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Improved longitudinal [^{18}F]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction

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ABSTRACT

Amyloid positron-emission-tomography (PET) offers an important research and diagnostic tool for investigating Alzheimer's disease (AD). The majority of amyloid PET studies have used the cerebellum as a reference region, and clinical studies have not accounted for atrophy-based partial volume effects (PVE). Longitudinal studies using cerebellum as reference tissue have revealed only small mean increases and high inter-subject variability in amyloid binding. We aimed to test the effects of different reference regions and PVE-correction (PVEC) on the discriminatory power and longitudinal performance of amyloid PET.

We analyzed [^{18}F]-AV45 PET and T1-weighted MRI data of 962 subjects at baseline and two-year follow-up data of 258 subjects. Cortical composite volume-of-interest (VOI) values (COMP) for tracer uptake were generated using either full brain atlas VOIs, gray matter segmented VOIs or gray matter segmented VOIs after VOI-based PVEC. Standard-uptake-value ratios (SUVR) were calculated by scaling the COMP values to uptake in cerebellum ($SUVR_{CBL}$), brainstem ($SUVR_{BST}$) or white matter ($SUVR_{WM}$). Mean SUV, SUVR, and changes after PVEC were compared at baseline between diagnostic groups of healthy controls (HC; N = 316), mild cognitive impairment (MCI; N = 483) and AD (N = 163). Receiver operating characteristics (ROC) were calculated for the discriminations between HC, MCI and AD, and expressed as area under the curve (AUC). Finally, the longitudinal [^{18}F]-AV45-PET data were used to analyze the impact of quantitation procedures on apparent changes in amyloid load over time.

Reference region SUV was most constant between diagnosis groups for the white matter. PVEC led to decreases of COMP-SUV in HC (−18%) and MCI (−10%), but increases in AD (+7%). Highest AUCs were found when using PVEC with white matter scaling for the contrast between HC/AD (0.907) or with brainstem scaling for the contrast between HC/MCI (0.658). Longitudinal increases were greatest in all diagnosis groups with application of PVEC, and inter-subject variability was lowest for the white matter reference.

Thus, discriminatory power of [^{18}F]-AV45-PET was improved by use of a VOI-based PVEC and white matter or brainstem rather than cerebellum reference region. Detection of longitudinal amyloid increases was optimized with PVEC and white matter reference tissue.

Abbreviations: Aß, ß-amyloid; AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale — cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; AUC, area under the curve; BST, brainstem; CBL, cerebellum; COMP, combined region of frontal, parietal, temporal and posterior cingulate cortices; CSF, cerebrospinal fluid; FAD, familiar Alzheimer's disease; FDA, Food and Drug Administration; FDG, fluorodeoxyglucose; FULL, full atlas VOIs; GM, gray matter; HC, cognitively healthy; MANOVA, multivariate analysis of covariance; MCI, mild cognitive impairment; MMSE, mini mental state examination; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; NIA, National Institute on Aging; NIBIB, National Institute of Biomedical Imaging and Bioengineering; PET, positron emission tomography; PVE, partial volume effect; PVEC, partial volume effect correction; R, Pearson's coefficient of correlation; REF, reference configuration from tracer validation; ROC, receiver operating characteristics; SAD, sporadic Alzheimer's disease; SUV, standard uptake value; SUVR, standard uptake value ratio; T1w, T1 weighted; VOI, volume of interest; WM, white matter; FWHM, Full-width-at-half-maximum.

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia; its incidence increases exponentially as a function of age, which is imposing an onerous burden on health care systems in societies with aging populations (Ziegler-Graham et al., 2008). Neurofibrillary tangles and amyloid plaques together comprise the hallmark neuropathology of AD (Braak and Braak, 1991). Elevated brain amyloid burden is now clearly associated with cognitive decline in the healthy elderly (HC) (Lim et al., 2012) and in cases of mild cognitive impairment (MCI) (Lim et al., 2014). Amyloid PET offers a feasible tool for the early detection of brain amyloidosis, and the recent development of fluorine-18 labeled amyloid radioligands such as [^{18}F]-AV45 has made this technique available to PET centers lacking an on-site cyclotron/radiochemistry facility.

In clinical PET practice, Aβ-positivity and -negativity are visually assessed with good inter- and intra-reader agreement (Clark et al., 2012). However, a semiquantitative approach is better suited especially to the requirements of longitudinal clinical trials of amyloidosis progression and treatment. The issue of defining an optimal reference region has been extensively discussed for normalization of [^{18}F]-fluorodeoxyglucose-(FDG) PET relative to cerebellum, pons/brainstem, global mean, or a reference cluster (Bohnen et al., 2012; Borghammer et al., 2009; Dukart et al., 2013; Yakushev et al., 2008).

