Impact of spillover from white matter by partial volume effect on quantification of amyloid deposition with $[^{11}C]$PiB PET

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Abstract

High non-specific uptake of $[^{11}C]$Pittsburgh compound B ($[^{11}C]$PiB) in white matter and signal spillover from white matter, due to partial volume effects, confound radioactivity measured in positron emission tomography (PET) with $[^{11}C]$PiB. We aimed to reveal the partial volume effect in absolute values of kinetic parameters for $[^{11}C]$PiB, in terms of spillover from white matter. Dynamic data acquired in $[^{11}C]$PiB PET scans with five healthy volunteers and eight patients with Alzheimer’s disease were corrected with region-based and voxel-based partial volume corrections. Binding potential ($BP_{ND}$) was estimated using the two-tissue compartment model analysis with a plasma input function. Partial volume corrections significantly decreased cortical $BP_{ND}$ values. The degree of decrease in healthy volunteers ($-52.7 \pm 5.8\%$) was larger than that in Alzheimer’s disease patients ($-11.9 \pm 4.2\%$). The simulation demonstrated that white matter spillover signals due to the partial volume effect resulted in an overestimation of cortical $BP_{ND}$ with a greater degree of overestimation for lower $BP_{ND}$ values. Thus, an overestimation due to partial volume effects is more severe in healthy volunteers than in Alzheimer’s disease patients. Partial volume corrections may be useful for accurately quantifying $A\beta$ deposition in cortical regions.

Keywords: Alzheimer’s disease, Amyloid, Compartment model analysis, Partial volume effect, PET

1. Introduction

Alzheimer’s disease (AD) is the most common form of neurodegenerative dementia, characterized by deposition of amyloid beta (Aβ) protein (Braak and Braak, 1991). This pathological characteristic of AD allows for in vivo imaging of Aβ deposition, which could serve as a biomarker for AD diagnosis and the evaluation of drug therapy. $[^{11}C]$Pittsburgh compound B ($[^{11}C]$PiB) was developed as a first generation radiotracer to measure Aβ plaque deposition in cortical gray matter regions with positron emission tomography (PET) (Klunk et al., 2004; Mathis et al., 2003), and has been widely used in clinical AD research (Buckner et al., 2005; Engler et al., 2006; Rowe et al., 2007; Kerbler et al., 2015; Klupp et al., 2015; Murray et al., 2014; Price et al., 2005).

Kinetic analysis with a compartment model has been performed to estimate blood flow and specific binding to receptors, enzymes, or other proteins in tissues (Watabe et al., 2006). Compartments model analysis requires arterial blood sampling to acquire a plasma time-activity curve (TAC) as an input function. Some simplified methods have been developed, which do not involve blood sampling, to estimate relative parameters to reference tissue (Ichise et al., 2003; Lammertsma and Hume, 1996; Logan et al., 1996). For $[^{11}C]$PiB PET, two tissue compartment models with four parameters (2TC) have been shown to be optimal for kinetic analysis with arterial input function (Price et al., 2005). For $[^{11}C]$PiB PET, two tissue compartment models with four parameters (2TC) have been shown to be optimal for kinetic analysis with arterial input function (Price et al., 2005). For $[^{11}C]$PiB PET, two tissue compartment models with four parameters (2TC) have been shown to be optimal for kinetic analysis with arterial input function (Price et al., 2005). For $[^{11}C]$PiB PET, two tissue compartment models with four parameters (2TC) have been shown to be optimal for kinetic analysis with arterial input function (Price et al., 2005). For $[^{11}C]$PiB PET, two tissue compartment models with four parameters (2TC) have been shown to be optimal for kinetic analysis with arterial input function (Price et al., 2005).

