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Short communication

Neuroinflammation in Parkinson's disease: A study with [^{11}C]PBR28 PET and cerebrospinal fluid markers

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ABSTRACT

Objective: To investigate neuroinflammation in Parkinson's disease (PD) with [^{11}C]PBR28 positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers, and the relationship to dopaminergic functioning measured with 6-[^{18}F]-fluoro-L-dopa ([^{18}F]FDOPA) PET.
Methods: The clinical cohort consisted of 20 subjects with PD and 51 healthy controls (HC). All HC and 15 PD participants underwent [^{11}C]PBR28 High Resolution Research Tomograph (HRRT) PET for the quantitative assessment of cerebral binding to the translocator protein (*TSPO*), a neuroinflammation marker. CSF samples were available from 17 subjects with PD and 21 HC and were examined for soluble triggering receptor expressed on myeloid cells 2 (sTREM2), chitinase 3-like 1 protein (YKL-40), neurogranin (NG), alpha-synuclein (aSyn) and oligo-alpha-synuclein. All subjects with PD underwent [^{18}F]FDOPA HRRT PET.
Results: While the subjects with PD and HC did not differ in the total volume of distribution (V_T) of [^{11}C]PBR28 in any studied brain regions, higher levels of neuroinflammation and neurodegeneration CSF biomarkers sTREM2 and NG, respectively were associated with more severe motor symptoms evaluated by The Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) ($r = 0.52$, $p = 0.041$ and $r = 0.59$, $p = 0.016$ respectively). Additionally, in the PD group increased [^{11}C]PBR28 V_T in the basal ganglia and substantia nigra (SN) was related to higher levels of neuroinflammation biomarker YKL-40 ($p < 0.01$).
Conclusion: Associations between CSF biomarkers, motor disability and [^{11}C]PBR28 V_T in the striatum and SN may support a role for neuroinflammation in PD.

1. Introduction

The aetiology of Parkinson's disease (PD) is still unclear but growing evidence suggests that neuroinflammation has a crucial role in its pathology. It has been associated with PD in studies of activated microglia and inflammatory cytokines and cerebrospinal fluid (CSF) [1]. Higher levels of inflammatory transmitters and activated immune defence cells have been detected in CSF and blood in subjects with PD, compared to healthy controls [1]. However, the relationship between neuroinflammation and neurodegeneration and clinical features of PD remains poorly understood.

Microglial mitochondria express an 18 kDa translocator protein

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(*TSPO*) which has a low expression in resident microglia but is significantly increased in activated microglia [2], which represents a hallmark in neuroinflammation. It is also overexpressed in the reactive astrocytes [2]. [^{11}C]PK11195 is a PET radioligand that binds to *TSPO* and has been widely used to image neuroinflammation in vivo. Subjects with PD showed significantly increased [^{11}C]PK11195 binding and the increased binding correlated with the severity of PD motor symptoms [3]. The findings have not, however, been consistently confirmed [3]. [^{11}C]PK11195 has a poor signal-to-noise ratio which has led to the development of so-called second-generation *TSPO* tracers, such as [^{11}C]PBR28. The binding of [^{11}C]PBR28 is affected by a single nucleotide polymorphism (rs6971) [4] and recently, it was demonstrated that also other biological factors may contribute to the binding, including body mass index (BMI), age and sex [5].

In this study, we examined the distribution and severity of neuroinflammation in PD with [^{11}C]PBR28 PET and CSF biomarkers for neuroinflammation, neurodegeneration, and alfa-synuclein levels with dopaminergic functioning measured with 6-[^{18}F]-fluoro-L-dopa ([^{18}F]FDOPA) PET.

2. Materials and methods

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland and was conducted according to the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and following Good Clinical Practice guidelines. Written informed consent was obtained from all participants according to the declaration of Helsinki.

The study included 20 subjects with PD and 10 healthy controls, all vetted for medical history and examined by a clinical neurologist. Participants with neurodegenerative disease or a significant neurological illness other than PD were excluded. An additional 41 controls from the CIRI (Cognition, Insulin Resistance and Inflammation) Study, focusing on Alzheimer's disease risk factors, were also incorporated with the permission of the corresponding researchers. All participants underwent rs6971 polymorphism genotyping for the TSPO gene prior to imaging to determine the high (HAB), mixed (MAB) and low-affinity binders (LAB). The low-affinity binders (LAB) were excluded from the study. PD participants matched the UK Brain Bank criteria for idiopathic PD. Demographics are presented in Table 1.

