

CHOLINERGIC SUBCORTICAL HYPERINTENSITIES: RELATIONSHIPS WITH COGNITIVE DYSFUNCTION AND HIPPOCAMPAL ATROPHY

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BACKGROUND

The presence of **subcortical hyperintensities (SH)** strategically located within the **cholinergic pathways** is believed to reflect cerebrovascular compromise of the cholinergic system in dementia [1, 2].

Hippocampal (HP) atrophy is a commonly used biomarker for Alzheimer's disease (AD) and has been shown to be associated with cognition and memory dysfunction [3, 4, 5].

PURPOSE & HYPOTHESIS

To examine the relationships between vascular burden in the cholinergic pathways, HP atrophy, and cognition, in a sample of AD patients (n=234).

We hypothesized that:

- Severity of chSH volumes would be related to executive and memory functioning.
- Hippocampal atrophy would be related to this strategic vasculopathy.

METHODS

Statistical analyses were conducted to examine the relationships between **chSH volumetric data**, **neuropsychological data** and **HP volumetric data**.

Subjects were evenly divided into low (n=117) and high (n=117) chSH groups based on the median split, after head size correction.

MRI-derived volumetrics:

- The cholinergic mask and chSH volumes were obtained using SABRE [6] and a modified version of Lesion Explorer (LE) [7], see figure 2 & 3. This method was highly correlated with the Cholinergic Pathways Hyperintensities Scale (CHIPS) [1] ($\rho=0.84$, $p<0.001$), see figure 1.