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parameters even in amyloid PET studies. Low spatial resolution of PET, typically between 5 and 7 mm full-width at half maximum (FWHM), results in spillout radioactivity from the region of interest and spill-in from marginal regions. The phenomenon is generally referred to as the ‘partial volume effect’ (Hoffman et al., 1979). Morphological changes in neurodegenerating brain tissue increase the partial volume effect. For example, gyri thinned by progressive atrophy in AD results in stronger spill-out from the gray matter regions, thereby underestimating cortical radioactivity, as well as overestimating the cortical radioactivity due to spillover from white matter. Additionally, $[^11]$C$PiB$ is highly distributed to the white matter, even though amyloid does not deposit in the white matter (Klunk et al., 2004). The high uptake in white matter makes more severe the spillover from the white matter into the gray matter, thereby confounding $[^11]$C$PiB$ radioactivity in the gray matter regions. Some techniques to correct partial volume effect have been developed (Alessio and Kinahan, 2006; Baete et al., 2004; Meltzer et al., 1990; Muller-Gartner et al., 1992; Rizzo et al., 1997; Rousset et al., 1998a, 1998b; Shidahara et al., 2009; Thomas et al., 2011). Partial volume correction (PVC) can improve the statistical power in group comparisons (Rullmann et al., 2015; Thomas et al., 2011) and longitudinal studies (Su et al., 2015). However, to the best of our knowledge, the effects of partial volume effect on absolute kinetic parameters, estimated by compartment model analysis, have not been investigated for $[^11]$C$PiB$ PET and are still required to validate the impact of partial volume effect on quantification of amyloid deposit in $[^11]$C$PiB$ PET studies.

The aim of the current study is to analyze the partial volume effect in absolute kinetic parameters for $[^11]$C$PiB$. In particular, we focused on the effect of spillover from white matter regions on kinetic parameters. To validate these effects, we applied region- and voxel-based PVC to dynamic $[^11]$C$PiB$ PET data acquired from healthy volunteers and AD patients, and then performed compartment model analysis with arterial input function. Goodness-of-fit with and without PVC was compared between three conventional models to determine whether partial volume effect alters the optimal model for $[^11]$C$PiB$ PET. Then, kinetic parameters estimated by a two-tissue-four-parameters compartment model (2TC) were compared between conditions with and without PVC. We also simulated TACs with spillover from white matter to interpret the observed changes in kinetic parameters with PVC.

2. Materials and methods

2.1. Subjects

AD patients were recruited from Chiba University Hospital and affiliated hospitals between October 2007 and January 2010. All AD patients were diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Cognitive healthy control volunteers (HVs) were recruited from the volunteer association of the National Institute of Radiological Sciences (NIRS). A board-certified neurologist confirmed that all HVs were not cognitively impaired and were not being treated with medications that affect the central nervous system. All subjects were classified using the Clinical Dementia Rating (CDR) scale (Morris, 1993); HVs corresponded to 0 and AD patients to 1 or 2. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was performed on all subjects to evaluate cognitive functions. Magnetic resonance (MR) imaging showed no notable brain tissue lesions in any healthy volunteers. All subjects did not have any comorbidities including severe cerebrovascular and neurodegenerative diseases other than dementia and AD. An expert for neuroradiology visually evaluated PiB-positive or negative with $[^11]$C$PiB$ PET image to confirm no HV with PiB-positive and AD with PiB-negative were included each subject group. We also confirmed $BP_{\text{ND}}$, estimated as described later, in whole cerebral cortex for all AD patients were larger than mean $+ 2.5$ SD of $BP_{\text{ND}}$ for the HV group.

The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan (approved on June 28, 2005 and April 30, 2008; approval numbers were not assigned), and were performed in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, issued by Ministry of Health, Labor and Welfare, Japan Government, as well as the Declaration of Helsinki. Written informed consent was obtained from all subjects or their close family members.

2.2. PET procedures

All PET scans were performed with an ECAT EXACT HR+ system (CTI-Siemens, Knoxville, TN, USA), which provides 63 sections with a 15.5-cm axial field-of-view. The intrinsic spatial resolution was 4.3 mm in-plane and 4.2 mm full-width at half-maximum (FWHM) axially (Brix et al., 1997). Data were acquired in the three-dimensional mode with scatter correction. The acquired count data were reconstructed by filtered-back projection with a Hanning filter (cut-off frequency: 0.4 cycles/pixel). Final in-plane resolution was 7.5 mm FWHM. A head fixation device with thermoplastic attachments for individual fit minimized head movement during PET scans.

