CHOLINERGIC PATHWAY SUBCORTICAL HYPERINTENSITY VOLUME CORRELATES WITH EXECUTIVE FUNCTION AND HIPPOCAMPAL VOLUME

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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=182) and normal elderly controls (NC: n=93).

We hypothesized that subjects who have poor cognitive function would have greater volumes of cholinergic SH (chSH) and cholinergic lacunes (ch-lacune) and that these volumes would be associated with HP atrophy.

METHODS

MRI-derived volumetrics:
- chSH and ch-lacune volumes were obtained using a modified version of Lesion Explorer (LE) [6].
- HP volumes were obtained using the Sunnybrook Hippocampal Volumetry (SBHV) Tool [7].

Neuropsychological Assessment [8]**:**

Executive:
- Verbal Fluency 'FAS' Test
- Wisconsin Card Sorting Test
  - number of decisions correct overall
  - perseverative errors to previous response
  - perseverative errors to previous category

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

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

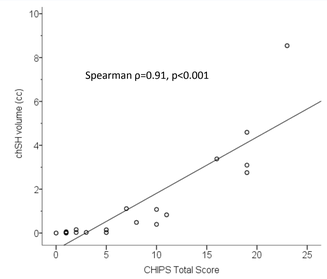

Figure 1. The chSH volume generated by LE was highly correlated with the Cholinergic Pathways Hyperintensities Scale (CHIPS)[1].

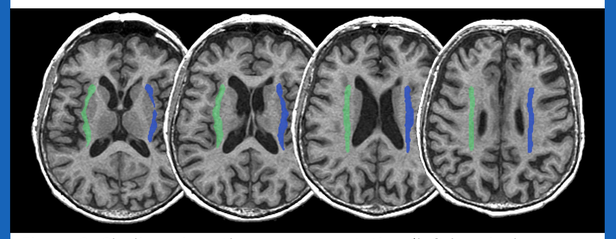

Figure 2. Cholinergic pathways segmentation (left hemisphere =blue, right hemisphere =green), overlaid on T1 weighted MRI

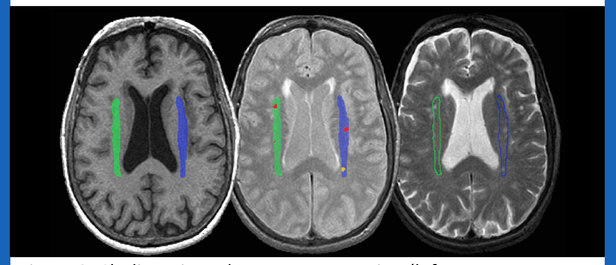

Figure 3. Cholinergic pathways segmentation (left hemisphere=blue, right hemisphere=green); overlaid on T1 (left), proton density (PD) with lesion mask (deep white SH=red, periventricular SH=yellow)(middle), and T2 (right)

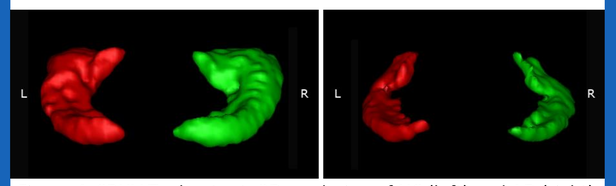

Figure 4. SBHV Tool output: 3D rendering of NC (left) and AD (right) HP, right HP=green, left HP=red
(Note: HP are depicted in neurological convention)

ANALYSIS

Correlations were performed for cognitive domain relationship testing between three groups (mild moderate and severe chSH, irrespective of diagnosis (Dx), determined using data ranking and quartile division based on chSH volume. Analyses were performed with age, sex, education, brain parenchymal fraction (BPF), global SH and Dx included as covariates when applicable.

