Changes in brain glutathione in patients with mild vascular cognitive impairment

Jinghan Jenny Chen [1], Nathan Herrmann, MD FRCPC[2,3,10], Jane Ding [2], Laiba Azhar [1], Sandra E. Black, MD FRCPC[3,4], Joel Ramirez, PhD[3,4], Ana C. Andreazza, PhD[1], Alex Kiss, PhD[5], Paul Oh, MD FRCPC[6,7], Damien Gallagher, MD MRCPsych FRCPC[2,3], Simon Graham, PhD [8,9], and Krista L. Lanctôt, PhD[1-4,10]

1. Department of Pharmacology and Toxicology, University of Toronto, Toronto, 2. Department of Psychiatry, Sunnybrook Research Institute, Toronto, 3. Brain Sciences Research Program, Sunnybrook Research Institute, Toronto, 4. Department of Neurology, Sunnybrook Research Institute, Toronto, ON, Canada 5. Department of Research Design & Biostatistics, Sunnybrook Health Sciences Centre, Toronto, 6. Cardiac Rehabilitation and Secondary Prevention Program-University Health Network, Toronto Rehabilitation Institute, Toronto, 7. Department of Medicine, University of Toronto, Toronto, 8. Department of Medical Biophysics, University of Toronto, Toronto, 9. Physical Sciences, Sunnybrook Research Institute, Toronto, 10. Department of Psychiatry, University of Toronto, Toronto,

Introduction & Background

- Oxidative stress (OS) is implicated in age-related neuro-degeneration, vascular dementia, and Alzheimer's disease
- Our previous meta analysis of peripheral and brain glutathione (GSH) in patients with Alzheimer Disease and Mild Cognitive Impairment:
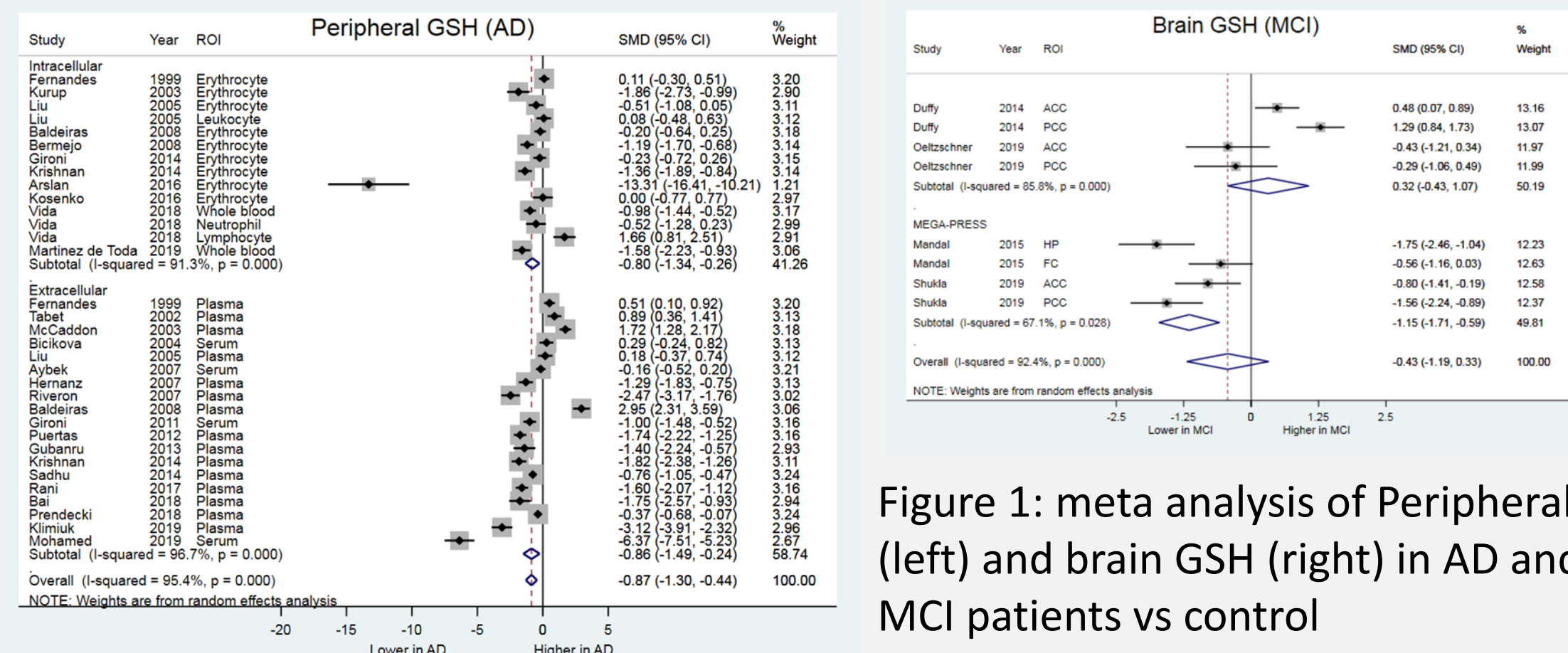

