Published in final edited form as:

J Clin Neurosci. 2017 October ; 44: 128–132. doi:10.1016/j.jocn.2017.05.008.

Agreement among neuropsychological and behavioral data and PiB findings in diagnosing Frontotemporal Dementia

Kelly A. Ryan, Ph.D.¹, Dustin Hammers, Ph.D.^{1,6}, Angeline DeLeon, B.S.¹, Hande Bilen¹, Kirk Frey, M.D., Ph.D.^{2,3}, James Burke, M.D.², Roger Albin, M.D.^{2,4,5}, Nancy Barbas, MD^{2,5}, Judith Heidebrink, MD^{2,5}, and Bruno Giordani, Ph.D.^{1,2,5}

¹Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

²Department of Neurology, University of Michigan, Ann Arbor, MI, USA

³Department of Radiology (Nuclear Medicine), University of Michigan, Ann Arbor, MI, USA

⁴Geriatrics Research, Education, and Clinical Centre, VAAHS, Ann Arbor, MI, 48105

⁵Michigan Alzheimer Disease Center, Ann Arbor, Michigan

⁶University of Utah Health Care, Salt Lake City, UT 84108, USA

Abstract

Diagnostic inaccuracies have been reported in Alzheimer's disease (AD) and Frontotemporal dementia (FTD) using clinical data alone. The [¹¹C]-PiB PET scan offers a new method of identifying AD based on the detection of amyloid deposits. Our study investigated whether there was an agreement between neuropsychological and behavioral data and PiB findings in the diagnosis of FTD. Participants were 32 patients diagnosed with suspected FTD by clinical consensus. All participants underwent neuropsychological testing and PiB imaging. In addition, caregivers completed behavioral ratings of participants' memory, frontal behaviors, and mood. Seventeen participants were classified as PiB positive (+). Results of MANOVA and subsequent ANOVA analyses showed a significant difference on memory performance between the PiB– and PiB+ groups, with the PiB– group performing better than the PiB+ group. There were no significant differences between the groups on cognitive or behavioral measures of executive/ frontal impairment, mood. Both groups showed similar severity of dementia. These findings provide evidence for the utility of the [¹¹C]-PiB PET scan in distinguishing between AD and FTD, with evaluation of memory at clinical diagnosis serving as a valuable indicator of the absence of FTD and consideration for an AD diagnosis. Our results would support the concern that patients who may present with primary behavioral or executive dysfunction may not necessarily have FTD, particularly if memory deficits are evident.

Corresponding Author for reprints: Kelly Ryan, 2101 Commonwealth Blvd, Suite C, Ann Arbor, MI 48105, karyan@umich.edu, Phone: 734-936-5524, Fax4-936-9262.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Alzheimer's disease; Frontotemporal dementia; [^{11}C]-PiB PET imaging; Neuropsychological Assessment

---

1. Introduction

Frontotemporal Dementia (FTD) has a high rate of clinical misdiagnosis when later reviewed via autopsy studies, especially when patients present to clinic early in the disease process¹. While the earliest states AD have been associated with primary memory deficits² and FTD has been associated with primary deficits in executive functioning and behavior (e.g., impaired planning and decision-making)³, the manifestation of behavioral dysfunction in preclinical AD and FTD appear to typically follow similar patterns. For example, caregivers of AD and FTD patients tend to initially report prominent changes in personality and social behavior, such as changes in distractibility, impulsivity, poor judgment, and social disinhibition⁴, resulting in diagnostic confusion at the early stages. The discovery of a frontal variant of AD further complicates the issue of accurate diagnosis. In addition to memory problems, a frontal-based manifestation of AD appears to share the cognitive deficits associated with FTD, including severe executive dysfunction and language impairment⁵. Furthermore, pathological evidence supports the existence of a frontal-AD subtype as a dense clustering of neurofibrillary tangles that can be found near the frontal lobes of patients with the frontal variant of AD⁶, rather than the temporal parietal clustering found in typical AD. As such, it has been difficult to clinically identify the proper etiology leading to cognitive decline in patients with presentation of behavioral disturbance.

