RESEARCH ARTICLE

# Imaging of dopamine transporters in Parkinson disease: a meta-analysis of $^{18}$F/$^{123}$I-FP-CIT studies

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## Abstract

**Objective:** $^{18}$F-FP-CIT and $^{123}$I-FP-CIT are widely used radiotracers in molecular imaging for Parkinson's disease (PD) diagnosis. Compared with $^{123}$I-FP-CIT, $^{18}$F-FP-CIT has superior tracer kinetics. We aimed to conduct a meta-analysis to assess the efficacy of using $^{18}$F-FP-CIT positron emission tomography (PET) and $^{123}$I-FP-CIT single-photon emission computed tomography (SPECT) of dopamine transporters in patients with PD in order to provide evidence for clinical decision-making. **Methods:** We searched the PubMed, Embase, Wanfang Data, and China National Knowledge Infrastructure databases to identify the relevant studies from the time of inception of the databases to 30 April 2020. We identified six PET studies, including 779 patients with PD and 124 healthy controls, which met the inclusion criteria. Twenty-seven SPECT studies with 1244 PD patients and 859 controls were also included in this meta-analysis. **Results:** Overall effect-size analysis indicated that patients with PD showed significantly reduced $^{18}$F-FP-CIT uptake in three brain regions [caudate nucleus: standardized mean difference (SMD) = −1.71, $Z$ = −3.31, $P$ = 0.0009; anterior putamen: SMD = −3.71, $Z$ = −6.26, $P$ < 0.0001; and posterior putamen: SMD = −5.49, $Z$ = −5.97, $P$ < 0.0001]. Significant decreases of $^{123}$I-FP-CIT uptake were also observed in the caudate (SMD = −2.31, $Z$ = −11.49, $P$ < 0.0001) and putamen (SMD = −3.25, $Z$ = −14.79, $P$ < 0.0001). **Interpretation:** In conclusion, our findings indicate that both $^{18}$F-FP-CIT PET and $^{123}$I-FP-CIT SPECT imaging of dopamine transporters can provide viable biomarkers for early PD diagnosis.

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder.[1] Its predominant pathological feature is the degeneration of dopaminergic neurons projecting from the substantia nigra pars compacta in the midbrain to the striatum (caudate and putamen nucleus). It clinically presents with motor impairment, including rigidity, bradykinesia, resting tremor, and postural imbalance.[2,3] However, early diagnosis of PD based on clinical signs and symptoms is difficult.[4] Furthermore, PD diagnosis solely based on clinical assessment is not always accurate since the clinical symptoms of PD could be similar to those of other neurodegenerative diseases. Moreover, studies have reported that at least 15% of the patients diagnosed with PD do not meet the clinical diagnostic criteria, while 20–25% were diagnosed with another condition, including atypical parkinsonian syndromes or essential tremor.[5–8]

Currently, apart from the clinical symptoms, some functional brain imaging modalities have been reported to increase the accuracy of PD diagnosis.[9,10] Dopaminergic dysfunction in patients with PD can be visualized through single-photon emission computed tomography (SPECT) and positron emission tomography (PET) using various radiotracers. SPECT derivatives include $^{123}$I-FP-CIT (DatScan™), $^{123}$I-beta-CIT (DopaScan™), $^{123}$I-altropane, and $^{99m}$Tc-TRODAT, while PET tracers include $^{11}$C-RTI-32, $^{11}$C-CFT, $^{11}$C-methylphenidate, $^{11}$C-nomifensine, $^{11}$C-dihydrotetrabenazine, $^{18}$F-DOPA, $^{18}$F-FE-PE2I, $^{18}$F-CFT, and $^{18}$F-FP-CIT.[11–18]

Compared with $^{18}$F-FP-CIT, $^{123}$I-FP-CIT has been shown to have a higher affinity for the presynaptic dopamine transporter and a longer half-life (6–13 h); furthermore, it has been commercially available for auxiliary diagnosis of PD using SPECT.[9,19] However, considering their higher nonspecific background signals, SPECT radiotracers, including $^{123}$I-FP-CIT and $^{123}$I-altropane, exhibit lower striatal/cerebellar uptake ratios.[16] $^{18}$F-DOPA, which is an effective substitute tracer for $^{123}$I-FP-CIT, has been reported to underestimate the degree of nigrostriatal impairment in SPECT imaging due to the upregulation of aromatic amino acid decarboxylase as a compensatory mechanism in the presynaptic dopaminergic nerve terminal.[6]

In contrast, $^{18}$F-FP-CIT has a shorter half-life (20–110 min) and superior tracer kinetics compared to other SPECT tracers; furthermore, it is well set up for detecting presynaptic dopaminergic deficiency in various parkinsonian syndromes.[20,21] Previous studies have reported a significantly faster decrease in striatal $^{18}$F-FP-CIT uptake in patients with PD compared to that in controls. Moreover, there are differences in the rates of decrease among the striatal subregions, namely, the caudate nucleus, anterior putamen, and posterior putamen, which indicate that $^{18}$F-FP-CIT may be more effective for the diagnosis of PD.[22–26]

However, there is heterogeneity among the studies, such as differences in the sample sizes, study design, and participant characteristics, as well as inadequate comparability and evidentiary value of findings from striatal subregion analysis. To the best of our knowledge, a meta-analysis of previous studies on $^{18}$F-FP-CIT PET/$^{123}$I-FP-CIT SPECT imaging of dopamine transporters for the diagnosis of PD has not been conducted to date. Therefore, we aimed to collectively evaluate $^{18}$F-FP-CIT PET/$^{123}$I-FP-CIT SPECT imaging findings of dopamine transporters in patients with PD, identify patterns of abnormalities, and propose evidence that can influence clinical decision-making with respect to the diagnosis of PD.

