NMDA receptor binding in focal epilepsies

C J McGinnity,1,2,3 M J Koepp,4,5 A Hammers,1,2,3,4,5,6 D A Riaño Barros,1,2 R M Pressler,7 S Luthra,8 P A Jones,8 W Trigg,8 C Micallef,7 M R Symms,4,5 D J Brooks,1,10 J S Duncan4,5

ABSTRACT

Objective To demonstrate altered N-methyl-d-aspartate (NMDA) receptor availability in patients with focal epilepsies using positron emission tomography (PET) and [18F]GE-179, a ligand that selectively binds to the open NMDA receptor ion channel, which is thought to be overactive in epilepsy.

Methods Eleven patients (median age 33 years, 6 males) with known frequent interictal epileptiform discharges had an [18F]GE-179 PET scan, in a cross-sectional study. MRI showed a focal lesion but discordant EEG changes in two, was non-localising with multifocal EEG abnormalities in two, and was normal in the remaining seven patients who all had multifocal EEG changes. Individual patient [18F]GE-179 volume-of-distribution (VT) images were compared between individual patients and a group of 10 healthy controls (47 years, 7 males) using Statistical Parametric Mapping.

Results Individual analyses revealed a single cluster of focal VT increase in four patients; one with a single and one with multifocal MRI lesions, and two with normal MRIs. Post hoc analysis revealed that, relative to controls, patients not taking antidepressants had globally increased [18F]GE-179 VT (28%; p<0.002), and the three patients taking an antidepressant drug had globally reduced [18F]GE-179 VT (29%; p<0.002). There were no focal abnormalities common to the epilepsy group.

Conclusions In patients with focal epilepsies, we detected primarily global increases of [18F]GE-179 VT consistent with increased NMDA channel activation, but reduced availability in those taking antidepressant drugs, consistent with a possible mode of action of this class of drugs. [18F]GE-179 PET showed focal accentuations of NMDA binding in 4 out of 11 patients, with difficulty to localise and treat focal epilepsy.

INTRODUCTION

N-methyl-d-aspartate (NMDA) receptors are ligand-gated and voltage-gated ion channels that mediate fast excitatory neurotransmission in the central nervous system (CNS).1,2 NMDA receptor-mediated neurotransmission is necessary for cognition, memory and neuronal survival, but excessive NMDA receptor activation mediates excitotoxic neuronal injury following acute cerebral insults,3 is associated with cell death4 and is thought to contribute to disorders of neuronal hyperexcitability, such as epilepsy and neuropathic pain, and chronic neurodegenerative diseases,5 depression6,7 and schizophrenia.8 In chemical models, administration of agonists of either the NMDA or α-amino-3-
Epilepsy

Epilepsy and control populations
This was a proof-of-principle, cross-sectional pilot study with targets of 12 participants per group. Eleven patients with refractory focal epilepsies (median age 33 years; range 20–50 years; 6 males) were recruited from the outpatient clinics at the National Hospital for Neurology and Neurosurgery. Demographics and clinical details are listed in Table 1. Their diagnoses were based on history, seizure semiology, prolonged and repeated interictal and ictal EEG recordings (where available), and MRI data. Patients were chosen who had frequent interictal spikes on previous EEG recordings, which we hypothesised would maximise our chances to detect increased binding to open NMDA receptors. None of the patients were taking an antiepileptic drug (AED) known to act at the NMDA receptor. Exclusion criteria included inability to provide informed consent, claustrophobia, standard MR contraindications, a positive urinary pregnancy test on the day of the PET scan and history of drug abuse. Patient 4, whose seizures consisted of a sustained ictal EG

PET image acquisition and data analysis
PET image acquisition has been described previously. Briefly, images were acquired using a Siemens/CTI ECAT EXACT 962 HR+PET camera (Siemens, Erlangen, Germany) at Hammersmith Imanet Limited. Each participant had a 90 min dynamic emission scan with a smooth bolus intravenous injection of median 187 MBq (range 173–192 MBq) [18F]GE-179 administered 30 seconds after starting image acquisition. For calculation of continuous decay-corrected and metabolite-corrected parent plasma input functions, discrete arterial blood samples were taken throughout the scan, with continuous arterial blood sampling for the first 15 minutes.

