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Cognition, glucose metabolism and amyloid burden in Alzheimer's disease

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Abstract

The authors investigated relationships between glucose metabolism, amyloid load, and measures of cognitive and functional impairment in Alzheimer's disease (AD). Patients meeting criteria for probable AD underwent ^{11}C-labeled Pittsburgh Compound-B ([^{11}C]PIB) and 18F-fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) imaging and were assessed on a set of clinical measures. The Pittsburgh Compound-B (PIB) Distribution volume ratios and fluorodeoxyglucose (FDG) scans were spatially normalized and average PIB counts from regions-of-interest (ROI) were used to compute a measure of global PIB uptake. Separate voxel-wise regressions explored local and global relationships between metabolism, amyloid burden, and clinical measures. Regressions reflected cognitive domains assessed by individual measures, with visuospatial tests associated with more posterior metabolism, and language tests associated with metabolism in the left hemisphere. Correlating regional FDG uptake with these measures confirmed these findings. In contrast, no correlations were found between either voxel-wise or regional PIB uptake and any of the clinical measures. Finally, there were no associations between regional PIB and FDG uptake. We conclude that regional and global amyloid burden does not correlate with clinical status or glucose metabolism in AD.

Keywords: Alzheimer's disease; Amyloid plaques; Amyloidosis; Cognition; Dementia severity; Fluorodeoxyglucose; Glucose metabolism; Pittsburgh Compound-B

Alzheimer's disease (AD) is a neurodegenerative disease with a distinct neuropathology involving extracellular neuritic β-amyloid (Aβ) plaques and intraneuronal neurofibrillary tangles (NFT) (Arnold et al., 1991; Braak and Braak, 1991; Braak and Braak, 1997). Triggered by findings that genetic defects in the amyloid precursor protein (APP) gene lead to overproduction of Aβ and early-onset familial AD (Goate et al., 1991; Naruse et al., 1991), it has been suggested that Aβ is in fact the primary cause of AD (Hardy and Higgins, 1992). According to this "amyloid cascade hypothesis," Aβ causes synaptic dysfunction, synapse loss, and neuronal death resulting in cognitive decline and dementia.

The clinicopathologic evidence supporting this hypothesis remains inconclusive. Several studies suggest a correlation between cognitive decline and Aβ plaque levels in AD (Bussiere et al., 2002; Cummings and Cotman, 1995; Cummings et al., 1996; Haroutunian et al., 1998; Kanne et al., 1998; McLean et al., 1999; Naslund et al., 2000; Parvathy et al., 2001) and in some cases more specifically a regional association between Aβ levels and dementia severity (Bussiere et al., 2002; Cummings et al., 1996; Naslund et al., 2000). However, other studies have challenged this view showing that dementia severity increases as a function of NFT and not plaque density (Arriagada et al., 1992; Berg et

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al., 1993; Berg et al., 1998; Bierer et al., 1995; Crystal et al., 1988; Duyckaerts et al., 1997; Giannakopoulos et al., 2003; Hof et al., 1992; Price et al., 1991). While these discrepancies could arise from technical factors such as sampling methods, (Bussiere et al., 2002), it is possible that differences in amyloid species or mediation of effects by NFT pathology (Bennett et al., 2004; Giannakopoulos et al., 2003) could be responsible.

