# Cerebrovascular reactivity (CVR) as a biomarker in VCID

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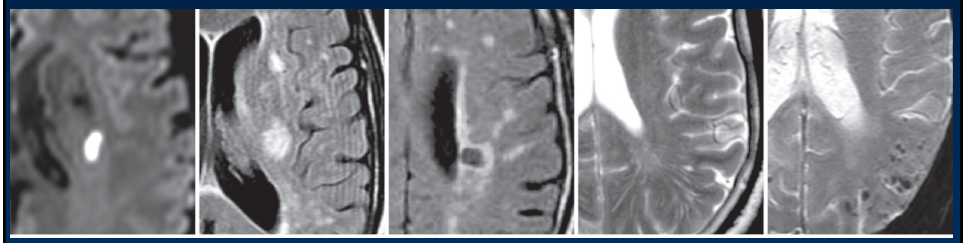
# Classic MRI hallmarks of small vessel diseases



Recent infarct | WMH | Lacune | Perivascular space | Micro-bleed

*Wardlaw et al. Lancet Neurol 12: 822, 2013*

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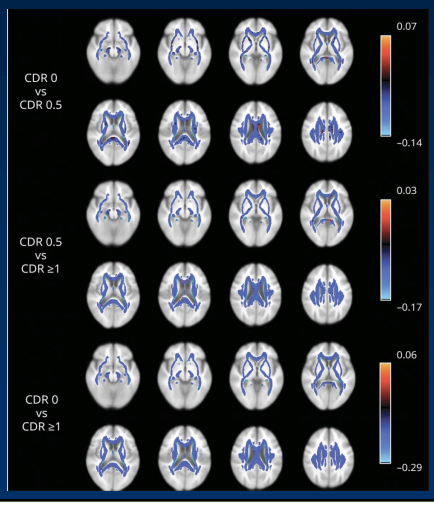
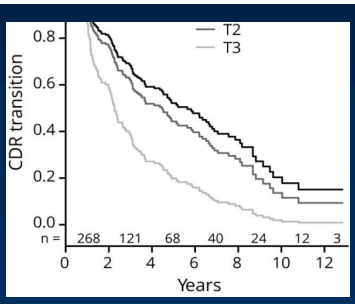
# Quantitative imaging biomarkers: Free-water estimation with diffusion MRI

$$\mathbf{A}_{\text{bi-tensor}}(\mathbf{D}, f) = \mathbf{C}_{\text{tissue}} + \mathbf{C}_{\text{water}} = f\mathbf{A}_{\text{tissue}}(\mathbf{D}) + (1-f)\mathbf{A}_{\text{water}}$$




*Pasternak et al. Magnetic Resonance in Medicine, 62:717, 2009*

*Maillard et al. Neurology, 92:2221, 2019*

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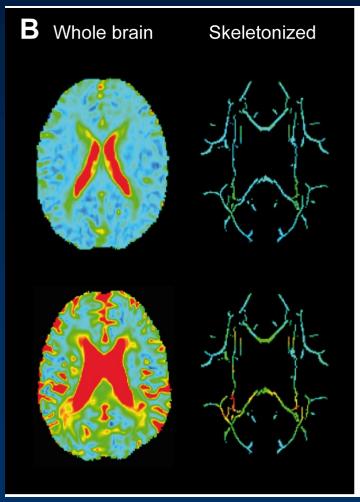
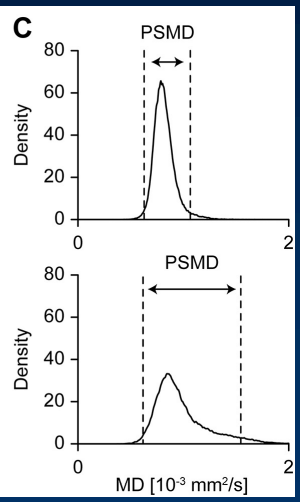
# Quantitative imaging biomarkers: Peak width of skeletonized mean diffusivity (PSMD)




*Baykara et al. Ann Neurol, 80:581, 2016*

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## Physiological markers in VCID

- Easy to interpret
- Precedes anatomic/structural changes
- More modifiable
- Size of change is big

