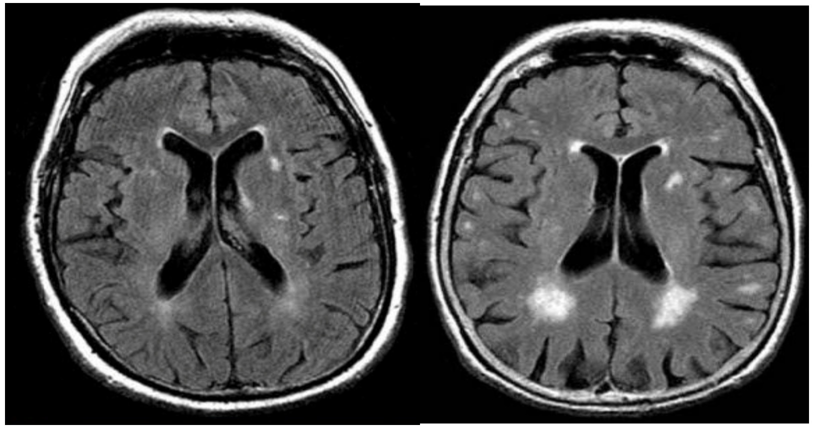
Preliminary CVR Findings from *(cerebrovascular reactivity)* the Canadian White Matter Hyperintensity Study

Joan Saary, MD, PhD, FRCPC, FACOEM, FAsMA
Kayley Marchena-Romero, MSc
Victoria Tucci, BSc (candidate)
Sandra Black, O.C., O.Ont., Hon DSc., MD, FRCP(C), FRSC, FAAN, FAHA, FANA
Bradley MacIntosh, PhD



Defence Research and Development Canada
Recherche et développement pour la défense Canada
University of Toronto
Sunnybrook Research Institute
White Matter Hyperintensity Study

The Team

Joan Saary, MD, PhD, FRCPC, FACOEM, FAsMA[1,4]
Sandra Black, O.C., O.Ont., Hon DSc., MD, FRCP(C),FRSC, FAAN, FAHA, FANA[3]
Oshin Vartanian, PhD[2]
Shawn Rhind, PhD[2]
Joel Ramirez, PhD[3]
Gary Gray, MD, PhD[1]
Bradley MacIntosh, PhD[3]
Fuqiang Gao, MD[3]
Maged Goubran, PhD[3]
Shamus Allen, BEng, BSc CD[1];
Miriam Palmer, MSc[1];
Christopher Scott, MSc[3];
Kayley Marchena-Romero, MSc[3]
Melissa Holmes, HBSc[3]
Victoria Tucci, BSc (candidate)[5]

1. Canadian Forces Environmental Medicine Establishment, Toronto Canada
2. Defence Research and Development, Toronto, Canada
3. Sunnybrook Research Institute, Toronto Canada
4. University of Toronto, Division of Occupational Medicine
5. McMaster University

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Disclosures

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ADM (DRDC)/People SFA:

The Assistant Deputy Minister (Defence Research and Development Canada)/ People (strategic focus area)

I will not discuss off-label use or investigational use in my presentation

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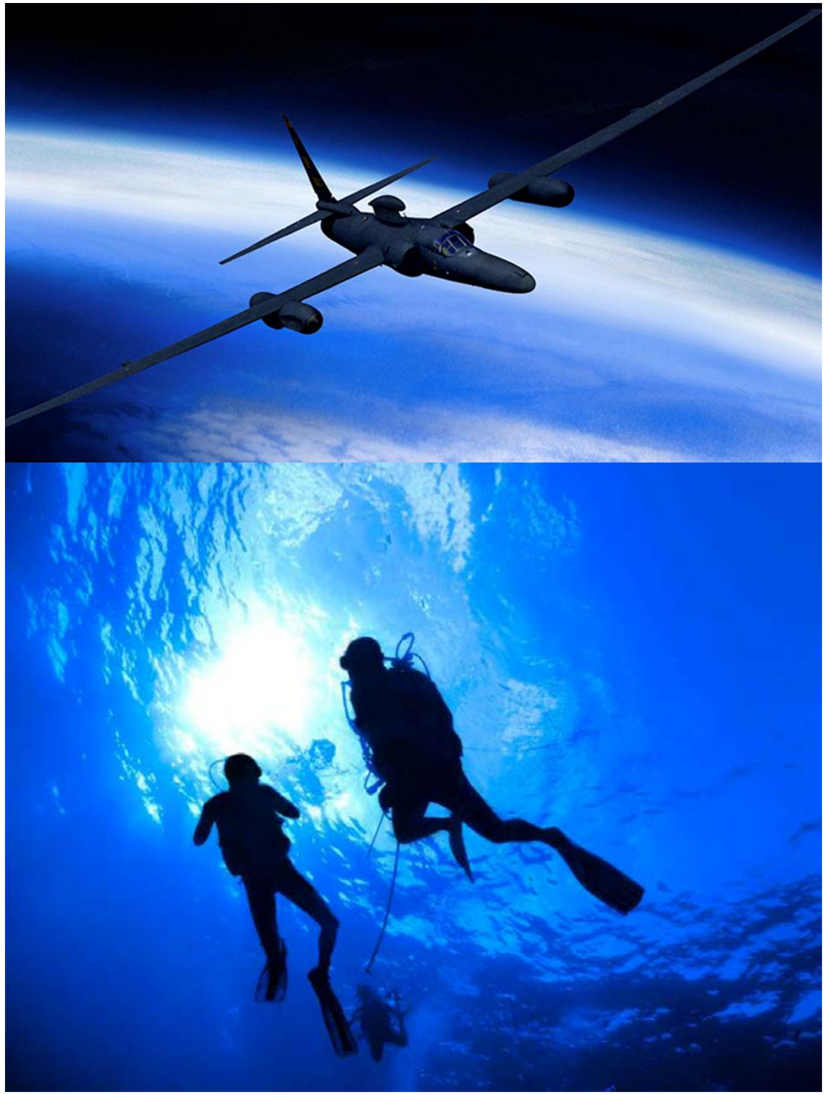
White Matter Hyperintensity Study

Background

White matter hyperintense lesions in the brain:

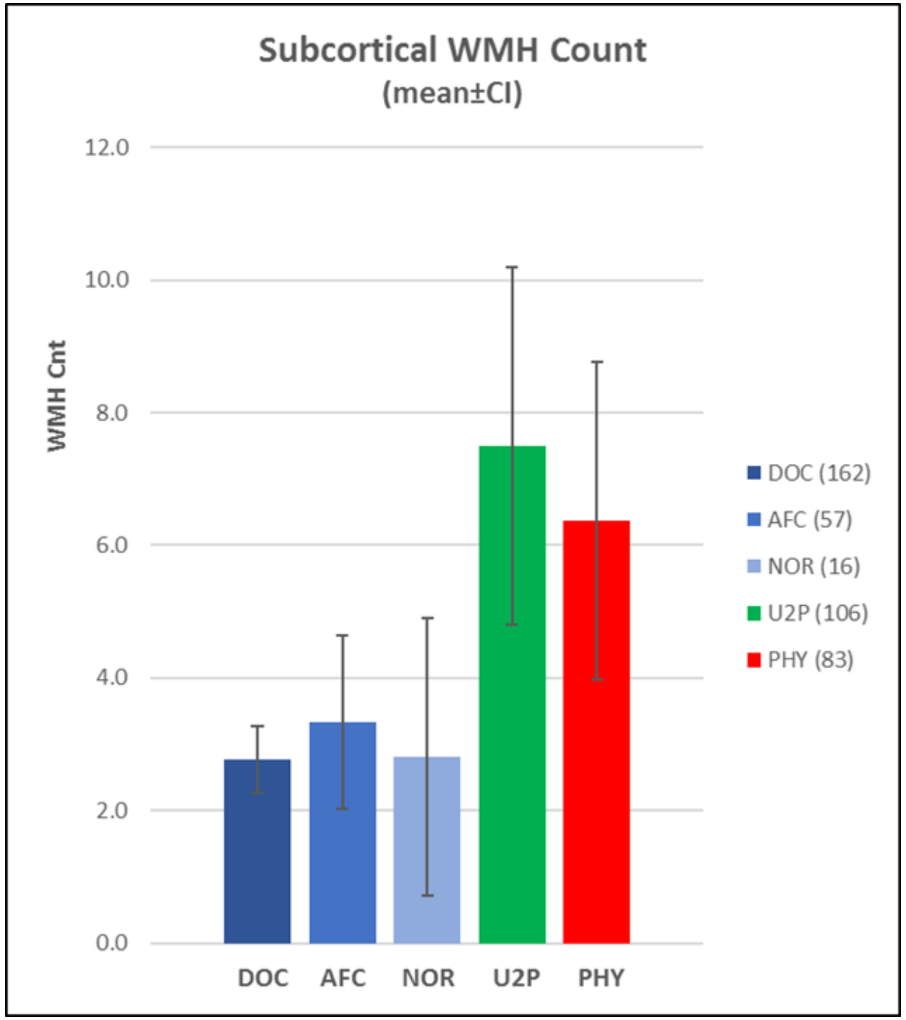
- are common in older adults
- are rarely found in young, healthy individuals
- have been found in individuals with occupational exposure to decompression stress



Background

U-2 pilots: subtle, sub-clinical decrements on cognitive testing that was correlated with increased WMH burden.

The long-term of developing consequences WMH at a relatively young age are unknown.



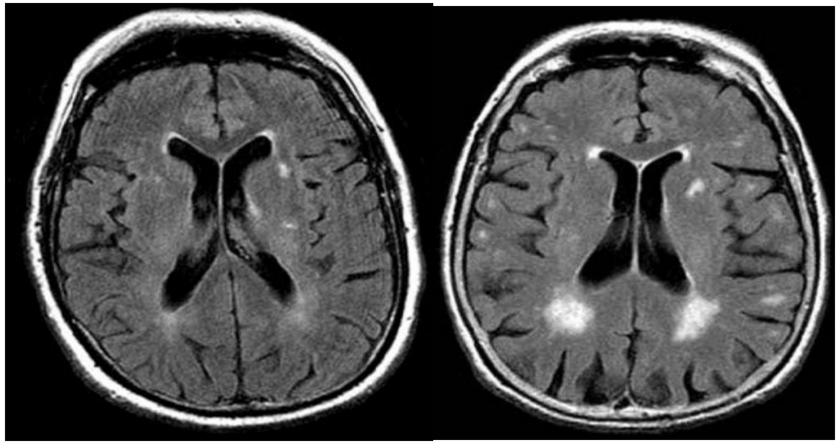
- *McGuire et al. Neurol 2013;81:729-735*
- *McGuire et al. Ann Neurol 2014;76:719-726*

DOC – doctorate controls
U2P – U-2 pilots
PHY – aerospace operational physiologists
AFC – aircrew fundamental course students

Significantly increased WMH count in U2 Pilots & Aerospace Physiologists

White Matter Hyperintensities

- **Etiology and pathophysiology are not well understood**
- Causes hypothesized:
  - **chronic ischemia** (ie restricted blood flow) from small vessel disease then leads to myelin loss and the characteristic appearance.
  - **Inflammation and amyloid angiopathy** (deposition of protein in blood vessels) (Gouw et al 2011; Prins et al, 2015; Simpson et al, 2007)



Hyperintense Lesions on T2 FLAIR

This Study

Day 1 (Wed): Travel to Toronto

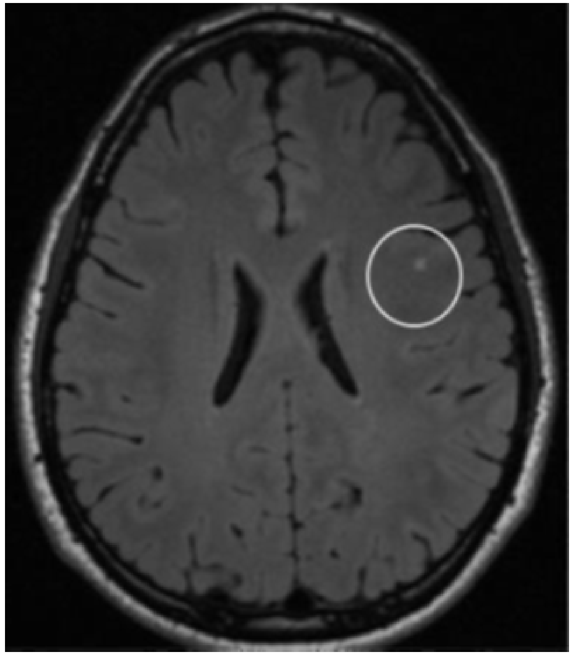
- Bring flight log book
- No alcohol, otherwise usual routine, coffee ok

Day 2 (Thurs): MRI brain scan

Day 3 (Fri):

- Occupational exposure history questionnaire;
- Physical exam;
- Computer-based cognitive testing;
- Blood sampling for peripheral biomarkers and cardiac risk markers;
- Agitated saline contrast echo to rule out PFO

Day 4 (Sat): Travel



Demographics

- All male
- Mean age 35 (range 25-57)
- All Caucasian except 1 Asian
- All non-smokers
- Most use EtOH sparingly (1-5 drinks per week)

Whole Brain Descriptives

Total N=26	Mean	Median	SD	Min	Max
Age, years	34.615	31.000	8.927	25.000	57.000
Supratentorial Intracranial Volume	1360.605	1351.241	94.501	1137.073	1576.999
White Matter	506.439	509.850	49.613	387.875	594.982
Gray Matter	656.744	647.571	52.209	575.563	807.581
Sulcal Cerebrospinal Fluid	178.884	181.078	29.712	123.934	250.938
Ventricular Cerebrospinal Fluid	18.168	13.821	15.348	6.509	87.455
Total White Matter Hyperintensities	0.330	0.288	0.293	0.293	0.281
Periventricular White Matter Hyperintensities	0.248	0.164	0.260	0.000	1.185
Deep White Matter Hyperintensities	0.082	0.054	0.096	0.000	0.353
Enlarged Perivascular Spaces	0.041	0.039	0.024	0.000	0.097

All data is presented in mL unless otherwise indicated.