Over the past several years, research has focused on improving the early detection and clinical differentiation of AD and FTD using various approaches. One method has incorporated the use of Positron Emission Tomography (PET) scans with the radiotracer [^{11}C] Pittsburgh Compound B (PiB⁷), which is known to bind with high specificity to amyloid-beta plaques. It has been proposed that by identifying the presence of amyloid plaques using a relatively non-invasive technique, PiB scanning offers a method of classifying AD based on physiological markers prior to autopsy⁸. While its efficacy as a diagnostic tool in detecting AD is still being evaluated, the presence of PiB pathology has been correlated well with neuropsychological and behavioral data in AD⁹. Similarly, PiB status has been identified as being related strongly to episodic memory in participants classified as healthy adults and individuals with Mild Cognitive Impairment (MCI¹⁰). Other research has reported the correlation of episodic memory and PiB retention in the posterior cingulum, frontal cortex, and temporal cortex, as well as conversion to a presence of amyloid pathology (PiB+) MCI cases (but absence of amyloid pathology, PiB-, MCI cases) to AD over a 2–16 month follow-up period (mean follow-up of 8 months)¹¹. Alternatively, PiB binding in FTD is thought to occur in much lower rates relative to AD, based on the decreased involvement of amyloid pathology in FTD. Rowe and colleagues¹² reported no PiB binding present in a clinically diagnosed FTD population, whereas others have identified PiB+ rates of 20–25% in clinically diagnosed FTD populations^{8,9,13}, although

these higher rates were suggested to be a function of the population having mixed FTD/AD dementia or frontal variant AD⁹.

Clinical diagnosis of FTD has not proven to be as reliable as the diagnosis of clinical AD or other related disorders when confirmation is undertaken using post-mortem autopsy. Because advancements in treatment options and the need for adequate family/patient counseling make early diagnosis imperative, it is important to evaluate the accuracy of the clinical diagnosis of FTD. The accurate differentiation of AD and FTD requires a collection of information from neuroimaging results, neuropsychological performance, and behavioral data. Although the nature of caregivers' reports tend to be similar between preclinical AD and FTD, frontal-related atrophy and the hallmark executive dysfunction associated with FTD³ suggest that caregivers should report relatively greater displays of inappropriate social behavior and poor judgment in rating FTD patients. Our group has previously shown that patients with a clinical consensus diagnosis of FTD but a molecular imaging (¹¹C-dihydrotetrabenazine PET imaging of striatal vesicular monoamine transporters and PiB imaging) diagnosis of AD, patients exhibited better memory functioning, more frequent behavioral complaints and a trend toward more impaired frontal lobe functioning as compared to those with a clinical consensus diagnosis of AD and concordant molecular imaging consistent with AD¹⁴. There were no differences between PiB+ and PiB- molecularly diagnosed FTD patients in neuropsychological performance when examining a brief battery of tests, though there were some significant behavioral differences. The lack of neuropsychological differentiation may have been due to the small sample size and reduced number of executive functioning tasks included in the battery, as well only limited behavioral/memory ratings. The clinician's ability to interpret behavioral data and to form a diagnostic opinion based on the presentation of clinical symptoms is a critical factor which influences the patient's course of treatment and, therefore, outcome. The current study examines the concordance between measures of behavior and neuropsychological performance with [¹¹C]-PiB-PET scanning in a larger subset of patients clinically diagnosed with FTD than we have previously reported and using a more extensive neuropsychological test battery and observer ratings scales.

In this current study, we examined patients who received a clinical diagnosis of FTD or MCI-executive type with suspicion of having a bvFTD and who underwent [¹¹C]-PiB PET scanning as part of a larger longitudinal project. Patients with FTD or probable FTD were identified as being either PiB positive or PiB negative (see Methods section), and the groups were compared on neuropsychological and behavioral profiles. We hypothesized that the presence of amyloid pathology would be associated with greater memory impairment and fewer frontal-related behavioral features as compared to the [¹¹C]-PiB negative group.

