Changes in brain glutathione in patients with mild vascular cognitive impairment

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Introduction & Background

- Oxidative stress (OS) implicated in dementia
- In vascular mild cognitive impairment (vMCI), elevated peripheral biomarkers of OS are reported
- High OS impairs cellular function & affect antioxidant balance, predicts poorer cognitive outcomes
- **The role of central antioxidant responses is still unclear**

Objectives & Hypotheses

- To investigate brain GSH in vMCI patients vs. cognitively normal controls
- Hypothesis: vMCI patients will have lower brain GSH compared to controls

Methods

- Patients (age 55-85) with ≥2 vascular risk factors or a previous vascular event were screened (Table 1) from a cardiac rehabilitation exercise program

Table 1: Scales used for cognitive testing

Domain		Scale
Global Cognition		Montreal Cognitive Assessment (MoCA)
National Institute of Neurological Disorders and Stroke – Canadian Stroke Network 60-min standardized battery	Executive Function (EF)	Trails making B, Semantic Fluency, Phonemic Fluency
	Working Memory	Digit Span
	Processing Speed	Digit Symbol-Coding
	Visual and Verbal Memory	Rey Complex Figure Test, Hopkins Verbal Learning Test–Revised

- vMCI: MoCA <28 AND ≤-1SD below norms in any domain
- Control: MoCA ≥28 OR ≥-1 SD below norms for all domains
- Brain GSH in the anterior cingulate (ACC) and occipital (OC) cortices (Figure 1-2) were quantified with MEscher–GArwood Point Resolved Spectroscopy (MEGA-PRESS) using Gannet (vers. 3.1), SPM12 and Matlab (vers. 2020b)

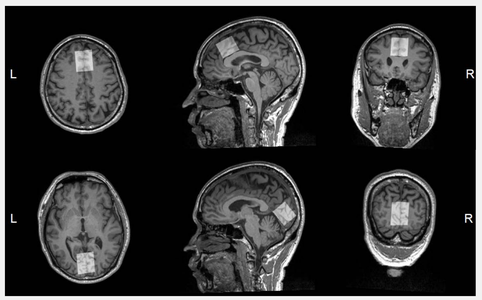

Figure 1: locations of 30x30x30mm MRS voxels of interest in axial, sagittal, and coronal views (left to right) in the ACC (top panel) and OC (bottom panel)

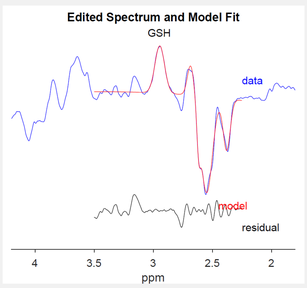

Figure 2: sample MRS spectra used to estimate voxel GSH level

Results

- 43 participants (vMCI n=22, Control n=21)

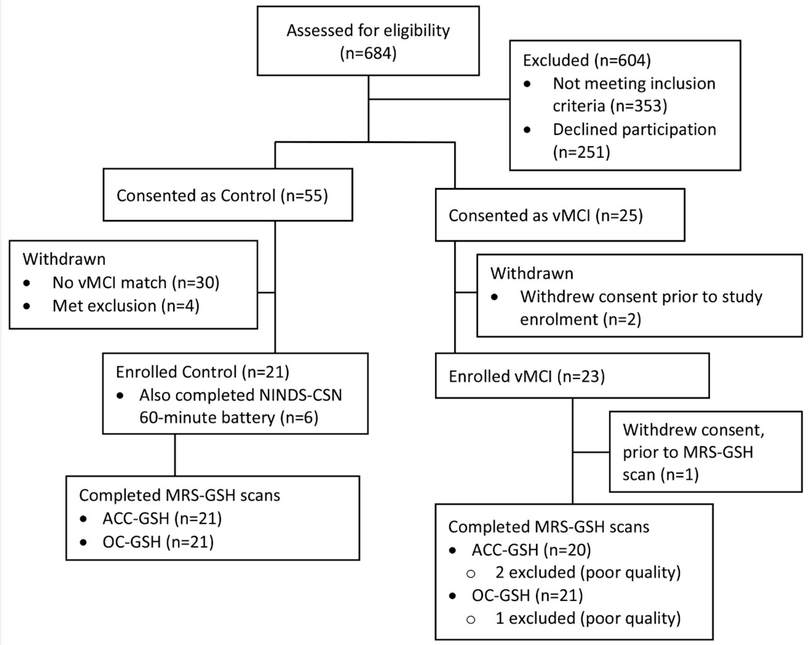

Figure 3: Flow chart of study recruitment. For controls, 15 participants had MoCA scores ≥ 28 and did not complete the NINDS-CSN 60-minute battery. One vMCI participant withdrew consent after enrolment but prior to MRS data collection and was excluded from the analysis.