RESULTS

Table 1. Demographics and raw volume data: AD and NC

	NC (n=93)	AD (n=182)	p	Cohen's d
Demographics				
Age (years)	69.3±8.1	71.4±9.8	ns	
Sex (male)	41	82	ns	
Education (years)	15.7±3.0	13.9±3.7	***	0.53
Volumetrics				
Global SH (cc)	5.4±9.3	8.2±11.1	**	0.26
Total chSH (cc)	0.2±0.7	0.4±0.9	***	0.20
Left chSH (cc)	0.1±0.4	0.2±0.5	***	0.21
Right chSH (cc)	0.1±0.4	0.2±0.4	***	0.17
Total ch-lacune (mm^3)	0.5±2.8	1.7±7.1	*	0.20
Left ch-lacune (mm^3)	0.2±0.9	0.9±4.4	*	0.05
Right ch-lacune (mm^3)	0.3±2.1	0.8±5.4	ns	
Total HP (cc)	5.7±0.6	4.7±0.8	***	1.39
Left HP (cc)	2.8±0.3	2.3±0.4	***	1.42
Right HP (cc)	2.9±0.3	2.4±0.4	***	1.15
BPF (%)	79.2±3.7	73.3±4.7	***	1.34

Data is presented as Mean±SD
Raw volumes are presented for illustrative purposes
*p<0.05, **p<0.01, ***p<0.001

Association between chSH and cognition

Table 2. Demographics, raw volume data and cognitive domain scores: mild, moderate and severe chSH groups

	Degree of SH in cholinergic pathways			
	Mild (n=92)	Moderate (n=91)	Severe (n=92)	p
Demographics				
Age (years)	66.1±8.6	70.5±9.2	75.4±7.6	***
Sex (male)	44	37	42	ns
Education (years)	15.0±3.7	14.6±3.5	13.9±3.3	ns
Volumetrics				
Global SH (cc)	1.7±1.9	3.8±3.1	16.3±14.0	***
Total chSH (mm^3)	0.6±1.5	33.5±23.0	899.8±1319.6	***
Left chSH (mm^3)	0.4±1.2	20.9±19.5	499.4±739.2	***
Right chSH (mm^3)	0.2±0.8	12.7±14.0	400.3±621.6	***
BPF (%)	77.3±5.0	75.0±6.0	74.0±4.3	***
Cognition				
Executive	-0.5±1.1	-0.7±1.0	-0.9±1.1	*
Memory	-2.3±2.6	-3.0±2.7	-4.2±2.6	***
Visuospatial	-1.7±2.7	-1.7±2.6	-1.8±2.4	ns

Data is presented as Mean±SD
Raw volumes are presented for illustrative purposes
*p<0.05, **p<0.01, ***p<0.001

Table 3. Tertile analysis: correlation between cognition and mild, moderate and severe chSH groups

	Degree of SH in cholinergic pathways						
	Mild (n=92)	Moderate (n=91)	Severe (n=92)				
			Left chSH		Right chSH		ch-Lacune	
Domain			ρ	r^2	ρ	r^2	ρ	r^2
Executive			-0.3**	0.09	-0.32**	0.10	-0.23*	0.05
Memory	ns	ns	ns		ns		ns	
Visuospatial			ns		-0.22*	0.05	ns	

ρ = Spearman's rho, correlation coefficient, *p<0.05, **p<0.01
r^2 = effect size

Association between chSH and HP atrophy

A significant relationship was found between right HP volume and right hemisphere chSH in NC (β=-0.25, p<0.05 r^2=0.05), indicating that a **1% decrease in right HP volume estimates a 0.25 SD increase in right hemisphere chSH.**

DISCUSSION

This study suggests that signs of vascular compromise within the cholinergic system may be related to executive and visuospatial dysfunction.

However, the relationship between chSH and cognition is only evident in cases from the severe chSH group. This suggests a threshold effect, where cognitive dysfunction is only detectable when a **chSH threshold is exceeded (0.5% of supra-tentorial intracranial capacity)** [9, 10].

The current study also suggests that chSH may be related to memory dysfunction, as HP volume is inversely associated with chSH (in the right hemisphere).

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