## Materials and Methods

### Search strategy and study selection

We searched for relevant studies in the PubMed, Embase, Wanfang Data, and China National Knowledge Infrastructure databases from the time of inception of the databases to 30 April 2020. This search included both English and Chinese articles. We used the following key terms: "$^{18}$F-FP-CIT," "$^{123}$I-FP-CIT," "Paralysis Agitans," "Parkinson's disease," "Idiopathic Parkinson disease," "Parkinsonism," "atypical Parkinsonism" "positron emission tomography," and "single-photon emission computed tomography." The references of the eligible articles were manually screened to retrieve potentially relevant studies deemed suitable for analysis. The inclusion criteria for studies in the meta-analysis were as follows: assessment of $^{18}$F-FP-CIT/$^{123}$I-FP-CIT uptake in the caudate nucleus or putamen (anterior and posterior putamen) while performing PET/SPECT and reporting of the corresponding outcomes [standardized uptake value ratio (SUVR)] in PD patients and healthy control subjects. We included cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials. We excluded case reports, letters to the editor not subjected to peer review, conference abstracts, as well as studies without well-defined cohorts of patients with PD, those without controls or consecutive patients seen in a unit, and those without quantitative outcomes.

Two independent investigators (Yanyan Kong and Chencheng Zhang) conducted the entire literature search and study selection process. In case of disagreements, the reviewers discussed their viewpoints, and a third investigator (Bomin Sun) was consulted if no consensus was reached. For studies that recruited participants within the same time period or from the same hospital, we only included the study with the largest sample size or the most pertinent outcomes to avoid duplication.

## Data extraction and statistical analysis

R software (version 3.6.1; The R Foundation, Vienna, Austria) and Statistical Analysis System (version 9.3; SAS Institute, Cary, NC) were used for statistical analysis. Several outcome measurements can be used in PET/SPECT studies on dopamine transporter binding in PD. Among them, regional SUVR or standardized uptake values measured using subject-specific FreeSurfer-generated volume of interest are considered the gold standard.[22] Two investigators (Yanyan Kong and Chencheng Zhang) independently extracted data from each study. The following variables were retrieved: name of the first author, year of publication, sample size, disease duration, age of the patients with PD and controls, and estimation of effects (means and standard deviations for the decrease in SUVR in the PD group compared with the healthy control group).

The standardized mean difference (SMD) and standard error (SE) of the SMD for the outcomes in the PD and control groups were calculated separately for the reported brain regions in each study. SMDs were used because the main outcomes of interest in PET/SPECT studies of dopamine transporter binding can be assessed by several possible outcome measurements.[27]. Random-effects meta-analysis using the DerSimonian and Laird method was considered due to high heterogeneity across the studies. $I^2$ statistics were used to assess the heterogeneity among the included studies. $P < 0.05$ was considered to indicate significant heterogeneity in the $I^2$ statistics test. Additionally, $I^2$ values of 0–25%, >25–50%, >50–75%, and >75% indicated insignificant, low, moderate, and high heterogeneity, respectively.[28] We had initially planned to assess the potential impact of moderator variables; however, the included studies did not provide adequate information for such examination. Given the small number of studies across all investigated domains, publication bias assessment using funnel plots was not suitable.[28–32] Therefore, publication bias was assessed using Rosenberg's Fail-safe N approach.[33] A fail-safe number represents the number of nonsignificant and unpublished (or missing) studies that must be included in the meta-analysis to render an observed statistically significant result nonsignificant.[33,34] We calculated the fail-safe N for each significant outcome, and results at $P < 0.05$ were considered statistically significant.

## Results

### Study selection and characteristics

The initial literature search yielded 1021 studies, from which we eliminated 259 duplicated studies and 643 articles that did not meet the inclusion criteria. The excluded articles included animal experiments (19), case reports (36), meeting abstracts (211), reviews (13), and topics not pertinent to the research question (303 were not ^{18}F-FP-CIT PET/^{123}I-FP-CIT SPECT studies, 37 were not PD studies, and 24 lacked quantitative outcomes). The preliminarily selected 119 full-text articles were reviewed for eligibility, after which 86 were excluded for reporting irrelevant variables and unobtainable data. We included the remaining 33 articles (six articles reported PET studies involving 779 patients with PD and 124 controls, and 27 reported SPECT studies involving 1244 PD patients and 859 controls) in this meta-analysis. These studies comprised cross-sectional surveys (10 studies), case-control studies (19 studies), and cohort studies (four studies).[17,22–26,35–61] Figure 1 illustrates the protocol for the literature search and study selection process. Table 1 summarizes the characteristics of the individual studies, including the sample sizes and participant characteristics. These studies were published from 1998 to 2019. Furthermore, except for one study on the caudate that did not report significant between-group differences, the remaining studies reported decreased ^{18}F-FP-CIT uptake.

### Estimates of effect size

The overall effect analysis of PET studies indicated a statistically significant decrease in the SUVR in the three striatum regions between PD patients and controls, as follows: caudate region, SMD = −1.71, 95% confidence interval (CI) [−2.73, −0.70], $Z = -3.31$, $P = 0.0009$; anterior putamen, SMD = −3.71, 95% CI [−4.87, −2.55], $Z = -6.26$, $P < 0.0001$; and posterior putamen, SMD = −5.49, 95% CI [−7.30, −3.69], $Z = -5.97$, $P < 0.0001$. Figures 2–4 show the forest plots for the estimates of the effect size. Compared with the controls, patients with PD showed significant decrease in the uptake level in both caudate and putamen in the 27 SPECT studies (caudate, SMD = −2.31, 95% CI [−2.71, −1.92], $Z = -11.49$, $P < 0.0001$; putamen, SMD = −3.25, 95% CI [−3.68, −2.82], $Z = -14.79$, $P < 0.0001$). Figures 5 and 6 show the forest plots for overall effect sizes of the SPECT studies.

### PET studies on atypical parkinsonism

Four studies[21,62–64] reported the application of ^{18}F-FP-CIT PET in atypical Parkinsonism. They suggested that ^{18}F-FP-CIT PETs could be useful for the differential diagnosis of atypical Parkinson.

### Heterogeneity

With respect to the assessment of ^{18}F-FP-CIT uptake, there was heterogeneity in the three striatal regions of interest (caudate: $I^2 = 90\%$, $P < 0.0001$; anterior

Records identified through database searching
(n=1021)
-PubMed :701
-Embase:301
-China National Knowledge Infrastructure:6
-Wanfang Data:13

Duplicates removed(n=259)

Records screened
(n=762)

Records excluded(n=643), with reasons
-animal experiment(n=19)
-case report(n=36)
-meeting abstract(n=211)
-review(n=13)
-topic not relevant for the research question(n=364)

Full texts assessed for eligibility
(n=119)

Full texts excluded(n=86), with reasons
-variable not relevant
-data unobtainable

Studies included in quantitative synthesis
(n=33)

**Figure 1.** Search results and flow chart for the inclusion of studies in the meta-analysis.

putamen: $I^2 = 91\%$, $P < 0.0001$; and posterior putamen: $I^2 = 95\%$, $P < 0.0001$). Statistical significance was observed in all heterogeneity tests (Figs. 2–4). The analysis also showed heterogeneity in the $^{123}$I-FP-CIT studies included (caudate, $I^2 = 89\%$, $P < 0.0001$; putamen, $I^2 = 91\%$, $P < 0.0001$) (Figs. 5–6).