Table 2: Participant characteristics, variables in colored rows (in tan) were significantly different between groups (p<.05) and were controlled for in *post hoc* analysis

	Control (n=21)	mVCI (n=22)
Age, mean (SD)	66.7 (7.8)	67.4 (7.3)
Male, n (%)	18 (86%)	16 (73%)
White, n (%)	16 (67%)	12 (54%)
History of smoking tobacco, n (%)	9 (43%)	6 (27%)
Years of education, mean (SD)	18.3 (2.9)	15.3 (3.4)
Mean Arterial Pressure, mmHg (SD)	87.5 (9.6)	96.3 (9.1)
Number of vascular risk factors, mean (SD)	1.1 (1.2)	1.8 (1.3)
MoCA, mean out of 30 (SD)	27.7 (1.2)	23.0 (2.0)

- Correcting for cerebrospinal fluid (CSF) volume, ACC-GSH was higher in mVCI (Figure 2), there was no difference in OC-GSH between groups

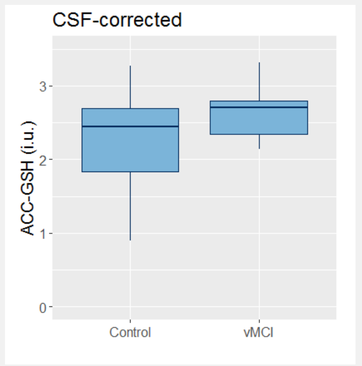

Figure 2 (right): Box and whisker plots denoting median, interquartile range, minimum, and maximum of CSF-corrected ACC-GSH level in control and vMCI participants. Abbreviations: ACC – anterior cingulate cortex, GSH – glutathione, i.u. – institutional units.

Post Hoc and Exploratory Results

- Adjusting for potential confounders (age, sex, years of education, mean arterial pressure), CSF-corrected ACC-GSH remained higher in vMCI cs. Controls (Table 3)

Table 3: *Post hoc* analysis of association between brain GSH and vMCI status (n=41), controlling for variables affecting GSH levels (age, sex) and characteristics significantly different between vMCI and controls (years of education, mean arterial pressure)

Outcome	Independent Variable	B [SE]	t, p	Model Significance	Adj R^2
CSF-corrected ACC-GSH	Controlling for age, sex, years of education, and mean arterial pressure				
	vMCI status	0.36 [0.18]	2.1, p=.048	$F_{(5,35)}$ = 3.2, p=.017	0.22
CSF-corrected OC-GSH	Controlling for age, sex, years of education, and mean arterial pressure				
	vMCI status	0.07 [0.11]	0.6, p=.5	$F_{(5,36)}$ = 1.4, p=.26	0.04

- In exploratory analysis, higher levels of CSF-corrected ACC-GSH, but not OC-GSH, was correlated with decreased executive function performance (Table 4) after controlling for education and diagnosis

Table 4: Exploratory analysis , association between brain GSH and executive function performance, controlling for years of education and diagnosis (vMCI status) (n=26)

Outcome	Independent Variable	B [SE]	t, p	Model Significance	Adj R^2
Executive Function	Controlling for years of education and vMCI status				
	CSF-corrected ACC-GSH	-0.50 [0.23]	-2.2, p=.04	$F_{(3, 22)}$=11.3, p<.001	0.55
Executive Function	Controlling for years of education and vMCI status				
	CSF-corrected OC-GSH	-0.20 [0.41]	-0.5,p=.63	$F_{(3, 23)}$=8.2 p=.006	0.46

Implications

- Contrary to central GSH decline reported in Alzheimer's disease, increased ACC-GSH was observed in vMCI
  - Compensation in response to OS challenges
- Higher ACC-GSH was correlated to poorer EF
  - Link between regional brain antioxidants and disease-relevant cognitive domains
- Changes in the antioxidant system may be etiologically implicated in the evolution of vMCI

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