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Chapter 10

Imaging herpes virus activity in the central nervous system of schizophrenic patients

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Abstract

Schizophrenia is a chronic, disabling brain disease with unknown etiology. Herpes viruses have been implicated in the etiology of schizophrenia and antibodies against herpes viruses were found to be associated with schizophrenia. In the present study, positron emission tomography (PET) with $[^{18}F]$-FHBG, a tracer for the viral thymidine kinase, was used to study the presence of active herpes viruses in the brain of schizophrenic patients during psychosis.

Eight schizophrenic patients were included for $[^{18}F]$-FHBG PET. Patients were assigned to a mildly or severely affected group, based on psychosis and memory as measured with the positive and negative syndrome scale and 15-word test, respectively.

The metabolic rate of $[^{18}F]$-FHBG in the temporal lobe of the severely affected group was 50% higher ($p<0.05$) than in the mildly affected group. No differences were found in any other brain region. No increased influx of $[^{18}F]$-FHBG was found, indicating that the higher metabolic rate is due to an increased phosphorylation of $[^{18}F]$-FHBG by the viral thymidine kinase.

The increased metabolic rate of $[^{18}F]$-FHBG in the temporal lobe of schizophrenic patients experiencing severe psychosis, suggests the focal presence of active herpes viruses. Additional studies are needed to confirm viral presence and to specify which of the herpes viruses are present in the schizophrenic brain.
Introduction

Schizophrenia is a chronic, disabling brain disease with unknown etiology. It has been suggested that herpes viruses play a role in schizophrenia [1-4]. An important characteristic of these viruses is that they establish latency in the central nervous system after primary infection. Both primary infection and reactivation of herpes viruses may sporadically result in herpes encephalitis, mostly caused by the herpes simplex virus type-1 (HSV-1) [5].

Post-mortem studies found the presence of herpes viruses in the brain, but there was no difference in herpes virus levels between schizophrenic patients and healthy volunteers [6,7]. However, these studies do not give any insight in whether the viruses were latent or actively replicating. Interestingly, herpes encephalitis patients may initially present with symptoms that resemble psychosis associated with schizophrenia [8,9]. It is possible that psychosis in schizophrenia represents a mild form of herpes encephalitis only caused by herpes viruses in an active state. We aimed to explore the hypothesis that active herpes viruses are present in the brain of schizophrenic patients during a psychotic and impaired cognitive state.

Imaging techniques like positron emission tomography (PET) provide the opportunity to study functional processes in patients. The PET tracer 9-(4-[18]F-fluoro-3-hydroxymethylbutyl)guanine ([18]F-FHBG) is a radiolabelled analog of the antiviral pro-drug penciclovir. After entering the cell, [18]F-FHBG can phosphorylated by a viral thymidine kinase (or a viral analogue), which results in trapping of [18]F-FHBG inside the cell (figure 1). Viral thymidine kinase is only expressed in active, replicating viruses, thus only in infected cells trapping of [18]F-FHBG can occur. Human thymidine kinase has high substrate specificity and does not phosphorylate the antiviral drug. [18]F-FHBG can be phosphorylated by HSV-1, HSV-2, Varicella-Zoster virus (VZV) [10], Epstein-Barr virus (EBV) [11], cytomegalovirus (CMV) [12] and possibly human herpes virus-6 (HHV-6). [18]F-FHBG was already evaluated as a PET tracer for imaging of viral thymidine kinase in transduced tumor cells [13] and for imaging of herpes simplex encephalitis in rats [14]. [18]F-FHBG was found to be a suitable PET tracer to image HSV thymidine kinase, but it has not been used to study replicating viruses in the CNS of schizophrenic patients. In the present study, it was determined if active herpes viruses could be detected with [18]F-FHBG PET in the brain of schizophrenic patients during a psychotic episode.
Methods

Chemicals
All chemicals were purchased from commercial suppliers and used without further purification.

