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Partial volume correction in quantitative amyloid imaging

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ABSTRACT

Amyloid imaging is a valuable tool for research and diagnosis in dementing disorders. As positron emission tomography (PET) scanners have limited spatial resolution, measured signals are distorted by partial volume effects. Various techniques have been proposed for correcting partial volume effects, but there is no consensus as to whether these techniques are necessary in amyloid imaging, and, if so, how they should be implemented. We evaluated a two-component partial volume correction technique and a regional spread function technique using both simulated and human Pittsburgh compound B (PiB) PET imaging data. Both correction techniques compensated for partial volume effects and yielded improved detection of subtle changes in PiB retention. However, the regional spread function technique was more accurate in application to simulated data. Because PiB retention estimates depend on the correction technique, standardization is necessary to compare results across groups. Partial volume correction has sometimes been avoided because it increases the sensitivity to inaccuracy in image registration and segmentation. However, our results indicate that appropriate PVC may enhance our ability to detect changes in amyloid deposition.

Introduction

Alzheimer's disease (AD) is the most common form of dementia (Holtzman et al., 2011). The prevalence of AD is expected to increase dramatically worldwide over the next 50 years (Brookmeyer et al., 2007). It is well established that the pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles (Holtzman et al., 2011). However, the underlying disease mechanisms remain under study.

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There currently are no proven disease-modifying treatments (Aisen, 2009; Aisen et al., 2011; Doody et al., 2013; Huang and Mucke, 2012). Evidence suggests that pathological changes begin 10 to 20 years before the onset of clinical symptoms (Bateman et al., 2012; Morris and Price, 2001), which implies that successful treatment of AD may require early intervention. Hence, validated surrogate biomarkers for AD are needed for the design of therapeutic trials in asymptomatic individuals (Aisen, 2009; Aisen et al., 2011).

Positron emission tomography (PET) imaging of beta-amyloid (Aβ) plaques with tracers such as [^{11}C]PiB (N-methyl-[^{11}C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole) (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), enables in vivo measurement of fibrillar Aβ deposition, which provides an early indicator of AD pathology. Accurate quantification of Aβ burden is essential to better understand disease mechanisms, to develop early diagnostic techniques, and to identify suitable surrogate indicators for treatment monitoring.

Partial volume effect (PVE) in positron emission tomography (PET) is a consequence of the poor spatial resolution of PET scanners, which typically is 5 to 6 mm full-width-half-max (FWHM). Because of PVE, the intensity of a particular voxel reflects the tracer concentration not only of the tissue within that voxel but also the surrounding area. In addition, PVE depends on the physical size and the shape of a region-of-interest (ROI) and its relative contrast with surrounding regions (Soret et al., 2007). When PET is used to measure amyloid burden, the impact of PVE becomes more complicated. Previous studies indicate that amyloid plaques primarily develop in the cortical and subcortical gray matter while the signal observed in white matter mainly comes from non-specific binding (Klunk et al., 2004). Non-specific PiB binding in white matter would not be a problem if the spatial resolution of PET permitted imaging gray matter without partial volume contributions from white matter. However, the resolution of PET is only ~5–6 mm. Hence, partial volume effect cannot be avoided. Without appropriate partial volume correction (PVC), quantification based on the raw PET images yields only a qualitative representation of the amyloid burden, not a quantitative one. Only when we apply appropriate PVC can we obtain quantitative measurement of amyloid burden. For a simple demonstration please refer to the Supplementary material.

Currently, the approach to addressing PVE differs from one group to another and there is no consensus regarding whether correction for PVE is necessary and, if so, what type of correction should be used. We believe that this uncertainty is attributable to the limited understanding of the impact of PVE on quantitative amyloid imaging. In a recent longitudinal study (Villemagne et al., 2011), PVC increased the estimated regional standard uptake value ratios (SUVRs), but similar trends were obtained with and without PVC. The authors elected to not report PVC results to avoid potential inaccuracies resulting from segmentation errors (Villemagne et al., 2011). Other groups (Aizenstein et al., 2008; Lopresti et al., 2005; Lowe et al., 2009) use two-component PVC (Meltzer et al., 1996), which defines two types of tissue, i.e., brain and non-brain, and corrects for the underestimation of signal due to PVE caused by non-brain tissue. In a comparative study of two- vs. three-component (gray matter, white matter, and non-brain) PVC, it was concluded that the two-component method is better because it is less sensitive to registration and segmentation errors, although the three-component method is capable of more accurate absolute quantification (Meltzer et al., 1999). In contrast, a more recent paper (Thomas et al., 2011) advocates a region-based voxel-wise correction method to improve quantitative accuracy.

