

Regional white matter injury modifies associations of β -amyloid with cognition and cortical thickness

Sarah K. Royse¹, Alexandria C. Reese¹, Beth E. Snitz¹, James B. Hengenius², Paul K. Crane³, Shubhabrata Mukherjee³, Seo-Eun Choi³, Daniel Willie-Permor¹, Cynthia Felix¹, Theodore J. Huppert¹, Rebecca E. Roush¹, Geraldine Cisneros¹, Katey Potopenko¹, Brian J. Lopresti¹, Ann D. Cohen¹, C. Elizabeth Shaaban¹

¹University of Pittsburgh, Pittsburgh, PA, USA, ²Universitaire Sainte-Justine, Montreal, QC, CA, ³University of Washington, Seattle, WA, USA

What did we find?

- The combined influence of co-localized white matter injury and β -amyloid on cognition varies by brain region, but these differences are not readily explained by underlying neurodegeneration.

Why is it important?

- Parietal white matter injury and β -amyloid may act synergistically to influence lower cognition and more neurodegeneration.
- The anterior cingulate may support a compensatory mechanism for preserving cognition, despite greater pathological burden in AD.

Background

- White matter injury is common in Alzheimer's disease (AD).
- Examining synergistic relationships of co-localized white matter injury and AD pathology on cognition and neurodegeneration is difficult with current white matter injury indices.
- Our objective** was to determine if co-localized white matter injury (indexed using our spatially precise measurement) and β -amyloid ($A\beta$) interact on (1) memory, executive functioning, and language and (2) co-localized cortical thickness.

Methods

Study Population

Connectomics in Brain Aging (CoBRA) participants who underwent neuroimaging and a standardized neuropsychological test battery at one time point

Predictors

- Regional unhealthy white matter connectivity (UWMC)**
 - The proportion of white matter connections between two brain regions that pass through white matter hyperintensities (WMH; Figs 1A-C)