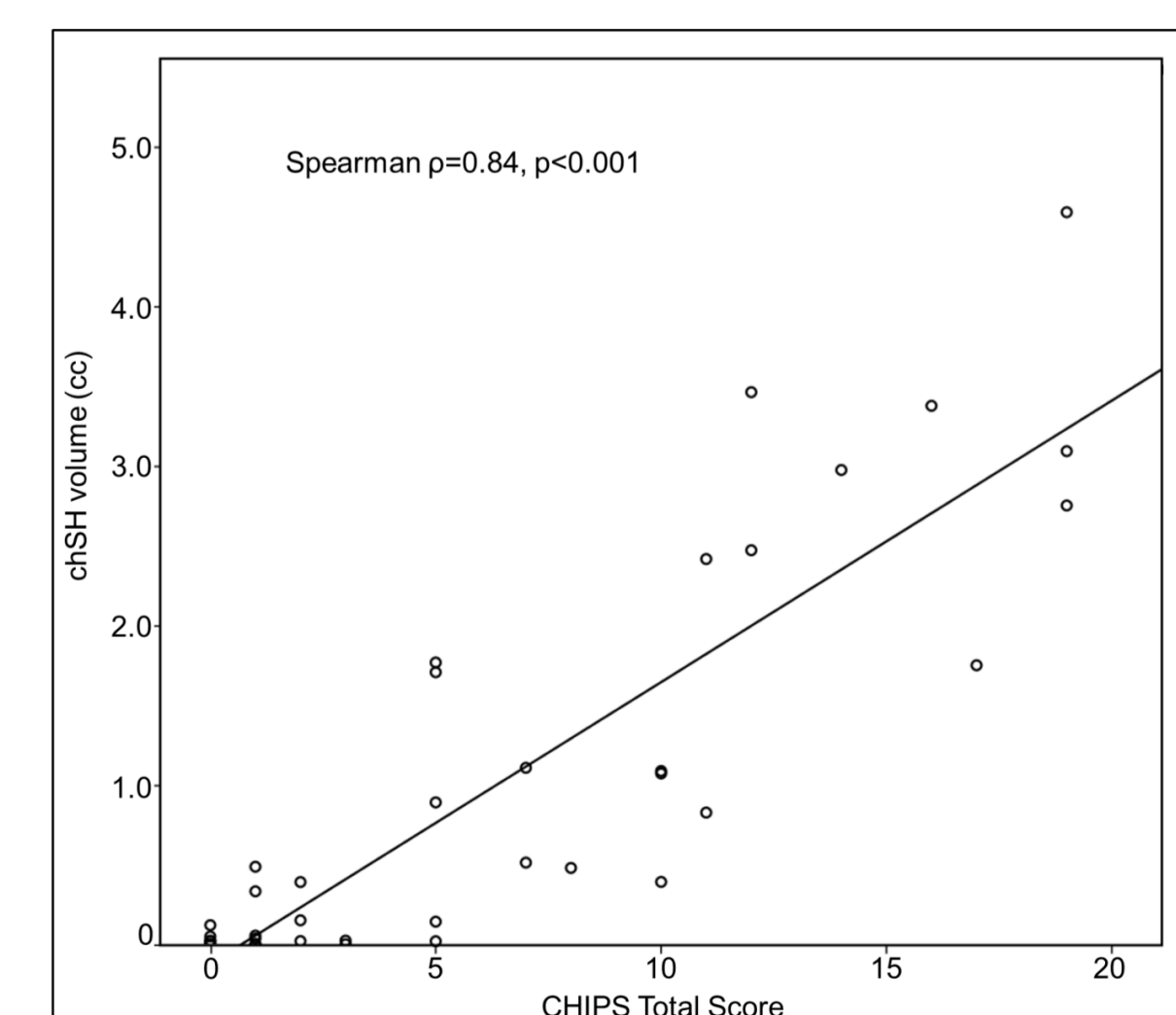


Figure 1 Correlation between chSH volume and CHIPS visual rating scale

- The individualized cholinergic pathway mask encompassed the lateral cholinergic fibre projections through the white matter starting from the most inferior point of the external capsule, reaching superiorly to the centre of the centrum semiovale, laterally to the insula and medially to the putamen, see figures 2 & 3.

