The use of synaptic vesicle glycoprotein 2A radiotracers with PET imaging could provide a way to measure synaptic density quantitatively in living humans. \(^{11}\)C-UCB-J ((R)-1-((3-(1\(^{11}\)C)methyl-1\(^{11}\)C)pyridin-4-yl) methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one), previously developed and assessed in nonhuman primates and humans, showed excellent kinetic properties as a PET radiogand. However, it is labeled with the short half-life isotope \(^{11}\)C. We developed a new tracer, an \(^{18}\)F-labeled difluoro-analog of UCB-J (\(^{18}\)F-SynVesT-1, also known as \(^{18}\)F-SDM-8), which displayed favorable properties in monkeys. The purpose of this first-in-human study was to assess the kinetic and binding properties of \(^{18}\)F-SynVesT-1 and compare with \(^{11}\)C-UCB-J. Methods: Eight healthy volunteers participated in a baseline study of \(^{18}\)F-SynVesT-1. Four of these subjects were also scanned after a blocking dose of the antiepileptic drug levetiracetam (20 mg/kg). Metabolite-corrected arterial input functions were measured. Regional time–activity curves were analyzed using 1-tissue-compartment (1TC) and 2-tissue-compartment (2TC) models and multilinear analysis 1 to compute total distribution volume (\(V_t\)) and binding potential (\(B_P^{\text{ND}}\)). The centrum semiovale was used as a reference region. The Lassen plot was applied to compute levetiracetam occupancy and nondisplaceable distribution volume. SUV ratio-1 (SUVR-1) over several time windows was compared with \(B_P^{\text{ND}}\). Results: Regional time–activity curves were fitted better with the 2TC model than the 1TC model, but 2TC \(V_t\) estimates were unstable. The 1TC \(V_t\) values matched well with those from the 2TC model (excluding the unstable values). Thus, 1TC was judged as the most useful model for quantitative analysis of \(^{18}\)F-SynVesT-1 imaging data. The minimum scan time for stable \(V_t\) measurement was 60 min. The rank order of \(V_t\) and \(B_P^{\text{ND}}\) was similar between \(^{18}\)F-SynVesT-1 and \(^{11}\)C-UCB-J. Regional \(V_t\) was slightly higher for \(^{11}\)C-UCB-J, but \(B_P^{\text{ND}}\) was higher for \(^{18}\)F-SynVesT-1, though these differences were not significant. Levetiracetam reduced the uptake of \(^{18}\)F-SynVesT-1 in all regions and produced occupancy of 85.7%. The SUVR-1 of \(^{18}\)F-SynVesT-1 from 60 to 90 min matched best with 1TC \(B_P^{\text{ND}}\). Conclusion: The novel synaptic vesicle glycoprotein 2A tracer, \(^{18}\)F-SynVesT-1, displays excellent kinetic and in vivo binding properties in humans and holds great potential for the imaging and quantification of synaptic density in neuropsychiatric disorders.

Key Words: PET; SV2A; brain imaging; kinetic modeling; synaptic density


DOI: 10.2967/jnumed.120.249144

S ynaptic vesicle glycoprotein 2A (SV2A) is located in the presynaptic vesicle membrane of virtually all synapses (J) and is the target of the anticonvulsant drug levetiracetam (2). We previously developed \(^{11}\)C-UCB-J ((R)-1-((3-(1\(^{11}\)C)methyl-1\(^{11}\)C)pyridin-4-yl) methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one) as a PET radiotracer, tested it in nonhuman primates and humans, and found it to have excellent imaging properties (3–5). SV2A PET could provide a way to measure synaptic density quantitatively in living humans and to track changes in synaptic density with disease. For example, SV2A PET imaging with \(^{11}\)C-UCB-J showed lower hippocampal SV2A specific binding in patients with Alzheimer disease than in cognitively normal subjects (6). In major depressive disorder (7), the severity of depressive symptoms was inversely correlated with SV2A density. Synaptic changes have also been found in Parkinson disease (8) and schizophrenia (9).