All PD participants were on their individual standard PD medication including dopamine agonists, levodopa and MAO-B inhibitors. The Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) was evaluated during the OFF stage (levodopa was discontinued for a minimum of 12 h in advance, dopamine agonists and MAO-B inhibitors 24h in advance). To confirm the clinical diagnosis of PD, the subjects with PD underwent [^{18}F]FDOPA PET examination showing typical findings for PD.

Table 1
Demographics and characteristics of all subjects with PD and healthy controls.

	PD	Healthy Controls	*p*-value
Number (Male/female)	20 (4/16)	51 (28/23)	0.008
Subjects with valid [11C] PBR28 data, PD n = 15, HC n = 51	15 (4/11)[a]	(41 (18/23))[c]	0.054[b]
Age (years), mean (SD)	66.2 (5.9) 66.0 (6.6)[a]	70.0 (4.9) (71.12 (3.2))[c]	0.003 0.011[b]
BMI, mean (SD) (subjects with valid [^{11}C] PBR28 data, PD n = 15, HC n = 51)	27.0 (6.6)[a]	26.3 (3.6) (26.5 (3.5))[c]	0.88
TSPO genotype (HAB/MAB) (Subjects with valid [^{11}C] PBR28 data, PD n = 15, HC n = 51)	12/5 (10/5)	28/23 (22/19)[c]	0.26 (0.56)[b]
Motor UPDRS score, mean (SD)	27.1 (8.0)	–	–
Duration of disease (years), mean (SD)	8.6 (5.2)	–	–
Hoehn and Yahr scale (Median (range))	2.5 (2.0–3.0)		

HAB: high-affinity binder, MAB: mixed-affinity binder.
[a] Subjects with valid [11C]PBR28 data in PD group (n = 15).
[b] PD subjects with valid [11C]PBR28 data (n = 15) compared to healthy controls (n = 51).
[c] CIRI study participants.

2.1. Cerebrospinal fluid

Thirty-eight subjects (17 PD (age years (SD): 66.7(6.1), F/M: 3/14) and 21 HC (age years (SD): 67.4(6.0), F/M 10/11) (age $p = 0.7$, sex $p = 0.02$) gave their consent to CSF sampling. CSF samples were centrifuged and aliquoted before being stored at −80 °C and transferred to the University of Gothenburg for analysis. Concentrations of sTREM2, NG, YKL-40, α-syn, and oligo-aSyn were measured using various assays, including in-house electrochemiluminescence, ELISA, and Simoa assays, as previously outlined [6–8].

2.2. Radiochemistry

The [^{11}C]PBR28 was prepared as described previously from its corresponding desmethyl-PBR28 precursor (PharmaSynth AS, Tartu, Estonia) [5].

2.3. PET imaging analyses

The PET data were realigned and co-registered with anatomical MR T1-weighted images using SPM12 software (Wellcome Trust Centre for Neuroimaging, London, UK) in MATLAB (The Mathworks, Natick, MA). Global grey matter and three bilateral regions of interest (ROIs) the thalamus, caudate nucleus, and putamen were automatically delineated with FreeSurfer software (vs 6). A bilateral substantia nigra ROI was created using the Hammers atlas.

For quantitative assessment of [^{11}C]PBR28 binding, regional distribution volumes (V_T) were estimated using Logan's method 30–70 min post-injection, with the metabolite-corrected arterial plasma time-activity curve as the input function. The reference tissue input Patlak method was applied to calculate the influx constant K_i^{ref} from 15 to 90 min post-[^{18}F]FDOPA injection, using the occipital region as reference [9,10].

