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Cognition and amyloid load in Alzheimer's imaged with florbetapir F 18 (AV-45) PET

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Abstract

Objectives—We examined the association between regional brain uptake of a novel amyloid PET tracer florbetapir F 18 ([¹⁸F]-AV-45) and cognitive performance in a pilot study.

Design—Cross-sectional comparison of florbetapir F 18 ([¹⁸F]-AV-45) in AD patients vs. controls.

Setting—3 specialty memory clinics

Participants—11 participants with probable Alzheimer's disease (AD) by NINDS/ADRDA criteria and 15 healthy comparison participants (HC).

Measurements—Participants underwent PET imaging following a 370 MBq (10 mCi) i.v. administration of florbetapir F 18. Regional/cerebellar standardized uptake value ratios (SUVRs) were calculated. Cognition was assessed using Mini-Mental State Exam, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Wechsler Logical Memory IA (immediate recall) test (LMIA), and verbal category fluency.

Results—Greater florbetapir F 18 SUVR was associated with poorer performance on all cognitive tests. In the HC group, occipital, parietal, precuneus, temporal, and cortical average SUVR was associated with greater ADAS-Cog, and greater anterior cingulate SUVR was

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Disclosure Statement

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associated with lower LMIA. Two HCs had florbetapir F 18 cortical/cerebellar SUVR > 1.5, one of whom had deficits in episodic recall and on followup met criteria for amnesic MCI.

Conclusions—Florbetapir F 18 SUVR in several brain regions was associated with worse global cognitive performance particularly in HC, suggesting its potential as a marker of preclinical AD.

Keywords

Amyloid; Alzheimer's; Cognition; Standardized uptake value ratios; Positron emission tomography; 18-Fluorine; PET tracer

BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative disease associated with aging. One of the hallmarks of AD pathology in the brain is the abundance of senile plaques, which are insoluble aggregates of amyloid- β , a metabolic product of the amyloid precursor protein. By the time AD is associated with clinical symptoms there is already significant amyloid deposition. It is increasingly apparent that imaging amyloid *in vivo* will be useful for diagnosis, prognosis and development of anti-amyloid therapies. Pittsburgh Compound B ($[^{11}\text{C}]\text{-PIB}$) is a positron emission tomography (PET) ligand that has been used to image amyloid in the human brain (1). PIB uptake is increased in AD compared to cognitively normal controls, and may be a useful biomarker for early and prodromal AD (2).

Due to the short half-life of $[^{11}\text{C}]$ -labeled compounds (20.4 minutes), clinical use of PET has been largely limited to $[^{18}\text{F}]$ -labeled compounds such as $[^{18}\text{F}]\text{-fluorodeoxyglucose}$, which allow for far greater flexibility of synthesis and imaging because of the longer half-life of $[^{18}\text{F}]$ (109.8 minutes). Among four candidate $[^{18}\text{F}]$ -labeled amyloid imaging tracers developed by Avid Radiopharmaceuticals, florbetapir F 18 was chosen as the most promising tracer due to its high affinity and specific binding for amyloid, and fast uptake and washout kinetics in brain (3). We have previously reported the kinetics of florbetapir F 18 PET imaging in humans with AD and cognitively healthy controls (HCs), as well as a comparison of cortical to cerebellar standard uptake value ratios (SUVRs) demonstrating increasing florbetapir uptake in AD patients compared to controls (4). Here we present the association of florbetapir F 18 SUVRs with cognitive performance in the same cohort. Prior results with $[^{11}\text{C}]\text{-PIB}$ offer mixed results: Pike et. al. report significant associations between PIB uptake and cognition in nondemented participants but not in AD participants (5), while Rentz et al. reported similar associations in demented and non-demented participants (6). Based on these results, our hypotheses were that greater florbetapir F 18 SUVRs would be associated with worse cognitive performance, and that this association would be most prominent in HCs.

METHODS

Participant recruitment and informed consent procedures

Eleven participants with AD and 15 healthy comparison participants (HC) were recruited from 3 sites: the Johns Hopkins University Alzheimer's Disease Research Center (ADRC) and Joint Memory Clinics (JHU) (Baltimore, MD), The Memory Enhancement Center (MEC) (Eatontown, NJ), and Community Health Center (CHC) (North East, MD). Local Institutional Review Boards approved study procedures and all participants or an appropriate representative signed informed consent consistent with established criteria (7). AD participants were > 50 years of age, had a probable diagnosis of AD according to the NINCDS-ADRDA criteria (8), and Mini-Mental State Examination (MMSE) (9) score

