


## BRIEF COMMUNICATION

# Neuroinflammation in frontotemporal lobar degeneration revealed by $^{11}\text{C}$ -PBR28 PET

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## Abstract

This study used  $^{11}\text{C}$ -PBR28 positron emission tomography (PET) imaging to determine whether levels of 18-kDa translocator protein (TSPO), an inflammation-specific biomarker, are increased in frontotemporal lobar degeneration (FTLD) patients.  $^{11}\text{C}$ -PBR28,  $^{18}\text{F}$ -FDG, and  $^{11}\text{C}$ -PIB brain PET scans, as well as magnetic resonance imaging (MRI), were conducted in four FTLD patients and 22 healthy controls.  $^{11}\text{C}$ -PBR28 scans revealed that all FTLD patients showed increased TSPO binding versus controls. Significantly greater increases in TSPO were observed in the frontal, lateral temporal, parietal, and occipital cortices, topographically consistent with individual clinical phenotypes and with brain MRI and  $^{18}\text{F}$ -FDG PET. Amyloid burden was not increased.

## Introduction

Frontotemporal lobar degeneration (FTLD) is the second most frequent cause of presenile neurodegenerative dementia.<sup>1</sup> Patients with clinical FTLD can present with one of three clinical syndromes: behavioral variant frontotemporal dementia (bvFTD), semantic dementia, and progressive nonfluent aphasia (PNFA).<sup>2</sup> Animal studies have demonstrated that abnormal neuroimmune responses associated with gene mutations can cause inherited forms of FTLD, suggesting that neuroinflammation may play a pathogenic role.<sup>3,4</sup> Thus, positron emission tomography (PET) scans using radioligands specific to active components of the neuroinflammatory process could be useful for monitoring disease-specific brain changes in living patients with FTLD.

Among the PET radioligands developed to quantify neuroinflammation, the most extensively studied in humans are those that bind to 18-kDa translocator protein (TSPO), a mitochondrial protein that is highly expressed in activated microglia. Only two published PET studies have examined TSPO in FTLD. One used the prototypical TSPO radioligand  $^{11}\text{C}$ -(R)-PK11195 in patients with FTLD<sup>5</sup> and the second used  $^{11}\text{C}$ -DAA1106 in presymptomatic carriers of the FTLD genetic mutation.<sup>6</sup> However,  $^{11}\text{C}$ -(R)-PK11195 has been shown to have low specific-to-nonspecific binding,<sup>7</sup> and further studies using improved radioligands have not yet been performed in symptomatic FTLD patients.

Previous studies using the second-generation TSPO radioligand  $^{11}\text{C}$ -PBR28 found strong correlations between brain uptake and the clinical severity or progression of

Alzheimer's disease (AD).<sup>8,9</sup> Another study found that the distribution of <sup>11</sup>C-PBR28 binding colocalized to neurodegeneration in different clinical subtypes of AD.<sup>10</sup> Building on this work, this study sought to investigate whether <sup>11</sup>C-PBR28 binding was increased in FTLD patients in their relevant affected brain areas. The expected affected brain regions were identified by clinical findings, brain magnetic resonance imaging (MRI), and <sup>18</sup>F-fluorodeoxyglucose (FDG) PET scan.

## Methods

### Subjects

Subjects were recruited by the Molecular Imaging Branch of the National Institute of Mental Health, National Institutes of Health (NIMH-NIH). All participants or their surrogate gave informed consent in accordance with the National Institutes of Health Combined Neurosciences Institutional Review Board. Four patients who met criteria for one of the clinical FTLD syndromes were recruited.<sup>2</sup> Twenty-two cognitively normal subjects from a previously described database<sup>11</sup> were retrospectively demographically matched with the FTLD patients to serve as a control group; subjects with significant comorbid medical or psychiatric illnesses were excluded. TSPO-binding affinity was determined by *in vitro* receptor binding to TSPO on leukocyte membranes,<sup>12</sup> and low-affinity binders were excluded. Although genetic testing was not available, none of the patients had a family history suggesting autosomal dominant inheritance.