2.4. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics (version 25) and JMP Pro 14. The data distribution was analyzed using Shapiro-Wilk's test alongside histograms. Differences in [^{11}C]PBR28 V_T across various ROIs between groups were probed using the General Linear Model (GLM), with BMI, TSPO, age and sex as adjustments. Sensitivity analyses on certain ROIs like CAU and SN, which showed non-normal distribution, were performed using log-transformed values. Additionally, subgroup evaluations based on the TSPO genotype were executed for the HAB subgroup through the same GLM approach, while the MAB subgroup underwent two-sample t-tests and the Mann-Whitney *U* test for non-normally distributed V_T values. The differences in [^{11}C]PBR28 V_T between males and females were explored with the two-samples *t*-test.

Correlations between [^{18}F]FDOPA K_i^{ref} and [^{11}C]PBR28 V_T in the putamen and caudate nucleus, both contralateral and ipsilateral to predominant motor symptoms, were conducted using Pearson partial correlation coefficients, adjusting for the TSPO genotype. Paired sample t-tests compared [^{18}F]FDOPA K_i^{ref} and [^{11}C]PBR28 V_T within these regions, with the substantia nigra distribution necessitating a Wilcoxon signed-rank test.

For correlations involving UPDRS-III, disease duration, and various biomarkers with [^{18}F] FDOPA K_i^{ref} in the PD group, the Pearson correlation coefficient was employed. No significant correlations were

observed between sex and any of the CSF markers and thus only age was included in the analyses as a covariate. The role of YKL-40 was scrutinized using Pearson partial correlation with age as a covariate, and the TSPO genotype-adjusted Pearson partial correlation was applied for other correlations with [^{11}C]PBR28 V_T. Spearman's correlation was utilized for non-normally distributed sTREM2 and correlations with [^{11}C]PBR28 in the PD group when the sample size was limited. CSF biomarker differences were analyzed with a two-sample *t*-test, while age-adjusted YKL-40 differences used GLM. All results with $p < 0.05$ were considered statistically significant.

3. Results

There was a significant negative correlation between BMI and [^{11}C]PBR28 V_T in all studied regions ($p < 0.01$). There was no significant difference in [^{11}C]PBR28 V_T between sexes or correlation between [^{11}C]PBR28 V_T and age ($p > 0.05$). There were no significant differences in the V_T between the PD group and healthy controls in the studied regions. In PD subjects there were no significant differences between the [^{11}C]PBR28 V_T in the contralateral and ipsilateral caudate nucleus (mean 2.79 vs 2.78, $p = 0.84$), putamen (mean 3.88 vs 3.92, $p = 0.54$) and substantia nigra (median 4.49 vs 4.03, $p = 0.39$). No significant relationship was found between [^{18}F]FDOPA K_i^{ref} and [^{11}C]PBR28 V_T in any studied region ($p > 0.1$).

UPDRS-III motor part total score and [^{11}C]PBR28 V_T did not correlate in any studied region ($p > 0.1$). No significant correlation was found between UPDRS-III and the duration of the disease ($p > 0.1$) nor between the duration of the disease and [^{11}C]PBR28 V_T ($p > 0.1$). Lower [^{18}F]FDOPA K_i^{ref} correlated with higher UPDRS-III scores but did not reach statistical significance in the (contralateral or ipsilateral) striatum ($p > 0.08$).

Age correlated with YKL-40 levels ($r = 0.59$, $p < 0.001$) but not with the level of sTREM2 ($r = 0.22$, $p = 0.30$) or NG ($r = 0.23$, $p = 0.11$). There were no differences between subjects with PD and controls in sTREM2 ($p = 0.07$) or YKL-40 ($p > 0.1$) levels (Fig. 1). Surprisingly, the control group had higher NG values than the PD group (median 162 vs 180, $p = 0.044$). There were no significant differences in aSyn, oligo-aSyn or their ratio between groups ($p > 0.1$).

UPDRS-III total score showed a positive correlation with sTREM2 and NG levels (Fig. 1, $r = 0.52$, $p = 0.041$ and $r = 0.59$, $p = 0.016$ respectively). A similar association was not observed between YKL-40 and UPDRS-III total score ($p = 0.15$, Fig. 1). Disease duration was not associated with any of the CSF marker levels. No significant correlations were observed between CSF markers and [^{18}F]FDOPA K_i^{ref} in substantia nigra, caudate nucleus, or putamen ($p > 0.1$). aSyn, oligo-aSyn or their ratio did not correlate with UPDRS-III nor with [^{18}F]FDOPA K_i^{ref} in substantia nigra, caudate nucleus, or putamen ($p > 0.1$).