[¹⁸F]-FHBG
A solution of 1 mg N²-(p-anisyldiphenylmethyl)-9-[(4-tosyl)-3-p-anisyldiphenylmethoxy-methylbutyl]guanine (ABX, Germany) in 0.5 ml of dry acetonitrile was added to dry [¹⁸F]KF/kryptofix 2.2.2 complex (5 mg K₂CO₃; 15 mg kryptofix) and heated for 30 min at 110°C. Then, 0.4 ml 1M HCl was added and the mixture was heated for 5 min at 90°C in an open vial to allow evaporation of acetonitrile. After cooling, the reaction mixture was neutralized with 1.5 ml 0.1M sodium phosphate buffer (pH 7.2). The reaction mixture was passed through a Waters alumina N seppak to remove unreacted fluoride. The product was purified by HPLC over a Hamilton PRP-1 column (250x10 mm, 10 µm) (Alltech, The Netherlands) with 7% of ethanol in water as the eluent at a flow rate of 5 ml/min. The HPLC fraction with the same retention time as an authentic reference sample was collected and sterilized over a Cathivex GS filter. A sample of the product was used for quality control prior to injection. The (radio)chemical purity and specific activity were determined by reversed phase HPLC (Nova-pak C18, 150x3.9 mm, 4 µm, 5% EtOH, 1 ml/min). The presence of unreacted [¹⁸F]fluoride was determined by TLC (silica, dichloromethane/methanol:7/3). [¹⁸F]-FHBG was obtained in 5-10% yield with a specific activity of 22-84 GBq/µmol. The radiochemical purity was always higher than 95%. Unknown impurities were <1 mg/l, kryptofix <10 mg/l and [¹⁸F]fluoride <5%.

Patients
Eight patients were recruited from psychiatric services based on the following inclusion criteria: 1) fulfilling DSM-IV criteria for schizophrenia (295.xx); 2) active psychosis (i.e. a minimum score of four on two items of the positive PANSS (positive and negative syndrome scale) [15] or a five or higher on one item; 3) age above eighteen; 4) ability to provide written informed consent. Exclusion criteria were 1) concomitant severe medical conditions; 2) substance abuse; 3) pregnancy and 4) use of anti-viral drugs. Patients were a-priori divided in severely and mildly affected groups.
Imaging herpes virus activity in schizophrenia

based on severity of psychosis and memory disorder. An increased risk for the presence of active herpes viruses was expected in patients with the most severe psychosis and memory disturbances, i.e. severely affected patients. The severely affected group consisted of patients with a score on the positive item of the PANSS higher than $1/3$ of the total score of 49, or of patients that scored below $1/2$ of the total score on the 15-word test (i.e. half of the total score of 120 on immediate recall, delayed recall and recognition). Because a memory disorder can be secondary to disturbances in attention, patients also underwent a continuous performance test (CPT) to test their sustained attention. The PANSS, 15-word test and CPT were taken by trained psychiatric nurses. Antibodies against the herpes viruses that phosphorylate $[^{18}\text{F}]-\text{FHBG}$ were determined using enzyme immunoassay.

A-priori division of patients into severely and mildly affected groups was preferred over inclusion of healthy volunteers, because no brain uptake of $[^{18}\text{F}]-\text{FHBG}$ was found in healthy volunteers [16].

The study was approved by the medical ethical committee of the University Medical Center Groningen. All patients provided written informed consent after detailed description of the study.

15-word test

Patients listened to a total of 15 words that were read aloud by the investigator, after which the patient was asked to repeat as many words as possible (immediate recall, representing short-term memory). This was repeated four times. After 15-30 minutes the patients were asked to repeat all the words that he/she still remembered, without hearing the words again (delayed recall, representing long-term memory). The test was ended by the investigator reading aloud a list of 30 words of which half of the words were from the list in the 15-word test. For each of the 30 words the patient had to indicate if the word was either present or not present in the list of the 15-word test (word recognition).

Continuous performance test

The test randomly presented numbers between 0 and 9 at the centre of the monitor at a constant rate of 1000 ms, with the number visible for 100 ms. The patients had to respond to the target number (7), by pressing a button, when it was preceded by the cue number (3). A total of 600 numbers with 90 targets were presented over 11
minutes. Outcome measurements were the reaction time and the sensitivity index \( (d') \), which measures the ability of the patients to discriminate the target stimuli from the non-target stimuli.

**PET protocol**

A catheter was inserted in the radial artery after testing for collateral circulation and injection of 1% lidocaine for local anesthesia. In the other arm, a catheter was inserted in the antebrachial vein. PET was performed with the ECAT EXACT HR+ camera (Siemens, Tennessee). Head movement was minimized with a head-restraining adhesive band and a neuroshield was used to attenuate radiation from the subject’s body. A 60-min emission scan in 3D-mode was performed, starting simultaneously with the intravenously injection of \([^{18}F]-FHBG\) (411±17 MBq) at a speed of 0.5 ml/sec (total volume of 8.3 ml).