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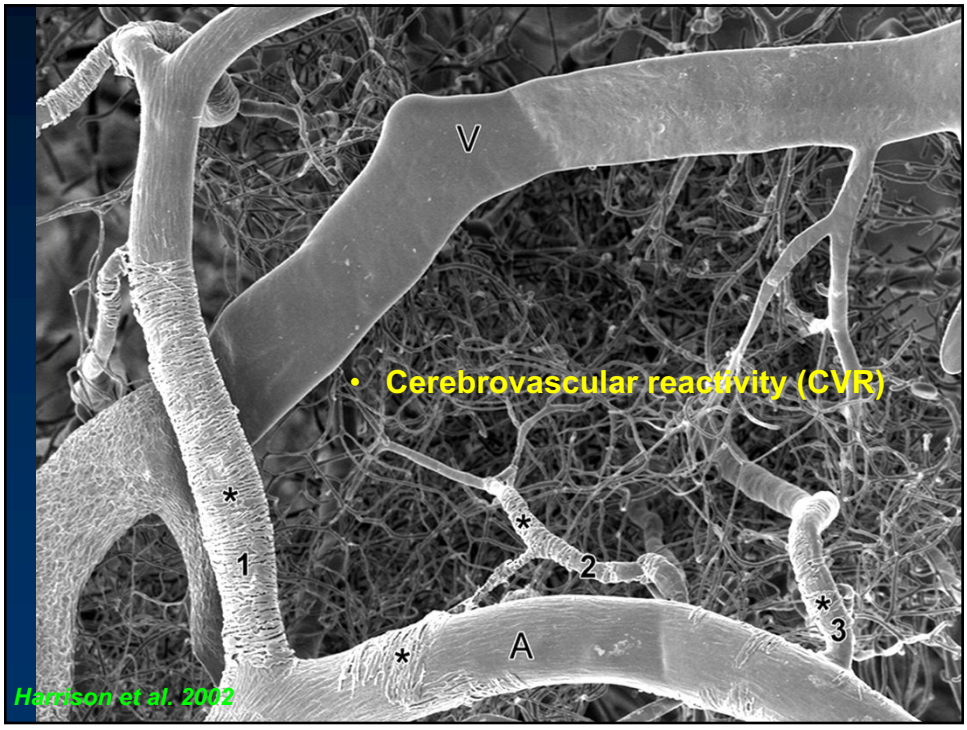


- Cerebrovascular reactivity (CVR)

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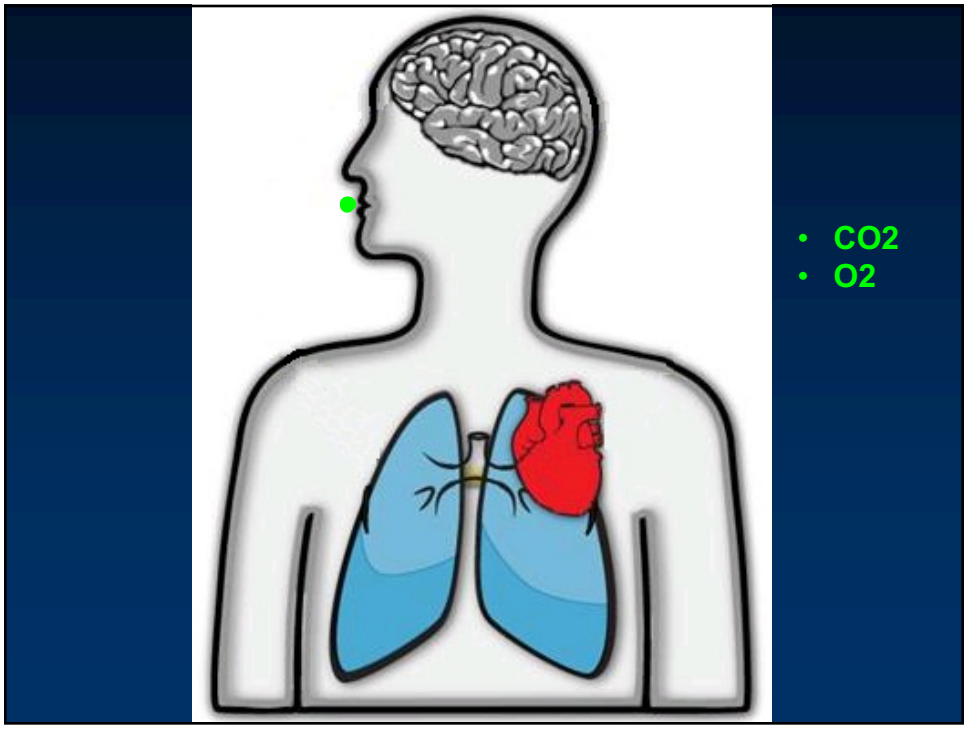