Interestingly, in an exploratory subgroup analysis including subjects with PD who had undergone both [^{11}C]PBR28 PET and CSF sampling ($n = 12$) YKL-40 levels were found to increase with higher [11C]PBR28 V_T in the ipsilateral putamen ($r = 0.65$, $p = 0.043$) and contralateral thalamus ($r = 0.66$, $p = 0.039$) when controlling for genotype and age. Due to the small sample size, this association was also explored with Spearman's correlation coefficient in which the two genotypes were

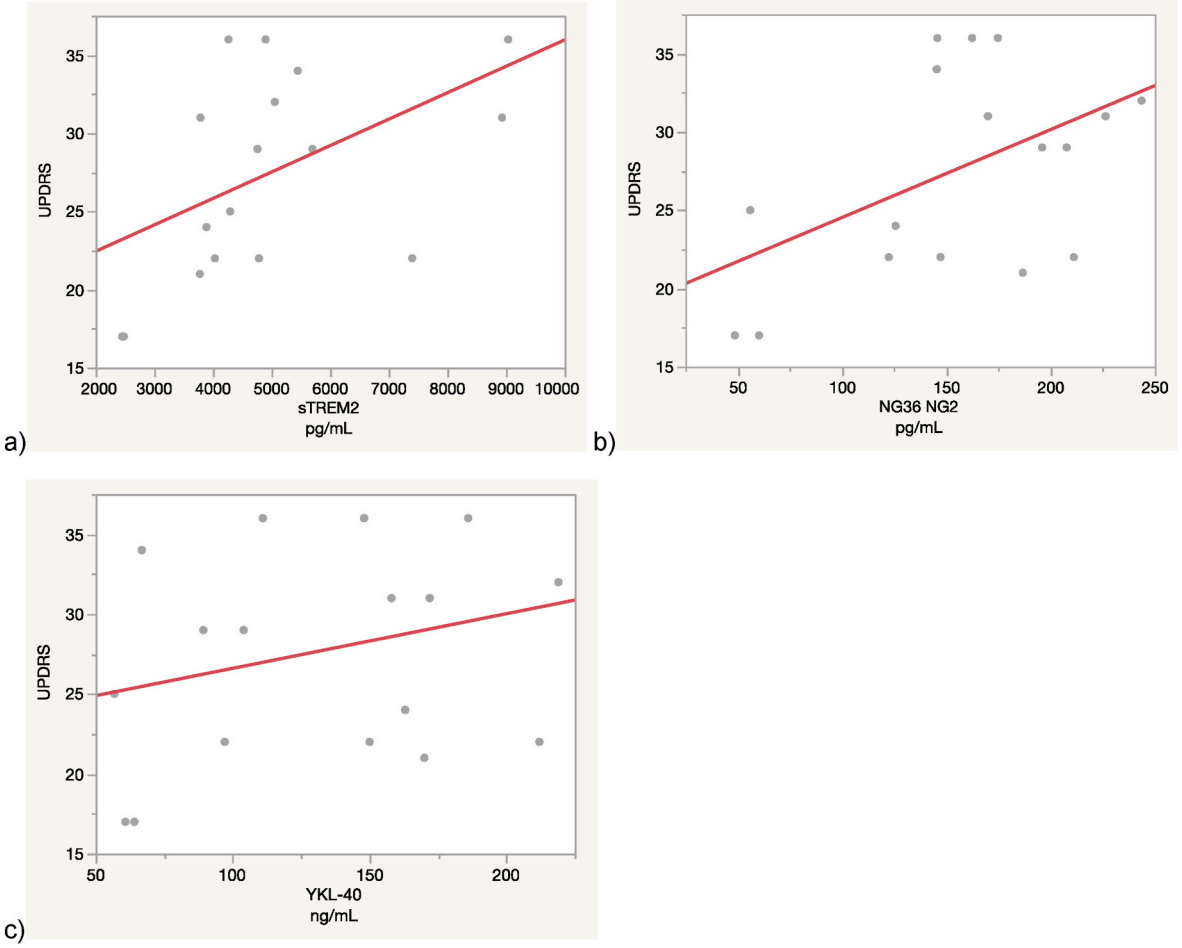

Fig. 1. UPDRS III total score in relation to CSF markers. A) sTREM2 $r_s = 0.52$, $p = 0.041$, b) NG $r = 0.59$, $p = 0.016$ and c) YKL-40 $r = 0.38$, $p = 0.15$.
r_s = Spearman correlation coefficient
r = Pearson correlation coefficient.