\(^{11}\)C-UCB-J has excellent test-retest reproducibility to measure distribution volume (\(V_t\)), with a short scan time (~60 min) (5). However, it has a half-life of 20 min, which requires the tracer to be produced on-site. An SV2A radiotracer labeled with \(^{18}\)F for PET imaging is attractive for clinical diagnostic applications. We therefore developed \(^{18}\)F-SynVesT-1 ((R)-4-(3-Fluoro-5-(fluoro-\(^{18}\)F)phenyl)-1-(3-methylpyridin-4-yl)methyl)pyrrolidin-2-one, the difluoro-analog of UCB-J) and demonstrated its suitability for imaging SV2A in rhesus monkeys. \(^{18}\)F-SynVesT-1 has the same favorable properties as \(^{11}\)C-UCB-J: high brain uptake and good specific binding signals (10). The previous identifier for this tracer was \(^{18}\)F-SDM-8, as it was part of a series of \(^{18}\)F-labeled UCB-J analogs developed as synaptic density markers (10). This tracer has also been studied elsewhere with the identifier \(^{18}\)F-MNI-1126 (11). The new name, \(^{18}\)F-SynVesT-1, was since agreed upon between the groups to eliminate future confusion in the field from use of 2 different names for the same radiogand.

In this study, we evaluated \(^{18}\)F-SynVesT-1 in healthy human volunteers and determined a suitable kinetic model for quantitative analysis of \(^{18}\)F-SynVesT-1 imaging data. A subgroup of volunteers also participated in a baseline and blocking study with \(^{18}\)F-SynVesT-1. A second group of healthy volunteers (2 men and 2 women; 38 ± 5 y old; body

MATERIALS AND METHODS

Radiotracer Synthesis

\(^{18}\)F-SynVesT-1 and \(^{11}\)C-UCB-J were synthesized as described previously (3,10).

Human Subjects

Four healthy volunteers (4 men; 44 ± 13 y old; body mass index, 30 ± 2) completed a baseline study with \(^{18}\)F-SynVesT-1. A second group of healthy volunteers (2 men and 2 women; 38 ± 15 y old; body...
mass index, 27 ± 4) were enrolled in a baseline-blocking study of 18F-SynVesT-1 and 11C-UCB-J using levetiracetam as the blocking drug. All subjects were screened with a physical exam, medical history, routine laboratory studies, pregnancy tests (for women), and electrocardiography to assess for eligibility. The institutional review board–approved study was also approved by the Yale–New Haven Hospital Radiation Safety Committee and was performed in accordance with federal guidelines and regulations of the United States for the protection of human research subjects contained in title 45, part 46, of the Code of Federal Regulations. All subjects gave written informed consent.

Brain PET Studies

PET Imaging. PET images were acquired using the High Resolution Research Tomograph (Siemens Medical Systems), which acquired 207 slices (1.2-mm slice separation) in list mode for 120 min for 18F-SynVesT-1 and 90 min for 11C-UCB-J. A 6-min transmission scan was conducted for attenuation correction. Dynamic scan data were reconstructed in 27 frames (6 × 30 s, 3 × 1 min, 2 × 2 min, and 16 × 5 min) for 11C-UCB-J, with 6 additional 5-min frames for 18F-SynVesT-1, with corrections for attenuation, normalization, scatter, randoms, and dead time using the motion-compensation ordered-subsets expectation maximization list-mode algorithm for resolution-recovery reconstruction (12). Event-by-event motion correction (13) based on measurements with the Polaris Vicra sensor (NDI Systems) was included in the reconstruction. Subjects were administered 18F-SynVesT-1 as an intravenous injection over 1 min by an automatic pump (PHD 22/2000; Harvard Apparatus). 11C-UCB-J was administered as a bolus for 2 subjects and as a bolus plus infusion for the other 2 subjects. The blocking scan was conducted 3 h after intravenous administration of levetiracetam (18F-SynVesT-1, 20 mg/kg; 11C-UCB-J, 10 mg/kg [n = 3] and 20 mg/kg [n = 1]).