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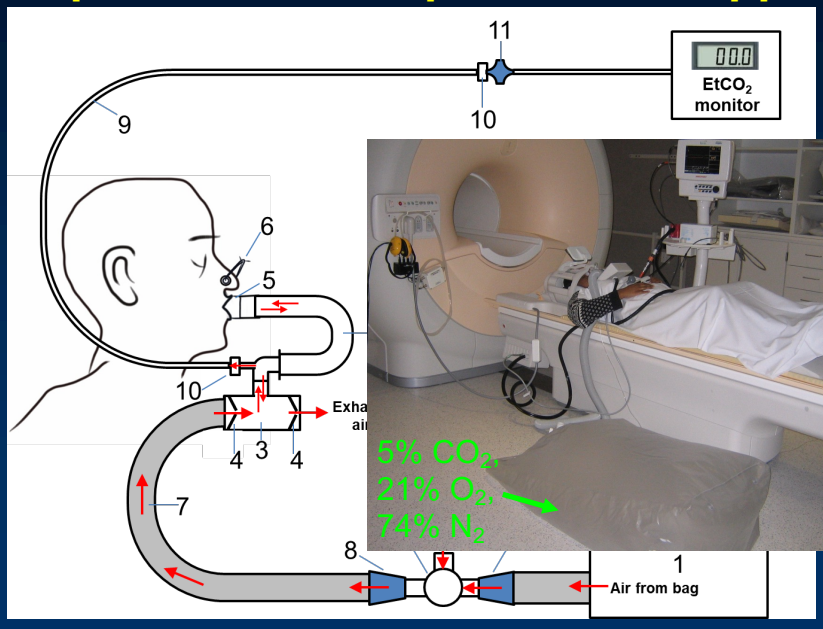
## Experimental setup for CVR mapping

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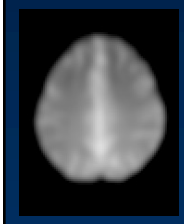
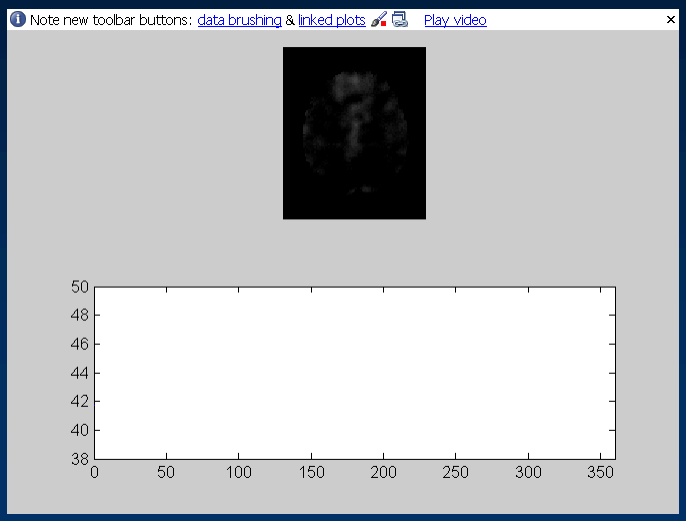
# MRI signal change due to breathing CO2






