG & WM): Semi-Automated Brain Region Extraction (SABRE) mask[9].

Table 1 – Baseline Demographics, Cognitive testing and VRS Volumetric summary statistics

	AD (n=61)	NC (n=39)	p
Demographics			
Age, years	69.05 (10.73)	70.18 (7.65)	-
Sex, %female	60.66	56.41	-
YOE	13.56 (3.38)	16.08 (2.47)	***
Inter-scan Interval	1.24 (0.19)	1.28 (0.20)	-
Cognitive Testing			
MMSE	24.14 (3.23)	28.92 (1.01)	***
Rey	23.81 (10.51)	33.33 (2.57)	***
TMT:A	79.63 (56.28)	31.47 (9.90)	***
TMT:B	183.64 (113.90)	67.45 (20.25)	***
VRS Volumetrics[a,b]			
Total VRS	56.68 (58.14)	56.68 (71.94)	-
BG VRS	17.44 (21.80)	24.71 (24.71)	-
WM VRS	40.70 (45.06)	36.34 (42.15)	-

*p<0.05, **p<0.01, ***p<0.001
[a] Values are median (IQR). Elsewhere values are mean (SD).
[b] Values are in mm^3 and are not reported as head size corrected.

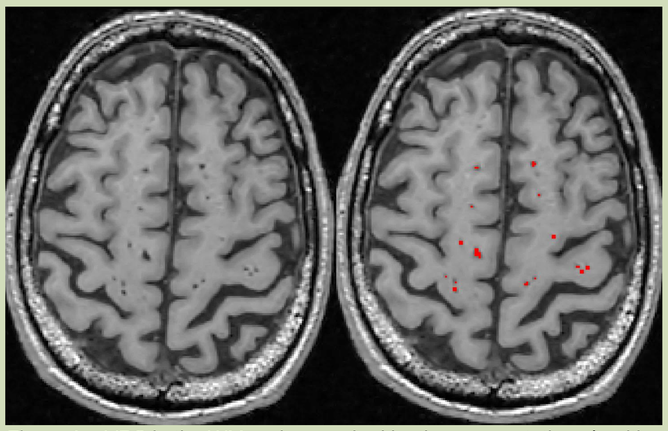

Figure 1 – VRS in the WM and as marked by the segmentation algorithm

RESULTS

Table 2 – Multiple Regression Analyses investigating if VRS volume change is predicted by sex and increasing age[1,2]

Response	Predictors	β	p	r^2
AD				
Δ Total VRS Volume	Sex	-0.069	-	0.001
	Δ Age	0.143	-	0.021
Δ BG VRS Volume	Sex	-0.221	-	0.011
	Δ Age	0.085	-	0.004
Δ WM VRS Volume	Sex	0.078	-	0.001
	Δ Age	0.144	-	0.021
NC				
Δ Total VRS Volume	Sex	0.763	*	0.152
	Δ Age	0.339	*	0.121
Δ BG VRS Volume	Sex	0.787	*	0.149
	Δ Age	0.122	-	0.016
Δ WM VRS Volume	Sex	0.389	-	0.040
	Δ Age	0.274	-	0.075

[2] Regression controlled for MMSE, years of education, brain parenchymal fraction and WMH volume change.

Table 3 – Multiple Regression Analyses investigating if cognitive decline is predicted by diagnosis and total VRS volume change[1,3]

Response	Predictors	β	p	r^2
Δ Rey (AD=52, NC=38)	Dx.	0.281	-	0.012
	Δ Volume	-0.797	*	0.008
	Interaction	0.510	*	0.062
Δ TMT:A (AD=45, NC=37)	Dx.	-0.389	-	0.023
	Δ Volume	-0.345	-	0.016
	Interaction	0.144	-	0.006
Δ TMT:B (AD=31, NC=36)	Dx.	-0.686	*	0.090
	Δ Volume	1.101	**	0.163
	Interaction	-0.563	*	0.105
Δ TMT:B-TMT:A (AD=31, NC=36)	Dx.	-0.632	*	0.085
	Δ Volume	1.448	***	0.273
	Interaction	-0.698	**	0.166
Δ TMT:B/TMT:A (AD=31, NC=36)	Dx.	-0.556	0.068	0.057
	Δ Volume	1.332	***	0.211
	Interaction	-0.611	**	0.114

[1] VRS volumes were head sized corrected.
[3] Regression controlled for age, sex, MMSE, years of education, brain parenchymal fraction and WMH volume change.