2. Methods

32 individuals clinically diagnosed with FTD (n = 20) using Neary criteria³ or with MCI-executive type (n=12)¹⁵ and suspected to be early in the clinical course of FTD. Participants were not suspected to have Primary Progressive Aphasia, but rather the bvFTD. There were no differences between the bvFTD and MCI-executive type groups in terms of PiB status, $\chi^2(1, n = 32) = 3.69, p = 0.08$, Cramer's V = 0.34, suggesting that they may be adequate to

combine into one group. Participants were enrolled as part of the longitudinal study of memory and aging (University of Michigan-Memory and Aging Project; UM-MAP) at the University of Michigan Alzheimer's Disease Center (MADC). Individuals were recruited from the Cognitive Disorders Clinic in the Department of Neurology, the Neuropsychology Section, or through MADC community outreach programs. Following screening for a history of stroke, Traumatic Brain Injury, and other medical conditions including intellectual disability, participants were enrolled in the MADC as part of the UM-MAP. Participants were evaluated by a neurologist and underwent neuropsychological testing with a trained technician and neuroimaging with [¹¹C]-PiB PET scans; the majority of participants underwent neuropsychological testing and neuroimaging either on the same day or within 48 hours of each other (68.8%, with 93.8% within three months of each other; 1 had a testing/scanning 6 months apart and another had them 19 months apart), and they completed a measure of current mood symptoms. Diagnosis of the participants was done at a consensus meeting consisting of at least one neuropsychologist and two neurologists. A study partners/caregiver for each participant completed measures relating to the patient's neurobehavioral symptoms. Caregivers were identified as a spouse, family member, or close friend who knew the participant well, could rate the participant's functioning, and "who provided care to the participant." UM-MAP is approved by the Institutional Human Use Review Board of the UMHS (IRBMED).

Caregiver Measures

Neuropsychiatric Inventory Questionnaire (NPI-Q¹⁶)—The NPI-Q assesses psychopathology commonly found in dementia patients through a semi-structured interview of a caregiver by a trained staff member. The version used evaluates delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. Higher scores reflect increased severity.

Frontal Behavioral Inventory (FBI¹)—The FBI is a rating scale of patients' frontal-behavioral functioning designed to help diagnose FTD. Caregivers are asked to rate changes in personality and behavior, such as apathy, judgment, and inflexibility. Higher scores reflect greater disturbance in negative behaviors and disinhibition.

Memory Complaint Questionnaire (MAC-Q¹⁷)—The MAC-Q is a measure of age-related memory decline, requiring caregivers to rate the participant's memory functioning in everyday situations relative to when they were younger. Higher scores indicate greater memory loss.

Blessed Rating Scale¹⁸—The Blessed Rating Scale is a measure of general functioning, as rated by a caregiver, which assesses changes in everyday activities, habits, and personality/interest/drive. Performance was partitioned into cognitive and functional subscales. Lower scores represent better daily functioning.

Participant measures

Neuropsychological assessment—All participants were administered a battery of neuropsychological tests as specified by the UDS test battery¹⁹ with additional tests specific to the UM-MAP. The test battery assessed basic orientation, memory functioning, executive functioning, and depressive symptoms. The Mini Mental Status Examination (MMSE) was used as a general measure of orientation and general cognition, and a study team neurologist also completed the Clinical Dementia Rating Scale (CDR²⁰), which is a measure of dementia severity. The CDR includes a global measure of dementia severity as well as a supplemental score that includes areas not rated in the CDR global rating; language dysfunction or alteration in personality and social behaviors. Memory functioning was assessed using raw score values from the Word List (WL) and Visual Reproduction (VR) subscales from the Wechsler Memory Scale-III, and executive functioning was assessed using the raw score for perseverative errors from the Wisconsin Card Sorting Test (WCST), the total time from the Trail Making Test Part B (TMT-B), and the number of words generated on the Controlled Oral Word Association Test (COWA). Patients also completed the Geriatric Depression Scale (GDS) short form as a measure of depressive symptoms. The entire testing process took approximately two hours to complete.

