Initial Evaluation of $^{18}$F-GE-179, A Putative PET Tracer for Activated N-Methyl d-Aspartate Receptors

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N-methyl-d-aspartate (NMDA) receptors for l-glutamate, the major excitatory neurotransmitter in the central nervous system (CNS), are linked to ligand- and voltage-gated ion channels (1). Excitatory synaptic transmission via these receptors mediates neuroplasticity and is necessary for learning and memory. In pathologic circumstances, however, NMDA receptor overactivation may be associated with cell death (2).

Excessive NMDA receptor activation mediates excitotoxic neuronal injury after acute cerebral insults (3) and is thought to contribute to disorders of neuronal hyperexcitability (e.g., epilepsy) and chronic neurodegenerative (e.g., Alzheimer, Huntington) (4) and psychotic (5) disorders. Hence, there is interest in the development of radioligands to allow assessment of NMDA receptor function in humans in vivo.

Imaging NMDA ion channel function in vivo in humans has been challenging because of low brain uptake, low affinity for the NMDA receptor, high rates of dissociation, rapid metabolism, and high nonspecific binding of candidate tracers. To date, only 6 of more than 60 radioligands designed for in vivo imaging of the NMDA receptor system (6) have progressed to PET or SPECT studies in humans (Table 1). Of these, 5 act at the phencyclidine recognition site (7), which lies within the NMDA ion channel pore, and hence these radioligands require receptor activation to allow binding. The diarylguanidine CNS 5161, a noncompetitive antagonist, is one such use-dependent ligand that demonstrated high uptake in the putamen and thalamus in human studies in vivo (8–10). Quantification of $^{11}$C-CNS 5161 proved to be difficult, its radiochemical yield low, and its metabolism fast; thus, it was not pursued as a PET radioligand.

In vitro evaluation of a $^{18}$F-labeled analog of CNS 5161 ($^{18}$F-GE-179 (11)) showed that $^{18}$F-GE-179 displaces $^3$H-TCP ($^3$H-N-[1-([thienyl] cyclohexyl)piperidine) from the phencyclidine site with a Ki (inhibition constant) of 2.4 nM (similar to that seen with $^3$H-MK-801 ($^3$H-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,j]cyclohepten-5,10-imine maleate) and CNS 5161 (12)) and GE-179 inhibits glutamate-mediated influx of Ca$^{2+}$ in teratocarcinoma 2 (NT2) cells differentiated to express human NMDA receptors in a dose-dependent manner (supplemental data; supplemental mate-
AUCmetabs or AUCIF.

179 did not significantly bind to any of the 60 receptors, channels, lipophilicity. In a binding study to characterize GE-179 binding to CNS 5161 (log

6

normal human brain. was to evaluate the kinetic behavior of the radioligand in vivo in GE-179 PET in healthy human subjects. Our primary objective

hibited by 3% or less at 10 nM or had not shown significant binding receptor was only inhibited by 8%; all other targets were either in-

sion to administer 18F-GE-179 was obtained from the Administration University College London Hospitals NHS Foundation Trust. Permis-

Royal Marsden Hospital, Imperial College Healthcare NHS Trust, and

the subjects are presented in Table 1.

11 previously described (Table 1.

PET Image Acquisition and Preprocessing

Images were acquired using an ECAT EXACT3D 962 HR+ PET camera (Siemens/CTI) with a 15.5-cm axial and 58.0-cm transaxial field of view. After a transmission scan, each subject underwent a 90-min dynamic emission scan following an intravenous bolus injection of median 186 MBq of 18F-GE-179. Thirty-four frames of increasing duration were acquired. Data were reconstructed with a Fourier rebinning algorithm (FORE; (14)) and 2-dimensional filtered backprojection (ramp, kernel 2.0 mm in full width at half maximum). The voxel size of the reconstructed images was 2.092 × 2.092 × 2.42 mm.

The images were acquired in a quiet, dimly lit room without background noise. Head position was monitored throughout with the camera’s laser light. Continuous arterial blood sampling at a rate of 5 mL per minute was performed from 0 to 15 min. Discrete arterial blood samples were taken at baseline and a further 8 times during the next 90.5 min. High-performance liquid chromatography was used to quantify radiolabeled metabolites in the plasma.