After injection, arterial blood radioactivity was continuously monitored with an automated sampling system (Veenstra Instruments, The Netherlands). An amount of 5 extra blood samples were collected at 10, 20, 30, 45 and 60 min after \([^{18}F]-FHBG\) injection to determine the amount of radioactivity in blood and plasma. In the arterial blood samples that were collected at 20 and 60 min after \([^{18}F]-FHBG\) injection, the fraction of intact tracer in plasma was also determined. Therefore, these blood samples were centrifuged at 3000 g for 3 min. Then 40 μl of 70% perchloric acid was added to 1.5 ml plasma. The plasma was mixed for 30 s and centrifuged at 3000 g for 5 min. After filtration over a Millex HV 45μm filter, a volume of 1 ml of the supernatant was injected into a HPLC system, consisting of a Waters 590 HPLC-pump (Waters Corporation, USA) and μBondapak C18 column (300x7.8 mm, 5 μm) (Alltech, The Netherlands). The mobile phase consisted of a mixture of 8% of acetonitrile in water. The flow-rate was set at 3.0 ml/min and samples were collected at time intervals of 30 s. The collected samples were counted for radioactivity using a gamma-counter (LKB Wallac, Finland).

**PET data-analysis**

Attenuation correction was performed with the separate ellipse algorithm. Images were reconstructed by filtered back projection in 21 successive frames of increasing duration (6x 10 sec, 2x 30 sec, 3x 1 min, 2x 2min, 2x 3 min, 3x 5min, 3x 10 min). Time-activity curves of the frontal, occipital, temporal and parietal lobe, thalamus, basal ganglia and cerebellum were created using manually drawn regions of interest.
and used for kinetic modelling with software developed in Matlab 7.1 (Mathworks, Massachusetts). Patlak analysis [17] was used to calculate the metabolic rate ($K_i$, i.e. the amount of phosphorylated tracer in relation to the amount of tracer that has been available in plasma, defined as $(K_1 k_3)/(k_2 + k_3)$), using a fixed blood volume of 3% (figure 1). The influx of $[^{18}F]$-FHBG into the brain was determined using two-compartment modeling with a fixed blood volume of 3% and an individual delay.

**Figure 1** Two-tissue compartment model to describe the kinetics of FHBG. Influx of FHBG from plasma to brain tissue is described by $K_1$ and the efflux of from brain tissue to plasma is described by $k_2$. In brain tissue, FHBG can be phosphorylated into FHBG-phosphate (FHBG-P) in cells expressing viral thymidine kinase, resulting in trapping of FHBG-P in these cells ($k_3$).

**Statistical analysis**

Statistical analysis was performed with SPSS 16.0. Correlations between the score on the PANSS, 15-word test and CPT, were assessed with Pearson’s product moment correlation coefficient ($r$). To determine the differences between the averages of the metabolic rate in severely and mildly affected groups, one-way ANOVA was used. Correlations and differences were considered to be significant when $p<0.05$.

**Results**

**Patient characteristics**

A total number of 8 psychotic patients (5 male and 3 female) were included (table 1). All patients were diagnosed as having schizophrenia (DSM-IV: 295.xx). The age of the patients was $42 \pm 13$ (n=8) (mean ± standard deviation), with the onset of
schizophrenia at an average age of 22±5 \( (n=8) \). All patients were recruited during psychosis and were using benzodiazepines and/or anti-psychotics in the period of the \[^{18}\text{F}]\)-FHBG scan. One patient (patient number 8) was diagnosed as having herpes encephalitis at the age of 13. At the age of 30, this patient experienced the first appearance of paranoid psychosis.

The presence of antibodies against the herpes viruses that phosphorylate \[^{18}\text{F}]\)-FHBG are displayed in table 1. All patients had antibodies against one or more herpes viruses.

<table>
<thead>
<tr>
<th>Pat#</th>
<th>Sex</th>
<th>Age</th>
<th>Onset</th>
<th>Total</th>
<th>Medication</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>44</td>
<td>22</td>
<td>6</td>
<td>Oxazepam</td>
<td>VZV, HHV-6</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>37</td>
<td>19</td>
<td>5</td>
<td>Risperidone, Diazepam, Venlafaxine</td>
<td>VZV, HHV-6</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>42</td>
<td>1</td>
<td>Risperidone, Diazepam</td>
<td>HSV-1, EBV, HHV-6</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>61</td>
<td>22</td>
<td>10</td>
<td>Zuclopetixol, Oxazepam, Lormetazepam, Esomeprazol, Amitriptyline, Temazepam</td>
<td>HSV-1, VZV, EBV, HHV-6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>30</td>
<td>13</td>
<td>1</td>
<td>Risperidone, Oxazepam, Temazepam</td>
<td>HHV-6</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>58</td>
<td>54</td>
<td>2</td>
<td>-</td>
<td>HSV-1, VZV, HHV-6</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>28</td>
<td>27</td>
<td>1</td>
<td>Olanzapine, Oxazepam, Temazepam</td>
<td>HSV-1, HSV-2, VZV, EBV, HHV-6</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>30</td>
<td>27</td>
<td>1</td>
<td>Olanzapine, Valproic acid, Lamotrigine</td>
<td>HSV-1, HHV-6</td>
</tr>
</tbody>
</table>