The area under the metabolite model curves (AUCmetabs) was used as a measure of the rate of metabolism for each individual. The AUCmetabs over t=0–30 minutes and t=0–90.5 minutes was compared between groups by multivariate general linear model (GLM), with gender as a fixed factor, and age and BMI as covariates. The residual sum of squares (RSSmetabs) for the metabolite model curve was compared between groups by univariate GLM. The threshold for statistical significance was p=0.05.

The VT of [18F]GE-179 was computed at the voxel level for each participant by exponential spectral analysis, as described previously.

The control group, 9 of whom have been described previously, comprised 10 healthy volunteers without history of neurological or psychiatric illness (median age 46 years; range 25–62 years; 7 males). Additional exclusion criteria were as described for the patients above. A further three seemingly healthy individuals were subsequently excluded; one due to excessive movement throughout the PET scan acquisition, one whose MRI revealed evidence of a cerebral infarct and one who was discovered to have a history of benzodiazepine abuse. The original control group data were used, rather than repeat imaging; the patient data were acquired at approximately the same time as those of the control group (i.e. within 12 months) using the same imaging protocol.

Median age and body mass index (BMI) were compared between patients and control groups by Mann-Whitney U statistic in SPSS. Gender balance was compared between groups with the (Pearson) χ² test.

MRI data acquisition
Three-dimensional volumetric T1-weighted coronal MRI sequences were acquired at Epilepsy Society (Chalfont St. Peter, UK), as previously described. MRIs were reviewed by an experienced neuroradiologist (CM). MRIs were not available for one control participant, in whom 3.0 T MRI was contra-indicated.

EEG
All patients had an EEG during the PET scan using a Trackit 18/8 (Lifelines Limited, Hants, UK) ambulatory EEG recorder and an ECI E1 Cap (Electro-Cap International, Eaton, Ohio, USA) with 19 electrodes placed according to the International 10–20 system. An additional reference electrode (Fpz) was sited just anterior to Fz. The O1 and O2 electrodes were removed from the cap prior to scanning for several patients in order to minimise discomfort. The participants were closely observed for evidence of seizures throughout the scan. EEGs were reviewed by an experienced clinical neurophysiologist (RMP). The number of IEDs during the first 30 min of scan acquisition was quantified and correlated with [18F]GE-179 global volume-of-distribution (VT) using Spearman’s ρ correlation coefficient.

