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## Face-name Associative Memory Performance is Related To Amyloid Burden in Normal Elderly

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### Abstract

Cerebral amyloid beta (A $\beta$ ) deposition occurs in a substantial fraction of cognitively normal (CN) older individuals. However, it has been difficult to reliably detect evidence of amyloid-related cognitive alterations in CN using standard neuropsychological measures. We sought to determine whether a highly demanding face-name associative memory exam (FNAME) could detect evidence of A $\beta$ -related memory impairment in CN. We studied 45 CN subjects (mean age = 71.7  $\pm$  8.8) with Clinical Dementia Rating (CDR) scores = 0 and MMSE  $\geq$  28, using Positron Emission Tomography with Pittsburgh Compound B (PiB PET). Memory factor scores were derived from a principal components analysis for FNAME name retrieval (FN-N), FNAME occupation retrieval (FN-O) and the 6-Trial Selective Reminding Test (SRT). Using multiple linear and logistic regression analyses, we related the memory factor scores to PiB distribution volume ratios (DVR, cerebellar reference) as either a continuous or a dichotomous variable in frontal cortex and a posterior cortical region representing the precuneus, posterior cingulate and lateral parietal cortices (PPCLP), co-varying for age and AMNART IQ (a proxy of cognitive reserve (CR)). A significant inverse relationship for FN-N was found with A $\beta$  deposition in frontal ( $R^2 = .29$ ,  $\beta = -2.2$ ,  $p = 0.02$ ) and PPCLP cortices ( $R^2 = .26$ ,  $\beta = -2.4$ ,  $p = 0.05$ ). In contrast, neither FN-O nor the SRT were significantly related to A $\beta$  deposition. Performance on a demanding test of face-name associative memory was related to A $\beta$  burden in brain regions associated with memory systems. Associative memory for faces and names, a common complaint among older adults, may be a sensitive marker of early A $\beta$ -related impairment.

### Keywords

Preclinical Alzheimer's Disease; Early Detection; Normal Aging; Amyloid Imaging

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## Introduction

Cognitively normal (CN) older individuals without evidence of cognitive or functional impairment are frequently found to harbor a substantial burden of fibrillar amyloid beta ( $A\beta$ ) pathology when imaged with Positron Emission Tomography (PET) using Pittsburgh Compound B (PiB) (Fagan, et al., 2006; Johnson, 2006; Mintun, et al., 2006). This observation is consistent with postmortem data indicating that substantial numbers of  $A\beta$  plaques are found in some individuals who showed no evidence of memory impairment or dementia during their lifetime (Bennett, et al., 2006; Katzman, et al., 1989; J. L. Price & Morris, 1999). Such individuals may represent a preclinical stage of Alzheimer's disease (AD) (Morris, et al., 2009; Sperling, et al., 2011), however, it has been difficult to reliably detect evidence of  $A\beta$ -related cognitive alternations in CN subjects using standard neuropsychological measures.

Several studies examining increased  $A\beta$  deposition with PiB PET imaging in CN subjects were unable to find a relationship between cognitive test performance and  $A\beta$  burden (Aizenstein, et al., 2008; Jack, et al., 2008; Mormino, et al., 2009; Villemagne, et al., 2011). One study (Pike, et al., 2007) of 32 healthy control subjects was able to find a modest relationship ( $r = -0.38$ ) between  $A\beta$  burden and episodic memory (EM) in CN subjects but the general findings were limited by sample selection bias toward family history and the presence of an apolipoprotein (APOE)  $\epsilon 4$  allele, primary risk factors for AD. Another study by Mormino et al. (Mormino, et al., 2009) found that PiB retention was related to EM and to hippocampal volume (HV) in a subset ( $N=20$ ) of the healthy control subjects studied. However, when HV and PiB were included in a regression model predicting EM, the HV variable was significant and the PiB variable was not. Storandt and colleagues (Storandt, Mintun, Head, & Morris, 2009) reported an association of  $A\beta$  burden with longitudinal cognitive decline prior to diagnosis of AD but a single time point of cognitive performance was not predictive of  $A\beta$ -related cognitive change.

As a potential confounding factor in the relationship between  $A\beta$  burden and cognitive performance, several studies, including our own, found that cognitive reserve (CR) may influence this association (Kemppainen, et al., 2008; Rentz, et al., 2010; Roe, et al., 2008; Roe, et al., 2010; Yaffe, et al., 2011). CR is a construct that indicates a reduced susceptibility to the clinical expression of a dementia, despite advanced neuropathology (Stern, 2009). This reduced susceptibility could be due to individual characteristics such as increased synaptic or neuronal capacity, greater efficiency engaging brain networks, or the use of alternative strategies to solve task demands. In a previous study with 66 CN subjects, the  $A\beta$  relation to cognitive performance was strongly attenuated in subjects with higher CR (Rentz, et al., 2010) suggesting that high CR subjects were performing normally on standardized cognitive tests despite increased  $A\beta$  burden. When a more challenging verbal associative memory task (i.e., Memory Capacity Test) was administered, we were able to find a significant relationship between memory performance and  $A\beta$  deposition but performance on the MCT was also sensitive to the modifying effects of CR.