## Publication bias

The calculation of Rosenberg's fail-safe numbers indicated that a large number of unpublished and non-significant studies (effect sizes of zero) would be needed to achieve a *P*-value >0.05 for the effect size of meta-

**Table 1.** Characteristics of the included studies.

| Study | PD (n) | HC (n) | PD age (years) | HC age (years) | PD sex (M/F) | HC sex (M/F) | Disease duration (years) | Tracer |
|---|---|---|---|---|---|---|---|---|
| Wang 2003 | 31 | 4 | 57 ± 8 | 59 ± 8 | – | – | – | ^{18}F-FP-CIT |
| Wang 2006 | 41 | 12 | 58 ± 8 | 59 ± 7 | – | – | 4.3 ± 3.4 | ^{18}F-FP-CIT |
| Song 2013 | 24 | 18 | 70 ± 8 | 70 ± 10 | 18/6 | 11/7 | 1.9 ± 0.7 | ^{18}F-FP-CIT |
| Kim 2015 | 56 | 71 | 61 ± 12 | 60 ± 10 | 31/25 | 39/32 | 2.7 ± 2.8 | ^{18}F-FP-CIT |
| Sung 2017 | 35 | 9 | 55 ± 12 | 70 ± 8 | 14/21 | 7/2 | 2.5 ± 2.8 | ^{18}F-FP-CIT |
| Yang 2017 | 592 | 10 | 70 ± 6 | 70 ± 8 | 40/502 | 2/8 | 6.0 ± 4.7 | ^{18}F-FP-CIT |
| Tissingh 1998 | 21 | 14 | 56 ± 10 | 54 ± 15 | 15/6 | 7/7 | 2.3 ± 1.3 | ^{123}I-FP-CIT |
| Booij 1999 | 19 | 10 | 57 | 53 | 18/1 | 1/9 | – | ^{123}I-FP-CIT |
| Booij 2001 | 32 | 36 | 53 ± 11 | 53 ± 18 | 24/8 | 16/20 | 2.0 ± 1.3 | ^{123}I-FP-CIT |
| Ceravolo 2004 | 20 | 8 | 67 ± 8 | 66 ± 9 | 13/7 | 5/3 | 4.3 ± 1.9 | ^{123}I-FP-CIT |
| O'Brien 2004 | 38 | 33 | 76 ± 5 | 75 ± 6 | 28/10 | 17/16 | 5.3 ± 7.3 | ^{123}I-FP-CIT |
| Tsuchida 2004 | 6 | 10 | 58 ± 12 | 36 ± 16 | 4/2 | 6/4 | 8.0 ± 4.7 | ^{123}I-FP-CIT |
| van Laere 2004 | 39 | 10 | 62 ± 11 | 60 ± 16 | 23/16 | 6/4 | 2.1 ± 1.3 | ^{123}I-FP-CIT |
| Varrone 2004 | 9 | 6 | 44 ± 3 | 51 ± 13 | 4/5 | 5/1 | – | ^{123}I-FP-CIT |
| Colloby 2005 | 20 | 22 | 74 ± 5 | 72 ± 4 | 14/6 | 13/9 | 4.5 ± 4.6 | ^{123}I-FP-CIT |
| Filippi 2005 | 29 | 18 | 61 ± 11 | 62 ± 8 | 16/13 | 9/9 | 2.2 ± 1.5 | ^{123}I-FP-CIT |
| Filippi 2006 | 21 | 20 | 64 ± 8 | 64 ± 7 | 12/9 | 9/11 | 2.7 ± 1.9 | ^{123}I-FP-CIT |
| Canesi 2007 | 38 | 14 | 66 ± 8 | – | 25/13 | – | 9.6 ± 4.0 | ^{123}I-FP-CIT |
| Isaias 2007 | 20 | 31 | 60 ± 11 | – | 11/9 | – | 1.5 ± 1.0 | ^{123}I-FP-CIT |
| Isaias 2008 | 47 | 31 | 62 ± 10 | 64 ± 10 | 28/19 | 13/18 | 3.0 ± 1.0 | ^{123}I-FP-CIT |
| Varrone 2008 | 24 | 6 | 46 ± 10 | 51 ± 13 | 16/8 | 5/1 | – | ^{123}I-FP-CIT |
| Isaias 2010 | 13 | 23 | 63 ± 9 | 71 ± 9 | 7/6 | 10/13 | 5.0 ± 2.8 | ^{123}I-FP-CIT |
| Kim 2010 | 14 | 12 | 67 ± 4 | 63 ± 6 | 11/3 | 8/4 | – | ^{123}I-FP-CIT |
| Cilia 2011 | 37 | 32 | 70 ± 5 | 70 ± 6 | 18/19 | 15/17 | 4.4 ± 2.9 | ^{123}I-FP-CIT |
| Djaldetti 2011 | 15 | 11 | 68 ± 9 | 61 ± 12 | 7/8 | – | 20.6 ± 6.3 | ^{123}I-FP-CIT |
| Isaias 2011 | 11 | 10 | 52 | 52 | 5/6 | 3/7 | – | ^{123}I-FP-CIT |
| Di Giuda 2012 | 21 | 17 | 60 ± 13 | 55 ± 14 | 14/7 | 7/10 | 4.0 ± 2.1 | ^{123}I-FP-CIT |
| Siepel 2014 | 339 | 158 | 61 ± 10 | 60 ± 11 | 219/120 | 98/60 | – | ^{123}I-FP-CIT |
| Roussakis 2016 | 28 | 12 | 69 ± 5 | 61 ± 9 | 19/9 | 7/5 | 9.8 ± 5.0 | ^{123}I-FP-CIT |
| Jakobson 2018 | 22 | 28 | 69 ± 8 | 70 ± 4 | – | – | 1.1 ± 0.8 | ^{123}I-FP-CIT |
| Nicastro 2019 | 280 | 208 | 70 ± 11 | 70 ± 11 | 148/132 | 83/125 | 1.3 ± 0.8 | ^{123}I-FP-CIT |
| Pilotto 2019 | 56 | 54 | 65 ± 10 | 61 ± 13 | 40/16 | 35/19 | 2.2 ± 2.1 | ^{123}I-FP-CIT |
| Wilson 2019 | 25 | 25 | 54 ± 8 | 46 ± 8 | 11/14 | 10/15 | 9.6 ± 3.9 | ^{123}I-FP-CIT |

