Automatic extraction of a reference region for the noninvasive quantification of translocator protein in brain using $^{11}$C-PBR28

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Abstract

Brain inflammation is associated with various types of neurodegenerative diseases, including Alzheimer’s disease. Quantifying inflammation with PET is a challenging and invasive procedure, especially in frail patients, because it requires blood sampling from an arterial catheter. A widely used alternative to arterial sampling is a supervised clustering algorithm (SVCA), which identifies the voxels with minimal specific binding in the PET images, thus extracting a reference region for noninvasive kinetic modeling. We tested this algorithm on a large population of subjects injected with the TSPO radioligand $^{11}$C-PBR28, and compared the kinetic modeling results obtained with the gold standard of arterial input function ($V_T/f_P$) with those obtained by SVCA (DVR with Logan plot). The study comprised 57 participants (21 healthy controls, 11 MCI, and 25 AD patients). We found that $V_T/f_P$ was greater in AD patients than in controls in the inferior parietal, combined middle and inferior temporal, and enthorinal cortices. SVCA-DVR identified increased binding in the same regions and in an additional one, the parahippocampal region. We noticed however that the average amplitude of the reference curve obtained from subjects with genetic high-affinity binding for $^{11}$C-PBR28 was significantly larger than that from subjects with moderate affinity. This suggests that the reference curve extracted by SVCA was contaminated by specific binding, likely from blood vessels or gray matter.

In summary, SVCA allows the noninvasive quantification of inflammatory biomarker TSPO measured with $^{11}$C-PBR28 but without the need of arterial sampling. Although the reference curves were contaminated with specific binding, the decreased variance of the outcome measure, SVCA DVR, allowed for an apparent greater sensitivity to detect regional abnormalities in brains of patients with Alzheimer’s disease.
Introduction

The need of arterial sampling to quantify the binding potential of PET tracers in the brain is probably the main obstacle to the widespread utilization of translocator protein (TSPO) radioligands in research protocols, let alone in clinical practice. In expert hands, placing an arterial catheter in the radial artery takes only few minutes, is well tolerated by patients and carries little risk, but it’s a logistically challenging and costly procedure. It requires trained personnel and special techniques to analyze the plasma samples, such as high-performance liquid chromatography. In addition, plasma measurements of parent concentrations and plasma free fraction are noisy and prone to errors (1). At least five approaches have been proposed as noninvasive alternatives to arterial sampling: 1) image-derived input function, 2) population-derived input function, 3) simultaneous estimation of the input function, 4) pseudoreference region, and 5) supervised clustering algorithm (SVCA), the approach examined in this paper. Image-derived input function from small brain vessels is seldom trustworthy: not only partial volume effects are very challenging to correct without scaling with blood samples, but PET images cannot distinguish the photons emitted by the parent compound from those of its radiometabolites. Template curves such as those used for population-derived input functions may not faithfully capture individual variability, and robust estimates are obtained only when at least one blood sample is used to properly scale the template curve. Although the simultaneous estimation of the input function needs at least one blood sample, together with the time-activity curves of several brain regions (2), Schain et al. validated this approach for 11C-PBR28 using a template curve and demonstrated that it was able to distinguish between healthy controls and patients with Alzheimer’s disease (3). However, a template curve still has to be previously generated from subjects scanned with arterial sampling, and the shape of the curve obtained from a population of healthy subjects may not necessarily reflect that of pathological conditions (3).