The fraction of plasma radioactivity attributable to the parent 18F-GE-179 was fitted to a sigmoid function normalized to unity at 0 min using CLICKFIT version1.7 (Hinz R, Cunningham VJ, Imaging Research Solutions Limited, London, U.K.) running in MATLAB 6.5 (The MathWorks Inc.) to generate a metabolite model for each participant.

The area under the metabolite model curve (AUCmetabs) was used as a measure of the rate of metabolism for each individual. Correlations between the AUCmetabs and age, weight, and body mass index (BMI) were examined by Spearman rank (p) correlation coefficient using SPSS (version 16.0 [SPSS Inc., IBM Corp.] for Windows [Micro-

soft]). The threshold of statistical significance (P < 0.05) was cor-

rected for multiple comparisons using the Bonferroni method.

Continuous decay- and metabolite-corrected parent plasma input functions were generated for all subjects using CLICKFIT, as de-

scribed previously (15). Briefly, the final input functions were gener-

ated by multiplication of the calibrated time course of radioactivity in the blood with the fits to the plasma-to-blood ratios and metabolite fractions. Rodent in vivo metabolism data showed that the likelihood of ingress of radiolabeled metabolites in to the CNS was low; this, therefore, was not accounted for (see supplemental data). The areas under the decay- and metabolite-corrected parent plasma input function curves (AUCIP) were calculated for each subject by summation of the counts in the parent plasma input function file, after correction for 18F radiodecay.

Correlations between the AUCIP and age, weight, BMI, and injected dose were examined by Spearman rank (p) correlation coefficient.

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**TABLE 1**

Healthy Participant Population Demographics, MR Imaging Findings, and 18F-GE-179 Injection Data

<table>
<thead>
<tr>
<th>Patient identification no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Handedness</th>
<th>Smoker</th>
<th>MR imaging</th>
<th>Injected dose (MBq)</th>
<th>Specific activity at time of injection (GBq/μmol)</th>
<th>Purity (%)</th>
<th>Coinjected mass (μg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>M</td>
<td>80</td>
<td>L</td>
<td>No</td>
<td>Normal</td>
<td>187.0</td>
<td>450.1</td>
<td>98</td>
<td>0.16</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>67</td>
<td>R</td>
<td>No</td>
<td>Normal</td>
<td>173.2</td>
<td>73.1</td>
<td>97</td>
<td>0.91</td>
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<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>83</td>
<td>R</td>
<td>Yes</td>
<td>WM foci</td>
<td>186.0</td>
<td>1428.0</td>
<td>97</td>
<td>0.05</td>
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<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>58</td>
<td>R</td>
<td>No</td>
<td>Tiny WM foci</td>
<td>180.4</td>
<td>769.5</td>
<td>96</td>
<td>0.09</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>65</td>
<td>R</td>
<td>No</td>
<td>Normal</td>
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<td>95</td>
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<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>53</td>
<td>R</td>
<td>No</td>
<td>WM foci</td>
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<tr>
<td>7*</td>
<td>25</td>
<td>F</td>
<td>81</td>
<td>R</td>
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<td>Normal</td>
<td>192.4</td>
<td>263.8</td>
<td>96</td>
<td>0.28</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>M</td>
<td>91</td>
<td>L</td>
<td>No</td>
<td>Normal</td>
<td>189.2</td>
<td>726.6</td>
<td>96</td>
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<tr>
<td>9</td>
<td>57</td>
<td>M</td>
<td>84</td>
<td>R</td>
<td>No</td>
<td>RF WM foci</td>
<td>186.9</td>
<td>311.9</td>
<td>96</td>
<td>0.23</td>
</tr>
<tr>
<td>Median/total</td>
<td>37</td>
<td>6 M</td>
<td>80</td>
<td>7 right</td>
<td>1 smoker</td>
<td>NA</td>
<td>186.0</td>
<td>450.1</td>
<td>96</td>
<td>0.16</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td></td>
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<td></td>
<td>2.8</td>
<td>70.0</td>
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<td>102</td>
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<tr>
<td>IQR</td>
<td>26–57</td>
<td>65–83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>183.7–187.0</td>
<td>263.8–769.5</td>
<td>96–97</td>
<td>0.09–0.28</td>
</tr>
<tr>
<td>Minimum</td>
<td>25</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>173.2</td>
<td>73.1</td>
<td>95</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximum</td>
<td>62</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>192.4</td>
<td>1428.0</td>
<td>98</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Participant 7 was a regular user of ibuprofen. Analysis by ANOVA failed to demonstrate any significant influence of this variable on AUCmetabs or AUCIP.

