Journal of Nuclear Medicine, published on April 12, 2019 as doi:10.2967/jnumed.119.227140

Presynaptic striatal dopaminergic function in atypical parkinsonisms: A meta-analysis of imaging studies

Valtteri Kaasinen[1,2,3], Tuomas Kankare[2], Juho Joutsa[1,2], Tero Vahlberg[4]

[1]Division of Clinical Neurosciences, Turku University Hospital, Finland

[2]Department of Neurology, University of Turku, Finland

[3]Turku PET Centre, University of Turku, Finland

[4]Department of Clinical Medicine, Biostatistics, University of Turku, Finland

Corresponding author:

Dr. Valtteri Kaasinen

Division of Clinical Neurosciences, Turku University Hospital,

POB 52, FIN-20521, Turku, Finland

Tel. +358-2-3131720, email: valtteri.kaasinen@tyks.fi

Short running title: Dopamine in atypical parkinsonisms

ABSTRACT

Background. Multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) have overlapping signs and symptoms with Parkinson's disease (PD), and these similarities complicate their clinical diagnostics. Although presynaptic dopaminergic brain imaging with PET and SPECT is clinically widely used for patients with suspected PD, the benefit of functional imaging in atypical parkinsonism syndromes remains unclear. We compared striatal presynaptic dopaminergic function in MSA parkinsonism variant (MSA-P), MSA cerebellar variant (MSA-C), PSP, CBS and PD using combined quantitative data from all published studies.

Methods. PubMed database was searched from inception to August 2018 for terms "dopamine" OR "dopaminergic" AND "PET" OR "SPECT" OR "SPET" and keywords related to PD, MSA, PSP and CBS. A total of 1711 publications were identified. PET or SPECT studies comparing patients with atypical parkinsonism to another diagnostic group (PD, MSA, PSP or CBS) were included. Tracers for dopamine transporter (DAT), aromatic amino acid decarboxylase (AADC) or vesicular monoamine type 2 (VMAT2) were investigated. Tracer binding data were extracted from the original articles. Heterogeneity of the data were examined using I^2 statistics and a random effect model was used to summarize data. Hedges *g* was used as an estimator of effect size in group comparisons. Results are reported according to PRISMA guidelines.

*Results.*Thirty-five studies (29 DAT, 6 AADC, no VMAT2 studies) with 356 MSA-P patients, 204 PSP patients, 79 CBS patients and 62 MSA-C patients were included in the meta-analysis. Caudate nucleus and putamen DAT functions were clearly lower in PSP as compared to PD (caudate: 34.1% difference, *g*=-1.08, 95%CI= -1.52 to -0.64; putamen:

18.2% , *g*=-0.86, 95%CI=-1.50 to -0.21) and MSA-P (striatum: 31.4%, *g*=-0.70, 95%CI=-1.21 to -0.19), and in MSA-P as compared to MSA-C (striatum: 46.0%, *g*=1.46, 95%CI=0.23 to 2.68). Although not significant due to limited data, aromatic L-amino acid decarboxylase (AADC) results paralleled the DAT findings.

Conclusions. Striatal presynaptic DAT function is clearly lower in PSP patients as compared to PD and MSA-P patients, and in MSA-P patients as compared to MSA-C patients.

Key words: PET, SPECT, dopamine, parkinsonism, multiple system atrophy, progressive supranuclear palsy, Parkinson's disease, human

INTRODUCTION

Multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) have been termed as atypical parkinsonian disorders and they are characterized by a more rapid progression and poorer prognosis than the typical parkinsonian disorder - Parkinson's disease (PD). Clinicopathological studies have pointed out that the diagnostic accuracy of atypical parkinsonisms is not optimal; these disorders are underdiagnosed, and many patients that carry a diagnosis of PD in fact have MSA, PSP or CBS (*1*). The sensitivities of the MSA and PSP diagnoses are low at 53% and 64%, respectively, when diagnosed by general neurologists, and at 88% and 84%, when diagnosed by movement disorders specialists (*2,3*). Given that there are distinct proteinopathic disease mechanisms in different atypical parkinsonian syndromes, and that there are active attempts to develop protein-specific therapies, biomarkers that could be used to improve diagnostic accuracy would be valuable.

Functional brain imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) enables the investigation of central neurotransmitter function at the system level *in vivo*. When PD patients are compared to healthy individuals via striatal dopaminergic PET/SPECT, the PD patients show a wide-spread presynaptic defect with practically no overlap with healthy controls (*4*). However, it remains unclear whether presynaptic dopamine imaging can be used in the differential diagnosis of atypical parkinsonisms. Protein-specific tracers for tau and alpha-synuclein hold promise as possible future diagnostic tools (*5*), but in the current clinical imaging of movement disorders, presynaptic dopaminergic imaging dominates the field. A major limitation in

individual dopaminergic neuroimaging studies of atypical parkinsonisms has been the small sample sizes, which has led to insufficient statistical power to make reliable clinical inferences.

A quantitative meta-analysis offers an opportunity to investigate a large number of small studies with improved power to detect differences. A previous meta-analysis using diagnostic odds ratios has suggested that presynaptic dopaminergic tracers cannot distinguish between PD and atypical parkinsonisms (*6*). To investigate the role of presynaptic dopaminergic PET and SPECT in the diagnosis of atypical parkinsonisms in more detail, we carried out a meta-analysis of all available imaging data using regional binding values in each study.

MATERIALS AND METHODS

Aims of Meta-Analysis

The primary aim of the meta-analysis was to investigate differences in striatal dopamine signaling as measured by PET/SPECT among atypical parkinsonism disorders as compared to PD. Ethics Committee approval was waived because this study did not involve any human participants or animals.

Study Collection and Screening

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed (*7*). Studies for initial screening were identified through PubMed for initial screening using a search query of keywords related to parkinsonism disorders (Fig. 1). The final database search was conducted on the 8th of August, 2018. The initial screening and assessment for eligibility were performed by two investigators (V.K. and T.K.). Criteria for screening and data extraction are presented in supplemental methods.

Statistical Analysis

The synthesis of study results and group comparisons were conducted using Meta-Essentials (Version 1.1, Erasmus Research Institute of Management, Rotterdam, The Netherlands) (*10*). Statistical significance was set at two-tailed P-value of <0.05. Hedges' *g* was used as an estimator of effect size in group comparisons using random effects model. Heterogeneity of the data was examined using I^2 statistics. If substantial heterogeneity (I^2 > 50%) was detected, meta-regression analyses of the moderators age, disease duration, and

disease severity as indicated by the motor UPDRS and Hoehn and Yahr scale scores were also performed.

RESULTS

Study Characteristics

Twenty-nine DAT studies (Supplemental Table 1) and 6 AADC studies (Supplemental Table 2) were included in the meta-analysis. There were no suitable VMAT2 studies. Four studies (*11-14*) that had combined MSA-P patients with MSA-C patients were excluded from the MSA-analysis (Supplemental Table 3). Only one study reported binding values also in PSP parkinsonism variant (PSP-P) patients (*15*), which were not included to the analysis. The final sample thus included 35 studies that described DAT or AADC binding in 958 PD, 356 MSA-P, 204 PSP, 79 CBS and 62 MSA-C patients. The demographic and clinical characteristics of the patients are presented in Table 1. The quality evaluation of the included studies is presented in Supplemental Table 4. Twenty-five studies received 5-6 stars and 10 studies received 3-4 stars (out of 6 stars) in the Newcastle-Ottawa scale. The overall quality of the studies was therefore sufficient but the PET/SPECT imaging methodology and resolution were suboptimal in studies that had been published in the 1990s. There was some variation in diagnostic criteria as well (Supplemental Table 5) although many studies used published and commonly used criteria for PD (*16*), PSP (*17*) and MSA (*18,19*).

The DAT-studies were published between 1998 and 2018. The tracers used were ^{123}I-β-CIT, ^{123}I-FP-CIT, ^{99m}Tc-TRODAT, ^{18}F-FP-CIT and ^{123}I-IPT. The majority of the included studies had calculated striatal specific binding ratios using the occipital cortex as the reference region, and the values were expressed as (region-of-interest – occipital cortex)/occipital cortex (Supplemental Table 1). The AADC-studies were published between 1990 and 1997 and used 6-^{18}F-fluoro-L-dopa as the tracer.