TABLE 2. Mean WMH Volume and Count by Group[a]

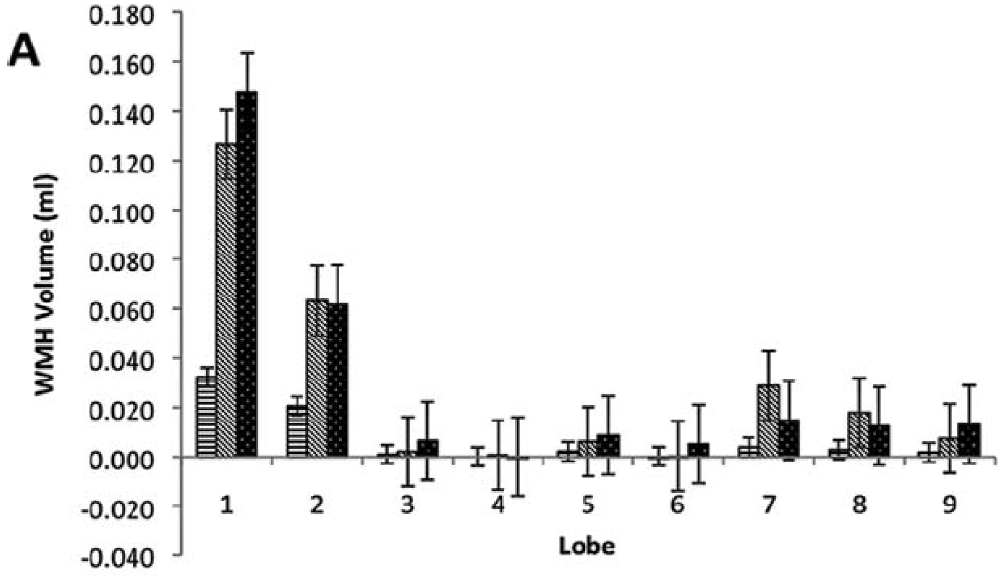
WMH	DOC, Mean ± SD (CI)	PHY, Mean ± SD (CI)	U2P, Mean ± SD (CI)	Mann–Whitney–Wilcoxon Significance, 2-Tailed		
				DOC:PHY	DOC:U2P	U2P:PHY
All subjects	n = 148	n = 83	n = 105			
Volume, ml	0.032 ± 0.058 (0.022–0.042)	0.126 ± 0.404 (0.040–0.212)	0.147 ± 0.296 (0.090–0.204)	$p = 0.011$	$p < 0.001$	$p = 0.237$
Count	2.6 ± 3.1 (2.1–3.1)	6.4 ± 11.1 (4.0–8.8)	9.7 ± 18.3 (6.2–13.2)	$p = 0.019$	$p < 0.001$	$p = 0.091$
All minus HTN/HLD	n = 132	n = 73	n = 85			
Volume, ml	0.033 ± 0.060 (0.023–0.043)	0.130 ± 0.428 (0.032–0.228)	0.114 ± 0.208 (0. 070–0.158)	$p = 0.045$	$p = 0.003$	$p = 0.397$
Count	2.6 ± 3.1 (2.1–3.1)	6.3 ± 11.5 (3.7–9.0)	7.4 ± 12.7 (4.7–10.1)	$p = 0.068$	$p < 0.001$	$p = 0.235$
All minus NDCS	n = 148	n = 81	n = 83			
Volume, ml	0.032 ± 0.058 (0.022–0.042)	0.126 ± 0.409 (0.038–0.214)	0.134 ± 0.303 (0.069–0.199)	$p = 0.039$	$p = 0.003$	$p = 0.404$
Count	2.6 ± 3.1 (2.1–3.1)	6.2 ± 11.1 (3.8–8.7)	9.2 ± 18.6 (5.2–13.2)	$p = 0.064$	$p < 0.001$	$p = 0.106$

[a]All subjects; all subjects after exclusion of HTN or HLD; all subjects after exclusion of clinical NDCS.
CI = confidence interval; DOC = doctorate degree, healthy, age-controlled volunteers; HLD = hyperlipidemia; HTN = hypertension; NDCS = neurological decompression sickness; PHY = altitude chamber operations personnel; SD = standard deviation; U2P = U-2 pilots; WMH = white matter hyperintensity.

Regional Volumetrics

N=26	Frontal		Temporal		Parietal		Occipital	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
White Matter	167.220	20.589	142.721	16.640	148.527	16.697	47.970	6.509
Gray Matter	223.277	19.497	207.173	16.210	153.053	15.266	73.242	8.256
Cerebrospinal Fluid	84.360	18.649	42.042	11.494	54.708	11.710	15.942	3.117
White Matter Hyperintensities	0.119	0.138	0.046	0.093	0.034	0.062	0.131	0.132
Enlarged Perivascular Spaces	0.004	0.005	0.036	0.025	0.003	0.005	0.000	0.001

All data is presented in mL unless otherwise indicated.



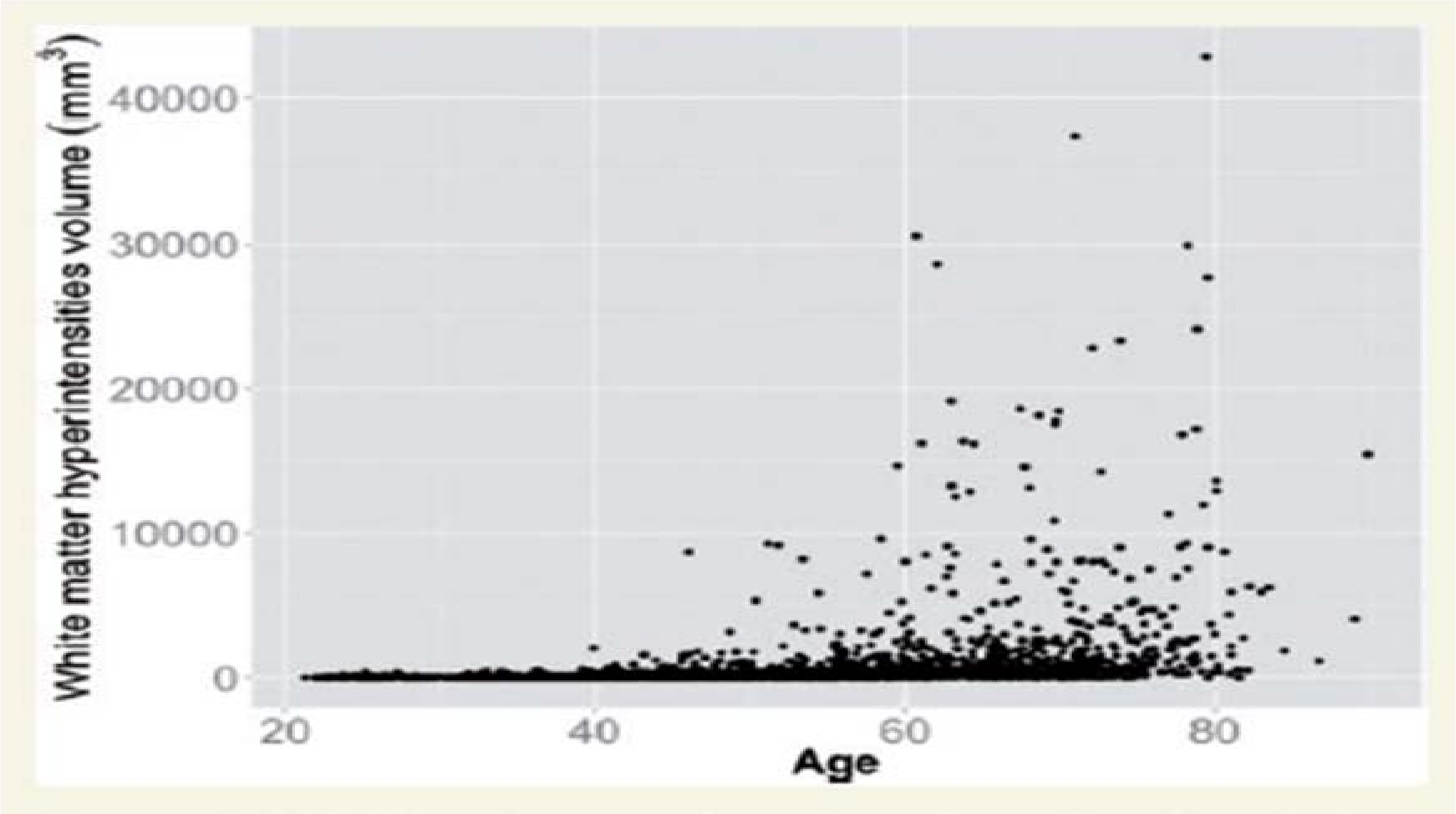
Screen capture of data reported in McGuire et al., *Annals Neurology*, 2014.

Lobe

FIGURE 3: Comparison of (A) white matter hyperintensity (WMH) volume and (B) WMH count per lobe by group. Horizontal stripes = doctorate degree, healthy, age-controlled volunteers; diagonal stripes = altitude chamber operations personnel; dots = U-2 pilots. Mean values are given with standard error. 1 = total; 2 = frontal; 3 = insular; 4 = interhemispheric; 5 = limbic; 6 = occipital; 7 = parietal; 8 = sublobar; 9 = temporal.

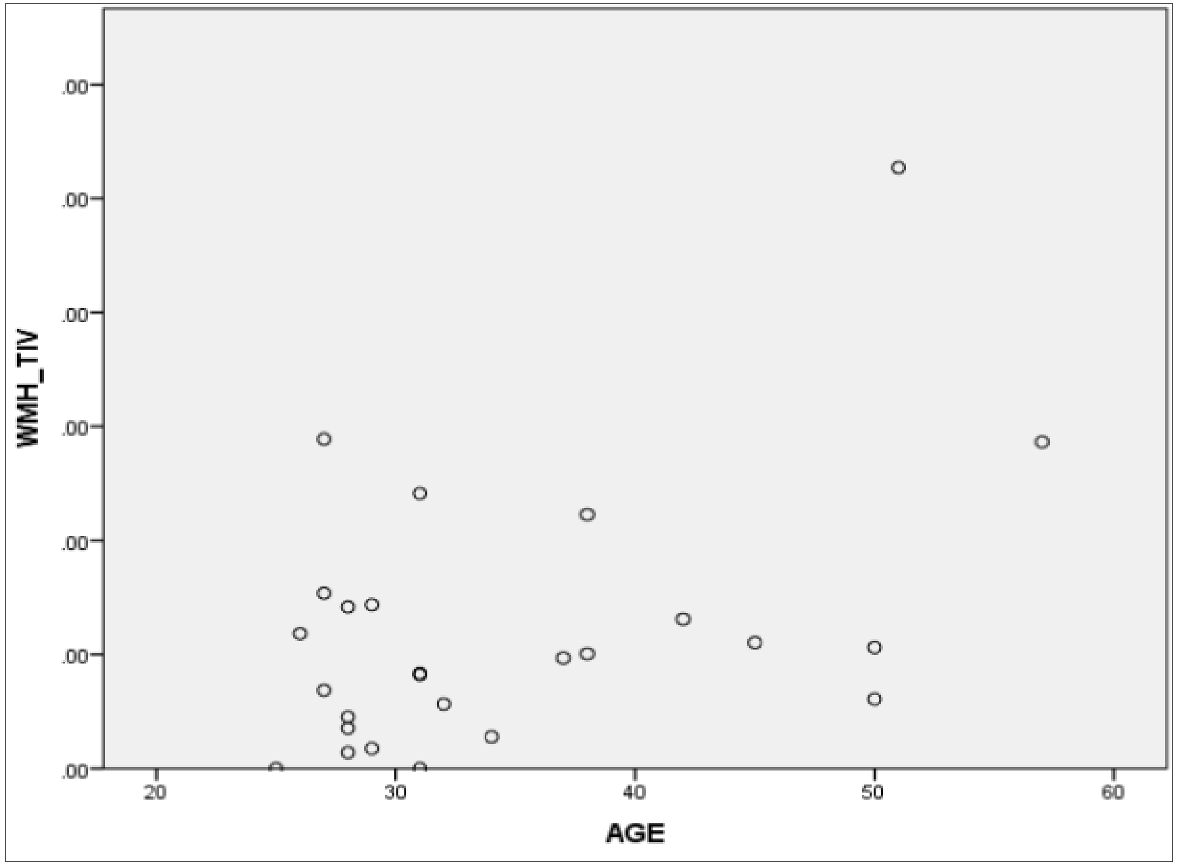
Age & WMH

General Populations



Ref: *Habes et al, 2016*

Age x WMH Volume Scatterplot (n=26)