*Yezhuvath et al. NMR in Biomedicine, 22:779, 2009*

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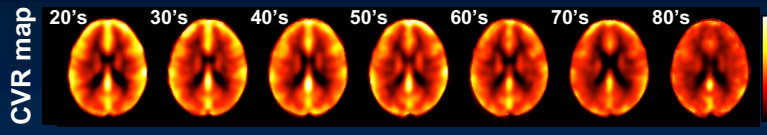
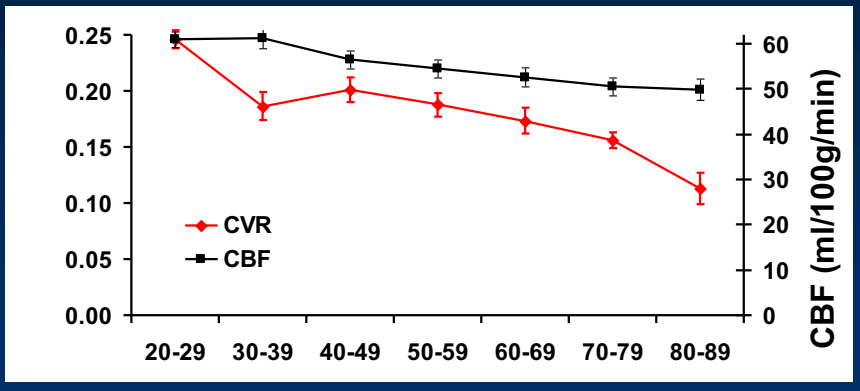
# Age-related decreases in CVR




*Lu et al. Cerebral Cortex, 21:1426, 2011*

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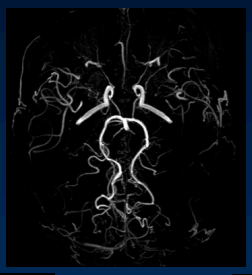
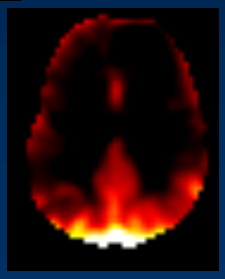
## CVR in large vessel disease





CBV

CVR

*Liu et al., Radiology, 299:419, 2021*

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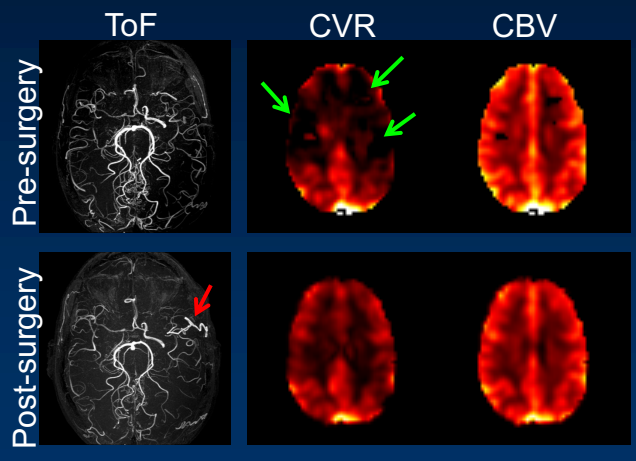
## CVR in detecting treatment effects

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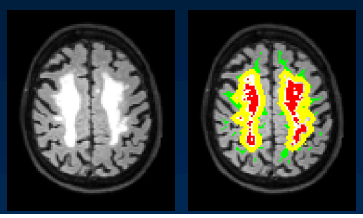
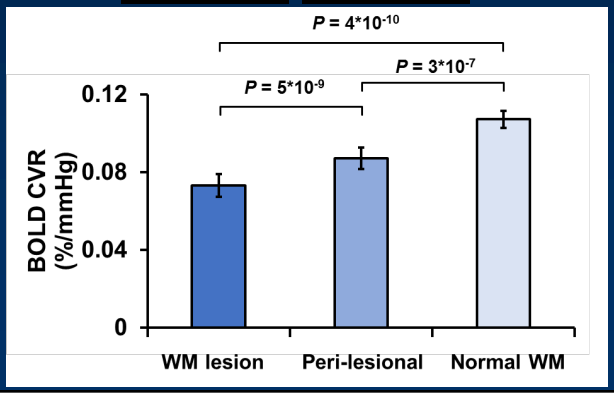
## FLAIR WMH regions have diminished CVR