$[^11]$C$PiB$ was produced according to previously described methods (Mathis et al., 2003). After intravenous bolus injection of $[^11]$C$PiB$ ($377.6 \pm 32.5$ MBq; $145.3 \pm 62.0$ GBq/μmol), dynamic scans were performed for 90 min, consisting of three 20-s, three 40-s, one 60-s, two 3-min, five 6-min, and five 10-min frames. A transmission scan for 10 min was first performed for attenuation correction. A total of 27 arterial blood samples were taken at 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 120 s, as well as at 4, 6, 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, and 85 min after $[^11]$C$PiB$ injection, to obtain arterial input function. The radioactivity fraction of parent compound in plasma was determined by high-performance liquid chromatography (HPLC). Seven blood samples from 70 s, and 4, 8, 20, 40, 60, and 70 min were measured with HPLC. The input function for parent compound was calculated by plasma activity and fraction interpolated by bi-exponential function.

2.3. MR imaging procedures

To acquire anatomical information for partial volume correction and other image processing, MR imaging scans were performed using a 1.5 T MR scanner (Philips Medical Systems, Best, the Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time: 9.2 ms; repetition time: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256 × 256; slice thickness: 1 mm).

2.4. Image processing and definition for volume of interest (VOI)

PET frames were resliced to an image averaged from frames during the first 10 min to correct for subject head motion during PET scans. All PET images were coregistered to space on MR images for each subject. Space transformations from Montreal Neurological Institute (MNI)/International Consortium for Brain Mapping (ICBM) 152 T1 templates for each subject space were estimated using non-linear image registration using a discrete cosine transformation (DCT) basis function (Ashburner and Friston, 1999).
All realignments and coregistrations were performed with a Statistical Parametric Mapping 8 (SPM8) package (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

Each voxel on MR images of the subject’s head was classified into gray matter, white matter, cerebrospinal fluid (CSF), bone, or soft tissue using the “NewSegment” toolbox in SPM8, which is based on a unified segmentation algorithm (Ashburner and Friston, 2005). NewSegment outputs “probability” maps for each class. To acquire the exact mask for each class, we assigned the largest probability on the voxel for each class. For example, if probabilities for gray matter, white matter, CSF, bone, and soft tissue on one voxel are 0.65, 0.20, 0.05, 0.10, and 0.00, respectively, this voxel would be assigned as gray matter.

Cortical and subcortical VOIs were drawn on each subject’s space using an inverse transformation from automated anatomical labeling (AAL) template on MNI/ICBM standard space (Tzourio-Mazoyer et al., 2002). The VOIs were masked with a mask for gray matter extracted from the segmentation process as described above, to extract gray matter VOIs precisely. The masks for white matter, CSF, bone, and soft tissue were regarded as VOIs. The VOIs for representative subjects are shown in Fig. 1. All extracted VOIs were used in the region-based PVC described below. Seven cortical (frontal cortex, parietal cortex, occipital cortex, lateral temporal cortex, medial temporal cortex, anterior cingulate, and posterior cingulate), hippocampal (hippocampus + parahippocampal gyrus), cerebellar, and white matter VOIs were investigated in the current study due to the strong interest in amyloid deposition for cortical regions and missegmentation in subcortical VOIs. VOI merged with the seven cortical VOIs was also investigated as ‘whole cerebral cortex’.

2.5. Partial volume correction (PVC)

We applied region-based PVC, referred to as the geometric transfer matrix (GTM) method (Rousset et al., 1998a), to determine the influence of partial volume effect on regional kinetic parameters. The GTM method assumes that radioactivity is homogenous over a region and is affected by spillover represented with GTM. The GTM contains the fractional radioactivity contribution from other VOIs into interested VOI, is calculated using the regional spread function (RSF), and is integrated by the point-spread function (PSF) over each VOI. The GTM method principles and details have been previously described (Rousset et al., 1998a). We calculated true radioactivities on VOIs drawn as described in the Section 2.4. A 7.5-mm FWHM Gaussian kernel was utilized as the PSF to calculate RSF in the current study, based on actual measurement of PSF with the PET scanner and preliminary validation for uniform PSF (see Supplementary materials).

The GTM method can recover true activities for multiple regions. However, it cannot recover voxel-wise computation. To generate images corrected for partial volume effect, we also applied voxel-based PVC, referred to as the modified Müller-Gärtner method (mMG) (Muller-Gartner et al., 1992; Rousset et al., 1998b). Briefly, true radioactivity in gray matter was estimated by subtraction with true radioactivity in white matter and other extra regions estimated with GTM and smoothed with PSF, and dividing with regional spread function of gray matter itself.

