Non-invasive assessment of Alzheimer’s disease neurofibrillary pathology using \(^{18}\)F-THK5105 PET

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Non-invasive imaging of tau pathology in the living brain would be useful for accurately diagnosing Alzheimer’s disease, tracking disease progression, and evaluating the treatment efficacy of disease-specific therapeutics. In this study, we evaluated the clinical usefulness of a novel tau-imaging positron emission tomography tracer \(^{18}\)F-THK5105 in 16 human subjects including eight patients with Alzheimer’s disease (three male and five females, 66–82 years) and eight healthy elderly controls (three male and five females, 63–76 years). All participants underwent neuropsychological examination and 3D magnetic resonance imaging, as well as both \(^{18}\)F-THK5105 and \(^{11}\)C-Pittsburgh compound B positron emission tomography scans. Standard uptake value ratios at 90–100 min and 40–70 min post-injection were calculated for \(^{18}\)F-THK5105 and \(^{11}\)C-Pittsburgh compound B, respectively, using the cerebellar cortex as the reference region. As a result, significantly higher \(^{18}\)F-THK5105 retention was observed in the temporal, parietal, posterior cingulate, frontal and mesial temporal cortices of patients with Alzheimer’s disease compared with healthy control subjects. In patients with Alzheimer’s disease, the inferior temporal cortex, which is an area known to contain high densities of neurofibrillary tangles in the Alzheimer’s disease brain, showed prominent \(^{18}\)F-THK5105 retention. Compared with high frequency (100%) of \(^{18}\)F-THK5105 retention in the temporal cortex of patients with Alzheimer’s disease, frontal \(^{18}\)F-THK5105 retention was less frequent (37.5%) and was only observed in cases with moderate-to-severe Alzheimer’s disease. In contrast, \(^{11}\)C-Pittsburgh compound B retention was highest in the posterior cingulate cortex, followed by the ventrolateral prefrontal, anterior cingulate, and superior temporal cortices, and did not correlate with \(^{18}\)F-THK5105 retention in the neocortex. In healthy control subjects, \(^{18}\)F-THK5105 retention was ~10% higher in the mesial temporal cortex than in the neocortex. Notably, unlike \(^{11}\)C-Pittsburgh compound B, \(^{18}\)F-THK5105 retention was significantly correlated with cognitive parameters, hippocampal and whole brain grey matter volumes, which was consistent with findings from previous post-mortem studies showing significant correlations of neurofibrillary tangle density with dementia severity or neuronal loss. From these results, \(^{18}\)F-THK5105 positron emission tomography is considered to be useful for the non-invasive assessment of tau pathology in the living brain. This technique would be applicable to the longitudinal evaluation of tau deposition and allow a better understanding of the pathophysiology of Alzheimer’s disease.
**Introduction**

Senile plaques and neurofibrillary tangles are considered the major pathological hallmarks of Alzheimer’s disease (Braak and Braak, 1991). Senile plaques consist of extracellular aggregates of amyloid-β peptide cleaved from a longer amyloid precursor protein (Masters et al., 2006). The neocortical deposition of senile plaques is considered one of the earliest pathological alterations in Alzheimer’s disease and is observed even in the presymptomatic stages (Mintun et al., 2006; Rowe et al., 2007; Price et al., 2009). Recently proposed research diagnostic criteria for preclinical Alzheimer’s disease include cognitively intact elderly with abnormal amyloid-β deposition in the brain (Sperling et al., 2011). Preclinical Alzheimer’s disease is associated with future cognitive decline and mortality (Vos et al., 2013); however, several neuro-pathological studies have shown no significant association between density of amyloid-β plaques and the severity of dementia or neuronal loss (Arriagada et al., 1992; Bierer et al., 1995; Gomez-Isla et al., 1997), suggesting the involvement of other key factors in Alzheimer’s disease-related neurodegeneration.

Neurofibrillary tangles are comprised of paired helical filaments that result from the abnormal aggregation of tau protein (Grundke-Iqbal et al., 1986a, b; Lee et al., 1991). Initial neurofibrillary tangle lesions occur in the trans-entorhinal cortex, followed by entorhinal cortex and hippocampus involvement, progressing to temporal neocortex and finally to the other neocortical areas (Arnold et al., 1991; Braak and Braak, 1991). In contrast with senile plaques, neurofibrillary tangle formation correlates well with cognitive impairment severity (Arriagada et al., 1992; Berg et al., 1993; Bierer et al., 1995), an association that is considered to continue throughout the disease course (Abner et al., 2011). Furthermore, the inhibition of abnormal tau hyperphosphorylation and its aggregation appear to be promising therapeutic strategies in Alzheimer’s disease. Thus, non-invasive imaging of tau pathology would be useful to assist in the early and differential diagnosis of dementia, track the progression of disease-related pathology, and monitor the efficacy of anti-tau treatments.