[¹¹C]-PiB PET imaging—A detailed review of University of Michigan PiB imaging procedures can be found in reviews^{13,21}. Briefly, participants underwent equilibrium [¹¹C]-PiB PET imaging on a Siemens ECAT HR+ camera operated in three-dimensional mode (septa retracted). [¹¹C]-PiB was administered as an intravenous bolus of 55% of the total dose followed by continuous infusion of the remaining 45% of the dose over the 80 minute duration of the study. [¹¹C]-PiB PET images were acquired as a dynamic series of 17 scan frames over the 80 min scan. Parametric [¹¹C]PiB distribution volume ratio images (DVR) were computed by averaging the last 4 scan frames (40–80 minutes) normalized to the mean value of the cerebellar hemisphere gray matter. The bolus+infusion administration provides steady-state conditions by 40 min post-injection, and hence allows direct estimation of the equilibrium distribution volume ratio (DVR). Standardized participant [¹¹C]-PiB PET transaxial image data sets stripped of identifiers were evaluated in a blinded manner by 1 expert interpreter (KF). Participants were divided into PiB positive (+) or PiB negative (–) groups based on the ratio of PiB frontal cortical binding to subcortical white matter binding. PiB deposition was judged abnormal if the cortical PiB deposition exceeded subjacent white matter deposition. Visual assessment of cortical PiB deposition has been found to exhibit accuracy comparable with quantitative analyses of PiB binding^{22,23}.

Data Analysis

For the primary behavioral and neuropsychological task analyses, a series of multivariate analyses of variance (MANOVAs) were performed using PiB status group (+/–) as the independent variable, and ANOVAs were run to determine specific group differences following significant omnibus tests. Chi-square analyses were performed for categorical variables with PiB status group as the independent variable. Measures of effect size were expressed as partial eta square (η^2) values (or Cramer's V values for non-parametric analyses).

3. Results

Of the 32 participants (age range 51–90 years old, education range 10–20 years, 40.6% female), 17 were classified as PiB+ and 15 were classified as PiB– following [^{11}C]-PiB PET imaging. Table 1 displays demographic, neuropsychological, and behavioral data. There were no significant differences among the PiB+ and PiB– groups with respect to age, $F(1, 29) = .09, p = .77, \eta^2 = .003$ and education, $F(1, 29) = 2.69, p = .11, \eta^2 = .09$. The PiB– group was more likely to include males, $\chi^2(1, n = 32) = 4.98, p = 0.04$, Cramer's $V = .39$. No significant differences existed between groups for the global CDR variable, $F(1, 29) = 0.63, p = 0.43, \eta^2 = .02$, or the MMSE, $F(1, 28) = 0.85, p = 0.36, \eta^2 = 0.0$; however, there was a significant difference between groups for the supplemental CDR variable, $F(1, 21) = 5.42, p = .03, \eta^2 = 0.21$. There was no difference between groups in terms of number of years with cognitive (memory and non-memory) decline, $F(1, 30) = 0.65, p = 0.80, \eta^2 = .002$.

Behavioral and Neuropsychological Measures

MANOVA analyses compared behavioral ratings and neuropsychological test performance between PiB+ and PiB– participants (Table 1). In general, no significant group differences existed for verbal memory tasks, Wilk's Lambda = .74, $F(4, 22) = 1.914, p = 0.14, \eta^2 = .26$. However, individual ANOVAs showed that the PiB+ group displayed a trend toward significantly worse performance on measures of Word List (WL) - % Retention, $F(1, 25) = 4.22, p = 0.05, \eta^2 = .14$, relative to the PiB– group, but not on WL-Learning Total Score, $F(1, 25) = 0.06, p = 0.81, \eta^2 = .002$, WL-Delayed Recall, $F(1, 25) = 2.75, p = 0.11, \eta^2 = .10$, and WL-Recognition, $F(1, 25) = 3.43, p = 0.08, \eta^2 = .12$. Significant differences were also observed for visual memory tests (Wilk's Lambda = .71, $F(2, 23) = 3.09, p = 0.047, \eta^2 = .29$, with VR immediate recall being, $F(1, 26) = 8.90, p = 0.006, \eta^2 = .26$ and VR Delayed Recall, $F(1, 25) = 8.12, p = 0.01, \eta^2 = .25$ being significantly worse for the PiB+ group. Alternatively, no differences existed for VR-% Retention, $F(1, 25) = 3.60, p = 0.07, \eta^2 = .13$ and VR-Recognition, $F(1, 25) = 1.71, p = 0.20, \eta^2 = .06$. Lastly, there were no significant group differences on the executive functioning measures, Wilk's Lambda = .84, $F(3, 14) = 0.92, p = 0.45, \eta^2 = .17$, with no differences between groups for the TMT-B, $F(1, 21) = 2.43, p = 0.13, \eta^2 = .10$, COWA, $F(1, 24) = 0.94, p = .34, \eta^2 = .03$, WCST perseverative errors, $F(1, 23) = 1.64, p = 0.21, \eta^2 = .07$.