As the field moves toward detecting and treating asymptomatic individuals during the very earliest stages of preclinical AD, it will be increasingly important to develop cognitive tests that are both sensitive to early pathological change and useful in subjects with all levels of CR. Since previous work with face-name associative memory tasks has demonstrated sensitivity to memory impairments related to preclinical AD (Clare, Wilson, Carter, Roth, & Hodges, 2002; Parra, et al., 2010; Werheid & Clare, 2007) and to impaired neural activity during face-name memory formation on fMRI tasks in subjects with amyloid deposition, (Sperling, et al., 2009; Vannini, et al., 2011) we speculated that this type of associative

memory task may help to clinically differentiate older individuals with early amyloid deposition, irrespective of CR. Here, we tested the hypothesis that performance on a highly demanding test of face-name associative memory (FNAME), is related to A $\beta$  burden in CN older adults and might be useful in overcoming the modifying effects of CR. In particular, we hypothesized that forming and retrieving novel cross-modal face-name associations (FN-N) would be particularly challenging, compared to face-occupation associations (FN-O), and might be a sensitive marker of early amyloid-associated memory impairment, even among the range of performance in CN older adults.

## Materials and Methods

### Subjects

Forty-five CN subjects enrolled in the Harvard Aging Brain Study at the Center for Alzheimer Research and Treatment at the Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) Alzheimer's Disease Research Center were studied using protocols and informed consent procedures approved by the Partners Human Research Committee.

The CN subjects were defined as having a Clinical Dementia Rating (CDR) (Morris, 1993) score of 0, a Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) score of greater than or equal to 28 and a Geriatric Depression Scale (GDS) score of less than 11 (Yesavage, et al., 1983) (See Table 1). A detailed review of medical history and functional performance as well as physical and neurological examinations confirmed their status as clinically normal (CN). Medical history profiles were typical of an aging sample with 13% having controlled hypertension, 3% with controlled hypercholesterolemia, 6% with remote history of resolved breast cancer, 4% with asthma and 2% with gastroesophageal reflux disease, atrial fibrillation, remote history of resolved prostate cancer and resolved depression. None of the participants had a history of alcoholism, drug abuse, head trauma or current serious medical or psychiatric illness.

**Neuropsychological (NP) evaluation**—Subjects were administered an extensive battery of NP tests that covered the cognitive realms of attention, executive functions, memory, language and visuospatial processing. For this study, we focused only on episodic memory (EM) tests because declines in EM are reportedly the earliest signs of preclinical AD; (Albert, Moss, Tanzi, & Jones, 2001; Johnson, et al., 2007a) and performance on tests of EM tend to decline 7 years before conversion to AD (Grober, et al., 2008). EM tests administered to our subjects included the 6-Trial Selective Reminding Test (SRT), (Masur, et al., 1989) the Free and Cued Selective Reminding Test (FCSRT) (Grober, Merling, Heimlich, & Lipton, 1997) and a challenging cross-modal associative memory test we developed based on fMRI experiments, called the Face-Name Associative Memory Exam (FNAME) (Sperling, et al., 2003a; Sperling, et al., 2001).

**FNAME Procedure**—The FNAME requires the subject to remember 16 unfamiliar face-name pairs and 16 face-occupation pairs for a total of 32 cross-modal paired associates to be remembered. The test has an initial study phase as well as free recall and cued recall trials.

**Initial Face Study Phase:** The test begins with an exposure to all 16 faces. Subjects are shown 4 faces to a page, one face in each quadrant. They are asked to look at each face for a total of 2 seconds until they have seen all 16 faces.

**Initial Study of Face-Name Pairs:** Subjects are then presented the same faces with names underneath and asked to study the name that goes with the face. To ensure that the subject is

learning the face-name pairs, the examiner points to the face and asks the subject to read the name associated with that face. After all 4 items are correctly identified; another 4 face-name pairs are presented until all 16 face-name pairs are studied. Subjects are given only one exposure to learn all 16 face-name pairs.

**Initial Recall of Face-Name Pairs:** The subjects are then shown the face and asked to recall the name that goes with the face. The correct number of face-name pairs is recorded as an initial learning score for names (ILN).

**Initial Study of Face-Occupation Pairs**—Subjects are then shown the same faces but this time with occupations underneath. The face-occupation pairs are presented in the same manner as the face-name pairs until all 16 face-occupation pairs are studied.

**Initial Recall of Face-Occupation Pairs:** Subjects are again shown the face and asked to recall the occupation that goes with the face. Correct recall of faces and occupations are tabulated as initial learning of occupations (ILO).

**FNAME Recall Trials**—The FNAME included both “free” and “cued” recall trials at immediate and delayed intervals.

**Free Recall Trials:** After the initial study phase, subjects are then asked to freely recall all the names (FRN) and occupations (FRO).

**Cued Recall Trials:** Following the Free Recall trial, subjects are shown the face and asked to recall the name (CRN) and occupation (CRO) that was associated with the face.

**30-Minute Delayed Free Recall:** Subjects are again asked to freely recall the names (FRN30) and occupations (FRO30) following a 30-minute delay.

**30-Minute Delayed Cued Recall:** Subjects are again shown the face and asked to recall the name (CRN30) and occupation (CRO30) associated with the face. A Reliability Analysis indicated good internal consistency among the 10 performance scores of the FNAME with a Cronbach alpha coefficient of .96. The mean inter-item correlation was 0.72 with values ranging from 0.48 to .93 suggesting a strong relationship among the items.

The distribution of scores on the FNAME was examined in relationship to performance on the SRT to determine the range of performance. We found that the FNAME did not exhibit the same ceiling effect in normal controls as other traditional memory measures (see Figure 1a and 1b). Furthermore, successful performance on the FNAME has been associated with increased activity in the brain networks subserving memory in both young and older individuals (Miller, et al., 2008).