Table 1: Patients with focal epilepsy and frequent IED—clinical details

<table>
<thead>
<tr>
<th>ID</th>
<th>Age/sex/handedness</th>
<th>Probable localisation MRI/EEG</th>
<th>Onset/duration (years)</th>
<th>Postictal interval</th>
<th>Treatment</th>
<th>Seizures</th>
<th>EEG</th>
<th>MEG</th>
<th>MRI</th>
<th>[18F]FDG-PET</th>
<th>Global [18F]GE-179 V1</th>
<th>Approximately N of observed IEDs (t=0–30 min)</th>
<th>[18F]GE-179 V1 increases</th>
<th>[18F]GE-179 V1 decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/M/R</td>
<td>L frontal</td>
<td>14.5/26.5</td>
<td>6.0 h</td>
<td>CBZ, LEV, LTG, ZNS</td>
<td>SPS, CPS, SGS</td>
<td>L frontotemporal</td>
<td>NA</td>
<td>R IFG lesion</td>
<td>L temporal</td>
<td>6.16</td>
<td>62</td>
<td>L frontal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22/M/R</td>
<td>L temporal</td>
<td>4/18</td>
<td>7.5 h</td>
<td>CBZ, LEV, LAC</td>
<td>CPS, SGS</td>
<td>L frontotemporal and R temporal</td>
<td>NA</td>
<td>L HS</td>
<td>L hemisphere</td>
<td>7.20</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>38/M/L</td>
<td>Multifocal MRI, EEG/MEG</td>
<td>2.5/36.5</td>
<td>45 min</td>
<td>CBZ, CLB, PHT, TPM, fexofenadine</td>
<td>SPS, CPS, SGS</td>
<td>R frontotemporal</td>
<td>R frontal, L and R temporal</td>
<td>Bilateral tubers: F, P, L-O, periventricular calc</td>
<td>Bilateral tubers: L and R frontal, L temporal, R parieto-occipital, L occipital</td>
<td>NA</td>
<td>4.53</td>
<td>EEG data corrupted</td>
<td>Brainstem; L temporal; R temporal</td>
</tr>
<tr>
<td>4</td>
<td>28/F/R</td>
<td>Multifocal MRI, EEG/MEG</td>
<td>10/18</td>
<td>20.5 h</td>
<td>LEV, sertraline, amlopidine</td>
<td>SPS (pupillary hippoc)</td>
<td>R temporoparietal</td>
<td>R parieto-occipital &gt;R temporal &gt;L occipital</td>
<td>Bilateral tubers: L and R frontal, L temporal, R parieto-occipital, L occipital</td>
<td>Bilateral tubers: L and R frontal, L temporal, R parieto-occipital, L occipital</td>
<td>NA</td>
<td>4.53</td>
<td>EEG data corrupted</td>
<td>Brainstem; L temporal; R temporal</td>
</tr>
<tr>
<td>5</td>
<td>50/F/R</td>
<td>MRI negative</td>
<td>11/39</td>
<td>39 days</td>
<td>LEV, PHT, lofepramine</td>
<td>CPS SGS</td>
<td>L=R temporal</td>
<td>L and R temporal</td>
<td>Neg</td>
<td>L temporal</td>
<td>5.32</td>
<td>26</td>
<td>R frontal</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>33/M/L</td>
<td>MRI negative</td>
<td>19/14</td>
<td>NA</td>
<td>CLN, Ruf, fluoxetine</td>
<td>CPS</td>
<td>L temporal</td>
<td>L frontotemporal</td>
<td>Neg</td>
<td>Neg</td>
<td>3.90</td>
<td>168</td>
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<tr>
<td>7</td>
<td>23/M/L</td>
<td>MRI-negative</td>
<td>16/7</td>
<td>3 days</td>
<td>CBZ, VAL</td>
<td>SPS, SGS</td>
<td>R frontal</td>
<td>NA</td>
<td>Neg</td>
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<td>L temporal; R frontal</td>
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<td>8</td>
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<td>MRI negative</td>
<td>12.5/28</td>
<td>11 days</td>
<td>CLB, LAC, OXC</td>
<td>SGS</td>
<td>L=R frontal</td>
<td>L F</td>
<td>Neg</td>
<td>8.40</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>24/M/R</td>
<td>MRI negative</td>
<td>7/17</td>
<td>6.5 h</td>
<td>LAC, LEV, LTG, OXC, CLB</td>
<td>SPS, CPS, SGS</td>
<td>R frontocentral</td>
<td>L frontal &gt;L insula. &gt;L frontotemporal</td>
<td>Neg</td>
<td>Neg</td>
<td>8.44</td>
<td>9</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>50/F/R</td>
<td>MRI negative</td>
<td>13/37</td>
<td>10+ years</td>
<td>LEV, LAC, LTG</td>
<td>CPS</td>
<td>L=R temporal</td>
<td>L and R T</td>
<td>Neg</td>
<td>NA</td>
<td>8.17</td>
<td>Cont epileptiform activity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>20/F/R</td>
<td>MRI negative</td>
<td>14/6</td>
<td>39.5 h</td>
<td>CLB, OXC,</td>
<td>CPS, SGS</td>
<td>R=L temporal</td>
<td>NA</td>
<td>Neg</td>
<td>8.88</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antidepressant drugs (patients 4–6) are displayed in bold font.