In terms of behavioral ratings, there were no differences in how caregivers of the two PiB groups rated their associated participant's memory using the MAC-Q, $F(1, 28) = 1.87, p = 0.18, \eta^2 = .06$, between groups in terms of the caregivers' rating of general functioning (Blessed Cognitive subscales, $F(1, 27) = .11, p = 0.74, \eta^2 = .004$, or Blessed Functional subscales, $F(1, 28) = 0.194, p = 0.66, \eta^2 = .007$ or measures of behavioral dysregulation using the FBI ($F(1, 17) = 0.286, p = 0.60, \eta^2 = .02$, and NPI-Q, $F(1, 29) = 2.81, p = 0.10, \eta^2 = .09$. Finally, PiB status groups did not differ in terms of mood using the GDS, $F(1, 28) = 1.16, p = 0.29, \eta^2 = .04$.

Volume of Interest-based Comparison using DVR value

Comparison of PiB status groups based on quantitative measure of equilibrium DVR, distribution volume ratio indicated group differences for the five regions of interest, posterior cingulate, $F(1, 30)=46.36$, $p<.001$), superior parietal, $F(1,30)=42.76$, $p<.001$), lateral frontal, $F(1,30)=40.20$, $p<.001$), medial frontal, $F(1,30)=51.99$, $p<.001$) and lateral temporal, $F(1,30)=35.56$, $p<.001$, with the PiB+ group having greater DVRs (Table 2). Further, there was a significant difference in the average of these five areas, $F(1, 30)=46.83$, $p<.001$), with the PiB+ group showing higher DVR. When comparing the bvFTD and MCI-executive type on DVR, there were no differences between these groups and the average DVR, $F(1,30)=3.82$, $p=.06$.

4. Discussion

The results of this study partially support our hypothesis that participants classified with positive PiB binding would display worse memory performance relative to participants with the absence of amyloid pathology. Our findings showed that the PiB+ group had weaker auditory memory retention, as well as weaker visual immediate and delayed recall. In general, these findings are not surprising given previous research suggesting the inverse relationship between episodic memory and PiB status^{9–11}, along with the high conversion of PiB+ status to AD pathology. The neuronal degeneration associated with AD involves the accumulation of neurofibrillary tangles and senile plaques in the brain²⁴, which results in gradual cognitive changes and a striking deficit in memory; consequently, positive PiB status denotes the presence of amyloid pathology in these participants and explains their decreased memory performance relative to the PiB– group.

When evaluating the executive functioning measures, there was no significant difference between PiB+ and PiB– groups clinically diagnosed with suspected FTD. As executive dysfunction is traditionally more pronounced in FTD than AD, we would anticipate worse performance in the FTD group or at least in the group with no amyloid pathology. This could be related to some heterogeneity of our sample, with two thirds suspected of bvFTD and the other third only at threshold for MCI-executive type and making it find to harder to find such an effect (although these two subgroups did not differ on cognitive or behavioral measures). Further, a review of the power analyses performed for the executive functioning measures suggests that given the small sample sizes for our current sample, our analyses had very limited power to detect true differences between the means (power equal to 0.09, 0.12, and 0.33 for the WCST, TMT-B, and COWA variables, respectively). Considering that a power value less than .80 is often viewed as insufficient²⁵, our null findings may not actually reflect a true lack of difference in the executive functioning measures, but rather high rates of type 2 error. While our small sample sizes are clearly a limitation for the study, we felt that the challenges associated with properly diagnosing FTD participants and maintaining them in a longitudinal study, the high cost and complexity of the scanning procedures, and the novelty of our study aims, outweighed our limited sample size and subsequent reduced power. Compared to prior results within our group that included fewer participants¹⁴ and a more limited evaluation battery, we now see memory as a differentiating feature between our PiB groups over that of executive functions.