Correlations with Age

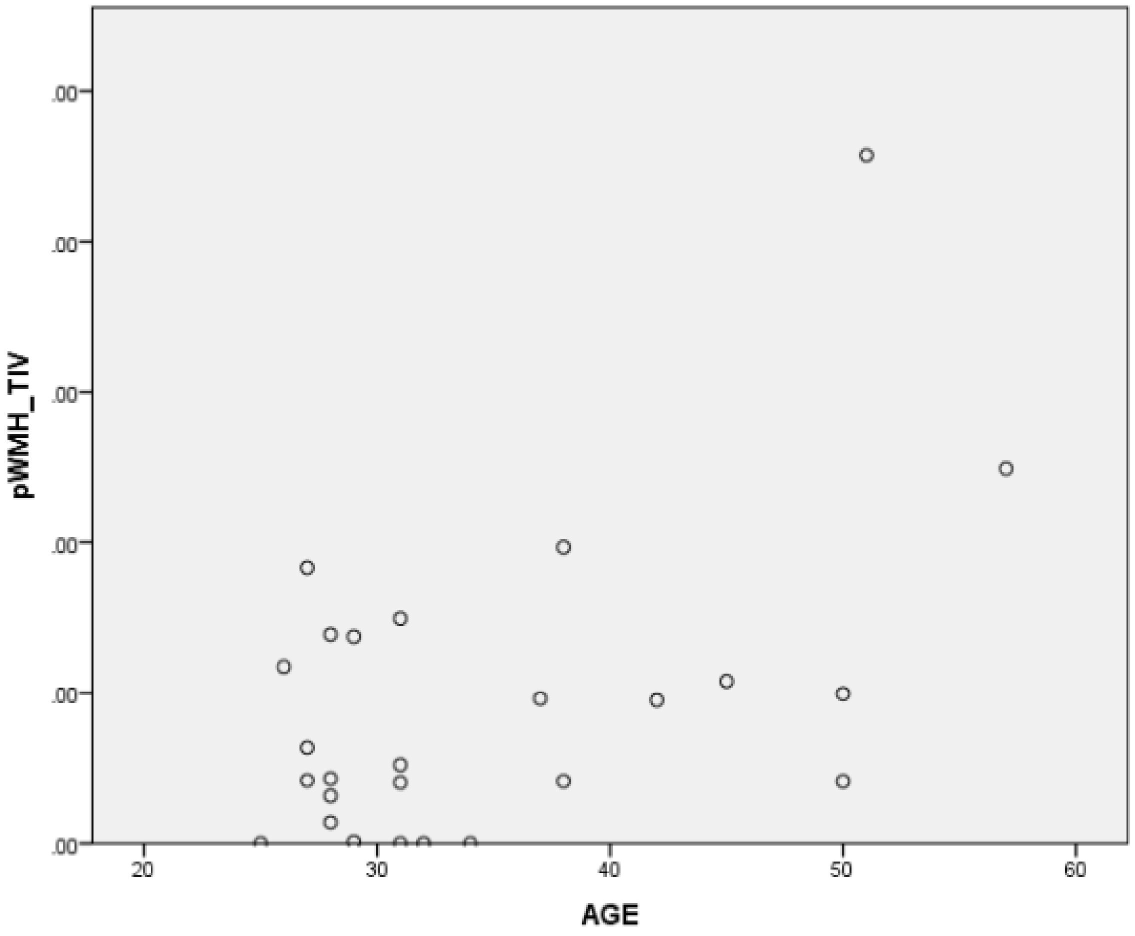
Correlations

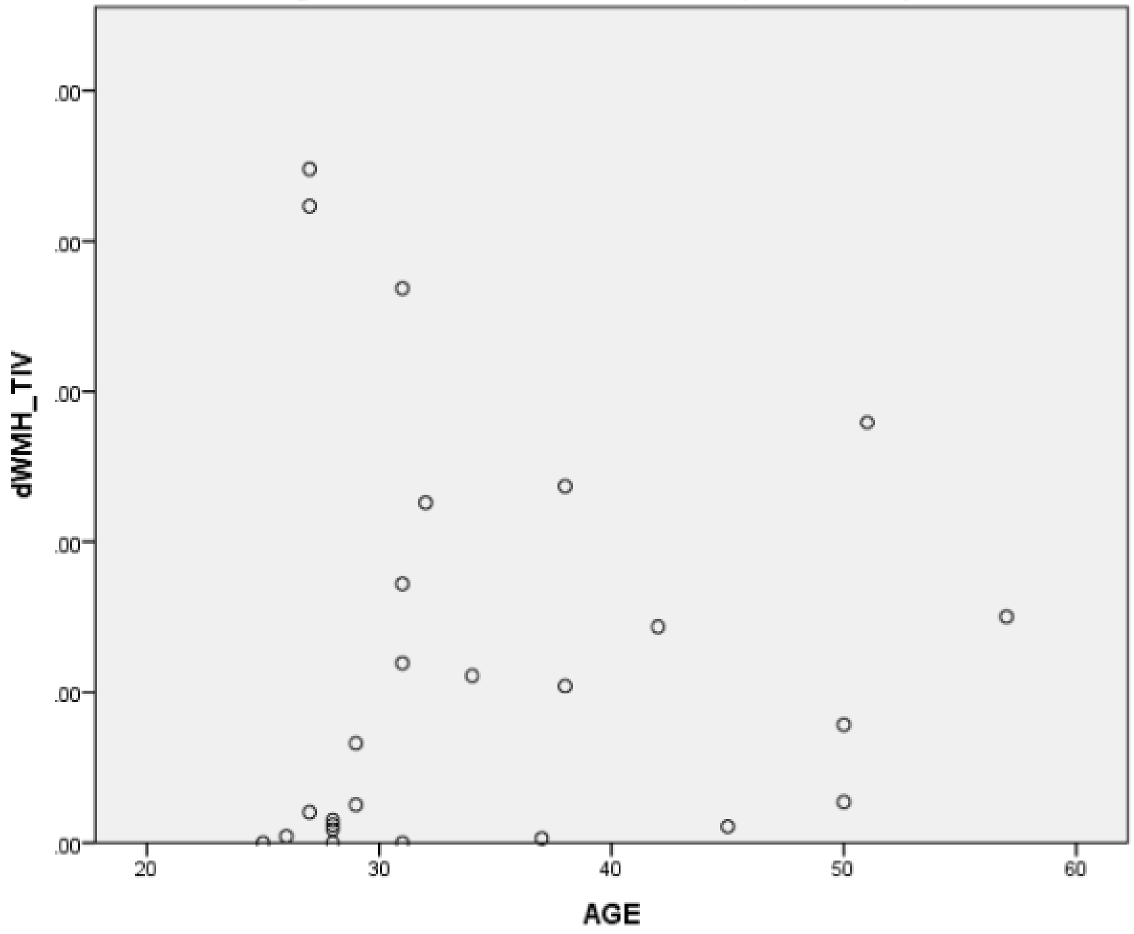
		AGE	ST_TIV	NAWM	NAGM	sCSF	vCSF	pWMH	dWMH	WMH	PVS
AGE	Pearson Correlation	1	-.071	-.020	-.358	.398*	.061	.515**	.016	.450*	.131
	Sig. (2-tailed)		.729	.923	.073	.044	.766	.007	.940	.021	.524
	N	26	26	26	26	26	26	26	26	26	26

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

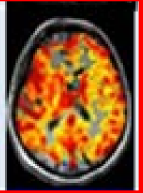
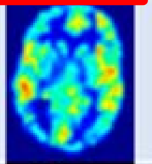
Periventricular vs Deep WMH by age





Scatterplots of age by MRI-derived head-size corrected periventricular WMH volumes (LEFT) and deep WMH volumes (RIGHT) in RCAF pilots (n=26).

MRI Sequences Used

DTI (Diffusion Tensor Imaging)	Measures the flow and direction of water in the brain	Used to measure white matter tract health	
CVR (Cerebrovascular Reactivity)	Measures the change of blood flow in response to a stimulus (CO_2)	Used to infer vascular health based on speed and pattern of responses	
pCASL (Pseudo-Continuous Arterial Spin Labelling)	Tracks blood as it flows from the neck into the brain	Used to measure cerebral blood flow	
Resting state f-MRI	Provides a measure of brain activity when you are doing nothing	Used to measure spontaneous brain activity during a task negative state	

Vascular Response to Hypercapnia:
Initial Dilation

Increased CO_2 causes an increase in cerebral blood flow

Mild to Moderate Hypercapnia

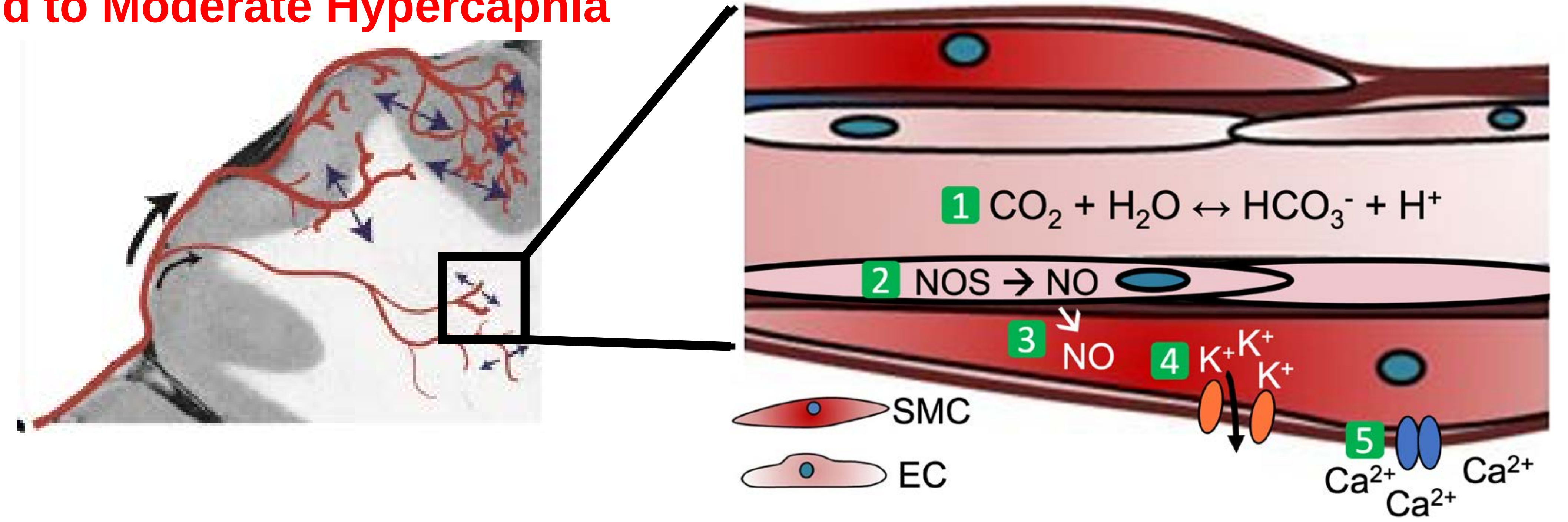
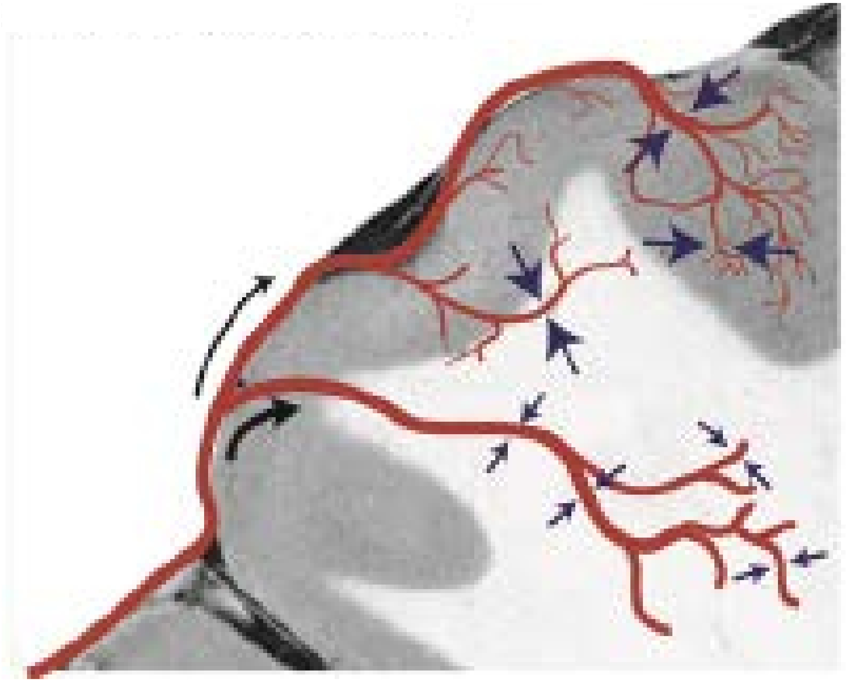
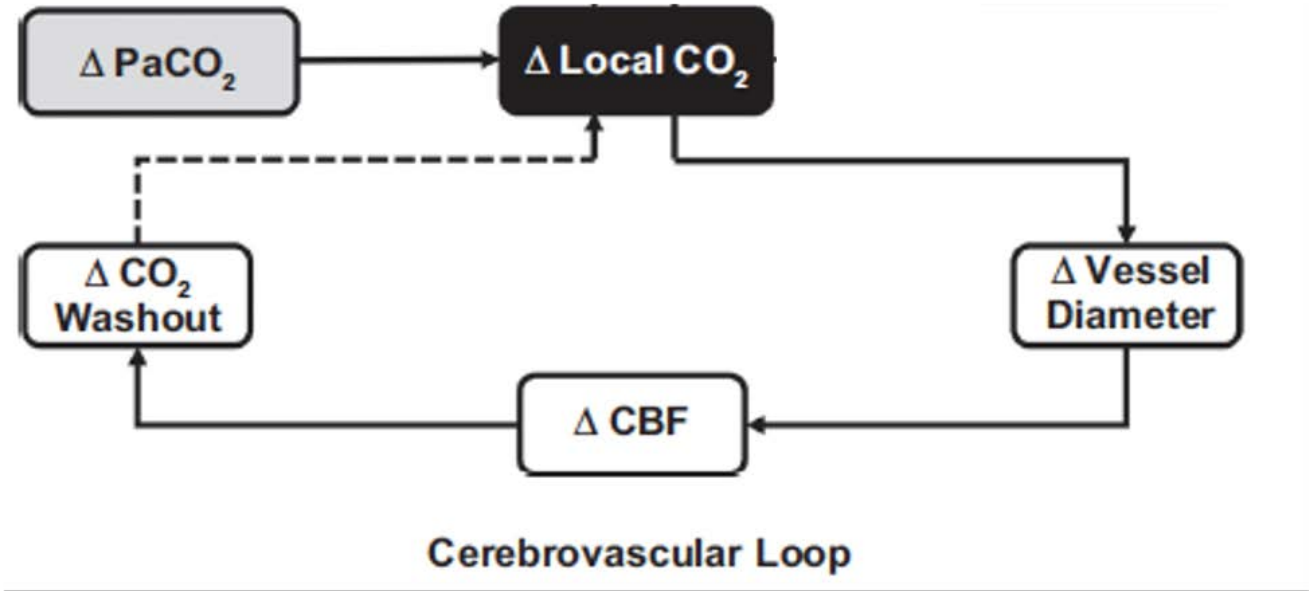