analyzed separately. In the HAB group (n = 8) YKL-40 increased with [^{11}C]PBR28 V_T in the substantia nigra (r = 0.88), caudate (r = 0.86), and putamen (r = 0.86) ($p < 0.01$, in all regions) but not in cortical regions. Similar associations were not observed between the other CSF markers and [^{11}C]PBR28 V_T or in the healthy controls ($p > 0.1$). Also, no significant correlations were observed between aSyn, oligo-aSyn or their ratio and [^{11}C]PBR28 V_T in PD or HC groups.

4. Discussion

In our study, both subjects with PD and healthy controls underwent PET examinations with the second-generation TSPO radioligand [^{11}C]PBR28. We found no significant differences in [^{11}C]PBR28 binding between the two groups. As an extension to previous studies, we identified a correlation between the severity of motor symptoms and higher levels of neuroinflammation markers in CSF.

A recent study reported no significant differences in [^{11}C]PBR28 binding between PD subjects with PD and healthy controls [11] which is supported by our results even when taking BMI as a covariate. In the current study, BMI correlated with [^{11}C]PBR28 binding which is consistent with our findings in an earlier study [5] indicating that BMI, age, and sex should be taken into account when analyzing [^{11}C]PBR28 binding as was done in the current study.

Previous PET studies utilizing the first-generation TSPO tracer [^{11}C]PK11195 have documented increased binding in PD patients, especially in substantia nigra, pons, basal ganglia, and cortical regions [3]. Factors such as age, disease stage, single nucleotide polymorphism (rs6971) and sex could influence these results, but the predominant determinant seems to be the tracer itself.

No significant relationship was found between [^{11}C]PBR28 binding and [18F]FDOPA or UPDRS-III scores in PD, consistent with previous studies [3,11]. [^{11}C]PK11195 binding has shown inverse correlation with putamen dopaminergic activity in early PD, but not in later stages [3]. The moderate disease stage of our patients may explain the lack of association observed here.

Higher sTREM2 and NG levels were associated with increased motor disability in PD subjects. This finding is supported by a recent study reporting that CSF sTREM2 is associated with the progression of PD motor symptoms evaluated by UPDRS total and motor part (III) scores [12]. Future studies should explore neuroinflammatory markers across different PD motor subtypes.

The higher neurogranin levels observed in the control group may be explained by sex differences, as elderly men have lower levels than women [13]. The PD group had more men (11 men, 4 women), while the control group had a more balanced distribution (23 men, 28 women), which could have influenced the results. It should be noted that the populations studied for CSF biomarkers and PET imaging partially overlap and one should therefore interpret these explorative analyses with caution.

While post-mortem studies show activated microglia in Parkinson's disease, [^{11}C]PBR28 PET in this in vivo study was unable to detect them, despite elevated CSF YKL-40 levels indicating neuroinflammation. This raises questions about whether [11C]PBR28 binding reflects microglial activation, astrocytes, or another mechanism. The relationship between TSPO expression and neuroinflammation remains unclear. Additionally, the patients in this study were in the moderately advanced stages of Parkinson's disease (H&Y stage 2–3). Since neuroinflammation could be an early event in the natural course of the disease, potential differences in [11C]PBR28 binding might be observed in earlier stages of the disease, and this factor may have influenced the current findings.

Our findings suggest neuroinflammation plays a role in PD, as indicated by CSF results, but [11C]PBR28 may not be the best PET tracer for this purpose. Further studies using advanced PET tracers and a range of biomarkers (GFAP, NFL) are needed to better understand neuroinflammation in PD.