When evaluating caregiver ratings, participants in the PiB+ and PiB- groups showed similar patterns of behavioral problems, executive dysfunction, memory problem via behavioral ratings, and general severity of dementia, which is consistent with previous research⁴. However, the supplemental CDR rating showed higher scores (e.g., more behavioral/ personality and language change) in the PiB negative group than in the PiB positive, suggesting that clinician ratings using these additional questions may be helpful better identifying those with bvFTD. Given that the MMSE and CDR values were statistically comparable between the PiB groups, global functioning did not appear to differ in our sample, which was likely reflected in the caregiver reports, and undoubtedly contributes to diagnostic complexities. Considering that true differences were observed in memory functioning, alone, this suggests that the caregivers may not be identifying perhaps subtle memory changes in the PiB+ group.

As alluded to previously, the current samples' small size likely reduced the statistical power necessary to detect moderate differences between group means. While this did not appear to negatively impact several of the memory measures, increased sample size would have likely reduced the variation around the mean and may have resulted in significance in other domains assessed. In addition, at the present time there is no 'gold standard' method of diagnosing FTD besides using autopsy, as there is with AD. As such, although research has presented promising results using diffusion tensor imaging to detect white matter degradation in FTD in vivo²⁶, particular neuropsychological deficits have not been empirically determined to correlate with FTD-specific biomarkers or post-mortem neuronal pathology, and the neuropsychological deficits observed in FTD (e.g., prominent executive impairment) may also resemble dysfunction based on other etiologies (e.g., depression, AD). While this speaks to the importance of our current study evaluating amyloid pathology and possible misdiagnosis in a sample of clinically diagnosed FTD participants, additional research should also be undertaken to identify possible histopathological underpinnings of FTD to ensure better accuracy of FTD diagnoses both clinically and in research.

In conclusion, our results suggest that a distinguishing feature between PiB+ and PiB- participants is not necessarily behavior, but objective memory impairment using neuropsychological tests, with PiB+ participants displaying significantly worse memory than those participants without amyloid binding. This neuropsychological distinction between PiB+ and PiB- groups supports the clinical differentiation between FTD and AD diagnoses^{2,3} and may raise questions regarding the diagnostic accuracy of these dementias using clinical data, alone. Consequently, the combination of [¹¹C]-PiB PET scanning with neuropsychological measures of cognitive function, particularly memory, may add to diagnostic accuracy in AD and FTD. Furthermore, evidence for clear memory deficits in addition to clinical behavioral signs may emphasize the need for consideration of the use of amyloid-based markers. Behavior ratings do not appear to add additional information, at least in the case of patients recruited to a large research center's dementia program. Given our rates of amyloid pathology in participants initially diagnosed as FTD, the current findings suggest evidence to support the hypothesis that many patients presenting with primary behavioral or executive dysfunction may actually have AD, rather than FTD, though autopsy studies would need to be completed before definitive conclusions are drawn. The consistent use of [¹¹C]-PiB PET scanning or other amyloid-based markers may enhance the

accuracy of clinical diagnoses and effectively resolve prevalent cases of misclassification. We continue to track this sample of participants in our larger longitudinal study until post-mortem analyses can be undertaken to confirm amyloid pathology in those participants believed to have AD, which will allow us to evaluate the accuracy of clinical FTD diagnoses and the utility of [^{11}C]-PiB PET scanning in such a population.