between 10 and 24 inclusive. HC participants were > 50 years of age with no evidence of cognitive impairment on clinical assessment, did not meet criteria for mild cognitive impairment (MCI) and had MMSE score of ≥ 29 . Exclusion criteria included 1) evidence of any other significant neurodegenerative or psychiatric disease, 2) clinically significant medical comorbidities that might pose a safety risk to the subject or interfere with interpretation of the scan, 3) participation in trials of investigational agents that target amyloid, 4) use of medications with narrow therapeutic windows including theophylline, warfarin, heparin, and other anticoagulant therapies. AD participants were included if they had been taking a cholinesterase inhibitor or memantine, as long as the dose was stable for three months prior to imaging.

Clinical Measures

Global cognitive function was assessed on the Mini-Mental State Exam (MMSE; range 0–30, with lower scores indicating worse performance)(9). The cognitive battery also included the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (10), a measure validated to be sensitive to change for AD trials and widely used for clinical characterization of cognitive deficits in AD. The range of ADAS-Cog total score is 1–70, with higher scores indicative of worse performance. Short-term episodic verbal recall was assessed with the Wechsler Logical Memory IA test (LMIA) (story A, immediate recall). The range of the LMIA is (0, 25) with higher scores indicating better recall (11) and verbal fluency was assessed by the number of animals and vegetables named in a 60 second period.

PET Methods

Data Collection—All three centers used GE PET scanners of similar design: Advance (GE Healthcare) (PET only, at JHU), Discovery LS (GE Healthcare) (PET/CT) at Community Health Center and The Memory Enhancement Center, and Discovery ST (GE Healthcare) (PET/CT) at The Memory Enhancement Center. Acquisition and cognitive test methods were identical at the three centers with the exception that a thermalplastic mask was used to minimize movement over the 90 minute scanning session at JHU only two centers. The doses of florbetapir F 18 were prepared individually on the day of administration in accordance with the Avid IND Master Batch Record and met QC release criteria. Radiotracer was made at the JHH cyclotron/radiochemistry lab for the JHH site and at the Avid, Philadelphia, PA for the remaining two centers. Subjects in the trial received an i.v. injection of approximately three hundred seventy (370) MBq (10 mCi) of florbetapir F 18 in 10 mL volume of 0.9% sterile saline containing 10% ethanol (USP) and 0.5% sodium ascorbate (USP). Dynamic brain PET images were collected for a period of approximately 90 minutes, beginning immediately after injection.

Data Analysis—We have previously reported PET analysis methods (4). Briefly, PET images for each subject were normalized to Talairach space, and volumes of interest (VOI) were created in the grey matter regions of cerebellum, frontal, temporal, parietal, and occipital cortex, anterior cingulate, posterior cingulate, and precuneus. A cortical average was calculated as the mean of these brain regions, calculated as a simple not weighted mean. Regional (or cortical average) to cerebellum standard uptake value ratios (SUVR) were then generated from count ratios from the relevant VOI for each imaging time frame. The period 50–60 minutes post injection of florbetapir F 18 was taken as the representative interval for image analysis (4).

Statistical Analyses—Mann-Whitney rank-sum tests were used to compare group means. Spearman's rank-order correlation was performed with cognitive performance as the dependent variable and regional (or cortical average) SUVRs as covariates. Spearman's r was calculated for each association. α level of 0.05 was used as the threshold for statistical

significance for all comparisons. No correction for multiple comparisons was made given the exploratory nature of the analyses.

RESULTS

The HC and AD participants did not differ on demographic characteristics with a mean age of 74.5 years (SD 10.4) ($z=.16$, $p=.87$), mean education of 17.3 years (SD 2.5) ($z=.68$, $p=.49$). 38.5% were female, 96% Caucasian, 42% reported self-defined “moderate” alcohol use and 50% were former smokers. Descriptive statistics for clinical variables are presented in table 1. AD participants had higher florbetapir F 18 SUVRs than HC participants in all 7 brain regions and the cortical average (Table 2) (previously reported(4)).

Combining AD and HC, higher florbetapir F 18 SUVRs in all 7 brain regions, and the cortical average, were associated with worse performance on all cognitive tests (Table 3). The associations between regional SUVRs and cognitive performance stratified by diagnosis are presented in Table 4. In the HC group, greater occipital, parietal, precuneus, temporal, and cortical average SUVR was associated with greater ADAS-Cog, and greater anterior cingulate SUVR was associated with lower LMIA. In the AD group, greater precuneus SUVR was associated with poorer verbal fluency. There were two HC subjects with cortical average SUVR > 1.5. One of these subjects had normal cognitive testing with (MMSE 30, ADAS-Cog 6, LMIA 12) while the other had deficits in episodic verbal recall (MMSE 29, ADAS-Cog 9, LMIA 5) and in subsequent assessments 1–2 years later met clinical criteria for amnesic MCI (data not shown).