Standardized uptake value (SUV) maps for PET images with and without PVC were calculated using the injected dose per body weight. To demonstrate maps for specific binding, SUV at the late phase (SUV60), which was 50–70 min after injection, was integrated.

2.6. Kinetic modeling for $[^{11}C]PiB$ PET with PVC

To determine whether PVC can alter the optimal $[^{11}C]PiB$ model, we compared goodness-of-fit for compartment model analysis between three models: i) two-tissue-four-parameters compartment model (2TC); ii) two-tissue-three-parameters compartment model (2TC3k), which assumes $k_4=0$ in 2TC; and iii) one-tissue compartment model (1TC). We determined the optimal model with the lowest Akaike information criteria (AIC) (Akaike, 1973). The arterial input function for unmetabolized $[^{11}C]PiB$ was acquired as described in section “PET procedures” and was used in all compartment model analysis. Blood component was considered in the all compartment model analysis, and blood volume ($V_b$) was estimated as well as rate constants ($K_1$, $k_2$, $k_3$, and $k_4$). All kinetic analyses were performed with PyBLD, which is a Python-based version of the BLD system (Carson et al., 1981) (http://www.rim.cric.tohoku.ac.jp/software/pybld/pybld.html).

2.7. Estimation of kinetic parameters for $[^{11}C]PiB$ PET with PVC

For subjects and regions fitted with 2TC best, binding potential relative to the nondisplaceable radiotracer concentration in the brain ($B_{NV60}$), and total distribution volume ($V_t$) were calculated as follows:

$$V_t = (K_1/k_2)(1 + k_3/k_4)$$ (1)
\[ \text{BP}_{\text{ND}} = k_3/k_4 \]  

Furthermore, to quantify the effect of PVC on kinetic parameters \( ((\text{parameter with PVC})/(\text{parameter without PVC})) \) was calculated as the “PVC factor.” The % change for all estimates \( (\text{parameter with PVC})-(\text{parameter without PVC})/(\text{parameter without PVC} \times 100) \) was also calculated to quantify changes with PVC. Differences between estimates with and without PVC were tested with the paired t-test.

For reference, we estimated and compared ratio of distribution volume (DVR) by Logan analysis with reference tissue input function (Logan et al., 1996). The details are described in Supplementary materials.

2.8. Simulation for spillover from white matter

We simulated TACs to reveal how spillover from white matter affects values for specific binding of \([11C]\text{PiB}\) and changes with amyloid deposition. First, we calculated the TAC in gray matter and white matter for healthy controls using the two-tissue-four-parameters compartment model. \( k_1, k_2, k_3, \) and \( k_4 \) values reported from a previous study (Price et al., 2005) \( [K_1'=0.2500\ \text{mL/mL/min}; \ k_2=0.1520\ \text{min}^{-1}; \ k_3=0.0152\ \text{min}^{-1}; \ k_4=0.0108\ \text{min}^{-1}] \) were used as healthy gray matter values. To validate the effect of spillover from white matter purely, the white matter TAC was calculated with fixing \( k_1/k_2 \) and \( k_3 \) between gray and white matters. \( k_1 \) in white matter \( (K_1^{\text{wm}}) \) was assumed as \( K_1^{\text{wm}}=(1/4) \times K_1 \) (Meyer et al., 1978), \( k_3 \) in white matter \( (k_3^{\text{wm}}) \) was roughly determined as 1.5 times of \( k_3 \) in gray matter based on SUV values reported in the previous study (Price et al., 2005). The blood volume was set to zero. The arterial input function averaged during HVs as below was used to calculate the TACs.

Second, to simulate changes in specific binding, we altered \( k_3 \) in the range of 0–0.0760 \text{min}^{-1}, \text{which corresponded to} \text{0–5 times as} \text{many values in gray matter for} \text{HV, and then calculated TACs. The change in} \text{k_3 mimics progress in amyloid deposition with AD. Next, TACs with the spillover from white matter were calculated from gray matter and white matter TACs simulated as above, using the following equation:}

\[ C_{\text{PET}} = p_{\text{gm}} C_{\text{gm}} + p_{\text{wm}} C_{\text{wm}} \]  

where \( C_{\text{PET}} \) was total radioactivity concentration, \( C_{\text{gm}} \) and \( C_{\text{wm}} \) were radioactivity concentrations in gray matter and white matter, respectively, and \( p_{\text{gm}} \) and \( p_{\text{wm}} \) were the proportions of gray matter and white matter in total radioactivity, respectively. \( p_{\text{gm}} \) and \( p_{\text{wm}} \) were fixed to 0.75 and 0.25, respectively, based on the regional spread function in gray matter calculated as described below (data not shown).