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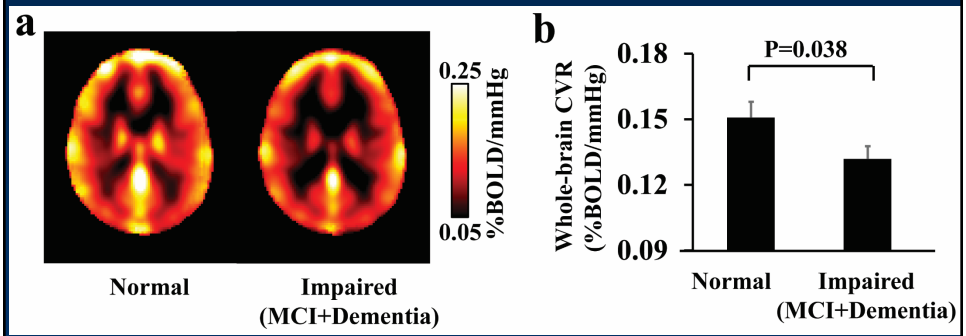
## CVR in small vessel disease

**CVR MRI:** 70-second room-air breathing blocks interleaved with 50-second CO2 breathing blocks. BOLD MRI. Total scan time: 7 min.




*Sur et al. Neurology, 95:962, (2020)*

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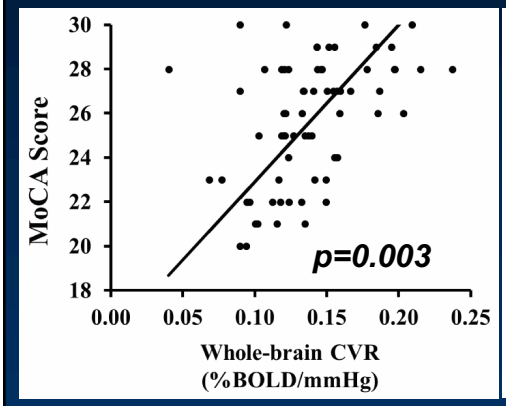
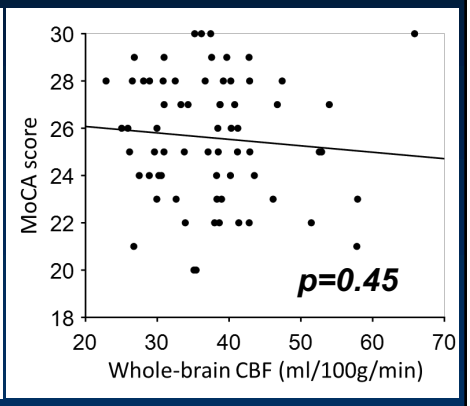
## CVR is associated with general cognitive function




*Sur et al. Neurology, 95:962, (2020)*

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## CVR and Aβ are independently associated with cognitive performance

| | | β (95% CI) |
|---|---|---|
| **MoCA score** | CVR | 29.64 (9.94 , 49.34)** |
| | Aβ42 | 0.002 (0.001, 0.004)* |
| | Tau | -0.001 (-0.001, 0.000006) |
| **Composite z** | CVR | 4.32 (0.05, 8.58)* |
| | Aβ42 | 0.001 (0.0003, 0.001)** |
| | Tau | -0.0001 (-0.0003, 0.00003) |

*Sur et al. Neurology, 95:962, (2020)*

**p<0.05*
***p<0.01*

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## CVR vs. specific cognitive domains

| | |
|---|---|
| **Language, z score** | 6.13 (0.75, 11.52), *p=0.027* |
| **Executive Function, z score** | 4.44 (-1.21, 10.08), *p=0.12* |
| **Episodic Memory, z score** | 2.94 (-3.87, 9.76), *p=0.39* |
| **Processing Speed, z score** | 7.65 (0.57, 14.72), *p=0.035* |