CRediT authorship contribution statement

H. Al-Abdulrasul: Writing – review & editing, Writing – original draft, Validation, Software, Investigation, Formal analysis, Data curation. **R. Ajalin:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. **J. Tuisku:** Writing – review & editing, Software, Formal analysis, Data curation. **H. Zetterberg:** Writing – review & editing, Investigation, Formal analysis, Data curation. **K. Blennow:** Writing – review & editing, Investigation, Formal analysis, Data curation. **T. Vahlberg:** Writing – review & editing, Methodology, Formal analysis, Data curation. **L. Ekblad:** Writing – review & editing, Investigation, Data curation. **S. Helin:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **S. Forsback:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **J.O. Rinne:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **A. Brück:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Haidar Al-Abdulrasul reports financial support was provided by Finnish Parkinson Foundation. Riikka Ajalin reports financial support was provided by Finnish Parkinson Foundation. Anna Bruck reports financial support was provided by Finnish Parkinson Foundation. Haidar Al-Abdulrasul reports financial support was provided by Helsinki University research funds. Anna Bruck reports financial support was provided by Finnish State Research Funding (VTR). Henrik Zetterberg reports a relationship with Swedish Research Council (2018 02532) that includes: funding grants. Henrik Zetterberg reports a relationship with The European Research Council (681 712) that includes: funding grants. Henrik Zetterberg reports a relationship with Swedish State Support for Clinical Research (ALFGBG 720931) that includes: funding grants. Henrik Zetterberg reports a relationship with the Alzheimer Drug Discovery Foundation (ADDF), USA (201 809 2016862) that includes: funding grants. Henrik Zetterberg reports a relationship with The AD Strategic Fund and the Alzheimer's Association (ADSF 21 831376C, ADSF 21 831381 C and ADSF 21 831377 C) that includes: funding grants. Henrik Zetterberg reports a relationship with the Olav Thon Foundation that includes: funding grants. Henrik Zetterberg reports a relationship with The Erling-Persson Family Foundation that includes: funding grants. Henrik Zetterberg reports a relationship with Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2019 0228) that includes: funding grants. Henrik Zetterberg reports a relationship with The European Union's Horizon 2020 research and innovation programme under the Marie Sktodowska Curie grant agreement No 860197 (MIRIADE) that includes: funding grants. Henrik Zetterberg reports a relationship with European Union Joint Program for Neurodegenerative Disorders (JPND2021 00694) that includes: funding grants. Henrik Zetterberg reports a relationship with the UK Dementia Research Institute at UCL that includes: funding grants. Kaj Blennow reports a relationship with Swedish Research Council (2017 00915) that includes: funding grants. Kaj Blennow reports a relationship with the Alzheimer Drug Discovery Foundation (ADDF), USA (RDAPB 201809 2016615) that includes: funding grants. Kaj Blennow reports a relationship with the Swedish Alzheimer Foundation (AF 742 881) that includes: funding grants. Kaj Blennow reports a relationship with Hjärnfonden, Sweden (FO2017 0243) that includes: funding grants. Kaj Blennow reports a relationship with the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG 715986) that includes: funding grants. Kaj Blennow reports a

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References

[1] M.G. Tansey, R.L. Wallings, M.C. Houser, M.K. Herrick, C.E. Keating, V. Joers, Inflammation and immune dysfunction in Parkinson disease, Nat. Rev. Immunol. 22 (2022) 657–673.

[2] S. Lavisse, M. Guillermier, A.-S.S. Hérard, F. Petit, M. Delahaye, N.V. Van Camp, L Ben Haim, V. Lebon, P. Remy, F. Dollé, T. Delzescaux, G. Bonvento, P. Hantraye, C. Escartin, L. Ben Haim, V. Lebon, P. Remy, F. Dollé, T. Delzescaux, G. Bonvento, P. Hantraye, C. Escartin, Reactive astrocytes overexpress TSPO and are detected by TSPO positron emission tomography imaging, J. Neurosci. 32 (2012) 10809–10818.

[3] L. Best, C. Ghadery, N. Pavese, Y.F. Tai, A.P. Strafella, New and old TSPO PET radioligands for imaging brain microglial activation in neurodegenerative disease, Curr. Neurol. Neurosci. Rep. 19 (2019) 24.