The goal of this study is to evaluate the impact of PVE on quantitative amyloid imaging in both cross-sectional and longitudinal studies using simulated and human research data. In addition, we specifically examine the impact of individual variability in cortical thickness and brain atrophy upon quantification. We also investigate the test–retest reliability of PVC attributable to variability in registration and segmentation.

Methods

Participants

Three cohorts were involved in this study (Table 1). The first cohort included 16 participants recruited from the Knight Alzheimer Disease Research Center (ADRC). One of the 16 participants had a CDR score of 0.5 (very mild dementia) while the CDR ratings for the rest were 0 (cognitively normal). This cohort was studied using a MRI test–retest (MRTRT) design to examine the sensitivity of PVC to uncertainty related to MRI images used as anatomical reference. Each participant in the MRTRT cohort underwent two separate MR scans on different days, using different MR sequences, and on different MR scanners, as described below in the imaging protocol. Another MRTRT experiment with anatomical MR acquired twice during the same imaging session was described in Supplementary material 2. The second cohort comprised 74 participants recruited at multiple sites as part of the international Dominantly Inherited Alzheimer Network (DIAN) initiative (Morris et al., 2012). The DIAN cohort included only individuals known to carry an autosomal dominant mutation leading to early onset AD. The DIAN cohort was analyzed to investigate the impact of PVC on cross-sectional studies. The estimated year-to-onset (EYO) was calculated for each individual in this cohort as the difference of the age of mutation carrier at the time of study and the parental age at onset (Bateman et al., 2012). EYO was used as the reference indicator of disease stage. The third cohort (LONG) included 42 participants from Knight ADRC, studied to investigate the impact of PVC on longitudinal studies. Six participants had a baseline CDR score of 0.5 while the rest had a CDR score of 0. Each LONG participant had a baseline visit and a follow-up visit at a mean interval of 2.2 years. The LONG cohort included only individuals with a baseline mean cortical binding potential (MCBP) greater than 0.06, as measured by PiB PET imaging (Mintun et al., 2006), to enhance the probability of observing an increase in amyloid deposition at the second visit (Sojkova et al., 2011). All three cohorts were independent and there was no overlap among the cohorts.

Ethics statement

All assessment and imaging procedures were approved by Washington University's (WashU) Human Research Protection Office. Written informed consent was obtained from all individuals or their caregivers. Local institutional review boards also approved the collection of scans for archiving and future study at each non-WashU study site.

Imaging

In all cohorts, PET imaging for quantitative estimation of amyloid deposition was performed using [^{11}C]PiB, prepared according to the published protocol (Mathis et al., 2003). In the MRTRT cohort, dynamic PET imaging was conducted for 1 h with a Biograph 40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany) in three-dimensional mode after intravenous administration of approximately 12 mCi of PiB. The images were reconstructed on a 128 × 128 × 109 matrix

Table 1
Demographics for this study.

Cohort	MRTRT	DIAN	LONG
N	16	74	42
Age (SD) years	63.0 (9.0)	39.1 (11.3)	70.7 (5.5)
EYO (SD) years	–	−8.1 (11.1)	–
Education (SD) years	15.5 (2.4)	14.4 (2.5)	15.6 (2.3)
Male (%)	8 (50.0)	36 (48.6)	16 (38.1)
CDR > 0 (%)	1 (6.3)	21 (28.4)	6 (14.3)
APOE4 + (%)	3 (19.7)	30 (40.5)	22 (52.4)
PET interval (SD) years	–	–	2.2 (0.85)

MRTRT (MR test–retest); DIAN (dominantly inherited Alzheimer's network); LONG (longitudinal cohort from Knight ADRC); CDR: clinical demential rating; APOE4+: carrier of at least one copy of E4 version of apolipoprotein gene; EYO; estimated year to onset.