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# Impact of partial volume correction on the regional correspondence between in vivo [C-11]PiB PET and postmortem measures of Aβ load

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ABSTRACT

The positron emission tomography (PET) radiotracer Pittsburgh Compound B ([C-11]PiB) demonstrates a high affinity for fibrillary amyloid-beta (Aβ) aggregates. However, [C-11]PiB's in vivo sensitivity and specificity is an ongoing area of investigation in correlation studies with postmortem measures of Aβ pathology. One potential confound in PET-to-postmortem correlation studies is the limited spatial resolution of PET and resulting partial volume effects (PVEs). In this work, we evaluated the impact of three partial volume correction (PVC) techniques – the Meltzer, the modified Müller-Gärtner, and the Region-Based Voxel-Wise – on correlations between region-matched in vivo [C-11]PiB standardized uptake value ratios (SUVRs) and postmortem measures of Aβ pathology in a unique cohort of nine subjects. Postmortem Aβ pathology was assessed histologically as percent area coverage of 6-CN-PiB positive and Aβ immunoreactive (4G8 antibody) deposits. The application of all three PVC techniques resulted in minimally reduced PET-to-postmortem correlations relative to no PVC. However, correlations to both 6-CN-PiB and 4G8 percent area across all PVC techniques and no PVC were statistically significant at $p < 0.01$, suggesting that PVC is of minimal importance in understanding the relationship between Aβ PET and neuropathologically assessed Aβ. Thus, the utility of PVC in Aβ PET imaging should continue to be examined on an application-specific basis.

## 1. Introduction

Alzheimer's disease (AD) is characterized clinically by impaired cognitive function (Förstl and Kurz, 1999) and neuropathologically by extracellular amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles of hyper-phosphorylated tau protein, and synaptic/neuronal loss resulting in regional hypometabolism and cortical atrophy (Mirra et al., 1991). To facilitate clinical diagnosis and early disease detection, several positron emission tomography (PET) radioligands were developed for imaging Aβ pathology in vivo, including $^{11}$C-radiolabelled Pittsburgh Compound B ([C-11]PiB) (Klunk et al., 2004; Engler et al., 2002), $^{18}$F-Florbetapir (Wong et al., 2010), $^{18}$F-Flutemetamol (Vandenberghe et al., 2010), and $^{18}$F-florbetaben (Rowe et al., 2008), the latter three of which have been FDA approved for clinical use (FDA approves 18F-florbetapir PET agent, 2012). Although these Aβ PET radioligands have high affinity for fibrillary Aβ aggregates in the grey matter (GM), characterization of their sensitivity and specificity is ongoing.

One important tool in this ongoing characterization is the comparison of in vivo Aβ PET measures with postmortem measures of Aβ deposition commonly held to be the "gold standard" (Bacskai et al., 2007; Ikonomovic et al., 2008; Cairns et al., 2009; Burack et al., 2010; Kadir et al., 2011; Sojkova et al., 2011; Kantarci et al., 2012; Ikonomovic et al., 2012; Driscoll et al., 2012; Seo et al., 2017). These comparisons typically result in good, but imperfect, correlations between the in vivo and postmortem quantifications. This could be due to differences

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**Table 1**
Demographics for nine subjects with postmortem measures of Aβ pathology load and in vivo [C-11]PiB PET and MR scans. Clinical diagnoses include probable Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and normal cognition (NC), and were determined through a battery of tests including the Mini Mental State Exam (MMSE).

| Subject | Diagnosis | Gender | Age at scan (years) | MMSE at scan | PET-death interval (months) | [C-11]PiB PET scan duration | MR scanner & sequence |
|---|---|---|---|---|---|---|---|
| Case#01 | AD | Male | 58 | 18 | 42.3 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#02 | DLB | Male | 77 | 10 | 17.2 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#03 | AD | Male | 54 | 19 | 30.4 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#04 | AD | Male | 74 | 21 | 10.5 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#05 | AD | Female | 66 | 21 | 34.6 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#06 | FTD | Male | 80 | 7 | 37.2 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#07 | AD | Female | 79 | 25 | 45.5 | 0–90 min | GE Signa 1.5 T SPGR |
| Case#08 | NC | Female | 80 | 28 | 31.8 | 40–70 min | GE Signa 1.5 T SPGR |
| Case#09 | NC | Male | 85 | 29 | 37.4 | 40–70 min | Siemens Tim Trio 3 T MPRG |

between what is actually detected by the in vivo PET Aβ tracers and the postmortem detection techniques, or it could be due to artifacts introduced by either the in vivo or postmortem analysis methods. Since most postmortem analyses quantify Aβ in microscopic fields limited only to brain cortex, one possible in vivo artifact could be created by the inclusion of tissues outside of the cortex caused by the relatively low spatial resolution of PET. This study looks at the effect of common methods to correct for this unintentional inclusion of non-cortical tissue in PET measurements of Aβ.