Acknowledgments

This study was supported by the Michigan Alzheimer's Disease Center

References

1. Kertesz A, Davidson W, Fox H. Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. *Can J Neurol Sci.* Feb; 1997 24(1):29–36. [PubMed: 9043744]
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* May; 2011 7(3): 263–269. [PubMed: 21514250]
3. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* Jan 9.1998 51:1546–1554. [PubMed: 9855500]
4. Levy ML, Miller BL, Cummings JL, Fairbanks LA, Craig A. Alzheimer disease and frontotemporal dementias: Behavioral distinctions. *Archives of Neurology.* 1996; 53(7):687–690. [PubMed: 8929178]
5. Woodward M, Jacova C, Black SE, Kertesz A, Mackenzie IR, Feldman H. Differentiating the frontal variant of Alzheimer's disease. *Int J Geriatr Psychiatry.* Jul; 2010 25(7):732–738. [PubMed: 19823987]
6. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer's disease. *Archives of Neurology.* 1999; 56(10):1233–1239. [PubMed: 10520939]
7. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* Mar; 2004 55(3):306–319. [PubMed: 14991808]
8. Engler H, Santillo AF, Wang SX, et al. In vivo amyloid imaging with PET in frontotemporal dementia. *Eur J Nucl Med Mol Imaging.* Jan; 2008 35(1):100–106. [PubMed: 17846768]
9. Rabinovici GD, Furst AJ, O'Neil JP, et al. ^{11}C -PiB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology.* Apr 10; 2007 68(15):1205–1212. [PubMed: 17420404]
10. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain.* Nov; 2007 130(Pt 11):2837–2844. [PubMed: 17928318]
11. Forsberg A, Engler H, Almkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging.* Oct; 2008 29(10):1456–1465. [PubMed: 17499392]
12. Rowe CC, Ng S, Ackermann U, et al. Imaging beta-amyloid burden in aging and dementia. *Neurology.* May 15; 2007 68(20):1718–1725. [PubMed: 17502554]
13. Hammers D, Spurgeon E, Ryan K, et al. Reliability of Repeated Cognitive Assessment of Dementia Using a Brief Computerized Battery. *Am J Alzheimers Dis Other Dement.* Jun 1.2011
14. Burke JF, Albin RL, Koeppe RA, et al. Assessment of mild dementia with amyloid and dopamine terminal positron emission tomography. *Brain: a journal of neurology.* Jun; 2011 134(Pt 6):1647–1657. [PubMed: 21555336]
15. Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine.* Sep; 2004 256(3):183–194. [PubMed: 15324362]
16. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* Dec; 1994 44(12):2308–2314. [PubMed: 7991117]

17. Crook TH 3rd, Feher EP, Larrabee GJ. Assessment of memory complaint in age-associated memory impairment: the MAC-Q. *Int Psychogeriatr*. Fall;1992 4(2):165–176. [PubMed: 1477304]
18. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. Jul; 1968 114(512):797–811. [PubMed: 5662937]
19. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. *Alzheimer Dis Assoc Disord*. Oct-Dec;2006 20(4):210–216. [PubMed: 17132964]
20. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. Nov; 1993 43(11):2412–2414.
21. Koeppe RA, Frey KA. Equilibrium analysis of [11C]PIB studies. *NeuroImage*. 2008; 41(Supplement 2(0)):T30.
22. Ng S, Villemagne VL, Berlangieri S, et al. Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*. Apr; 2007 48(4):547–552.
23. Suotunen T, Hirvonen J, Immonen-Raiha P, et al. Visual assessment of [(11)C]PIB PET in patients with cognitive impairment. *European journal of nuclear medicine and molecular imaging*. Jun; 2010 37(6):1141–1147. [PubMed: 20143064]
24. Zuberko GS. Molecular neurobiology of Alzheimer's disease (syndrome?). *Harv Rev Psychiatry*. Nov-Dec;1997 5(4):177–213. [PubMed: 9427013]
25. Pallant, J. *SPSS Survival Manual*. 3. New York, NY: Open University Press; 2007.
26. Zhang Y, Schuff N, Du AT, et al. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain*. Sep; 2009 132(Pt 9):2579–2592. [PubMed: 19439421]

Highlights

- [^{11}C]-PiB PET scan can distinguish between AD and FTD
- Patients with behavioral dysfunction may not have FTD if memory deficits are evident
- The consistent use of [^{11}C]-PiB PET may enhance the accuracy of clinical diagnoses.