A relative method of measurement, by comparing the uptake of the target region to that of a region devoid of receptors, would obviate the need of arterial sampling and arguably reduce the variability of the estimates, since the input function and the free fraction are common to both regions. However, since TSPO is expressed ubiquitously in the brain, a proper reference region does not exist. Nevertheless, Lyoo et al. successfully quantified 11C-PBR28 in a clinical protocol by using a pseudoreference region (4). A pseudoreference region is a one that has a certain amount of specific binding, but is not affected by the course of the disease. Using this approach,
Lyoo et al. re-analyzed a large database of 57 subjects, comprising healthy controls, patients with mild cognitive impairment (MCI), and patients with Alzheimer’s disease (AD) (5). By using the SUV ratio (SUVR) over the cerebellum, they were able to replicate the findings obtained with full kinetic modeling. They showed that TSPO binding was greater in AD patients than in either healthy or MCI subjects, and also identified 1 additional region, suggesting that this approach may have greater sensitivity (4). Of course, an important limitation of this method is that it requires previous knowledge that the designated pseudoreference region is not affected by the disease under study. In the study of Lyoo and colleagues, the use of the cerebellum as a pseudoreference region was justified by several lines of evidence: during Alzheimer’s disease, the cerebellum is relatively spared from neurodegeneration and the morphology of its microglia differs from that of the activated microglia in the neocortex. In addition, similar values were observed for \( V_t/f_o \) and SUV in the cerebellum among the healthy controls, MCI and AD patients (4).

A few years ago, Turkheimer et al. described a supervised clustering algorithm (SVCA) (6). SVCA uses predefined kinetic classes to segment the tissue and to automatically extract reference curves, defined as the average curve of all voxels where the specific binding component is minimal. This algorithm, initially validated for \(^{11}\text{C-}(R)\)-PK11195, would allow the noninvasive quantification of TSPO across a variety of diseases, independently of the availability of a reference region. Indeed, it has been used in different clinical conditions associated with microglial activation (7-10). However, \(^{11}\text{C-}(R)\)-PK11195 is a radioligand with very low specific binding, and there seems to be an inverse relationship between the affinity of the tracer and the successful implementation of SVCA (11). Recently Garcia-Lorenzo et al. (12) showed that SVCA can also be applied to \(^{18}\text{F-DPA-714}\), a TSPO tracer with intermediate affinity for TSPO (~1.5 fold that of \(^{11}\text{C-}(R)\)-PK11195 (13)). \(^{11}\text{C-PBR28}\) is one the most widely used TSPO tracer worldwide and has high affinity for TSPO (~5 to 6 fold that of \(^{11}\text{C-}(R)\)-PK11195 (13)).

The aim of this work was to test the suitability of SVCA to quantify \(^{11}\text{C-PBR28}\) noninvasively. We attempt to replicate the results of the same large database analyzed by Lyoo and colleagues, which comprised healthy controls, MCI, and AD patients. This also allowed a direct comparison with the pseudoreference approach.
MATERIALS AND METHODS

Subjects

All data from the previous study were included and re-analyzed for the current study (4). We included 57 participants (21 healthy controls, 11 MCI, and 25 AD patients). All MCI and AD patients were positive for amyloid-β after screening with 11C-Pittsburgh Compound B PET scan studies. Therefore, AD patients met the criteria for probable AD dementia with evidence of AD pathophysiological process (14), and MCI patients met the criteria for MCI due to high or intermediate likelihood of developing AD (15). Individual TSPO binding affinity was determined by using the leukocyte binding assay (16). All participants were included in our previous study (4), and image data were reanalyzed for the current study.

This study was approved by the Combined Neuroscience Institutional Review Board of the NIH Intramural Research Program. All subjects or their surrogate provided written informed consent to participate.

Acquisition of PET and MR images

PET images were acquired in a GE Advance PET scanner (GE Healthcare). Prior to the emission scan, a 68Ge transmission scan was acquired for 8 minutes for later attenuation correction. After the intravenous injection of 678.2 ± 35.5 MBq of 11C-PBR28 for one minute, dynamic PET data were acquired for 90 minutes, and arterial blood was sampled 23 times with time interval ranging from 0.25 to 15 minutes during the emission scan. In 27 time frames with increasing the scan duration from 0.5 to 5 minutes, a 3D-dynamic PET images were reconstructed with filtered back projection algorithm in 128 x 128 x 35 matrix with 2 x 2 x 4.25mm of voxel size. Sampled arterial blood was corrected for metabolite fraction measured by reverse-phase chromatography, and a plasma input function was obtained. The $f_P$ of radiotracer was measured by ultrafiltration and normalized to standard plasma (17).

