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# Utilizing the Centiloid scale in cross-sectional and longitudinal PiB PET studies

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ABSTRACT

Amyloid imaging is a valuable tool for research and diagnosis in dementing disorders. Successful use of this tool is limited by the lack of a common standard in the quantification of amyloid imaging data. The Centiloid approach was recently proposed to address this problem and in this work, we report our implementation of this approach and evaluate the impact of differences in underlying image analysis methodologies using both cross-sectional and longitudinal datasets. The Centiloid approach successfully converts quantitative amyloid burden measurements into a common Centiloid scale (CL) and comparable dynamic range. As expected, the Centiloid values derived from different analytical approaches inherit some of the inherent benefits and drawbacks of the underlying approaches, and these differences result in statistically significant ($p < 0.05$) differences in the variability and group mean values. Because of these differences, even after expression in CL, the 95% specificity amyloid positivity thresholds derived from different analytic approaches varied from 5.7 CL to 11.9 CL, and the reliable worsening threshold varied from −2.0 CL to 11.0 CL. Although this difference is in part due to the dependency of the threshold determination methodology on the statistical characteristics of the measurements. When amyloid measurements obtained from different centers are combined for analysis, one should not expect Centiloid conversion to eliminate all the differences in amyloid burden measurements due to variabilities in underlying acquisition protocols and analysis techniques.

## 1. Introduction

Alzheimer's disease (AD) is the most common form of dementia (Holtzman et al., 2011) and the prevalence of AD is expected to increase dramatically within the next 50 years (Alzheimer's, 2014). Currently, there are no proven disease-modifying treatments (Aisen, 2009; Aisen et al., 2011; Doody et al., 2013; Huang and Mucke, 2012); further research and development are in urgent need to prevent and/or treat this disease. It is well established that AD pathologies including amyloid plaques and neurofibrillary tangles begin to accumulate well before clinical symptoms appear (Bateman et al., 2012; Benzinger et al., 2013; Holtzman et al., 2011; Jack et al., 2010; Jansen et al., 2015; Morris and Price, 2001). Therefore, there is an increasing consensus that early intervention is necessary to effectively treat AD or slow down its progression (Aisen, 2009; Aisen et al., 2011). To enable the design of therapeutic trials, especially in asymptomatic individuals, validated surrogate biomarkers for AD pathology are necessary (Aisen, 2009; Aisen et al., 2011). As the primary pathological process in AD, accurate assessment of amyloid deposition in the brain may serve as an effective biomarker for the investigation of AD and marker in treatment trials.

To achieve this goal, positron emission tomography (PET) imaging tracers such as [$^{11}$C]Pittsburgh Compound-B (PiB) (Klunk et al., 2004), [$^{18}$F]florbetapir (Wong et al., 2010), [$^{18}$F]florbetaben (Rowe et al., 2008) and [$^{18}$F]flutemetamol (Vandenberghe et al., 2010), were developed to enable in vivo measurement of fibrillar beta-amyloid (Aβ) deposition. However, differences in these imaging tracers can lead to

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different estimations of the amyloid burden in the brain (Klunk et al., 2015; Landau et al., 2013). In addition to tracer differences, there is also substantial variability in the methods different groups use to quantify amyloid burden (Su et al., 2016), leading to difficulties in comparing and interpreting numeric results reported from different groups (Klunk et al., 2015).

To address these issues and facilitate standardization of PET based amyloid burden measurements, the Centiloid Working Group outlined the procedures for establishing the Centiloid scale and converting group specific amyloid burden measurements into the standard scale (Klunk et al., 2015). This group also made the dataset used for defining the Centiloid scale publicly available at the Global Alzheimer's Association Information Network (GAAIN; http://www.gaain.org). In this approach, two anchor points were used to define the Centiloid scale: the mean amyloid burden of the young control (YC) group who are assumed to have no amyloid pathology in their brain (defined as 0 in the Centiloid scale) and the mean amyloid burden of the AD group in the GAAIN dataset (defined as 100 in the Centiloid scale). A standard image analysis procedure estimating the standard uptake value ratio (SUVr) of a global cortical target region (CTX) over whole cerebellum (WC) for PiB PET images acquired within the 50 to 70 min post-injection time window was described to calculate the standard Centiloid SUVr, which was then mapped to the Centiloid scale based on the two anchor points. The outcome measure of any other analysis techniques can then be converted to the Centiloid scale using a linear transformation based on the GAAIN dataset (or other datasets that meets the criteria for Centiloid calibration), i.e. level-2 calibration (Klunk et al., 2015). The initial Centiloid paper also described the requirements and steps to scale amyloid burden measurements obtained using other PET tracers to the Centiloid scale (Klunk et al., 2015). Since its inception, the research community has gradually adopted the Centiloid approach (Jack et al., 2017; Leuzy et al., 2016; Weiner et al., 2017), and calibrations of [$^{18}$F]-NAV4694 (Rowe et al., 2016) and [$^{18}$F]-florbetaben (Rowe et al., 2017) based amyloid burden measurements to the Centiloid scale have been published recently.