Finally, we estimated \( K_1, k_2, k_3, \) and \( k_4 \) for simulated TACs with and without the spillover from white matter using the two-tissue compartment model analysis, and then calculated the binding potential \( (\text{BP}_{\text{ND}}=k_3/k_4) \). The %bias for estimates to value without the spillover \( ((x – x_{\text{true}})/x_{\text{true}} \times 100) \) was also calculated.

3. Results

3.1. Subjects

All AD patients and no HVs were classified as PiB-positive (AP-positive) according to visual assessment of SUV images. Eight AD patients and five age-matched HVs were included in further analyses. Demographic and clinical profiles of participants are summarized in Table 1. There was no significant difference in age and gender between the HV and AD groups \( (p=0.428 \text{ [Welch’s t-test]} \) and \( p=1.000 \text{ [Fisher’s exact test]} \), respectively). Significant differences were observed in MMSE and CDR between HV and AD groups \( (p<0.001 \text{ [Welch’s t-test} \) and Mann-Whitney U test, respectively]).

3.2. Images and TACs corrected for the partial volume effect

A higher contrast between gray matter and white matter was observed in images with PVC than ones without PVC, as shown in Fig. 1. TACs drawn on the top of Fig. 2 depict higher tracer uptake and faster clearance in the whole cerebral cortex with PVC than ones without PVC. Similar trends were also observed in TACs for each cortical region. Trends for white matter TACs were opposite to those for cortical gray matter regions, and lower uptake and slower clearance than TACs without PVC was also observed.

3.3. Modeling for dynamic \([11C]\text{PiB} \) PET data with PVC

The numbers of regions best fitted with 2TC, 2TC3k, or 1TC are shown in Fig. 3. 2TC was fitted most appropriately for most of the regions, even with PVC. Optimal model conversions from 2TC to 2TC3k with PVC were observed in eight regions of three HVs and two AD patients, including one occipital cortex, four medial temporal cortex regions, and three cerebellum regions. From the 2TC analysis of these cases, the \( k_3 \) and \( k_4 \) estimations were instable \([\text{CoV (constant error/estimated value)} > 100\%]\). In the cerebellum of one AD patient, 2TC3k was optimal both with and without PVC. There was no observed case that fitted best with 1TC.

We mention later only results for cases that fit best with 2TC.

3.4. Changes in kinetic parameters with PVC

The \( \text{BP}_{\text{ND}} \) in cortical regions for both HVs and AD patients decreased significantly by PVC with GTM \( (p<0.05) \), as shown in Table 2, S1, and S2. The \( \text{BP}_{\text{ND}} \) in white matter regions increased significantly by PVC, which was in contrast to cortical gray matter regions. The differences in cortical \( \text{BP}_{\text{ND}} \) with and without PVC in HVs were higher than in AD patients, as shown in Fig. 4.

The relationship between \( \text{BP}_{\text{ND}} \) with PVC and the PVC factor for \( \text{BP}_{\text{ND}} \) in cortical VOIs is shown in Fig. 5. In AD patients with moderate and high \( \text{BP}_{\text{ND}} \) (>1) with PVC, the PVC factors were approximately identical. In HVs with low \( \text{BP}_{\text{ND}} \) with PVC ( <1), PVC factors <1 were observed, indicating larger partial volume effect to \( \text{BP}_{\text{ND}} \) than in the AD patients.

\( K_1 \) was significantly increased by PVC in all gray matter regions for both HVs and AD patients, as shown in Table 2, S1, and S2. The \( K_1 \) increase in gray matter corresponded to decreases of \( K_1 \) in white matter regions. \( V_T \) was also significantly increased in cortical gray matter regions by PVC, but not in the hippocampus and cerebellum. SUV60 in HVs was significantly decreased, whereas it
was increased in AD patients. Significant increase in $V_b$ by PVC was observed in some cortical regions. The estimated parameters in cortical regions corrected with mMG were nearly identical to those with GTM (less than 5% differences from GTM), except for those in the medial temporal cortex.