Atypical Parkinsonisms vs PD

The PSP patients had lower DAT binding than did the PD patients in the mean caudate (weighted relative difference=34.1%, Table 2), mean putamen (18.2%, Table 2), mean striatum, contralateral caudate, ipsilateral caudate and anterior putamen (Fig. 2, Table 2, Supplemental Table 7). The MSA-P patients had lower DAT binding than did the PD patients in the mean caudate (Fig. 2, Table 2, Supplemental Table 7). There were no differences between the PD patients and patients with MSA-C or CBS but the total numbers of patients and studies were low (Table 2). There were no differences in AADC activity between the PD and PSP or MSA-P patients although directions of differences were similar to the DAT analysis (Supplemental Table 5). There were insufficient data for other AADC comparisons.

Differences Between Atypical Parkinsonisms

The PSP patients had 31.4% lower mean striatal DAT binding (weighted relative difference) than did the MSA-P patients (Table 2, Supplemental Table 7). The MSA-P patients had 46.0% lower DAT binding than did the MSA-C patients in the striatum (Table 2, Supplemental Table 7). No other significant differences were observed. The primary results with DAT imaging remained the same when only studies that had used similar diagnostic criteria (Supplemental Table 5) were included in the analysis. There were no suitable studies that had compared PSP to MSA-C patients, or CBS patients to those with other atypical parkinsonisms. There were no differences in AADC activity between PSP and MSA-P patients, and there were insufficient data for other comparisons (Supplemental Table 6).

Meta-Regression Analyses and Publication Bias

There were no significant associations in meta-regression analyses using disease duration or the mean motor UPDRS values as moderators. The only significant relationship observed was between the H&Y stage and the effect size for caudate DAT binding in the PD vs MSA-P comparison (Supplemental Table 8), indicating that a higher difference in the H&Y stage scores between the PD and MSA-P groups was associated with a greater difference in caudate nucleus DAT binding between these groups. Funnel plots of the comparisons that had sufficient numbers of studies, did not suggest missing studies that would have suggested publication bias (Egger regressions, $p>0.05$).

DISCUSSION

The results of this meta-analysis indicate that the striatal DAT binding is lower in PSP patients than in both MSA-P and PD. Another important finding was that the caudate DAT binding is lower in MSA-P than in PD patients without significant differences in the putamen. The third major finding was that the striatal DAT binding is clearly lower in MSA-P than in MSA-C patients. Although not significant due to limited data, AADC results paralleled the findings with DAT. The data concerning VMAT2 and CBS are currently insufficient.

Dopaminergic Function in PSP is Lower than in both MSA-P and PD

Our results show that presynaptic dopaminergic function, as measured by DAT binding, is up to 34% lower in PSP than in MSA-P and PD. It has been demonstrated that there is a profound loss of nigral dopaminergic neurons in PSP (*20*) and on the basis of the present results, this loss may exceed that seen in other degenerative parkinsonisms, at least when patients are examined by means of functional brain imaging 3-5 years after symptom onset. Comparative neuropathological data are needed to investigate whether the greater loss of presynaptic dopamine function in PSP is present at all disease stages and whether this loss of dopamine function is based on greater neuronal loss or a functional difference in the nigrostriatal tract. There are data suggesting that PD and PSP patients may have similar losses of A9 dopamine neurons in the substantia nigra (*21*), whereas the number of A10 neurons is clearly lower in PSP than in PD (*22*). From a clinical perspective, it is important to note that the markedly lower DAT binding in the PSP patients compared to the PD or MSA-P patients does not seem to be directly related to clinical differences in motor symptom severity. For example, although the motor symptoms of the PSP patients were less advanced

compared to those of the MSA-P patients (motor UPDRS score 33 vs 37, respectively), the striatal dopaminergic degeneration was clearly more progressed (31.4% lower in the PSP patients than in the MSA-P patients).

Relative differences in the striatal DAT binding between PSP and MSA-P/PD were large, at 18-34% (Hedges' $g > 0.70$). The magnitudes are possibly diagnostically significant. Currently, many semi-automatic analysis systems used clinically for DAT SPECT have taken advantage of published cohorts of healthy subjects (e.g. Varrone et al.(*23*)) and clinical diagnostics is aided by the automatic flagging of abnormal striatal values as compared to the reference values. In the future, automated analysis could possibly be extended to atypical parkinsonisms by including reference values for PD, PSP, MSA-P and MSA-C. However, this would not be an easy task, as the level of pathology is not constant across the disease course, and the system would need to contain information about not only the age and sex of the patients, but also the motor symptom severity and disease duration. This may not be possible in the immediate future, but an endeavor for this purpose could possibly be carried out via the international collection of large numbers of scans of patients with atypical parkinsonisms (*24*).

Caudate Dopaminergic Loss Differentiates MSA-P from PD

The results also showed that while there does not seem to be a difference in putaminal dopaminergic function between MSA-P and PD, there is a difference in the caudate nucleus. Indeed, one previously suggested possibility for improving the dopaminergic diagnostic accuracy of atypical parkinsonisms is the utilization of caudate-putamen or putamen-caudate ratios, as it has been suspected that the rostro-caudal gradient of the dopaminergic deficit is

lost in atypical parkinsonisms (e.g. (*25,26*)). We were unable to perform meta-analytical calculations of these ratios because the measurements were variably reported. Nevertheless, the results indirectly support the notion that the caudate-putamen ratio may be affected in MSA. This is another issue that merits the further large multisite collection of clinical scans for comparison. An automated comparison of the caudate-putamen ratio to those from a large pool of clinically well-characterized patients with PD and atypical parkinsonisms could prove valuable. These data would optimally be based on measurements from PET scans due to the superior spatial resolution which allows clearer separation of striatal subregions in PET as compared to SPECT (*25*). In the included studies, the binding values for the hemispheres contra- and ipsilateral to the predominant motor symptoms were also only sporadically reported. The lack of reported subregional and hemispheric values conveys a message to the neuroimaging community. To successfully perform similar meta-analyses in the future, more precise reporting of regional binding values (each contra- and ipsilateral region for each group together with SDs) or open data sharing is needed.

MSA-P and MSA-C Differ in Striatal Dopamine Function

There was a strikingly large 46.0% difference in striatal DAT binding between the MSA-P and MSA-C patients (Hedges' g = 1.46, four studies with 133 patients). DAT imaging therefore appears useful in the differentiation of MSA subtypes. However, rather than being dichotomically different pathological entities, MSA-P and MSA-C are likely to represent a neuropathological continuum with mixed neuropathology (*27*). It is possible that MSA-P and MSA-C patients included in neuroimaging trials are particularly well characterized and represent extreme ends of the continuum. Therefore, the large difference in striatal DAT binding between the MSA-P and MSA-C patients possibly does not fully represent clinical

reality, where patients with mixed phenotypes are more frequent. Nevertheless, the magnitude of the difference is noteworthy, and we argue that striatal DAT imaging could be one of the auxiliary diagnostic tools for patients with mild parkinsonism, dysautonomic features and variable levels of cerebellar findings. The second consensus diagnostic criteria of MSA suggested that in the absence of parkinsonian features in a patient with cerebellar ataxia, imaging evidence of a nigrostriatal presynaptic deficit points to the diagnosis of MSA-C (*19*). The present results do not directly contradict this interpretation, but the results demonstrate that it is not the MSA-C subtype but rather the MSA-P phenotype that shows the robust loss of dopamine function. Further studies comparing MSA-C to other degenerative parkinsonisms will be of importance.

