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Amyloid burden and neural function in people at risk for Alzheimer's Disease

Sterling C. Johnson [a,b,c,*], Bradley T. Christian [b,d], Ozioma C. Okonkwo [a,b], Jennifer M. Oh [a,b], Sandra Harding [a,b], Guofan Xu [b,e], Ansel T. Hillmer [d], Dustin W. Wooten [d], Dhanabalan Murali [d], Todd E. Barnhart [d], Lance T. Hall [e], Annie M. Racine [b], William E. Klunk [g], Chester A. Mathis [h], Barbara B. Bendlin [a,b], Catherine L. Gallagher [a,b], Cynthia M. Carlsson [a,b], Howard A. Rowley [b,e], Bruce P. Hermann [b,c], N. Maritza Dowling [a,b,f], Sanjay Asthana [a,b,c], Mark A. Sager [b,c]

[a] Geriatric Research Education and Clinical Center, Wm. S. Middleton Memorial VA Hospital, Madison, WI, USA
[b] Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[c] Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[d] Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[e] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[f] Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[g] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[h] Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

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ABSTRACT

To determine the relationship between amyloid burden and neural function in healthy adults at risk for Alzheimer's Disease (AD), we used multimodal imaging with [C-11]Pittsburgh compound B positron emission tomography, [F-18]fluorodeoxyglucose, positron emission tomography , and magnetic resonance imaging, together with cognitive measurement in 201 subjects (mean age, 60.1 years; range, 46–73 years) from the Wisconsin Registry for Alzheimer's Prevention. Using a qualitative rating, 18% of the samples were strongly positive Beta-amyloid (Aβ+), 41% indeterminate (Aβi), and 41% negative (Aβ−). Aβ+ was associated with older age, female sex, and showed trends for maternal family history of AD and APOE4. Relative to the Aβ− group, Aβ+ and Aβi participants had increased glucose metabolism in the bilateral thalamus; Aβ+ participants also had increased metabolism in the bilateral superior temporal gyrus. Aβ+ participants exhibited increased gray matter in the lateral parietal lobe bilaterally relative to the Aβ− group, and no areas of significant atrophy. Cognitive performance and self report cognitive and affective symptoms did not differ between groups. Amyloid burden can be identified in adults at a mean age of 60 years and is accompanied by glucometabolic increases in specific areas, but not atrophy or cognitive loss. This asymptomatic stage may be an opportune window for intervention to prevent progression to symptomatic AD.

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1. Introduction

Beta-amyloid (1–42) (Aβ42) accumulation, a hallmark feature of Alzheimer's disease (AD), is putatively a major cause of neural dysfunction (Palop and Mucke, 2010) and eventual cognitive decline to dementia (Hardy and Higgins, 1992). The first major stage of presymptomatic AD might be a period of brain Aβ42 accumulation denoted by a positive amyloid positron emission tomography (PET) scan or abnormal levels of Aβ in the cerebrospinal fluid (CSF) (Sperling et al., 2011). A subset of healthy older adults have substantial amyloid burden in the brain when measured with amyloid PET imaging and associations with poorer cognitive function have been observed (Lim et al., 2012; Mathis et al., 2013; Rodrigue et al., 2012; Sperling et al., 2013). Because amyloid PET labels extracellular insoluble aggregates, a presumed reason for associations with cognition is via cumulative neurotoxicity resulting in eventual cognitive decline (Jack et al., 2011a). The specifics of the hypothesized model (Sperling et al., 2011) of preclinical amyloid staging are being elucidated empirically (Jack et al., 2011b, 2012; Jagust et al., 2012; Knopman et al., 2012, 2013), but the temporal relationship between amyloid burden and neural and cognitive dysfunction in the earliest stages of preclinical AD is complex (Bateman et al., 2012; Reiman et al., 2012), and causality is incompletely understood (Chetelat, 2013). An important model for studying disease

* Corresponding author at: William S. Middleton Memorial VA Hospital, 2500 Overlook Terrace (11G), GRECC, Madison, WI 53705, USA. Tel.: +1 608 256 1901 x11946; fax: +1 608 280 7165.
E-mail address: scj@medicine.wisc.edu (S.C. Johnson).

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course in presymptomatic AD is to examine people who harbor risk factors for the disease. Other than age, having a first-degree relative (Okonkwo et al., 2012a; Sager et al., 2005; Xiong et al., 2011) and possessing the epsilon4 allele of the apolipoprotein E gene (APOE4) are by far the most substantive risk factors for AD and these have been associated with Aβ42 load and earlier age of Aβ42 accumulation using imaging methods (Fleisher et al., 2013; Morris et al., 2010; Mosconi et al., 2013; Rowe et al., 2010; Xiong et al., 2011). In the present study, the effect of amyloid burden on neural function in a subset of a cognitively healthy at-risk cohort known as the Wisconsin Registry for AD Prevention (WRAP) was examined. The cohort consisted of >1500 persons aged 40–65 at study entry enriched with parental family history and APOE4 who were followed serially (Sager et al., 2005). A major goal was to examine the rate of amyloid positivity (Aβ+) and its associated demographic, cognitive, and imaging characteristics in this sample. We hypothesized that Aβ+ would be associated with risk factors for AD, and with signs of neural dysfunction measured using glucometabolic imaging, volumetric gray matter atrophy, and cognition.

