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The use of Centiloids for applying [^{11}C]PiB classification cutoffs across region-of-interest delineation methods

Dana L. Tudorascu[a,*], Davneet S. Minhas[b], Patrick J. Lao[c,d], Tobey J. Betthauser[c,d], Zheming Yu[b], Charles M. Laymon[b], Brian J. Lopresti[b], Chet A. Mathis[b], William E. Klunk[e], Benjamin L. Handen[e], Bradley T. Christian[c,d], Ann D. Cohen[e]

[a]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[b]Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[c]Department of Medical Physics, University of Wisconsin–Madison, School of Medicine, Madison, WI, USA
[d]Waisman Center, University of Wisconsin–Madison, School of Medicine, Madison, WI, USA
[e]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Abstract

Introduction: Centiloid standardization was developed to establish a quantitative outcome measure of amyloid burden that could accommodate the integration of different amyloid positron emission tomography radiotracers or different methods of quantifying the same tracer. The goal of this study was to examine the use of Centiloids for establishing amyloid classification cutoffs for differing region-of-interest (ROI) delineation schemes.

Methods: Using ROIs from hand-drawn delineation in native space as the gold standard, we compared standard uptake value ratios obtained from the 6 hand-drawn ROIs that determine amyloid-positivity classification with standard uptake value ratio obtained from 3 different automated techniques (FreeSurfer, Statistical Parametric Mapping, and superimposed hand-drawn ROIs in Pittsburgh Compound B template space). We tested between-methods reliability using repeated measures models and intraclass correlation coefficients.

Results: We found high reliability between the hand-drawn standard method and other methods for almost all the regions considered. However, small differences in standard uptake value ratio were found to lead to unreliable classifications when the hand-drawn native space-derived cutoffs were used across other ROI delineation methods.

Discussion: The use of Centiloid standardization greatly improved the agreement of Pittsburgh Compound B classification across methods and may serve as an alternative method for applying cutoffs across methodologically different outcomes.

Keywords: Amyloid; Centiloid standardization; Down syndrome; ROI delineation in PET studies; ROI cutoff PET

1. Introduction

Amyloid positron emission tomography (PET) data are typically quantified using regions of interest (ROIs) delineated on structural MRI images using manual, or more recently, automated methods [1–7]. However, ROI segmentation on magnetic resonance imaging (MRI) images can be challenging in populations with brain structure abnormalities, such as Alzheimer's disease (AD) or Down syndrome (DS), particularly when automated processing routines are employed [8]. Differences in ROI delineation could substantially affect statistical outcomes when quantifying [^{11}C]Pittsburgh Compound B (PiB) PET standardized uptake value ratio (SUVR), which play a crucial role in studying the progression of AD in the elderly [9,10], autosomal dominant AD mutation carriers [11], and

*Corresponding author. Tel.: (412) 246-5692; Fax: (412) 246-6873.
E-mail address: dlt30@pitt.edu

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DS populations [8]. Therefore, a standardized method of ROI delineation would be useful in characterizing these disease populations when using SUVR outcomes.

ROIs manually defined in native space are particularly robust, as trained manual raters can better account for structural abnormalities, poor signal-to-noise ratio, and motion artifacts in MRI data. However, manual ROI tracings are susceptible to individual variability, and the process is time consuming, especially for larger studies [12]. Often, the task of manual ROI tracing for an imaging study is shared by several analysts resulting in inter-rater differences between subjects for the same region in the same cohort. As cohort sizes have increased in amyloid PET imaging studies, automated ROI delineation techniques have become more popular [3,6,13], yet the relative performance of these automated techniques in an integrated standardized framework remains unexplored.