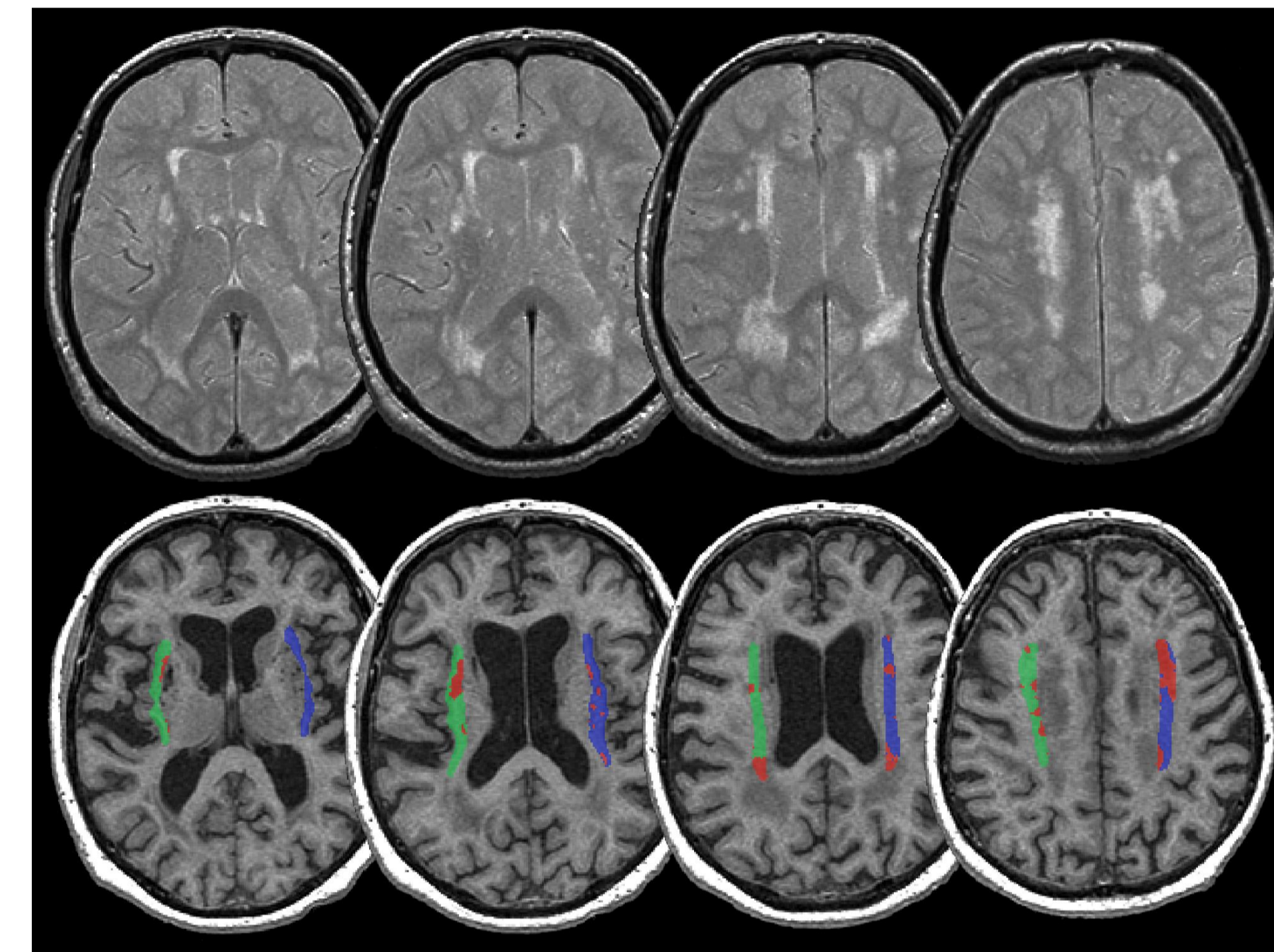


Figure 2 Anatomical boards of SABRE cholinergic pathway segmentation: Proton Density (top) and axial T1 weighted (bottom) MRI with left (blue) and right (green) cholinergic segmentation and SH (red) overlay