The goal of the Centiloid scale is to standardize PET based amyloid burden measurements to make comparisons of results from different research groups easier and facilitate the use of amyloid PET imaging as a diagnostic tool. However, it remains unknown how comparable Centiloid values derived from different analysis pipelines are, and what the impact of variability in the implementation of Centiloid analysis will be to cross-sectional and longitudinal studies. To answer these questions, we compared Centiloid values obtained from different analysis techniques using the GAAIN dataset and PiB PET imaging data from Knight Alzheimer Disease Research Center (ADRC) Memory and Aging Project. Specifically, 1) the GAAIN dataset was used to establish Centiloid conversion equations for 13 different methods to quantify global amyloid burden using PiB PET and then used to compare the variability of the measured amyloid burden within young controls who have no amyloid in their brain; 2) the impact of quantification methods to cross-sectional amyloid burden measurements after the Centiloid conversion was further evaluated in the Knight ADRC cohort; 3) longitudinal Knight ADRC data was used to examine the variability of amyloid burden measurements and assess the sensitivity to longitudinal changes in amyloid burden; and finally 4) we estimated amyloid positivity threshold in Centiloid scale and compared the thresholds obtained from different quantification methods.

## 2. Methods

### 2.1. Participants

The dataset used to define the Centiloid scale (downloaded from the GAAIN website: http://www.gaain.org) consists of 34 YCs (age ≤ 45 yrs) and 45 clinically diagnosed AD patients ages 50 to 89 who had a clinical dementia rating (CDR) (Morris, 1993) > 0. A subset (GAAIN_SUB) of the GAAIN dataset (18 YCs and 18 ADs) had sufficient dynamic PiB PET data to allow all of our analysis techniques (e.g., binding potential calculation) to be performed. These numbers exceeded the number of participants recommended by the Centiloid working group for level-2 calibration (Klunk et al., 2015)) and were successfully processed with our local processing pipeline (Su et al., 2015; Su et al., 2013) and passed quality control.

The Knight ADRC cohort included 590 participants with at least a single PiB PET session, with a mean age of 67.7 ± 10.0 yrs., 37.6% APOE4 carriers, and 91 of them were CDR positive (> 0). A subset of 243 participants had two longitudinal PiB PET data points with a mean baseline age of 65.8 ± 9.4 yrs., 32.5% of them were APOE4 carriers, and 16 of them were CDR positive. The mean follow-up interval was 3.2 ± 1.5 yrs.

#### 2.1.1. Ethics statement

All assessment and imaging procedures were approved by Washington University's Human Research Protection Office. Written informed consent was obtained from all individuals or their authorized representatives.

### 2.2. Imaging

The imaging protocols for the GAAIN dataset have been described previously (Klunk et al., 2015). The PiB PET from the GAAIN dataset includes PET images acquired within the 50–70 min post-injection window at a minimum. The GAAIN_SUB dataset had full dynamic multiframe PET imaging data acquired between 0 and 70 min after injection of PiB. T1-weighted MRI was also available to provide anatomical information and facilitate PET quantification.

For the Knight ADRC cohort, dynamic PET imaging was conducted for 1 h with a Siemens/CTI EXACT HR+ scanner or a Biograph 40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany) in three-dimensional mode after intravenous administration of approximately 12 mCi of PiB. Anatomic MRI was acquired with a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence using a Siemens 1.5 T or 3 T scanner.

### 2.3. Image analysis

Standard Centiloid processing was performed on the GAAIN dataset as described in the initial Centiloid paper (Klunk et al., 2015). In summary, a summed PET image of the 50–70 min post-injection window was created from raw PET data. Both PET and MRI data for each subject were re-oriented to match the Montreal Neurological Institute (MNI)-152 T1-weighted template provided with the Statistical Parametric Mapping version 8 (SPM8) software (Ashburner, 2009). Subjects' MRIs were then coregistered to the MNI template and subsequently, the PET images were coregistered to the individual MRI. Spatial normalization was performed using the unified segmentation method (Ashburner and Friston, 2005) implemented in SPM8 to allow quantification in the MNI-152 atlas space. Standard Centiloid SUVr was calculated based on the CTX region and WC region described in (Klunk et al., 2015).

In addition to standard Centiloid processing, our local processing pipeline (PUP; https://github.com/ysu001/PUP) was also used to process the GAAIN_SUB dataset and Knight ADRC data. Details of PUP processing have been discussed previously (Su et al., 2015; Su et al., 2013). Standard FreeSurfer (v5.3; Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA; https://surfer.nmr.mgh.harvard.edu/fswiki) based PUP processing (Su et al., 2015; Su et al., 2013) includes scanner resolution harmonization filter (Joshi et al.,