### 3.5. Simulation of spillover from white matter

TACs simulated for spillover from white matter are shown in Figure S1. A larger bias of $BP_{ND}$ estimated from TACs with spillover was observed in lower true $k_s$. The bias trends correspond to results observed in HVs and AD patients in the current study (see also Fig. 5).

#### 4. Discussion

4.1. Spillover from white matter

Significantly decreased kinetic parameters for $BP_{ND}$ by PVC at the cortical gray matter regions demonstrate the overestimation of kinetic parameters by partial volume effect. The simulation results demonstrated that the overestimation of cortical $BP_{ND}$ was due to spillover of signals between gray and white matter regions. Especially, the amounts of overestimation were large, in particular in cases with much lower $BP_{ND}$ in gray matter than in white matter, such as HVs. These results reflect the effect of spillover from white matter is predominant in the low $BP_{ND}$ cases. A uniform PVC factor of $BP_{ND}$ was observed in cases with moderate and high $BP_{ND}$ ratios, which corresponded with most AD patient cases. The PVC factors corresponded to difference in $BP_{ND}$ between gray matter and white matter regions. These findings indicate that spillover from white matter can induce a considerable bias in $BP_{ND}$ in cases where white matter accumulation is high relative to gray matter.

Previous studies have demonstrated higher uptake in white matter than in cortical regions, and white matter uptake affects visual assessment in $[^{11}C]PiB$ PET (Hosokawa et al., 2015, 2014). Another recent study comparing pre-mortem $[^{11}C]PiB$ PET and post-mortem amyloid deposition showed that accumulation at white matter and its spillover can result in an increased number of false positives during early detection of amyloid deposition (Villeneuve et al., 2015). These previous findings imply that spillover from white matter could be problematic during early detection of amyloid deposition. Findings from the present study indicated that PVC could remove the spillover effect from white matter, even with considerable uptake on white matter relative to gray matter, such as in early AD. Therefore, PVC could help with detection of subtle amyloid deposition in early AD patients.
Further cross-sectional and longitudinal studies with well-controlled and equivocal population are required to reveal the usefulness of PVC to detect subtle amyloid and diagnose early AD. Our findings show that [11C]PiB PET could extend to studies with other radiotracers, which are highly distributed to the white matter region, for amyloid. In general, 18F-labeled ligands are regarded to have higher non-specific binding in the white matter than 11C-labeled ligands due to greater lipophilicity (Kepe et al., 2013). For example, [18F]flutemetamol has been reported to distribute to the white matter region more than [11C]PiB (Mountz et al., 2015; Rowe et al., 2010). Thus, more severe overestimation of BPND by white matter spillover could be observed in amyloid PET studies with 18F-labeled ligands. However, further PET studies with the other radiotracers that have a low distribution to the white matter, such as [11C]AZD2184 (Nyberg et al., 2009), are needed.

