IC-P-015 HIGH AMYLOID LOAD IS ASSOCIATED WITH EPISODIC MEMORY DECLINE AND INCIDENT MILD COGNITIVE IMPAIRMENT IN MIDDLE-AGED ADULTS IN THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION (WRAP)

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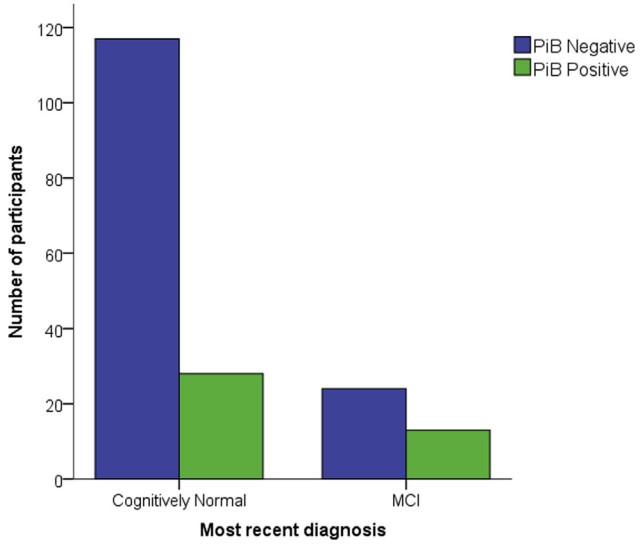
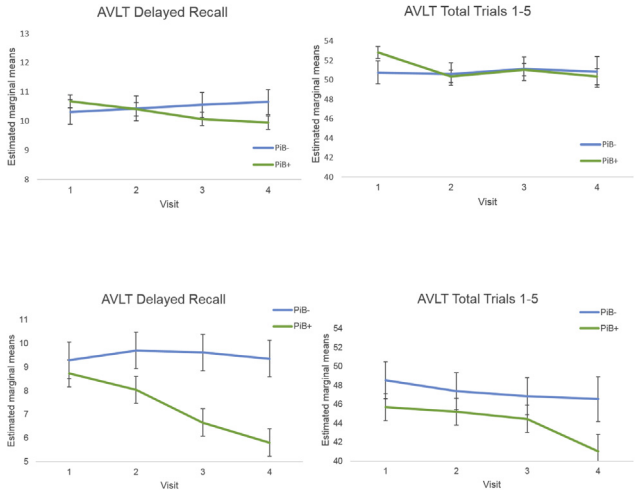
Background: This study investigated the relationship between amyloid burden and cognition in a cohort of late middle-aged participants enriched for family history of Alzheimer's disease (AD) enrolled in the WRAP Study. **Methods:** 182 WRAP participants completed a PET-PiB scan approximately 5 years after baseline cognitive testing. A composite cortical measure of amyloid burden was calculated and a DVR cutpoint of 1.12 (derived from an ROC analysis) was used to classify participants as PiB+ (n= 41) or PiB- (n=141). Additionally, participants were classified as having psychometric mild cognitive impairment (MCI; n=37) if at least two neuropsychological performances within a cognitive domain or least one measure in three cognitive domains (immediate memory, delayed memory, executive functioning) were ≤ 1.5 standard deviations below the mean of a robust normative group. Rates of PiB positivity by cognitive group (MCI or cognitively normal [CN]) were compared and a linear mixed-effects regression model examined longitudinal trajectories on the Rey Auditory Verbal Learning Test (RAVLT) by PiB and MCI status. The model included fixed effects for amyloid group (PiB+/PiB-), amyloid group x time, age, and gender, and random effects for participant and time.





Outcome variables were either RAVLT total trials 1-5 or RAVLT delayed recall raw scores. **Results:** The MCI group had a greater proportion of PiB+ participants compared with the CN group (X2=4.23; p<.05; see Figure 1). Linear mixed-effects models revealed a significant interaction between amyloid group and time on RAVLT delayed recall (β = -.34, p<.05), indicating steeper decline in the PiB+ group (see Figure 2). Other significant fixed effects included age (β =-.08, p<.01) and female sex (β =2.14, p<.001). There was a trend in the same direction for the amyloid by time interaction on RAVLT total trials (β = -.84, p=.08; see Figure 2). Models were re-run in the MCI group only and again indicated a significant interaction between amyloid group and time on RAVLT delayed recall (β =-1.05, p<.01), but not on RAVLT total trials (see Figure 3). **Conclusions:** Greater amyloid burden in late middle-age is associated with increased rates of MCI and steeper memory decline.

IC-P-016 AMYLOID IMAGING IN THERAPEUTIC TRIALS: THE QUEST FOR THE OPTIMAL REFERENCE REGION

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Background: The reference region (RR) approach was initially proposed for the kinetic analysis of neuroimaging radiotracers to remove the need of a metabolite-corrected plasma input function. The RR was described as a brain region with similar cellular and blood flow characteristics as the target region but lacking specific (saturable) binding sites. It relied on two basic assumptions: that the degree of nonspecific binding and the volume of distribution of the free compartment were the same in the RR and target regions. The use of a RR was later applied to semiquantitative tissue ratio

Table 1
Reference region stability across diagnoses, across time, and across Aβ status