MRI. Each subject underwent MRI for PET image registration. The MRI sequence was a 3-dimensional magnetization-prepared rapid acquisition with a gradient-echo pulse, using an echo time of 2.78 ms, a repetition time of 2,500 ms, an inversion time of 1,100 ms, and a flip angle of 7° on a 3-T whole-body scanner (Trio; Siemens Medical Systems) with a circularly polarized head coil.

Arterial Input Function Measurement. Discrete blood samples were manually drawn every 10 s from 10 to 90 s; every 15 s from 90 s to 3 min; and then at 3, 5, 6.5, 8, 12, 15, 20, 25, 30, 45, 60, 75, and 90 min for both tracers, with 2 additional samples taken at 105 and 120 min for 18F-SynVesT-1. Samples were centrifuged to obtain plasma and then counted with a calibrated well counter.

Radiotracer metabolism was analyzed using plasma samples collected at 3, 8, 15, 30, 60, and 90 min after injection for both tracers, with an additional sample at 120 min for 18F-SynVesT-1. Metabolites were analyzed using the column-switching high-performance liquid chromatography method (14) to determine the parent fraction, as previously described (10). An ultrafiltration-based method (Centrifree; Millipore) was used to measure the plasma free fraction (10).

Image Registration and Regions of Interest. PET images were corrected for motion by frame-by-frame registration to a summed image (0–10 min after injection) using a 6-parameter mutual information algorithm (FLIRT; FSL). The summed PET image was then coregistered to the subject’s T1-weighted MR image (6-parameter affine registration), which was subsequently coregistered to the automated anatomic labeling template (15) in Montreal Neurologic Institute (16) space using a non-linear transformation (BioImage Suite) (17). Using the combined transformations from template-to-PET space, regional tissue time–activity curves were generated in the following regions: amygdala, anterior cingulate cortex, caudate nucleus, cerebellum, frontal cortex, globus pallidus, hippocampus, insular cortex, occipital cortex, parietal cortex, posterior cingulate cortex, putamen, temporal cortex, and thalamus. The region of interest for the centrum semiovale (CS) was designed to minimize the partial-volume effect (18).

Quantitative Analysis

For 18F-SynVesT-1, regional total distribution volume (VT) was computed from the time–activity curves using 1-tissue-compartment (1TC) and 2-tissue-compartment (2TC) models. The relative fit quality of 1TC and 2TC models was compared with the F test. Percentage SE (%SE) was estimated from the theoretic parameter covariance matrix. Multilinear analysis 1 (MA1) (19) was also applied to estimate VT by changing the starting time t° (from 10 to 60 min with 10-min increments). The choice of best kinetic model for 18F-SynVesT-1 was based on analysis of data from the 8 baseline scans.

For comparison of parametric images to 11C-UCB-J, which used the 1TC model (5), parametric VT images for 18F-SynVesT-1 were also generated with the 1TC model using a basis function method, with k2 limited to the range of 0.01–1.0 min⁻¹ and without postsmoothing. All modeling was performed with in-house programs using IDL, version 8.0 (ITT Visual Information Solutions).

The minimal scan duration for VT quantification was evaluated by considering shorter datasets (30–120 min in 10-min increments, n = 8) using the selected kinetic model. The percentage differences in VT derived using data from the shorter intervals and 120 min were calculated. The choice of minimum scan time was based on criteria defined previously (20).

The CS region was used as a reference region to compute regional binding potential (BPND) from VT. The Lassen plot was used to determine target occupancy by levetiracetam and the nondisplaceable distribution volume (VND) (21). The VND from gray matter regions was compared with baseline VT in CS to test the suitability of CS as a reference region.