### Table 2

| Healthy volunteers (n = 5) Regions | K (g/mL/min) | BPND | VT (g/mL) | SUV60 |
|----------------------------------|--------------|------|----------|-------|
| Whole cerebral cortex  | Without PVC | 0.214 (13.1) | 0.86 (27.3) | 2.21 (20.1) | 0.575 (23.2) |
|                               | With PVC    | 0.320 (11.3) | 0.42 (41.3) | 2.36 (18.5) | 0.514 (23.6) |
| % Change                        | Without PVC | 49.9 ± 3.8   | −52.7 ± 5.8  | 7.2 ± 2.5  | −5.4 ± 5.9  |
| p                               | <0.001      | <0.001   | <0.001    | 0.001    |
| Cerebellum                      | Without PVC | 0.222 (17.1) | 0.46 (9.9) | 1.91 (14.6) | 0.516 (20.1) |
|                               | With PVC    | 0.302 (22.1) | 0.26 (12.2) | 1.96 (14.5) | 0.429 (26.4) |
| % Change                        | Without PVC | 35.2 ± 6.5   | −43.3 ± 11.4 | 2.4 ± 4.3  | −8.8 ± 10.2 |
| p                               | <0.001      | <0.001   | <0.001    | 0.001    |
| White matter                    | Without PVC | 0.177 (13.7) | 1.65 (14.9) | 2.88 (24.7) | 0.770 (28.3) |
|                               | With PVC    | 0.134 (17.0) | 2.49 (21.3) | 3.37 (27.7) | 0.950 (31.1) |
| % Change                        | Without PVC | −24.6 ± 4.0  | 49.6 ± 9.2  | 16.1 ± 6.1 | 112 ± 12.2  |
| p                               | <0.001      | 0.003    | 0.010     | 0.007    |
| AD patients (n = 8) Regions     | K (g/mL/min) | BPND | VT (g/mL) | SUV60 |
| Whole cerebral cortex  | Without PVC | 0.161 (34.2) | 2.93 (49.2) | 3.47 (33.3) | 0.873 (25.9) |
|                               | With PVC    | 0.238 (33.3) | 2.58 (47.8) | 4.61 (32.5) | 1.123 (30.4) |
| % Change                        | Without PVC | 47.8 ± 3.8   | −119 ± 4.2  | 33.3 ± 3.5 | 13.7 ± 15.8 |
| p                               | <0.001      | 0.004    | <0.001    | <0.001    |
| Cerebellum                      | Without PVC | 0.186 (33.4) | 1.41 (41.1) | 2.07 (18.0) | 0.549 (20.8) |
|                               | With PVC    | 0.249 (33.4) | 0.85 (53.5) | 1.97 (23.8) | 0.474 (31.5) |
| % Change                        | Without PVC | 33.4 ± 2.7   | −41.9 ± 13.2 | −5.3 ± 9.1 | −7.7 ± 10.8 |
| p                               | <0.001      | 0.022    | 0.292     | 0.010    |
| White matter                    | Without PVC | 0.142 (32.8) | 3.24 (52.5) | 3.31 (30.9) | 0.862 (21.7) |
|                               | With PVC    | 0.116 (32.8) | 3.95 (62.0) | 3.33 (30.6) | 0.884 (19.2) |
| % Change                        | Without PVC | −18.4 ± 3.3  | 19.1 ± 8.6  | 1.0 ± 5.4  | 1.7 ± 5.6   |
| p                               | <0.001      | 0.034    | 0.754     | 0.338    |

AD: Alzheimer’s disease; PVC: Partial volume correction. Values on rows “Without PVC” and “With PVC” indicate mean (%CoV). %CoV = SD/mean × 100%. Values on the row “% Change” indicate mean ± SD. %Change = (values with PVC − values without PVC)/values without PVC × 100%.

Fig. 4. Boxplot (left) and line plots (center: HV; right: AD) of BPND in whole cerebral cortex without and with PVC (GTM).

Fig. 5. Scatter plot of PVC factor for BPND in cortical VOIs. Gray line indicates simulated profiles for ratio between true BPND and those estimated from TACs with white matter spillover, with the PVC factor in the simulation. Dashed line indicates identical PVC factor.


4.2. Partial volume effect on kinetic analysis in $[^{11}C]$PiB PET

The compartment model analysis with arterial input function allows us to expect the partial volume effect influence on kinetic parameters estimated from the reference tissue input function method. For example, significantly increased cortical $V_t$ with PVC was observed, although there was no significant change in cerebellar $V_t$, which suggests that PVC could elevate apparent values of $DVR$ and $BP_{ND}$ [$DVR - 1$] calculated with reference tissue input function. Indeed, a previous study showed elevated $BP_{ND}$ by PVC in $[^{11}C]$PiB PET, which was estimated using the Logan analysis with reference tissue input function (Su et al., 2015). Findings from the compartment model analysis in the present study could provide a better understanding of the partial volume effect in kinetic analysis using the reference tissue input function method in previous amyloid PET studies (Su et al., 2015; Thomas et al., 2011).

The increase in $K_i$ and $V_b$ values with PVC reflects an under-estimation of $[^{11}C]$PiB uptake due to spillover from gray matter regions by partial volume effect. These results imply that PVC can correct the signal underestimation due to atrophy with partial volume effect, as well as the overestimation of specific binding by white matter spillover. These findings demonstrate the usefulness of PVC for accurately estimating kinetic parameters in $[^{11}C]$PiB PET.