Table 1

Demographic, traditional neuropsychological, and behavioral outcome variables

Measure	[¹¹ C]PiB Positive (n=17)	[¹¹ C]PiB Negative (n=15)	P value	Effect Size
Age	69.76 (8.99)	70.77 (9.37)	0.768	0.003
Gender (% male)	41.2%	80.0%	0.036	0.394
Education	15.47 (3.83)	13.46 (2.50)	2.690	0.088
Onset of cognitive decline (years)	4.47 (1.60)	4.27 (2.57)	0.800	0.002
<u>General Areas/Severity</u>				
MMSE	23.00 (4.74)	24.47 (3.93)	0.364	0.030
CDR Global	0.59 (0.42)	0.70 (0.32)	0.433	0.021
CDR Supplemental	1.10 (0.81)	1.88 (0.79)	0.030	0.205
Blessed-Cognitive	1.07 (1.12)	1.21 (1.28)	0.743	0.004
Blessed-Functional	0.44 (0.89)	0.57 (0.76)	0.663	0.007
<u>Memory Measures</u>				
WL- Learning Total	19.258 (6.05)	18.73 (5.23)	0.814	0.002
WL-Delayed Recall	1.18 (2.29)	2.53 (2.00)	0.110	0.099
WL-Recognition	17.67 (2.54)	19.73 (3.13)	0.076	0.121
WL-% Retention	17.50 (29.70)	42.27 (32.20)	0.051	0.144
VR- IR	36.93 (14.54)	55.38 (18.18)	0.006	0.255
VR-Delayed Recall	11.20 (9.83)	32.58 (27.02)	0.009	0.245
VR-Recognition	36.41 (3.20)	38.33 (4.48)	0.203	0.064
VR-% Retention	30.07 (21.78)	51.08 (35.41)	0.069	0.126
<u>Frontal Measures</u>				
WCST Persv. errors	20.87 (7.77)	16.20 (7.77)	0.213	0.066
TMT-B	141.42 (59.95)	183.45 (69.44)	0.134	0.104
COWA	24.43 (13.29)	19.50 (12.41)	0.341	0.038
<u>Behavioral Measures</u>				
MAC-Q	28.94 (5.11)	26.86 (2.68)	0.183	0.063
FBI	11.89 (9.41)	14.30 (10.15)	0.600	0.017
GDS	2.37 (1.75)	3.50 (3.74)	0.290	0.040
NPI-Q	2.68 (3.93)	5.40 (5.04)	0.104	0.088

[¹¹C]PiB Positive/Negative = participants divided into PiB +/- groups based on ratio of PiB frontal cortical binding to subcortical white matter binding., MMSE = Mini-mental status examination, CDR Global = Clinical Dementia Rating Scale overall score, Blessed = Blessed Rating Scale, WL = Word List, VR = Visual Reproduction, IR = Immediate Recall, WCST = Wisconsin Card Sorting Test, TMT-B = Trail Making Test Part B, COWA = Controlled Word Association Test, MAC-Q = Memory Complaint Questionnaire, FBI = Frontal Behavioral Inventory, GDS = Geriatric Depression Scale (short-form, cut-off 5/15), NPI-Q = Neuropsychiatric Inventory Questionnaire. Effect Sizes were measured using partial eta squared values (η^2), or Cramer's V values for categorical variable.

Table 2

Distribution Volume Ratio for PiB Positive and PiB Negative groups

Measure	[¹¹ C]PiB Positive (n=17)	[¹¹ C]PiB Negative (n=15)	P value
Average DVR	1.62 (0.31)	1.07 (0.06)	<.001
Posterior Cingulate	1.56 (0.27)	1.08 (0.07)	<.001
Superior Parietal	1.57 (0.31)	1.04 (0.07)	<.001
Lateral Frontal	1.65 (0.35)	1.07 (0.03)	<.001
Medial Frontal	1.74 (0.34)	1.09 (0.07)	<.001
Lateral Temporal	1.58 (0.32)	1.07 (0.07)	<.001