Values are means ± standard deviation or n.
PD, Parkinson's disease; HC, healthy controls; M, male; F, female.
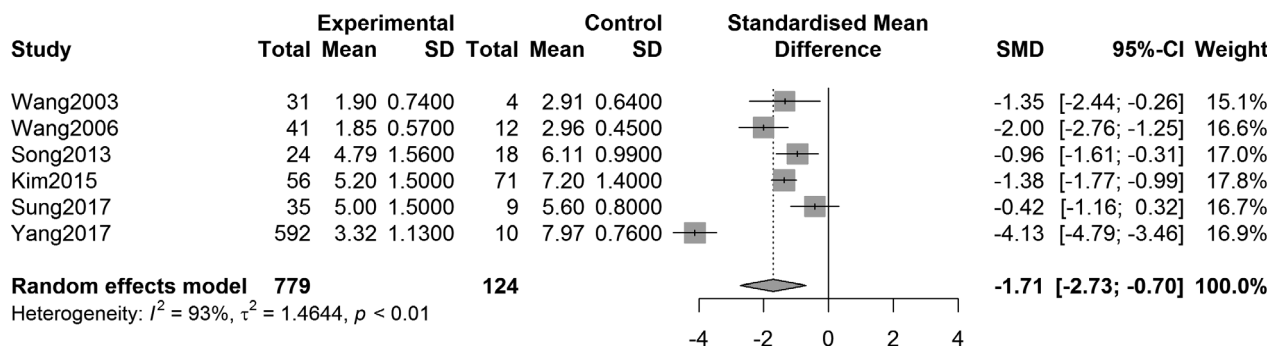


**Figure 2.** Forest plot for ^{18}F-FP-CIT PET studies assessing the decrease in SUVR in the caudate.

analyses of both PET and SPECT studies. A total of 418, 1966, and 4172 studies would be required to achieve $P > 0.05$ in meta-analyses of ^{18}F-FP-CIT PET imaging of the caudate, anterior putamen, and posterior putamen regions, respectively. Furthermore, for ^{123}I-FP-CIT SPECT studies, Rosenberg's fail-safe numbers were 18556 and 41260 for the pooled analysis of the caudate and putamen.

| Study | Experimental | | | Control | | | Standardised Mean Difference | SMD | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Mean | SD | Total | Mean | SD | | | | |
| Wang2003 | 31 | 1.56 | 0.6100 | 4 | 3.90 | 0.7900 | | -3.64 | [-5.02; -2.26] | 14.8% |
| Wang2006 | 41 | 1.55 | 0.5400 | 12 | 3.74 | 0.5200 | | -4.03 | [-5.05; -3.00] | 16.3% |
| Song2013 | 24 | 4.34 | 0.6500 | 18 | 6.43 | 0.8600 | | -2.75 | [-3.62; -1.88] | 16.9% |
| Kim2015 | 56 | 4.60 | 1.3000 | 71 | 9.20 | 1.4000 | | -3.37 | [-3.92; -2.82] | 17.9% |
| Sung2017 | 35 | 4.00 | 1.4000 | 9 | 7.20 | 1.1000 | | -2.33 | [-3.22; -1.44] | 16.8% |
| Yang2017 | 592 | 3.35 | 1.1600 | 10 | 10.38 | 0.8600 | | -6.07 | [-6.79; -5.36] | 17.4% |
| **Random effects model** | **779** | | | **124** | | | | **-3.71** | **[-4.87; -2.55]** | **100.0%** |
| Heterogeneity: $I^2 = 91\%$, $\tau^2 = 1.8841$, $p < 0.01$ | | | | | | | | | | |

