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Featured Article

Defining imaging biomarker cut points for brain aging and Alzheimer's disease

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Abstract

Introduction: Our goal was to develop cut points for amyloid positron emission tomography (PET), tau PET, flouro-deoxyglucose (FDG) PET, and MRI cortical thickness.
Methods: We examined five methods for determining cut points.
Results: The reliable worsening method produced a cut point only for amyloid PET. The specificity, sensitivity, and accuracy of cognitively impaired versus young clinically normal (CN) methods labeled the most people abnormal and all gave similar cut points for tau PET, FDG PET, and cortical thickness. Cut points defined using the accuracy of cognitively impaired versus age-matched CN method labeled fewer people abnormal.
Discussion: In the future, we will use a single cut point for amyloid PET (standardized uptake value ratio, 1.42; centiloid, 19) based on the reliable worsening cut point method. We will base lenient cut points for tau PET, FDG PET, and cortical thickness on the accuracy of cognitively impaired versus young CN method and base conservative cut points on the accuracy of cognitively impaired versus age-matched CN method.

Keywords: Alzheimer's disease; Alzheimer's imaging; Alzheimer's MRI; Amyloid PET; Tau PET; FDG PET; Alzheimer's biomarkers; Quantitative imaging

1. Introduction

Imaging and biofluid biomarkers of Alzheimer's disease (AD) are increasingly important to the study of brain aging and dementia. Although every biomarker exists on a continuum, dichotomizing biomarker values is necessary in certain situations. Clinical trials require a normal/abnormal classification when a biomarker is used to determine eligibility [1,2]. Additionally, modern criteria for AD across the cognitive spectrum label an individual's biomarker as normal or abnormal [3–7]. The goal of our study was to develop amyloid positron emission tomography (PET), tau PET, flouro-deoxyglucose (FDG) PET, and structural magnetic resonance imaging (MRI) biomarker cut points.

In brain aging and dementia research, defining a normal/abnormal cut point for quantitative amyloid PET has received

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significant attention. Various methods have been used [8–15] including the 10th percentile of clinically diagnosed AD dementia [16]. We adopted this last approach in 2012 [16] for amyloid PET, FDG PET, and structural MRI with the assumption that the same method should be used to select cut points for all biomarkers. However, we now believe that it may be appropriate to select cut points for different AD biomarkers using different methods. In particular, it seems reasonable to treat amyloid biomarkers differently from others. Defining cut points using individuals that meet certain clinical criteria without regard to evidence of amyloidosis is problematic [17]. The field has reached a consensus that biomarker evidence of amyloidosis is necessary for an accurate diagnosis of AD in living persons [3,4,6]. Of individuals with clinically diagnosed AD dementia, 10%–30% do not have AD at autopsy [18] or have no biomarker evidence of amyloidosis [19,20]. Therefore, using a clinical diagnosis of AD dementia to define an "affected" group of cases with AD when selecting biomarker cut points has significant inherent error. Similarly, around 30% of clinically normal elderly individuals have AD at autopsy [21] or have biomarker evidence of amyloidosis [22–24], and therefore, a clinically defined "unaffected" non-AD control group also has significant inherent error [17].

Tau PET has recently been introduced [25–34], and defining a normal/abnormal cut point is needed to place this modality on the same footing with other AD biomarkers. This in turn provides an opportunity to revisit the issue of defining cut points for more established imaging biomarkers used in AD research. Our objective was to examine different methods for defining cut points for amyloid PET, structural MRI, FDG PET, and tau PET. Identifying a single "best" cut point for each biomarker would provide the most straightforward outcome. However, "best" depends on the context of use [35], and therefore, it is reasonable that different cut points might apply for a given biomarker when used for different purposes [36].

In practice, biomarkers vary in terms of whether numerically high or low values are more abnormal. To simplify our presentation, we have reversed the axes for FDG PET and cortical thickness so that from left to right or bottom to top values are increasingly abnormal. In our general discussion of biomarkers, we treat higher values as more abnormal.

2. Methods

2.1. Participants

All clinically normal (CN) individuals in this study were participants enrolled in the Mayo Clinic Study of Aging (MCSA) [37]. Individuals with mild cognitive impairment (MCI) or AD dementia were participants enrolled in either the MCSA or the Mayo Alzheimer's Disease Research Center (ADRC). Beginning in 2004, the MCSA enrolled individuals aged 70–89 years; in 2012, the MCSA began enrolling individuals 50+ years; and, in 2015, the MCSA began enrolling individuals 30+ years. From 2006 to 2015, the imaging battery consisted of MRI, FDG PET, and amyloid PET. In 2015, tau PET was added to this battery, and FDG PET became optional.

All individuals included in this study completed MRI and amyloid PET imaging. However, owing to changes in the MCSA enrollment protocol, not all completed tau PET and FDG PET. Because of its recent introduction, only 508 individuals have tau PET scans. To take advantage of all available data, we created two separate samples for our analyses. The first sample included all individuals with tau PET, amyloid PET, and MRI (many of whom also had FDG PET). We refer to this sample as the "tau/amyloid/MRI sample." The second sample included all individuals with amyloid PET, FDG PET, and MRI. We refer to this sample as the "amyloid/FDG/MRI sample." Some of these individuals also had tau PET imaging. If individuals had multiple imaging visits, we used the first available visit with the necessary modalities.

The evolution of the MCSA described above has several practical implications. First, there are relatively few individuals under age 50 years. As the start of tau PET scanning coincided with enrolling this younger age group, all who consented to imaging had tau PET, amyloid PET, and MRI. Second, serial imaging data are only available in individuals age 50 years or older and only available for amyloid PET, FDG PET, and MRI.

2.2. Standard protocol approvals, registrations, and patient consents

These studies were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards and written informed consent was obtained from all participants.

2.3. Experimental design

2.3.1. Imaging methods

Amyloid PET imaging was performed with Pittsburgh Compound B [38] and tau PET with AV1451 [29]. Computed tomography was obtained for attenuation correction. Late uptake amyloid PET images were acquired from 40–60 minutes, FDG from 30–40 minutes, and tau PET from 80–100 minutes after injection. PET images were analyzed with our in-house fully automated image processing pipeline [39], where image voxel values are extracted from automatically labeled regions of interest (ROIs) propagated from an MRI template. An amyloid PET standardized uptake value ratio (SUVR) was formed from the voxel-number weighted average of the median uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs normalized to the cerebellar crus gray median. Amyloid PET values are expressed both in SUVR units and in centiloid units. The SUVR to centiloid conversion was done as recommended in Klunk et al [40]. An AD-signature FDG PET composite