In addition, a simplified outcome measure, the SUV ratio (SUVR), was evaluated in comparison to BPND. Static SUVR-1, which would equal BPND at equilibrium, was computed for 9 time windows of 30-min duration (10–40, 20–50, 30–60, 40–70, 50–80, 60–90, 70–100, 80–110, and 90–120 min) and compared with BPND calculated from regional VT ratio (target/reference) − 1. All outcome measures were computed from regional time–activity curve analysis of baseline scans.

RESULTS

Human Injection and Scan Parameters

The mean administered dose of 18F-SynVesT-1 had an activity of 180 ± 7 MBq (range, 167–186 MBq) and 180 ± 4 MBq (range, 175–185 MBq) for the baseline (n = 8) and blocking (n = 4) scans, respectively. Injection and scan parameters are listed in Table 1.

Safety

No significant clinical changes were observed with the administration of 18F-SynVesT-1 in an injected-mass dose of up to 0.55 μg.

Plasma Analysis

Data from plasma analysis are displayed in Figure 1. At 60 min after radiotracer injection, the fraction of radioactivity corresponding to the parent compound was 26% ± 9% (n = 8, baseline) and 26% ± 9% (n = 4, blocking) for 18F-SynVesT-1 and 23% ± 8% (n = 2, baseline) and 23% ± 10% (n = 2, blocking) for 11C-UCB-J. The plasma free fraction was 0.31 ± 0.01 (n = 8, baseline) and 0.30 ± 0.02 (n = 4, blocking) for 18F-SynVesT-1 and 0.27 ± 0.02 (n = 4, baseline) and 0.28 ± 0.02 (n = 4, blocking) for 11C-UCB-J. The parent fraction at 60 min and free fraction in plasma did not significantly differ between baseline and blocking conditions with 18F-SynVesT-1.

Brain Distribution and Kinetics

Typical time–activity curves and their fitting are shown in Figure 2. High uptake was seen in gray matter regions and low uptake in
white matter regions. The order of regional uptake levels was similar between \(^{18}\text{F}\)-SynVesT-1 and \(^{11}\text{C}\)-UCB-J. SUV in brain regions peaked at 5–20 min and 10–25 min after injection for \(^{18}\text{F}\)-SynVesT-1 and \(^{11}\text{C}\)-UCB-J, respectively.

The 2TC model was favored over the 1TC model by the \(F\) test (66% of fits), and the differences were found predominantly in the cerebellum, hippocampus, and neocortical regions. In particular, a moderate lack of fit was seen in the cerebellum with the 1TC model. Although the 2TC fits were excellent, kinetic parameters were not reliably estimated (\(\%\text{SE} > 100\%\) in 32% of the fits for \(k_1\) and 77% of the fits for \(k_3\)), leading to poor estimation of 2TC \(V_T\) in 60% of fits (\(\%\text{SE} > 10\%\)). In stable \(V_T\) cases (\(\%\text{SE} < 10\%\)), the estimated \(k_3\) was not small (~0.02). But, in unstable \(V_T\) cases (\(\%\text{SE} > 100\%\)), the estimated \(k_3\) was very small (<10~). The ratio of \(k_3/k_4\) was also unstable (\(\%\text{SE} > 1,000\%\)). Excluding the unreliable 2TC \(V_T\) estimates, 1TC \(V_T\) values matched exceptionally with those from 2TC (1TC \(V_T = 1.01 \times 2TC\) \(V_T = 0.32, R^2 = 1.00\)). The MA1 method was also tested with a range of \(t^*\) settings. If \(t^*\) has a very small effect on \(V_T\), then the 1TC model is appropriate. The results showed that MA1 \(V_T\) values derived with different \(t^*\) settings did not differ from those estimated by 1TC: the percentage differences ranged from 0.2% ± 0.3% (\(t^* = 10\) min) to 2.7% ± 0.8% (\(t^* = 60\) min). The largest difference was seen in the cerebellum and hippocampus with a \(t^*\) of 60 min (4%–5%). Given the insensitivity of \(V_T\) estimates to \(t^*\) settings in MA1, the quality of fitting by 1TC, and the excellent settings in MA1, the quality of fitting by 1TC, and the excellent

For the hippocampus and cerebellum, 40 min for the anterior cingulate cortex, and 30 min for other regions (Table 2).