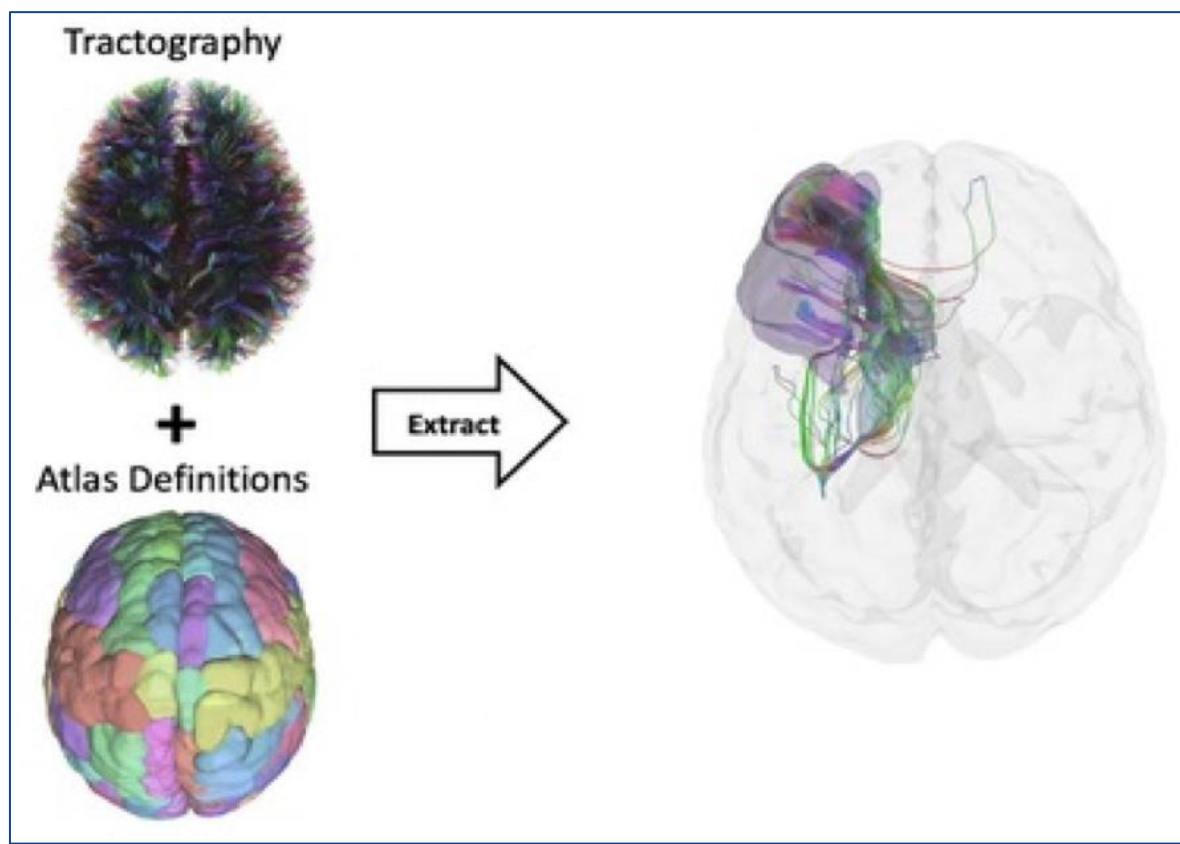


Fig 1A. Pairwise connectivity definitions

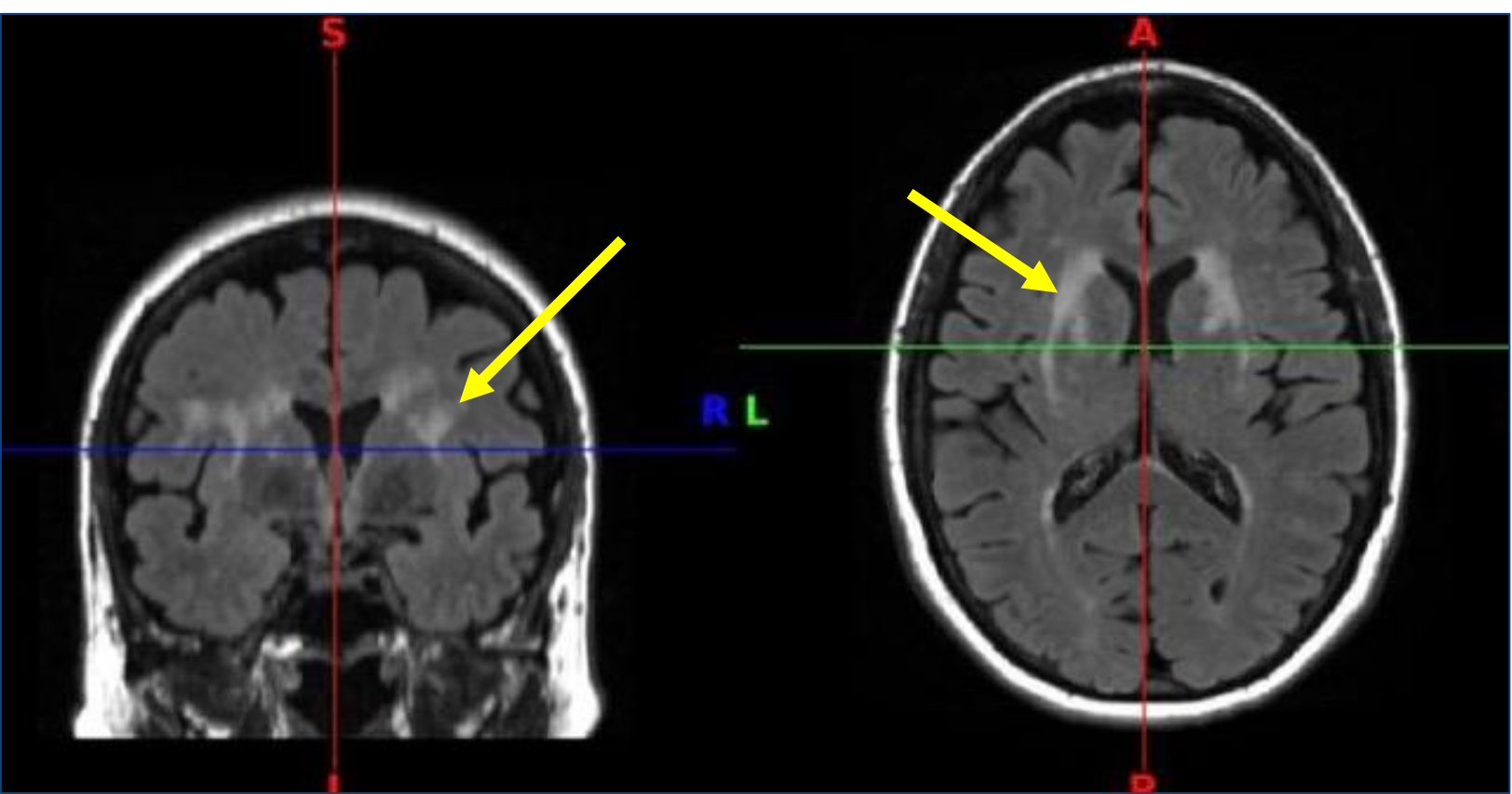


Fig 1B. WMH (yellow arrows) in a participant

Outcomes

- Memory, executive functioning, language domain composite scores**
 - Created via item-response theory
- Regional cortical thickness**

Statistical analyses

- Individual robust regression models**
 - Tested interactions between corresponding pairs of regional UWMC and [¹¹C]PiB SUVR with each cognitive domain score
 - Repeated replacing cognitive domain scores → corresponding cortical thickness
 - Covariates: age, sex, racialized group, education, *APOE**4, hypertension, diabetes, and high cholesterol