Image retrieved from Bhogal et al. *Neuroimage.* 2015

Cerebrovascular Loop Clears CO_2

Return to Normocapnia





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Positive Effect
Negative Effect

Image retrieved from Bhogal et al. *Neuroimage.* 2015
[1] MacKay et al. *Adv Physiol Educ*. 2016

Cerebrovascular Reactivity

- Is defined as the change in blood flow in response to a vasoactive stimulus
- Indicator of vascular health

Cerebrovascular Reactivity in Special Operations Forces Combat Soldiers

Patricia R. Roby,[1,2] Avinash Chandran,[1,6] Nikki E. Barczak-Scarboro,[1,2] Stephen M. DeLellis,[3] Cassie B. Ford,[1,7] Marshall L. Healy,[4] Gary E. Means,[4] Shawn F. Kane,[1,5] James H. Lynch,[4] and Jason P. Mihalik[1,2]

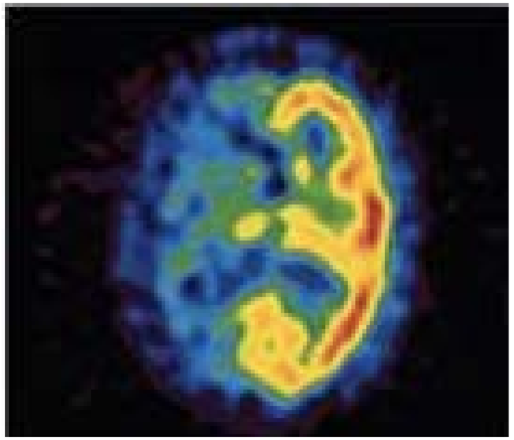
Acute Gravitational Stress Selectively Impairs Dynamic Cerebrovascular Reactivity in the Anterior Circulation Independent of Changes to the Central Respiratory Chemoreflex

*Hironori Watanabe[1], Shotaro Saito[1], Takuro Washio[1,2], Damian Miles Bailey[2,3] and Shigehiko Ogoh[1,3]**

CVR Imaging Modalities

GE SPECT/ CT System[1]

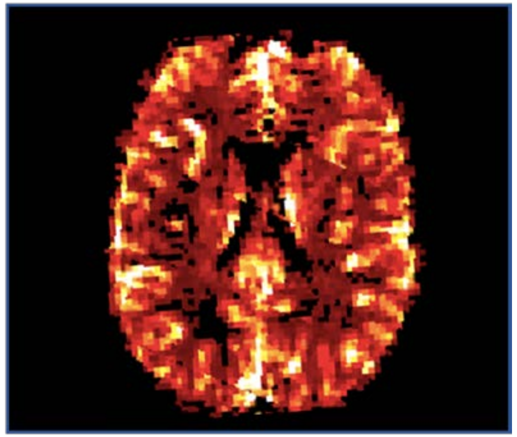
SPECT-CVR



63 y.o. male w/ right ICA occlusion[3]

Siemens Prisma MRI Scanner[2]

BOLD-CVR

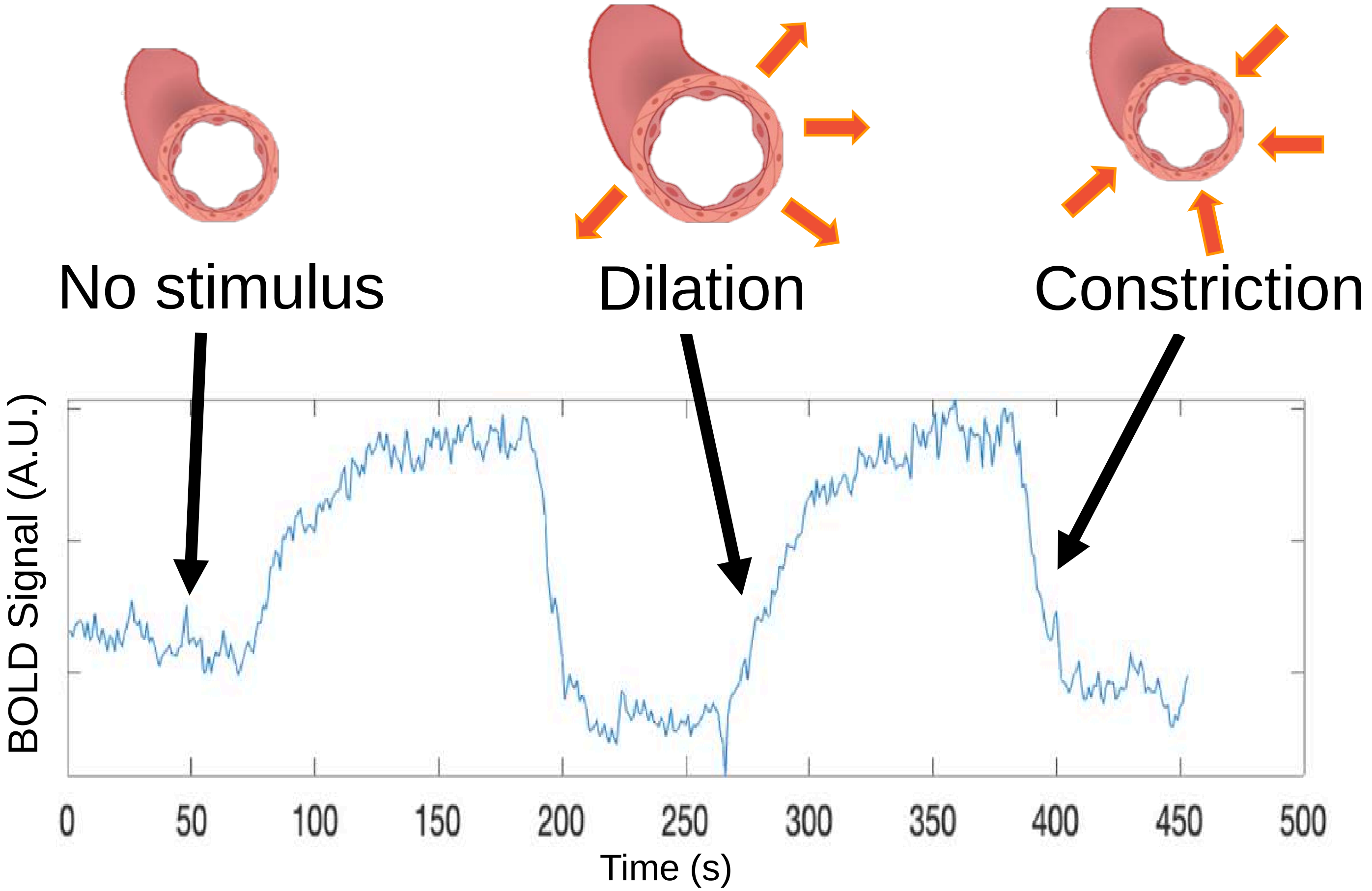


Healthy 31 y.o. RCAF pilot

[1] https://www.itnonline.com/content/ge-healthcare-introduces-performance-spectct-systems
[2] https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/3t-mri-scanner/magnetom-prisma
[3] Matano et al., *NMC Case Report Journal*, 2017

Blood Oxygenation Level Dependent (BOLD)-fMRI

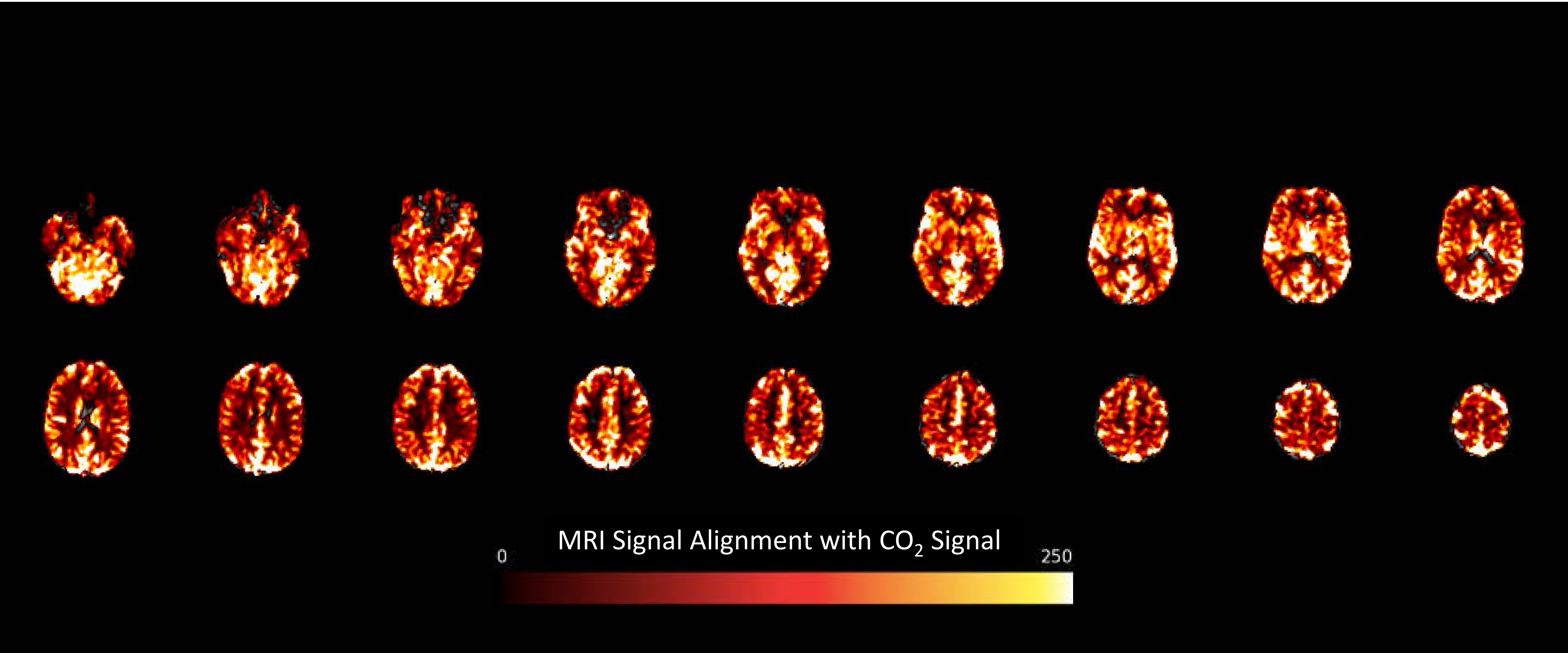
Measures change in local ratio of oxygenated blood to deoxygenated blood