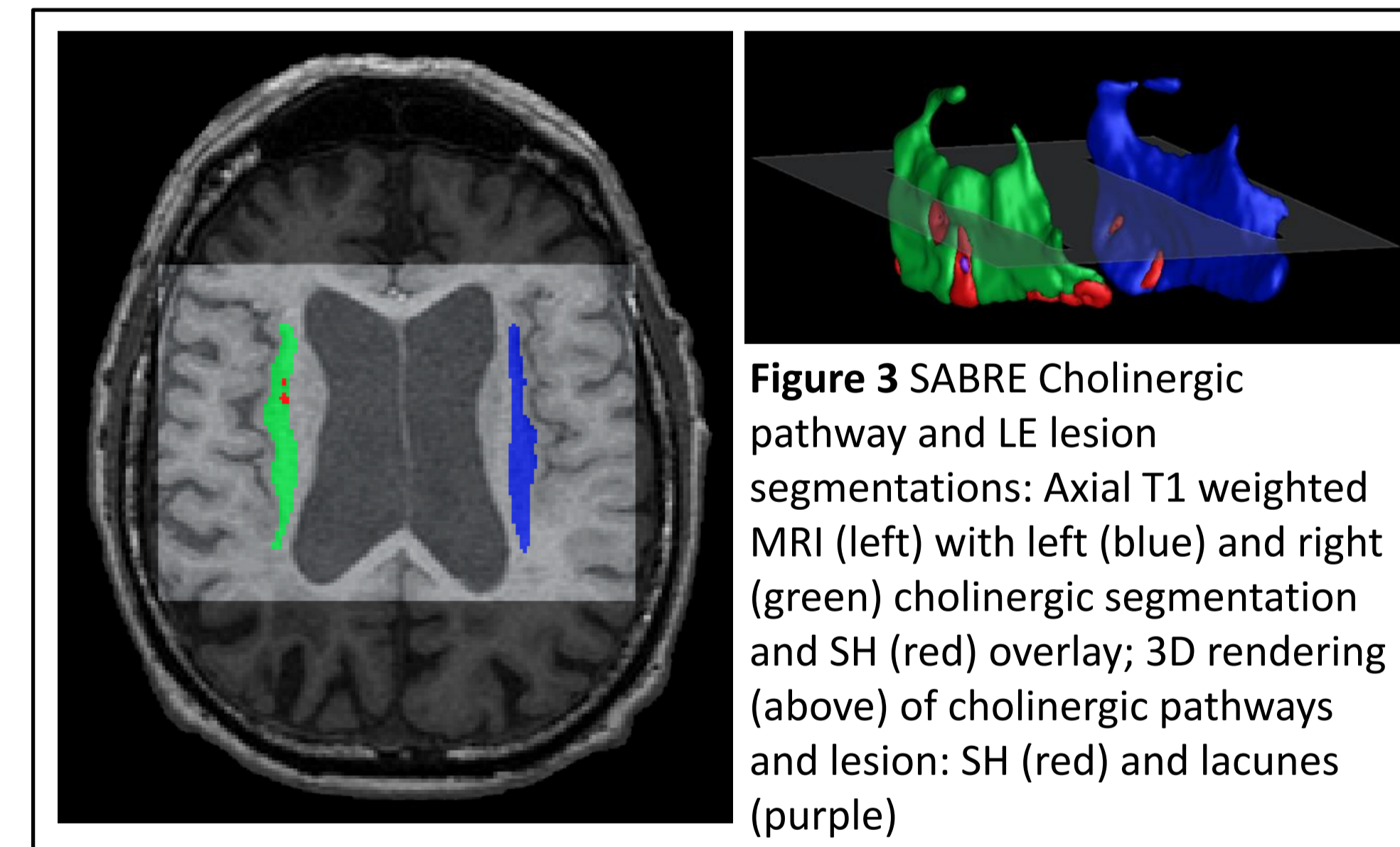


Figure 3 SABRE Cholinergic pathway and LE lesion segmentations: Axial T1 weighted MRI (left) with left (blue) and right (green) cholinergic segmentation and SH (red) overlay; 3D rendering (above) of cholinergic pathways and lesion: SH (red) and lacunes (purple)

- Automatic HP volumes were acquired using the SunnyBrook Hippocampal Volumetry (SBHV) Tool [8], an in house multi-atlas segmentation tool.