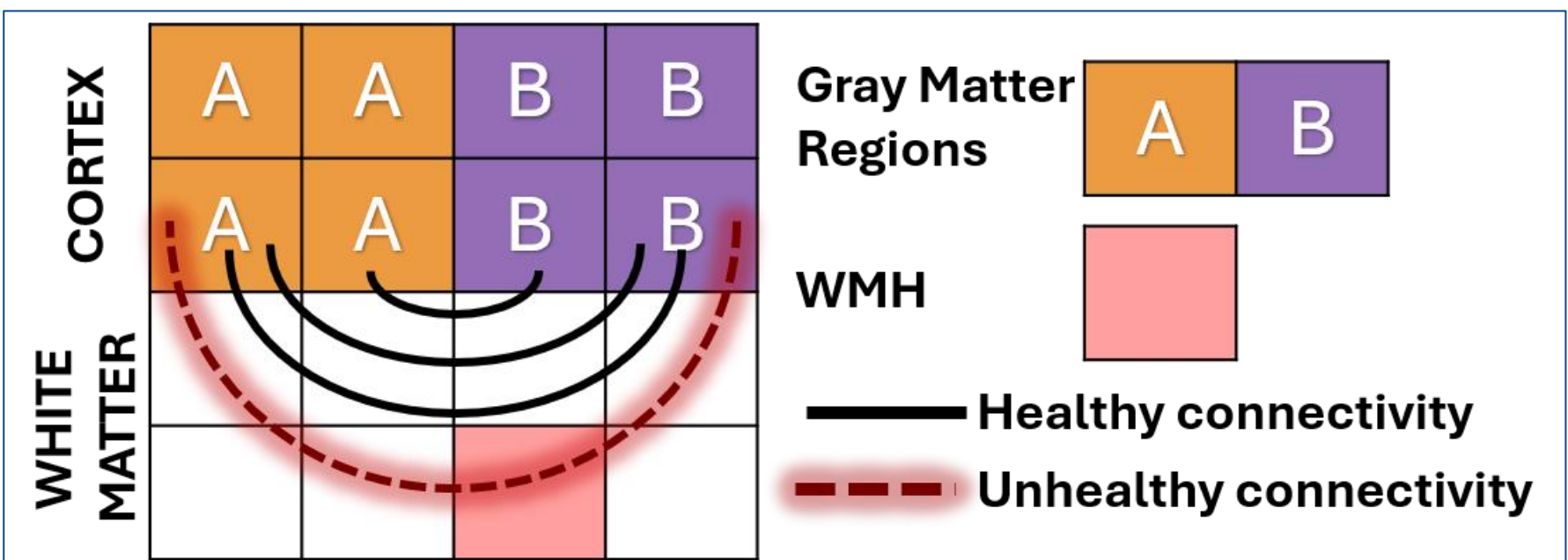


Fig 1C. Healthy vs. unhealthy pairwise connectivity

Results

Table 1. Participant characteristics

	Total N = 207	Global [¹¹ C]PiB SUVR + N = 31		Global [¹¹ C]PiB SUVR – N = 176	
		High global UWMC N = 10	Low global UWMC N = 21	High global UWMC N = 93	Low global UWMC N = 83
Demographics					
Age	62.0 (57.0, 70.0)	72.5 (72.0, 77.0)	71.0 (68.0, 79.0)	61.0 (57.0, 67.0)	60.0 (55.0, 69.0)
Female	136 (65.7%)	6 (60.0%)	8 (38.1%)	72 (77.4%)*	50 (60.2%)*
White	98 (47.3%)	4 (40.0%)*	20 (95.2%)*	38 (40.9%)	36 (43.4%)
Education	15.0 (12.0, 17.0)	16.0 (16.0, 18.0)	18.0 (14.0, 19.0)	14.0 (12.0, 16.0)	14.0 (12.0, 17.0)
<i>APOE</i> *4	65 (31.4%)	4 (40.0%)	10 (47.6%)	24 (25.8%)	27 (32.5%)
Cardiovascular					
Hypertension	85 (41.1%)	7 (70.0%)*	4 (19.0%)*	36 (38.7%)	38 (45.8%)
Diabetes	36 (17.4%)	2 (20.0%)	1 (4.76%)	18 (19.4%)	15 (18.1%)
High cholesterol	69 (33.3%)	4 (40.0%)	10 (47.6%)	28 (30.1%)	27 (32.5%)
Cognition					
Memory	0.69 (0.27, 1.02)	0.73 (0.08, 1.10)	0.68 (0.30, 0.99)	0.64 (0.24, 0.95)	0.72 (0.38, 1.07)
Executive function	0.91 (0.50, 1.31)	0.51 (-0.20, 1.08)	1.08 (0.64, 1.48)	0.81 (0.38, 1.25)	0.99 (0.66, 1.26)
Language	0.48 (0.14, 0.88)	0.19 (-0.10, 0.96)	0.87 (0.52, 1.10)	0.35 (0.12, 0.69)	0.53 (0.16, 0.89)
MoCA	25.0 (23.0, 27.0)	23.5 (20.0, 26.0)*	27.0 (25.0, 28.0)*	25.0 (23.0, 26.5)*	26.0 (23.0, 27.0)*
CU	153 (73.9%)	5 (50.0%)	14 (66.7%)	69 (74.2%)	65 (78.3%)