18F-FDDNP has been reported to detect neurofibrillary tangle deposition (Shoghi-Jadid et al., 2002) and successfully differentiate subjects with Alzheimer’s disease and mild cognitive impairment from those with no cognitive impairment (Small et al., 2006). However, this tracer detects the combined signals of senile plaques and neurofibrillary tangles (Shoghi-Jadid et al., 2002). Several radiotracers have been developed for the selective visualization of neurofibrillary tangles in the living brain (Chien et al., 2013, 2014; Maruyama et al., 2013). Early clinical PET studies successfully differentiated patients with Alzheimer’s disease from cognitively normal elderly. However, the selective binding ability of these radiotracers to tau has not been fully validated in vivo.

For the development of a selective tau radiotracer, we screened β-sheet-binding small molecules and identified novel quinoline derivatives with high binding selectivity to tau deposits in Alzheimer’s disease brain samples (Okamura et al., 2005; Fodero-Tavoletti et al., 2011; Harada et al., 2013). Through a compound optimization process, we developed a novel 18F-labelled 2-arylquinoline derivative, 18F-THK5105 (Fig. 1), which showed high binding affinity and selectivity to tau protein deposits in Alzheimer’s disease brain sections (Okamura et al., 2013). This 18F-labelled radiotracer also exhibited high blood–brain barrier permeability and no defluorination in mice (Okamura et al., 2013). The present clinical study evaluated whether 18F-THK5105 PET could selectively bind to tau pathology in living patients with Alzheimer’s disease.

**Materials and methods**

**Participants**

Sixteen subjects, including eight patients with probable Alzheimer’s disease (three male and five females, age range 66–82 years) and eight age-matched healthy control subjects (three male and five females, age range 63–76 years), underwent both 18F-THK5105 and 11C-labelled Pittsburgh compound B (11C-PiB) PET scans (Table 1). Written informed consent was obtained from all participants. Study approval was obtained from the Austin Health Human Research Ethics Committee. Elderly healthy controls were recruited by advertisement in the community, and patients with Alzheimer’s disease were recruited from tertiary Memory Disorders Clinics or physicians who sub-specialize in dementia care. All participants were reviewed and classified on the basis of their clinical and neuropsychological performance by the consensus of a neurologist and a neuropsychologist who were blind to their PET results. The diagnosis of Alzheimer’s disease was made according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

**Neuropsychological evaluation**

Cognitive impairment and dementia severity were evaluated with the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) and the CDR scale sum of boxes (CDR-SOB). In addition, composite episodic memory and non-memory scores were generated as previously described (Villemagne et al., 2011). Briefly, a composite episodic memory score was calculated by taking the average of the z-scores for the Rey Complex Figure Test, the long delay California Verbal Learning Test, Second Edition, and the Logical Memory II subscale of the Wechsler Memory Scale. A composite non-memory score was calculated by taking the average of the z-scores for the Boston Naming Test, letter fluency, category fluency, digit span forwards and backwards, digit symbol-coding, and Rey Complex Figure Test copy.

**Keywords:** Alzheimer’s disease; Alzheimer’s disease pathology; amyloid; positron emission tomography; PET

**Abbreviations:** CDR = clinical dementia rating; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SOB = sum of boxes; SUV = standardized uptake value; SUVR = ratio of regional SUV to cerebellar cortex SUV ratio
**Image acquisition**

MRI scanning was performed on a 3 T Siemens TRIO magnetic resonance system (Siemens Healthcare) using the ADNI 3D MPRAGE sequence with 1 × 1 mm in-plane resolution and 1.2 mm slice thickness, repetition time/echo time/inversion time = 2300/2.98/900, flip angle 9°, field of view 240 × 256, and 160 slices. T2 fast spin echo and FLAIR sequences were also obtained.