T1-weighted magnetic resonance (MR) images were acquired in a 3T Philips Achieva scanner (Philips) using turbo field echo (TFE) sequence (repetition time (TR) = 8.1 msec, echo time (TE) = 3.7 msec, flip angle = 8, matrix = 181 x 256 x 256, voxel size = 1 x 0.983 x 0.983 mm).
Image processing steps

FreeSurfer 5.1 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu) was used for creation of participant-specific volume-of-interest (VOI). In brief, T1-weighted MR images were processed with inhomogeneity correction, skull-stripping, and segmentation into gray and white matter based on the intensity gradient and connectivity of voxels. After tessellation into trigones, 3D-gray and white matter surfaces were created. Cerebral cortex was segmented into smaller cortical areas with the probabilistic labelling algorithm by inflating the white matter surface and overlaying curvature information on the inflated surface (18, 19). Subcortical structures were also segmented by using the probabilistic registration technique (20). Composite VOI mask images including 112 cortical and subcortical regions were created. Finally, we created participant-specific composite VOI mask images for 12 cortical (prefrontal, sensorimotor, inferior parietal, superior temporal, middle and inferior temporal, precuneus, anterior cingulate, posterior cingulate, occipital, entorhinal, parahippocampal cortices, and hippocampus) and 3 subcortical regions (striatum, thalamus, and cerebellar cortex) by merging the anatomically-related regions.

Statistical parametric mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK) and in-house programs implemented in MATLAB R2015b (MathWorks, Natick, MA, USA) was used to process the PET images. Except for the first three time frames, dynamic PET images were realigned to correct head motion during the scan time. For the VOI analysis, the mean PET images were coregistered to individual T1-weighted MR images, and then all time frames of realigned dynamic PET images were coregistered by using the transformation matrix coregistering mean PET to MR images. By overlaying the composite VOI masks, regional time-activity-curves (TACs) were obtained.

For the SVCA procedure, four types of tissue mask images (normal gray matter, normal white matter, sinus, and pathological gray matter) were created in the MR space. To create white matter mask least affected by the activity from the surrounding gray matter, we first extracted binarized gray matter and cerebrospinal fluid (CSF) masks from the composite VOI mask. After smoothing these masks by using the Gaussian kernel with 7 mm full-width half maximum, we chose the white matter voxels affected by less than 1% of gray matter and CSF activity and created white matter mask image in the MR space. Pathological gray matter masks were created with the voxels for the inferior parietal and middle and inferior temporal cortices in which $^{11}$C-
PBR28 binding was significantly increased in AD patients (5). Sinus masks were manually drawn on the PET images coregistered to MR images with reference to first three time frames of the dynamic PET images.

**SVCA procedure**

We used a modification of optimized SVCA method with four kinetic classes (10). Three kinetic classes (normal gray and white matter and blood) were obtained from 21 controls, and one (pathological gray matter) from the 25 AD patients. First, the means and standard deviations of activities for each time frame were calculated within the whole brain masks. The activities of coregistered dynamic PET images were then standardized by subtracting the means and dividing by the standard deviations. By overlaying the masks for each tissue type on the standardized PET images, standardized TACs for each kinetic class were obtained in each individual. Finally, four kinetic classes were established after averaging TACs. Additionally, two sets of kinetic classes were separately established for each TSPO genotype.

For each voxel in the activity-standardized PET images, the non-negative least squares algorithm was used to find four coefficients for each kinetic class that would minimize the difference between the estimated TAC and the standardized TAC (6). Thereby, each coefficient was mapped. Finally, the SVCA reference TAC was established by using the coefficient map for normal gray matter within the gray matter mask to reduce the contamination from noisy white matter TAC (6, 10). The whole procedure is summarized in Figure 1.

**Kinetic analysis**

$^{11}$C-PBR28 binding values were quantified as DVR using a Logan reference plot, with $k_2'$ set at 0.13 min$^{-1}$ (21). The SVCA-derived Logan-DVR values were compared to the gold standard of total distribution volume, obtained with a two-tissue compartment model, and corrected for plasma-free fraction $(V_T/f_P)$.