In vivo uptake of the radiotracer ^{18}F-fluorodeoxyglucose (FDG) is strongly correlated to cerebral synaptic density and activity (Rocher et al., 2003) and has been extensively employed to study metabolic decline in AD. Significant metabolic reductions in association cortex including the precuneus and posterior cingulate have been found to be closely associated with disease severity and to differentiate normal controls (NC) from AD patients (Heiss et al., 1991a; Heiss et al., 1991b; Herholz et al., 2002; Ichimiya et al., 1994; Langbaum et al., 2009; Mielke et al., 1994; Minoshima et al., 1995b). Global and regional effects of Aβ deposition on brain function can now be assessed by combining FDG with the recently developed PET ligand [*N*-methyl-11C]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, more commonly known as Pittsburgh Compound B (PIB), which specifically binds to fibrillar amyloid both *in vitro* (Klunk et al., 2003) and *in vivo* (Bacskai et al., 2003; Klunk et al., 2004). PIB has been used to study AD, normal aging, mild cognitive impairment (MCI), frontotemporal and other amyloid-associated dementias (Aizenstein et al., 2008; Boxer et al., 2007; Engler et al., 2006; Forsberg et al., 2008; Frisoni et al., 2009; Gomperts et al., 2008; Jack et al., 2009; Johnson et al., 2007; Mintun et al., 2006; Mormino et al., 2009; Pike et al., 2007; Rabinovici et al., 2007; Rowe et al., 2007; Sperling et al., 2009). Combining both tracers, some authors (Edison et al., 2007; Klunk et al., 2004) have found negative correlations between β-amyloid load and glucose metabolism in temporal and parietal regions but only when either PIB negative healthy controls or PIB negative AD patients were included. Similarly, others (Li et al., 2008) initially found inverse intraregional correlations between FDG and PIB uptake when combining data of NC, MCI, and AD patients but none of these correlations survived within the three diagnostic groups. Only a few studies have looked at the relationship between cognition and *in vivo* amyloid burden as measured by PIB in AD. Three studies reported no significant correlations between PIB uptake and either the Mini-Mental Status Exam (MMSE) (Klunk et al., 2004; Pike et al., 2007; Rowe et al., 2007) or composite episodic memory scores (Pike et al., 2007). One study (Engler et al., 2006) found inverse correlations between regional PIB uptake and MMSE scores at baseline but this finding could not be replicated at the 24-month follow-up. Another (Edison et al., 2007) reported correlations between PIB uptake and scores on the Warrington Recognition Memory Test which were, however, dependent on the inclusion of two PIB negative AD patients (i.e., patients with no amyloidosis). A more recent study (Grimmer et al., 2008) found that scores on the Clinical Dementia Rating "sum of boxes" (CDRSB) explained 11–22% of the regional variance of PIB uptake in frontal cortex, anterior cingulated, and nucleus lentiformis, but in subsequent voxel-wise regressions these correlations were not reliable once age was included as a nuisance variable.

Taken together these studies suggest that the impact of Aβ on cognition and brain metabolism differs according to diagnosis and in the case of clinical AD pathology it is, in fact, questionable whether there is any considerable effect in patients with genuine amyloid pathology. Clarity on the latter issue is obviously of crucial importance for the future development and assessment of appropriate disease modifying therapies (Aisen, 2009). The current study was specifically aimed at investigating this relationship in a large cohort of patients diagnosed with probable AD and we hypothesized that FDG would be more strongly associated with cognitive status than PIB.

1. Materials and methods

1.1. Subject selection

Patients were recruited from an AD research cohort followed at the University of California, San Francisco Memory and Aging Center (UCSF-MAC). The clinical evaluation included a history and physical examination by a neurologist, a structured caregiver interview administered by a nurse, and a comprehensive battery of neuropsychological tests (Kramer et al., 2003). Clinical diagnoses were assigned by consensus at a multidisciplinary conference using standard research criteria (McKhann et al., 1984). In the current study we used a subset of clinical measures which included the MMSE (Folstein et al., 1975), the CDRSB (Morris, 1993), copy of the modified Rey-Osterrieth figure (ModRey) and a phonemic verbal fluency test (VbFlu) to assess functional status, visuo-spatial memory and executive functions (Kramer et al., 2003). The mean interval between testing and PET was 90 $\pm$ 83 days. Although meeting criteria for probable AD one of our patients scored 0 on the CDRSB. However, she has recently declined to a score of one which is consistent with the original diagnosis.

Patients were considered eligible for the study if they had a clinical diagnosis of probable AD and did not have significant comorbid medical, neurological or psychiatric illness. Patients were recruited between April 2005 and January 2009, and all who consented to participate were enrolled. Two subjects were excluded from the final analysis for technical reasons (motion artifact, incomplete study, etc.). Our final cohort consisted of 39 patients with probable AD.

The study was approved by the Institutional review boards of all participating institutions.