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Featured Article

PET staging of amyloidosis using striatum

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Abstract

Introduction: Amyloid PET data are commonly expressed as binary measures of cortical deposition. However, not all individuals with high cortical amyloid will experience rapid cognitive decline. Motivated by postmortem data, we evaluated a three-stage PET classification: low cortical; high cortical, low striatal; and high cortical, high striatal amyloid; hypothesizing this model could better reflect Alzheimer's dementia progression than a model based only on cortical measures.

Methods: We classified PET data from 1433 participants (646 normal, 574 mild cognitive impairment, and 213 AD), explored the successive involvement of cortex and striatum using 3-year follow-up PET data, and evaluated the associations between PET stages, hippocampal volumes, and cognition.

Results: Follow-up data indicated that PET detects amyloid first in cortex and then in striatum. Our three-category staging including striatum better predicted hippocampal volumes and subsequent cognition than a three-category staging including only cortical amyloid.

Discussion: PET can evaluate amyloid expansion from cortex to subcortex. Using striatal signal as a marker of advanced amyloidosis may increase predictive power in Alzheimer's dementia research.

Keywords: Amyloid PET imaging; Structural MRI; Striatum; Cortex; Cognitive aging; MCI; Alzheimer's disease; Classification; Staging

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1. Introduction

Brain amyloid β (Aβ) deposition, one of the defining pathologies of Alzheimer's disease, is now detectable *in vivo* with high specificity using PET, as confirmed at autopsy [1–3]. It is well established that elevated PET measures of brain Aβ increase risk for subsequent cognitive decline in both cognitively impaired [4] and normal populations [5–8], and Aβ measures have been widely adopted as part of eligibility criteria for anti-Aβ therapeutic trials. However, the subsequent decline of clinically normal (CN) individuals with elevated Aβ occurs slowly over several years [9], and alternative PET measures that could predict decline over a shorter interval could potentially improve the efficiency of prevention trials.

We explored an alternative PET measure seeking to stage Aβ pathology *in vivo* based on the established Thal-Phase postmortem ordinal system for regional extent of Aβ pathology [10–12]. We evaluated the predictive value of a PET measure from striatum, a subcortical structure in which Aβ is typically detected at autopsy only after cortical deposition [10] and in which corresponding PET measures are readily available [3]. We reasoned that because striatal involvement reflects a more progressive amyloidosis at postmortem, an *in vivo* striatal PET measure could provide predictive information that differs from the typical cortical PET measure and have a stronger relation to cognitive decline. Specifically, we used data from two large observational studies to test two hypotheses: First, we used serial PET imaging data to confirm *in vivo* that Aβ accumulates later in striatum than in cortex. Second, we hypothesized that participants with elevated cortical Aβ plus elevated striatal Aβ had a more advanced clinical syndrome, greater tau deposition, lower hippocampal volume, and greater cognitive decline than those with elevated cortical and low striatal Aβ.

2. Methods

2.1. Study design

This prospective study analyzed data from 1433 participants enrolled in either the Harvard Aging Brain study (HABS) or the Alzheimer's Disease Neuroimaging Initiative (ADNI). HABS is an ongoing, longitudinal, monocentric study conducted at Massachusetts General Hospital (USA). ADNI is an ongoing, longitudinal, multicenter study conducted in 59 sites across the USA and Canada. Eligibility criteria and study designs of HABS and ADNI are similar: Normal participants, aged 55 to 94 years, are recruited from the community together with patients having mild cognitive impairment (MCI) or Alzheimer's dementia (AD). MRI and PET imaging data are acquired shortly after inclusion (baseline); cognitive follow-up data are acquired annually for virtually all participants, and imaging follow-up data are available in a subset of the participants. Exclusion criteria include history of alcoholism, drug abuse, head trauma, or serious medical or psychiatric condition. Cholinesterase inhibitors and memantine are only allowed in MCI or AD patients if stable for three months before screen. Antidepressants are allowed for both normal and impaired participants if they are not depressed at the time of screen and do not have a history of major depression within the past 1 year. In both cohorts, institutional review board approvals and informed consents were obtained before all procedures.

For the purpose of this research, we did not include participants who had no PET data available. We also excluded from our analyses cognitive data that were acquired more than six months before PET was conducted. PET-Aβ data used in this study were first acquired in ADNI in May 2010 and in HABS in September 2010. Data used in the present report were thus collected between November 2009 and July 2016, when data from both cohorts were downloaded for analyses. The clinical dementia rating (CDR) obtained at the clinical assessment closest to baseline PET was used as a diagnostic criterion for CN (CDR = 0), MCI (CDR = 0.5), and AD dementia (CDR ≥ 1). Baseline MMSE in CN and MCI participants was greater than or Q3 equal to 24/30.

2.2. Neuropsychology

Cognitive performances, as assessed using MMSE, episodic memory, and executive function tests were evaluated at baseline and then followed annually in both HABS and ADNI. Z-scores specific to each cohort were computed: the Preclinical Alzheimer Cognitive Composite (PACC) [13] in HABS and memory [14] and executive function [15] factor scores in ADNI. Cognitive follow-up data were not analyzed in participants who had AD dementia at baseline because our aim in analyzing cognitive changes was to evaluate the predictive power of striatal compared to cortical PET-Aβ in nondemented individuals. Patients with AD dementia at baseline were only included in the descriptive statistics and in the longitudinal PET data analyses.

2.3. Imaging

Aβ burden was assessed using C^{11} Pittsburgh compound B (PiB) in HABS and F^{18} Florbetapir (FBP) in ADNI. PiB data were expressed as distribution volume ratios (DVR; 40–60 minutes) scaled on cerebellar gray after partial volume correction using geometric transfer matrix [16]. FBP data were expressed as standard uptake volume ratios (SUVs; 50–70 minutes) scaled on a composite reference region including whole cerebellum and hemispheric white matter [17]. Data from both cohorts were coregistered to each participant's MRI and anatomically parcellated using FreeSurfer v5.1. We used previously published cortical aggregates [16,17], specific to each cohort and tracer, and the striatum region consisted of a volume-weighted