Limitations

The results presented herein were derived almost solely from DAT imaging using various tracers. We did not identify suitable VMAT2 studies, and also the number of AADC studies was low (six studies published in the 1990s). Therefore, we do not currently know if the diagnostic value of DAT imaging in atypical parkinsonisms is superior to or worse than other presynaptic imaging targets. Although AADC function may be somewhat upregulated in PD and the DAT is possibly downregulated (*28*), we do not consider it likely that the differences reported herein would be markedly different if VMAT2 or AADC was the target. Another limitation is that the level of the present evidence precludes definitive conclusions about the dopaminergic function in CBS because the numbers of studies and patients were low. It is also debatable whether it is useful to classify PSP and CBS as different disorders (*29,30*). It should also be noted that the results of the present meta-analysis do not necessarily represent well the clinical diagnostic reality as many of the included studies were

performed with patients that had already been clinically diagnosed at the time of imaging. Finally, medications were variably reported and it was therefore impossible to perform subanalyses between treatment groups.

CONCLUSION

The results of this meta-analysis demonstrate that PSP is associated with the greatest presynaptic dopaminergic loss compared to other degenerative parkinsonian syndromes. The observed large difference between MSA-P and MSA-C may also be clinically useful in patients with dysautonomia. Given the magnitude of the differences between the diagnostic groups, an effort could be initiated for the collection and analysis of clinical scans that could be used to create reference and of cut-off values for research and clinical work.

ACKNOWLEDGEMENTS

This research was supported by the Päivikki and Sakari Sohlberg Foundation and the Turku University Hospital (ERVA-funds). J.J. was funded by the Academy of Finland (grant #295580).

Statement of Disclosure

No potential conflicts of interest relevant to this article exist.

Key points

Question: It is unclear whether presynaptic dopamine imaging with PET or SPECT can be used in the differential diagnosis of atypical parkinsonisms.

Pertinent findings: Striatal dopamine transporter (DAT) function was clearly lower in progressive supranuclear palsy (PSP) as compared to Parkinson's disease and parkinsonism variant of multiple system atrophy (MSA-P), and in MSA-P as compared to the cerebellar variant (MSA-C).

Implications for patient care: The results demonstrate group-level differences in presynaptic dopamine function between atypical parkinsonism syndromes.

REFERENCES

1. Kim HJ, Jeon BS, Jellinger KA. Diagnosis and differential diagnosis of MSA: boundary issues. *J Neurol.* 2015;262:1801-1813.

2. Joutsa J, Gardberg M, Röyttä M, Kaasinen V. Diagnostic accuracy of parkinsonism syndromes by general neurologists. *Parkinsonism Relat Disord.* 2014;20:840-844.

3. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain.* 2002;125:861-870.

4. Kaasinen V, Vahlberg T. Striatal dopamine in Parkinson disease: A meta-analysis of imaging studies. *Ann Neurol.* 2017;82:873-882.

5. Strafella AP, Bohnen NI, Perlmutter JS, et al. Molecular imaging to track Parkinson's disease and atypical parkinsonisms: New imaging frontiers. *Mov Disord.* 2017;32:181-192.

6. Vlaar AM, van Kroonenburgh MJ, Kessels AG, Weber WE. Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. *BMC Neurol.* 2007;7:27.

7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.

8. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Method*. 2005;5:13

9. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed on 20MAR2019.

10. Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: A free and simple tool for meta-analysis. *Res Synth Methods.* 2017;8:537-553.

11. Otsuka M, Kuwabara Y, Ichiya Y, et al. Differentiating between multiple system atrophy and Parkinson's disease by positron emission tomography with 18F-dopa and 18F-FDG. *Ann Nucl Med.* 1997;11:251-257.

12. Pirker W, Asenbaum S, Bencsits G, et al. [123I]beta-CIT SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. *Mov Disord.* 2000;15:1158-1167.

13. Berding G, Brücke T, Odin P, et al. [[123I]beta-CIT SPECT imaging of dopamine and serotonin transporters in Parkinson's disease and multiple system atrophy. *Nuklearmedizin.* 2003;42:31-38.

14. Plotkin M, Amthauer H, Klaffke S, et al. Combined 123I-FP-CIT and 123I-IBZM SPECT for the diagnosis of parkinsonian syndromes: study on 72 patients. *J Neural Transm (Vienna).* 2005;112:677-692.

15. Lin WY, Lin KJ, Weng YH, et al. Preliminary studies of differential impairments of the dopaminergic system in subtypes of progressive supranuclear palsy. *Nucl Med Commun.* 2010;31:974-980.

16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55:181-184.

17. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology.* 1996;47:1-9.

18. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci.* 1999;163:94-98.

19. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* 2008;71:670-676.

20. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain.* 2005;128:1247-1258.

21. Hardman CD, Halliday GM, McRitchie DA, Cartwright HR, Morris JG. Progressive supranuclear palsy affects both the substantia nigra pars compacta and reticulata. *Exp Neurol.* 1997;144:183-192.

22. Murphy KE, Karaconji T, Hardman CD, Halliday GM. Excessive dopamine neuron loss in progressive supranuclear palsy. *Mov Disord.* 2008;23:607-610.

23. Varrone A, Dickson JC, Tossici-Bolt L, et al. European multicentre database of healthy controls for [(123)I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. *Eur J Nucl Med Mol Imaging.* 2013;40:213-227.

24. Alingment and standardisation of neuroimaging methods in atypical parkinsonism, specifically synucleinopathies and tauopathies. Report of a JPND working group on harmonisation and alignment in brain imaging methods. http://www.neurodegenerationresearch.eu/wp-content/uploads/2018/04/JPND-Brain-Imaging-Working-Group-Report_ASAP-SynTau.pdf.

25. Oh M, Kim JS, Kim JY, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med.* 2012;53:399-406.

26. Im JH, Chung SJ, Kim JS, Lee MC. Differential patterns of dopamine transporter loss in the basal ganglia of progressive supranuclear palsy and Parkinson's disease: analysis with [(123)I]IPT single photon emission computed tomography. *J Neurol Sci.* 2006;244:103-109.

27. Jellinger KA. Neuropathology of multiple system atrophy: new thoughts about pathogenesis. *Mov Disord.* 2014;29:1720-1741.

28. Lee CS, Samii A, Sossi V, et al. In vivo positron emission tomographic evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. *Ann Neurol.* 2000;47:493-503.

29. Ling H, Macerollo A. Is it Useful to Classify PSP and CBD as Different Disorders? Yes. *Mov Disord Clin Pract.* 2018;5:145-148.

30. Lang AE. Comment on "Is it Useful to Classify PSP and CBD as Different Disorders?". *Mov Disord Clin Pract.* 2018;5:564-565.

31. Messa C, Volonté MA, Fazio F, et al. Differential distribution of striatal [123I]beta-CIT in Parkinson's disease and progressive supranuclear palsy, evaluated with single-photon emission tomography. *Eur J Nucl Med.* 1998;25:1270-1276.

32. Kim GM, Kim SE, Lee WY. Preclinical impairment of the striatal dopamine transporter system in sporadic olivopontocerebellar atrophy: studied with [(123)I]beta-CIT and SPECT. *Eur Neurol.* 2000;43:23-29.

33. Parkinson Study Group. A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism. *Neurology.* 2000;55:1540-1547.

34. Varrone A, Marek KL, Jennings D, Innis RB, Seibyl JP. [(123)I]beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. *Mov Disord.* 2001;16:1023-1032.

35. Kim YJ, Ichise M, Ballinger JR, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. *Mov Disord.* 2002;17:303-312.

36. Antonini A, Benti R, De Notaris R, et al. 123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Neurol Sci.* 2003;24:149-150.

37. Lai SC, Weng YH, Yen TC, et al. Imaging early-stage corticobasal degeneration with [99mTc]TRODAT-1 SPET. *Nucl Med Commun.* 2004;25:339-345.

38. Lu CS, Weng YH, Chen MC, et al. 99mTc-TRODAT-1 imaging of multiple system atrophy. *J Nucl Med.* 2004;45:49-55.

39. Scherfler C, Seppi K, Donnemiller E, et al. Voxel-wise analysis of [123I]beta-CIT SPECT differentiates the Parkinson variant of multiple system atrophy from idiopathic Parkinson's disease. *Brain.* 2005;128:1605-1612.

40. Swanson RL, Newberg AB, Acton PD, et al. Differences in [99mTc]TRODAT-1 SPECT binding to dopamine transporters in patients with multiple system atrophy and Parkinson's disease. *Eur J Nucl Med Mol Imaging.* 2005;32:302-307.