Two radiotracers, 18F-THK5105 and 11C-PiB, were prepared in the Centre for PET at Austin Hospital. 18F-THK5105 was synthesized by nucleophilic substitution of the tosylate precursor as described previously (Okamura et al., 2013). The decay-corrected average radiochemical yield of the production of 18F-THK5105 was 45%, with a radiochemical purity >95% and a specific activity of 229.6 GBq/μmol (6.2 ± 3.3 Ci/μmol). 11C-PiB was synthesized using the one-step 11C-methyl triflate approach as previously described (Rowe et al., 2007). The decay-corrected average radiochemical yield for 11C-PiB was 30%, with a radiochemical purity >98% and a specific activity of 30 ± 7.6 GBq/μmol.

A list-mode emission acquisition on an Allegro™ PET camera (Philips Medical Systems) was performed in 3D mode from 0–50 min and between 90–120 min after injection of 200 MBq 18F-THK5105. List-mode raw data for the initial 50 min of the acquisition were sorted off-line into 6 × 30-s, 7 × 1-min, 4 × 2.5-min, 2 × 5-min, and 6 × 10-min frames. The final 30 min were acquired as 6 × 5-min frames. The sorted sinograms were reconstructed using a 3D RAMLA algorithm. A 30-min acquisition (6 × 5-min frames) on an Allegro™ PET camera began 40 min after intravenous injection of 300 MBq 11C-PiB.

**Hippocampal analysis**

Hippocampal and cortical grey matter volumes were obtained using an automated volumetric measurement program (NeuroQuant: CorTechs Labs Inc) applied to the 3D MP RAGE MRI images. The primary MRI outcome measures were the grey cortical matter and hippocampal volumes normalized to total intracranial volume.

PET images were processed using a semi-automatic region of interest method. Firstly, standardized uptake value (SUV) images of 18F-THK5105 and 11C-PiB were obtained by normalizing tissue radioactivity concentration by injected dose and body weight. Subsequently, individual MRI T1 images were anatomically co-registered into individual PET images using Statistical Parametric Mapping software (SPM8: Wellcome Trust Centre for Neuroimaging, London, UK). Co-registered MRI and PET images were then spatially normalized to an MRI T1 template in Talairach space using SPM8. After spatial normalization, a region of interest template was placed on individual axial images in the cerebellar hemisphere, ventrolateral frontal cortex [Brodmann areas (BA) 10, 44, 45 and 46], lateral and medial orbitofrontal cortex (BA 11 and 12), superior temporal cortex (BA 22), inferior temporal cortex (BA 20 and 37), parietal cortex (BA 39 and 40), lateral occipital cortex (BA 18 and 19), anterior cingulate cortex, posterior cingulate cortex, mesial temporal cortex (BA 27, 28, 34 and 35), putamen, pons, and subcortical white matter. Regional SUVs were sampled using PMOD software (PMOD Technologies, Ltd). The ratio of regional SUV to cerebellar cortex SUV ratio (SUVR) was used as an index of tracer retention. Neocortical tau and amyloid-β burden were expressed as the average SUVR for the following cortical regions of interest: frontal, parietal, lateral temporal, and posterior cingulate for THK5105 and PiB, respectively. As in previous studies, a PiB SUVR threshold of 1.5 was used to categorize high and low amyloid-β burden.

**Statistical analysis**

Mann-Whitney’s U-tests were applied for comparison of the Alzheimer’s disease and healthy control groups. For comparison of regional radiotracer uptake, one-way repeated measures analysis of variance (ANOVA) followed by Bonferroni’s tests were performed. To examine the regional difference of tracer retention between neocortex and mesial temporal cortex, Wilcoxon matched-pairs signed rank tests were performed. Effect size coefficients (Cohen’s d) were calculated for the evaluation of group differences in PET measurements. Statistical significance for each analysis was defined as \( P < 0.05 \). Data are presented as mean ± standard deviation (SD).

**Results**

Healthy control and Alzheimer’s disease subject demographics are shown in Table 1. There were no significant differences between healthy control and Alzheimer’s disease groups with regard to age.
or gender; however, the Alzheimer’s disease group was significantly less educated than the healthy control group. As expected, significant differences between the two groups were observed for CDR and CDR-SOB scores, cognitive performance (MMSE, episodic memory, and non-memory scores), and brain volumetrics (grey matter and hippocampal volumes).