Figure 4 shows examples of Lassen plots using \(V_T\) measured with \(^{18}\text{F}\)-SynVesT-1 and \(^{11}\text{C}\)-UCB-J in the baseline blocking study with levetiracetam (Table 3). The occupancy by a 20 mg/kg dose of levetiracetam was 85.3% ± 4.7% as measured by \(^{18}\text{F}\)-SynVesT-1 and 82.5% as measured by \(^{11}\text{C}\)-UCB-J, whereas occupancy produced by the 10 mg/kg dose was 76.4% ± 5.6% as measured by \(^{11}\text{C}\)-UCB-J. The \(V_{ND}\) determined as the \(x\) intercepts from the Lassen plots, was 2.38 ± 0.33 mL/cm\(^3\) for \(^{18}\text{F}\)-SynVesT-1 and 3.13 ± 0.40 mL/cm\(^3\) for \(^{11}\text{C}\)-UCB-J. The gray matter \(V_{ND}\) was lower than the baseline CS \(V_T\) by 32% ± 16% for \(^{18}\text{F}\)-SynVesT-1 and 29% ± 13% for \(^{11}\text{C}\)-UCB-J; these offsets did not significantly differ between the tracers (P = 0.83). If \(V_{ND}\) in CS equals that in gray matter, these data indicate that the \(BP_{ND}\) for CS is 0.47 and 0.41 for \(^{18}\text{F}\)-SynVesT-1 and \(^{11}\text{C}\)-UCB-J, respectively. However, we previously showed that \(V_{ND}\) is greater in CS than in gray matter (18).

Regional \(BP_{ND}\) was compared between the 2 tracers using either baseline CS \(V_T\) or Lassen plot \(V_{ND}\) as reference values (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). By either reference method, \(^{18}\text{F}\)-SynVesT-1 had higher \(BP_{ND}\) than \(^{11}\text{C}\)-UCB-J, but the difference was not statistically significant.

Using the CS as a reference region for calculation of \(BP_{ND}\) from regional \(V_T\), the mean 1TC \(BP_{SD}\) ranged from 2.5 ± 0.5 in the globus pallidus to 4.5 ± 0.5 in the putamen for \(^{18}\text{F}\)-SynVesT-1 (Table 2). These values were then compared with SUVRs using different 30-min windows. Percentage differences between SUVR-1 and \(BP_{ND}\)
The smallest percentage difference was seen when the window for SUVR-1 calculation was 60–90 min. The regression line was as follows: SUVR-1 (60–90 min) = 0.95 × \(BP_{ND}\) 0.15 (\(R^2 = 0.97\)).

DISCUSSION

This first-in-human study of the SV2A PET tracer \(^{18}\)F-SynVesT-1 included baseline PET scans to evaluate methods for kinetic analysis of imaging data, levetiracetam occupancy scans to assess nonspecific binding, and comparison with the established tracer \(^{11}\)C-UCB-J.

In choosing the best kinetic analysis method, we compared the ITC and 2TC models. The 2TC model was preferred for analysis of \(^{18}\)F-SynVesT-1 imaging data based on the \(F\) test in 66% of fits. However, \(k_3\) and \(k_4\) were poorly estimated by the 2TC model, resulting in unreliable \(V_T\) estimation. When such unreliable estimates were excluded, the ITC and 2TC models provided almost