41. Filippi L, Manni C, Pierantozzi M, et al. 123I-FP-CIT in progressive supranuclear palsy and in Parkinson's disease: a SPECT semiquantitative study. *Nucl Med Commun.* 2006;27:381-386.

42. Seppi K, Scherfler C, Donnemiller E, et al. Topography of dopamine transporter availability in progressive supranuclear palsy: a voxelwise [123I]beta-CIT SPECT analysis. *Arch Neurol.* 2006;63:1154-1160.

43. Roselli F, Pisciotta NM, Pennelli M, et al. Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. *Mov Disord.* 2010;25:1853-1859.

44. Goebel G, Seppi K, Donnemiller E, et al. A novel computer-assisted image analysis of [123I]β-CIT SPECT images improves the diagnostic accuracy of parkinsonian disorders. *Eur J Nucl Med Mol Imaging.* 2011;38:702-710.

45. Cilia R, Rossi C, Frosini D, et al. Dopamine Transporter SPECT Imaging in Corticobasal Syndrome. *Plos One.* 2011;6:e18301.

46. Nocker M, Seppi K, Donnemiller E, et al. Progression of dopamine transporter decline in patients with the Parkinson variant of multiple system atrophy: a voxel-based analysis of [123I]β-CIT SPECT. *Eur J Nucl Med Mol Imaging.* 2012;39:1012-1020.

47. Jakobson Mo S, Linder J, Forsgren L, Holmberg H, Larsson A, Riklund K. Pre- and postsynaptic dopamine SPECT in idiopathic Parkinsonian diseases: a follow-up study. *Biomed Res Int.* 2013;2013:143532.

48. Hammesfahr S, Antke C, Mamlins E, et al. FP-CIT- and IBZM-SPECT in Corticobasal Syndrome: Results from a Clinical Follow-Up Study. *Neurodegener Dis.* 2016;16:342-347.

49. Kim HW, Kim JS, Oh M, et al. Different loss of dopamine transporter according to subtype of multiple system atrophy. *Eur J Nucl Med Mol Imaging.* 2016;43:517-525.

50. Joling M, Vriend C, van den Heuvel OA, et al. Analysis of Extrastriatal. *J Nucl Med.* 2017;58:1117-1123.

51. Ohta Y, Yamashita T, Hishikawa N, et al. Potential multisystem degeneration in Asidan patients. *J Neurol Sci.* 2017;373:216-222.

52. Saari L, Kivinen K, Gardberg M, Joutsa J, Noponen T, Kaasinen V. Dopamine transporter imaging does not predict the number of nigral neurons in Parkinson disease. *Neurology.* 2017;88:1461-1467.

53. Nicastro N, Garibotto V, Burkhard PR. 123I-FP-CIT SPECT Accurately Distinguishes Parkinsonian From Cerebellar Variant of Multiple System Atrophy. *Clin Nucl Med.* 2018;43:e33-e36.

54. Brooks DJ, Salmon EP, Mathias CJ, et al. The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure, and Parkinson's disease, studied with PET. *Brain.* 1990;113 (Pt 5):1539-1552.

55. Brooks DJ, Ibanez V, Sawle GV, et al. Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol.* 1990;28:547-555.

56. Burn DJ, Sawle GV, Brooks DJ. Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal 18F-dopa PET data. *J Neurol Neurosurg Psychiatry.* 1994;57:278-284.

57. Otsuka M, Ichiya Y, Kuwabara Y, et al. Nigrofrontal dopaminergic function as assessed by 18F-dopa PET. *Nucl Med Commun.* 1995;16:1021-1025.

58. Antonini A, Leenders KL, Vontobel P, et al. Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease. *Brain.* 1997;120 (Pt 12):2187-2195.

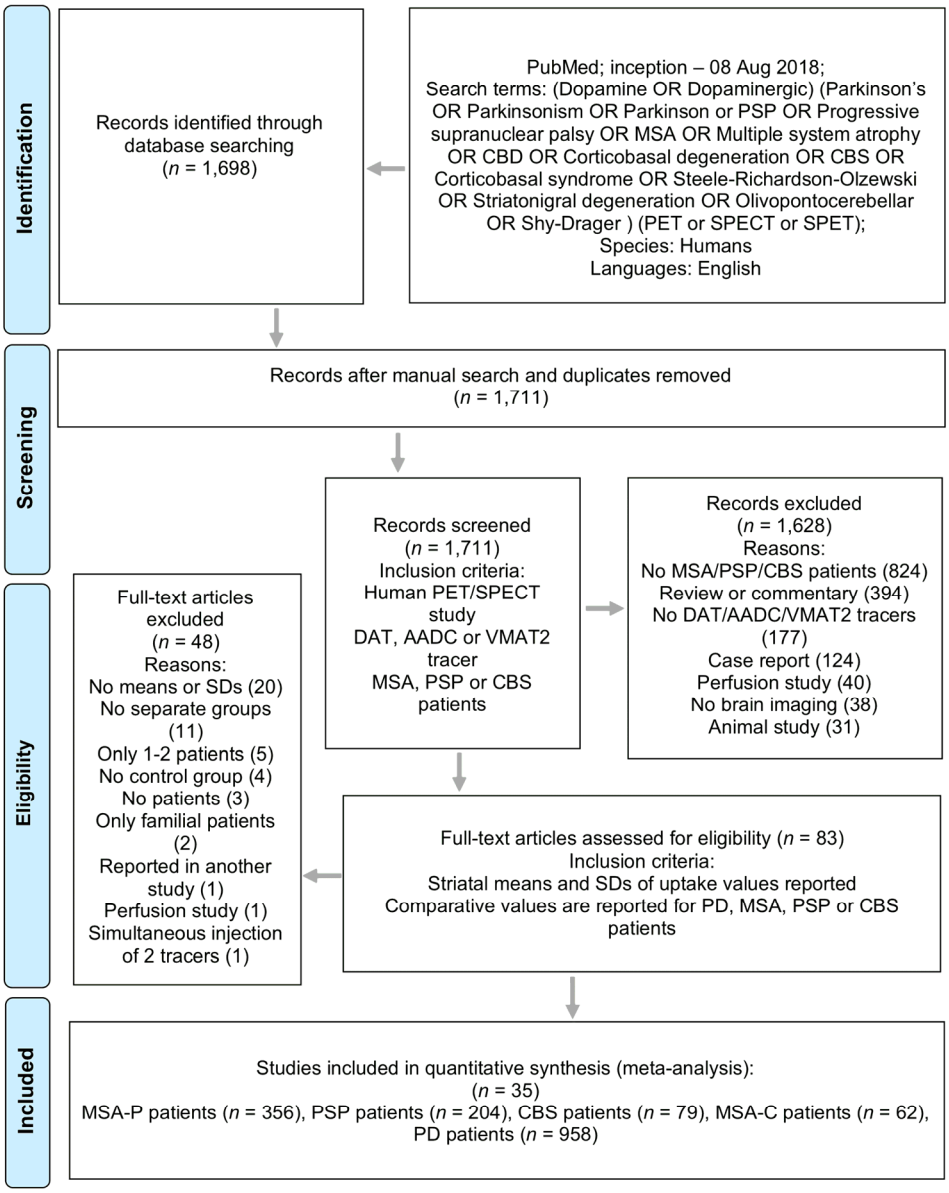

Figure 1. Flow chart of study inclusion and exclusion. PSP=progressive supranuclear palsy, MSA=multiple system atrophy, CBD=corticobasal degeneration, CBS=corticobasal syndrome, PET=positron emission tomography, SPECT=single photon emission computed tomography, DAT=dopamine transporter, AADC=aromatic amino acid decarboxylase, VMAT2=vesicular monoamine transporter type 2, SD=standard deviation, MSA-P=multiple system atrophy parkinsonism variant, MSA-C=multiple system atrophy cerebellar variant.