Figure 1: meta analysis of Peripheral (left) and brain GSH (right) in AD and MCI patients vs control

- Mild Vascular Cognitive Impairment (mVCI) is a prodromal stage of dementia defined by cognitive deficits associated with cerebrovascular disease
- Brain GSH has not been characterized in mVCI, in whom oxidative stress may be particularly high

Objectives & Hypotheses

- To investigate the change in brain GSH of patients with mVCI compared to age- sex-matched controls with similar cardiovascular risk factors
- **Hypothesis:** Brain GSH in the anterior cingulate and occipital cortices regions will be decreased in mVCI patients compared to cognitively healthy controls

Methods

- mVCI patients (1 standard deviation (SD) below norm in 1 of the 5 domains: executive function, verbal memory, working memory, processing speed, visuospatial function) were matched (sex and age +/- 5 years) to cognitively-normal (CN) controls (Table 1) and recruited from a cardiac rehabilitation program
- GSH is measured using the Mescher-Garwood Point Resolved Spectroscopy (MEGA-PRESS)[2] pulse sequence in the anterior cingulate (AC) and the occipital cortex (OC) regions (Figure 2)

Methods

- MRS analysis used open-source Gannet toolkit (Matlab)[3]; the edited GSH peak is integrated using nonlinear least-squares fitting, giving GSH level relative to water (Figure 3)
- CSF-corrected GSH using T1-weighted images (SPM12)