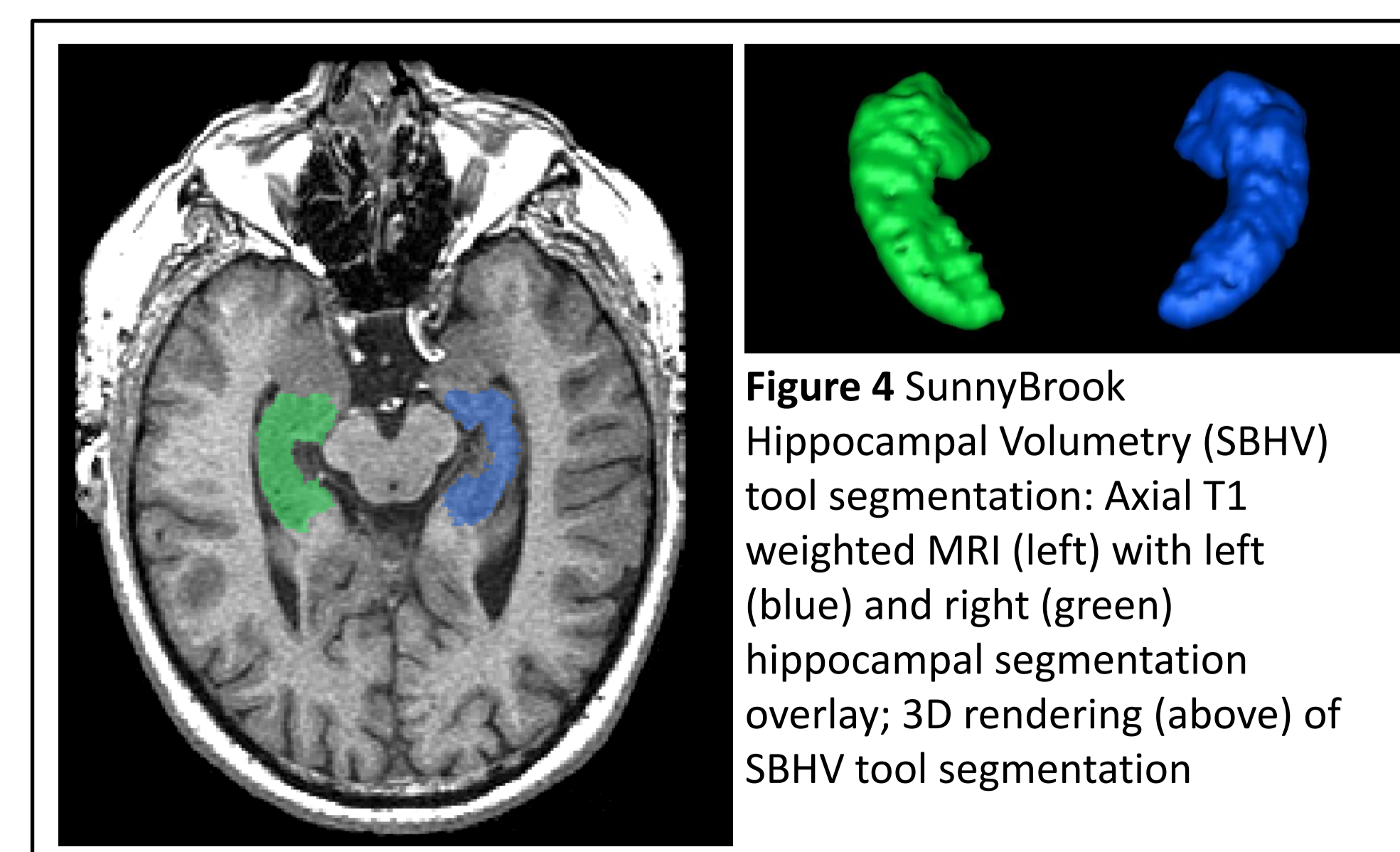


Figure 4 SunnyBrook Hippocampal Volumetry (SBHV) tool segmentation: Axial T1 weighted MRI (left) with left (blue) and right (green) hippocampal segmentation overlay; 3D rendering (above) of SBHV tool segmentation

Neuropsychological Assessment [9]:

Executive:

- Verbal Fluency 'FAS' Test
- Wisconsin Card Sorting Test

Visuospatial:

- Benton Judgement of Line Orientation Test
- Rey-Osterrieth Complex Figure Copy Test

Memory:

- California Verbal Learning Test
- Visual Reproduction
- Dementia Rating Scale, Memory

RESULTS

Association Between chSH and Cognition

| | Degree of SH in cholinergic pathways | | p | Cohen's d |
|----------------------------------|--------------------------------------|---------------|-----|-----------|
| | Low (n=117) | High (n=117) | | |
| Demographics | | | | |
| Age, years | 69.0 (9.5) | 75.0 (7.4) | *** | 0.70 |
| Sex, n (% male) | 59 (50.4) | 39 (33.3) | ** | - |
| Education, years | 14.2 (3.8) | 13.6 (3.8) | ns | - |
| MMSE/30 | 23.0 (4.7) | 23.5 (4.1) | ns | - |
| DRS/144 | 117.3 (15.2) | 120.2 (11.9) | ns | - |
| Volumetrics | | | | |
| BPF, % | 72.8 (4.9) | 73.2 (4.3) | ns | - |
| Global SH | 2.2 (2.0) | 12.5 (10.7) | *** | 1.75 |
| Total chSH, mm ³ | 6.7 (9.7) | 639.0 (997.4) | *** | 1.88 |
| Total ch-lacune, mm ³ | 0.0 (0.3) | 1.5 (7.0) | *** | 0.48 |
| Total HP | 4.7 (0.7) | 4.5 (0.8) | * | 0.29 |
| Cognition | | | | |
| Executive, z-score | -1.2 (1.1) | -1.2 (1.1) | ns | - |
| Memory, z-score | -4.7 (1.8) | -5.1 (1.8) | * | 0.22 |
| Visuospatial, z-score | -2.9 (2.9) | -2.3 (2.7) | ns | - |