**Figure 3.** Forest plot for ^{18}F-FP-CIT PET studies assessing the decrease in SUVR in the anterior putamen.

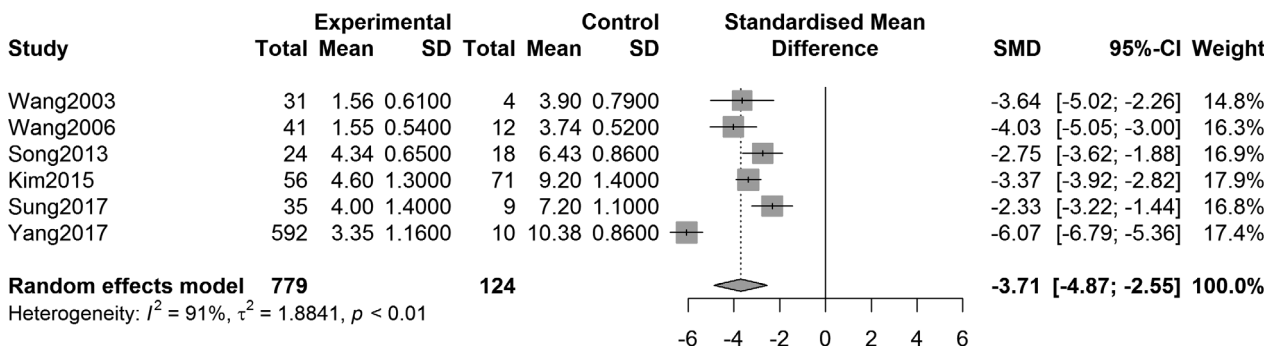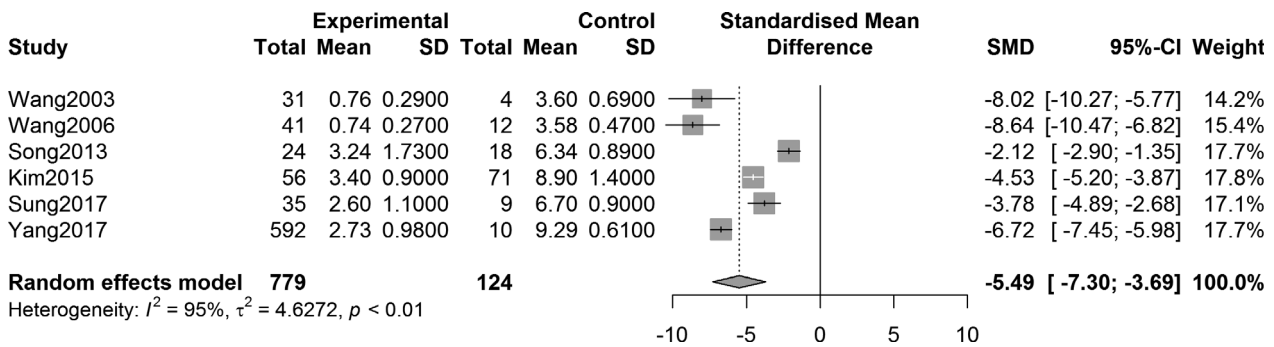| Study | Experimental | | | Control | | | Standardised Mean Difference | SMD | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Mean | SD | Total | Mean | SD | | | | |
| Wang2003 | 31 | 0.76 | 0.2900 | 4 | 3.60 | 0.6900 | | -8.02 | [-10.27; -5.77] | 14.2% |
| Wang2006 | 41 | 0.74 | 0.2700 | 12 | 3.58 | 0.4700 | | -8.64 | [-10.47; -6.82] | 15.4% |
| Song2013 | 24 | 3.24 | 1.7300 | 18 | 6.34 | 0.8900 | | -2.12 | [-2.90; -1.35] | 17.7% |
| Kim2015 | 56 | 3.40 | 0.9000 | 71 | 8.90 | 1.4000 | | -4.53 | [-5.20; -3.87] | 17.8% |
| Sung2017 | 35 | 2.60 | 1.1000 | 9 | 6.70 | 0.9000 | | -3.78 | [-4.89; -2.68] | 17.1% |
| Yang2017 | 592 | 2.73 | 0.9800 | 10 | 9.29 | 0.6100 | | -6.72 | [-7.45; -5.98] | 17.7% |
| **Random effects model** | **779** | | | **124** | | | | **-5.49** | **[-7.30; -3.69]** | **100.0%** |
| Heterogeneity: $I^2 = 95\%$, $\tau^2 = 4.6272$, $p < 0.01$ | | | | | | | | | | |

**Figure 4.** Forest plot for ^{18}F-FP-CIT PET studies assessing the decrease in SUVR in the posterior putamen.

## Discussion

### Summary of the findings

It is well-known that findings from studies with small sample sizes are less powerful.[65] Consequently, meta-analyses are considered to be powerful and widely used tools that compile results from different studies to draw more meaningful conclusions than those of individual reports.[27,66] In the meta-analysis of PET studies, the mean number of participants in the PD and control groups in each included study was 129 and 21, respectively. This disparity in the sample sizes mainly resulted from the imbalance in the number of participants recruited in Yang's study (592 patients with PD and 10 controls). As shown in Table 1, the number of participants in the other five included studies met the sample size requirements for a typical molecular imaging study.[67–75] With respect to individual studies, all included studies, except one (findings in the caudate nucleus in Sung's study[24]), reported a significant decrease in the SUVR for ^{18}F-FP-CIT uptake in the three striatum regions (caudate nucleus, anterior putamen, and posterior putamen) in patients with PD compared to that in the controls. Moreover, the overall effect size indicated significantly decreased ^{18}F-FP-CIT

uptake in the targeted cerebral regions. In addition, we performed a meta-analysis of ^{123}I-FP-CIT SPECT imaging studies. A total of 27 studies with 1244 PD patients and 859 healthy control subjects were included. The studies showed that patients with PD exhibited a significant decrease in uptake level in both the caudate and putamen compared to controls.