WM = white matter; RF = right frontal; NA = nonapplicable.
The median asymmetry indices (AIs) were calculated to compare radioactivity concentration (RC) in the ROIs highlighted by the survey, according to the following formula:

$$AI = \frac{RC_{Left} - RC_{Right}}{(RC_{Left} + RC_{Right})/2}$$

Compartmental Modeling of $^{18}$F-GE-179 Cerebral Tissue Kinetics

Six gray matter–only ROIs were defined a priori for modeling purposes according to the known distribution of the NMDA receptor (21) and sampled with left and right sides combined. In order of decreasing approximate receptor density, the ROIs were the putamina, thalami, superior frontal gyri, parahippocampal gyri, occipital lobes, and cerebellum. The entire brain gray matter and white matter ROIs were also sampled. Each participant’s attenuation- and motion-corrected dynamic PET image was sampled over all 34 time frames. Time–activity curves for each ROI were produced using CLICKFIT from the scanner information file and a weights file that had been generated for each ROI from the sampled dynamic PET data.

Analyses of $^{18}$F-GE-179 cerebral tissue kinetics were performed using the following standard compartmental models: 1-brain-compartment, 2-rate constant (1c2kbv, reversible binding); 2-brain-compartment, 3-rate constant (2c3kbv, irreversible binding); 2-brain-compartment, 4-rate constant (2c4kbv, reversible binding); and 3-brain-compartment, 6-rate constant (3c6kbv, reversible binding). All models incorporated a variable blood volume component and were used to calculate the delay between plasma and tissue time–activity curves.

The model fit was assessed using the Akaike Information Criterion (AICw) and the intraregion and between-subject coefficient of variation (CV) of volume-of-distribution ($V_T$) estimates.

Strengths of regional $V_T$ and $K_1$ correlations were assessed by Spearman rank ($\rho$) correlation coefficients, pooling all ROI data for the 9 participants.

The correlations between gray matter $V_T$ and age, weight, BMI, injected dose, specific radioactivity at the time of injection, and AUC$_{IF}$ were similarly interrogated with the Spearman rank ($\rho$) statistic, with correction for multiple comparisons using Bonferroni method.

Generation of Parametric $V_T$ Images

Parametric $V_T$ images were generated by voxelwise rank-shaping regularization of exponential spectral analysis (RS-ESA) (22). RS-ESA is a development of the model-free exponential spectral analysis...
estimation method (23) that has been optimized for noisy datasets by incorporating a singular value decomposition of the exponential base. Time constants were specified as 5 and 5,100 s. The noise fraction was specified as 0.15. The median VT was computed within the ROIs and compared with the VTs derived via compartmental modeling. The correlations between regional VTs derived using each method were assessed by Spearman rank ($r$) correlation coefficient, pooling all ROI data for the 9 participants.

RESULTS

Metabolism

Unmetabolized 18F-GE-179 accounted for a mean of 50% of the plasma radioactivity at approximately 16 min and 25% at 44 min (Fig. 1).

There was a significant negative correlation between the AUCC$_{\text{metabs}}$ and BMI ($r = -0.86, P = 0.002$). There were no significant correlations with other variables.

Decay- and Metabolite-Corrected Parent Plasma Input Functions

The parent plasma input functions peaked at a median of 71.5 s (interquartile range [IQR], 65.6–81.7 s) and decreased to less than 10% of the peak activity concentration within 5 min (Fig. 2). The radioactivity concentrations in plasma at the peak of the parent plasma input functions had a median of 47.3 kBq/mL (IQR, 43.4–65.1 kBq/mL), equivalent to 0.02% of the injected dose/mL.