No toxic event was observed in the current clinical PET study. After intravenous administration of $^{18}$F-THK5105, all subjects showed rapid entry of the tracer into grey matter areas. The SUV time activity curves of $^{18}$F-THK5105 PET are shown in Fig. 2. The peak uptake and clearance rates of $^{18}$F-THK5105 in the cerebellar cortex were similar between healthy control (Fig. 2A) and Alzheimer’s disease (Fig. 2B) groups. In patients with Alzheimer’s disease, the inferior temporal cortex, which is an area known to contain high densities of neurofibrillary tangles in Alzheimer’s disease (Bouras et al., 1994), showed $^{18}$F-THK5105 retention compared to the cerebellum, especially at the later time points. In contrast, time activity curves in the inferior temporal cortex of healthy control subjects were nearly identical to those in the cerebellum. The subcortical white matter region showed relatively lower entry and slower clearance than grey matter areas, but no significant differences were observed for time activity curves between healthy control and Alzheimer’s disease groups (data not shown). The ratio of inferior temporal cortex to cerebellar SUVR became constant in all participants ~90 min after injection of $^{18}$F-THK5105 (Fig. 2C). Therefore, we selected SUVR values from 90–100 min post-injection for the following analysis.

Summed SUVR images from 90–100 min post-injection for healthy control and Alzheimer’s disease subjects are shown in Fig. 3. Contrasted with a lack of remarkable $^{18}$F-THK5105 retention in the grey matter of healthy control subjects, patients with Alzheimer’s disease showed high grey matter $^{18}$F-THK5105 retention in the lateral and mesial temporal regions. $^{18}$F-THK5105 retention was additionally observed in the brain stem; however, similar retention in these areas was detected in healthy control subjects. When comparing the 90–100 min regional SUVR in Alzheimer’s disease and healthy control subjects, $^{18}$F-THK5105 SUVRs for the ventrolateral prefrontal, medial orbitofrontal, superior, and inferior temporal, parietal, posterior cingulate, and mesial temporal cortices were significantly higher in patients with Alzheimer’s disease (Table 2 and Fig. 4). Notably, SUVR in the inferior temporal cortex showed no overlap between the Alzheimer’s disease and healthy control groups (Fig. 4). $^{18}$F-THK5105 retention in other neocortical areas was relatively lower than in the inferior temporal area. The SUVR in the parietal cortex was elevated in 62.5% (5/8) of patients with Alzheimer’s disease; however, $^{18}$F-THK5105 retention in the ventrolateral prefrontal cortex was only elevated in 37.5% (3/8) of patients with Alzheimer’s disease. Mesial temporal $^{18}$F-THK5105 retention was significantly higher in patients with Alzheimer’s disease than in healthy control subjects. However, a substantial overlap of SUVR was observed between both groups. The SUVR values in the pons and subcortical white matter were nearly identical in both groups, but higher than other neocortical regions. The effect size value between Alzheimer’s disease and healthy control subjects was highest in the inferior temporal cortex, followed by the superior temporal, posterior cingulate, parietal, and medial orbitofrontal cortices and was lowest in the other regions examined (Table 2). Regional difference of $^{18}$F-THK5105 retention was additionally examined in healthy control subjects. As a result, mesial temporal $^{18}$F-THK5105 retention (mean SUVR = 1.17) was significantly higher than neocortical $^{18}$F-THK5105 retention (mean SUVR = 1.05) in healthy control subjects.
As reported in previous PET studies (Klunk et al., 2004; Mintun et al., 2006; Rowe et al., 2007), \(^{11}\text{C}-\text{PiB}\) SUVR values were significantly greater in the neocortical regions of patients with Alzheimer’s disease compared to healthy control subjects (Table 3). All patients with Alzheimer’s disease showed marked and extensive PiB retention in neocortical areas. On the other hand, neocortical PiB retention in healthy control subjects was not significant, except for one healthy control case that only showed high \(^{11}\text{C}-\text{PiB}\) retention in the frontal cortex. In contrast