Table 1: Brief summary of study inclusion and exclusion criteria

| Inclusion	Exclusion
mVCI: - Males or females 55-85 years old - Montreal Cognitive Assessment (**MoCA**) <28 - At least 1.0 SD below population norm in one or more domains of the NINDS-CSN 60 minute neuro-psychological battery **Cognitively-normal (CN) control:** - Montreal Cognitive Assessment (**MoCA**) ≥28 OR does not meet criteria for mVCI using NINDS-CSN 60 minute neuro-psychological battery	- History of stroke or epilepsy - Presence of severely impaired organ function - Current major psychiatric or neurological condition - Contraindication to MRI/MRS scan
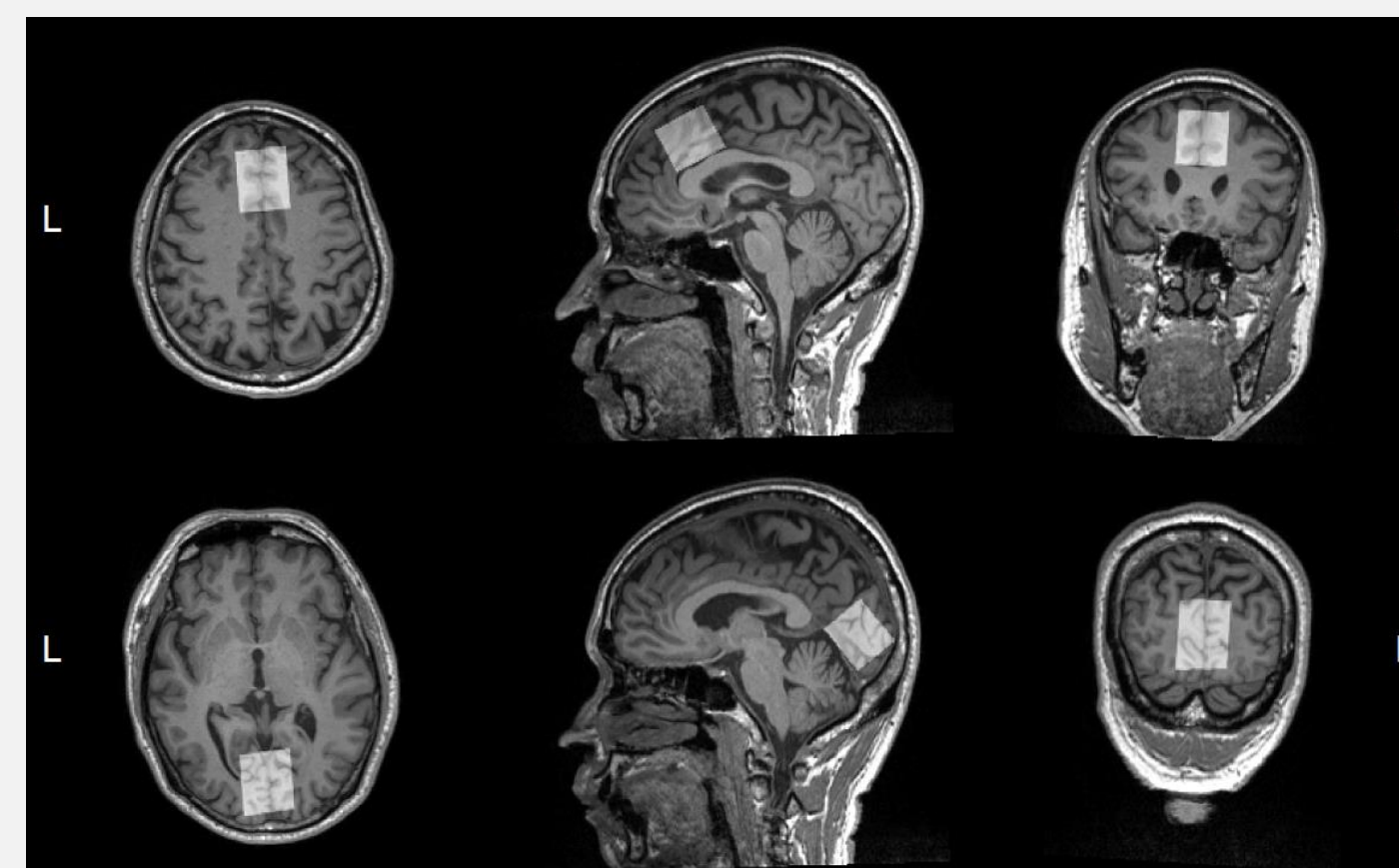
Figure 2: locations of 30x30x30mm MRS voxels of interest in axial, sagittal, and coronal views (left to right) in the AC (top panel) and OC (bottom panel)
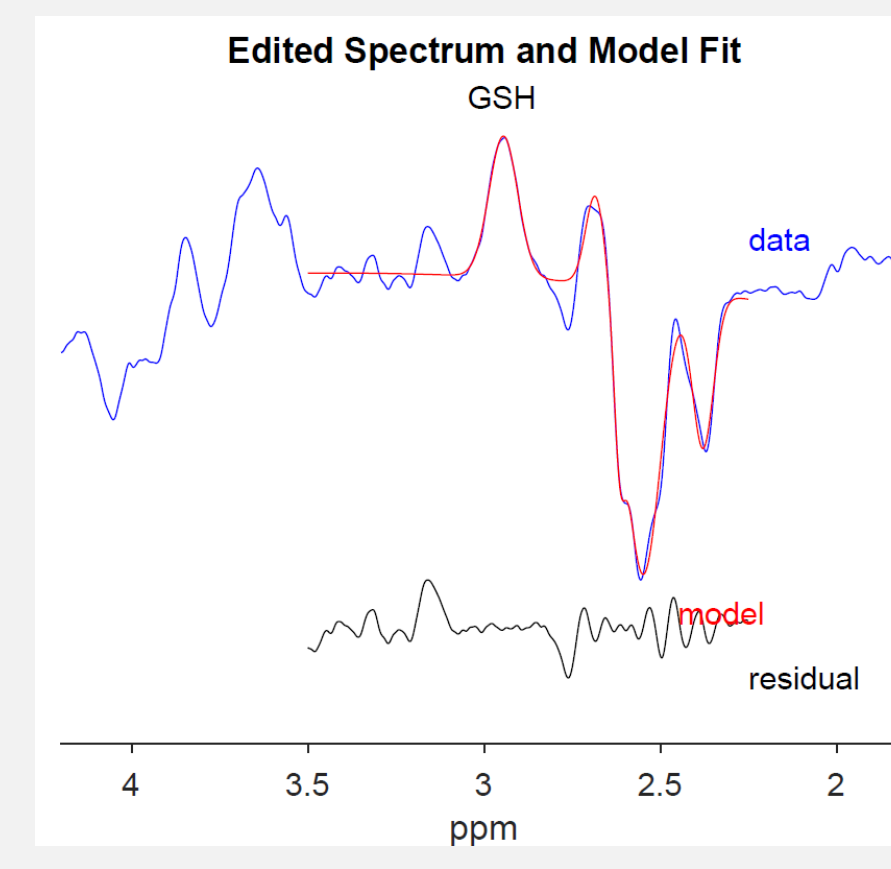