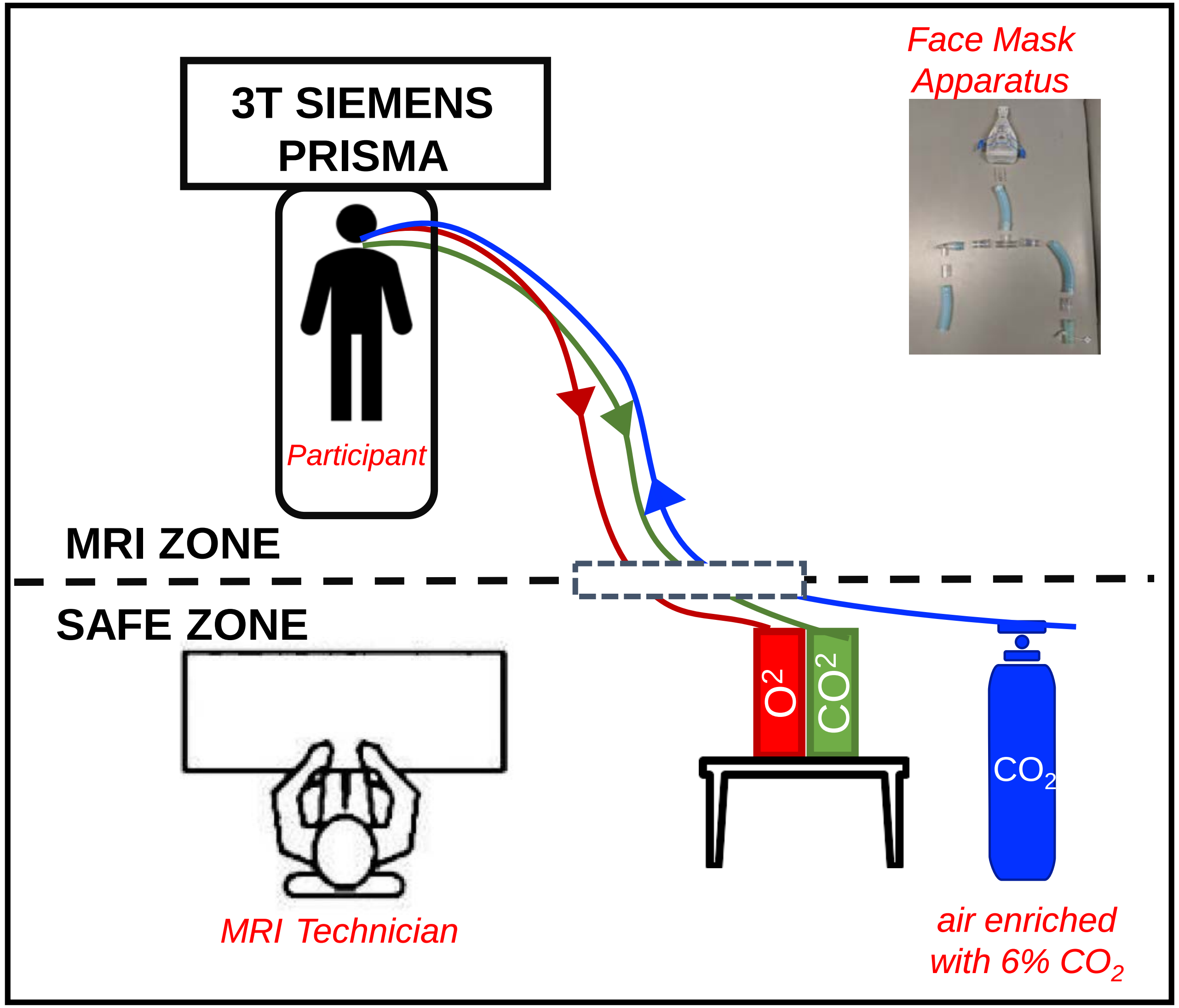
CVR signal overlayed on T1 image (grayscale)

Whole-brain CVR

in a 31-year-old male RCAF pilot

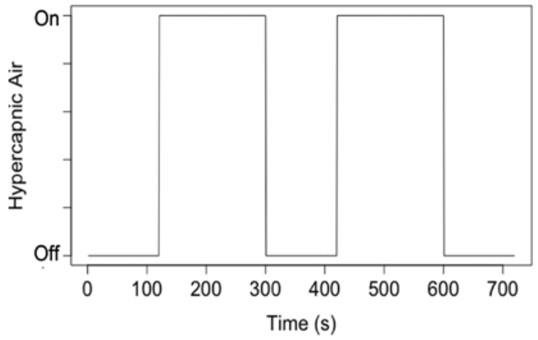


Data Collection



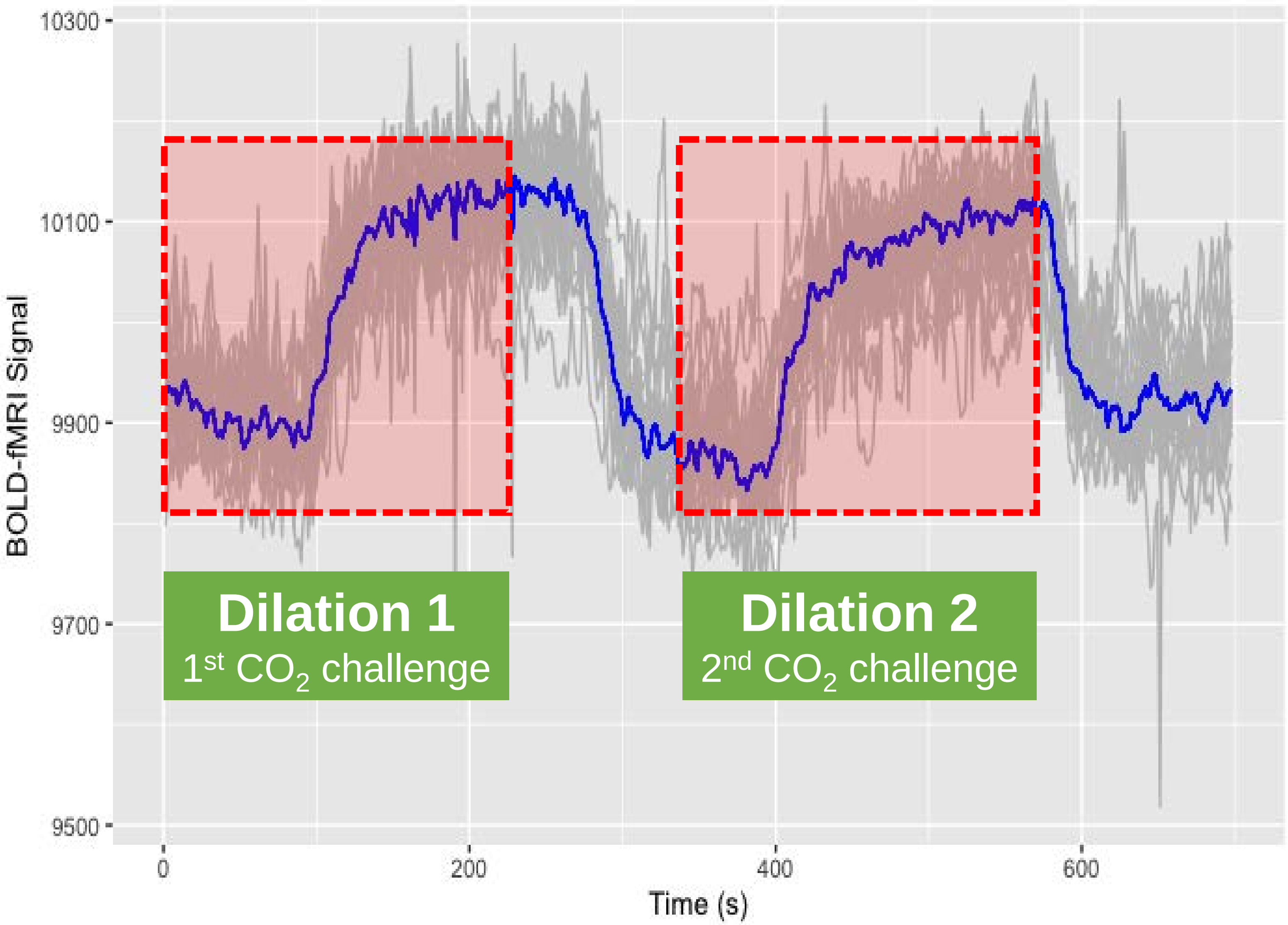
BIOPAC Monitoring System

Breathing Challenge



ON = 6% CO_2 administered 3 mins
OFF = Room air administered 2 mins

Isolating Temporal Features

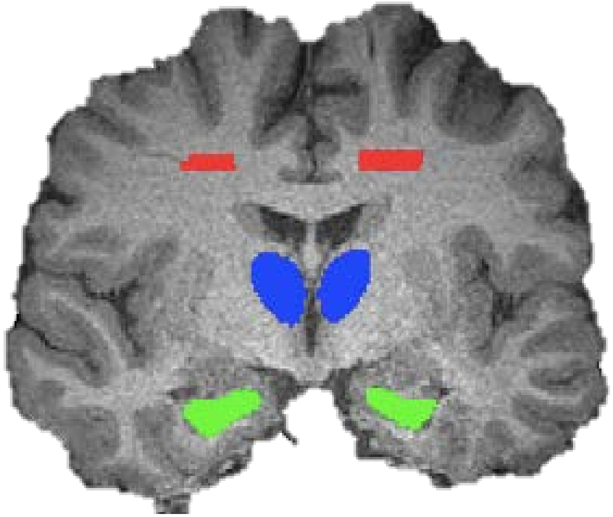


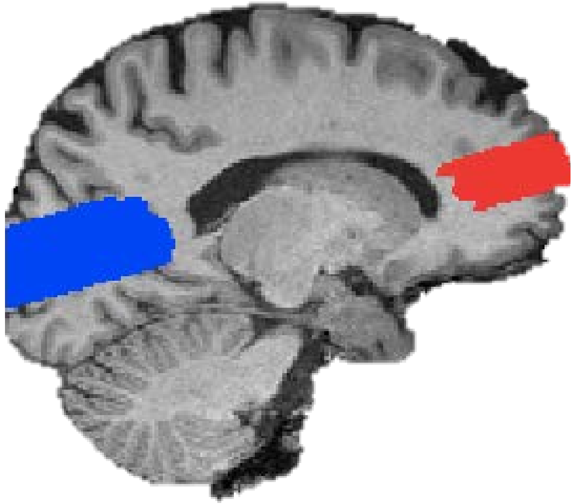
Dilation Measure

How much does BOLD signal increase?

$$\text{CVR} = \frac{\%\,\Delta\,\text{BOLD signal}}{\Delta\,\text{CO}_2\ (\text{in mmHg})}$$

Brain Regions of Interest





Centrum Semiovale

- Typically associated white matter hyperintensities[1]

Thalamus

- Responsible for relaying sensory information[2]

Hippocampus

- Pilot performance associated with hippocampal size[3]

Anterior Cerebral Artery

- Longest travel to front of brain

Posterior Cerebral Artery

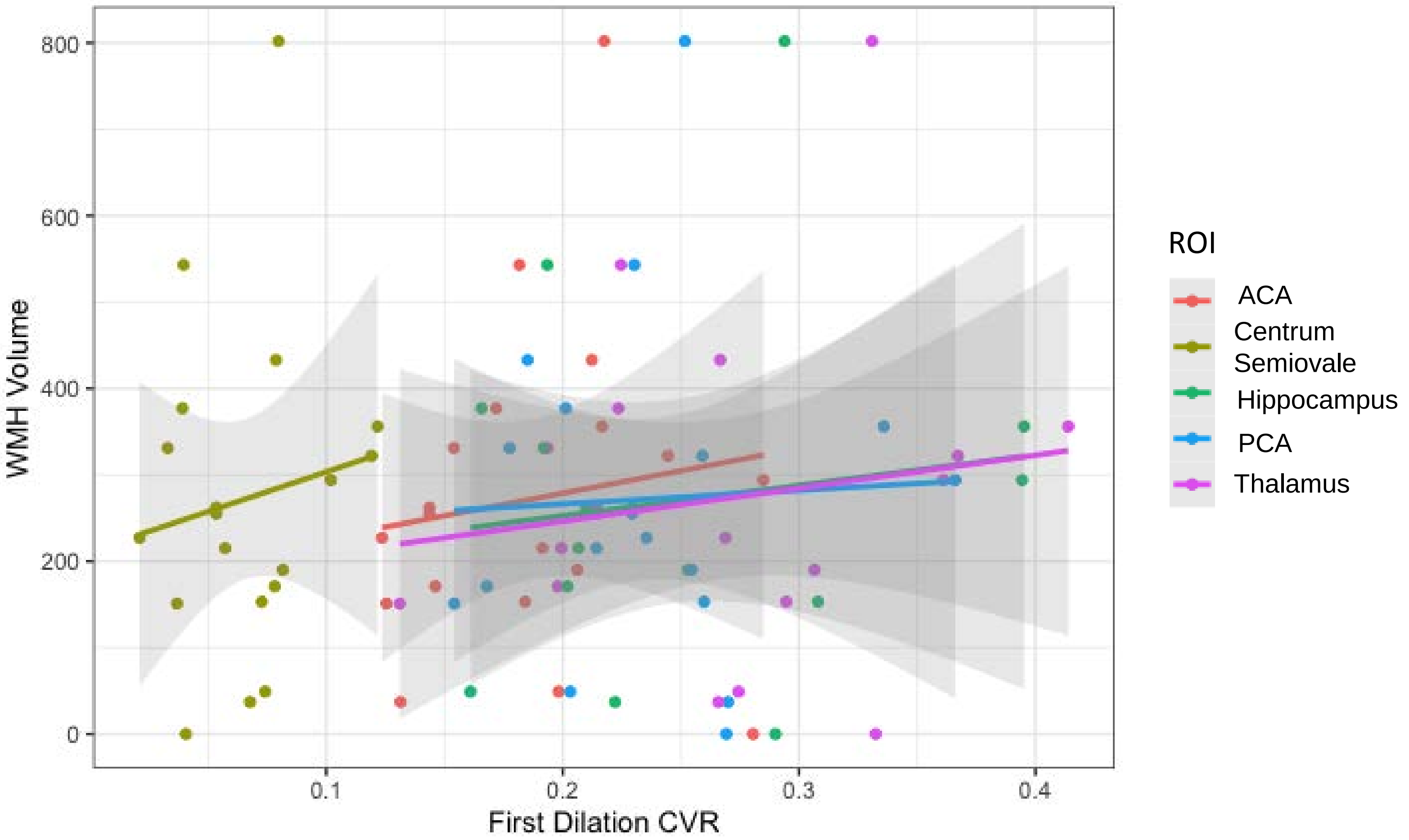
- Longest travel to back of brain

[1] Wardlaw et al. *Lancet Neurol*. 2013
[2] Torrico and Munakomi. *StatPearls*. 2021
[3] Adamson et al. *Aviat Space Environ Med.* 2012