Table 1 Demographics, raw volume data and cognition by severity: low and high chSH groups
Note: Data are presented as Mean (SD) unless otherwise stated. Raw volumes are presented for transparency, statistical analyses were performed on normalized, head size corrected data. Volumetrics are reported in cc unless otherwise stated.
*p<0.05, **p<0.01, ***p<0.001

A significant difference was found between low and high chSH group memory scores ($p<0.05$, $d=0.22$) independent of age, sex, YOE, BPF, DRS score and Global SH, see figure 5.

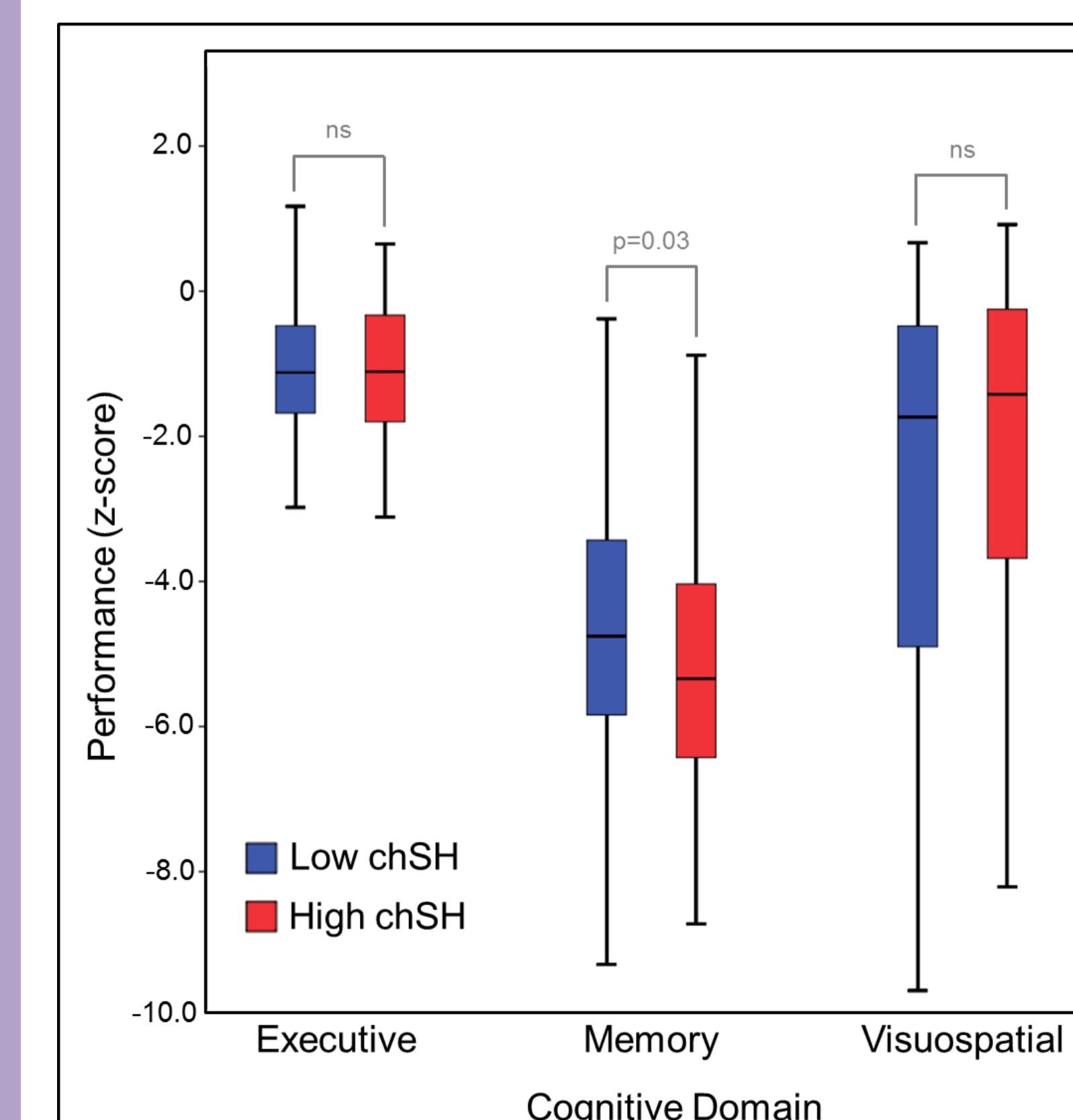


Figure 5 Boxplot displaying chSH group differences in executive, memory and visuospatial cognitive domain performance. The high chSH group's (red) memory performance was significantly worse than the low chSH group (blue) ($p=0.03$). Whiskers represent maximal and minimal values, excluding outliers.

Association Between chSH and HP Atrophy

A significant difference was found between HP volume in the low and high chSH groups ($p<0.05$, $d=0.29$).

DISCUSSION

This study presents a novel method that allows for volumetric quantification of SH within the cholinergic tracts.

Strategic signs of SVD within the cholinergic projections may be associated with specific cognitive dysfunction in cases with high cholinergic SH load. This suggests a possible threshold effect [10, 11], where cognitive dysfunction is only detectable when a chSH threshold is exceeded.

Damage to the cholinergic fibres, independent of global SH may be related to HP atrophy and memory dysfunction in AD. More research is needed to fully understand the etiology and impact of this damage in order to assess the efficacy of cholinergic therapies in AD with SVD.