### Quality of meta-analysis

$I^2$ statistical analysis was used to assess heterogeneity among the included studies. We found high heterogeneity in the results for the three investigated cerebral regions with $I^2$ values ranging from 90% to 95%. Moreover, we conducted a statistical analysis using a random effects model. The heterogeneity could be attributed to differences in the study designs, sample sizes, study locations, characteristics of the study populations, the severity of PD at the time of imaging, disease duration, category of complications, and correction for relevant factors. There are some limitations to this meta-analysis. In the course of designing the study, we attempted to evaluate the potential impact of moderator variables using meta-regression analysis; however, the included studies did not provide adequate information. Notably,
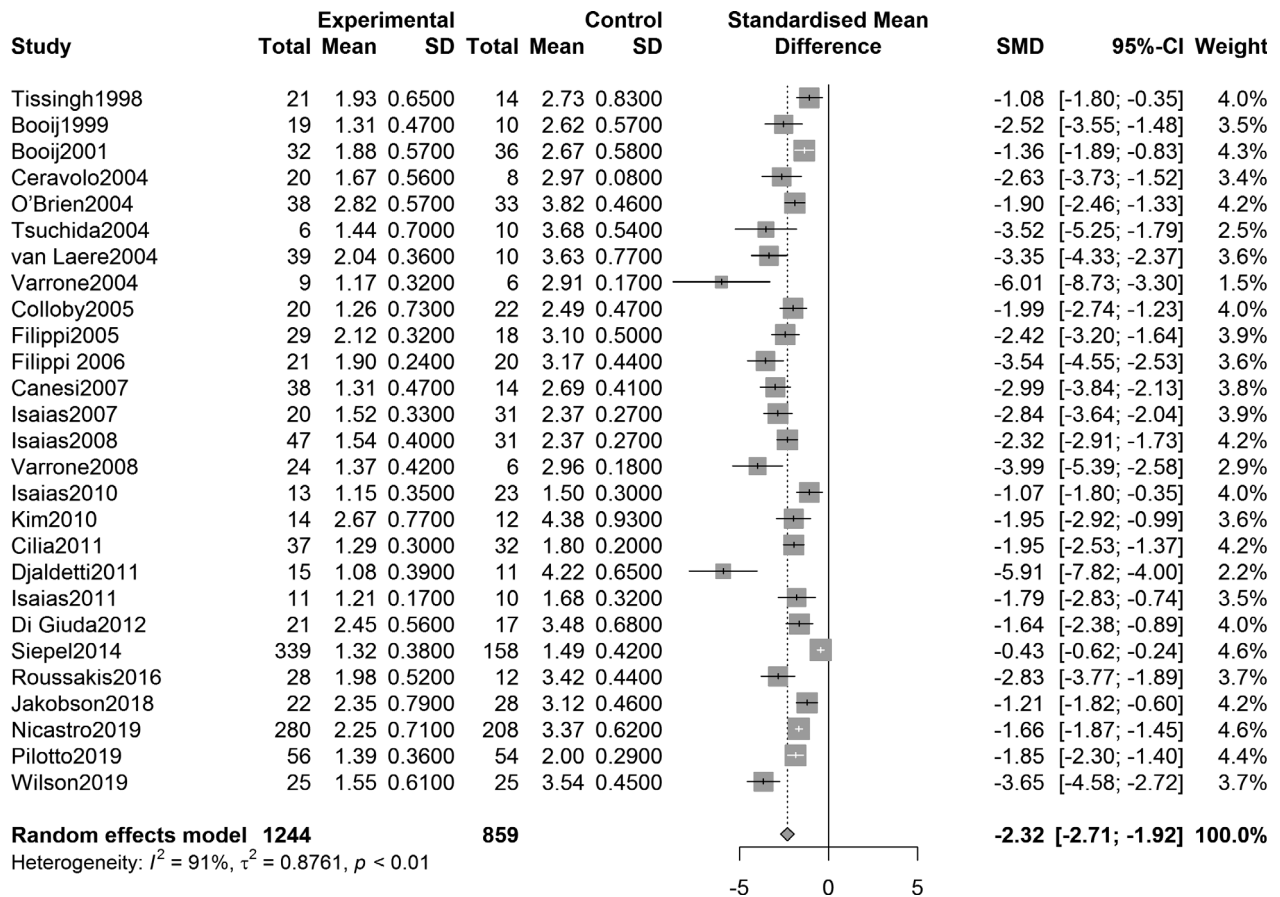
| Study | Total | Experimental Mean | SD | Total | Control Mean | SD | Standardised Mean Difference | SMD | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|---|---|
| Tissingh1998 | 21 | 1.93 | 0.6500 | 14 | 2.73 | 0.8300 | | -1.08 | [-1.80; -0.35] | 4.0% |
| Booij1999 | 19 | 1.31 | 0.4700 | 10 | 2.62 | 0.5700 | | -2.52 | [-3.55; -1.48] | 3.5% |
| Booij2001 | 32 | 1.88 | 0.5700 | 36 | 2.67 | 0.5800 | | -1.36 | [-1.89; -0.83] | 4.3% |
| Ceravolo2004 | 20 | 1.67 | 0.5600 | 8 | 2.97 | 0.0800 | | -2.63 | [-3.73; -1.52] | 3.4% |
| O'Brien2004 | 38 | 2.82 | 0.5700 | 33 | 3.82 | 0.4600 | | -1.90 | [-2.46; -1.33] | 4.2% |
| Tsuchida2004 | 6 | 1.44 | 0.7000 | 10 | 3.68 | 0.5400 | | -3.52 | [-5.25; -1.79] | 2.5% |
| van Laere2004 | 39 | 2.04 | 0.3600 | 10 | 3.63 | 0.7700 | | -3.35 | [-4.33; -2.37] | 3.6% |
| Varrone2004 | 9 | 1.17 | 0.3200 | 6 | 2.91 | 0.1700 | | -6.01 | [-8.73; -3.30] | 1.5% |
| Colloby2005 | 20 | 1.26 | 0.7300 | 22 | 2.49 | 0.4700 | | -1.99 | [-2.74; -1.23] | 4.0% |
| Filippi2005 | 29 | 2.12 | 0.3200 | 18 | 3.10 | 0.5000 | | -2.42 | [-3.20; -1.64] | 3.9% |
| Filippi 2006 | 21 | 1.90 | 0.2400 | 20 | 3.17 | 0.4400 | | -3.54 | [-4.55; -2.53] | 3.6% |
| Canesi2007 | 38 | 1.31 | 0.4700 | 14 | 2.69 | 0.4100 | | -2.99 | [-3.84; -2.13] | 3.8% |
| Isaias2007 | 20 | 1.52 | 0.3300 | 31 | 2.37 | 0.2700 | | -2.84 | [-3.64; -2.04] | 3.9% |
| Isaias2008 | 47 | 1.54 | 0.4000 | 31 | 2.37 | 0.2700 | | -2.32 | [-2.91; -1.73] | 4.2% |
| Varrone2008 | 24 | 1.37 | 0.4200 | 6 | 2.96 | 0.1800 | | -3.99 | [-5.39; -2.58] | 2.9% |
| Isaias2010 | 13 | 1.15 | 0.3500 | 23 | 1.50 | 0.3000 | | -1.07 | [-1.80; -0.35] | 4.0% |
| Kim2010 | 14 | 2.67 | 0.7700 | 12 | 4.38 | 0.9300 | | -1.95 | [-2.92; -0.99] | 3.6% |
| Cilia2011 | 37 | 1.29 | 0.3000 | 32 | 1.80 | 0.2000 | | -1.95 | [-2.53; -1.37] | 4.2% |
| Djaldetti2011 | 15 | 1.08 | 0.3900 | 11 | 4.22 | 0.6500 | | -5.91 | [-7.82; -4.00] | 2.2% |
| Isaias2011 | 11 | 1.21 | 0.1700 | 10 | 1.68 | 0.3200 | | -1.79 | [-2.83; -0.74] | 3.5% |
| Di Giuda2012 | 21 | 2.45 | 0.5600 | 17 | 3.48 | 0.6800 | | -1.64 | [-2.38; -0.89] | 4.0% |
| Siepel2014 | 339 | 1.32 | 0.3800 | 158 | 1.49 | 0.4200 | | -0.43 | [-0.62; -0.24] | 4.6% |
| Roussakis2016 | 28 | 1.98 | 0.5200 | 12 | 3.42 | 0.4400 | | -2.83 | [-3.77; -1.89] | 3.7% |
| Jakobson2018 | 22 | 2.35 | 0.7900 | 28 | 3.12 | 0.4600 | | -1.21 | [-1.82; -0.60] | 4.2% |
| Nicastro2019 | 280 | 2.25 | 0.7100 | 208 | 3.37 | 0.6200 | | -1.66 | [-1.87; -1.45] | 4.6% |
| Pilotto2019 | 56 | 1.39 | 0.3600 | 54 | 2.00 | 0.2900 | | -1.85 | [-2.30; -1.40] | 4.4% |
| Wilson2019 | 25 | 1.55 | 0.6100 | 25 | 3.54 | 0.4500 | | -3.65 | [-4.58; -2.72] | 3.7% |
| **Random effects model** | **1244** | | | **859** | | | | **-2.32** | **[-2.71; -1.92]** | **100.0%** |