[4] S. Paul, E. Gallagher, J.S. Liow, S. Mabins, K. Henry, S.S. Zoghbi, R.N. Gunn, W. C. Kreisl, E.M. Richards, P. Zanotti-Fregonara, C.L. Morse, J. Hong, A. Kowalski, V. W. Pike, R.B. Innis, M. Fujita, Building a database for brain 18 kDa translocator protein imaged using [11C]PBR28 in healthy subjects, J. Cerebr. Blood Flow Metabol. 39 (2019) 1138–1147.

[5] J. Tuisku, P. Plavén-Sigray, E.C. Gaiser, L. Airas, H. Al-Abdulrasul, A. Brück, R. E. Carson, M.K. Chen, K.P. Cosgrove, L. Ekblad, I. Esterlis, L. Farde, A. Forsberg, C. Halldin, S. Helin, E. Kosek, M. Lekander, N. Lindgren, P. Marjamäki, E. Rissanen, M. Sucksdorff, A. Varrone, K. Collste, J.D. Gallezot, A. Hillmer, Y. Huang, C. O. Höglund, J. Johansson, A. Jucaite, J. Lampa, N. Nabulsi, B. Pittman, C. M. Sandiego, P. Stenkrona, J. Rinne, D. Matuskey, S. Cervenka, Effects of age, BMI and sex on the glial cell marker TSPO — a multicentre [11C]PBR28 HRRT PET study, Eur. J. Nucl. Med. Mol. Imag. 46 (2019) 2329–2338.

[6] M. Gisslén, A. Heslegrave, E. Veleva, A. Yilmaz, L.-M.M. Andersson, L. Hagberg, S. Spudich, D. Fuchs, R.W. Price, H. Zetterberg, CSF concentrations of soluble TREM2 as a marker of microglial activation in HIV-1 infection, Neurol Neuroimmunol NeuroInflammation 6 (2019) e512.

[7] M.T.M.M. Clarke, A. Brinkmalm, M.S. Foiani, I.O.C.C. Woollacott, C. Heller, A. Heslegrave, A. Keshavan, N.C. Fox, J.M. Schott, J.D. Warren, K. Blennow, H. Zetterberg, J.D. Rohrer, CSF synaptic protein concentrations are raised in those with atypical Alzheimer's disease but not frontotemporal dementia, Alzheimer's Res. Ther. 11 (2019) 105.

[8] M. von Euler Chelpin, L. Söderberg, J. Fälting, C. Möller, M. Giorgetti, R. Constantinescu, K. Blennow, H. Zetterberg, K. Höglund, Alpha-synuclein protofibrils in cerebrospinal fluid: a potential biomarker for Parkinson's disease, J. Parkinsons Dis. 10 (2020) 1429–1442.

[9] C.S. Patlak, R.G. Blasberg, Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations, J. Cerebr. Blood Flow Metabol. 5 (1985) 584–590.

[10] A. Brück, S. Aalto, E. Rauhala, J. Bergman, R. Marttila, J.O. Rinne, A follow-up study on 6-[18F]Fluoro-L-dopa uptake in early Parkinson's disease shows nonlinear progressionin the putamen, Mov. Disord. 24 (2009) 1009–1015.

[11] K. Varnäs, Z. Cselényi, A. Jucaite, C. Halldin, P. Svenningsson, L. Farde, A. Varrone, PET imaging of [11 C]PBR28 in Parkinson's disease patients does not indicate increased binding to TSPO despite reduced dopamine transporter binding, Eur. J. Nucl. Med. Mol. Imag. 46 (2019) 367–375.

[12] X. Zhang, X. Zhong, L. Wang, H. Li, L. Yang, X. Li, X. Yu, A. Xie, Effects of soluble TREM2 on motor progression in Parkinson's disease, Neurosci. Lett. 807 (2023).

[13] M.M. Mielke, J.A. Syrjanen, K. Blennow, H. Zetterberg, I. Skoog, P. Vemuri, M. M. Machulda, J. Graff-Radford, D.S. Knopman, C.R. Jack, R.C. Petersen, S. Kern, Comparison of variables associated with cerebrospinal fluid neurofilament, total-tau, and neurogranin, Alzheimer's Dementia 15 (2019) 1437–1447.