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Parallel ICA of FDG-PET and PiB-PET in three conditions with underlying Alzheimer's pathology

Robert Laforce Jr[a,c,1,*], Duygu Tosun[b], Pia Ghosh[a,c], Manja Lehmann[a,c], Cindee M. Madison[a], Michael W. Weiner[b], Bruce L. Miller[c], William J. Jagust[a,d], Gil D. Rabinovici[a,c,d]

[a]Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA
[b]Center for Imaging of Neurodegenerative Diseases, Department of Radiology and Biomedical Imaging, University of California San Francisco, CA, USA
[c]Memory and Aging Center, Department of Neurology, University of California San Francisco, CA, USA
[d]Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, USA

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ABSTRACT

The relationships between clinical phenotype, β-amyloid (Aβ) deposition and neurodegeneration in Alzheimer's disease (AD) are incompletely understood yet have important ramifications for future therapy. The goal of this study was to utilize multimodality positron emission tomography (PET) data from a clinically heterogeneous population of patients with probable AD in order to: (1) identify spatial patterns of Aβ deposition measured by (^{11}C)-labeled Pittsburgh Compound B (PiB-PET) and glucose metabolism measured by FDG-PET that correlate with specific clinical presentation and (2) explore associations between spatial patterns of Aβ deposition and glucose metabolism across the AD population. We included all patients meeting the criteria for probable AD (NIA–AA) who had undergone MRI, PiB and FDG-PET at our center ($N = 46$, mean age 63.0 ± 7.7, Mini-Mental State Examination 22.0 ± 4.8). Patients were subclassified based on their cognitive profiles into an amnestic/dysexecutive group (AD-memory; $n = 27$), a language-predominant group (AD-language; $n = 10$) and a visuospatial-predominant group (AD-visuospatial; $n = 9$). All patients were required to have evidence of amyloid deposition on PiB-PET. To capture the spatial distribution of Aβ deposition and glucose metabolism, we employed parallel independent component analysis (pICA), a method that enables joint analyses of multimodal imaging data. The relationships between PET components and clinical group were examined using a Receiver Operator Characteristic approach, including age, gender, education and apolipoprotein E ϵ4 allele carrier status as covariates. Results of the first set of analyses independently examining the relationship between components from each modality and clinical group showed three significant components for FDG: a left inferior frontal and temporoparietal component associated with AD-language (area under the curve [AUC] 0.82, $p = 0.011$), and two components associated with AD-visuospatial (bilateral occipito-parieto-temporal [AUC 0.85, $p = 0.009$] and right posterior cingulate cortex [PCC]/precuneus and right lateral parietal [AUC 0.69, $p = 0.045$]). The AD-memory associated component included predominantly bilateral inferior frontal, cuneus and inferior temporal, and right inferior parietal hypometabolism but did not reach significance (AUC 0.65, $p = 0.062$). None of the PiB components correlated with clinical group. Joint analysis of PiB and FDG with pICA revealed a correlated component pair, in which increased frontal and decreased PCC/precuneus PiB correlated with decreased FDG in the frontal, occipital and temporal regions (partial $r = 0.75$, $p < 0.0001$). Using multivariate data analysis, this study reinforced the notion that clinical phenotype in AD is tightly linked to patterns of glucose hypometabolism but not amyloid deposition. These findings are strikingly similar to those of univariate paradigms and provide additional support in favor of specific involvement of the language network, higher-order visual network, and default mode network in clinical variants of AD. The inverse relationship between Aβ deposition and

Abbreviations: AD or AD-memory, Alzheimer's disease; AUC, area under the curve; AD-language or LPA, logopenic variant primary progressive aphasia; PCA or AD-visuospatial, posterior cortical atrophy; PCC, posterior cingulate cortex; PPC, posterior parietal cortex.

[1] Present address: Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec — Hôpital de l'Enfant-Jésus 1401, 18ième rue, Québec G1J 1Z4, Canada.

[*] Corresponding author:
E-mail address: robert.laforce@fmed.ulaval.ca (R. Laforce Jr).

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glucose metabolism in partially overlapping brain regions suggests that Aβ may exert both local and remote effects on brain metabolism. Applying multivariate approaches such as pICA to multimodal imaging data is a promising approach for unraveling the complex relationships between different elements of AD pathophysiology.

1 Introduction

The relationships between amyloid, metabolism and clinical phenotype in Alzheimer's disease (AD) are incompletely understood. Previous studies have yielded mixed results within typical amnestic AD and across different AD phenotypes. For example, in three clinical variants of AD (AD-memory, AD-language, AD-visuospatial), clinical syndromes were strongly linked to patterns of glucose metabolism, whereas (^{11}C)-labeled Pittsburgh Compound B (PiB-PET) binding was similar across clinical phenotypes (Cohen et al., 2009; de Souza et al., 2011; Lehmann et al., 2013a; Leyton et al., 2011; Rabinovici et al., 2008; Rosenbloom et al., 2011). Correlations between increased β-amyloid and decreased metabolism have been found in some studies (Cohen et al., 2009; Edison et al., 2007; Engler et al., 2006) but not in others (Furst et al., 2012; Li et al., 2008). Some studies have suggested that the relationships between amyloid and glucose metabolism vary by brain region and disease state (Cohen et al., 2009; La Joie et al., 2012).