Pilot Demographics for Preliminary Results

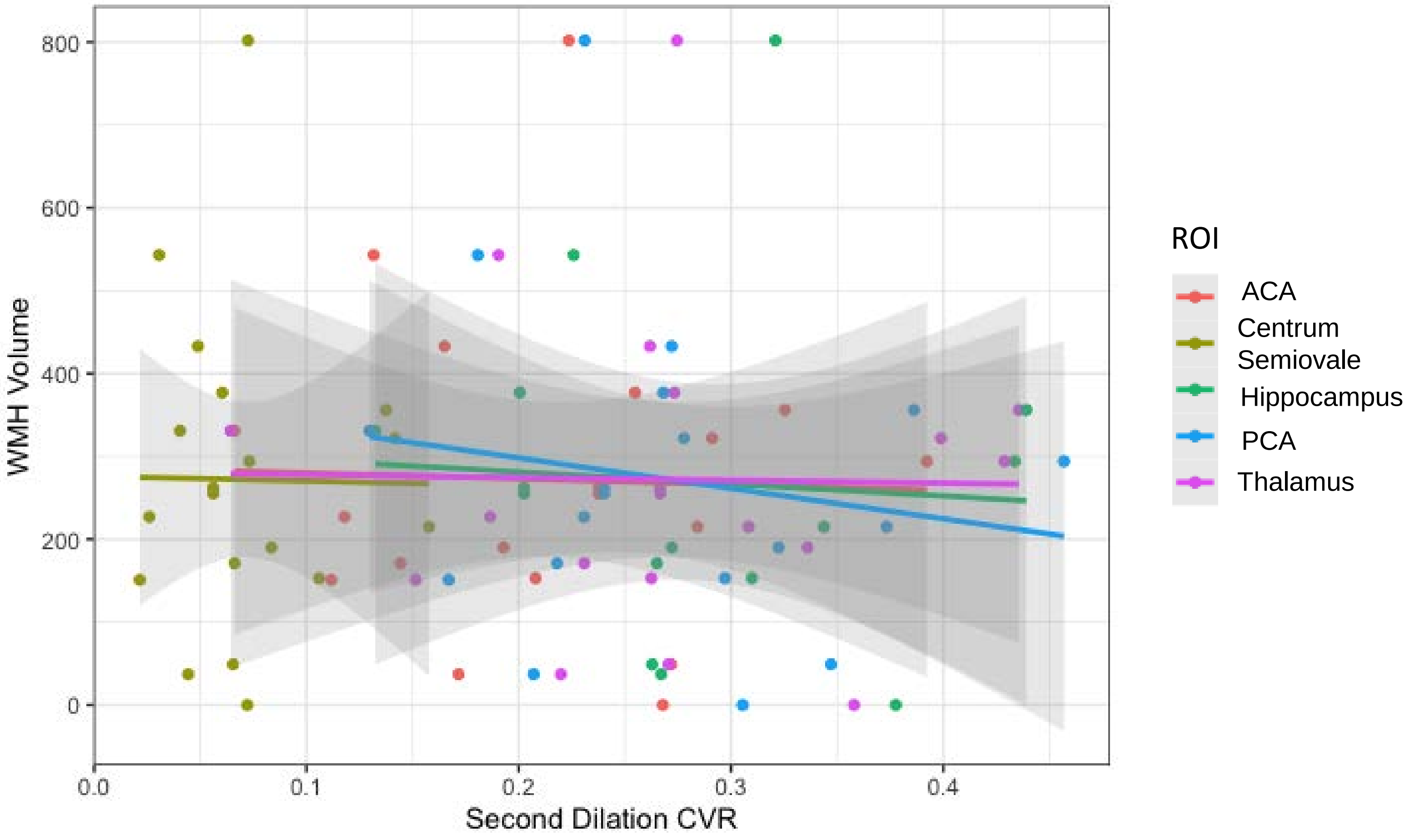
Demographic Details	
Sample Size	27
Age (years)	36 ± 8
WMH Volume (mL)	.271 ± .176

WMH Volume Not Associated with First Dilation Response



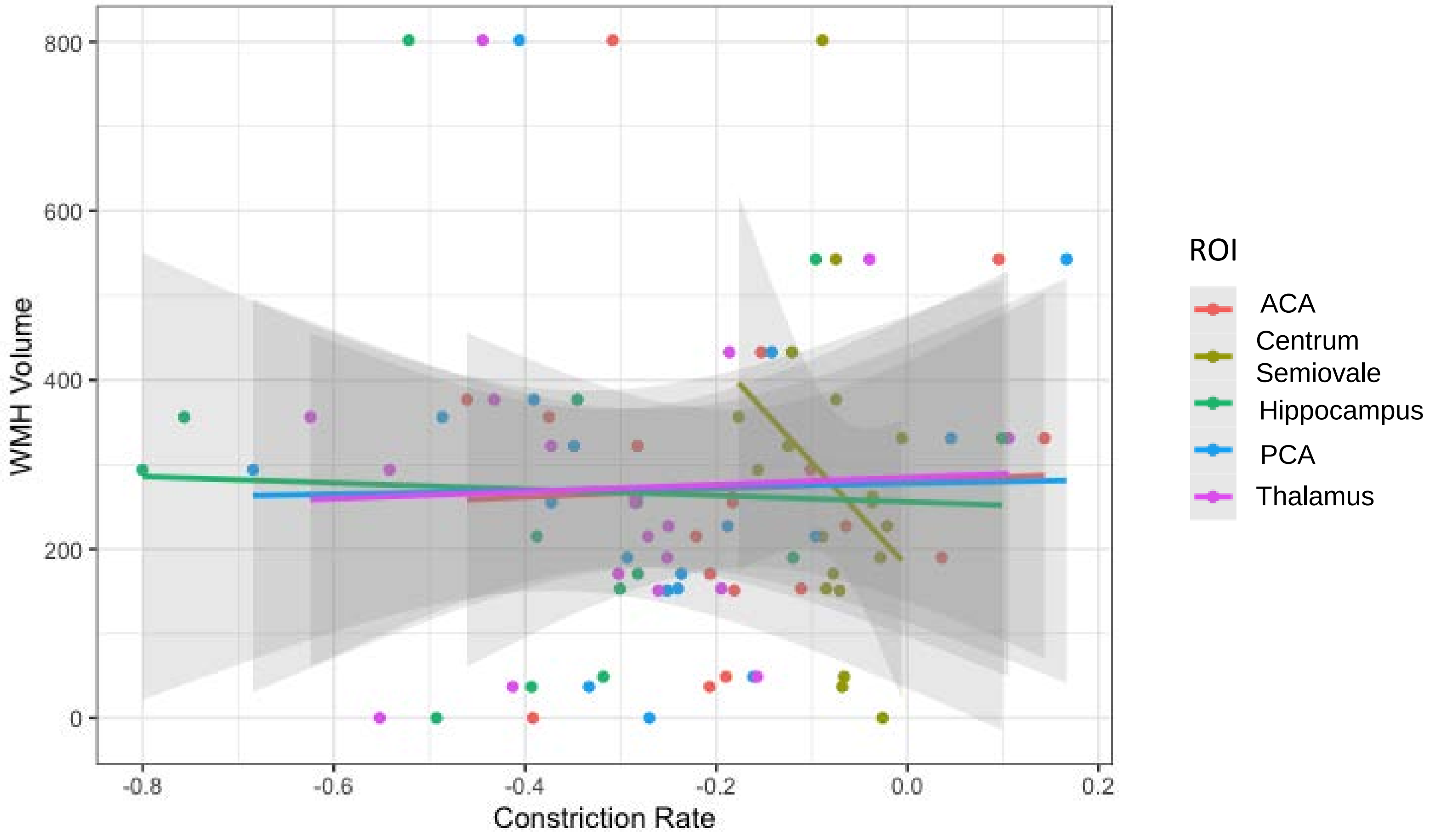
ROI	r
ACA	0.13
Centrum Semiovale	0.14
Hippocampus	0.13
PCA	0.04
Thalamus	0.15

WMH Volume Not Associated with Second Dilation Response



ROI	r
ACA	-0.01
Centrum Semiovale	-0.01
Hippocampus	-0.06
PCA	-0.16
Thalamus	-0.02

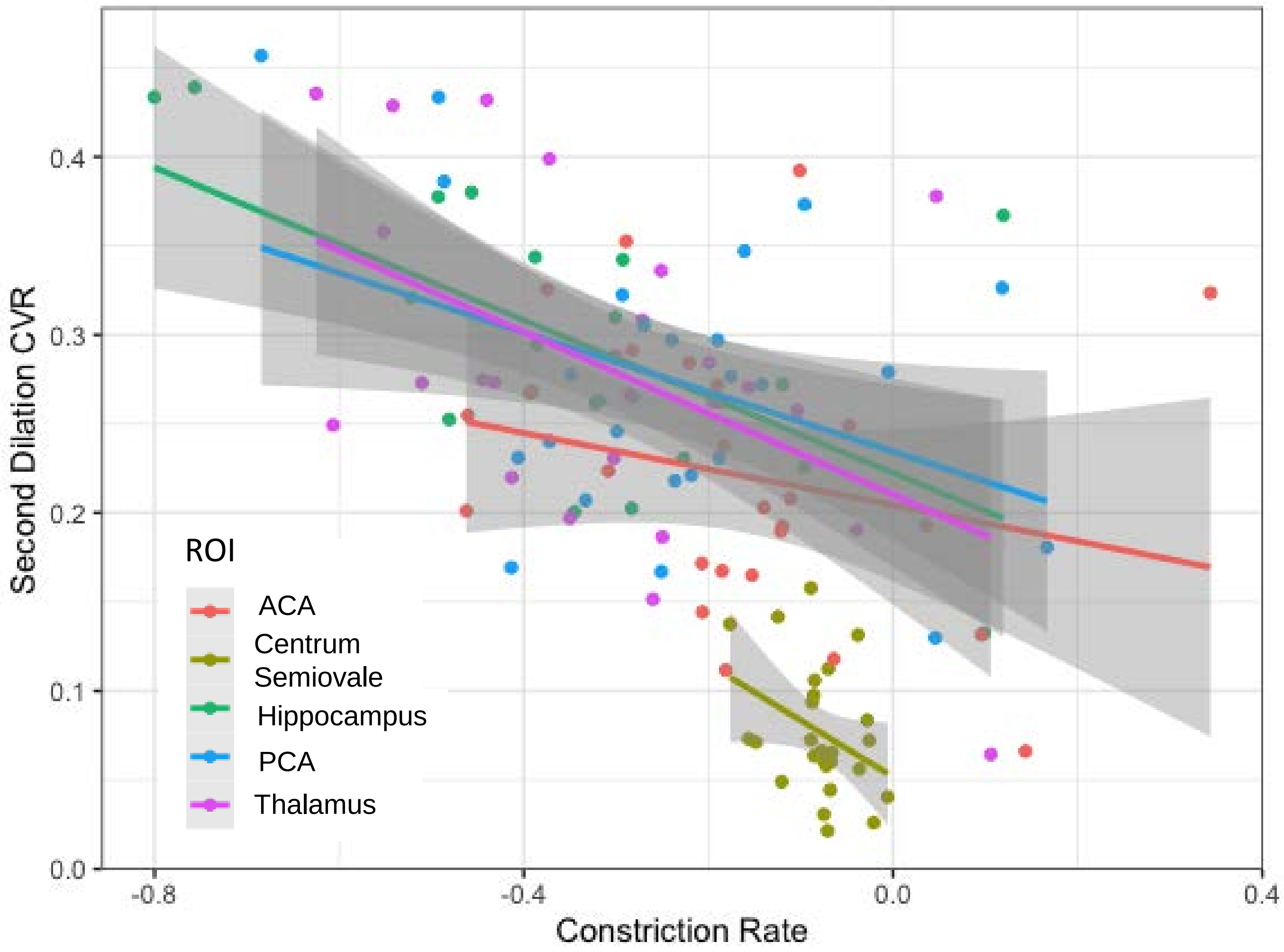
WMH Volume Not Associated with Constriction