**Development of Composite Factor Scores**—To avoid capitalizing on chance due to multiple comparisons, the memory test battery was subjected to a principal components analysis to derive composite factor scores. The initial analysis revealed 5 factors among all the memory tests, explaining 86% of the variance (51%, 17.1%, 7.3%, 6.1% and 4.9% respectively). The Kaiser-Meyer-Olkin value of .83 and Bartlett’s Test of Sphericity ( $p < .001$ ) supported the factorability of the correlation matrix. However, the scree plot revealed a clear break after the third factor and it was decided to retain only those 3 factors. This resulted in excluding the MC and MC30 of the SRT and FRsrt and FCsrt of the FCSRT. The three-factor solution explained a total of 88% of the variance. Factor 1 contributed to 60.4% of the variance and was associated with the FNAME Name scores. Factor 2 contributed to 20.4% of the variance and was associated with the SRT scores. Factor 3 contributed to 7.3%

of the variance and was associated with the FNAME Occupation scores. Table 2 displays the tests that loaded on the 3 factors. The Kaiser-Meyer-Okin value of .86 and Bartlett's Test of Sphericity ( $p < .001$ ) again supported the factorability of the correlation matrix. The component correlation matrix revealed that the FNAME Name Composite (FN-N) was correlated with the SRT-Memory Composite ( $r = 0.547$ ,  $p < 0.01$ ) as well as the FNAME Occupation Composite (FN-O) ( $r = 0.367$ ,  $p = 0.01$ ). The FN-N and FN-O Composites were also highly correlated with each other ( $r = 0.693$ ,  $p < 0.01$ ). In light of these 3 identified factors, we derived regression weighted factor composite scores for each subject. We used these 3 factor composites to explore the relationship of EM performance in CN subjects to A $\beta$  deposition in frontal association and parietal/posterior cingulate cortices that encompass a widely distributed memory network (Buckner, et al., 2005). These regions were chosen because they are associated with early A $\beta$  deposition (Mintun, et al., 2006) and EM in the default network (Buckner, et al., 2005; Sperling, et al., 2009). The average factor composite scores are given in Table 1. The mean (sd) time between PET imaging and testing was 3.4 (5.5) months.

**Positron Emission Tomography—PiB** was prepared as described by Mathis et al (Mathis, et al., 2003) and PiB PET acquisitions were performed as described previously (Gomperts, et al., 2008; Johnson, et al., 2007b; Rentz, et al., 2010). Following a transmission scan, 8.5 – 15 mCi  $^{11}\text{C}$ -PiB was injected as a bolus and followed immediately by a 60-minute dynamic acquisition. PiB PET data were reconstructed with ordered set expectation maximization, corrected for attenuation. Each frame was evaluated to verify adequate count statistics and absence of head motion. The Logan graphical analysis method (Logan, et al., 1996; J. C. Price, et al., 2005) with cerebellar cortex as the reference tissue input function was used to evaluate specific PiB retention expressed as the distribution volume ratio (DVR) (Archer, et al., 2006; Fagan, et al., 2006; Johnson, et al., 2007b; Lopresti, et al., 2005). We calculated the DVR (with cerebellar grey reference) in aggregate cortical regions-of-interest (ROI) for the frontal association and precuneus, posterior cingulate, and lateral parietal (PPCLP) cortices, particularly including brain regions responsible for memory. The ROIs were defined according to the automated anatomical labeling (AAL) parcellation scheme (Tzourio-Mazoyer, et al., 2002) applied to data warped to the Montreal Neurological Institute (MNI) standard space using Statistical Parametric Mapping software. The Frontal association cortex ROI consisted of inferior (opercularis, triangularis, orbitalis), superior and middle gyri as well as the supplementary motor area. The PPCLP ROI comprised the posterior cingulate, parietal lobe, supramarginal gyrus, angular gyrus, and precuneus.”(see Figure 3 in Tzourio-Mazoyer, et al., 2002).

**Statistical Analysis—**We performed multiple regression analyses relating PiB retention (DVR, cerebellar reference) as a continuous variable in cortical regions, co-varying for age and AMNART IQ, as a proxy for CR (Rentz, et al., 2007; Rentz, et al., 2010) and the interaction (cross-product) of CR and amyloid burden to the 3 memory factor scores. A logistic regression was performed to determine if PiB positivity was related to the 3 memory factor scores, covarying for age and AMNART-IQ. As reported previously (Rentz, et al., 2010), we chose a cut-point for amyloid PiB-positive to be a global mean PiB  $\geq 1.15$  ( $n = 17$ ). PiB-negative was defined as a global mean PiB  $< 1.15$  ( $n = 28$ ). We chose 1.15 because (1) it is the cutoff used in other studies published by our group (Gomperts, et al., 2008; Hedden, et al., 2009; Rentz, et al., 2010); (2) because in a previous study combining CN, MCI and AD subjects it represented a cut point that best separated those with from those without focally elevated PiB retention (Gomperts, et al., 2008); and (3) because it represented a lower limit for PiB retention seen in AD patients (Gomperts, et al., 2008; Johnson, et al., 2007).