Figure 3: sample MRS spectra used to estimate voxel GSH level

Preliminary Results

- To date, 18 CN controls and 17 mVCI participants are enrolled (Table 2), recruitment is still ongoing
- As expected, mVCI scored lower in global cognition (MoCA), $F_{(1, 29)}=91.8$, p<.001

Table 2: Participant demographics

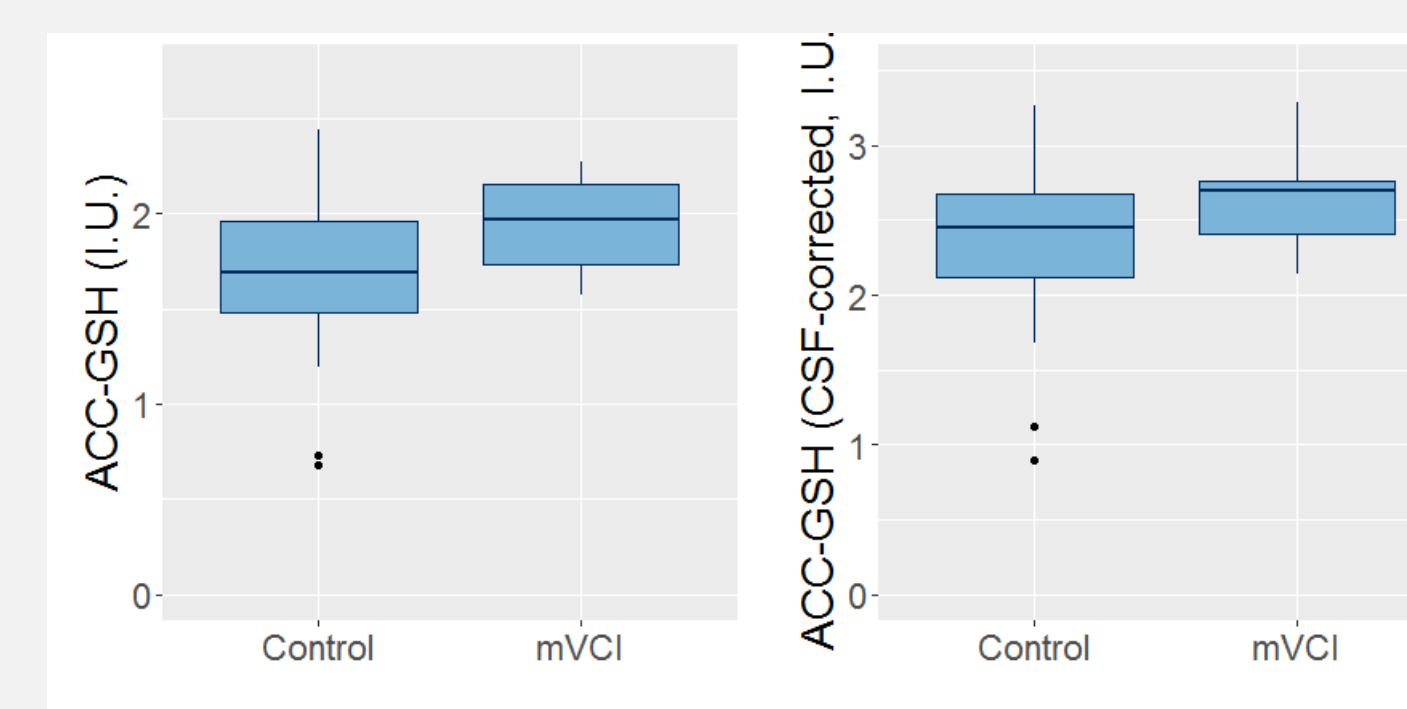|	Control (n=18)	mVCI (n=17)
Age (mean ± SD)	66.8 ± 7.4	67.4 ± 8.1
Male (%)	89%	71%
Caucasian (%)	67%	41%
History of smoking (%)	39%	19%
Years of education (mean ± SD)	18.1 ± 3.0	15.9 ± 2.6
Retired (%)	50%	53%
MoCA (mean out of 30 ± SD)	27.6 ± 1.3	22.6 ± 1.7

Preliminary Results

Figure 4: boxplots of brain ACC-GSH level in CN control and mVCI patients (left) and after correcting for voxel CSF volume (right)

- Higher brain ACC-GSH in mVCI compared to controls, $F_{(1, 26.9)}=5.38$, p=.03, difference remains after correcting for CSF volume $F_{(1, 26.6)}=4.71$, p=.04 (Figure 4)

- MoCA total score negatively correlated with GSH in the ACC but not the OC (Table 3, Figure 5), this relationship remains significant after CSF-correction.