<table>
<thead>
<tr>
<th>Region</th>
<th>(V_T) (mL/cm(^3)) (baseline, (n = 8))</th>
<th>(BP_{ND}) (baseline, (n = 8))</th>
<th>Minimum scan time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>19.3 (14%)</td>
<td>4.5 (11%)</td>
<td>30</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>18.8 (16%)</td>
<td>4.3 (13%)</td>
<td>30</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>18.6 (15%)</td>
<td>4.3 (13%)</td>
<td>30</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>17.7 (16%)</td>
<td>4.0 (15%)</td>
<td>30</td>
</tr>
<tr>
<td>Amygdala</td>
<td>17.6 (11%)</td>
<td>4.0 (12%)</td>
<td>30</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>17.4 (18%)</td>
<td>3.9 (17%)</td>
<td>30</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>17.2 (15%)</td>
<td>3.9 (13%)</td>
<td>40</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>16.9 (15%)</td>
<td>3.8 (12%)</td>
<td>30</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>15.3 (15%)</td>
<td>3.3 (12%)</td>
<td>30</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>14.2 (27%)</td>
<td>3.0 (29%)</td>
<td>30</td>
</tr>
<tr>
<td>Thalamus</td>
<td>13.5 (12%)</td>
<td>2.8 (12%)</td>
<td>30</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>13.0 (12%)</td>
<td>2.7 (15%)</td>
<td>60</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>13.0 (11%)</td>
<td>2.7 (14%)</td>
<td>60</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>12.6 (20%)</td>
<td>2.5 (19%)</td>
<td>30</td>
</tr>
<tr>
<td>CS</td>
<td>3.5 (11%)</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>
Regional $V_T$ values derived from parametric images matched well with those from time–activity curve analysis. Because the statistical quality of $V_T$ images was similarly high for $^{18}$F-SynVesT-1 and $^{11}$C-UCB-J, no spatial smoothing was required for either tracer. For centers with the ability to produce $^{11}$C tracer, ultimately it will be of interest to assess which tracer provides the best image quality with matched radiation dose.

The CS has been proposed as a suitable reference region because of its negligible SV2A level in the baboon brain, as observed by Western blot analysis (4). Since CS has been used as a reference region to quantify $^{11}$C-UCB-J specific binding (6,22), we also evaluated the use of CS as a reference region to compute the BP$_{ND}$ and SUVR of $^{18}$F-SynVesT-1. Rossano et al. (18) investigated the CS reference region for $^{11}$C-UCB-J quantification and optimized the location and size of the region of interest, which were adopted in the current study. As observed previously with $^{11}$C-UCB-J, a decrease in $^{18}$F-SynVesT-1 was seen in the CS after SV2A blockade with levetiracetam. For both tracers, the VND determined from the occupancy plot was about 30% lower than the CS V$_T$. Thus, use of the CS as a reference region might lead to underestimation of BP$_{ND}$ and SUVR. Nonetheless, the CS may still serve as a useful reference region if there is a consistent relationship between CS V$_T$ and VND, as was shown for $^{11}$C-UCB-J (18).

Overall, mean V$_T$ was slightly higher for $^{11}$C-UCB-J than for $^{18}$F-SynVesT-1 across all brain regions, including the CS (Table 3). When the CS was used as a reference region, $^{18}$F-SynVesT-1 gave a higher BP$_{ND}$ than did $^{11}$C-UCB-J, with the ratio of BP$_{ND}$ ($^{11}$C-UCB-J)/BP$_{ND}$ ($^{18}$F-SynVesT-1) being 0.84 ± 0.16 (Supplemental Table 1). When the VND derived from the Lassen occupancy plots was used, a similar BP$_{ND}$ ratio of 0.79 ± 0.36 was obtained. That is, the mean BP$_{ND}$ of $^{18}$F-SynVesT-1 was about 20% higher than that of $^{11}$C-UCB-J. Note, however, that with the small size of this study ($n = 4$), these differences were not statistically significant. The lower logD of $^{18}$F-SynVesT-1 (2.32 vs. 2.53 for $^{11}$C-UCB-J) contributes to a higher free fraction of ligand in the nondisplaceable tissue compartment ($f_{ND}$) (0.130 vs. 0.086 for $^{11}$C-UCB-J) and a lower VND (2.38 vs. 3.13 for $^{11}$C-UCB-J). However, the relative values of BP$_{ND}$ (=f$_{ND}$/$K_d$) also depend on the in vivo $K_d$. The average in vitro $K_d$ was 3.3 nM for SynVesT-1 and 2.7 nM for UCB-J, taken from 2 sets of measurements published previously ($K_d$ of 2.2 and 4.7 nM, respectively, for SynVesT-1 and 1.5 and 3.0 nM, respectively, for UCB-J) (23) and 1 set of our own measurements ($K_d$ of 3.1 nM for SynVesT-1 and 3.7 nM for UCB-J; unpublished data, December 2019) using $^3$H-UCB-J and human cortex homogenates. Using these in vitro $K_d$ averages as surrogates for in vivo $K_d$, we found that [f$_{ND}$/K_d] ($^{11}$C-UCB-J)/[f$_{ND}$/K_d] ($^{18}$F-SynVesT-1) = 0.81, which matches well with the 0.79 found in the present study for BP$_{ND}$ ($^{11}$C-UCB-J)/BP$_{ND}$ ($^{18}$F-SynVesT-1).

