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Memory decline shows stronger associations with estimated spatial patterns of amyloid deposition progression than total amyloid burden

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ABSTRACT

The development of amyloid imaging compounds has allowed in vivo imaging of amyloid deposition. In this study, we examined the spatial patterns of amyloid deposition throughout the brain using Pittsburgh Compound Blue (^{11}C-PiB) positron emission tomography data from the Baltimore Longitudinal Study of Aging. We used a new methodology that allowed us to approximate spatial patterns of the temporal progression of amyloid plaque deposition from cross-sectional data. Our results are consistent with patterns of progression known from autopsy studies, with frontal and precuneus regions affected early and occipital and sensorimotor cortices affected later in disease progression—here, disease progression means lower-to-higher total amyloid burden. Furthermore, we divided participants into subgroups based on longitudinal change in memory performance, and demonstrated significantly different spatial patterns of the estimated progression of amyloid deposition between these subgroups. Our results indicate that the spatial pattern of amyloid deposition is related to cognitive performance and may be more informative than a biomarker reflecting total amyloid burden, the use of which is the current practice. This finding has broad implications for our understanding of the relationship between cognitive decline/resilience and amyloid deposition, as well as for the use of amyloid imaging as a biomarker in research and clinical applications.

1. Introduction

The hallmark pathologies of Alzheimer's disease are histology-confirmed amyloid plaques and neurofibrillary tangles. Currently, disease progression must usually be estimated from cross-sectional data and is defined as lower-to-higher total pathology. As shown in a large series of post-mortem brains studied by Braak and Braak (Braak and Braak, 1997b), the progression of amyloid plaque deposition (both diffuse and neuritic) follows characteristic spatially unique stages rather than uniform deposition throughout the brain. There are substantial interindividual variations in spatial patterns of amyloid deposition, but frontal, lateral temporal, and parietal regions are affected early, with relative sparing of the occipital lobe and motor cortices until later in disease progression.

Spatial heterogeneity of patterns of amyloid deposition have also been found using recently developed in vivo amyloid tracers (Lockhart et al., 2007). Across studies, elevated amyloid deposition has been found in frontal cortex, lateral temporal cortex, and precuneus, especially in subjects with dementia of the Alzheimer type (DAT), with less consistent binding in the occipital cortex (Klunk et al., 2004; Lopresti et al., 2005; Rowe et al., 2008; Wong et al., 2010). A significant proportion of cognitively normal subjects also display elevated cortical amyloid burden (Jack et al., 2008; Pike et al., 2007), with some likely in the preclinical stages of DAT. In addition, patients with mild cognitive impairment (MCI) show a bimodal distribution, such that some subjects exhibit amyloid deposition similar to that of DAT subjects while other subjects exhibit deposition similar to healthy controls (Mintun et al., 2006; Villemagne et al., 2008; Villemagne et al., 2011). Furthermore, MCI subjects who exhibit amyloid burden similar to DAT subjects are more likely to progress to DAT, compared to subjects who exhibit levels of amyloid burden similar to that in healthy controls (Forsberg et al., 2008).

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Mean or regional cortical amyloid burden are the typical biomarkers measured in in vivo amyloid imaging studies. Advances in in vivo imaging technique methods now allow us to investigate temporal changes in amyloid deposition and relation to other imaging modalities in greater detail (Shoghi-Jadid et al., 2002; Sojkova et al., 2011). Moreover, the spatiotemporal dynamics of amyloid deposition have not been studied in detail, in part due to the relatively recent availability of amyloid imaging radiotracers and the time lag in acquiring sufficient longitudinal data. In the current study, we use a pseudo-dynamic image analysis method, similar to that used by Braak and Braak (1997b), estimating the progression of amyloid deposition from cross-sectional images of older individuals. In particular, nonlinear regional fits are used to determine regional amyloid burden as a function of total amyloid load, thereby generating maps that indicate how much amyloid must be accumulated globally in the brain before a given brain region is affected. This is accomplished by making an assumption that total amyloid burden is related to temporal dynamics, that is, a cortex will have lower total amyloid load earlier in the disease progression, and progressively higher amyloid load later in the disease progression, although a spline smoothing process is used to handle deviations from this assumption. Pseudo-temporal maps can then be generated from cross-sectional data. These maps are herein found to provide insights into the dynamics of amyloid spread throughout the brain that are not evident in conventional group comparisons.

Although cross-sectional studies of relationships between amyloid burden and cognition have yielded mixed results, higher amyloid burden has been associated with greater longitudinal memory decline in a number of studies (reviewed by Resnick and Sojkova, 2011). In prior work, we have demonstrated associations between rates of longitudinal change in verbal episodic memory performance and structural/functional changes in the cortex (Clark et al., 2012). Thus, in the present study, we aimed to use rates of change in California Verbal Learning Test (CVLT) scores to group participants for comparison of amyloid progression patterns. Decline in verbal episodic memory is typically the earliest change during the prodromal phase of DAT (Grober et al., 2008).