**Table 2** Regional \(^{18}\text{F}-\text{THK5105}\) SUVR values in healthy control and Alzheimer’s disease subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy controls</th>
<th>Alzheimer’s disease</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventrolateral prefrontal</td>
<td>1.08 ± 0.08</td>
<td>1.23 ± 0.14*</td>
<td>1.33</td>
</tr>
<tr>
<td>Lateral orbitofrontal</td>
<td>1.01 ± 0.08</td>
<td>1.15 ± 0.13</td>
<td>1.32</td>
</tr>
<tr>
<td>Medial orbitofrontal</td>
<td>1.17 ± 0.06</td>
<td>1.29 ± 0.09*</td>
<td>1.55</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>1.04 ± 0.06</td>
<td>1.22 ± 0.07*</td>
<td>2.75</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>1.09 ± 0.04</td>
<td>1.32 ± 0.08*</td>
<td>3.58</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.99 ± 0.08</td>
<td>1.16 ± 0.13*</td>
<td>1.59</td>
</tr>
<tr>
<td>Lateral occipital</td>
<td>1.07 ± 0.06</td>
<td>1.18 ± 0.15</td>
<td>1.01</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>1.07 ± 0.11</td>
<td>1.12 ± 0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>1.04 ± 0.08</td>
<td>1.20 ± 0.12*</td>
<td>1.61</td>
</tr>
<tr>
<td>Mesial temporal</td>
<td>1.17 ± 0.05</td>
<td>1.26 ± 0.10*</td>
<td>1.17</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.41 ± 0.10</td>
<td>1.52 ± 0.17</td>
<td>0.83</td>
</tr>
<tr>
<td>Pons</td>
<td>1.88 ± 0.14</td>
<td>1.89 ± 0.23</td>
<td>0.03</td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>1.22 ± 0.15</td>
<td>1.22 ± 0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Neocortex</td>
<td>1.05 ± 0.05</td>
<td>1.23 ± 0.08*</td>
<td>2.68</td>
</tr>
</tbody>
</table>

\(^{*}\)P < 0.05 by the Mann–Whitney U test.

**Figure 3** \(^{18}\text{F}-\text{THK5105}\) PET images from 60–80 min post-injection in a healthy control subject (72-years-old, CDR 0, MMSE 29) and a patient with Alzheimer’s disease (68-years-old, CDR 1.0, MMSE 20).

**Figure 4** Regional \(^{18}\text{F}-\text{THK5105}\) SUVR values from 60–80 min post-injection in healthy control and Alzheimer’s disease (AD) subjects.

\(^{*}\)P < 0.05 by the Mann–Whitney U test.
Table 3 Regional 11C-PiB SUVR values in healthy control and Alzheimer’s disease subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy controls</th>
<th>Alzheimer’s disease</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventrolateral prefrontal</td>
<td>1.32 ± 0.39</td>
<td>2.92 ± 0.82*</td>
<td>2.49</td>
</tr>
<tr>
<td>Lateral orbitofrontal</td>
<td>1.08 ± 0.25</td>
<td>1.66 ± 0.50*</td>
<td>1.46</td>
</tr>
<tr>
<td>Medial orbitofrontal</td>
<td>1.36 ± 0.23</td>
<td>2.38 ± 0.63*</td>
<td>2.15</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>1.11 ± 0.13</td>
<td>2.67 ± 0.67*</td>
<td>3.22</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>1.08 ± 0.08</td>
<td>2.42 ± 0.66*</td>
<td>2.88</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.22 ± 0.17</td>
<td>2.56 ± 0.51*</td>
<td>3.54</td>
</tr>
<tr>
<td>Lateral occipital</td>
<td>1.25 ± 0.11</td>
<td>2.07 ± 0.61*</td>
<td>1.86</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>1.39 ± 0.28</td>
<td>2.79 ± 0.70*</td>
<td>2.64</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>1.31 ± 0.24</td>
<td>3.15 ± 0.78*</td>
<td>3.22</td>
</tr>
<tr>
<td>Mesial temporal</td>
<td>1.29 ± 0.15</td>
<td>1.65 ± 0.32*</td>
<td>1.42</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.48 ± 0.20</td>
<td>2.64 ± 0.62*</td>
<td>2.50</td>
</tr>
<tr>
<td>Pons</td>
<td>2.04 ± 0.33</td>
<td>2.04 ± 0.40</td>
<td>0.00</td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>2.02 ± 0.38</td>
<td>2.06 ± 0.66</td>
<td>0.07</td>
</tr>
<tr>
<td>Neocortex</td>
<td>1.21 ± 0.14</td>
<td>2.75 ± 0.66*</td>
<td>3.21</td>
</tr>
</tbody>
</table>

*P < 0.05 by the Mann–Whitney U test.