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.8761$, $p < 0.01$

**Figure 5.** Forest plot for ^{123}I-FP-CIT SPECT studies assessing the decrease in SUVR in the caudate.

Yang's study enrolled 592 patients with PD and only 10 controls; therefore, we also performed a meta-analysis after excluding this study. This led to a decrease in the $I^2$ values from 90% to 59%, 91% to 50%, and 95% to 94% in the caudate nucleus, anterior putamen, and posterior putamen, respectively. This indicated that allocation of participants to the PD and control groups in Yang's study may be a potential source of bias. In this meta-analysis, the number of studies included across all investigated domains was too small to assess publication bias using funnel plots; this may have reduced the statistical power of this study.[28–32] Consequently, we calculated Rosenberg's fail-safe numbers, which were quite high as follows: $N_C = 418$, $N_{AP} = 1966$, and $N_{PP} = 4172$ (C: caudate, AP: anterior putamen, PP: posterior putamen). It has been suggested that possible publication bias could be safely ignored when the fail-safe numbers are high.[33,34] Considering the limitations discussed above, the results of this analysis may have limited reference value and the observed correlations should be interpreted with caution.

## Clinical implications

Despite the limitations of this meta-analysis, the overall effects showed significantly reduced ^{18}F-FP-CIT/^{123}I-FP-CIT uptake in patients with PD compared to that in the controls in cerebral regions of interest, which was consistently noted in the original studies included in this analysis. Therefore, ^{18}F-FP-CIT/^{123}I-FP-CIT are efficient tracers for primary PD diagnosis. Moreover, the six PET studies included reported that ^{18}F-FP-CIT was effective not only in differentiating patients with PD from the healthy controls but also in determining the severity of PD.[22,24–26,35] The progression rates differed significantly according to the various striatal subregions.[24] In PET studies, the posterior putamen is the most severely affected region in the striatum while the caudate nucleus is relatively spared.[76–78] However, data from some of these studies were not appropriate for assessment in this meta-analysis. Nevertheless, we believe that our findings are robust, given the number of studies included. Well-designed longitudinal studies are warranted to address issues regarding the
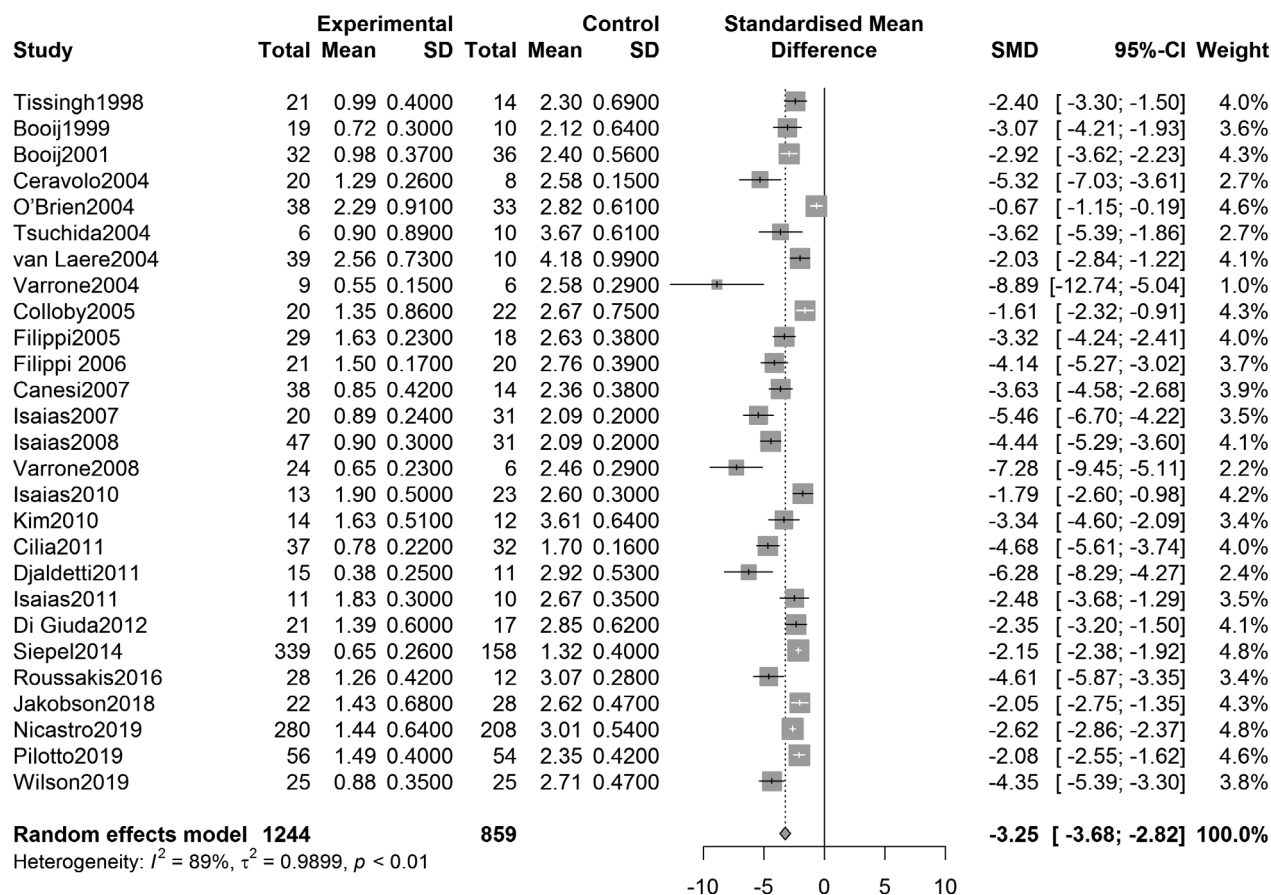
| Study | Total | Experimental Mean | SD | Total | Control Mean | SD | Standardised Mean Difference | SMD | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|---|---|
| Tissingh1998 | 21 | 0.99 | 0.4000 | 14 | 2.30 | 0.6900 | | -2.40 | [ -3.30; -1.50] | 4.0% |
| Booij1999 | 19 | 0.72 | 0.3000 | 10 | 2.12 | 0.6400 | | -3.07 | [ -4.21; -1.93] | 3.6% |
| Booij2001 | 32 | 0.98 | 0.3700 | 36 | 2.40 | 0.5600 | | -2.92 | [ -3.62; -2.23] | 4.3% |
| Ceravolo2004 | 20 | 1.29 | 0.2600 | 8 | 2.58 | 0.1500 | | -5.32 | [ -7.03; -3.61] | 2.7% |
| O'Brien2004 | 38 | 2.29 | 0.9100 | 33 | 2.82 | 0.6100 | | -0.67 | [ -1.15; -0.19] | 4.6% |
| Tsuchida2004 | 6 | 0.90 | 0.8900 | 10 | 3.67 | 0.6100 | | -3.62 | [ -5.39; -1.86] | 2.7% |