Post-hoc multiple regression analyses were performed to examine the specificity of the relationship between cognitive performance and A $\beta$  burden in frontal and PPCLP regions. The dependent variable was each subtest of the FNAME, the individual cognitive tests for the various domains of attention (Digit Span forward, Trails A), executive functions (Trails B, FAS, Digits Backward), semantic processing (category generation to animals, vegetables and fruit), language (Boston Naming Test) and visuospatial processing (Visual Form Discrimination Test) as well as an executive z-score composite consisting of Trails B, FAS and Digits Backward. The covariates were age, AMNART IQ and the PiB DVR. We also explored in a post-hoc analysis, the relationship of A $\beta$  deposition in frontal and PPCLP regions with APO  $\epsilon$ 4 carrier status and memory performance, again controlling for age and AMNART IQ. Significance was set *a priori* as  $p < 0.05$ . All data were analyzed using SPSS v18.0.

## Results

### Subject Characteristics

The subject characteristics are provided in Table 1. The sample had an average age of 72 years (46–88 years). Figure 2 displays global amyloid deposition across the age range. There were no significant differences between the numbers of men and women in the sample, with 42% of the sample being men and 58% women. Men were more educated than women (Mann-Whitney U Test,  $p = .01$ ), but there were no significant differences between men and women on any of the other variables.

### Relationship between Amyloid and Memory Performance, Multiple Regression Analysis

We initially explored whether A $\beta$  deposition in cortical regions was associated with memory performance using the 3-factor scores co-varied for age and AMNART IQ. Table 3 provides the results of the multiple regression analyses. We found a significant inverse relationship for the FN-N Composite such that lower performances were associated with A $\beta$  deposition in frontal ( $R^2 = 0.29$ ,  $\beta = -2.2$ ,  $p = 0.02$ ) and PPCLP cortices ( $R^2 = 0.26$ ,  $\beta = -2.4$ ,  $p = 0.05$ ) (see Figure 3a). There were no significant associations found with the SRT Memory Composite (see Figure 3b) or the FN-O Composite (see Figure 3c). No significant relationships were found between FN-N Composite scores, FN-O Composite scores, amyloid deposition and CR.

### Logistic Regression Analysis

To explore whether PiB positivity was related to memory performance on the 3 factor scores, we performed a logistic regression co-varying for age and AMNART IQ. We found a significant relationship between the PiB-positive classification and lower performance on the FN-N Composite ( $\chi^2 = 11.13$ ,  $\beta = -1.32$ ,  $p = 0.04$ ) but there were no significant relationships with the FN-O or SRT Composites (see Figure 4).

### Post-Hoc Analyses

In post-hoc analyses we explored whether specific aspects of the FNAME were related to amyloid burden in frontal and PPCLP regions. We found that performance on all subtests of the FN-N portion of the FNAME were significant with frontal amyloid deposition including initial learning (ILN,  $r^2 = .38$ ,  $p = .02$ ) free recall (FRN,  $r^2 = .28$ ,  $p = .01$ ) and cued recall (CRN,  $r^2 = .28$ ,  $p = .03$ ), as well as free (FRN30,  $r^2 = .23$ ,  $p = .04$ ) and cued delayed recall (CRN30,  $r^2 = .20$ ,  $p = .05$ ). The relationship between performance on these subtests and PPCLP amyloid deposition showed a similar pattern, but was not as significant across all FN-N subtests of the FNAME (ILN,  $r^2 = .38$ ,  $p = .02$ ; FRN,  $r^2 = .23$ ,  $p = .05$ ; CRN,  $r^2 = .25$ ,  $p = .08$ ; FRN30,  $r^2 = .21$ ,  $p = .08$ ; CRN30,  $r^2 = .16$ ,  $p = .16$ ). We did not find a significant

relationship with amyloid deposition and performance on any of the FN-O subtests of the FNAME. These findings suggest that all aspects of FN-N are similarly challenging and significantly related to amyloid burden.

We also explored whether A $\beta$  burden in frontal and PPCLP regions was related to other cognitive functions. We did not find any significant relationships ( $p > 0.15$ ) with A $\beta$  burden in frontal or PPCLP regions with tests representing the cognitive domains of attention, executive function, language and visuospatial processing.

Finally, we reran the above regression analyses to determine if there was a relationship between APOE status and memory performance. Thirty-two of the 45 subjects had APOE genotyping available. The remaining 13 individuals did not differ from the 32 subjects in either demographics or performance on the memory factor scores or any of the other cognitive measures. Of these 32 subjects, 8 were  $\epsilon 4$  carriers and 24 were non- $\epsilon 4$  carriers. We reran the regression models as described above but added one or no copies of the APOE  $\epsilon 4$  allele as a dummy-coded predictor variable. We found that APOE status was not a significant predictor of memory performance on any of the memory composite scores. We also failed to find a significant relationship between APOE carrier status and degree of amyloid deposition in either frontal, PPCLP, precuneus, and global PiB DVR regions (all  $p > 0.30$ ) in this sample.

## Discussion

In this study, we report an association of A $\beta$  burden with performance on a highly challenging test of face-name associative memory, namely (FN-N) of the FNAME, in CN older adults. Similar to other reports (Aizenstein, et al., 2008; Mormino, et al., 2009; Rentz, et al., 2010; Storandt, et al., 2009), we were unable to find this association with less challenging tests of EM, such as face-occupation retrieval (FN-O) or the SRT. The findings of this study suggest that FN-N, in particular, may be a more sensitive probe of A $\beta$ -related memory dysfunction when examining CN older adults.