M, male; F, female; VZV, Varicella-Zoster virus; HHV-6, human herpes virus 6; HSV-1, herpes simplex virus type-1; EBV, Epstein-Barr virus; HSV-2, herpes simplex virus type-2

The average score on the positive scale of the PANSS was 18±4 \( (n=8) \) (table 2), 22±6 \( (n=8) \) on the negative scale and 43±8 \( (n=8) \) on the global scale. The patients with a score on the positive item of the PANSS higher than \( \frac{1}{3} \) of the total score of 49, i.e. 16.3, where assigned to the severely affected group. The severely affected group regarding psychosis included patient number 2, 4, 6 and 8. The average score on the immediate recall in the 15-word test was 27±10 \( (n=8) \), on the delayed recall 3.8±2.8 \( (n=8) \) and on the recognition 27±3 \( (n=8) \). No correlations were found between immediate and delayed recall, and the scores on both items did not correlate to either of the items on the PANSS \( (p>0.1) \). The score on recognition showed a significantly negative correlation to the score on the positive scale of the PANSS \( (r=0.87; p=0.005) \), but not to the negative \( (r=0.20; p=0.628) \) and the global scale of the
PANSS (r=0.30; p=0.478). No correlation was found between the immediate recall, delayed recall and recognition in the 15-word test and the d’ on the CPT (p>0.1), suggesting that the memory disturbances are not secondary to attention deficits. Patients that had a score lower than $1/2$ of the total score on the 15-word test, which is a score of 60, were assigned to the severely affected group for memory disorder (i.e. patient 2, 4, 6 and 8). These were the same patients as the patients assigned to the severely affected group of psychosis.

**Table 2** Patient scores on the PANSS, the 15-word test and the continuous performance test

<table>
<thead>
<tr>
<th>Pat#</th>
<th>Pos</th>
<th>Neg</th>
<th>Global</th>
<th>Imm. recall</th>
<th>Del. recall</th>
<th>Recognition</th>
<th>Total score</th>
<th>RT (ms)</th>
<th>d'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>25</td>
<td>33</td>
<td>34</td>
<td>2</td>
<td>30</td>
<td>66</td>
<td>636</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>28</td>
<td>42</td>
<td>23</td>
<td>2</td>
<td>22</td>
<td>47</td>
<td>648</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>24</td>
<td>51</td>
<td>27</td>
<td>6</td>
<td>29</td>
<td>62</td>
<td>744</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>30</td>
<td>53</td>
<td>12</td>
<td>2</td>
<td>28</td>
<td>42</td>
<td>377</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>11</td>
<td>41</td>
<td>43</td>
<td>8</td>
<td>30</td>
<td>81</td>
<td>692</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>23</td>
<td>52</td>
<td>15</td>
<td>2</td>
<td>22</td>
<td>39</td>
<td>833</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>19</td>
<td>32</td>
<td>27</td>
<td>7</td>
<td>29</td>
<td>63</td>
<td>639</td>
<td>2.7</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>15</td>
<td>39</td>
<td>33</td>
<td>1</td>
<td>24</td>
<td>58</td>
<td>622</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Pos, positive; Neg, negative; 15 WT, 15-word test; Imm., immediate; Del., delayed; CPT, continuous performance test; RT, reaction time

**[18F]-FHBG PET**

The [18F]-FHBG images showed low brain uptake (figure 2). No radioactive metabolites were found in plasma at 20 and 60 minutes after the injection of [18F]-FHBG (data not shown). Two-tissue compartment modeling revealed a low influx of [18F]-FHBG into brain tissue ($K_1 = 0.022\pm0.018$) (n=8). No differences in the influx were found between the severely and mildly affected group (p>0.200). A significantly higher metabolic rate was found in the temporal lobe of the severely affected group when compared to the mildly affected group ($3.9\times10^4\pm1.0\times10^4$ vs. $5.9\times10^4\pm1.1\times10^4$, p=0.035) (table 3). The increased metabolic rate of [18F]-FHBG could not be attributed to a single herpes virus.

In the patient that had herpes encephalitis at the age of 13 (patient 8), no significant deviation in influx or metabolic rate of [18F]-FHBG was found in any of the examined brain areas, when compared to the severely and mildly affected groups.
Figure 2 Sagittal view of the $[^{18}\text{F}]-\text{FHBG}$ PET images. A Summation of the first 2 min of the PET scan. B Summation of the last 55 min of the PET scan.