**Statistical analysis**

For direct comparison with the pseudoreference region approach, we replicated the same statistical analyses performed by Lyoo et al. (4). SVCA-derived Logan DVR values of $^{11}$C-PBR28 were compared among the three groups using factorial ANOVA with TSPO genotype as
a fixed factor, to correct for affinity differences related to the rs6971 single nucleotide polymorphism (22). Age was entered as covariate. Bonferroni correction for multiple comparisons was used for comparisons between groups. SPSS (SPSS Inc.) was used for the statistical analysis.

The coefficient of variation (%COV) was calculated as SD/mean × 100 and used to determine the variability of binding values. The correlation between the binding values and the severity of dementia was explored in two stages: first by obtaining the standardized residuals of the Clinical Dementia Rating scale – sum-of-boxes scores and the DVR values in combined middle and inferior temporal cortex after adjusting for age and TSPO genotype, and second by calculating the Pearson’s correlation between the two standardized residuals.

Results

The SVCA-derived DVR values of the present study were greater in AD than controls in the inferior parietal, combined middle and inferior temporal, parahippocampal, and enthorinal cortices. Compared to MCI patients, SVCA-DVR values were greater in AD in the combined temporal region and in the enthorinal cortex, although the enthorinal cortex did not survive correction for multiple comparisons (Table 1). The results of the present study closely replicated those of Kreisl et al. (5) and are virtually identical to those of Lyoo et al. (4). Indeed, Kreisl et al. found that $V_{T/f_p}$ was greater in AD patients than controls in the inferior parietal, combined middle and inferior temporal and enthorinal cortices, and greater than MCI subjects in the combined middle and inferior temporal and enthorinal cortices (5). With the pseudoreference region approach, Lyoo et al found an additional significant result in the parahippocampal region (4), the same additional region found in the present study.

SVCA-DVR values in the combined middle and inferior temporal cortex were positively correlated with the Clinical Dementia Rating sum-of-boxes scores. The level of significance was greater for SVCA-DVR (P < 0.001) than that of either $V_{T/f_p}$ (P < 0.01) or SUVR (P < 0.01) (Figure 2). Notably, simple SUV values did not show any significant group difference and were not significantly correlated to $V_{T/f_p}$ values (data not shown).

The variability of SVCA-DVR was much lower than that of $V_{T/f_p}$, and similar to that of SUVR values (4) (Table 2). Similar to SUVR results, the SVCA-DVR values in MAB were
paradoxically greater than those of HAB in all diagnostic groups and all regions (mean SVCA-
DVR among all regions [HAB vs. MAB]: 1.00 vs. 1.04 in HC, 1.00 vs. 1.07 in MCI, and 1.01 vs.
1.08 in AD) (Table 3).

Discussion

In this study we showed that a non-invasive supervised clustering algorithm (SVCA)
could accurately replicate the quantitative results obtained with arterial sampling in a large
clinical study involving healthy controls, MCI, and AD patients. SVCA appears to be more
sensitive than modeling obtained with arterial sampling, as it identified an additional region
(parahippocampal gyrus) that differed between controls and AD patients. This same additional
region was found in this same population of subjects also using the pseudoreference region
approach (4). Compared to full kinetic modeling, SVCA shares with the pseudoreference region
approach the important advantage of not relying on blood data. Indeed, measuring plasma
concentrations of radioactivity, separating the parent from its radiometabolites, and measuring
the free fraction are complex procedures (1) which introduce an element of variability that is
avoided when using DVR or SUVR. For instance, a recent test-retest study of 11C-PBR28 SUVR
values in Alzheimer’s disease yielded low variability and high intraclass correlation coefficient,
and compared favorably with published values of 11C-PBR28 variability (23). In our study, the coefficient of variation was 13-36% for $V_t/f_p$ and only 2-11% for DVR (Table
2). However, the obvious advantage of SVCA over SUVR is that a suitable pseudoreference
region does not need to be identified beforehand and may not even exist. Thus, this technique
can potentially be applied to any population and any disease.