Forming face-name associations is widely acknowledged to be particularly difficult due to the inherent unrelatedness of a face with a name (Werheid & Clare, 2007). Remembering proper names is the most common memory complaint of older adults (Leirer, Morrow, Sheikh, & Pariente, 1990; Zelinski & Gilewski, 1988). Whereas, forming an association of a face with other biographical information about someone (i.e., occupations, hobbies) is easier (Cohen, 1990; McWeeny, Young, Hay, & Ellis, 1987). Even in paradoxical situations where “Baker” is used as both a name and an occupation, Baker presented as a name was harder to recall than when it was presented as an occupation (McWeeny, et al., 1987). Since there are no contextual properties with which to formulate an associative link, binding a proper name to a unique face can be considered much more effortful, requiring a higher level of cognitive demand, than other less demanding memory tasks that can be associated with previously stored semantic knowledge, such as occupations in the FN-O task, or recalling words that can be associated with well known categories such as on the California Verbal Learning Test or the Free and Cued Selective Reminding Test. It is unknown whether other tests of high cognitive demand would be associated with amyloid deposition. However, based on our analyses, we did not find an association with amyloid deposition and other frontal executive tasks, including Trails B. Consistent with this theory, we found that forming an association between a face and a name was not only more difficult for CN older subjects but also associated with A $\beta$  burden in brain regions related to memory.

Previous fMRI work from multiple groups has suggested that the successful formation and retrieval of face-name pairs required coordinated activity in a distributed memory network

(Fletcher & Henson, 2001; Miller, et al., 2008; Rugg, Otten, & Henson, 2002; Sperling, et al., 2003b; Vannini, et al., 2010; Zeineh, Engel, Thompson, & Bookheimer, 2003) This network includes not only the hippocampus and related structures in the medial temporal lobe, but a distributed set of cortical regions, collectively known as the default network (Buckner, et al., 2005; Raichle, et al., 2001). Of particular relevance to our current findings, is the observation that the precuneus/posterior cingulate appears to be a key node in the default network involved in both encoding and retrieval of associative memories (Miller, et al., 2008; Rugg, Otten, & Henson, 2002; Vannini, et al., 2010).

The brain regions particularly vulnerable to early A $\beta$  deposition appear to overlap the anatomic distribution of the default network (Buckner, et al., 2005; Sperling, et al., 2009). Regions within the default network show structural and functional connectivity that converge on the posterior cingulate extending into the precuneus which is strongly interconnected with the hippocampus (Greicius, Srivastava, Reiss, & Menon, 2004). Our previous work, as well as that of other groups, has suggested that A $\beta$  deposition in the default mode network is associated with functional disruption within the default network in cognitively normal older individuals (Hedden, et al., 2009; Sperling, et al., 2009; Vannini, et al., 2011). Thus it is perhaps not surprising that we found an association between reduced performances in FN-N and increased A $\beta$  burden in these brain regions. We did not observe an association between A $\beta$  deposition in medial temporal lobe regions and performance on any cognitive measures. This likely reflects the fact that there is relatively less amyloid pathology in the human hippocampus compared to neocortical regions found in aging or early Alzheimer's disease.

Another important finding of this study is the association between FN-N and A $\beta$  burden in frontal cortices, in addition to parietal regions. Converging evidence has shown that in addition to medial temporal involvement, cortical regions of the frontal lobe also play an important role in associative memory formation and retrieval (Cabeza, et al., 1997; Fletcher & Henson, 2001) including the forced choice recognition of memory for face-name pairs (Jackson & Schacter, 2004; Vannini, et al., 2010; Werheid & Clare, 2007). When we explored whether specific subtests of the FNAME were related to amyloid deposition in frontal and PPCLP regions, we found that all aspects of FN-N including initial learning, recall and delayed recall were similarly challenging and significantly related to A $\beta$  burden in frontal and PPCLP regions. While it is known that declines in EM and executive functions are predictive of subsequent cognitive decline to AD, (Albert, Moss, Tanzi, & Jones, 2001; Blacker, et al., 2007; Chen, et al., 2000; Grober, et al., 2008), an association of memory and executive dysfunction with A $\beta$  burden in frontal cortex has not been reported in CN older adults. We found that impairments in FN-N were related to A $\beta$  burden in frontal cortices which are also vulnerable to early A $\beta$  deposition (Klunk, et al., 2004).

The findings in this study are consistent with other reports that have suggested that paired associative learning tasks are particularly sensitive in detecting early impairment and preclinical AD, sometimes well before significant deterioration occurred on standard neuropsychological tests (Blackwell, et al., 2004; de Jager, Milwain, & Budge, 2002; Elias, et al., 2000; Fowler, Saling, Conway, Semple, & Louis, 2002; Linn, et al., 1995). In fact, face-name associative memory may be particularly sensitive in dissociating memory impairments related to preclinical AD from those associated with normal aging. Others have also found that face-name associative memory, provides highly sensitive indices of episodic and semantic memory performance in preclinical AD (Clare, Wilson, Carter, Roth, & Hodges, 2002; Parra, et al., 2010; Werheid & Clare, 2007), as was a shape-color associative visual memory task in predicting familial AD (Parra, et al., 2010). It remains to be known whether there are other types of paired associative learning tasks that are equally sensitive to



A $\beta$  burden but the development of more challenging tests of memory are needed as future clinical trials move to target individuals in preclinical stages of AD.