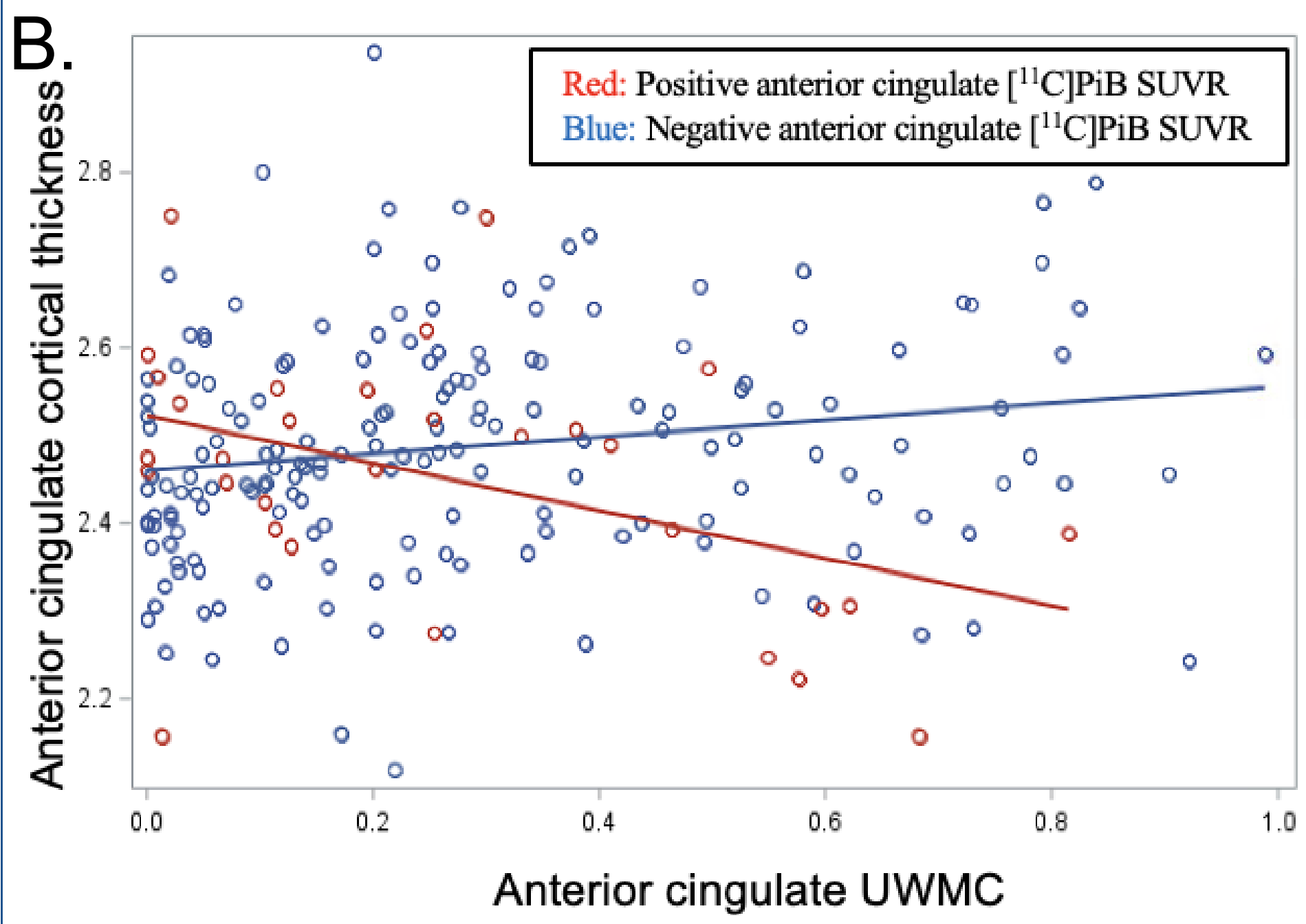
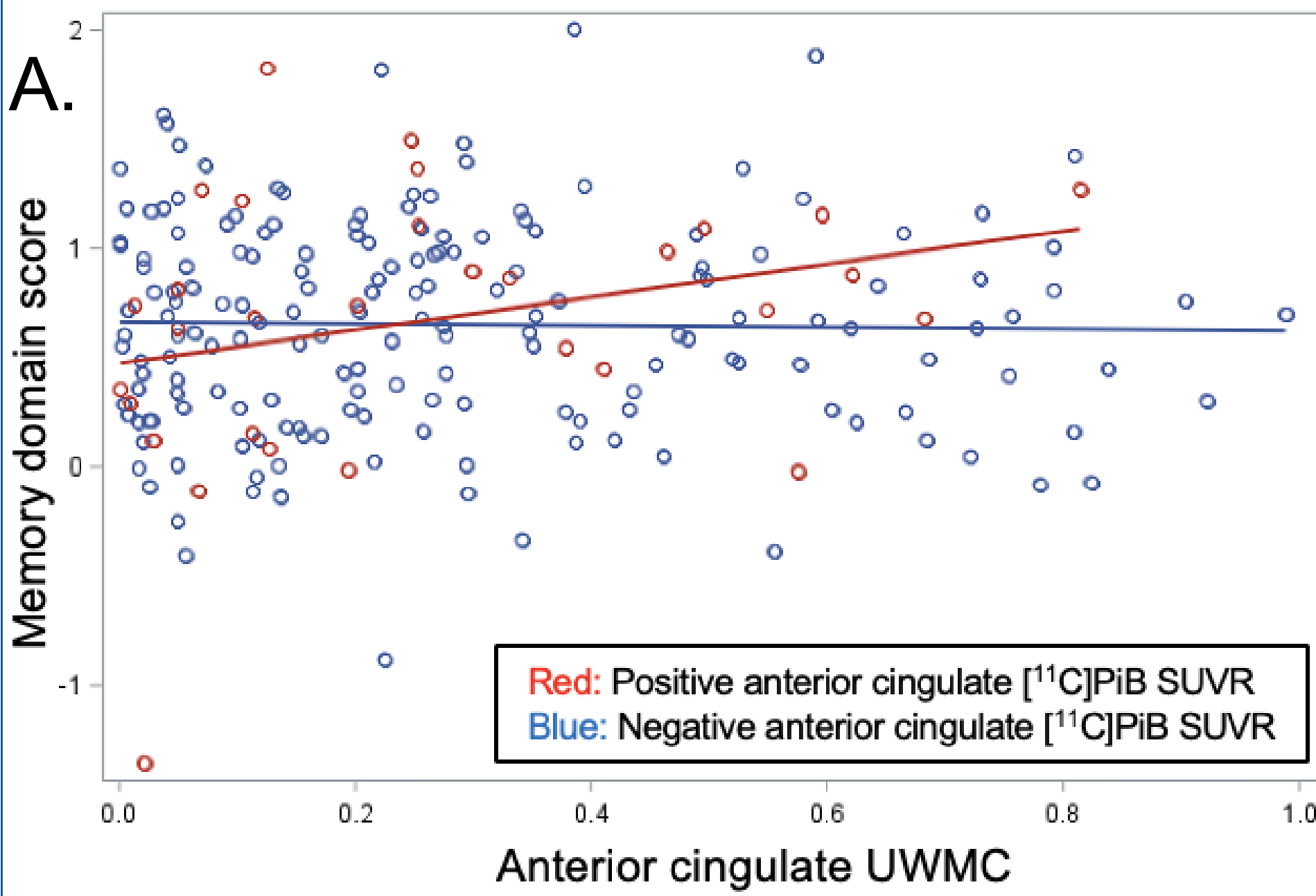