By design, SVCA selects reference tissue voxels which are assumed to be without specific
binding (6). Of course, no voxel is actually entirely devoid of TSPO, because this protein is
ubiquitously, if heterogeneously, distributed in the brain. For instance, TSPO is highly expressed
in the vascular endothelium (24). SVCA was initially validated, and then repeatedly used (7-9),
to quantify $^{11}$C-($R$)-PK11195, a tracer with a very low specific binding. Recently, Rizzo et al.
analyzed three different TSPO tracers ($^{11}$C-($R$)-PK11195, $^{18}$F-DPA-714, and $^{11}$C-PBR28) and
argued that there may be an inverse relationship between binding affinity and suitability for
clustering. An increase in affinity would also be associated with a lower tissue contrast. Specifically, tracer affinity would modulate the contrast between tissue kinetics, by acting on both parenchymal and vascular binding. High-affinity compounds would display a higher vascular binding, and thus the tissue contrast would be lower and the clustering more difficult (11).

In this study, the tracer with the highest affinity, \(^{11}\text{C-PBR28}\), displayed the highest similarity of tissue kinetics between the grey and white matter classes (as defined by the trigonometric angle between the kinetic vectors of the classes), \(^{18}\text{F-DPA-714}\) had intermediate similarity values, and \(^{11}\text{C-(R)-PK11195}\) had the lowest similarity. SVCA was subsequently validated for \(^{18}\text{F-DPA-714}\) (12), although the nonspecific curves of high- and mixed-affinity binders were not compared, as we did in the present study. Despite having the highest classes similarity, in this study we showed that \(^{11}\text{C-PBR28}\) can be amenable to quantification with SVCA and we were able to accurately replicate the results obtained with standard kinetic modeling.

To further probe the suitability of \(^{11}\text{C-PBR28}\) for cluster analysis, we compared the non-specific curves in high- and mixed-affinity binders. If SVCA could perfectly extract the non-specific curve from \(^{11}\text{C-PBR28}\) scans, this curve would have the same amplitude in both populations, since the TSPO polymorphism only affects the specific component. However, as shown in Figure 3, the non-specific curves of high-affinity binders are significantly higher than those of mixed-affinity binders. This is of course due to the contamination of the reference curves by the different amount of specific binding. Notably, the difference between HABs and MABs is evident even in the healthy brain, where the level of TSPO expression is very low (25). This could be explained by the presence of TSPO in cells other than microglia or astrocytes, in particular endothelial cells (24, 25). Recently, Matheson and colleagues warned against hasty implementation of reference models and ratio methods (26), as both SUVR and DVR showed little to no association with \(^{11}\text{C-PBR28}-VT\). Specifically, they showed that almost all variability between brain regions can be attributed to a single underlying dimension of variance, and the ratio between a target region and a highly correlated reference region leaves minimal residual differences between individuals (26). Although they used only a small number of healthy subjects, whose restricted range of \(VT\) values may have affected the correlation, and they did not correct the \(VT\) values for the plasma free fraction, we do share their concern. A truly non-specific reference curve should not be affected by genotype, but it did affect our SVCA-
derived analyses, strongly suggesting that the analysis is biased by specific binding contaminating the reference curve. Despite this bias, the current results with SVCA-DVR perfectly replicated those from pseudoreference region (4). Both methods showed apparently greater sensitivity than the gold standard method using an arterial input function \((V_t/f_P)\) presumably because of the decreased variance in these two bloodless methods compared to the arterial input function.

In summary, using a noninvasive SVCA algorithm, we were able to accurately replicate the findings of a clinical protocol on a large population of healthy controls, MCI and Alzheimer’s disease patients. In addition, we were able to identify an additional significant region, likely because SVCA analyses do not require delicate and error-prone blood analyses and thus are more sensitive. Although the current results with SVCA-DVR perfectly replicated those from pseudo reference region, the extracted reference curves were biased to some extent, because they are not entirely free of specific binding. The large population and effect size of this study may have facilitated its replication, despite the bias present in the extracted reference curves. It would be plausible that in a study with less statistical power (e.g. fewer patients) a biased SVCA would produce falsely negative results. Therefore, the impact of this bias should be investigated thoroughly before envisioning a widespread application of this technique.