### Imaging procedures and analysis

Both FTLD patients and healthy controls underwent brain MRI as well as PET imaging with <sup>11</sup>C-PBR28. <sup>18</sup>F-FDG PET scans were obtained in all four patients with FTLD, and <sup>11</sup>C-Pittsburgh Compound B (PIB) PET scans were obtained in three of the four FTLD patients. <sup>11</sup>C-PIB PET data were also available for all healthy controls older than 45 years ( $N = 15$ ), and were confirmed to be "PIB-negative" using a dichotomizing method adapted from Jack and colleagues.<sup>13</sup> Brain MRI, <sup>18</sup>F-FDG, <sup>11</sup>C-PIB, and <sup>11</sup>C-PBR28 PET procedures and preprocessing steps were performed as previously described.<sup>10</sup>

For region-of-interest (ROI)-based analysis of <sup>11</sup>C-PBR28 PET images, the realigned PET images were coregistered to the MR images using SPM8 software (Wellcome Center for Human Neuroimaging, London, UK). A set of 83 predefined regions from the Hammers N30R83 maximum probability atlas was adjusted to the MRI scan of individual subjects using the PNEURO module of PMOD 3.9 (PMOD Technologies, Zurich, Switzerland).<sup>14</sup> These

were segmented from the spatially normalized individual MRIs and applied to the dynamic PET images. Partial volume effects were corrected within each PET image using a region-based voxel-wise method provided in PNEURO/PMOD.<sup>15</sup> For better representation and noise reduction, the 83 ROIs were combined into 11 ROIs via weighted averaging. Total distribution volume ( $V_T$ ) in each ROI was calculated using the two-tissue compartment model and corrected for free fraction of radioligand in plasma ( $f_p$ ). Data were also analyzed using a simplified ratio method as previously described, with cerebellum as a pseudoreference region.<sup>16</sup> For visual comparison of TSPO distribution in the FTLD patients and two representative healthy controls, <sup>11</sup>C-PBR28 parametric images – where each voxel represents  $V_T/f_p$  – were generated using the Logan plot and arithmetic tools in PMOD.

For the three FTLD patients whose <sup>11</sup>C-PIB PET data were available, parametric images of <sup>11</sup>C-PIB distribution volume ratio were generated using the Logan reference model.<sup>17</sup> In all FTLD patients, standardized uptake value ratio images of <sup>18</sup>F-FDG PET were generated using cerebellum as a reference region.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics 25 (Chicago, IL, USA). Demographic variables were compared using the Mann–Whitney U-test and the Chi-squared test. The ROI-based comparisons of <sup>11</sup>C-PBR28 binding were conducted using the Mann–Whitney U-test. To correct for TSPO-binding affinity, each ROI value of <sup>11</sup>C-PBR28  $V_T/f_p$  in mixed-affinity binders was multiplied by 1.2 before comparison, based on a previous study that determined the ratio of <sup>11</sup>C-PBR28 binding for high-affinity binders and mixed-affinity binders.<sup>11</sup> This correction was not conducted with the simplified ratio method because differences in TSPO-binding affinity are cancelled out in the ratio.

## Results

### Subject characteristics

Demographic characteristics are described in Table 1. Three of the four FTLD patients met criteria for bvFTD<sup>18</sup> and one had PNFA.<sup>2</sup> No significant differences in age, sex, education level, or TSPO-binding affinity was noted between the patient and control groups.

### Patterns of TSPO binding

All four patients showed higher <sup>11</sup>C-PBR28 binding than healthy controls, regardless of TSPO-binding affinity

**Table 1.** Demographic and clinical characteristics

Variable	FTLD		P value
	(n = 4)	HC (n = 22)	
Age (y)	54.3 ± 6.9	54.4 ± 14.1	0.66*
Sex	1F, 3M	7F, 15 M	1.00**
Education (y)	17.0 ± 3.5	16.2 ± 2.6	0.66*
TSPO-binding affinity type (HAB:MAB)	2:2	8:14	0.63**
Mini-Mental State Examination score	17.0 ± 11.4	29.9 ± 0.3	<0.001*

Abbreviations: FTLD, frontotemporal lobar degeneration; HC, healthy control; TSPO, 18-kDa translocator protein; HAB, high-affinity binder; MAB, mixed-affinity binder.

\*By Mann–Whitney *U*-test;

\*\*By Chi-squared test.