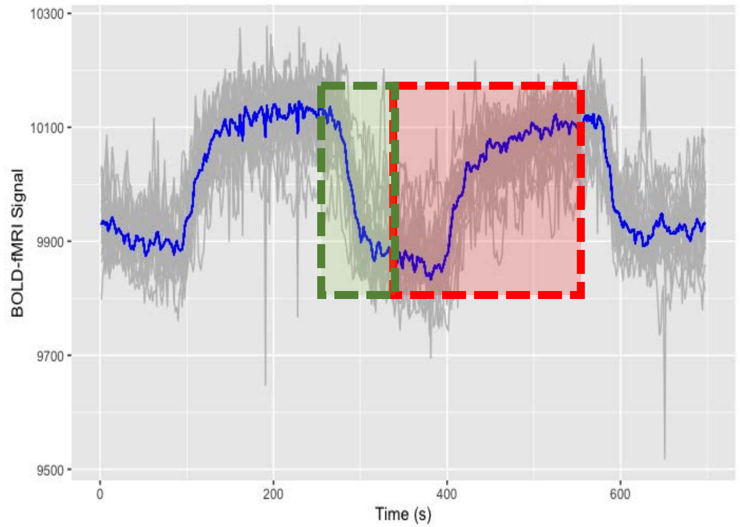


ROI	r
ACA	0.04
Centrum Semiovale	-0.30
Hippocampus	-0.04
PCA	0.02
Thalamus	0.04

Increased Responsiveness to CO2 on Second Administration

Linear association between constriction and dilation

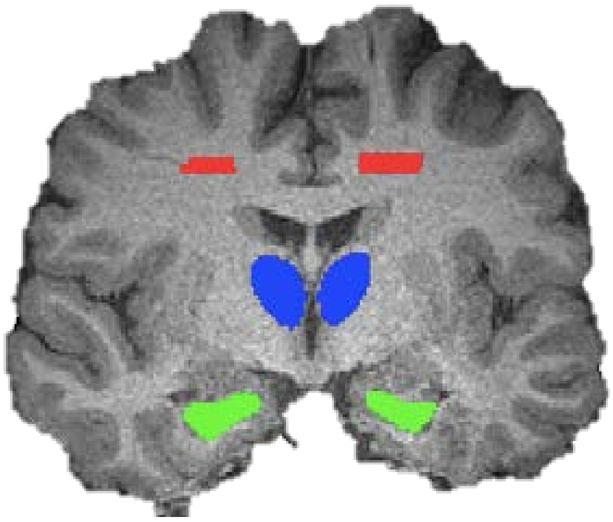


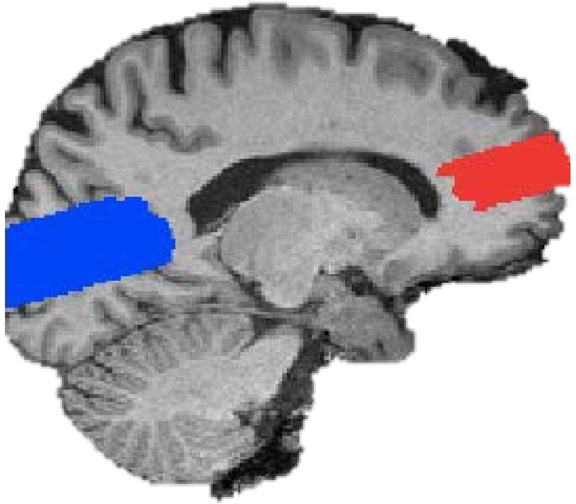


Interpretation

- Constriction is strongly associated with dilation
- Faster constriction predicts a greater CVR response
- Hippocampus showed strongest association

Recall: Brain Regions of Interest





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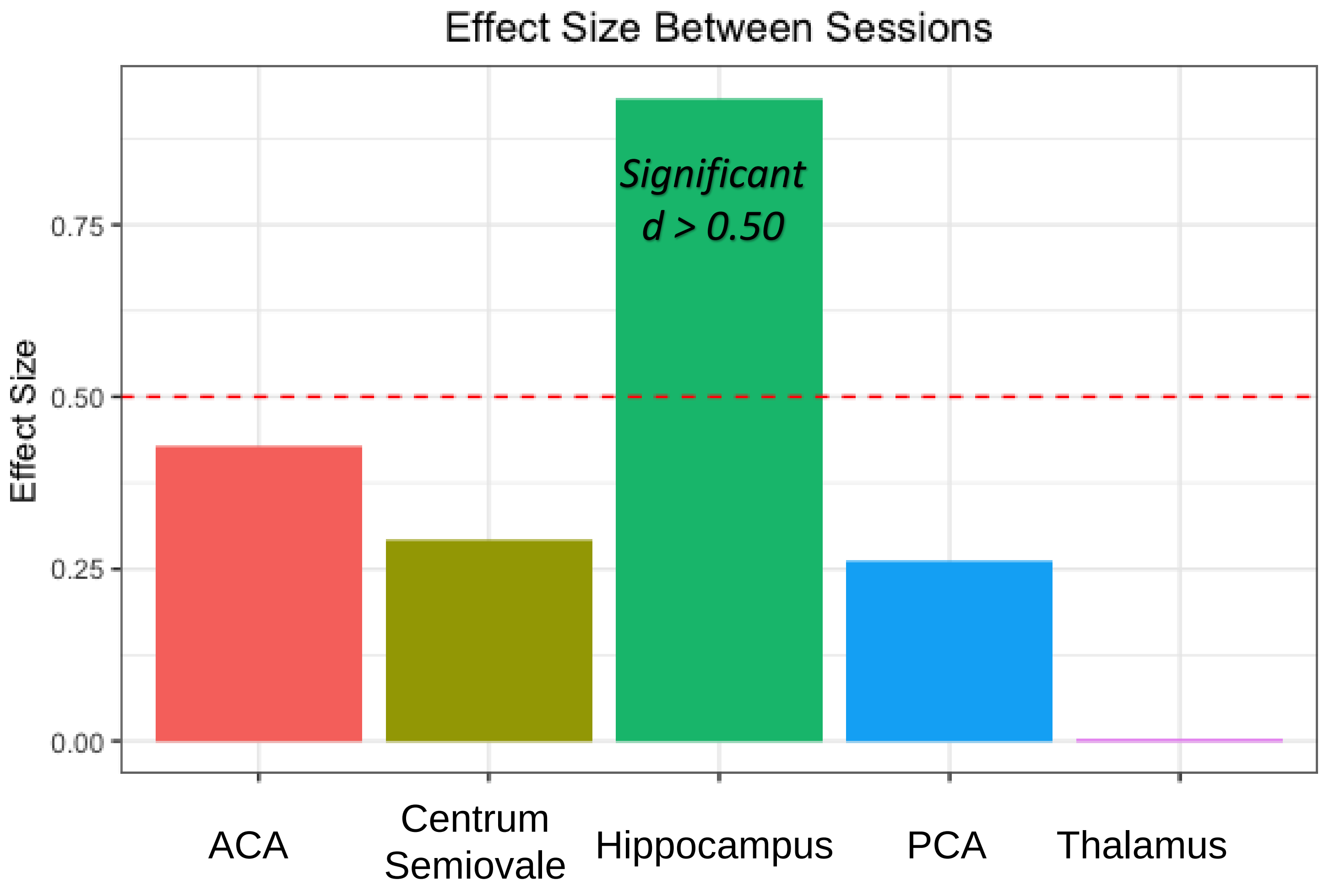
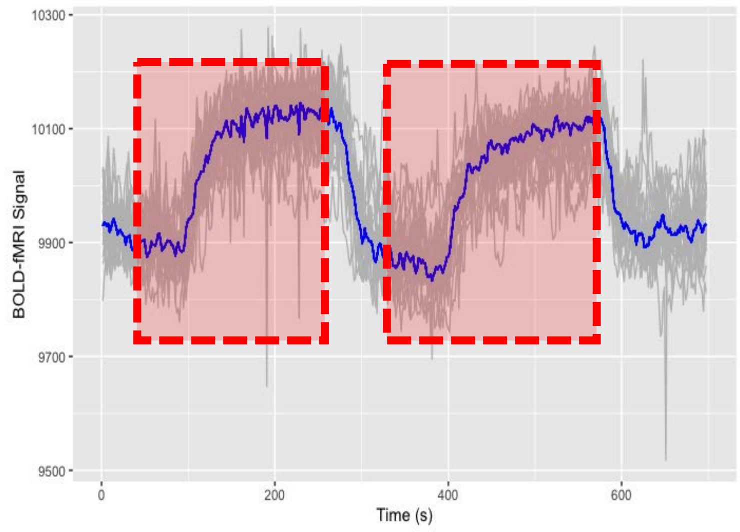
[3] Adamson et al. *Aviat Space Environ Med.* 2012

Session Effect - Hippocampus





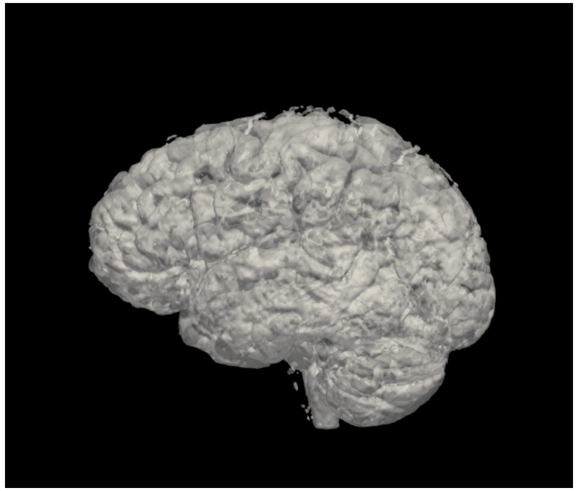
Interpretation

- Significant difference between first and second dilation response in hippocampus

Key Takeaways…

- No evidence of reduced CVR in WM among pilots

- Given that the hippocampus:
  - Is involved in memory formation
    - this population has better short-term memory scores
  - Is sensitive to hypoxia
  - Is a marker for neurodegeneration when there is a decrease in volume/function



…then…

What is the significance of this new finding of increased hippocampal reactivity among fighter pilots?

- Could it be protective?
- Selection bias or environmental factor?
- Anatomic variation?

Recommended Reading

- Fierstra J, Sobczyk O, Battisti-Charbonney A, et al. **Measuring cerebrovascular reactivity: what stimulus to use?**. *J Physiol.* 2013;591(23):5809-5821. doi:10.1113/jphysiol.2013.259150

- Sleight E, Stringer MS, Marshall I, Wardlaw JM, Thrippleton MJ. **Cerebrovascular Reactivity Measurement Using Magnetic Resonance Imaging: A Systematic Review.** *Frontiers in Physiology*. 2021;12. doi:10.3389/fphys.2021.643468.

- MacKay CM, Skow RJ, Tymko MM, et al. **Central respiratory chemosensitivity and cerebrovascular CO2 reactivity: a rebreathing demonstration illustrating integrative human physiology.** *Adv Physiol Educ*. 2016;40(1):79-92. doi:10.1152/advan.00048.2015