Discussion

In this study, the novel radiotrace 18F-THK5105 successfully differentiated patients with Alzheimer’s disease from healthy control subjects. The pattern of 18F-THK5105 distribution in patients with Alzheimer’s disease appears similar to the reported neurofibrillary tangle distribution in the post-mortem Alzheimer’s disease brain. 18F-THK5105 retention in the inferior temporal cortex, where neurofibrillary tangle accumulation is highest in Alzheimer’s disease, was observed in most patients with Alzheimer’s disease. In contrast to the high frequency of 18F-THK5105 retention in the temporal cortices of Alzheimer’s disease cases, ventrolateral prefrontal 18F-THK5105 retention was less frequent (3/8) and was only observed in cases with moderate-to-severe Alzheimer’s disease (MMSE range 10–17). This finding is consistent with neurofibrillary tangle distribution in post-mortem Alzheimer’s disease brain, where there is a higher frequency of neurofibrillary tangles in the temporal cortex than the frontal cortex (Arnold et al., 1991; Bouras et al., 1994; Haroutunian et al., 1999). It is also in agreement with recent PET results using other novel radiotracers (18F-T807 and 18F-T808) that demonstrated higher radiotracer retention in the lateral temporal lobe compared to the frontal lobe and selective binding ability to paired helical filament tau (Chien et al., 2013, 2014). These findings suggest a spreading
of tau pathology (Soto, 2012; Mohamed et al., 2013) from temporal areas to the other association cortices. A longitudinal assessment of tau pathology will help elucidate the spatial patterns of tau pathology progression in the living brain. In addition, as observed in $^{18}$F-T807 and $^{18}$F-T808 PET studies (Chien et al., 2013, 2014), $^{18}$F-THK5105 retention in the mesial temporal area was relatively lower than in the lateral temporal area in patients with Alzheimer’s disease, which conflicts with microscopic observations showing higher neurofibrillary tangle density in the entorhinal cortex and hippocampus of Alzheimer’s disease brain compared to the neocortex (Arnold et al., 1991). One possible explanation for this phenomenon is the partial volume effect of radiotracer signals (Muller-Gartner et al., 1992). $^{18}$F-THK5105 retention in the mesial temporal cortex might be underestimated in patients with severe hippocampal atrophy.

$^{18}$F-THK5105 retention in patients with Alzheimer’s disease was closely associated with dementia severity. This finding is consistent with results from previous post-mortem studies showing significant correlations of neurofibrillary tangle density with dementia severity (Arriagada et al., 1992; Bierer et al., 1995; Berg et al., 1998). Our results further demonstrate that hippocampal atrophy is significantly correlated with $^{18}$F-THK5105 retention but not with $^{11}$C-PiB retention in the same area. In addition, the neocortical grey matter volume was negatively correlated with global $^{18}$F-THK5105 retention in the neocortex. These findings correspond with the neuropathological observation that the density of neurofibrillary tangles, but not senile plaques, is closely associated with neuronal loss (Gomez-Isla et al., 1996, 1997). Intriguingly, $^{18}$F-THK5105 retention in healthy control subjects was significantly higher in the mesial temporal cortex (SUVR = 1.17) than in the neocortex (SUVR = 1.05). This finding is likely to reflect age-related tau accumulation in this area. In future studies, the association of mesial temporal $^{18}$F-THK5105 retention with ageing should be evaluated in a large population. It is also still unclear whether or not tau accumulation precedes neuronal loss. To answer this question, mesial temporal cortex tau density should be evaluated in the mild cognitive impairment population, as well as cognitively normal individuals with amyloid-$\beta$ deposition, and these results should be compared with fluorodeoxyglucose and brain atrophy in a longitudinal analysis.

The amount of neocortical $^{18}$F-THK5105 retention (SUVR = 1.23) was considerably lower than that of $^{11}$C-PiB (SUVR = 2.75) in patients with Alzheimer’s disease. This is thought to result from higher concentrations of amyloid-$\beta$ fibrils than tau fibrils in the Alzheimer’s disease brain (Villemagne et al., 2012). Therefore, a tau-specific radiotracer must be highly sensitive and selective to tau protein fibrils. Our previous study demonstrated that the binding affinity of $^{18}$F-THK5105 for tau fibrils (Kd = 1.45 nM) was 25-times higher than to amyloid-$\beta$ fibrils (Kd = 35.9 nM) (Okamura et al., 2013). Autoradiography studies