2. Methods

Two hundred and one adults were recruited from the WRAP registry either by in-person invitation at their main WRAP study visit or by mailed invitation. The mean age was 60.1 years (SD = 5.9 years), mean years of education was 16.1 (SD = 2.3), and 139 (67%) were women. Fifty-nine (29%) individuals reported no family history (FH) of AD; 95 (46%) had a maternal history of AD (mFH+); 44 (21%) had a paternal history (pFH+), and 9 (4%) had both parents afflicted with AD (mpFH+). APOE genotype was as follows: APOE e2/e2 = 0; e2/e3 = 23; e2/e4 = 7; e3/e3 = 96; e3/e4 = 69; e4/e4 = 6. The characteristics of this study sample did not differ significantly from the larger WRAP registry.

The method for determining the presence or absence of AD in the parent has been described previously (La Rue et al., 2008; Sager et al., 2005). The University of Wisconsin Institutional Review Board approved all study procedures and each subject provided signed informed consent before participation.

2.1. Imaging methods

The procedures involved undergoing a [C-11]Pittsburgh compound B ([C-11]PiB) positron emission tomography (PET) scan, an Fluorodeoxyglucose ([F-18] FDG PET) scan, (both on a the same Siemens EXACT HR+ scanner and typically occurring the same day), and a 3.0 Tesla magnetic resonance imaging (MRI) scan.

2.1.1. [C-11]PiB radiochemical synthesis

[C-11]PiB was synthesized using a captive solvent method (Wilson et al., 2000). N-methylation of the 2-(4′-amino-phenyl)-6-OH-benzothiazole (6-OH-BTA-0) precursor (ABX, Inc, Radeberg, Germany) was accomplished using [C-11] methyl triflate produced via an automated chemistry module and subsequently purified using high-performance liquid chromatography. Typical yields of final [C-11]PiB product were in excess of 2 GBq, with specific activities of 150–600 GBq/μmol. [F-18] FDG was purchased from a commercial vendor.

2.1.2. PiB PET scanning

The [C-11]PiB PET data were acquired in 3-D mode. Participants were positioned head first, supine with the canthomeatal line parallel to the in-plane field of view. A 6 minute transmission scan was acquired for attenuation correction. A 70-minute dynamic [C-11]PiB PET acquisition was then initiated with the injection of a 15 mCi target dose of [C-11]PiB bolus (mean 15.3 mCi, SD = 0.9), injected over 30 seconds. Dynamic acquisition frames included 5 × 2 minutes and 12 × 5 minutes for a total of 17 time frames. The PET data were reconstructed using a filtered back-projection algorithm (Direct inverse Fourier Transformation; DIFT) with sinogram trimming to a voxel size of 2.57 mm × 2.57 mm × 2.43 mm and matrix dimension of 128 × 128 × 63 and corrected for random events, attenuation of annihilation radiation, dead time, scanner normalization, and scatter radiation using the ECAT v7.2.2 software with segmented attenuation correction. The reconstructed time series of PET data were realigned using SPM8 (www.fil.ion.ucl.ac.uk/spm) to correct for subject motion during the course of the study and a denoising algorithm was applied to the voxel-based time series (Christian et al., 2010; Floberg et al., 2012). The PET time series was coregistered into the space defined according to the T1-weighted MRI scan based on coregistration with the time-integrated (i.e., sum image) [C-11] PET scan using mutual information.

2.1.3. Distribution volume ratio maps

The data were then transformed into voxel-wise parametric images representing [C-11]PiB binding using the cerebellar cortex as a reference region of negligible binding (Price et al., 2005). The cerebellar time–activity curve was extracted from the PET data using a cerebellar gray matter (GM) mask image derived from the coregistered T1-weighted MRI using FreeSurfer 5.3 software (http://surfer.nmr.mgh.harvard.edu/). Voxel-based parametric images using Logan graphical analysis were created as described previously (Lopresti et al., 2005). For the Logan graphical method (Logan et al., 1996), linear regression was applied to the transformed data using the 35–70 minute (7 points) interval and a mean efflux constant of 0.149/min. The resulting distribution volume ratio (DVR) images were each inspected for quality and rated for amyloid burden using a rating system described in (Section 2.1.4). Using SPM8, the DVRs were also spatially normalized to the International Consortium for Brain Mapping 152 atlas (ICBM 152, i.e., Montreal Neurological Institute [MNI] space) and smoothed with an 8-mm full width at half maximum Gaussian kernel and entered into voxel-wise group analyses.

2.1.4. Qualitative PiB rating

A qualitative score for amyloid burden was used for greater clinical applicability and to allow for the possibility of regional heterogeneity in this age range when amyloid burden may only be emerging. The visual rating of PiB positivity was achieved on the native space DVR images that were all scaled uniformly from 0.0 to 2.0, and displayed using a color map (the ACTC activation color map) that provided distinct shades of color for demarcating PiB positivity (approximately 1.2 or greater). After establishing high inter- and intrarater reliability (intraclass correlation coefficients of 0.95 and 0.96, respectively) on a set of 33 consecutively selected examinations, the entire set of examinations was rated in 1 session by a single rater (SCJ) blind to subject characteristics. Examinations were rated on a 4-point scale, where 0 represented no cortical amyloid burden or only nonspecific white matter uptake; 1 represented non-significant patchy or diffuse cortical GM binding not resembling an AD pattern (significant uptake in the basal ganglia was common and not considered in the amyloid score); 2 represented an indeterminate (Aβi) classification where GM binding was present in the cortex of at least 3 lobes resembling an AD disease pattern but less intense than an overtly positive scan; 3 represented unambiguous positive amyloid binding in the cortex (Aβ+). Category 0 occurred rarely (9 cases, too few to study as its own class) so 0 and 1 ratings were subsequently combined to form an amyloid negative (Aβ−) group. Fig. 1 depicts the rating categories with examples.