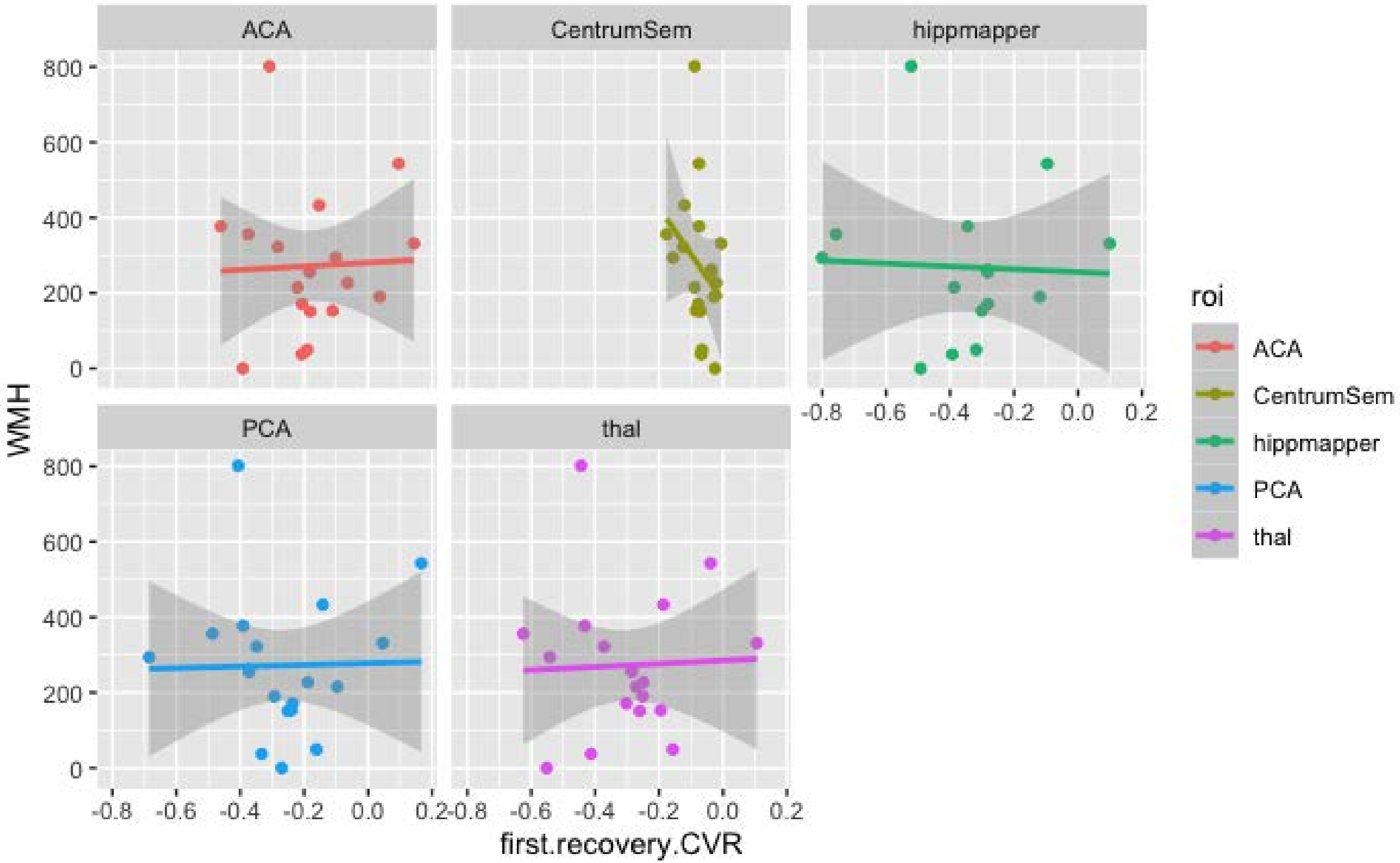
Extra Slides

RCAF CVR Metrics Association with WMH

Kayley Marchena

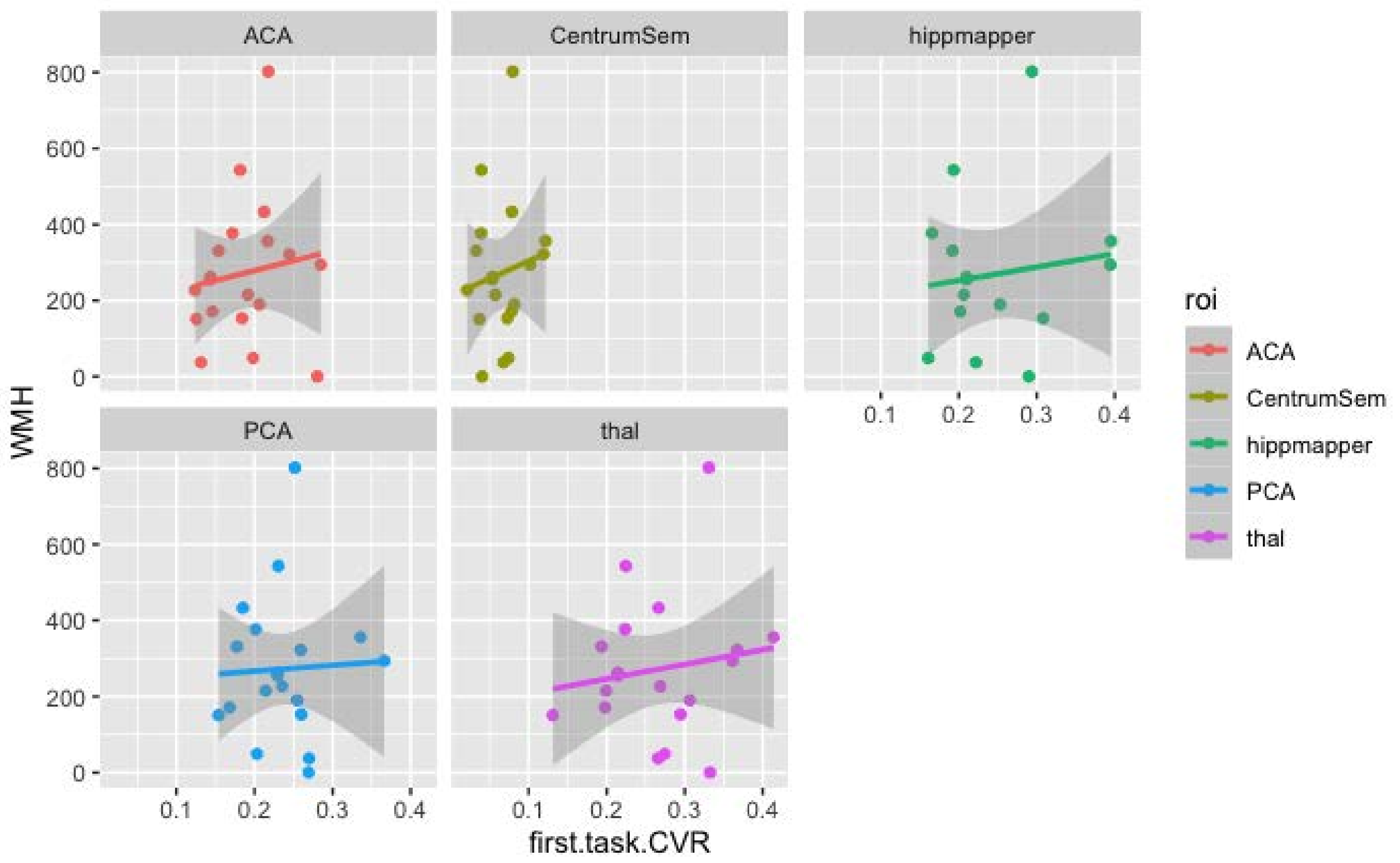
February 10, 2022

WMH Association with Constriction



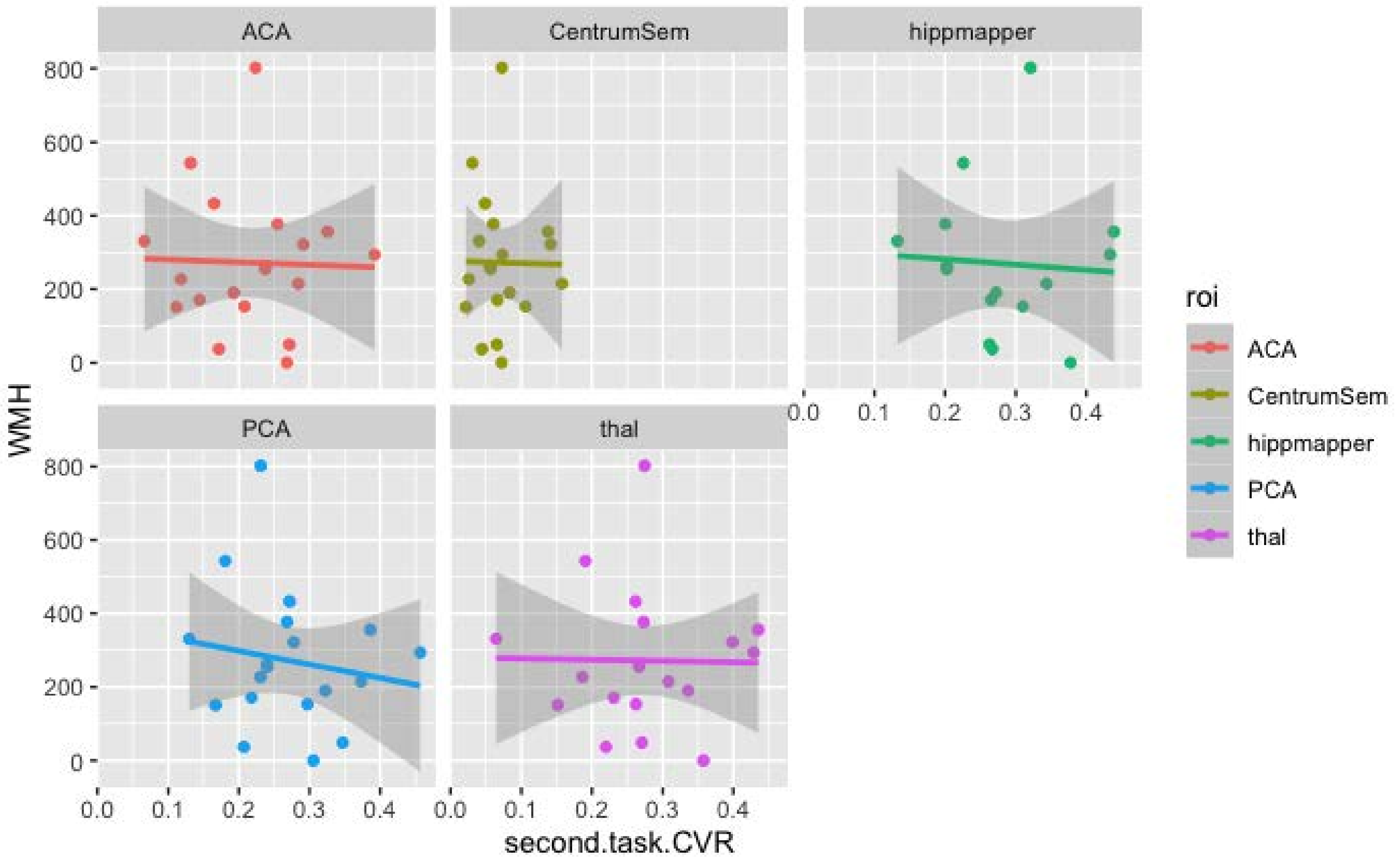
ROI	r2
ACA	0.001
Centrum Semiovale	0.1
Hippocampus	0.002
PCA	0.0005
Thalamus	0.002

WMH Association with First CVR

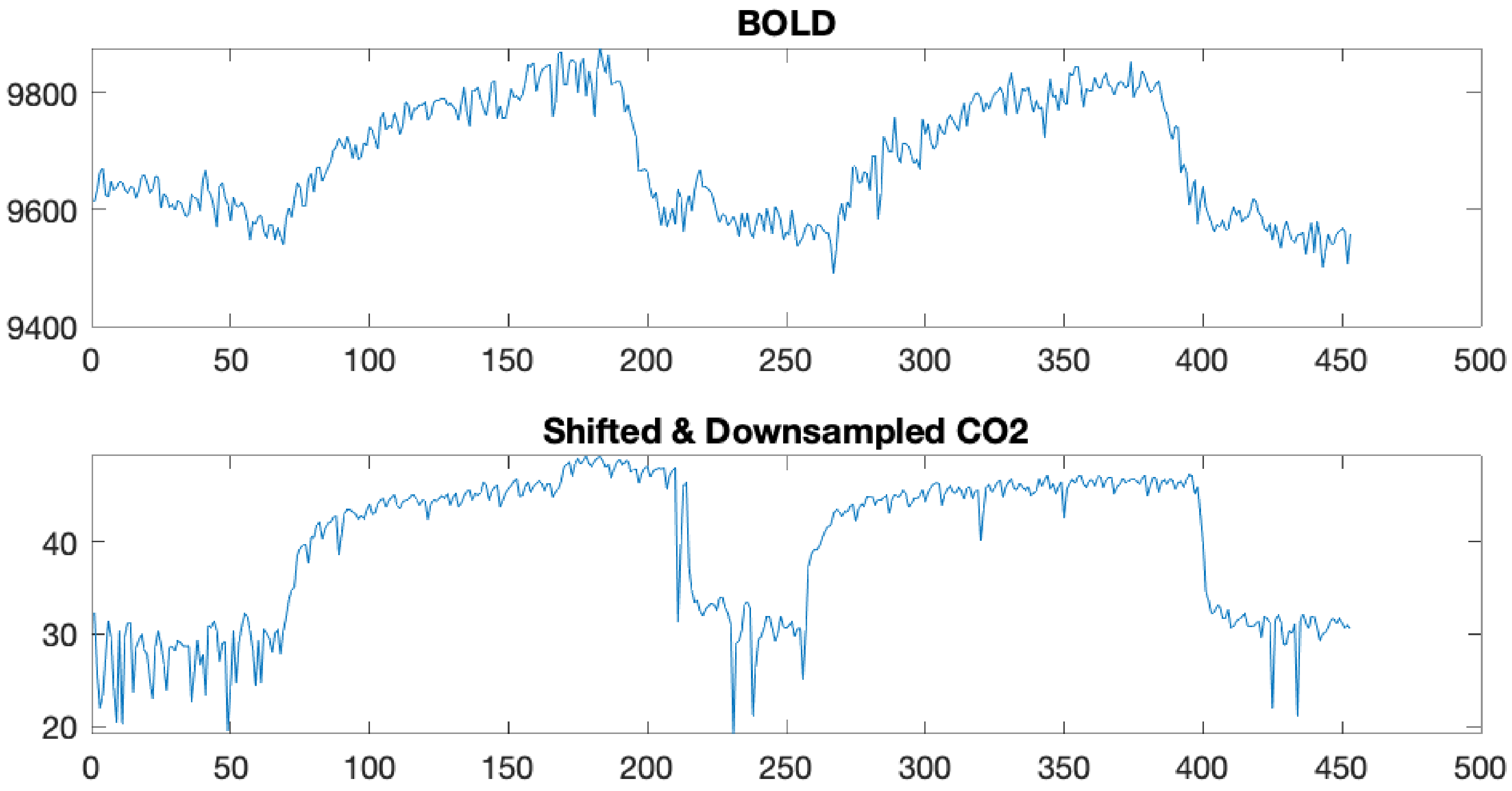


ROI	r2
ACA	0.018
Centrum Semiovale	0.019
Hippocampus	0.016
PCA	0.002
Thalamus	0.21

WMH Association with Second CVR



ROI	r2
ACA	0.0009
Centrum Semiovale	0.0001
Hippocampus	0.004
PCA	0.03
Thalamus	0.0003



R2CVR: 0.5962
% CVR: 0.1027