The poor spatial resolution of Aβ PET imaging relative to magnetic resonance (MR) imaging and X-ray computed tomography (CT) is due to technical factors including detector size, positron range, and non-collinearity (Saha, 2010). The spatial resolution of PET characterized by a point spread function (PSF) corresponds to the image of a point source and is modeled as a Gaussian function with a defined full width at half maximum (FWHM). Whole-body PET scanner spatial resolutions typically range from 4 mm to 6 mm FWHM. Quantification of radioactivity concentration in structures which are large in comparison to this resolution scale (> 2xFWHM) is reasonably accurate (Hoffman et al., 1979). However, in PET brain imaging, volume of interest (VOI) size typically falls below this threshold resulting in reduced measurement accuracy due to the blurring of activity between regions, i.e. activity spill-in/spill-out between adjacent VOIs. Resolution-induced inaccuracy is often referred to as the partial volume effect (PVE) (Hoffman et al., 1979; Mazziotta et al., 1981). PVEs may confound quantification of Aβ PET imaging, particularly in elderly subjects where cortical atrophy, with the expansion of CSF spaces and thinning of cortex, may result in the underestimation of tracer uptake in CSF-bordering cortical grey matter (GM). Furthermore, non-specific white matter (WM) uptake (common to all currently available Aβ PET radioligands) can cross-contaminate cortical GM, potentially inflating the signal in Aβ-free healthy controls or reducing apparent retention signal in AD patients with high Aβ burden.

To address PVEs, several protocols were developed with variable success; these are referred to as partial volume correction (PVC) techniques and include: 1) the Meltzer method, which addresses spill-out of activity from the brain to CSF space but does not account for heterogeneity within tissue (Meltzer et al., 1990; Meltzer et al., 1999; Price et al., 2005; Lopresti et al., 2005); 2) the modified Müller-Gärtner (mMG) method, which addresses cross-contamination between GM and WM but does not account for heterogeneity within WM or GM (Rousset et al., 1998a); 3) the geometric transform matrix (GTM) method (Rousset et al., 1998b); and 4) the Region-Based Voxel-Wise (RBV) method (Thomas et al., 2011). The latter two methods account for within-tissue type heterogeneity through parcellating the brain into contiguous non-overlapping regions. Each of these methods rely on anatomical information typically provided by a co-registered MR image, and model the observed PET image as a convolution of the true image by a point spread function.

The impact of PVC techniques in Aβ PET studies is an ongoing area of investigation. Mikhno et al. (2008) demonstrated that voxel-based analysis with the mMG method improved separation of AD and healthy control groups. Rabinovici et al. (2010) obtained similar results using the Meltzer method in their study of healthy controls, early-onset AD, and late-onset AD. However, Drzezga et al. (2008) observed that when the mMG method was used, differences in [C-11]PiB PET uptake between semantic dementia and AD groups were less prominent. Recently, Su et al. (2015) demonstrated that PVEs, if uncorrected, can lead to underestimated measures of longitudinal change in Aβ pathology in the presence of decreasing cortical thickness. Schwarz et al. (2017) observed that the use of Meltzer PVC increased longitudinal plausibility, that is the percent of subjects not decreasing in [C-11]PiB retention between baseline to follow-up scans. However, another study examining the regional correlations between [C-11]PiB and postmortem Aβ pathology found correlations were consistent between uncorrected and mMG partial volume-corrected SUVR data (Seo et al., 2017).

In our investigations of the correspondence between [C-11]PiB PET and postmortem measures of Aβ pathology, we previously applied a modified form of the Meltzer PVC method to [C-11]PiB PET measures in two case reports (Ikonomovic et al., 2008; Ikonomovic et al., 2012), but uncorrected [C-11]PiB measures were not examined. In the current work, we compared the effects of three PVC techniques on the correspondence between region-matched in vivo PET and postmortem measures of Aβ pathology in nine subjects who had an in vivo [C-11]PiB PET scan and later underwent postmortem neuropathology examination.

## 2. Materials and methods

### 2.1. Subject data

Nine subjects ($n$ = 6 male, $n$ = 3 female) with in vivo [C-11]PiB PET and MR scans and postmortem histological assessments of Aβ pathology were included in this study (Table 1). One case has been reported previously (Ikonomovic et al., 2012) (Case#02). Clinical diagnosis of AD was based on a standardized University of Pittsburgh Alzheimer's Disease Research Center (ADRC) evaluation at a Consensus Conference, utilizing Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et al., 1984). Neuropathological diagnosis was determined by a board-certified neuropathologist (RLH or JKK) using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Mirra et al., 1991) and National Institute on Aging-Reagan Institute (NIA-RI) consensus (Ronald and G. National Institute, 1998) criteria (Table 1).

Based on the last in vivo clinical diagnosis at time of scan, five subjects had probable AD, one subject had dementia with Lewy Bodies (DLB), one subject had frontotemporal dementia (FTD), and two