(Fig. 1). The frontotemporal cortex showed the most prominent increase despite substantial interindividual variability. In the ROI-based analysis, FTLD patients had 1.4- to 1.8-fold greater  $V_T/f_p$  in frontal cortex (*P* value ranged between 0.002 and 0.04) and 1.4- to 1.5-fold greater  $V_T/f_p$  in lateral temporal, parietal, and occipital

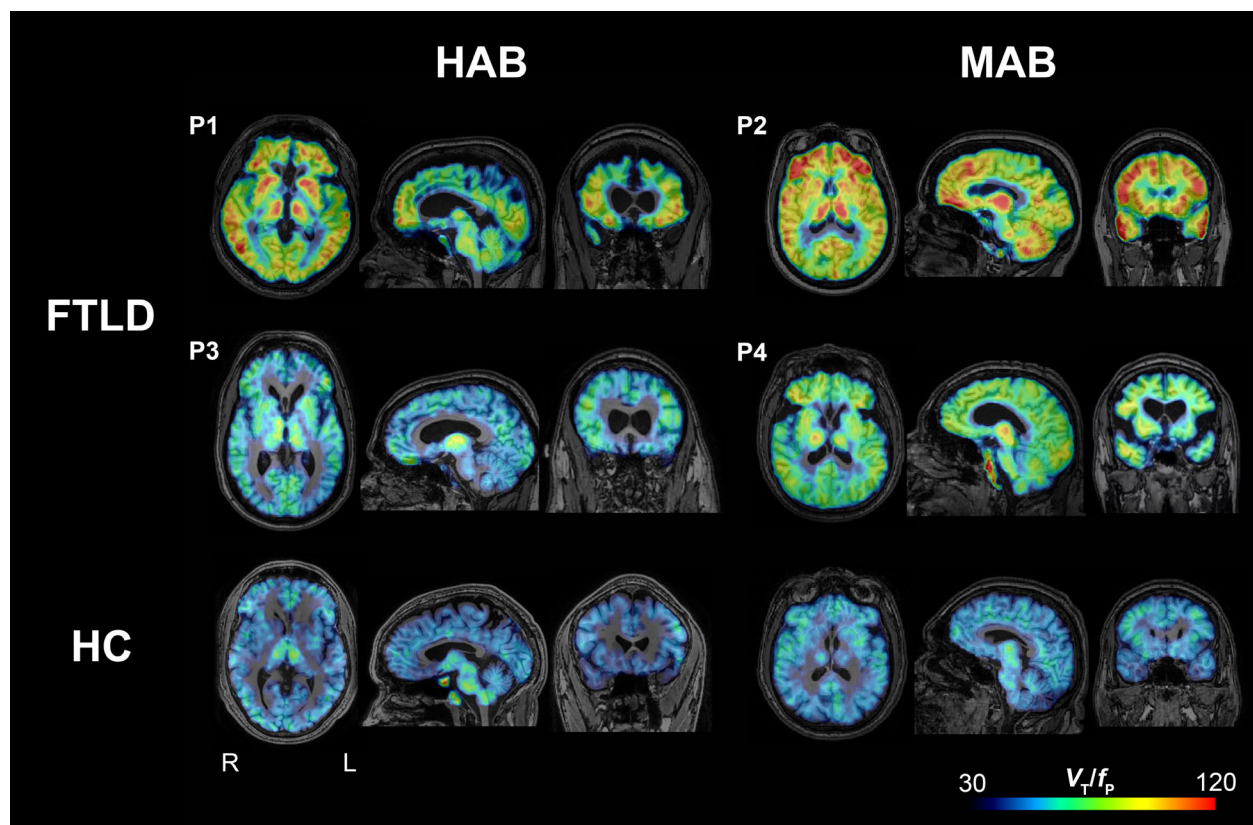
cortices (*P* value ranged between 0.02 and 0.03) than healthy controls. Results obtained using the simplified ratio method were similar except that no difference was observed in the occipital cortex (*P* = 0.66).