The median AUC$_{\text{IF}}$ was 4782.0 kBq/cm$^3$ (IQR, 4,165.4–5,754.8 kBq/mL). There was a significant negative correlation between the AUC$_{\text{IF}}$ and weight and AUC$_{\text{IF}}$ and BMI (both $r = -0.721, P = 0.019$). There were no significant correlations with other variables.

Regional Distribution of Radioactivity

The median gray matter radioactivity concentration was 7.3 kBq/mL (IQR, 5.9–9.2 kBq/mL) in the 5- to 30-min summation images. The highest median radioactivity concentration was identified in the putamina, followed by (in descending order) the cunei, lingual gyri, thalami, and cerebellum (Table 2). The between-subject CVs for the gray matter radioactivity concentration ranged from 25.4% to 29.2%.

The lowest median radioactivity concentration in gray matter was observed in the anterior medial temporal lobes, followed by (in ascending order) the parahippocampal gyri, hippocampi, and superior frontal gyri (Table 2).

Left–Right Asymmetry of 18F-GE-179 Radioactivity Concentration

The range of median asymmetry indices in the regions reported above was from –0.03 (IQR, –0.05–0.01) in the thalami to 0.03 (IQR, 0.00–0.05) in the lingual gyri (Table 2).
TABLE 3

$^{18}$F-GE-179 $V_T$ and $K_1$ as Calculated by Regional 2-Brain-Compartment, 4-Rate-Constant Model

<table>
<thead>
<tr>
<th>Region</th>
<th>$\Delta$ICw</th>
<th>IQR</th>
<th>$K_1$ ($\times 10^{-3}$)</th>
<th>$V_T$ Median</th>
<th>IQR</th>
<th>Between-subject CV in $V_T$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Whole-brain) gray matter*</td>
<td>-207.7</td>
<td>-203.1 to -219.8</td>
<td>3.6</td>
<td>8.9</td>
<td>8.5–9.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Putamina</td>
<td>-149.1</td>
<td>-115.3 to -159.3</td>
<td>4.6</td>
<td>11.7</td>
<td>9.9–12.7</td>
<td>15.9</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-146.6</td>
<td>-145.1 to -147.4</td>
<td>4.5</td>
<td>11.8</td>
<td>10.4–13.0</td>
<td>15.8</td>
</tr>
<tr>
<td>Superior frontal gyri</td>
<td>-182.4</td>
<td>-142.9 to -186.7</td>
<td>3.9</td>
<td>8.6</td>
<td>8.4–9.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Occipital lobes</td>
<td>-207.1</td>
<td>-198.6 to -212.4</td>
<td>4.1</td>
<td>9.5</td>
<td>8.8–10.7</td>
<td>13.7</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>-191.6</td>
<td>-186.6 to -209.6</td>
<td>4.0</td>
<td>8.9</td>
<td>8.0–10.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Parahippocampal gyri</td>
<td>-160.9</td>
<td>-149.7 to -179.2</td>
<td>3.1</td>
<td>9.3</td>
<td>8.1–9.7</td>
<td>16.0</td>
</tr>
</tbody>
</table>

*Data are derived from 8 participants as model failure noted in (whole-brain) gray matter for participant 4.

**Time–Activity Curves**

The mean gray matter radioactivity concentration peaked at 8.9 kBq/mL, equivalent to a mean of 0.0048 percentage injected dose (%ID) at 7.5 min. The mean white matter radioactivity peaked at 5.1 kBq/mL (0.0028 %ID) at 13 min. The radioactivity declined more slowly than in the other gray matter regions (68% in the parahippocampal gyri, later than in other ROIs, but also declined more slowly than in the other gray matter regions (68% of the peak at 91.5 min).

The highest mean gray matter radioactivity concentration was seen in the putamina, which peaked at 10.4 kBq/mL (0.0056 %ID) at 7.5 min (Fig. 3), followed by the thalami, occipital lobes, cerebellum, superior frontal gyri, and parahippocampal gyri. The radioactivity concentration in the putamina decreased to approximately 58% of the peak at 91.5 min, to 63% in the thalami, 53% in the occipital lobes, 51% in the cerebellum, and 64% in the superior frontal gyri. The radioactivity concentration peaked at 13 min in the parahippocampal gyri, later than in other ROIs, but also declined more slowly than in the other gray matter regions (68% of the peak at 91.5 min).