Another way to compare specific binding between tracers is to use the graphical method of Guo et al. (Guo plot) (24), where the sign of the y-intercept predicts which tracer has a higher specific binding signal. However, when the Guo plot was applied to compare $^{18}$F-SynVesT-1 and $^{11}$C-UCB-J, the y-intercept could not be reliably estimated because all the data points were far from the origin.

Of the 4 subjects with both $^{11}$C-UCB-J and $^{18}$F-SynVesT-1 scans, 2 had their $^{11}$C-UCB-J scans conducted under a bolus-plus-infusion protocol, and the other 2 received a bolus injection of the radiotracer. This difference in tracer administration methods should not affect the results, since the outcome measure, V$_T$, was based on kinetic analysis, which accounts for the difference in input function. Although the number of subjects with $^{11}$C-UCB-J scans was limited in this study, the small difference in V$_T$, which was observed for $^{18}$F-SynVesT-1 and $^{11}$C-UCB-J, is consistent with the general trend of the present study.
study, their regional $V_T$ values were close to those in the literature (5,18). For comparison of regional time–activity curves, input functions, and parent fraction curves between tracers, we used the data from the subjects receiving bolus injections of the radiotracers.

To simplify the imaging and analysis protocol for $^{18}$F-SynVesT-1, shorter scan times and simplified quantification method are desirable. By comparing $V_T$ values from different scan lengths to those derived from the 120-min scan data, we found that a scan time of 60 min was sufficient to provide stable $V_T$ estimates for $^{18}$F-SynVesT-1. For quantification without arterial sampling, we assessed the possibility of using SUVR-1 as a surrogate for $BP_{ND}$. The SUVR-1 underestimated $BP_{ND}$ at early time windows, and the difference between SUVR-1 and $BP_{ND}$ monotonically increased by shifting the time window. The best match was seen when the time window for SUVR-1 calculation was 60–90 min. Thus, SUVR-1 calculated from 60 to 90 min after injection of $^{18}$F-SynVesT-1 can be used as an appropriate substitute for $BP_{ND}$ as a measure of specific binding signal, thus simplifying the imaging and quantification protocols for this SV2A radiotracer. Note, this result was obtained in healthy control baseline scans and could be affected by disease or drug administration. Indeed, SUVR-1 from 60 to 90 min was about 20% lower than $BP_{ND}$ in the levetiracetam blocking scans.

CONCLUSION

This study showed that $^{18}$F-SynVesT-1 is an excellent PET tracer for SV2A. $^{18}$F-SynVesT-1 exhibited properties as good as those of the existing radiotracer $^{11}$C-UCB-J: high brain uptake, fast and reversible kinetics, and high specific binding. The 1TC model was chosen as best for quantitative kinetic analysis of $^{18}$F-SynVesT-1 imaging data. Regional $BP_{ND}$ levels of $^{18}$F-SynVesT-1 were higher than those of $^{11}$C-UCB-J. SUVR-1 from 60 to 90 min after injection provided an excellent match with the 1TC $BP_{ND}$ of $^{18}$F-SynVesT-1 and thus can serve as a surrogate quantitative measurement of specific binding in a short scan time without invasive arterial sampling. The longer half-life of this tracer will facilitate its broad application in studies of synaptic density in many neurodegenerative and neuropsychiatric populations.