*EEG revealed continuous ongoing focal epileptiform activity in patient 10, who had not shown clinically evident seizure activity within the preceding 10 years. Underline indicates concordance between the cluster of increase and the location of the presumed epileptogenic zone, where known.

Calc, calcification; CBZ, carbamazepine; CLB, clonazepam; CLN, clonazepam; CPS, complex partial seizures; EEG, electroencephalography; F, frontal lobe; F/M, female/male; [18F]FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; HS, hippocampal sclerosis; ID, identifying number; IED, interictal epileptiform discharges; IFG, inferior frontal gyrus; L/R, left/right; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MEG, magnetoecephalography; MRI, magnetic resonance imaging; NA, not available; Neg, negative, that is, no significant findings; O, occipital; OXC, oxcarbazepine; P, parietal lobe; PHT, phenytoin; RUF, rufinamide; SGS, secondary generalised seizures; SPS, simple partial seizures; TPM, topiramate; VAL, valproate; V1, volume-of-distribution; ZNS, zonisamide.
RESULTS
There was no difference between patient and control group in terms of age (p=0.70), BMI (p=0.99) or gender mix (p=0.47).

There were no significant differences in the AUCmetabs or the RSSmetabs between the groups (p=0.19 and p=0.47, respectively). Age, BMI and gender also did not significantly influence the AUCmetabs (all p>0.09).

Global changes in VT
Global VT was higher in the focal epilepsy group (median 7.51, range 3.77–8.66) than in controls (median 6.21, range 5.37–7.56), although this did not reach statistical significance (p=0.40). There were two distinct subgroups of patients with higher (n=8) and lower (n=3) than normal global VT. To explore this distribution in patients further, post hoc analysis revealed large and significant differences in global VT between patients with focal epilepsy who were not taking antidepressant drugs (median 7.97, range 6.04–8.66; +28% relative to controls), and those who were taking antidepressant drugs (median 4.40, range 3.77–5.15; −29% relative to controls), and controls (6.21, range 5.37–7.56; all p<0.002; figure 1).

There were no differences (in gender, age, AUCmetabs, RSSmetabs, BMI, number of IEDs in the first 30 min postinjection) to explain the occurrence of high-VT and low-VT patients other than their use of antidepressants.

Frequent IEDs were noted in the EEG of eight patients throughout the first 30 min of scan acquisition. Global VT did not correlate with the frequency of IEDs measured in the first 30 min after radiotracer injection.

In the following analyses, in order to detect focal increases in activated NMDA receptors over and above global increases, the contribution of global VT to variance was removed by an ANCOV A by group.

Focal changes—group comparisons
There were no common areas of relative focal decrease or focal accentuations of the globally increased [18F]GE-179 VT in the patient group compared with controls.

Relative decreases in VT—individual comparisons
A focal decrease in [18F]GE-179 VT was seen in two healthy control participants (control 3 mid-parietal; control 4 frontal pole). A relative focal decrease in [18F]GE-179 VT was seen in two patients (table 2). None of these changes reached significance after correction for multiple comparisons. In one patient (patient 10), the area of relatively decreased VT was concordant with one of the multiple tubers seen on MRI.

Relative increases in VT—individual comparisons
Focal increases in [18F]GE-179 VT were seen in one control participant (control 4), maximal in the left parieto-occipital region. A focal increase above global baseline increase in [18F]GE-179 VT was seen in four patients (table 3 and figure 2). Where known, the largest cluster was localised to the lobe of the presumed epileptogenic zone in one, as was the second largest cluster of a further two patients.