Table 3 Metabolic rate, as determined by Patlak analysis. Averages ± standard deviation of patients groups based on the severity of psychosis and memory disorder.

<table>
<thead>
<tr>
<th></th>
<th>Mildly affected (n=4)</th>
<th>Severely affected (n=4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>6.9E-04 ± 2.3E-04</td>
<td>6.6E-04 ± 3.4E-04</td>
<td>n.s.</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>4.9E-04 ± 1.2E-04</td>
<td>3.6E-04 ± 1.7E-04</td>
<td>n.s.</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>3.7E-04 ± 1.7E-04</td>
<td>5.4E-04 ± 6.0E-05</td>
<td>n.s.</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>3.8E-04 ± 1.0E-04</td>
<td>5.9E-04 ± 1.1E-04</td>
<td>0.035</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.7E-04 ± 1.8E-04</td>
<td>3.8E-04 ± 1.4E-04</td>
<td>n.s.</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>4.2E-04 ± 1.9E-04</td>
<td>4.7E-04 ± 1.1E-04</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>5.2E-04 ± 2.9E-04</td>
<td>3.0E-04 ± 1.7E-04</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s., non-significant

Discussion

In the present study, a significantly higher metabolic rate of $[^{18}\text{F}]-\text{FHBG}$ was found in the temporal lobe of severely affected patients, based on severity of psychosis and memory deficit. Herpes viruses that are hypothesized to play a role in the etiology of schizophrenia have thus far only been found in post-mortem brains, in undefined
latent or active state. This $[^{18}F]$-FHBG PET study provided the first evidence of the presence of active herpes viruses in living schizophrenic patients.

The increased metabolic rate of $[^{18}F]$-FHBG in the temporal lobe suggests the presence of active herpes viruses. However, the metabolic rate is a function of the influx of $[^{18}F]$-FHBG ($K_1$), the efflux ($k_2$) and the phosphorylation ($k_3$) ($[K_1*k_3]/[k_2+k_3]$) and consequently an increased metabolic rate could also be caused by an increased $[^{18}F]$-FHBG influx. Since no differences were found in the influx, the increased metabolic rate is due to increased phosphorylation the thymidine kinase of active herpes viruses.

The finding of an increased metabolic rate of $[^{18}F]$-FHBG in the temporal lobe is consistent with the involvement of this brain area in schizophrenia. The temporal lobe is involved in, amongst others, memory and the processing of both auditory and visual information, which is disturbed in schizophrenia, especially during psychosis [18]. The severely affected group in the present study showed a high score on the positive item of the PANSS and memory disturbances, consistent with the involvement of the temporal lobe in psychosis in schizophrenia. In addition, HSV-1, VZV and EBV infection of the brain was found to mainly involve the temporal lobe [19,20]. Interestingly, we recently found evidence for an increased activation of microglia cells, indicative of neuroinflammation, in the hippocampus of schizophrenic patients during psychosis [21]. Since the hippocampus is part of the temporal lobe, the presence of active herpes viruses in the temporal lobe can be responsible for the observed neuroinflammation.

The activity of herpes viruses in the temporal lobe may cause psychosis and memory disturbances in the severely affected patients. However, it is important to keep in mind that the viral hypothesis of schizophrenia may only account for a subgroup of the patients and that the presence of active virus alone may not be sufficient for the development of schizophrenia.

**Conclusion**

The increased metabolic rate of $[^{18}F]$-FHBG in the temporal lobe of schizophrenic patients experiencing severe psychosis, suggests the presence of active herpes viruses and supports the viral hypothesis of schizophrenia. Additional studies are needed to confirm the presence of the active herpes viruses and to specify which herpes virus is present in the schizophrenic brain.
Acknowledgement

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Reference List

1 Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. Arch.Gen.Psychiatry 2003; 60:466-472


3 Prasad KM, Shirts BH, Yolken RH, Keshavan MS, Nimgaonkar VL. Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. Mol.Psychiatry 2007; 12:105-113

4 Shirts BH, Prasad KM, Pogue-Geile MF, Dickerson F, Yolken R, Nimgaonkar VL. Antibodies to cytomegalovirus and Herpes Simplex Virus 1 associated with cognitive function in schizophrenia. Schizophr.Res. 2008; 106:268-274


14 Doorduin J, Klein HC, Dierckx RA, de Vries EF. Herpes simplex encephalitis in rats: a positron emission tomography study with [18F]-FHBG, [11C]-(R)-PK11195 and [18F]-FDG. Neuroimage. 2008; 41:T110-