DISCLOSURE

This publication was made possible by CTSA grant UL1 RR024139 jointly from the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS).

| TABLE 3 | Total Distribution Volumes Derived with 1TC Model for $^{18}$F-SynVesT-1 and $^{11}$C-UCB-J Under Baseline and Levetiracetam Blocking Conditions |
| Region | 18F-SynVesT-1 ($n = 4$) | 18F-SynVesT-1 ($n = 4$) |
| Baseline | Blocking | Baseline | Blocking |
| Putamen | 18.7 (18%) | 5.1 (14%) | 20.5 (14%) | 7.2 (10%) |
| Insular cortex | 18.4 (21%) | 4.9 (13%) | 19.8 (15%) | 6.9 (11%) |
| Temporal cortex | 18.8 (20%) | 4.6 (8%) | 20.4 (15%) | 6.8 (7%) |
| Parietal cortex | 18.1 (21%) | 4.3 (6%) | 20.1 (15%) | 6.6 (7%) |
| Amygdala | 17.4 (13%) | 4.7 (12%) | 19.1 (13%) | 7.0 (13%) |
| Occipital cortex | 17.7 (24%) | 4.2 (6%) | 19.5 (20%) | 6.3 (4%) |
| Anterior cingulate cortex | 17.6 (21%) | 4.8 (16%) | 19.0 (20%) | 7.0 (15%) |
| Frontal cortex | 17.1 (18%) | 4.3 (8%) | 18.8 (12%) | 6.4 (8%) |
| Caudate nucleus | 15.9 (15%) | 4.3 (12%) | 17.6 (14%) | 6.3 (12%) |
| Posterior cingulate cortex | 15.9 (32%) | 4.0 (9%) | 16.9 (28%) | 5.9 (19%) |
| Thalamus | 13.3 (14%) | 4.0 (13%) | 14.5 (12%) | 5.7 (6%) |
| Cerebellum | 13.0 (17%) | 3.6 (12%) | 13.7 (13%) | 5.2 (5%) |
| Hippocampus | 13.2 (13%) | 3.8 (11%) | 14.1 (10%) | 5.5 (10%) |
| Globus pallidus | 11.9 (27%) | 4.2 (14%) | 12.5 (18%) | 5.6 (6%) |
| CS | 3.6 (13%) | 2.4 (6%) | 4.5 (10%) | 3.4 (4%) |

Data in parentheses represent %COV (percentage coefficient of variation [intersubject variability]).
components of the National Institutes of Health (NIH). The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of NIH. Financial support was received from R01AG052560, the Michael J. Fox Foundation, and R01AG065474. The radioligand 18F-SynVesT-1 (formerly referred to as 18F-SDM-8) is the subject of international patent application PCT/US2018/018388, “Radiolabeled Pharmaceuticals and Methods of Making and Using Same,” filed on February 15, 2018 (inventors: Yiyun Huang, Zhengxin Cai, Songye Li, Nabeel Nabulsi, and Richard E. Carson). No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENT

We appreciate the excellent technical assistance of the staff at the Yale University PET Center.

KEY POINTS

QUESTION: Does 18F-SynVesT-1 show kinetic properties suitable for quantifying SV2A density in humans, in comparison with the existing SV2A tracer, 11C-UCB-J?

PERTINENT FINDINGS: 18F-SynVesT-1 showed excellent in vivo properties, with high brain uptake, reversible kinetics, and high specific binding, similar to 11C-UCB-J.

IMPLICATIONS FOR PATIENT CARE: This longer-half-life tracer will be more useful for clinical studies in terms of allowing off-site production and distribution.

REFERENCES