*Sur et al. Neurology, 95:962, (2020)*

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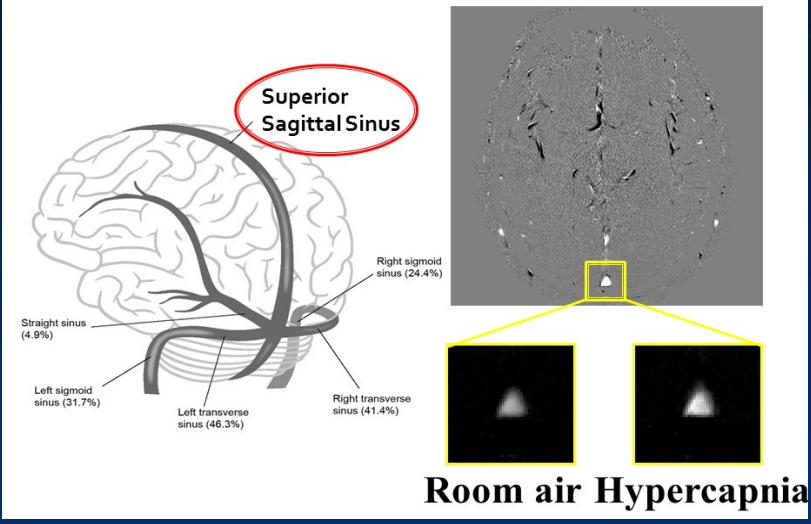
## Measurement of CVR based on cerebral blood flow MRI technique

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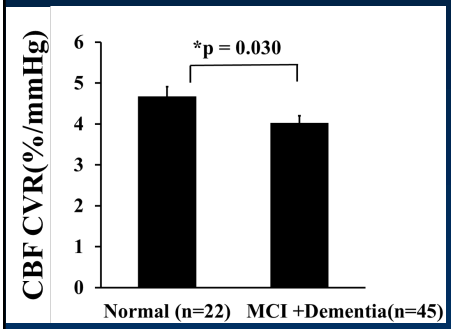
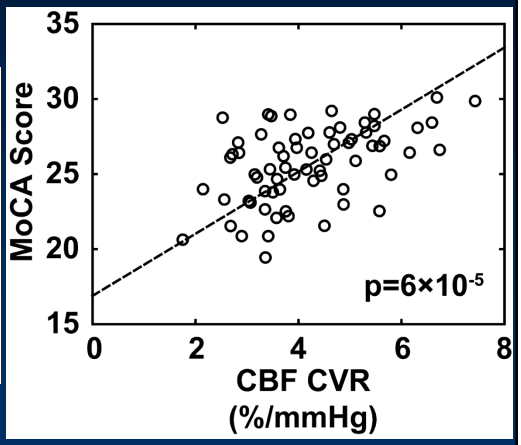
# CBF-based CVR is associated with MoCA and diagnostic category

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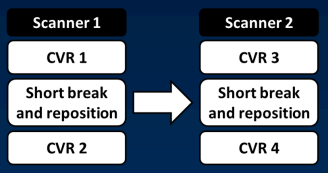
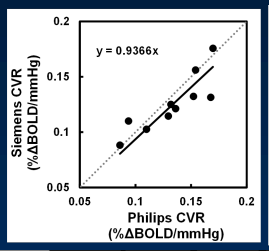
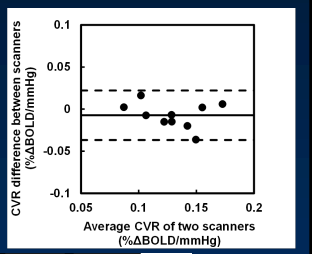
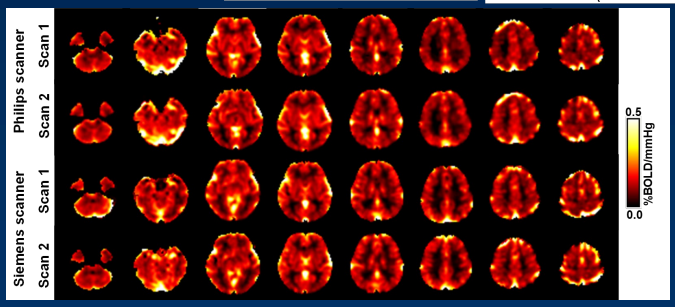
# Inter-scanner reproducibility

N=10 (3F/7M; age 24.0±2.4 yrs)