This study has several important limitations. The sample size was small and the fact that we did not find an interaction with CR may be due to a lack of power or may suggest that CR plays less of a role in more challenging EM tasks. Another limitation of this report is the lack of APOE genotyping in all subjects, the limited number of APOE  $\epsilon$ 4 carriers and the absence of any  $\epsilon$ 4 homozygotes in the study. Previous studies with larger sample sizes, including subjects with family history of AD (Morris, et al., 2010) or recruited specifically to find APOE  $\epsilon$ 4 carriers (Reiman, et al., 2009) have reported that accelerated memory decline (Caselli, et al., 2009) and fibrillar A $\beta$  as measured with PiB PET imaging was significantly associated with APOE  $\epsilon$ 4 carrier status in cognitively normal individuals. Future work will be required to determine if APOE has an independent contribution to our observed findings. Finally, the relationship between frontal and PPCLP amyloid and FN-N appears to be driven primarily by a small number of individuals with high amyloid burden. Data from our group, as well as reports from multiple other groups studying amyloid imaging, suggest that the relationship between A $\beta$  burden and cognitive performance, as well as functional and structural imaging variables, is often driven by the subset of individuals with very high levels of PiB retention (Becker, et al., 2011; Hedden, et al., 2009; Sheline, et al., 2010; Sperling, et al., 2009). Although we believe that there is a continuum of A $\beta$  burden, it is likely that these few individuals with very high A $\beta$  deposition represent those at highest risk for subsequent clinical decline, and that these individuals are of particular interest.

In conclusion, we found that performance on a demanding test of face-name retrieval, a common complaint of many normal older individuals, was associated with A $\beta$  burden in frontal and PPCLP cortices, thought to be critical brain regions in a distributed memory network. Challenging tests of associative memory retrieval in clinically normal older individuals may prove to be sensitive markers for detecting the early effects of A $\beta$  deposition.

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Figure 1a

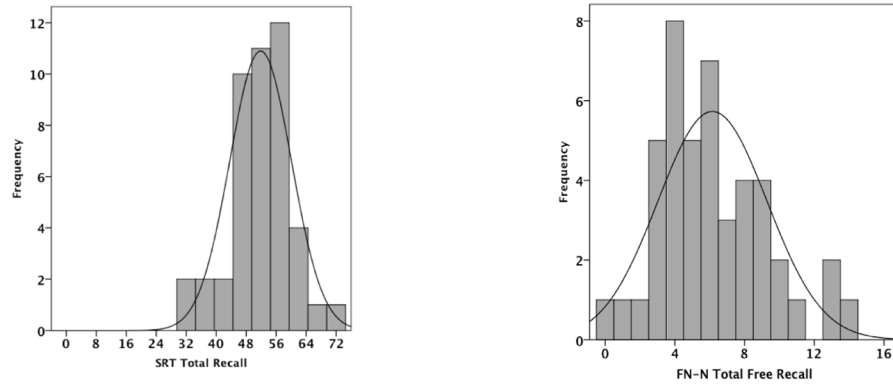
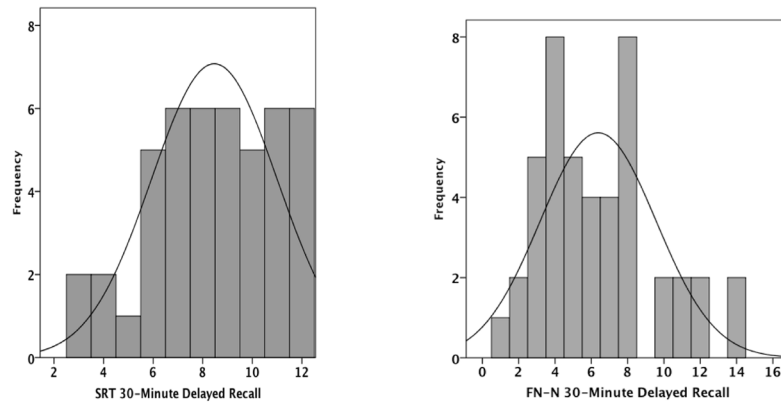
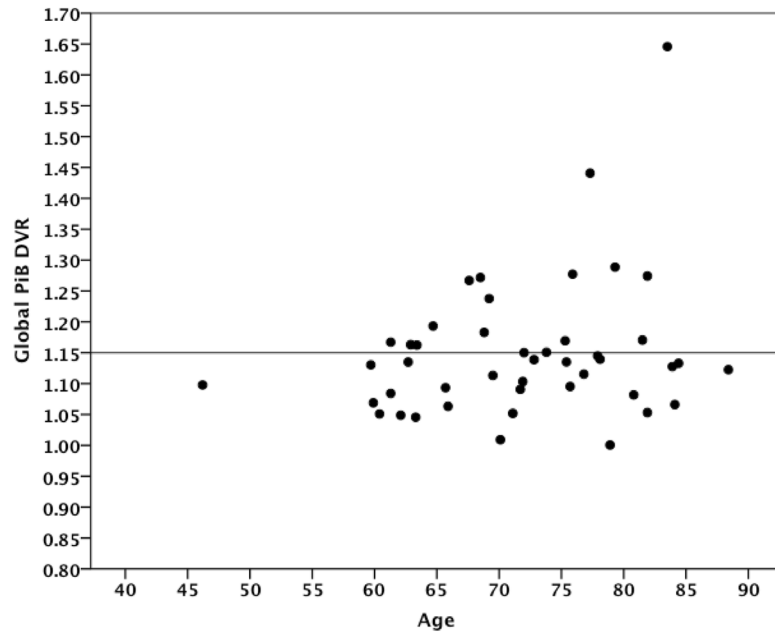


Figure 1b



**Figure 1.** Figure 1a and 1b: Histograms of the frequency of SRT Total Recall and FN-N Total Free Recall as well as SRT 30-Minute Delayed Recall and FN-N 30-Minute Delayed Recall shows that the FN-N distribution of scores has less of a ceiling effect than the SRT scores. (Scales on the x-axis represent the highest score possible on the test)



**Figure 2.** Scatterplot of age and global A $\beta$  deposition. Line at 1.15 indicates the separation between amyloid negative and amyloid positive individuals based on a combined sample of 140 subjects representing the lower limit for PiB retention in AD patients.