| van Laere2004 | 39 | 2.56 | 0.7300 | 10 | 4.18 | 0.9900 | | -2.03 | [ -2.84; -1.22] | 4.1% |
| Varrone2004 | 9 | 0.55 | 0.1500 | 6 | 2.58 | 0.2900 | | -8.89 | [-12.74; -5.04] | 1.0% |
| Colloby2005 | 20 | 1.35 | 0.8600 | 22 | 2.67 | 0.7500 | | -1.61 | [ -2.32; -0.91] | 4.3% |
| Filippi2005 | 29 | 1.63 | 0.2300 | 18 | 2.63 | 0.3800 | | -3.32 | [ -4.24; -2.41] | 4.0% |
| Filippi 2006 | 21 | 1.50 | 0.1700 | 20 | 2.76 | 0.3900 | | -4.14 | [ -5.27; -3.02] | 3.7% |
| Canesi2007 | 38 | 0.85 | 0.4200 | 14 | 2.36 | 0.3800 | | -3.63 | [ -4.58; -2.68] | 3.9% |
| Isaias2007 | 20 | 0.89 | 0.2400 | 31 | 2.09 | 0.2000 | | -5.46 | [ -6.70; -4.22] | 3.5% |
| Isaias2008 | 47 | 0.90 | 0.3000 | 31 | 2.09 | 0.2000 | | -4.44 | [ -5.29; -3.60] | 4.1% |
| Varrone2008 | 24 | 0.65 | 0.2300 | 6 | 2.46 | 0.2900 | | -7.28 | [ -9.45; -5.11] | 2.2% |
| Isaias2010 | 13 | 1.90 | 0.5000 | 23 | 2.60 | 0.3000 | | -1.79 | [ -2.60; -0.98] | 4.2% |
| Kim2010 | 14 | 1.63 | 0.5100 | 12 | 3.61 | 0.6400 | | -3.34 | [ -4.60; -2.09] | 3.4% |
| Cilia2011 | 37 | 0.78 | 0.2200 | 32 | 1.70 | 0.1600 | | -4.68 | [ -5.61; -3.74] | 4.0% |
| Djaldetti2011 | 15 | 0.38 | 0.2500 | 11 | 2.92 | 0.5300 | | -6.28 | [ -8.29; -4.27] | 2.4% |
| Isaias2011 | 11 | 1.83 | 0.3000 | 10 | 2.67 | 0.3500 | | -2.48 | [ -3.68; -1.29] | 3.5% |
| Di Giuda2012 | 21 | 1.39 | 0.6000 | 17 | 2.85 | 0.6200 | | -2.35 | [ -3.20; -1.50] | 4.1% |
| Siepel2014 | 339 | 0.65 | 0.2600 | 158 | 1.32 | 0.4000 | | -2.15 | [ -2.38; -1.92] | 4.8% |
| Roussakis2016 | 28 | 1.26 | 0.4200 | 12 | 3.07 | 0.2800 | | -4.61 | [ -5.87; -3.35] | 3.4% |
| Jakobson2018 | 22 | 1.43 | 0.6800 | 28 | 2.62 | 0.4700 | | -2.05 | [ -2.75; -1.35] | 4.3% |
| Nicastro2019 | 280 | 1.44 | 0.6400 | 208 | 3.01 | 0.5400 | | -2.62 | [ -2.86; -2.37] | 4.8% |
| Pilotto2019 | 56 | 1.49 | 0.4000 | 54 | 2.35 | 0.4200 | | -2.08 | [ -2.55; -1.62] | 4.6% |
| Wilson2019 | 25 | 0.88 | 0.3500 | 25 | 2.71 | 0.4700 | | -4.35 | [ -5.39; -3.30] | 3.8% |
| **Random effects model** | **1244** | | | **859** | | | | **-3.25** | **[ -3.68; -2.82]** | **100.0%** |

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.9899$, $p < 0.01$

-10   -5   0   5   10

**Figure 6.** Forest plot for ^{123}I-FP-CIT SPECT studies assessing the decrease in SUVR in the putamen. Std., standard; CI, confidence interval; SUVR, standardized uptake value ratio.

detection of PD progression through ^{18}F-FP-CIT PET/^{123}I-FP-CIT SPECT imaging. Furthermore, the region of interest approach is a semi-quantitative analysis method; more advanced neuroimaging techniques that can improve the diagnostic accuracy for PD or the differentiation of atypical Parkinsonism from PD are needed. Interestingly, studies on statistical parametric mapping, source-based morphometry, and dual-time ^{18}F-FP-CIT reported promising findings with respect to the diagnosis of PD.[25,79,80]

In conclusion, our data indicate that ^{18}F-FP-CIT PET and ^{123}I-FP-CIT SPECT imaging of dopamine transporters is helpful in the diagnosis of PD. We propose that the application of PET or SPECT imaging modalities in combination with advanced approaches would be beneficial.

## Conflict of Interest

No potential conflict of interest relevant to this article exist.

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