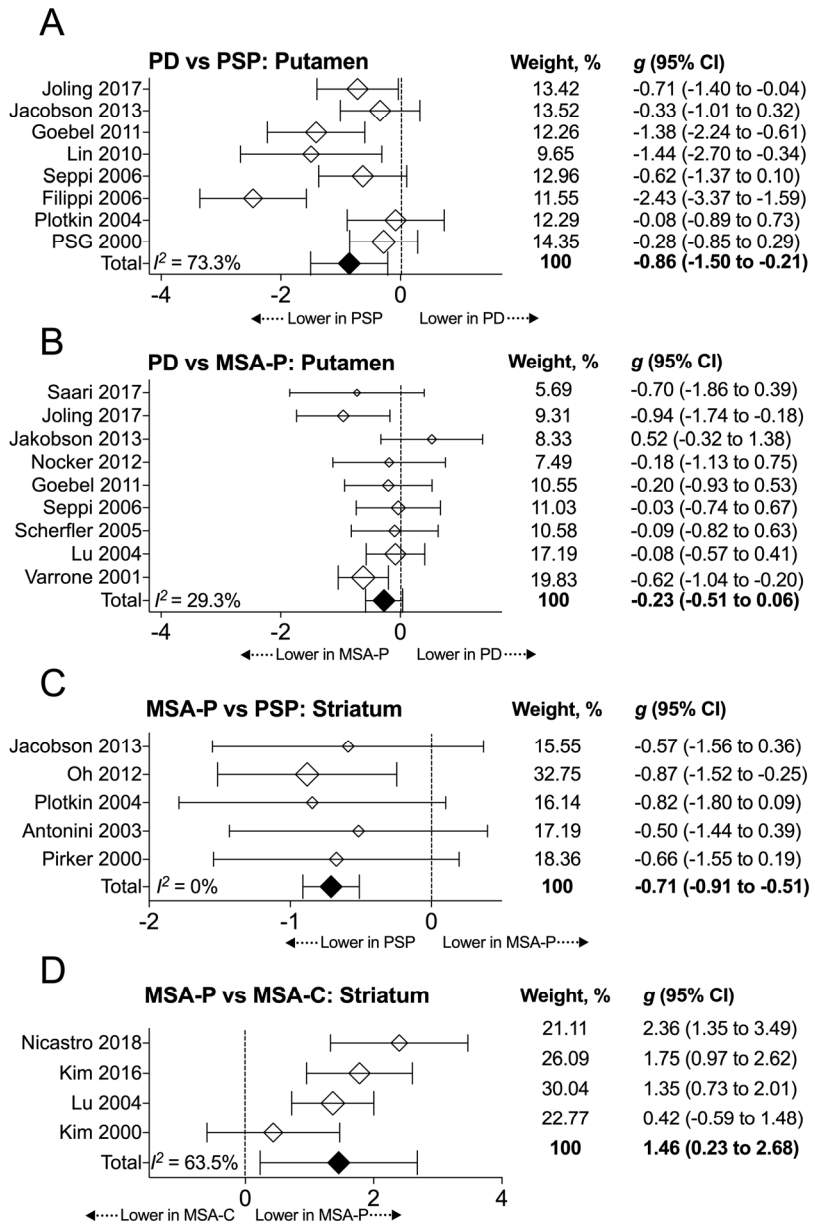

Figure 2. Forest plots of key comparisons in DAT studies. A. Significant putaminal difference between PD and PSP. B. Non-significant putaminal difference between PD and MSA-P. C. Significant striatal difference between MSA-P and PSP. D. Significant striatal difference between MSA-P and MSA-C.

Table 1. Summary of demographic and clinical details of the samples in the included studies. N or weighted* mean values and weighted standard deviations are presented.

Target	Variable	PD	MSA-P	PSP	CBS	MSA-C
DAT	Samples (n)	26	18	16	5	5
	Patients (n)	877	285	181	77	62
	Age (yrs)	64(9)	63(9)	67(7)	68(8)	62(8)
	Sex (m/f ratio)	1.5	1.0	1.3	0.7	1.1
	Disease duration (yrs)	4.6(3.6)	3.2(1.9)	3.2(1.9)	3.0(1.3)	3.2(1.9)
	H&Y score	2.1(0.7)	3.4(0.8)	3.2(0.9)	3.0(0.8)	3.5(1.1)
	Motor UPDRS score	23(11)	37(13)	33(11)	35(13)	30(11)
AADC	Samples (n)	6	5	3	1	0
	Patients (n)	81	71	23	2	0
	Age (yrs)	58(6)	57(7)	66(5)	65(5)	-
	Sex (m/f ratio)	2.1	1.6	3.3	1.0	-
	Disease duration (yrs)	8.3(6.3)	4.7(3.3)	3.3(1.8)	4.0(0)	-
	H&Y score	2.7(0.8)	3.3(0.8)	3.3(-)	-	-
	Motor UPDRS score	-	-	-	-	-

*Weighted for number of subjects for each study

Table 2. Summary of DAT results. *g* = Hedges' *g*, CI = 95% confidence interval for *g,* n = number of studies/number of patients, I^2= heterogeneity index. There were no available studies that have compared MSA-C patients to PSP or CBS patients. There were also insufficient data for an MSA-P vs. CBS comparison. Statistically significant comparisons are highlighted with bold text. Hemispheric values and ratios are presented in Supplemental Table 6.

	PD vs MSA-P	**PD vs PSP**	**PD vs MSA-C**	**PD vs CBS**	**MSA-P vs PSP**	**MSA-P vs MSA-C**	**PSP vs CBS**
Caudate	***g*=-0.39 CI=-0.77 to -0.01 n=10/609, I^2=63.2%**	***g*=-1.08 CI=-1.52 to -0.64 n=11/356, I^2=56.6%**	*g*=0.73 CI=-1.18 to 2.63 n=2/92, I^2=0.0%	*g*=-0.33 CI=-1.08 to 0.43 n=3/122, I^2=0.0%	*g*=-0.37 CI=-1.13 to 0.39 n=5/114, I^2=47.7%	*g*=1.20 CI=-0.20 to 2.59 n=3/99, I^2=45.6%	Insufficient data n=1/17
Putamen	*g*=-0.27 CI=-0.58 to 0.04 n=9/451, I^2=29.5%	***g*=-0.86 CI=-1.50 to -0.21 n=8/291, I^2=73.3%**	*g*=1.51 CI=-0.57 to 3.59 n=2/92, I^2=0.0%	*g*=0.55 CI=-0.42 to 1.53 n=3/122, I^2=26.8%	*g*=-0.47 CI=-1.22 to 0.28 n=4/101, I^2=27.5%	***g*=1.87 CI=0.46 to 3.29 n=3/99, I^2=34.1%**	Insufficient data n=1/17
Striatum	*g*=-0.34 CI=-1.01 to 0.33 n=4/255, I^2=46.6%	***g*=-1.05 CI=-1.68 to -0.43 n=9/390, I^2=73.3%**	Insufficient data n=1/55	*g*=0.98 CI=-0.65 to 2.62 n=4/142, I^2=81.3%	***g*=-0.70 CI=-1.21 to -0.19 n=3/83, I^2=0.0%**	***g*=1.46 CI=0.23 to 2.68 n=4/133, I^2=63.5%**	*g*=1.30 CI=-5.49 to 8.09 n=2/29, I^2=40.1%

Supplemental Methods

Study Collection and Screening

This study is an extension to a previously reported meta-analytical comparison between PD patients and healthy controls, using the same methodology (*4*). Studies were first screened on the basis of relevance in the title and abstract. Full-text articles were obtained and assessed if the articles were deemed relevant to the analysis, if their eligibility could not be determined from the title and abstract alone, or if the abstract was not available on PubMed. Dopaminergic synaptic mechanisms included in the analysis were aromatic L-amino acid decarboxylase (AADC), dopamine transporter (DAT) and vesicular monoamine transporter type 2 (VMAT2). Other criteria for inclusion are shown in Fig. 1. MSA studies that reported separate binding values for MSA-P patients or MSA-C patients or both were included. Studies that did not specifically state MSA subgroups were considered to involve MSA-P, the more common subtype, if supported by the clinical features (i.e. the patients had parkinsonism). Studies that combined the binding values of MSA-P and MSA-C patients were excluded from the MSA comparisons. In the PSP studies, only Richardson syndrome (PSP-RS) phenotype patients were included.