In PET imaging with [^{18}F]-AV45- and [^{11}C]-PiB, the entire cerebellum and the cerebellar gray matter (GM) have emerged as the most widely used reference regions for quantitation of amyloid burden (Weiner et al., 2013). However, a recent longitudinal [^{11}C]-PiB PET study of mild cognitive impairment (MCI) and AD showed high inter-subject variability based on a cerebellar GM reference (van Berckel et al., 2013). Furthermore, amyloid PET results are potentially biased by partial volume effects (PVE), which have a considerable impact in patients with pronounced atrophy (Thomas et al., 2011), which is particularly problematic in longitudinal studies.

Given these considerations, we aimed to compare systematically the quantitation of [^{18}F]-AV45-PET results for different reference regions, using as our material the Alzheimer's Disease Neuroimaging Initiative (ADNI)-dataset, which includes more than 1000 amyloid PET cases. Furthermore, we set about to investigate the impact of a volume-of-interest (VOI)-based partial volume effect correction (PVEC) on the semiquantitative analyses. Receiver operating characteristics (ROC) were obtained for the baseline discrimination of HC from MCI and AD cases in order to identify the most sensitive amyloid-PET analysis. Finally, two-year longitudinal [^{18}F]-AV45-PET data from 258 patients used to test the impact of the above factors on apparent changes in amyloid load with time.

Materials and methods

Alzheimer's disease neuroimaging initiative

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California — San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

Data from ADNI-GO/-2 were included in this work. Pre-processed brain [^{18}F]-AV45-PET images and temporally corresponding T1-weighted MPRAGE images were downloaded from the ADNI database as available on Jan 16th, 2014.

Patient selection and study design

1018 subjects from ADNI-GO and ADNI-2 who had undergone brain [^{18}F]-AV45-PET and T1 weighted MPRAGE (T1w) MRI at their study baseline were included in this investigation. Clinical diagnoses as provided by the ADNI database at the time of PET-imaging were: 336 HC, 508 MCI and 174 AD. A subgroup of 278 subjects (94 HC, 158 MCI and 26 AD) who underwent a second [^{18}F]-AV45-PET and T1w MRI at two-year follow-up was used for longitudinal analyses.

Image data

ADNI [^{18}F]-AV45-PET acquisition and pre-processing

The [^{18}F]-AV45-PET images had been acquired using Siemens, GE and Philips PET scanners according to a standard dynamic 50–70 min protocol following the intravenous injection of 370 ± 37 MBq of [^{18}F]-AV45. Data were corrected for both scatter and measured attenuation, which was determined using the CT scan for PET/CT scanners, or a transmission scan with [^{68}Ge] or [^{137}Cs] rotating rod sources for PET-only scanners. Images were reconstructed using scanner-specific algorithms, and sent to the University of Michigan, where they were reviewed for artifacts and transmitted to the Laboratory of NeuroImaging (LONI) for storage.

Downloaded [^{18}F]-AV45-PET images in DICOM format had been pre-processed in four steps: 1) motion correction by co-registration of single five minute frames; 2) time frame averaging (50–70 min p.i.); 3) co-registration of longitudinal data to the baseline scan and reorientation in a standardized 160 × 160 × 96 matrix with 1.5 mm cubic voxels; 4) smoothing with a scanner-specific filter function to an isotropic resolution of 8 mm. Further details are provided in Supplement 1.

ADNI MRI acquisition and pre-processing

T1-weighted MRI scans had been acquired using Siemens, GE or Philips MRI scanners according to a standard protocol (Jack et al., 2008) involving acquisitions of two 3-D MPRAGE imaging sequences per subject. Of the two images acquired per subject and time-point, the ADNI quality assurance team selected the better image for pre-processing, based on the presence and severity of commonly occurring image artifacts.

MRI preprocessing involved: 1) application of a scanner-specific correction for gradient nonlinearity distortion (Gradwarp) (Jovicich et al., 2006); 2) correction for image intensity non-uniformity (B1) (Jack et al., 2008); 3) histogram peak sharpening algorithm for bias field correction (N3) (Sled et al., 1998.); 4) application of spatial scaling factors obtained by phantom measurements. For images acquired on Philips scanners, B1 correction was already implemented, and the gradient systems with this instrument tended to be linear (Jack et al., 2008).