To date, most studies have investigated these relationships using univariate analyses, but this approach may fail to capture distributed variations across brain networks. A number of recent studies have demonstrated that multivariate statistical paradigms (e.g., principal component analysis or independent component analysis [ICA]), where distributed variations in multiple neuroimaging data and their inter-relationships are assessed together, provide a better framework for integrative analysis of imaging data. Multivariate techniques have been shown to be more sensitive for early diagnosis of AD and capture patterns of normal age-associated atrophy (Brickman et al., 2007). Parallel independent component analysis (pICA; Calhoun et al., 2006), a variation of ICA which allows estimation of independent components as well as multimodal patterns or mixed coefficients, has recently been used to study the mechanisms by which amyloid-β deposition leads to neurodegeneration and cognitive decline (Tosun et al., 2011). This is particularly relevant in light of possible distant (Bourgeat et al., 2010) rather than local (Cohen et al., 2009) effects of β-amyloid on glucose metabolism.

In this study we applied a multivariate approach to explore the relationships between metabolism and amyloid accumulation across AD phenotypes. To this end, we recruited patients with three phenotypes of AD cited in the new clinical diagnostic guidelines (McKhann et al., 2011): 1) a group of prototypical AD, or AD-memory, characterized by predominant episodic memory impairment and executive dysfunction (Dubois et al., 2007), 2) a group with language variant AD (AD-language, also called *logopenic variant primary progressive aphasia*) characterized by progressive word-finding difficulties and deficits in sentence repetition (Gorno-Tempini et al., 2004, 2011), and 3) a group with the visuospatial variant of AD (AD-visuospatial, also referred to as *posterior cortical atrophy*) marked by predominant visuospatial and visuoperceptual dysfunctions. We then applied pICA to 1) identify specific components from each modality that correlated with clinical presentation and 2) identify relationships between spatial patterns of PiB and FDG across AD patients. Based on previous results applying univariate statistics from our group and others, we hypothesized that FDG but not PiB would generate individual components that correlated with diagnosis. We further aimed to capture relationships between spatial patterns of glucose metabolism and amyloid deposition in this clinically and anatomically diverse cohort which may not be apparent using traditional univariate methods.

2. Subjects and methods

2.1. Subject selection and characteristics

We identified all patients seen at the University of California San Francisco (UCSF) Memory & Aging Center who met the criteria for probable AD according to the National Institute on Aging–Alzheimer's Association (NIA–AA) guidelines (McKhann et al., 2011), were PiB-positive and had available FDG and MRI scans. Patients were excluded if they had clinical or imaging evidence of previous stroke, or had a high burden of white matter hyperintensities (defined as Scheltens grade ≥ 4) (Scheltens et al., 1998). All patients were recruited between April 2005 and July 2011. Patients underwent a history and physical examination by a behavioral neurologist, a structured caregiver interview by a nurse, and a battery of neuropsychological tests (Kramer et al., 2003). All patients had mild-to-moderate dementia based on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the Clinical Dementia Rating (CDR; Morris, 1993) scale. Diagnosis was made in a consensus clinical conference incorporating clinical and neuropsychological profiles but blinded to imaging data. Patients were subclassified as AD-memory, AD-language, and AD-visuospatial using published criteria (Gorno-Tempini et al., 2011; McKhann et al., 2011; Tang-Wai et al., 2004). The AD-memory group was composed of patients meeting the NIA–AA criteria for probable AD but not AD-language or AD-visuospatial criteria. The final cohort consisted of 27 patients with probable AD-memory, ten with AD-language and nine with AD-visuospatial (see Table 1).

2.2. Imaging

Acquisition parameters for all scanners have been described in previous publications (Mormino et al., 2012; Mueller et al., 2009; Rabinovici et al., 2007; Rosen et al., 2002; Zhou et al., 2012).

2.3. Structural imaging

T_1-weighted scans were collected at UCSF or Lawrence Berkeley National Laboratory (LBNL) on different MRI units, including two 1.5 T units (Magnetom Avanto System, Siemens Medical Systems, Erlangen, Germany; Magnetom VISION system, Siemens Inc., Iselin, NJ), a 3 T unit (Siemens Tim Trio scanner), and a 4 T unit (BrukerMedSpec). The proportions of subjects studied on each scanner were balanced across the three AD groups. In patients with multiple MRIs, the MRI closest to the date of the PET scan was used for data preprocessing.