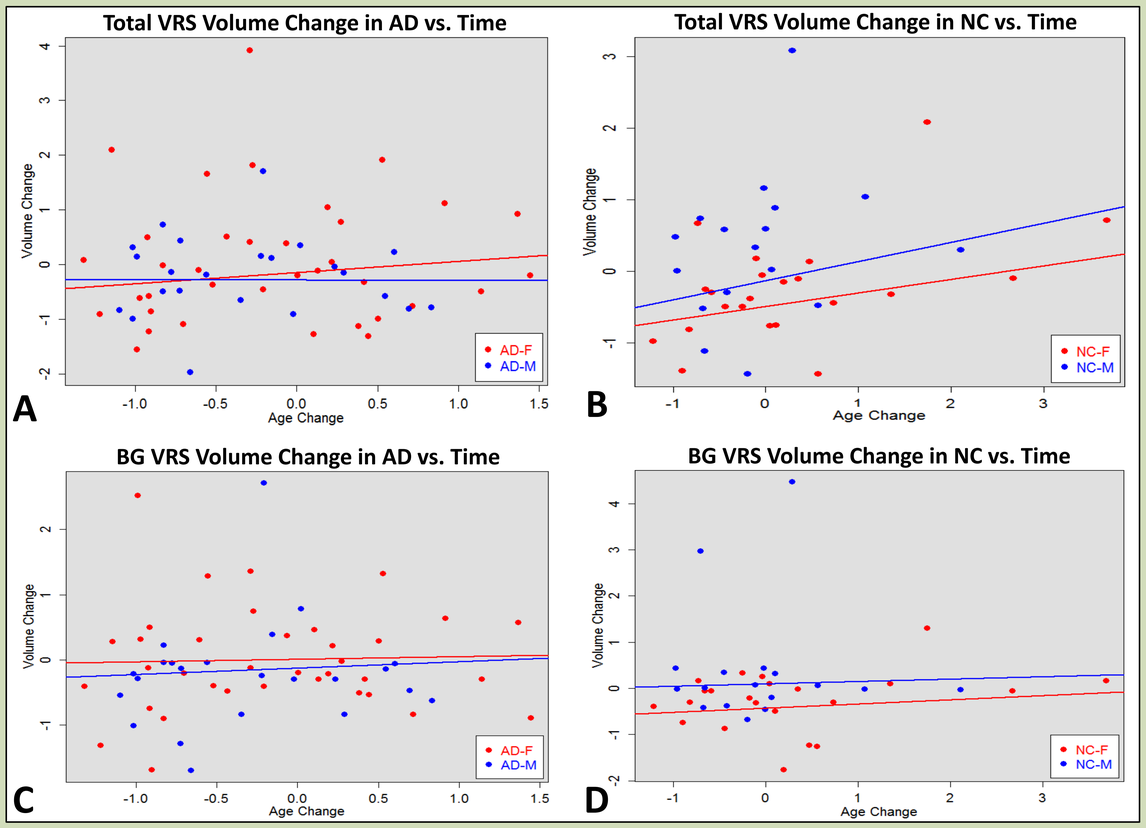

Figure 2 – Change in Total VRS volume as a function of change in age in (A) AD and (B) NC subjects and change in BG VRS volume as a function of change in age in (C) AD and (D) NC subjects

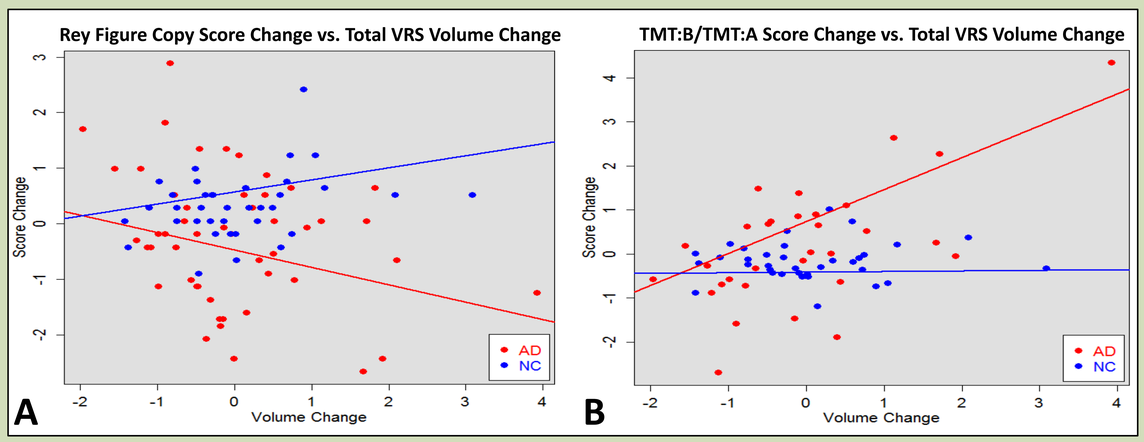

Figure 3 – Change in (A) visuospatial skills and (B) set-shifting as a function of changing total VRS volume

DISCUSSION AND CONCLUSION

- This study suggests total VRS volume increases with time but only in normal elderly, revealing a possible ceiling effect in VRS development in Alzheimer's disease.
- Total and BG VRS developed faster in normal males than females.
- Increasing Total VRS volume was linked to declining visuospatial ability in AD patients, independent of age and white matter hyperintensity volume, but had a surprising protective effect in NC subjects.
- Increase in VRS load was not linked to processing speed as measured by Trails-A but was associated with executive function in AD as measured by Trails-B.
- The negative relationship between VRS volume and derived minus and quotient Trails scores suggests greater volume correlates with set-shifting decline but only in AD.
- This is the first longitudinal study investigating volumetric progression of VRS over time in an AD and NC population.
- This is also the first study demonstrating that a cognitive domain is affected in AD, but not in normal elderly, as total VRS volume increases.

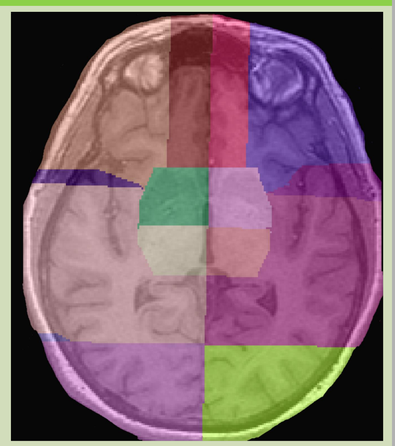

Figure 4 – SABRE parcellation mask

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