**Compartmental Modeling of $^{18}$F-GE-179 Cerebral Tissue Kinetics**

The 2c4kbv model best described the radioligand’s kinetics in gray matter ($\Delta$ICw = -207; Table 3; Fig. 4), with a slight bias toward underestimation of $V_T$, relative to that derived from the $2c3kbv$ model, was observed (Fig. 7).

A representative example of an $^{18}$F-GE-179 $V_T$ image is provided in Figure 6. RS-ESA yielded $V_T$s (Table 4) that correlated with those derived from regional compartmental modeling (Spearman $\rho = 0.398$; $P = 0.003$; Fig. 5). There was a positive correlation between gray matter $V_T$ and age (Spearman $\rho = 0.803$; $P = 0.009$). There were no significant correlations with other variables.

**DISCUSSION**

To our knowledge, we describe the first use of $^{18}$F-GE-179 as a PET radioligand in humans.

Brain penetration of $^{18}$F-GE-179 was high, with a mean peak radioactivity concentration of 8.9 kBq/mL in gray matter, which is greater than that achieved when using the NMDA radioligands $^{11}$C-memantine (24), $^{11}$C-AcL703 (25), and $^{11}$C-CNS 5161 (8), normalized to injected volume. The mean peak global and gray matter radioactivity concentrations have not been reported with other radioligands targeted at the NMDA receptor (26–30).

The distribution of radioactivity in gray matter after injection of $^{18}$F-GE-179 was relatively homogeneous, with the highest concentration (in the absence of correction for partial-volume effects) observed in the putamina, a region of moderate NMDA receptor density (31). Peak and summed (5–30 min) radioactivity concentrations in the white matter, often considered a reference region for nonspecific binding (32), were just over half that of the putamina. High radioactivity concentration was observed in the cerebellar cortex, in keeping with the documented existence of NMDA receptors in this region (33).

The channel maximal open probability of the NR2A subunit is approximately 2–5 times higher than that of the NR2B subunit.
VT suggests partial cerebral blood flow-dependency. A dose-escalation safety study with CNS 5161 was abandoned because of the rate of uptake of the radioligand, a second baseline scan at rest would be required, and the increased local concentration might be expected to increase specific binding in certain brain regions, such as an episodic memory task, during radioligand injection.

Ideally, the specificity of 18F-GE-179 binding in vivo would be quantified by coadministration of unlabeled GE-179 or another unlabeled agent with high affinity and selectivity for the phencyclidine-binding site. However, this is not feasible in humans because of poor tolerability of blocking doses of NMDA antagonists. A dose-escalation safety study with CNS 5161 was abandoned after a sustained systolic blood pressure increase in 1 of 2 participants administered 750 μg (38). The performance of a cognitive task, such as an episodic memory task, during radioligand injection might be expected to increase specific binding in certain brain areas, that is, in the medial temporal lobe. However, such a paradigm would have to be performed for approximately 20 min or more because of the rate of uptake of the radioligand, a second baseline scan at rest would be required, and the increased local cerebral blood flow would confound the analyses. Focal epileptic activity could also be hypothesized to increase (specific) binding in the medial temporal lobe regions. 18F-GE-179 will be investigated in participants with epilepsy in a subsequent study. Additional limitations of this first-in-human study include the small sample size and lack of test–retest data. A further study is required to demonstrate acceptable within-subject (i.e., test–retest) variability for the quantification of 18F-GE-179 VT. However, in view of the low NMDA–channel opening probability at baseline, test–retest data at rest without control over cognitive and emotional state might not be helpful.