DISCUSSION
Using [18F]GE-179 PET, we identified global increases in NMDA receptor ion binding availability for patients with focal epilepsies who were not taking antidepressants, whereas tracer binding was globally decreased in those patients with epilepsy who were also taking antidepressant drugs. Increases in [18F]GE-179 VT are consistent with an increase in activated/open NMDA receptors in actively discharging cortex as shown in preclinical work. We suggest that increased NMDA activation in patients with chronic focal epilepsy extends beyond the presumed epileptogenic zone and is a global phenomenon, as reflected in the increased global VT.

Our group analyses did not identify any focal redistribution of activated NMDA receptor availability in this group of heterogeneous patients with focal epilepsies arising from different cortical locations; this is perhaps not surprising given the heterogeneity and small sample size. For this pilot study, patients were selected based on the frequency of IEDs on previous EEGs, to maximise our chances of detecting increases in NMDA binding. Concordance of [18F]GE-179 foci with EEG, structural and functional imaging in individual patients is difficult to assess.

Figure 1  [18F]GE-179 VT by subgroup. The top row (A) depicts the mean [18F]GE-179 VT patients with focal epilepsy who were taking an antidepressant drug; the middle row (B) for the controls; and the bottom row (C) for the patients with focal epilepsy who were not taking an antidepressant drug. Images are displayed according to radiological convention (ie, ‘left is right’). L, left; R, right; VT, volume-of-distribution.
given that some of our cohort had normal or EEG-discordant MRI and poorly defined epileptogenic zones: the epileptogenic zone could not be localised using high-resolution MRI, ictal EEG recordings, magnetoencephalography and fluorodeoxyglucose PET (FDG-PET) in four patients, and could only be lateralised to one lobe in four of the remaining seven patients. In contrast, our individual $[^{18}F]$GE-179 PET analysis identified focal clusters of increased NMDA receptor activation in four patients with focal epilepsy, and these were concordant with the location of the presumed epileptogenic zone in two of those three patients, in whom this could be lateralised to one lobe. Patient 1 was one of the best-localised cases in our cohort, having concordant scalp EEG, $[^{18}F]$FDG-PET and ictal single-photom emission CT findings. An intracranial EEG recording over the left temporal lobe revealed a diffuse ictal onset, consistent with spread from a nearby lobe. Consistent with these data, a large cluster of increased $V_T$ was observed in the left frontal lobe for this participant.

Interestingly, a focal increase in $[^{18}F]$GE-179 $V_T$ was seen in the brainstem of the patient with ictal pupillary hippus in addition to left and right temporal lobe increases (patient 4). The patient is now seizure-free after resection of the tuber in the right parieto-occipital region. Our finding suggests the unusual ictal manifestation might result from a broad epileptogenic network that encompassed the brainstem in close proximity to the nuclei of the oculomotor (III) nerve.

The proportion of NMDA receptors that are active in the resting physiological state is unknown, and the power to detect subtle regional changes in channel opening superimposed on global differences in binding, induced by the epileptic brain or reduced by concomitant use of antidepressants, was limited by our small sample size and conservative thresholds. Studies of unequivocally unifocal epilepsies are now needed to determine whether focal increases of $[^{18}F]$GE-179 binding may be apparent at epileptic foci. If these initial findings are replicated, $[^{18}F]$GE-179 PET might find clinical application in the presurgical localisation of epileptogenic foci in patients with refractory focal epilepsy with non-contributory MRI.

Interrictal regional cerebral blood flow (rCBF) studies usually show reduced perfusion in focal epilepsy, and significant increases in rCBF scans were only seen with prolonged discharges of 8–105 seconds after electrostimulation. Our findings are unlikely to reflect changes in cerebral blood flow (rCBF) or altered $[^{18}F]$GE-179 availability as decreased perfusion in the epileptogenic zone would likely result in decreased $[^{18}F]$GE-179 availability and thus $V_T$. While NMDA receptor ion channel opening and the excitatory postsynaptic current are extremely rapid events, grey matter uptake and the metabolism of $[^{18}F]$GE-179 occurs over minutes. Hence, we interpret the $V_T$ data as indicative of the integrated extent of NMDA receptor activation during the tracer uptake phase (first 30 min) of the scan.