### Visual comparisons with brain MRI, <sup>18</sup>F-FDG PET, and <sup>11</sup>C-PIB PET

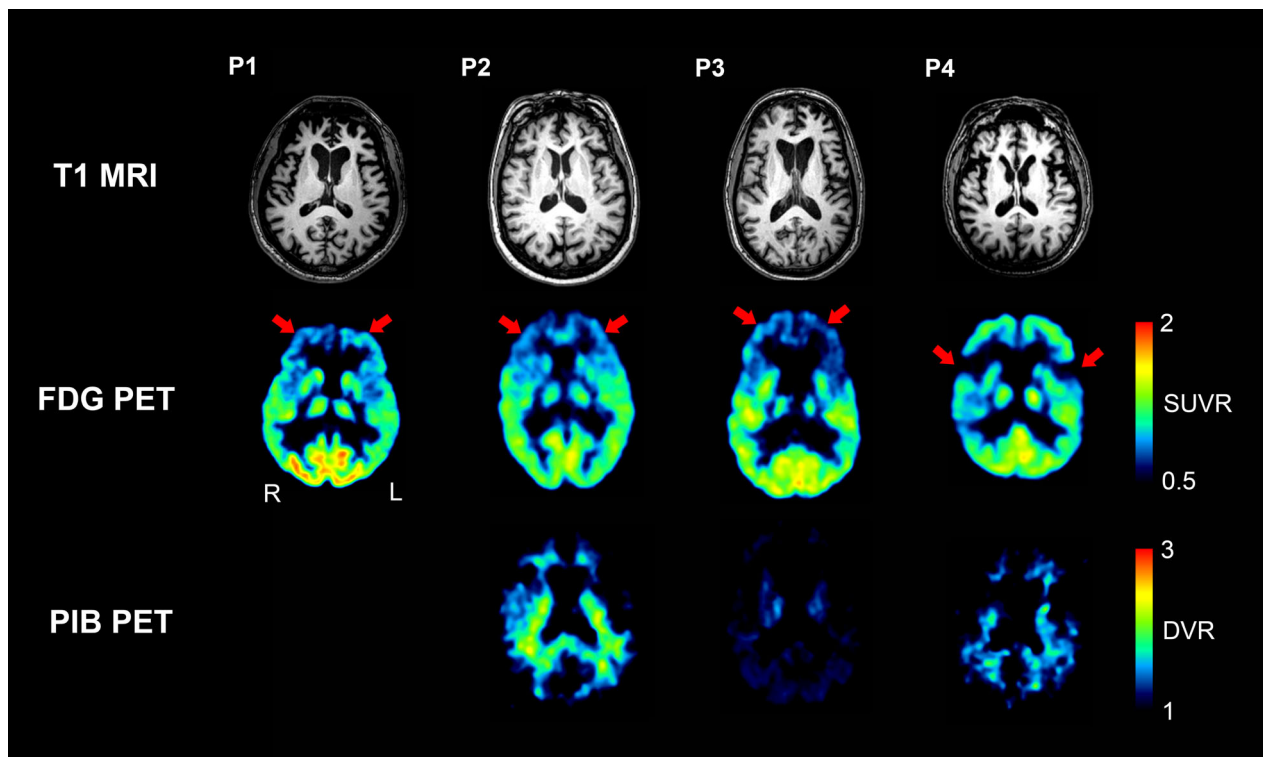
On T1-weighted MR and <sup>18</sup>F-FDG PET images, all three patients with bvFTD showed significant atrophy and hypometabolism in the bilateral anterior frontal cortices, and the PNFA patient showed prominent atrophy and hypometabolism in the bilateral perisylvian areas (Fig. 2). None of the patients who underwent amyloid PET scans showed increased <sup>11</sup>C-PIB uptake in any gray matter region.

### Discussion

In this study, <sup>11</sup>C-PBR28 binding was increased in the brain of FTLD patients although the amount of increase varied between patients. Regions of increased <sup>11</sup>C-PBR28



**Figure 1.** Parametric images of <sup>11</sup>C-PBR28 total distribution volume corrected by plasma-free fraction ( $V_T/f_p$ ) in four patients with frontotemporal lobar degeneration (FTLD) (P1, P2, P3, and P4) and two representative healthy control subjects (bottom row). When visually compared to healthy control subjects, FTLD patients had greater <sup>11</sup>C-PBR28 binding in frontotemporal cortices and other brain areas. Abbreviations: HAB, high-affinity binder; MAB, mixed-affinity binder; HC, healthy control.