Table 3: Summary of Pearson's correlation results of brain GSH to MoCA score

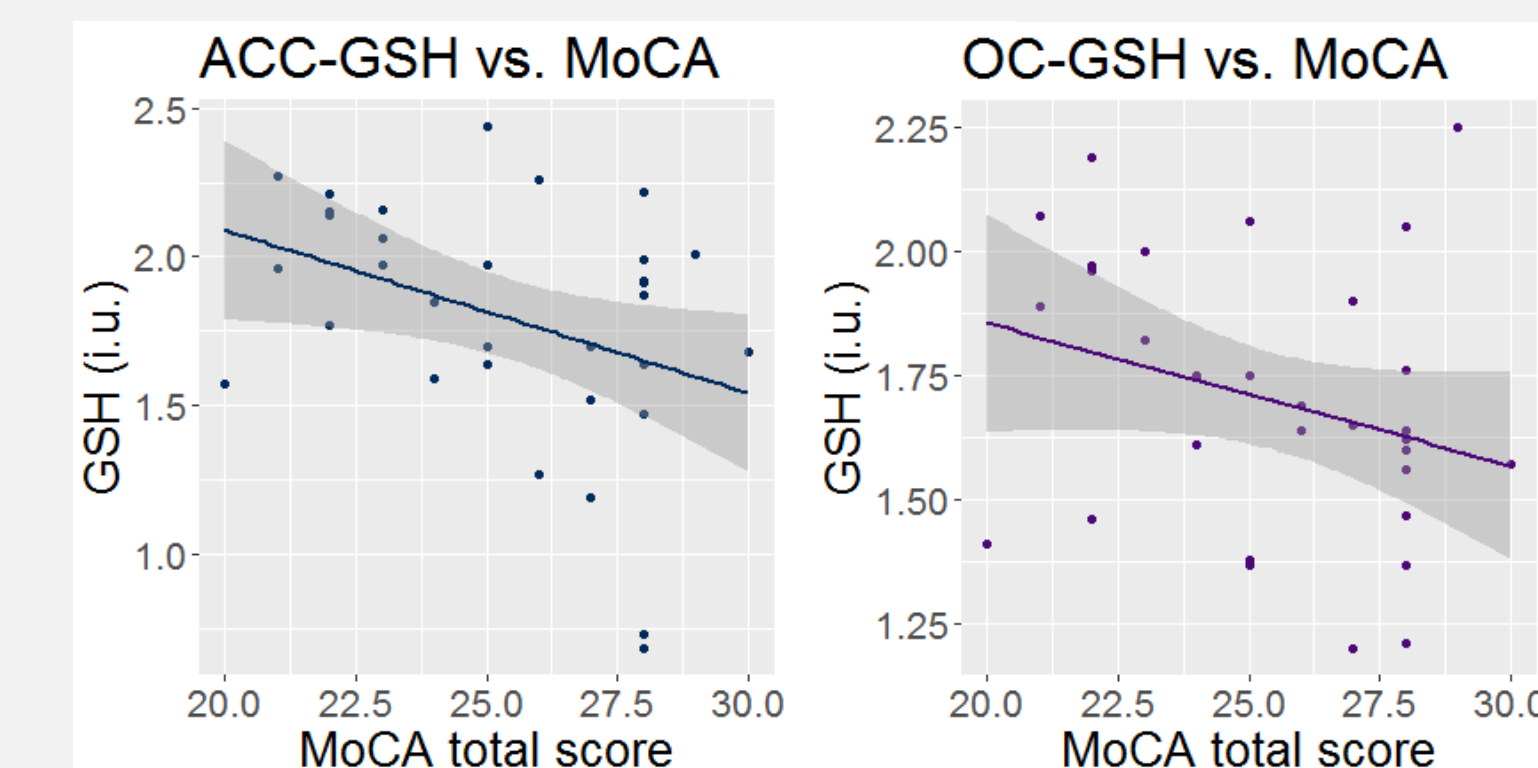| Brain GSH vs. MoCA total score	Pearson Correlation
Anterior Cingulate	r (30)=-0.44, p=.012
Anterior Cingulate (CSF-corrected)	r (30)=-0.44, p=.011
Occipital Cortex	r (29)=-0.39, p=.031
Occipital Cortex (CSF -corrected)	r (29)=-0.32, p=.08

Figure 5: scatterplots of of brain ACC-GSH vs. MoCA score (left, line of best fit r (30)=-0.44, p=.012 with 95% confidence interval); and OC-GSH vs. MoCA score (right, line of best fit r (30)=-0.39, p=.031 with 95% confidence interval).

Implications

- Preliminary data suggests an upregulation in ACC-GSH in mVCI, suggesting a compensatory increase in antioxidants in view of oxidative stress previously reported in these patients
- Additional participants are needed to confirm findings
- Findings may suggest the GSH antioxidant pathway as a therapeutic target for prevention of vascular cognitive impairment and vascular dementia