*Liu et al. Neuroimage, 245: 118754, 2021*

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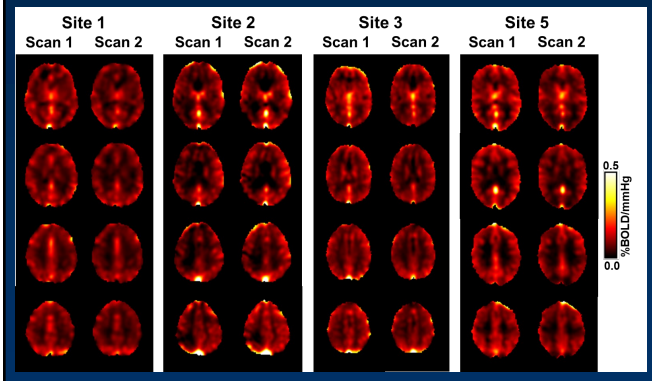
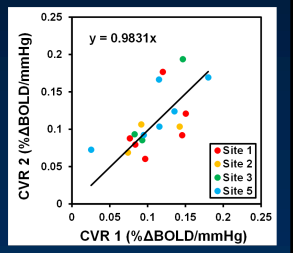
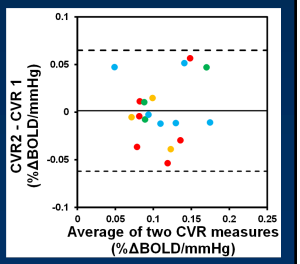
# Test-retest repeatability

JHU (Site 1): N=6
UKY (Site 2): N=4
USC (Site 3): N=4
UTHSCSA (Site 5): N=6




*Liu et al. Neuroimage, 245: 118754, 2021*

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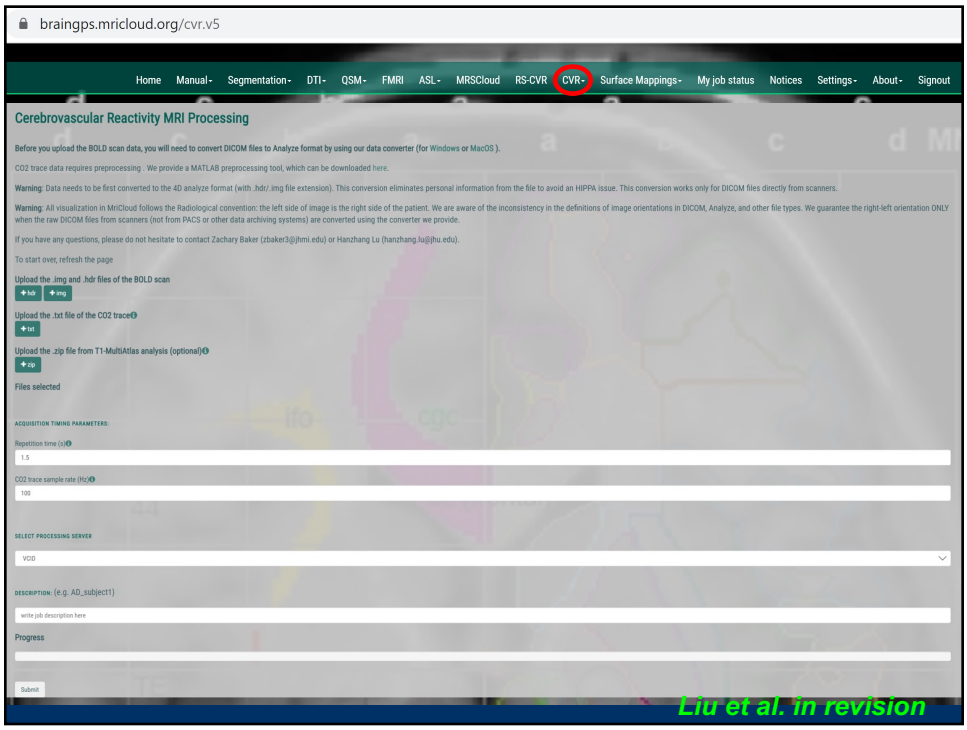