**Conflict of Interest**

No potential conflicts of interest relevant to this article exist
REFERENCES


Figure 1

Processing steps for acquiring four template kinetic classes

(a) By using FreeSurfer, T1-weighted MR images were segmented into 112 regions. (b) After merging the regions in parcellated segments, masks for whole brain, gray and white matter, and composite VOI mask images were created. (c) White matter VOI masks least affected by the activity of surrounding structures were created for each control. (d and e) PET images were coregistered to T1-MR image by using the mean PET image. (f) Sinus masks for each control were created. (g) In AD patients, masks for pathological gray matter (pGM) were created. (h) Activity of PET images were standardized by using the whole brain masks. (i) Standardized
TACs for normal white matter (nWM), normal gray matter (nGM), and blood were obtained from the 21 controls. Likewise, standardized TAC for pGM was obtained from 25 AD patients. (j) By averaging the standardized TACs, template TACs for four kinetic classes were established.
Figure 2

Correlation between the binding values of combined middle and inferior temporal cortex and the sum-of-boxes of clinical dementia rating (CDR) score. SVCA-derived DVR values show a similar, and even slightly stronger, correlation compared to those with $V_T/f_p$ and SUVR, as reported by Lyoo et al. (4)
Figure 3

Comparison of the SVCA-extracted reference curves between HAB (black dots) and MAB (white dots). Errors bars are the standard deviations. In all populations the area under the curve was significantly higher for HAB (all p < 0.005), which suggests that the SVCA-reference curve is not completely free of specific uptake and the amount of this uptake depends on genotype status.
**Table 1.** Level of statistical significance by region with the different quantification methods

<table>
<thead>
<tr>
<th>Region</th>
<th>$V_{f_p}/V_{T}$</th>
<th>$p$</th>
<th>SUVR</th>
<th>SVCA-DVR</th>
<th>$V_{f_p}/V_{T}$</th>
<th>$p$</th>
<th>SUVR</th>
<th>SVCA-DVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior parietal</td>
<td>0.028</td>
<td>&lt;0.0005</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>mid. &amp; inf. temporal</td>
<td>0.023</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>0.043</td>
<td>0.010</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>NS</td>
<td>0.048*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>0.048</td>
<td>0.009</td>
<td>0.001</td>
<td>0.048</td>
<td>NS</td>
<td>0.025*</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Parahippocampal</td>
<td>NS</td>
<td>0.006</td>
<td>0.003</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Did not survive region-wise correction for multiple comparisons

NS= not significant

P values were obtained from univariate ANOVA. Diagnosis and genotype were used as fixed factors.
Table 2. Coefficients of variation for $V_t/f_p$, SUVR obtained with a pseudoreference region, and Logan-DVR obtained with SVCA

<table>
<thead>
<tr>
<th></th>
<th>$V_t/f_p$</th>
<th>SUVR</th>
<th>SVCA-DVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAB</td>
<td>13 - 27%</td>
<td>1 - 9%</td>
<td>2 - 7%</td>
</tr>
<tr>
<td>MAB</td>
<td>16 - 36%</td>
<td>4 - 13%</td>
<td>3 - 11%</td>
</tr>
</tbody>
</table>
Table 3. Regional $^{11}$C-PBR28 binding values in patients with Alzheimer’s disease, individuals with mild cognitive impairment, and healthy controls, stratified by TSPO genotype.