Figure 3a

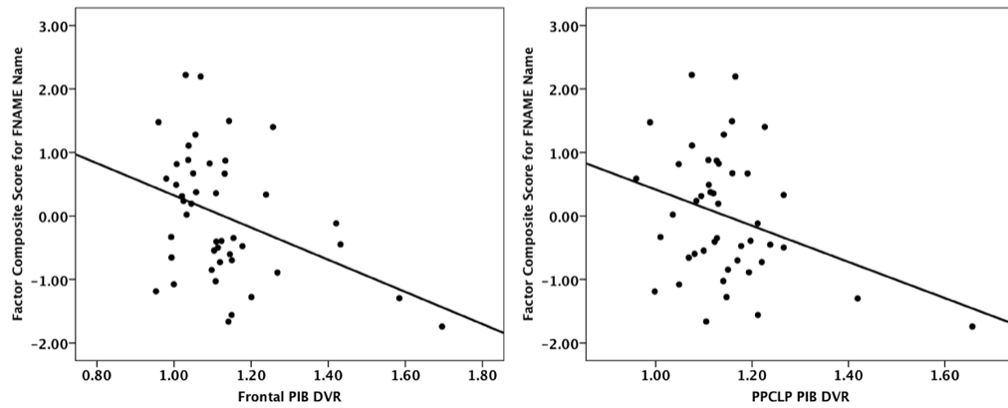


Figure 3b

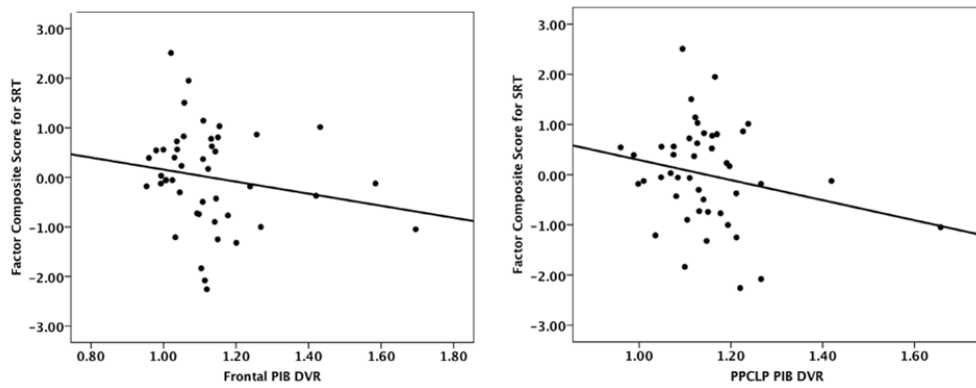
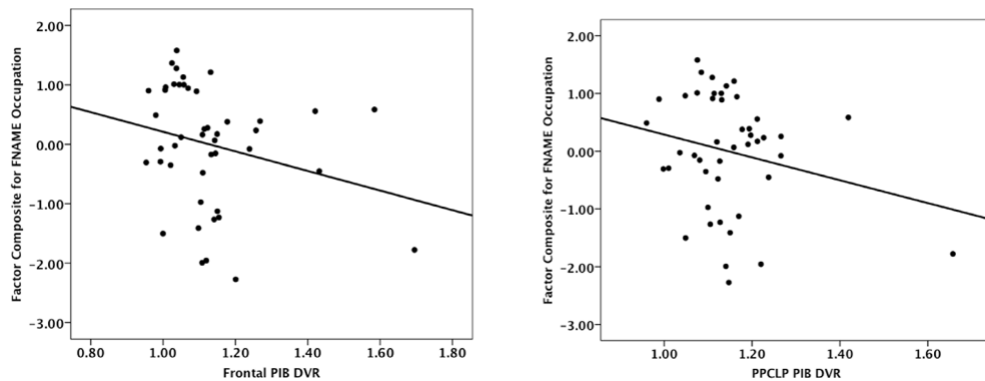
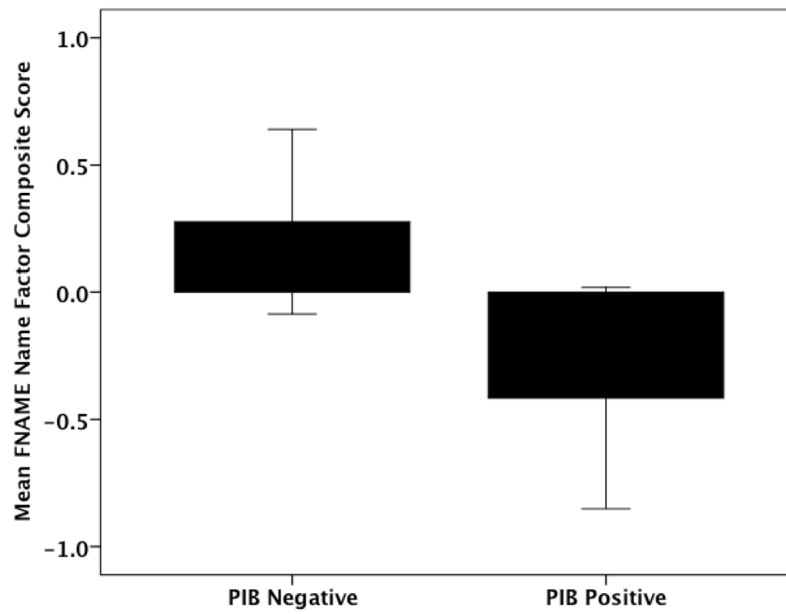


Figure 3c



**Figure 3.** Figure 3a to 3c: Performances on the FN-N Composite (3a) the SRT Memory Composite (3b) and the FN-O Composite (3c) were inversely related to PiB retention in frontal and PPCLP cortices but only the FN-N Composite reached statistical significance. Analyses were co-varied for age and AMNART IQ.