The lack of focal increases in $V_T$ for 7 of the 11 patients with focal epilepsy did not appear to relate to the frequency of scalp-detected IEDs. Global $[^{18}F]$GE-179 $V_T$ was not significantly correlated with the number of IEDs in the first 30 min following injection. The true extent of epileptic activity will not be detectable on scalp EEG, which may explain the lack of correlation between focal spike activity and global $[^{18}F]$GE-179 uptake. Moreover, it would be oversimplistic to assume a linear relation between global $[^{18}F]$GE-179 $V_T$ and IED frequency. We expect that NMDA receptors involved in generation of the IED would rapidly internalise or desensitise following their activation. Individual short IEDs would be very difficult to visualise over a 90 min PET scan with $[^{18}F]$GE-179. We assume any observed increase of $[^{18}F]$GE-179 binding to be related to underlying generalised baseline overactivity, rather than to transient NMDA channel opening over a few milliseconds. In the only other in vivo PET study of NMDA ion channel activity in epilepsy, Kumlien did not detect focal increases in receptor availability using (S)-[N-methyl-$^{11}$C]ketamine.

### Table 2: Focal decreases in $[^{18}F]$GE-179 $V_T$—individual patients versus 10 controls

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Probable localisation (EEG)</th>
<th>MRI</th>
<th>$[^{18}F]$GE-179 $V_T$ decreases</th>
<th>Cluster size (mm$^3$/voxels)</th>
<th>Peak voxel coordinates (x, y, z; mm)</th>
<th>$Z_{max}$</th>
<th>Cluster level p (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Multifocal</td>
<td>Multiple tubers</td>
<td>R parietal</td>
<td>4864/608</td>
<td>62–32 38</td>
<td>3.62</td>
<td>0.002</td>
</tr>
<tr>
<td>7</td>
<td>R frontal</td>
<td>Negative</td>
<td>L temporal</td>
<td>3968/496</td>
<td>−58–20–22</td>
<td>4.32</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R frontal</td>
<td>1704/213</td>
<td>10 20–20</td>
<td>3.89</td>
<td>0.040</td>
</tr>
</tbody>
</table>

The cluster(s) reaching significance at p<0.05 uncorrected are listed. The contribution of global $V_T$ to variance was removed by an ANCOVA by group. ANCOVA, analysis of covariance; EEG, electroencephalography; ID, identifying number; L/R, left/right; mm, millimeters; MRI, magnetic resonance imaging; $V_T$, volume-of-distribution.

### Table 3: Focal increases in $[^{18}F]$GE-179 $V_T$—individual patients versus 10 controls

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Probable localisation (EEG)</th>
<th>MRI</th>
<th>$[^{18}F]$GE-179 $V_T$ increases</th>
<th>Cluster size (mm$^3$/voxels)</th>
<th>Peak voxel coordinates (x, y, z; mm)</th>
<th>$Z_{max}$</th>
<th>Cluster level p (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L frontotemporal</td>
<td>R IFG lesion</td>
<td>L frontal</td>
<td>7000/875</td>
<td>−322 234</td>
<td>4.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>Multifocal</td>
<td>Multiple tubers</td>
<td>Brainstem</td>
<td>5152/644</td>
<td>06–28–38</td>
<td>4.58</td>
<td>0.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>L temporal</td>
<td>3264/408</td>
<td>−32 04–36</td>
<td>4.09</td>
<td>0.007</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>R temporal</td>
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<td>18 04–30</td>
<td>3.97</td>
<td>0.039</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral temporal L&gt;R</td>
<td>Negative</td>
<td>R frontal</td>
<td>3360/420</td>
<td>381 024</td>
<td>4.43</td>
<td>0.006</td>
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<td>7</td>
<td>R frontal</td>
<td>Negative</td>
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<td>0.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>R frontal</td>
<td>4512/564</td>
<td>061 840</td>
<td>4.23</td>
<td>0.002</td>
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</table>