DISCUSSION

We previously reported that florbetapir F 18 SUVRs are higher in AD vs. controls in several brain regions (4). The current report additionally presents the associations between florbetapir F 18 SUVRs and cognitive performance from the same cohort. Across all study participants, greater florbetapir F 18 SUVR in all 7 brain regions studied (and cortical average) was associated with poorer performance on a global measure of cognition (ADAS-Cog), as well as on measures of episodic memory (LMIA), and verbal fluency (category fluency). Since high AV-45 SUVR and poorer cognitive performance are both associated with AD diagnosis, we expected to find this association. But after stratifying for diagnosis we found additional associations at an exploratory level of hypothesis generation. In HCs, greater florbetapir F 18 SUVR in several brain regions studied (and cortical average), was associated with poorer performance on a global measure of cognition (ADAS-Cog), and greater florbetapir F 18 anterior cingulate SUVR was associated with poorer episodic recall (LMIA). In AD, greater florbetapir F 18 precuneus SUVR was associated with poorer verbal fluency, but no other associations met threshold for statistical significance.

The finding that some healthy controls have levels of amyloid binding in the range of those for AD patients, as assessed on florbetapir PET scans(4), is consistent with the neuropathology literature, as well as data from other biomarker studies which show that 10 to 50% of cognitively normal elderly subjects (depending on age and ApoE status) have evidence of amyloid pathology(12–15). The question then is what does this amyloid aggregation in a healthy control mean. The present study provides preliminary evidence that this amyloid deposition as evidenced by florbetapir PET is early evidence of pathology.

Although admittedly exploratory, the present results suggest that flobetapir F 18 SUVR is associated with poorer cognitive performance particularly in the HC group. These results conceptually concur with recent reports that greater [^{11}C]-PIB uptake is associated with poorer episodic memory in individuals with MCI as well as cognitively normal controls (5,

6, 16–20)(21) and that hippocampal amyloid plaque number (quantitated in autopsy samples) is associated with memory impairment(22). In our cohort, one of two HC participants with cortical SUVRs well within the AD range had evidence of impairment in episodic recall and has been observed to develop memory complaints on followup, suggesting that that participant now meets criteria for amnesic MCI. In view of these recent findings, our results suggest that florbetapir F 18 PET imaging may detect amyloid deposition associated with subtle changes in cognitive performance consistent with preclinical AD.

Limitations of this report include a small sample size with concomitant risk of both type I and type II errors. That relatively high cortical/cerebellar SUVR values were obtained in some HC participants only at site 1 may partly be due to the small sample size. The probability of amyloid pathology increases with age and the HC subjects with elevated SUVR were all at least 80. Among this small sample of subjects the HCs at site 1 tended to be older than the HCs at site 2 and 3. Similarly, as this was a first pilot study, we only administered a small number of cognitive tests, and most importantly did not carefully assess executive function, an important mediator of functional decline from MCI to AD (23). Larger studies assessing a range of cognitive domains in individuals ranging from HC to MCI to AD and that include longitudinal follow-up are now nearing completion and should shed further light on the utility of florbetapir F 18 PET imaging. Most importantly, the findings in Table 4 may be due to random chance rather than true statistical association. With 64 comparisons, if there are no true associations one would expect 3 type I errors using $p=.05$ as the statistical threshold. We report 6 such associations, and thus the possibility that these are due to random chance must be acknowledged. For these reasons we present these results as preliminary data and do not make the assertion that they are strong enough to be regarded as definitive hypothesis-testing.

Early identification of subjects with amyloid accumulation will likely be critical to the development and therapeutic application of potential disease modifying therapies because amyloid targeted therapies, may not be effective once latter stages of cascade have begun. However, the evidence to date is not sufficient to support routine use of PET amyloid imaging for screening cognitively normal subjects, even in the presence of risk factors. Although the present study suggests that amyloid accumulation seen on a florbetapir-PET scan may be associated with early signs of cognitive decline, longitudinal studies are required to understand how likely and how long it will be before such subjects progress to more serious levels of impairment. On the other hand, the present study provides further evidence to suggest that florbetapir-PET identifies a clinically relevant pathology and raises hope that PET amyloid imaging might someday allow earlier and more specific diagnosis and may possibly identify patients with AD, before the point where irreversible damage precludes effective treatment.