Data Extraction

The study site and imaging method information as well as the tracer binding values were extracted from the included studies. Variables extracted were the study year, first author name and institution, tracer compound and target, method of calculation for binding values,

scanner model, sample sizes, mean (SD) age, mean (SD) duration of disease, mean (SD) motor and total Unified Parkinson's Disease Rating Scale (UPDRS) scores, mean (SD) and minimum/maximum Hoehn and Yahr scale scores, mean pre-scan carbidopa dose (mg) in the AADC studies, mean or range of dose of injected tracer (MBq), scan duration (min), and binding values for each brain region analyzed. Hemispheric values were used to derive bilateral mean values if these were not provided in the original publication. If only medians and ranges of the variables were reported, the missing mean values and standard deviations were generated statistically as described (*8*). If necessary, the mean values and ranges were calculated using the individual patient data from the original articles when possible. For longitudinal studies, the time-point from which the most data could be gathered was chosen to represent the study. When mean binding ratios were reported (BR = ROI/ref), they were converted to specific binding ratios (SBR = (ROI-ref)/ref) by subtracting 1 (SBR = BR–1).

The most common investigated brain regions were the mean (bilateral) caudate nucleus (studies n=25), mean putamen (n=21), mean striatum (n=15), contralateral caudate nucleus (n=11), ipsilateral caudate nucleus (n=11), mean posterior putamen (n=9), mean anterior putamen (n=8), contralateral putamen (n=8) and ipsilateral putamen (n=8). Asymmetry indices for the putamen were reported in 6 studies, and putamen/caudate ratios were reported in 6 studies. For the AADC studies, sufficient data were available only for the mean caudate nucleus and mean putamen.

Risk of Publication Bias and Quality of Studies

The risk of publication bias was considered and examined using funnel plots of the studies included in the synthesis (comparisons with 10 or more samples). The quality of the included studies was evaluated according to the Newcastle-Ottawa scale (*9*).

Supplemental Table 1. Characteristics of DAT studies. Values are n or mean (SD/range) unless specified otherwise.

Study	Site	Groups	n (m/f)	Age (yrs)	Disease duration (yrs)	Motor UPDRS	Hoehn & Yahr	Injected dose (MBq)	Scan dur (min)	Tracer/ Scanner	Analysis method
Messa et al 1998(*31*)	MIL	PD	13 (8/5)	59 (13)	2.2 (1.4)	-	2.2 (0.2)	130	30	^{123}I-β-CIT Ceraspet	(str-occ)/occ
		PSP	5 (4/1)	66 (8)	3.8 (1.3)	-	3 (0)				
Kim et al 2000(*32*)	SEO	MSA-P	7 (4/3)	55 (9)	-	-	-	185-370	30	^{123}I-β-CIT Triad XLT	str/occ
		MSA-C	9 (5/4)	53 (7)	2.4 (1.5)	-	-				
Parkinson Study Group 2000(*33*)	MUL	PD	43 (30/13)	68 (8)	-	-	-	185	30	^{123}I-β-CIT 5 different scanners	(str-occ)/occ
		PSP	17 (10/7)	72 (6)	-	-	-				
Pirker et al 2000(*12*)	VIE	PD	48 (27/21)	68 (10)	8.6 (5.2)	35 (13)	3.5 (0.5)	89-197	40	^{123}I-β-CIT Siemens Multispect 3	(str-cer)/cer
		MSA	18 (7/11)	63 (11)	3.6 (2.2)	37 (10)	3.9 (0.5)				
		PSP	8 (6/2)	65 (6)	3.3 (2.1)	32 (11)	4.3 (0.5)				
		CBS	4 (1/3)	68 (9)	2.3 (1.0)	42 (9)	3.8 (0.5)				
Varrone et al 2001(*34*)	NEW	PD	157 (102/55)	61 (34-84)	4.0 (0.3-23)	18 (6-40)	1.7 (1-4)	217	-	^{123}I-β-CIT Picker PRISM 3000 XP	(str-occ)/occ
		MSA	26 (19/7)	66 (48-81)	4.0 (0.2-10)	31 (10-73)	2.8 (1-5)				
Kim et al 2002(*35*)	TOR	PD	12 (6/6)	62 (10)	3.5 (3.1)	18 (7)	1.9 (0.6)	-	-	^{123}I-β-CIT Picker PRISM 3000 XP	B_{max}/K_dV_2 (fcx as reference)
		MSA	7 (5/2)	62 (14)	3.4 (1.4)	50 (17)	4.0 (0)				
		PSP	6 (5/1)	63 (7)	3.6 (0.8)	27 (11)	3.3 (0.8)				
Berding et al 2003(*13*)	HAN	PD	14 (7/7)	57 (9)	13 (5)	-	3.9 (0.7)	-	120	^{123}I-β-CIT Siemens Multispect 3	(str-ref)/ref (ref = occ and cer)
		MSA	10 (2/8)	63 (7)	2.5 (1.7)	32 (12)	3.2 (1.1)				
Antonini et al 2003(*36*)	MIL	PD	70 (-)	62 (13)	5.0 (4.0)	-	-	110-140	-	^{123}I-FP-CIT Prism 3000	(str-occ)/occ
		MSA-P	10 (-)	60 (8)	4.0 (2.0)	-	-				
		PSP	10 (-)	64 (8)	4.0 (3.0)	-	-				
Lai et al 2004(*37*)	TAO	PD	10 (3/7)	60 (16)	1.9 (0.7)	22 (10)	1.8 (0.6)	925	-	^{99m}Tc-TRODAT-1 Siemens Multispect 3	(str-occ)/occ
		CBS	5 (4/1)	59 (16)	1.6 (0.9)	30 (7)	1.9 (1.2)				
	TAI	PD	36 (20/16)	63 (7)	4.8 (3.5)	30 (14)	2.3 (0.9)	925	-	^{99m}Tc-TRODAT-1	