Analyses of amyloid deposition patterns in relation to cognitive performance that have been based on region-of-interest or voxel-wise approaches have resulted in heterogeneous findings. Generally, the regions that appear to be more involved in episodic memory changes include the precuneus, also the frontal, posterior cingulate, and lateral parietal cortices (Rentz et al., 2011), and the (frontal and lateral) temporal regions (Chetelat et al., 2011; Resnick et al., 2010). Although these analyses begin to address differential associations between cognition and amyloid deposition across the cortex, they are confounded by high interindividual variability introduced by the fact that different individuals enrolled in a study are generally at different stages of amyloid progression, which may obscure relationships between the spatial distribution and progression of amyloid and cognition. In other words, the same value of amyloid burden at a given spatial location might relate differently to cognitive decline, depending on the overall spatial pattern of deposition and the stage of the disease. Moreover, amyloid imaging, based on conventional measurements obtained from cross-sectional snapshots, is not very informative of the dynamics of disease progression. To mitigate this problem, we undertook to investigate spatial patterns of amyloid deposition as a function of total amyloid burden throughout the brain, such that total amyloid burden is used as a proxy for the underlying stage of disease progression in the absence of a more precise measure. Furthermore, we sought to determine whether the spatial patterns of amyloid deposition between subgroups would show a striking and significant divergence when individuals were classified according to longitudinal change in cognitive performance. A varying spatial pattern may indicate an earlier involvement of many specific brain regions in cognitively declining (CD) individuals compared with a relatively more constrained amyloid spread in cognitively stable (CS) individuals.

2. Method

2.1. Participants

A series of 64 participants (35 men and 29 women; mean age [SD] = 76.61 years [6.89 years]; cortical distributed volume ratio [SD] 1.16 [0.26]) from the Baltimore Longitudinal Study of Aging (BLSA) neuroimaging substudy were included. Additional participants were evaluated but excluded because of clinical stroke (n = 2), brain injury (n = 1), and intolerance of magnetic resonance imaging (MRI) (n = 1). At baseline, BLSA neuroimaging participants were excluded for the following conditions: central nervous system (CNS) disease, severe cardiovascular disease, severe pulmonary disease, or metastatic cancer. The participants included in this study were representative of the entire BLSA group with respect to baseline age, sex, race/ethnicity, and education. For participants with multiple ^{11}C-PiB scans, only the last available scan was included for analysis.

All participants also underwent thorough neuropsychological evaluation in conjunction with each neuroimaging visit. Participants were followed for an average of 12 years (SD = 1.8 years) and were tested approximately once per year, resulting in an average of 11 test time-points per participant (SD = 1.57). A battery of 12 neuropsychological tests was administered at each neuroimaging visit to evaluate mental status, word knowledge and verbal ability, memory, language, verbal fluency, attention, executive function, and spatial ability. Mental status was assessed with the Mini-Mental State Examination (MMSE), verbal memory with the CVLT, and visual memory with the Benton Visual Retention Test (BVRT). Ten participants had a score of 0.5 or higher on the Clinical Dementia Rating (CDR) scale (Morris, 1997), of whom 3 were clinically diagnosed with MCI at the time of the scan, and 1 participant had a dementia diagnosis with subsequent autopsy-confirmed DAT. The CDR scale, typically informant based, was administered in conjunction with ^{11}C-PiB positron emission tomography (PET) imaging, and was also administered during earlier imaging visits if participants scored 3 or higher on the Blessed Information Memory Concentration test and at each visit for autopsy study participants (~50% of the sample) (Blessed et al., 1968).

2.2. ^{11}C-PiB PET imaging

Dynamic ^{11}C-PiB PET studies (29 time frames over 70 minutes) were performed in 3-dimensional (3D) mode on a GE Advance scanner (General Electric, Milwaukee, WI). Participants were fitted with a thermoplastic mask for PET imaging to minimize motion artifacts. The PET scanning started immediately after intravenous bolus injection of a mean (SD) of 14.65 (0.9) mCi of ^{11}C-PiB. Dynamic images were reconstructed using filtered back-projection with a ramp filter (image size = 128 × 128, pixel size = 2 × 2 mm, slice thickness = 4.25 mm), yielding a spatial resolution of approximately 4.5 mm FWHM at the center of the field-of-view.

2.3. Quantification of ^{11}C-PiB distribution volume ratios

In conjunction with ^{11}C-PiB PET imaging, each participant also underwent structural MRI imaging with a T1-weighted volumetric protocol. MRI images were co-registered to the mean of the first 20-minute dynamic PET images for each participant using the mutual information method in the Statistical Parametric Mapping