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References

1. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004; 55:306–319. [PubMed: 14991808]

2. Okello A, Koivunen J, Edison P, et al. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology*. 2009; 73:754–760. [PubMed: 19587325]
3. Choi SR, Golding G, Zhuang Z, et al. Preclinical properties of 18F-AV-45: a PET agent for Abeta plaques in the brain. *J Nucl Med*. 2009; 50:1887–1894. [PubMed: 19837759]
4. Wong DF, Rosenberg PB, Zhou Y, et al. *In Vivo* Imaging of Amyloid Deposition in Alzheimer's Disease using the Novel Radioligand [¹⁸F]AV-45. *J Nucl Med*. 2010 (in press).
5. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain*. 2007; 130:2837–2844. [PubMed: 17928318]
6. Rentz DM, Locascio JJ, Becker JA, et al. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol*. 2010; 67:353–364. [PubMed: 20373347]
7. Alzheimer's Association. Research consent for cognitively impaired adults: recommendations for institutional review boards and investigators. *Alzheimer Dis Assoc Disord*. 2004; 18:171–175. [PubMed: 15494623]
8. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
9. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
10. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984; 141:1356–1364. [PubMed: 6496779]
11. Wechsler, D.; Stone, CP. Manual: Wechsler Memory Scale. 1973.
12. Hulette CM, Welsh-Bohmer KA, Murray MG, et al. Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *J Neuropathol Exp Neurol*. 1998; 57:1168–1174. [PubMed: 9862640]
13. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol*. 1999; 45:358–368. [PubMed: 10072051]
14. Mintun MA, Larossa GN, Sheline YI, et al. 11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology*. 2006; 67:446–452. [PubMed: 16894106]
15. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement*. 2010; 6:221–229. [PubMed: 20451870]
16. Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated {beta}-amyloid deposition in elderly subjects. *Brain* [serial online]. Nov 28.2008
17. Resnick SM, Sojkova J, Zhou Y, et al. Longitudinal cognitive decline is associated with fibrillar amyloid-beta measured by [11C]PiB. *Neurology*. 2010; 74:807–815. [PubMed: 20147655]
18. Storandt M, Mintun MA, Head D, et al. Cognitive decline and brain volume loss as signatures of cerebral amyloid-beta peptide deposition identified with Pittsburgh compound B: cognitive decline associated with Abeta deposition. *Arch Neurol*. 2009; 66:1476–1481. [PubMed: 20008651]
19. Jack CR Jr, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009; 132:1355–1365. [PubMed: 19339253]
20. Grimmer T, Henriksen G, Wester HJ, et al. Clinical severity of Alzheimer's disease is associated with PIB uptake in PET. *Neurobiol Aging*. 2008
21. Chetelat G, Villemagne VL, Bourgeat P, et al. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol*. 2010; 67:317–324. [PubMed: 20373343]
22. Reitz C, Honig L, Vonsattel JP, et al. Memory performance is related to amyloid and tau pathology in the hippocampus. *J Neurol Neurosurg Psychiatry*. 2009; 80:715–721. [PubMed: 19258354]

Figure 1.

Scatter plot showing ADAS-cog scores as a function of cortical average SUVR for individual HC (diamond) and AD (circle) participants. Study sites are distinguished by color. For HC subjects, Spearman's $\rho = .52$, $p = .045$. For AD subjects, Spearman's $\rho = .35$ and $p = .29$.

Table 1

Demographic and clinical variables

Variable	HC (N=15)			AD (N=11)		
	Mean	SD	Range	Mean	SD	Range
Age (yrs)	74.2	11.3	55, 87	75	9.5	55, 88
MMSE	29.8	.41	29, 30	19.1	3.6	13, 24
ADAS-Cog	6.3	2.8	1, 12	22.4	7.7	9, 40
WMS	14.3	4.0	5, 20	4.5	3.6	0, 10
Fluency	30.3	6.0	20, 40	14.3	6.6	6, 23

SUVr outcomes (previously reported in {{2095 Wong, D.F. 2010}}}, Table 2) The ratio of regional (or cortical average) SUV to cerebellar SUV is reported as mean/standard deviation (SD) stratified by diagnosis (healthy comparison subjects [HC] vs. Alzheimer’s disease [AD]). SUVr’s were compared between HC and AD using Mann-Whitney two-sample test. $p<.05$ was used as the threshold for statistical significance.