*Liu et al. in revision*

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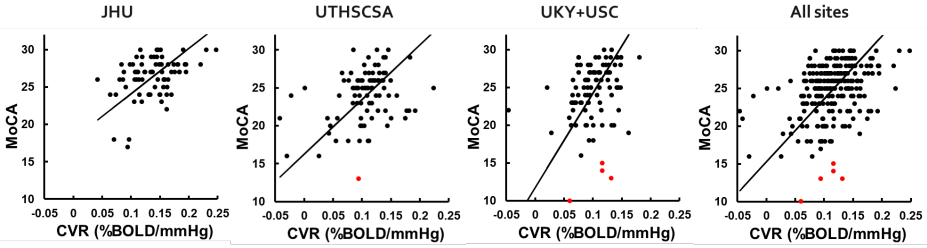
# Multi-site study of CVR marker in MarkVCID 1




| Site | JHU | | | UTHSCSA | | | UKY/USC | | | All sites | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | β | p | N | β | P | N | β | P | N | β | P |
| All MoCA | 77 | 22.08 | 0.003 | 92 | 20.48 | 0.005 | 95 | 21.83 | 0.05 | 264 | 23.36 | $7x10^{-7}$ |
| MoCA>15 | 77 | 22.08 | 0.003 | 91 | 19.43 | 0.004 | 91 | 26.68 | 0.006 | 259 | 23.54 | $5x10^{-8}$ |

*Liu et al. in-prep*

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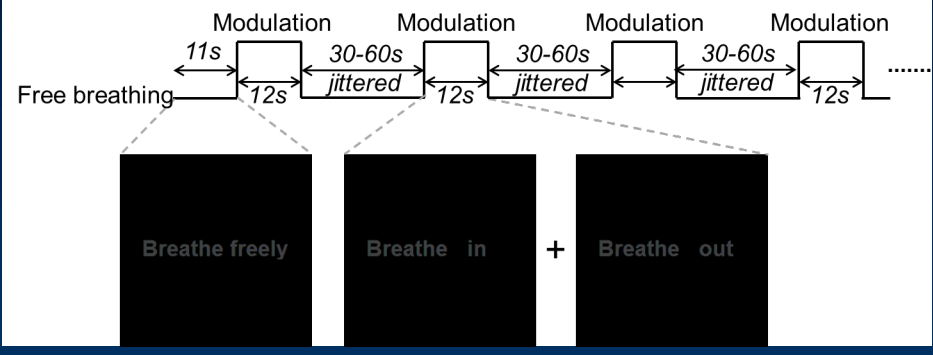
# Non-gas CVR mapping




- **6s-mod**: 3s breath in/3s breath out; 3s breath in/3s breath out

*Liu et al. Neuroimage. 215:116787, (2020)*

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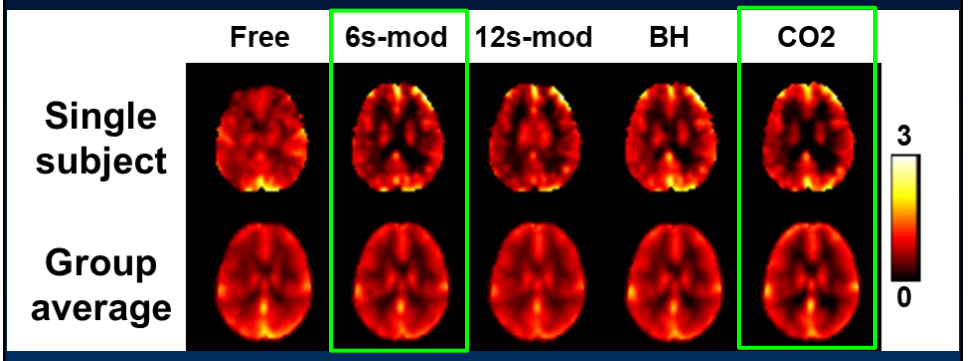
## CVR maps




Spatial correlation with CO2-CVR:

| Free | 6s-mod | 12s-mod | BH |
|---|---|---|---|
| 0.77±0.21 | 0.90±0.05 | 0.81±0.20 | 0.89±0.05 |

*Liu et al. Neuroimage. 215:116787, (2020)*

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## Take-home messages

- CVR measures vasodilatory capacity of the brain vessels.
- CVR is associated with cognitive function and clinical status, independent of Alzheimer's pathology.
- CVR as a potential marker in VCID is scalable and reproducible.

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Rong Zhang
Binu Thomas
Jinsoo Uh
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Kevin King
Feng Xu
Chenguang Zhao
Uma Yezhuvath
Lisa Krishnamurthy
Min Sheng
Sina Aslan
Bart Rypma
Sandi Chapman


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UF1 NS100588
R01 NS106702
R01 NS106711
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P41 EB031771
R01 AG064792


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***Thank you!***

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