$2TC$ was an optimal fit in most cases, irrespective of PVC. Results suggest that partial volume effect and its correction do not affect the kinetic model choice for $[^{11}C]$PiB. In several regions of some subjects, $2TC3k$ was the optimal fit, corresponding to results from a previous study showing that fittings with $2TC$ were not achieved in several regions for some subjects (Price et al., 2005). These results showed the existence of a subtype with $[^{11}C]$PiB kinetic indicating $k_d = 0$. However, the computational instability in the $k_d$ estimation with $2TC$ can also explain the optimal fit with $2TC3k$ in some cases.

$V_b$ without and with PVC were also estimated with the compartment model including blood component in the current study. However, interpretation of the estimated $V_b$ should be carefully considered for the following reasons. In theory, degrees of partial volume effect could be different between the tissue and blood components; these regions have different object sizes. To the best of our knowledge, there is no PVC method which can handle the tissue and blood components separately. The sum of both the components are usually applied as PVC factors in the existing MR-based PVC methods. The present results, the significantly larger $V_b$ in some regions with PVC, can be simply due to the increase in apparent tissue uptake of $[^{11}C]$PiB at early phase by PVC. The $V_b$ estimates with PVC are not true estimates free from partial volume effect, and rather, should be considered as merely a parameter to fit curves. Interpretation of blood volume with PVC still remains an open question.

PVC can amplify instability of the compartment model analysis due to propagation of noise in the PET signal. Indeed, the error in $k_d$ estimation with $2TC$ was larger with PVC than without PVC in some cases. A previous study recommended the use of a reference tissue input function method for studies requiring statistical stability, such as discriminatory and longitudinal studies (Lopresti et al., 2005). We suggest that the reference tissue input function method with PVC is a better choice for discriminatory and longitudinal studies. However, it is important to note that the present study focused on validating the partial volume effect in kinetic parameters, which was the reason for selecting the compartment model analysis with arterial input function.

GTM method assumes tracer uptake homogenous in each region. The assumption can be violated in cases with inhomogeneous lesion such as local amyloid deposition and white matter pathology. The violation could affect kinetic parameters in each voxel and thus visual inspection of amyloid deposition with parametric map. In the current study, the similar values in kinetic parameters averaged in each VOI between GTM and mMG methods were observed because the averaging in VOI canceled the effect in the violation of homogeneity. Further studies to investigate the effect of PVC in voxelwise analysis are required. mMG could not be the best PVC method for voxelwise analysis in amyloid PET studies because the method assumes homogeneous radioactivity per tissue fractional volume in whole gray matter; amounts of spillover in the GM regions are calculated only from the MR segmented tissue fractions (Muller-Gartner et al., 1992; Rousset et al., 1998b). This assumption causes erroneous PVC results, especially in voxels surrounded by high uptake regions, as pointed out in the previous report (Thomas et al., 2011). We should consider differences in characteristic of methods in choice of PVC methods. Some other voxel-based PVC methods (Bousse et al., 2012; Thomas et al., 2011) can be candidates in voxelwise analysis and visual inspection with parametric maps.

Another limitation in the present study is misalignment between transmission and emission scans due to subjects’ head motion during the scan, which can be problematic especially in scans with AD patients. The misalignment between transmission and emission scans were not considered in the present study, whereas the motion correction during emission frames was performed. The previous amyloid PET study has indicated head motion increases variability of $DVR$ (Wardak et al., 2010). Thus, the misalignment between transmission and emission can affect statistical power of kinetic parameters in amyloid PET study. Further studies are required to reveal the effect of the misalignment in partial volume effect on amyloid PET.

5. Conclusions

The results from the present study revealed an overestimation of specific binding for $[^{11}C]$PiB by white matter spillover associated with partial volume effect. This remarkable overestimation was observed in cases with considerable white matter uptake relatively to gray matter uptake such as HVs, rather than AD patients. The underestimation of $K_i$ and $V_t$ due to partial volume effect were also demonstrated. The appropriate PVC can avoid the over- and under-estimation of kinetic parameters. These findings demonstrate that PVC can help to better understand the true kinetic for $[^{11}C]$PiB and can be useful for accurately estimating amyloid deposition in $[^{11}C]$PiB PET.

Disclosure

The authors declare that there is no conflict of interest.

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