**Figure 2.** Brain magnetic resonance (MR), <sup>18</sup>F-FDG PET, and <sup>11</sup>C-PIB PET images of patients with frontotemporal lobar degeneration (FTLD). Patients 1, 2, and 3, who had behavioral variant frontotemporal dementia (P1, P2, and P3), showed atrophy and hypometabolism in the bilateral anterior frontal cortices on MRI and <sup>18</sup>F-FDG PET, respectively. Patient 4, who had progressive nonfluent aphasia (P4), showed bilateral perisylvian atrophy and hypometabolism on MRI and <sup>18</sup>F-FDG PET, respectively. <sup>11</sup>C-PIB uptake was not increased in these areas or other gray matter areas for any of the patients. <sup>11</sup>C-PIB PET imaging was not available for Patient 1. Abbreviations: FDG, fluorodeoxyglucose; PIB, Pittsburgh Compound B.

binding in FTLD patients corresponded with the expected neurodegeneration predicted by clinical phenotype as well as MRI and <sup>18</sup>F-FDG PET scans. Amyloid burden, as measured by <sup>11</sup>C-PIB, was not increased in any gray matter region in FTLD patients, consistent with the nonamyloid pathology of FTLD. The results also confirm that the simplified ratio method of <sup>11</sup>C-PBR28 developed for use in AD can be extended for use in FTLD.

In contrast to a previous study using <sup>11</sup>C-(R)-PK11195 that found increased TSPO binding mainly in medial temporal, subcortical, and some frontal cortical regions,<sup>5</sup> the present <sup>11</sup>C-PBR28 study found that the highest increases in binding were observed in neocortical regions – including frontal, lateral temporal, parietal, and occipital cortices – with no significant increase in medial temporal or subcortical regions.<sup>5</sup> While these differences may be partially attributable to clinical and pathological heterogeneity among FTLD patients, <sup>11</sup>C-PBR28 would also be expected to be more sensitive and specific than <sup>11</sup>C-(R)-PK11195 given the greater specific-to-nonspecific binding of <sup>11</sup>C-PBR28.<sup>7</sup> Another study that used <sup>11</sup>C-DAA1106 imaging found the greatest increase in the occipital, posterior cingulate, and medial frontal cortex;

these differences may be due to the fact that they included only presymptomatic *MAPT* mutation carriers.<sup>6</sup>

The distribution of in vivo TSPO binding in this study is consistent with previous postmortem findings demonstrating that microglial activation is increased in frontal and lateral temporal cortical gray and subcortical white matter in FTLD brain tissue, regardless of histological or genetic subtype.<sup>19</sup> Other studies also found that different types of pathologies linked to tau and progranulin were commonly associated with abnormal microglial response.<sup>3,20</sup> In addition, major proteins and their coding genes associated with certain familial types of FTLD are thought to be functionally linked to microglial activity.<sup>3,4</sup> Taken together, the results suggest that, in FTLD, early heterogeneous pathological processes involve a variety of genes and proteins, and that neuroinflammation may be a subsequent convergent process; this, in turn, may explain why diverse genotypes and proteinopathies result in the small number of common phenotypes seen in FTLD. In this regard, further investigations with larger patient populations are warranted to determine whether correlations exist between in vivo neuroinflammation measured by TSPO imaging and clinical severity or progression of

FTLD. The hope is TSPO imaging may serve as a useful pharmacodynamic biomarker, enhancing the efficiency of early phase clinical trials for FTLD.

In summary, this study used an improved TSPO radioligand to confirm that neuroinflammation levels are increased in FTLD. The ability to use TSPO imaging to evaluate the *in vivo* status of neuroinflammation in FTLD is promising for future investigations into the underlying pathophysiology of this disorder and to the concomitant discovery of relevant therapeutic targets.

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## Author Contributions

VP, RI, and WK contributed to the conception and design of the study; MJK, MM, KJ, JS, CM, and SZ contributed to the acquisition and analysis of data; MJK, JS, RI, and WK drafted the text and prepared the figures and table.

## Conflict of Interest

The authors have no other conflicts of interest to disclose, financial or otherwise.

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