Lu et al 2004 (*38*)		MSA-P	30 (12/18)	62 (8)	4.5 (3.3)	43 (15)	3.5 (1.3)			Siemens Multispect 3	(str-occ)/occ
		MSA-C	19 (9/10)	64 (7)	4.0 (2.5)	30 (13)	3.7 (1.2)				
Plotkin et al 2005(*14*)	BER	PD	25 (18/7)	60 (13)	4.0 (4.1)	-	1.8 (0.8)	200	-	^{123}I-FP-CIT Siemens Multispect 3	str/fcx
		MSA	13 (6/7)	64 (8)	4.0 (2.3)	-	-				
		PSP	8 (6/2)	67 (7)	3.0 (1.9)	-	-				
		CBS	9 (4/5)	63 (11)	3.0 (1.6)	-	-				
Scherfler et al 2005(*39*)	INN	PD	15 (10/5)	61 (7)	1.7 (0.8)	22 (7)	1.9 (0.9)	148-185	43	^{123}I-β-CIT ADAC Vertex-Plus	(str-occ)/occ
		MSA	15 (8/7)	62 (9)	2.0 (0.8)	39 (11)	2.6 (0.7)				
Swanson et al 2005(*40*)	PHI	PD	130 (87/43)	63 (10)	6.4 (5.4)	-	-	740	-	^{99m}Tc-TRODAT-1 Picker PRISM 3000 XP	(str-ref)/ref[B]
		MSA-P	25 (17/8)	66 (9)	4.9 (3.6)	-	-				
Im et al 2006(*26*)	SEO	PD	20 (10/10)	62 (7)	2.8 (1.7)	-	2 (0)	251	30	^{123}I-IPT Triad XLT 24	(str-occ)/occ
		PSP	9 (6/3)	56 (11)	1.8 (0.8)	-	-				
Filippi et al 2006(*41*)	ROM	PD	21 (12/9)	64 (8)	2.7 (1.9)	-	-	185	-	^{123}I-FP-CIT Millenium VG	(str-occ)/occ
		PSP	15 (9/6)	64 (6)	2.7 (1.2)	-	-				
Seppi et al 2006(*42*)	INN	PD	17 (10/7)	62 (7)	2.0 (1.1)	22 (7)	-	148-185	-	^{123}I-β-CIT ADAC Vertex-plus	(str-occ)/occ
		MSA	15 (8/7)	62 (9)	2.0 (0.8)	39 (11)	-				
		PSP	14 (6/8)	67 (-)[A]	2.2 (0.7)	36 (7)	-				
Roselli et al 2010(*43*)	BAR	PD	15 (9/4)	78 (6)	3.5 (2.5)	25 (8)	2.5 (-)	111	22	^{123}I-FP-CIT GE Infinia	(str-occ)/occ
		PSP	10 (5/5)	66 (8)	1.5 (1.2)	25 (19)	1.8 (-)				
Lin et al 2010(*15*)	TAO	PD	10 (7/3)	61 (7)	4.6 (2.3)	25 (9)	2.1 (0.5)	925	40	^{99m}Tc-TRODAT-1 Siemens E.CAM	(str-occ)/occ
		PSP	6 (2/4)	64 (3)	5.2 (1.9)	47 (13)	3.7 (1.0)				
Goebel et al 2011(*44*)	INN	PD	15 (10/5)	61 (7)	1.7 (0.8)	22 (7)	-	148-185	43	^{123}I-β-CIT ADAC Vertex-plus	(str-occ)/occ
		MSA	15 (8/7)	62 (9)	2.0 (0.8)	39 (11)	-				
		PSP	15 (7/8)	66 (7)	2.0 (0.9)	35 (7)	-				
Cilia et al 2011(*45*)	MIL	PD	37 (18/19)	70 (5)	4.4 (2.9)	22 (8)	1.9 (0.7)	110-185	30-45	^{123}I-FP-CIT Prism 3000	(str-occ)/occ
		CBS	36 (16/20)	71 (7)	3.9 (1.6)	39 (13)	3.1 (0.8)				
Oh et al 2012(*25*)	SEO	PD	49 (21/28)	62 (11)	5.1 (6.0)	20 (13)	2.0 (1.0)	185	10	^{18}F-FP-CIT Biograph 40	(str-occ)/occ
		MSA	24 (8/16)	62 (11)	3.0 (1.7)	35 (17)	4.0 (1.2)				
		PSP	19 (9/10)	68 (8)	3.9 (2.1)	26 (13)	3.4 (1.3)				
Nocker et al 2012(*46*)	INN	PD	11 (7/4)	61(6)	2.4 (1.2)	19 (8)	1.9 (0.5)	148-185	43	^{123}I-β-CIT ADAC Vertex-plus	(str-occ)/occ
		MSA	8 (4/4)	60 (8)	2.4 (1.0)	40 (5)	3.0 (0)				
	UME	PD	29 (18/11)	74 (4)	1.5 (0.8)	27 (11)	2.0 (0.6)	185	60	^{123}I-FP-CIT	str/occ

Jacobson Mo et al 2013(*47*)		MSA	7 (-)	71 (14)	1.3 (0.9)	22 (11)	2.8 (1.0)			GE Infinia	
		PSP	13 (-)	76 (9)	1.9 (1.5)	34 (15)	2.9 (1.0)				
Hammesfahr et al 2016(*48*)	DÜS	PD	18 (6/12)	65 (7)	1.9 (0.9)	18 (11)	-	184	-	^{123}I-FP-CIT Prism 2000	str/occ
		CBS	19 (6/13)	67 (8)	2.0 (0.9)	28 (15)	-				
Kim et al 2016(*49*)	DAE	MSA-P	13 (-)	-	-	-	-	185	10	^{18}F-FP-CIT Biograph 40	(str-occ)/occ
		MSA-C	21 (-)	-	-	-	-				
Joling et al 2017(*50*)	AMS	PD	30 (16/14)	66 (8)	3.6 (3.0)	27 (12)	-	185	30	^{123}I-FP-CIT E.Cam, Siemens	(str-cer)/cer
		MSA-P	9 (2/7)	61 (10)	3.2 (2.6)	41 (23)	-				
		MSA-C	7 (3/4)	68 (11)	3.6 (1.4)	37 (8)	-				
		PSP	13 (7/6)	70 (6)	5.7 (4.7)	33 (12)	-				
Ohta et al 2017(*51*)	OKA	PD	21 (8/13)	70 (11)	6.3 (5.8)	37 (12)	-	-	-	^{123}I-FP-CIT -	-
		PSP	13 (8/5)	70 (6)	4.5 (3.3)	37 (8)	-				
Saari et al 2017(*52*)	TUR	PD	11 (10/1)	69 (7)	1.5 (1.5)	-	-	185	-	^{123}I-FP-CIT ^{123}I-β-CIT Picker, ADAC Vertex, GE Infinia	(str-occ)/occ
		MSA	5 (2/3)	53 (7)	1.3 (0.7)	-	-				
Nicastro et al 2018(*53*)	GEN	MSA-P	28 (13/15)	70 (10)	2.6 (2.4)	36 (11)	3.0 (0.7)	185	-	^{123}I-FP-CIT GCA-9300A/UI Toshiba	-
		MSA-C	6 (4/2)	62 (8)	1.6 (1.1)	20 (8)	2.8 (0.8)				

MIL = Milan, Italy; SEO = Seoul, Korea; MUL = Multisite; VIE = Vienna, Austria; NEW = New Haven, CT, USA; TOR = Toronto, Canada; HAN = Hannover, Germany; TAO = Taoyuan, Taiwan; TAI = Taipei, Taiwan; BER = Berlin, Germany; INN = Innsbruck, Austria; PHI = Philadelphia, PA, USA; ROM = Rome, Italy; BAR = Bari, Italy; UME = Umeå, Sweden; DÜS = Düsseldorf, Germany; DAE = Daegu, Korea; AMS = Amsterdam, The Netherlands; OKA = Okayama, Japan; TUR = Turku, Finland; GEN = Geneva, Switzerland

[A] Extremely large SD for the age of PSP patients, an apparent typographical error

[B] Reference region = supratentorial structures above the basal ganglia

Supplemental Table 2. Characteristics of AADC studies. All included studies performed with 6-^{18}F-fluoro-L-dopa as the tracer. Values are n or mean (SD/range) unless specified otherwise. None of the studies reported motor UPDRS values.

Study	Site	Groups	n (m/f)	Age (yrs)	Disease duration (yrs)	Hoehn & Yahr	Injected dose (MBq)	Scan duration (min)	Scanner	Analysis method
Brooks et al 1990a(*54*)	LON	PD	8 (7/1)	64 (6)	10.6 (8.7)	3.0 (0.8)	111-185	90	CTI 931/08/012	Ki^{occ}
		MSA	10 (6/4)	59 (9)	4.4 (3.2)	3.6 (1.0)				
Brooks et al 1990b(*55*)	LON	PD	16 (11/5)	56 (11)	9.2 (5.1)	2.7 (1-4)	74-185	90	CTI 981/08/012	Ki^{occ}
		MSA	18 (13/5)	56 (10)	4.1 (3)	3.2 (1-5)				
		PSP	10 (10/0)	68 (4)	3.5 (2.2)	3.3 (2-5)				
Burn et al 1994(*56*)	LON	PD	28 (-/-)	61 (38-77)	7.2 (0.5-20)	- (1-4)	111-185	94	CTI 931/08/012	Ki^{occ}
		MSA	25 (-/-)	58 (40-73)	4.4 (1-10)	- (2-5)				
		PSP	10 (-/-)	68 (62-75)	3.5 (0.5-8)	- (3-4)				
Otsuka et al 1995(*57*)	FUK	PD	4 (-/-)	-	-	-	110-240	127	Headtome III	ROI/cer
		PSP	3 (0/3)	56 (6)	1.7 (0.6)	-				
		CBS	2 (1/1)	65 (5)	4.0 (0)	-				
Otsuka et al 1997(*11*)	FUK	PD	15 (8/7)	49 (10)	7.0 (7.1)	1.9 (0.9)	110-240	127	Headtome III	ROI/occ
		MSA	9 (4/5)	52 (14)	6.4 (5.5)	2.4 (0.5)				
Antonini et al 1997(*58*)	VIL	PD	10 (7/3)	63 (5)	10 (5)	3.7 (0.6)	90-160	124	CTI 933/04-16	Ki^{occ}
		MSA	9 (5/4)	57 (7)	5 (2)	3.9 (0.9)				

LON = London, UK; FUK = Fukuoka, Japan; VIL = Villigen, Switzerland, Disdur = disease duration, ROI = region of interest, occ = occipital cortex, cer = cerebellum

Supplemental Table 3. MSA subgroups in included studies. Values are n.