The cluster(s) reaching significance at p<0.05 uncorrected are listed. The contribution of global $V_T$ to variance was removed by an ANCOVA by group. Underline indicates concordance between the cluster of increase and the location of the presumed epileptogenic zone, where known. ANCOVA, analysis of covariance; EEG, electroencephalography; ID, identifying number; IFG, inferior frontal gyrus; L/R, left/right; mm, millimeters; MRI, magnetic resonance imaging; $V_T$, volume-of-distribution.
Interestingly, each participant in that temporal lobe epilepsy (TLE) cohort showed temporal hypometabolism on [18F]FDG-PET, so the results could have been significantly confounded by cerebral hypoperfusion. Four of our patients had normal [18F]FDG-PET, one of whom had a focal increase in [18F]GE-179 VT. The absence of hypometabolism may have facilitated visualisation of activated NMDA receptors in our cohort. Alternatively, our cohort might have had more actively spiking cortex, and thus possibly greater NMDA receptor activation.

A striking and unanticipated finding of our study was reduced VT in the small number of patients with focal epilepsies who were taking antidepressants, suggesting that either depression or the use of antidepressant drug constituted an additional confounder. Our finding is in keeping with the mounting evidence for the action of antidepressant drugs at NMDA receptors including tricyclics, and serotonin-selective reuptake inhibitors, such as fluoxetine, the two classes used by patients in this study. While our finding may represent the first in vivo evidence of an NMDA-mediated mechanism of action of antidepressants (the extent of which is likely to vary between drugs), caution is warranted as, given the sample size, the result could be due to random chance. Hence, in order to better understand [18F]GE-179 binding, a larger study is required, which would compare [18F]GE-179 binding between unmedicated patients with depression and those taking antidepressants. It will also be of interest to ascertain whether AEDs that are characterised by use-dependent inhibition of NMDA receptor function (such as felbamate) or certain combinations of AEDs, affect NMDA receptor binding.

A recent multicentre review concluded that administration of the NMDA receptor antagonist ketamine ‘likely’ or ‘possibly’ contributed to the achievement of control in 32% of (19 of 60) episodes, whereas treatment was discontinued due to adverse events in approximately 8%. Smaller series have reported greater success. Similarly to [18F]GE-179, ketamine binds to the PCP site in the NMDA ion channel pore. Hence, the demonstration of increased NMDA receptor activation via [18F]GE-179 PET might aid the stratification of patients with refractory status epilepticus.

Limitations of this proof-of-principle study include the small and heterogeneous population. While [18F]GE-179 has a low affinity for other CNS receptors in vitro, we cannot exclude the possibility that non-specific binding confounded the analyses. Further studies are needed to confirm our findings, and to quantify reproducibility and specificity of [18F]GE-179 binding in vivo.

In conclusion, our results provide in vivo evidence for widespread increases in activated NMDA receptor availability in patients with focal epilepsies. A PET radioligand that reliably demonstrates focal increases in NMDA receptor activity in humans in vivo would hold potential as a method to investigate epileptogenesis in vivo after brain injury, to investigate the role of activated NMDA receptor availability in other conditions, and possibly in the presurgical investigation of patients with refractory focal epilepsy.

Author affiliations
1Division of Neuroscience, Department of Medicine, Imperial College London, London, UK
2Medical Research Council Clinical Sciences Centre, London, UK
3Division of Imaging Sciences & Biomedical Engineering, Faculty of Life Sciences & Medicine, King’s College London, London, UK
4Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK
5MRI Unit, Epilepsy Society, Chalfont St. Peter, UK
6The Neurolab Foundation, CERM, Imagerie du Vivant, Lyon, France
7Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children NHS Trust, London, UK
8GE Healthcare plc, The Grove Centre, Amersham, UK
9National Hospital for Neurology and Neurosurgery, London, UK
10Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

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Data sharing statement

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