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 Canadian Partnership for Stroke Recovery.

REFERENCES

- C.Bocti et al., A new visual rating scale to assess strategic white matter hyperintensities within cholinergic pathways in dementia, *Stroke*. 36 (2005) 2126-2131.
- P.Behl et al., Strategic subcortical hyperintensities in cholinergic pathways and executive function decline in treated Alzheimer patients, *Arch.Neurol.* 64 (2007) 266-272.
- P.T.Francis et al., The cholinergic hypothesis of Alzheimer's disease: a review of progress, *Journal of Neurology, Neurosurgery, and Psychiatry*. 66 (1999) 137-147.
- T.den Heijer et al., A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline, *Brain*. 133 (2010) 1163-1172.
- M.L.Schroeter et al., Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients, *Neuroimage*. 47 (2009) 1196-1206.
- Dade, et al., Semiautomatic brain region extraction: a method of parcellating brain regions from structural magnetic resonance images. *Neuroimage*. 22, (2004) 1492-1502.
- J.Ramirez et al., Lesion Explorer: A comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue, *Neuroimage*. 54 (2011) 963-973.
- S.M.Nestor et al., A direct morphometric comparison of five labeling protocols for multi-atlas driven automatic segmentation of the hippocampus in Alzheimer's disease, *Neuroimage*. 66C (2013) 50-70.
- M.D.Lezak, *Neuropsychological assessment*, 4 ed., Oxford University Press, New York, 2004.
- K.B.Boone et al., Neuropsychological correlates of white-matter lesions in healthy elderly subjects. A threshold effect, *Arch.Neurol.* 49 (1992) 549-554.
- C.Decarli, et al., The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults, *Neurology*. 45 (1995) 2077-2084.

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