**Figure 4.** Logistic regression revealed a significant relationship between PiB positive classification and lower performance on the FN-N Composite.

**Table 1**

Sample Characteristics (N=45)

Sex, M/F, (Percent)	19 (42%)	26 (58%)		
	Mean	SD	Range	
Age	71.72	8.81	46.2	88.4
Education	16.73	2.64	12.0	20.0
AMNART IQ	123.47	7.05	102.0	132.0
MMSE	29.27	0.75	28.0	30.0
GDS	3.07	3.27	0.0	10.0
FNAME Name Composite	0.02	0.96	-1.65	2.16
FNAME Occupation Composite	-0.01	0.94	-2.16	1.50
SRT Composite	-0.02	0.78	-1.74	1.95
Frontal DVR <b>Median</b>	<b>1.11</b>	0.15	0.95	1.70
PPCLP DVR <b>Median</b>	<b>1.13</b>	0.11	0.96	1.66

AMNART IQ= American National Adult Reading Test Intelligence Quotient; MMSE= Mini Mental State Exam, GDS= Geriatric Depression Scale, FNAME- Face Name Associative Memory Exam, SRT= Selective Reminding Test, DVR= Distribution Volume Ratio, PPCLP= Precuneus, Posterior Cingulate and Lateral Parietal

**Table 2**

Pattern and structure matrix for PCA with oblim rotation of 3-factor solution from which regression weighted factor scores were derived for each individual.

Tests	Pattern Coefficients			Structure Coefficients			
	Component			Tests	Component		
	1	2	3		1	2	3
FRN30	<b>.991</b>	.010	.045	FRN30	<b>.966</b>	.527	.623
CRN30	<b>.976</b>	.022	.048	CRN	<b>.965</b>	.544	.667
CRN	<b>.921</b>	.035	.037	CRN30	<b>.956</b>	.530	.614
FRN	<b>.899</b>	.016	.096	FRN	<b>.955</b>	.501	.693
ILN	<b>.890</b>	.009	.022	ILN	<b>.900</b>	.478	.616
LTR	.029	<b>1.008</b>	.008	LTR	.508	<b>.989</b>	.324
LTS	.034	<b>1.005</b>	.041	LTS	.480	<b>.972</b>	.288
CR	.025	<b>1.000</b>	.039	CR	.487	<b>.972</b>	.293
CLTR	.015	<b>.941</b>	.019	TR	.539	<b>.951</b>	.381
TR	.001	<b>.931</b>	.055	CLTR	.508	<b>.942</b>	.320
DR30	.029	<b>.824</b>	.083	DR30	.528	<b>.869</b>	.390
DR	.086	<b>.764</b>	.004	DR	.500	<b>.812</b>	.328
FRO	.081	.024	<b>.962</b>	CRO	.659	.422	<b>.955</b>
CRO30	.037	.051	<b>.946</b>	CRO30	.643	.299	<b>.953</b>
CRO	.027	.110	<b>.935</b>	ILO	.702	.342	<b>.927</b>
FRO30	.025	.039	<b>.885</b>	FRO30	.639	.362	<b>.915</b>
ILO	.167	.037	<b>.828</b>	FRO	.551	.269	<b>.899</b>

Factor 1: FRN30= FNAME free recall of names at 30 minutes; CRN30= FNAME cued recall of names at 30 minutes; CRN= FNAME cued recall of names; FRN= FNAME free recall of names; ILN= FNAME initial learning of names; Factor 2: LTR= SRT long-term retrieval; LTS= SRT long-term store; CR= SRT continuous retrieval; CLTR= SRT continuous long-term retrieval; TR= SRT total recall; DR30= SRT delayed recall at 30-minutes; DR= SRT delayed recall at 10-minutes; Factor 3: FRO= FNAME free recall of occupations; CRO30= FNAME cued recall of occupations at 30-minutes; CRO= FNAME cued recall of occupations; FRO30= FNAME free recall of occupations at 30-minutes; ILO= FNAME initial learning of occupations.

**Table 3**

Multiple regression analyses of the memory factor composite scores and PIB DVR in frontal and PPCLP regions. All models covaried for age and AMNART IQ.

ROI	Factor 1			Factor 2			Factor 3		
	FNAME Name Composite			SRT Composite			FNAME Occupation Composite		
	<i>a</i> R <sup>2</sup>	<i>b</i> β	p	R <sup>2</sup>	β	p	R <sup>2</sup>	β	p
Frontal	0.29	-2.21	0.02	0.12	-1.17	0.25	0.22	-1.19	0.22
PPCLP	0.26	-2.44	0.05	0.14	-1.99	0.14	0.21	-1.44	0.26

*a* R<sup>2</sup> = Full model R-Square

*b* β = unstandardized partial regression coefficient