<table>
<thead>
<tr>
<th></th>
<th>inferior parietal</th>
<th>mid. &amp; inf. temporal</th>
<th>precuneus</th>
<th>occipital</th>
<th>hippocampus</th>
<th>entorhinal</th>
<th>parahippocampal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (mL·cm$^{-3}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>4.7 ± 1.0</td>
<td>4.8 ± 1.1</td>
<td>4.5 ± 0.9</td>
<td>4.3 ± 0.9</td>
<td>4.4 ± 1.1</td>
<td>4.8 ± 1.1</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>HAB MCI</td>
<td>3.6 ± 1.1</td>
<td>3.8 ± 1.0</td>
<td>3.8 ± 0.9</td>
<td>3.6 ± 1.0</td>
<td>3.7 ± 0.9</td>
<td>3.8 ± 1.0</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>HC</td>
<td>4.4 ± 1.1</td>
<td>4.3 ± 1.1</td>
<td>4.3 ± 1.0</td>
<td>4.3 ± 1.0</td>
<td>4.3 ± 1.2</td>
<td>4.5 ± 1.1</td>
<td>4.0 ± 1.1</td>
</tr>
<tr>
<td>AD</td>
<td>3.0 ± 1.1</td>
<td>3.1 ± 1.1</td>
<td>3.0 ± 1.1</td>
<td>2.8 ± 0.9</td>
<td>2.9 ± 1.1</td>
<td>3.2 ± 1.1</td>
<td>2.6 ± 0.9</td>
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<tr>
<td>MAB MCI</td>
<td>3.0 ± 0.6</td>
<td>3.0 ± 0.6</td>
<td>3.1 ± 0.7</td>
<td>2.8 ± 0.5</td>
<td>3.0 ± 0.6</td>
<td>3.1 ± 0.6</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>HC</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>2.7 ± 0.7</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>$V_T$/$f_P$ (mL·cm$^{-3}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>130.9 ± 28.0</td>
<td>135.1 ± 26.5</td>
<td>125.1 ± 24.6</td>
<td>119.9 ± 26.8</td>
<td>123.6 ± 25.3</td>
<td>134.9 ± 24.1</td>
<td>112.9 ± 24.5</td>
</tr>
<tr>
<td>HAB MCI</td>
<td>98.0 ± 20.5</td>
<td>102.9 ± 18.5</td>
<td>104.8 ± 17.6</td>
<td>97.3 ± 17.8</td>
<td>100.0 ± 13.1</td>
<td>103.9 ± 14.2</td>
<td>89.9 ± 14.4</td>
</tr>
<tr>
<td>HC</td>
<td>104.2 ± 25.2</td>
<td>103.7 ± 28.1</td>
<td>104.6 ± 28.0</td>
<td>103.0 ± 25.9</td>
<td>102.8 ± 27.6</td>
<td>109.7 ± 29.0</td>
<td>94.1 ± 22.3</td>
</tr>
<tr>
<td>AD</td>
<td>79.4 ± 25.8</td>
<td>81.2 ± 29.2</td>
<td>78.8 ± 28.2</td>
<td>74.4 ± 22.5</td>
<td>76.3 ± 29.5</td>
<td>85.7 ± 29.5</td>
<td>68.4 ± 24.4</td>
</tr>
<tr>
<td>MAB MCI</td>
<td>68.9 ± 13.7</td>
<td>68.7 ± 13.2</td>
<td>70.7 ± 13.9</td>
<td>66.1 ± 10.3</td>
<td>69.1 ± 15.6</td>
<td>71.6 ± 17.5</td>
<td>60.1 ± 11.5</td>
</tr>
<tr>
<td>HC</td>
<td>65.9 ± 20.5</td>
<td>66.7 ± 19.0</td>
<td>65.8 ± 19.3</td>
<td>66.9 ± 20.8</td>
<td>65.2 ± 17.2</td>
<td>69.1 ± 21.6</td>
<td>59.3 ± 16.2</td>
</tr>
<tr>
<td>SUVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>1.056 ± 0.041</td>
<td>1.081 ± 0.068</td>
<td>1.054 ± 0.071</td>
<td>1.022 ± 0.043</td>