The rate of metabolism of 18F-GE-179 was less rapid than that of 11C-CNS 5161 (8) and 123I-CNS 1261 (29) but not 18F-memantine (24) (data not reported for other NMDA-receptor radioligands). Our analyses assumed radiolabeled metabolites did not penetrate the brain, although 1 more polar compound was identified in rodent brains at 30 min after injection (GE Healthcare, unpublished data, on file, 2009). Parent 18F-GE-179 accounted for 84% of the cerebral radioactivity at this point. In humans, the slower plasma metabolism of the radioligand suggests it should account for an even greater proportion at this time point. 18F-GE-179 exhibited faster gray matter tissue uptake and washout than 11C-CNS 5161 (8) and also 123I-MK-801 (28,30), 18F-memantine (24), and 11C-AcL703 (25)). Model fits indicated a better fit for the reversible model. Our data indicate that quantification of regional 18F-GE-179 VT is achievable with a 2c4kbv model with variable blood component. Voxelwise quantification of 18F-GE-179 VT by RS-ESA yielded comparable estimates and parametric maps of acceptable visual quality; this will also allow for comparison of VT between populations without a priori delineation of ROI whereas voxelwise compartmental modeling is hampered by noise. When ROI quantification is preferred, we suggest that the 2c4kbv model is used to avoid the negative bias associated with RS-ESA. However, the choice of quantification method will also be informed by test–retest variability, when such data become available.

18F-GE-179 uptake and VT have acceptable between-subject variability in healthy participants, as evidenced by regional between-subject CVs of less than 16%. A positive correlation between VT and age was observed and so future studies, especially if involving poorly matched subgroups, should model this as a covariate in the analyses. This finding appears at odds with the age-related declines in cerebral blood flow (39) and NMDA receptor function (40). However, it is possible that the relationship between 18F-GE-179 VT and age is nonlinear. In such a case, the positive correlation we have identified might reflect the limited age spread (range, 25–62 y) of our cohort. As expected, participants of higher weight or BMI had a lower parent plasma input than the remaining controls. Moreover, regional VT was seen to correlate with the first rate constant (i.e., linked to cerebral blood flow).

CONCLUSION

Our first-in-human evaluation of 18F-GE-179 has demonstrated several properties that are desirable in PET radioligands, such as

**FIGURE 6.** VT of 18F-GE-179 for representative participant (1), as calculated by RS-ESA. Image has been smoothed by isotropic gaussian filter of 6 mm at full width at half maximum.
high brain uptake and acceptable between-subject variability. Quantification of $V_T$ appears feasible within ROIs and at the voxel level. The specificity of $^{18}$F-GE-179 binding requires further characterization and could potentially limit its application. Further in vivo evaluation of $^{18}$F-GE-179 is warranted.

**DISCLOSURE**

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This study was supported by the Medical Research Council (MRC) Clinical Sciences Centre; GE Healthcare plc; the Department of Health NIHR Biomedical Research Centre (G108/585); and the Neurodis Foundation. Sajinder K. Koepp have received fees from GE Healthcare plc but are not current or former employees of the organization. John S. Duncan has received fees for organizing symposia and lecturing for UCB Pharma, Eisai, GSK, and GE Healthcare. Alexander Hammers receives license fees for atlas variants that are not used in this study from Imperial Innovations. No other potential conflict of interest relevant to this article was reported.

**ACKNOWLEDGMENTS**

We thank the staff of Hammersmith Imanet Limited and the Epilepsy Society MRI Unit for their assistance with data acquisition and preparation.

**REFERENCES**


**TABLE 4**

$^{18}$F-GE-179 $V_T$ as Calculated by Voxelwise RS-ESA

<table>
<thead>
<tr>
<th>Region</th>
<th>Median</th>
<th>IQR</th>
<th>Between-subject CV in $V_T$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Whole-brain) gray matter</td>
<td>8.4</td>
<td>7.7–9.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Putamina</td>
<td>10.9</td>
<td>9.5–12.5</td>
<td>14.8</td>
</tr>
<tr>
<td>Thalamus</td>
<td>11.1</td>
<td>9.4–11.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Superior frontal gyri</td>
<td>8.2</td>
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<td>11.6</td>
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<tr>
<td>Occipital lobes</td>
<td>8.2</td>
<td>8.2–8.8</td>
<td>12.6</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>8.3</td>
<td>7.4–9.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Parahippocampal gyri</td>
<td>7.8</td>
<td>7.2–8.1</td>
<td>13.2</td>
</tr>
</tbody>
</table>

**FIGURE 7.** Tukey mean-difference plot for comparison of $^{18}$F-GE-179 $V_T$ as calculated by voxelwise RS-ESA and by regional 2c4kbv model. Data from 6 bilateral ROIs are shown for each participant.