

# Imaging pro-inflammatory microglia in Parkinson's disease using [11C]SMW139 PET: a multi-center study

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## Abstract

**Background:** Several TSPO PET studies have shown increased glial cell density in Parkinson's disease (PD). However, TSPO PET cannot discriminate between pro- and anti-inflammatory microglia, thereby limiting the understanding of pro-inflammatory contributions to PD pathogenesis. Therefore, this study focused on the novel radiotracer [<sup>11</sup>C]SMW139 targeting the P2X7 receptor (P2X7R), which is specifically expressed on pro-inflammatory microglia. We aim to investigate pro-inflammatory signals in PD using [<sup>11</sup>C]SMW139 PET.

**Method:** 15 PD patients (age: 67, 67% male) and 15 controls (HC) (age: 64, 47% male) were included from Amsterdam UMC, Turku University Hospital and Karolinska Institutet. All participants underwent a 90 min [<sup>11</sup>C]SMW139 PET scan with arterial sampling, resulting in the outcome measure  $V_{Tp}$  (Volume of distribution). [<sup>11</sup>C]SMW139  $V_{Tp}$  was quantified in several regions of interest (ROIs)(Figure 1). Differences in [<sup>11</sup>C]SMW139  $V_{Tp}$  between PD and HC were assessed using linear mixed models with post hoc testing. Associations between motor symptom severity as measured by UPDRS-III, disease duration and [<sup>11</sup>C]SMW139  $V_{Tp}$  were assessed using linear regressions.

**Result:** In the a-priori ROIs, PD patients showed significantly higher  $V_{Tp}$  in the putamen ( $\beta=0.04$ ,  $p=0.046$ ) and whole cortex ( $\beta=0.04$ ,  $p=0.043$ ) compared to HC, indicating higher pro-inflammatory activity (Figure 1). In an exploratory analysis, PD patients

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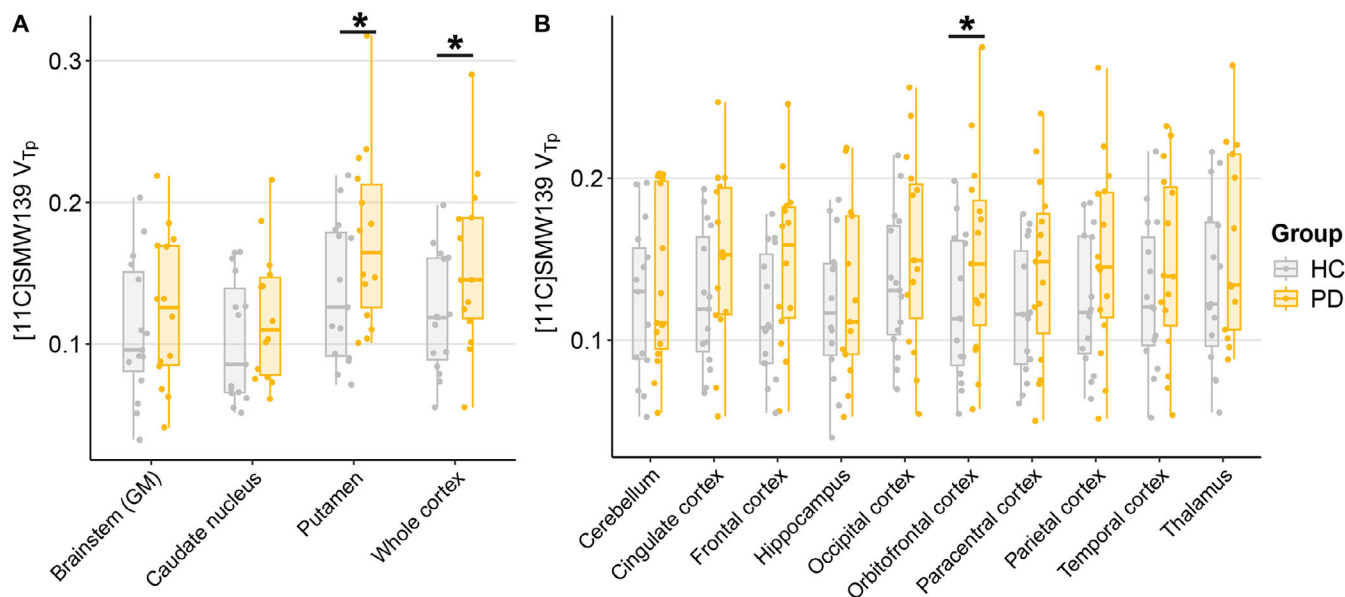
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also showed higher  $V_{Tp}$  in the orbitofrontal cortex ( $\beta = 0.04$ ,  $p = 0.041$ ). There was no significant association between  $V_{Tp}$  and symptom severity (brainstem:  $\beta = -0.002$ ,  $p = 0.084$ ; caudate nucleus;  $\beta = -0.002$ ,  $p = 0.164800$ ; putamen:  $\beta = -0.002$ ,  $p = 0.265$ , whole cortex:  $\beta = -0.002$ ,  $p = 0.119$ ) or disease duration in PD (brainstem:  $\beta = -0.01$ ,  $p = 0.055$ ; caudate nucleus;  $\beta = -0.005$ ,  $p = 0.282$ ; putamen:  $\beta = -0.01$ ,  $p = 0.113$ , whole cortex:  $\beta = -0.007$ ,  $p = 0.217$ ) (Figure 2). However, there was a negative trend indicating higher pro-inflammatory activation earlier in the disease trajectory, which warrants further investigation (Figure 2 & 3).