The Centiloid Project was developed to standardize quantitative amyloid imaging measures on a 0–100 scale, with this scale being anchored at zero by young controls and 100 by AD patients. One of the major goals in the development of the Centiloid scale was to facilitate direct comparison of results across different analysis methods and tracers [14]. The goal of this work was to examine the use of Centiloid standardization [14] on [^{11}C]PiB SUVR classification. This was accomplished using an existing DS population dataset [8] to provide a comparison between [^{11}C]PiB SUVR outcomes determined from hand-drawn in native space (HD_{NS}) ROI and 3 automated methods of ROI analysis. SUVR threshold values for amyloid positivity have been previously described by our group based on tracing of 6 cortical HD_{NS} ROIs associated with amyloid β deposition in AD [1,12].The hand-drawn native space method was compared with the following automated methods: FreeSurfer [15,16], Statistical Parametric Mapping (SPM) using the Wake Forest University PickAtlas [17] extraction, and a hand-drawn method in PiB template space. Although the Centiloid method specifies a standard cortical + striatum target region and a whole-cerebellum reference region for initial analysis, smaller ROIs are accommodated by either (1) generation of a parametric Centiloid image for sampling smaller ROIs or (2) linear regression [14]. Here, we apply the Centiloid standardization linear regression approach to the global and striatum ROIs to examine its impact on [^{11}C]PiB SUVR classification.

Of all the forms of AD, DS has one of the most homogeneous and best understood initiating events in the overproduction of amyloid β due to 3 copies of chromosome 21 and the *APP* gene present in this chromosome. Adults with DS are uniformly affected by AD pathology by their fourth decade [18–20]. Furthermore, the early striatal pattern of amyloid deposition in DS is similar to that in autosomal dominant AD mutation carriers [21]. Adults with DS in their seventh decade have a 70%–80% chance of developing clinical dementia [22,23]. DS can be viewed in relation to AD as one of amplified sensitivity to risk and protective factors that moderate the relationship between amyloid β, neurodegeneration, and clinical dementia. Thus, DS provides a unique opportunity to study AD.

2. Methods

2.1. Subjects

A total of 83 adults with confirmed DS were recruited as previously described [24]. Participants were assessed for dementia using the Dementia Scale for Down Syndrome [25]. Three individuals who received a cognitive cutoff score > 3 (indicating dementia) were removed from this analysis. Thus, 80 subjects underwent the image processing described in the following.

2.2. Data acquisition

For PET scans, [^{11}C]PiB scans were acquired on Siemens ECAT HR + PET scanners at both sites using a nominal dose of 15 mCi of radiotracer. Preprocessing of dynamic [^{11}C]PiB data was performed in AIR, version 3.0 [26]. Dynamic PET data were corrected for inter frame motion and averaged over 50–70 min after injection. Parametric SUVR images were generated using a cerebellar gray matter ROI. For MRI scans, T1-weighted MRIs were acquired on a 3.0 T GE SIGNA 750 at the University of Wisconsin-Madison site and on a 3.0 T Siemens Magnetom Trio at the University of Pittsburgh Medical Center site. The SIGNA 750 acquisition used high-resolution volumetric spoiled gradient sequence (TI/TE/TR = 450/3.2/8.2 ms, flip angle = 12°, slice thickness = 1 mm no gap, matrix size = 256 × 256 × 156), whereas the Magnetom Trio acquisition used a magnetization prepared rapid acquisition gradient echo sequence (TI/TE/TR = 900/2.98/2300 ms, flip angle = 9°, slice thickness = 1.2 mm, matrix size = 160 × 240 × 256).

2.2.1. ROIs hand-drawn in native space

HD_{NS} ROIs were generated as previously described [1,12]. MR images were manually skull-stripped and reoriented such that the axial image planes were parallel to the anterior-posterior commissure line. [^{11}C]PiB images were registered to skull-stripped MRIs using AIR, version 3.0, and MRI images were resliced to PET resolution.

Manual ROI tracing was performed on skull-stripped MR images in PET native space using ROI Tool software (Siemens Medical Systems, Knoxville, TN). HD_{NS} ROIs included the anterior cingulate gyrus (ACG), anterior ventral striatum (AVS), frontal cortex (FRC), lateral temporal cortex (LTC), parietal cortex (PAR), precuneus cortex (PRC), and cerebellar gray matter. A global region (GBL) was created by generating a voxel-weighted average of the 5 cortical ROIs and the striatal ROI.

2.2.2. ROIs hand-drawn in MNI space

Spatial normalization of standardized uptake value PET images was performed using a DS-specific PET template