Figure 6 Correlation of neocortical $^{18}$F-THK5105 and $^{11}$C-PiB SUVR with MMSE scores (upper) and CDR-SOB scores (lower). Data from eight healthy control subjects (open circles) and eight patients with Alzheimer’s disease (AD, filled circles) are shown.
further confirmed the preferential binding ability of $^{18}$F-THK5105 to tau protein deposits in Alzheimer’s disease brain sections. In this PET study, all Alzheimer’s disease cases were PiB-positive and showed remarkable PiB retention in broad neocortical areas. As reported by many researchers, these patients with Alzheimer’s disease showed prominent PiB retention in the ventrolateral prefrontal cortex (SUVR $< 2.0$), reflecting high amyloid-$\beta$ pathology in this area. In contrast, $^{18}$F-THK5105 retention in the frontal cortex was not elevated in more than half of the Alzheimer’s disease cases (Fig. 4). In addition, one healthy control case showing PiB retention in the frontal cortex showed no retention of $^{18}$F-THK5105 in this area. These results support the low sensitivity of $^{18}$F-THK5105 to amyloid-$\beta$ plaques.

Compared with previous $^{18}$F-THK523 PET data, specific $^{18}$F-THK5105 retention in grey matter was considerably higher whereas white matter retention was considerably lower than those observed for $^{18}$F-THK523. This observation is consistent with previous in vitro autoradiograms showing a higher signal-to-background ratio of $^{18}$F-THK5105 than $^{18}$F-THK523 in Alzheimer’s disease brain sections (Okamura et al., 2013). This is probably due to the higher binding affinity of $^{18}$F-THK5105 to tau protein fibrils. The peak brain entry of $^{18}$F-THK5105 (cerebellar SUV = 4.5), which was observed before 6 min post-injection, was higher than for $^{18}$F-THK523 and other reported radiotracers ($^{18}$F-T807, $^{18}$F-T808 and $^{11}$C-PBB3) and almost identical to the reported SUV value of $^{11}$C-PiB (Klunk et al., 2004). In addition, $^{18}$F-THK5105 did not accumulate in the skull, which is often the result of defluorination and interferes with visual PET image inspection. These pharmacokinetic properties are unique advantages of $^{18}$F-THK5105 over the other reported radiotracers. Conversely, one of the drawbacks of $^{18}$F-THK5105 is the existence of non-specific tracer retention in the brainstem, thalamus, and subcortical white matter, which reflects the binding of tracer to $\beta$-sheet structures present in myelin basic protein, similar to that observed for $^{11}$C-PiB (Stankoff et al., 2011). Nevertheless, the $^{18}$F-THK5105 signal in the subcortical white matter was not visually noticeable as compared with $^{18}$F-THK523 and $^{11}$C-PiB. The relatively slower kinetics of $^{18}$F-THK5105 cause the high background signals in grey matter, which may make the white matter signals less noticeable. Actually, the clearance of $^{18}$F-THK5105 from normal grey matter tissue was slower than that of PiB because of higher lipophilicity for $^{18}$F-THK5105 (LogP = 3.03) than PiB (LogP = 1.20). As another tau-imaging radiotracer candidate, we have developed a 2-arylquinoline derivative named $^{18}$F-THK5117 (Okamura et al., 2013), which is more hydrophilic and shows faster pharmacokinetics in mice than $^{18}$F-THK5105. It is expected to show faster clearance from normal brain tissue in humans and higher signal-to-background ratio than $^{18}$F-THK5105. A clinical trial testing $^{18}$F-THK5117 is currently underway.
Tau deposits are also present in non-Alzheimer’s disease tauopathies including frontotemporal lobe degeneration, corticobasal degeneration, progressive supranuclear palsy and chronic traumatic encephalopathy. Although THK523 failed to detect tau deposits in these non-Alzheimer’s disease tauopathies, we recently observed in vitro binding ability of THK5105 and THK5117 to glial tau pathology in corticobasal degeneration and progressive supranuclear palsy. Therefore, clinical PET study in non-Alzheimer’s disease tauopathies will be necessary to decide whether \(^{18}\)F-THK5105 is applicable to the study of a broad range of tauopathies.

The results of the current study indicate that \(^{18}\)F-THK5105 has adequate safety to be used as a clinical PET tracer. \(^{18}\)F-THK5105 PET demonstrated high tracer retention in sites susceptible to paired helical filament-tau deposition in patients with Alzheimer’s disease and distinctly differentiated patients with Alzheimer’s disease from age-matched healthy controls. Collectively, these findings suggest that \(^{18}\)F-THK5105 is useful for the non-invasive evaluation of tau pathology in humans and could be employed to study longitudinal tau deposition in healthy and pathological ageing.

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