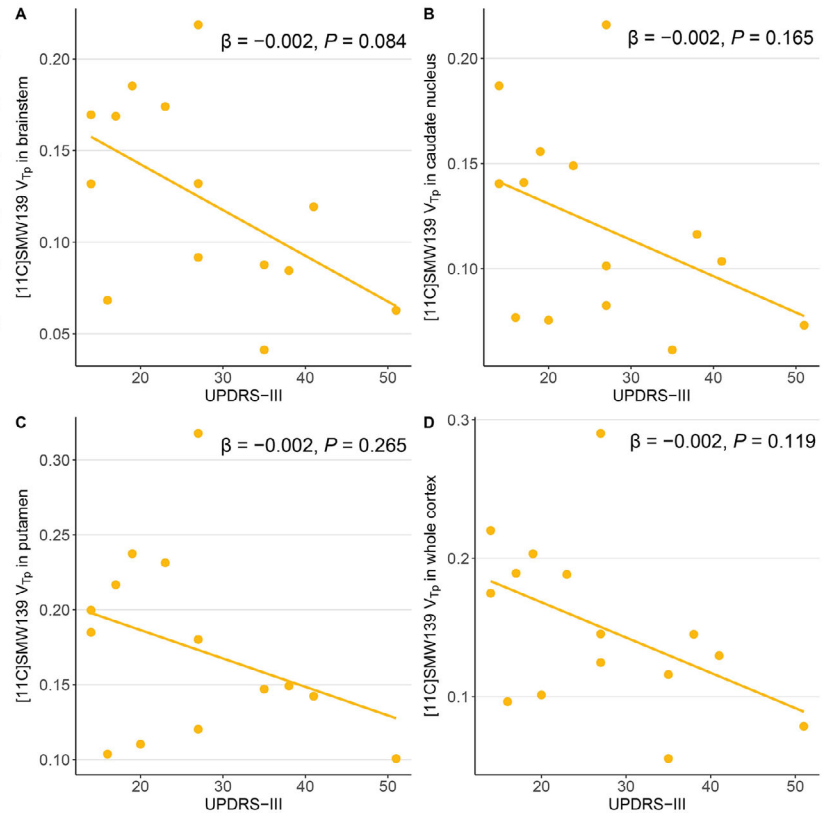
**Conclusion:** PD patients showed increased P2X7R binding in the putamen and brain cortex, as assessed by [<sup>11</sup>C]SMW139 PET, suggesting the presence of increased levels of pro-inflammatory microglia.



**Figure 1** Comparison of [<sup>11</sup>C]SMW139  $V_{Tp}$  between PD patients and HC. Boxplot showing [<sup>11</sup>C]SMW139  $V_{Tp}$  between patients with PD and healthy controls (HC) in the a priori ROIs (A) and all other ROIs (B). The reported p-values were derived from post-hoc group x region analyses of age, sex- and center-adjusted linear mixed models with random intercept for subject.

\*:  $p < 0.05$

**Figure 2 Association between [<sup>11</sup>C]SMW139 V<sub>Tp</sub> and UPDRS-III.** Scatterplots showing the associations between [<sup>11</sup>C]SMW139 V<sub>Tp</sub> and symptom severity measured by UPDRS-III score in brainstem (A), caudate nucleus (B), putamen (C), and whole cortex (D). PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.



**Figure 3 Association between [<sup>11</sup>C]SMW139 V<sub>Tp</sub> and disease duration.** Scatterplots showing the associations between [<sup>11</sup>C]SMW139 V<sub>Tp</sub> and disease duration in years in brainstem (A), caudate nucleus (B), putamen (C), and whole cortex (D). PD = Parkinson's disease; y = years.

