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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 (Aβ) 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 Aβ-related memory impairment in CN. We studied 45 CN subjects (mean age = 71.7 ± 8.8) with Clinical Dementia Rating (CDR) scores = 0 and MMSE ≥ 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 Aβ deposition in frontal ($R^2 = 0.29$, $\beta = -2.2$, $p = 0.02$) and PPCLP cortices ($R^2 = 0.26$, $\beta = -2.4$, $p = 0.05$). In contrast, neither FN-O nor the SRT were significantly related to Aβ deposition. Performance on a demanding test of face-name associative memory was related to Aβ 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 Aβ-related impairment.

1. 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 (Aβ) 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 Aβ 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; 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 Aβ-related cognitive alternations in CN subjects using standard neuropsychological measures.

Several studies examining increased Aβ deposition with PiB PET imaging in CN subjects were unable to find a relationship between cognitive test performance and Aβ 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 Aβ 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) ε4 allele, primary risk factors for AD. Another study by 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, Mintun, Head, and Morris (2009) reported an association of Aβ burden with longitudinal cognitive decline prior to diagnosis of AD but a single time point of cognitive performance was not predictive of Aβ-related cognitive change.

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As a potential confounding factor in the relationship between Aβ 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, 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 Aβ 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 Aβ 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 Aβ 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 Aβ 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.

2. Materials and methods

2.1. 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.

2.2. 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., 2007) 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, Bates, et al., 2003; Sperling et al., 2001).

Table 1
Sample characteristics ($N = 45$).

Sex, M/F (%)	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 median	1.11	0.15	0.95	1.70
PPCLP DVR median	1.13	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.

2.3. 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 s 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).

2.4. 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).

2.5. FNAME recall trials

The FNAME includes 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-Min delayed free recall:* subjects are again asked to freely recall the names (FRN30) and occupations (FRO30) following a 30-min delay. *30-Min 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 0.96. The mean inter-item correlation was 0.72 with values ranging from 0.48 to 0.93 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 Fig. 1a and b). 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).

2.6. 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 compos-