ACROSS DX	Cb GM	WCb	PONS	Cb WM	SWM	SWMKCER	WCb+PONS	SWM+PONS	SWMKCER +PONS	SWM+WCB +PONS	SWMKCER+ WCb+PONS
FLUTEMETAMOL	***n.s***	***n.s***	***n.s***	***n.s***	*p=0.05*	***n.s***	***n.s***	***n.s***	***n.s***	n.s	***n.s***
FLORBETAPIR	n.s	n.s	n.s	n.s	n.s.	***n.s***	n.s	n.s	n.s	n.s	n.s
FLORBETABEN	***n.s.***	*p=0.026*	*p=0.0007*	*p=0.0015*	*p=0.001*	*p=0.004*	*p=0.013*	*p=0.002*	*p=0.002*	*p=0.003*	*p=0.005*
ACROSS TIME											
FLUTEMETAMOL	***n.s***	***n.s***	***n.s***	***n.s***	n.s	***n.s***	***n.s***	***n.s***	***n.s***	n.s	***n.s***
FLORBETAPIR	*p=0.025*	*p=0.013*	*p=0.014*	*p=0.029*	n.s	***n.s***	*p=0.013*	*p=0.03*	*p=0.04*	*p=0.03*	*p=0.05*
FLORBETABEN	***n.s***	n.s	n.s	n.s	n.s	n.s	n.s	n.s	n.s	n.s	n.s
ACROSS Aβ status											
FLUTEMETAMOL	***n.s***	***n.s***	***n.s***	***n.s***	*p=0.001*	***n.s***	***n.s***	***n.s***	***n.s***	*p=0.03*	***n.s***
FLORBETAPIR	n.s	n.s	n.s	n.s	*p=0.004*	***n.s***	n.s	*p=0.04*	n.s	*p=0.02*	n.s
FLORBETABEN	***n.s***	n.s	n.s	n.s	*p=0.04*	n.s	n.s	*p=0.04*	n.s	n.s	n.s

Abbreviations: Cb GM: Cerebellar Grey Matter; WCb: Whole cerebellum; Cb WM: Cerebellar white matter; SWM: Subcortical white matter (centrum semiovale); SWMKCER: Subcortical white matter (extending from the centrum semiovale to the corpus callosum as proposed by Kewei Chen and Eric Reiman) n.s.: not significant

Significantly different ($p<0.05$)

Reference regions that remained stable under all conditions examined

approaches, as the ones widely used for Aβ imaging studies. With the advent of therapeutic anti-Aβ trials there has been a renewed interest in optimizing outcomes by reducing the variance of Aβ burden measurements. The purpose of this study was to first assess the stability of different RR and then look at the stable RR that yielded the lowest variance for Aβ burden estimates obtained with three FDA-approved Aβ imaging tracers. **Methods:** 653 participants were evaluated (258 w/flutemetamol-FLUTE-; 184 w/florbetapir-FBP- and 211 w/florbetaben-FBB-) where 237 had longitudinal scans (81 w/FLUTE; 87 w/FBP and 69 w/FBB). We assessed the SUV of 11 either pure grey (GM) or white matter (WM) RR, and their combinations (Table 1) across clinical conditions, across Aβ status, and across time. Stable RR were then used to assess the variance of the Aβ burden estimates. **Results:** For FLUTE, GM and most WM RR were stable under all conditions, with the composite SWM+pons yielding the lowest Aβ burden variance both cross-sectionally and longitudinally. While a subcortical WM RR (SWMKCER, extending from the centrum semiovale to the corpus callosum as proposed by Kewei Chen and Eric Reiman) was stable under all conditions for FBP, Cerebellar GM (CbGM) was the only stable RR for FBB. The Aβ burden variances obtained with the aforementioned RR were similar for all tracers. **Conclusions:** SWM+pons for FLUTE, CbGM for FBB, and SWMKCER for FBP remained stable across the examined conditions, yielding the lowest variance of the Aβ burden estimates. To optimize outcomes in ongoing therapeutic trials, tracer-specific RR should be applied.

IC-P-017 CEREBRAL AMYLOID DEPOSITION ITSELF IS NOT RELATED TO DEPRESSIVE SYMPTOMS IN ELDERLY INDIVIDUALS WITH NORMAL COGNITION, MCI, AND ALZHEIMER'S DISEASE

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Table 1
Subjects characteristics

	All (n=76)	CN (n=26)	MCI (n=23)	AD (n=27)	P
Age, year	70.32±7.36	71.541 5.29	70.481 7.66	69.00+ 8.74	0.457
Gender, n (M/F)	18/58	10/16	4/19	4/23	0.090
Education, year	9.28±4.89	11.1214.67	8.87+4.63	7.85+4.93	0.045*
ApoE ε4 carrier, n (%)	37 (48.7)	12 (46.2)	10 (43.5)	15 (55.6)	0.662
CDR					<0.001
0	26	26	0	0	
0.5	38	0	23	15	
≥ 1	12	0	0	12	
CDR-SOB	1.78±2.22	0+0	1.17+0.51	4.02+2.29	<0.001*‡
GDS	11.0717.12	8.00+5.70	11.70+7.13	13.48+7.50	0.015*
HAM-D	2.3013.15	0.58+0.99	2.48+3.25	3.81+3.66	<0.001*
Vascular risk score, %	0.96+0.74	0.85+0.73	1.09+0.73	0.96+0.76	0.529
Global amyloid burden	1.3110.32	1.09+0.22	1.31+0.28	1.54+0.29	<0.001*†
PiB positive, n (%)	35 (46.1)	3 (11.5)	11 (47.8)	21 (77.8)	<0.001

CDR-SOB, clinical dementia rating-sum of boxes; GDS, Geriatric depression scale; HAM-D, Hamilton depression rating scale. Comparison of three diagnostic groups was done by ANOVA with post hoc contrasts using Tukey's methods: *CN vs AD, †MCI vs AD, ‡CN vs MCI. Chi-square test was performed to compare the categorical variables