Fig 4. Regional anterior cingulate UWMC vs. outcome (A. memory domain score; B. cortical thickness) by [¹¹C]PiB +

- The relationship between more parietal UWMC and worse memory (Table 2), executive functioning (*P*=0.01), and language (*P*=0.01) composite scores was stronger with higher [¹¹C]PiB SUVR.
- Greater anterior cingulate UWMC was associated with better memory composite score in those with higher, versus lower, [¹¹C]PiB SUVR (Table 2).

- Parietal UWMC and [¹¹C]PiB SUVR did not interact on co-localized cortical thickness (Table 3).
- The association between more anterior cingulate UWMC and lower cortical thickness was stronger with higher [¹¹C]PiB SUVR (Table 3).

Table 2. Linear models with memory

	Standardized β (<i>P</i> value)		
	UWMC	[¹¹ C]PiB SUVR	Interaction
Anterior Cingulate	0.003 (0.93)	-0.02 (0.70)	0.08 (0.03)*
Anterior Ventral Striatum	0.02 (0.64)	-0.05 (0.21)	0.02 (0.65)
Superior Frontal	-0.04 (0.29)	-0.02 (0.63)	0.05 (0.35)
Orbitofrontal	-0.01 (0.84)	-0.01 (0.88)	0.07 (0.07)
Insula	0.03 (0.38)	-0.01 (0.74)	0.07 (0.18)
Lateral Temporal	-0.03 (0.43)	-0.04 (0.30)	-0.04 (0.28)
Parietal	-0.06 (0.08)	-0.03 (0.37)	-0.14 (0.0003)*
Posterior Cingulate	0.01 (0.77)	-0.04 (0.36)	-0.002 (0.96)
Precuneus	-0.08 (0.049)*	-0.08 (0.049)*	-0.06 (0.30)

Table 3. Linear models with cortical thickness

	Standardized β (<i>P</i> value)		
	UWMC	[¹¹ C]PiB SUVR	Interaction
Anterior Cingulate	0.01 (0.52)	-0.02 (0.14)	-0.03 (0.003)*
Superior Frontal	-0.01 (0.23)	-0.04 (0.66)	0.01 (0.52)
Orbitofrontal	0.01 (0.33)	0.01 (0.29)	0.01 (0.14)
Insula	-0.02 (0.11)	-0.03 (0.01)*	-0.02 (0.28)
Lateral Temporal	-0.02 (0.046)*	-0.01 (0.55)	0.01 (0.38)
Parietal	-0.01 (0.28)	-0.02 (0.07)	-0.02 (0.06)
Posterior Cingulate	-0.02 (0.01)*	0.01 (0.80)	0.01 (0.38)
Precuneus	-0.01 (0.17)	-0.01 (0.08)	0.0002 (0.99)

Conclusions

- Strengths:** More spatially precise index of white matter injury allowed us to more closely interrogate its combined influence with $A\beta$ on cognition and co-localized cortical thickness
- Limitations:** Sample of participants is fairly small and healthier than the general older adult population
- Future directions:** Explore interactions of regional white matter injury with other AD markers

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Contact



sak225@pitt.edu



Sarah Royse, PhD, MPH