<td>0.996 ± 0.057</td>
<td>1.009 ± 0.091</td>
<td>0.920 ± 0.056</td>
</tr>
<tr>
<td>HAB MCI</td>
<td>0.939 ± 0.011</td>
<td>0.980 ± 0.051</td>
<td>1.019 ± 0.072</td>
<td>0.948 ± 0.035</td>
<td>0.934 ± 0.084</td>
<td>0.921 ± 0.063</td>
<td>0.853 ± 0.059</td>
</tr>
<tr>
<td>HC</td>
<td>0.985 ± 0.045</td>
<td>0.975 ± 0.071</td>
<td>1.006 ± 0.050</td>
<td>0.997 ± 0.023</td>
<td>0.948 ± 0.024</td>
<td>0.946 ± 0.054</td>
<td>0.877 ± 0.026</td>
</tr>
<tr>
<td>AD</td>
<td>1.117 ± 0.101</td>
<td>1.148 ± 0.060</td>
<td>1.111 ± 0.115</td>
<td>1.068 ± 0.053</td>
<td>1.062 ± 0.092</td>
<td>1.154 ± 0.060</td>
<td>0.993 ± 0.053</td>
</tr>
<tr>
<td>MAB MCI</td>
<td>1.084 ± 0.122</td>
<td>1.100 ± 0.104</td>
<td>1.121 ± 0.147</td>
<td>1.047 ± 0.062</td>
<td>1.085 ± 0.075</td>
<td>1.118 ± 0.066</td>
<td>0.976 ± 0.039</td>
</tr>
<tr>
<td>HC</td>
<td>1.011 ± 0.061</td>
<td>1.046 ± 0.067</td>
<td>1.024 ± 0.055</td>
<td>1.029 ± 0.053</td>
<td>1.027 ± 0.053</td>
<td>1.070 ± 0.081</td>
<td>0.945 ± 0.058</td>
</tr>
<tr>
<td>SVCA-DVR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>1.046 ± 0.037</td>
<td>1.060 ± 0.041</td>
<td>1.070 ± 0.043</td>
<td>1.062 ± 0.042</td>
<td>0.980 ± 0.049</td>
<td>0.973 ± 0.064</td>
<td>0.914 ± 0.052</td>
</tr>
<tr>
<td>HAB MCI</td>
<td>0.981 ± 0.031</td>
<td>0.993 ± 0.037</td>
<td>1.084 ± 0.053</td>
<td>1.009 ± 0.021</td>
<td>0.933 ± 0.045</td>
<td>0.903 ± 0.037</td>
<td>0.864 ± 0.033</td>
</tr>
<tr>
<td>HC</td>
<td>1.008 ± 0.023</td>
<td>0.980 ± 0.042</td>
<td>1.061 ± 0.026</td>
<td>1.042 ± 0.034</td>
<td>0.938 ± 0.048</td>
<td>0.909 ± 0.042</td>
<td>0.873 ± 0.044</td>
</tr>
<tr>
<td>AD</td>
<td>1.112 ± 0.074</td>
<td>1.135 ± 0.053</td>
<td>1.138 ± 0.099</td>
<td>1.099 ± 0.043</td>
<td>1.035 ± 0.088</td>
<td>1.102 ± 0.065</td>
<td>0.982 ± 0.058</td>
</tr>
<tr>
<td>MAB MCI</td>
<td>1.079 ± 0.097</td>
<td>1.080 ± 0.082</td>
<td>1.151 ± 0.131</td>
<td>1.076 ± 0.064</td>
<td>1.053 ± 0.081</td>
<td>1.044 ± 0.054</td>
<td>0.957 ± 0.048</td>
</tr>
<tr>
<td>HC</td>
<td>1.026 ± 0.026</td>
<td>1.041 ± 0.037</td>
<td>1.066 ± 0.046</td>
<td>1.062 ± 0.029</td>
<td>1.011 ± 0.048</td>
<td>1.018 ± 0.065</td>
<td>0.935 ± 0.044</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; HC = healthy control; $V_T$ = total distribution volume; $V_T$/$f_P$ = total distribution volume/free fraction of radioligand; SVCA-DVR = distribution volume ratio calculated with Logan and SVCA as the reference region; SUVR = standardized uptake value ratio; HAB = high affinity binder; MAB = mixed affinity binder. Data are presented with mean ± SD.