Table 2

SUVr (ROI/cerebellum)	Healthy comparison subjects (HC) (N=15)		Alzheimer’s disease (AD) (N=11)		p
	Mean	SD	Mean	SD	
Anterior cingulate	1.30	.31	1.79	.30	.003
Frontal	1.20	.30	1.67	.21	.001
Occipital	1.13	.13	1.36	.26	.016
Parietal	1.17	.19	1.57	.27	.002
Posterior cingulate	1.31	.21	1.64	.19	<.001
Precuneus	1.30	.27	1.85	.24	<.001
Temporal	1.31	.20	1.77	.20	<.001
Cortical average	1.25	.18	1.67	.17	<.001

COGNITIVE PERFORMANCE VS. SUVR IN ALL SUBJECTS

Table 3

Cognitive performance vs. SUVRs for preselected ROIs and cortical average in 26 participants, (15 HC and AD). Cognitive tests include Mini-Mental State Exam (MMSE), Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Wechsler Logical Memory Scale IA (LMIA), and the sum of animal + vegetable category fluency (60 sec. each) (Fluency). Spearman’s rank-order correlation was performed with cognitive performance as the dependent variable and the ratio of regional (or cortical average) SUV to cerebellar SUV as covariate. Spearman’s r and p-values are shown for each ROI.

SUVR (ROI/cerebellum)	MMSE		ADAS-Cog		LMIA		Fluency	
	r	p	r	p	r	p	r	p
Anterior cingulate	−0.53	0.005	0.59	0.002	−0.68	<.001	−0.60	0.001
Frontal	−0.54	0.004	0.58	0.002	−0.56	0.003	−0.59	0.002
Occipital	−0.50	0.009	0.56	0.003	−0.51	0.008	−0.44	0.03
Parietal	−0.58	0.002	0.69	<.001	−0.66	<.001	−0.55	0.004
Posterior cingulate	−0.61	<.001	0.51	0.008	−0.58	0.002	−0.52	0.006
Precuneus	−0.75	<.001	0.78	<.001	−0.70	<.001	−0.68	<.001
Temporal	−0.74	<.001	0.78	<.001	−0.74	<.001	−0.72	<.001
Cortical average	−0.74	<.001	0.78	<.001	−0.74	<.001	−0.66	<.001

COGNITIVE PERFORMANCE VS. SUVR, STRATIFIED BY DIAGNOSIS

Table 4

Cognitive performance vs. SUVRs for preselected ROIs and cortical average in AD (N=11) and HC subjects (N=15).. Cognitive tests include Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Wechsler Logical Memory Scale IA (LMIA), and the sum of animal + vegetable category fluency (60 sec. each) (Fluency). Spearman's rank-order correlation was performed with cognitive performance as the dependent variable and the ratio of regional (or cortical average) SUVR to cerebellar SUVR as covariate. Spearman's r and p-values are shown for each ROI.

Healthy comparison participants (HC) (N=15)										
SUVR	MMSE		ADAS-Cog		LMIA		Fluency			
	r	p	r	p	r	p	r	p		
(ROI/cerebellum)										
Anterior cingulate	-.19	.49	.28	.31	-.52	.05	-.39	.15		
Frontal	.23	.41	.07	.81	.12	.68	.05	.85		
Occipital	-.27	.33	.52	.05	-.06	.81	.13	.63		
Parietal	-.34	.20	.71	.002	-.18	.52	-.12	.66		
Posterior cingulate	.04	.89	-.16	.57	.22	.44	.37	.17		
Precuneus	-.30	.26	.62	.01	.002	.99	.13	.64		
Temporal	-.23	.41	.52	.05	-.24	.38	-.20	.48		
Cortical average	-.19	.49	.52	.05	-.15	.60	.18	.51		

Alzheimer's Disease (AD) (N=11)										
SUVR	MMSE		ADAS-Cog		LMIA		Fluency			
	r	p	r	p	r	p	r	p		
(ROI/cerebellum)										
Anterior cingulate	.32	.34	.23	.50	.12	.72	-.08	.82		
Frontal	.19	.57	.15	.65	.05	.88	-.36	.27		
Occipital	-.18	.58	.16	.65	-.38	.24	-.49	.12		
Parietal	.16	.64	.14	.69	-.37	.26	-.009	.98		
Posterior cingulate	.10	.78	-.02	.96	-.28	.40	-.50	.11		
Precuneus	.04	.91	.005	.99	-.19	.57	-.66	.03		
Temporal	0	1.0	.37	.27	-.07	.83	-.24	.47		
Cortical average	-.08	.81	.35	.29	-.26	.43	-.41	.21		