Study	MSA total	Subgroups [A]			Comment
		MSA-P/SND	MSA-C/OPCA	SDS	
Brooks et al. 1990a	10	-	-	-	-
Brooks et al. 1990b	18	-	-	-	-
Burn et al 1994	25	-	-	-	-
Otsuka et al 1997	9	4	5	-	No separate mean values reported for subgroups
Antonini et al 1997	9	-	-	-	-
Kim et al. 2000	16	7	9	-	Separate mean values reported for MSA-P and MSA-C
Pirker et al. 2000	19	15	3	-	No separate mean values reported for subgroups
Varrone et al. 2001	26	14	-	12	Separate mean values reported for SND and SDS
Kim et al. 2002	7	7	-	-	-
Berding et al 2003	10	7	3	-	No separate mean values reported for subgroups
Antonini et al. 2003	10	10	-	-	-
Lu et al 2004	49	30	19	-	Separate mean values reported for MSA-P and MSA-C
Plotkin et al 2005	13	8	5	-	No separate mean values reported for subgroups
Swanson et al. 2005	25	25			
Scherfler et al 2005	15	15	-	-	-
Seppi et al 2006	15	15	-	-	-
Goebel et al 2011	15	15	-	-	-
Oh et al 2012	24	24	-	-	-
Nocker et al 2012	8	8	-	-	-
Jacobson Mo et al 2013	7	-	-	-	-
Kim et al. 2016	34	13	21	-	Separate mean values reported for MSA-P and MSA-C
Joling et al 2017	16	9	7	-	Separate mean values reported for MSA-P and MSA-C
Saari et al 2017	5	-	-	-	-
Nicastro et al 2018	34	28	6	-	Separate mean values reported for MSA-P and MSA-C

MSA = multiple system atrophy, MSA-P = parkinsonism varian multiple system atrophy, SND = striatonigral degeneration, MSA-C = cerebellar variant multiple system atrophy, OPCA = olivopontocerebellar atrophy, SDS = Shy-Drager syndrome

[A] Studies that did not report subgroups were included in the MSA-P group for the analysis (4 AADC studies and 2 DAT studies).

Supplemental Table 4. Quality of the included studies (Newcastle-Ottawa Scale).

Study	Case definition	Age-/sex-differences between groups	PET/SPECT imaging methodology & resolution	Disease duration	UPDRS/UMSARS/ HY-scale	Analysis method	Total Score
Brooks et al 1990a	*	*	-	*	*	*	5
Brooks et al 1990b	*	-	-	*	*	*	4
Burn et al 1994	*	-	-	*	-	*	3
Otsuka et al 1995	*	*	-	-	-	*	3
Otsuka et al 1997	*	*	-	*	*	*	5
Antonini et al 1997	*	*	-	*	*	*	5
Messa et al 1998	*	*	-	*	*	*	5
Kim et al 2000	*	*	-	-	-	*	3
PSG 2000	*	*	-	-	-	*	3
Pirker et al 2000	*	*	*	*	*	*	6
Varrone et al 2001	*	*	*	*	*	*	6
Kim et al 2002	*	*	*	*	*	-	5
Berding et al 2003	*	-	*	*	*	*	5
Antonini et al 2003	*	-	*	*	-	*	4
Lu et al 2004	*	*	*	*	*	*	6
Lai et al 2004	*	-	*	*	*	*	5
Plotkin et al 2005	*	*	*	*	-	-	4
Swanson et al 2005	*	*	*	*	-	-	4
Scherfler et al 2005	*	*	*	*	*	*	6
Im et al 2006	*	*	*	*	-	*	5
Filippi et al 2006	*	*	*	*	-	*	5
Seppi et al 2006	*	*	*	*	*	*	6
Roselli et al 2010	*	-	*	*	*	*	5
Lin et al 2010	*	*	*	*	*	*	6
Goebel et al 2011	*	*	*	*	*	*	6
Cilia et al 2011	*	*	*	*	*	*	6
Oh et al 2012	*	*	*	*	*	*	6
Nocker et al 2012	*	*	*	*	*	*	6
Jakobson et al 2013	*	-	*	*	*	*	5

Kim et al 2016	*	-	*	-	-	*	3
Hammesfahr et al 2016	*	*	*	*	*	*	6
Joling et al 2017	*	-	*	*	*	*	5
Ohta et al 2017	*	*	*	*	*	-	5
Saari et al 2017	*	-	*	*	-	*	4
Nicastro et al 2018	*	*	*	*	*	-	5

Supplemental Table 5. Clinical diagnostic criteria for PD, MSA, PSP and CBS in the included studies.

Study	Diagnostic criteria
Messa et al 1998	PD: Calne et al. Ann Neurol 1992;32:S125-S127, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Kim et al 2000	MSA-C: Criteria modified from Yamaguchi et al. J Neurol Sci 1994;125:56-61, MSA-P: Quinn, J Neurol Neurosurg Psychiatry 1989;special suppl:8-89
Parkinson Study Group 2000	PD: 1. At least two of the following: resting tremor, rigidity, bradykinesia, postural reflex impairment, and freezing phenomenon 2. Hoehn and Yahr stage of 1.0 to 3.028 3. Has a known positive response to antiparkinsonian medications 4. No other known or suspected cause of parkinsonism PSP: 1. At least two of the following: axial rigidity, bradykinesia, postural reflex impairment, speech impairment 2. Ophthalmoparesis including restriction of downgaze 3. No significant response to antiparkinsonian medication 4. Ability to ambulate without assistance 5. No other known or suspected cause of parkinsonism
Pirker et al 2000	MSA: Quinn, Movement Disorders 3 1994;262-281, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), CBD: Litvan et al. Neurology 1997;48:119-125
Varrone et al 2001	PD: Age older than 35 years, and at least two of the following: bradykinesia, resting tremor, rigidity, postural instability, or freezing phenomena (one of which is rest tremor or bradykinesia). MSA: A known negative, unsustained, or inadequate response to L-dopa, with at least two of the following: resting tremor, bradykinesia, postural reflex impairment, or freezing phenomenon; and with a concurrent presence of cerebellar dysfunction, symptomatic autonomic failure, or pyramidal signs.
Kim et al 2002	

	PD: Hughes et al J Neurol Neurosurg Psychiatry 1992;55:181-184, MSA: Quinn, Movement Disorders 3 1994;262-281, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Berding et al 2003	Not reported.
Antonini et al 2003	Not reported.
Lai et al 2004	CBD: Lang et al. In: Calne DB (editor). Neurogenerative Disease. Philadelphia: W.B. Saunders 1994;877-894
Lu et al 2004	PD: Calne et al. Ann Neurol 1992;32:S125-S127, MSA: Gilman et al. J Neurol Sci 1999;163:94-98
Plotkin et al 2005	PD: Hughes et al J Neurol Neurosurg Psychiatry 1992;55:181-184, MSA: Gilman et al. J Neurol Sci 1999;163:94-98, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Scherfler et al 2005	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, MSA: Gilman et al. Clin Auton Res 1998;8:359-362
Swanson et al 2005	PD: Ward & Gibbs. In: Streifler et al (eds). Advances in neurology: anatomy, pathology and therapy. New York: Raven, 1990, MSA: Gilman et al. J Neurol Sci 1999;163:94-98
Im et al 2006	PD: CAPIT Committee, Mov Disord 1992;7:2-13, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Filippi et al 2006	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Seppi et al 2006	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), MSA: Gilman et al. Clin Auton Res 1998;8:359-362
Roselli et al 2010	PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Lin et al 2010	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Goebel et al 2011	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), MSA: Gilman et al. Clin Auton Res 1998;8:359-362

Cilia et al 2011	CBS: Mahapatra et al. Lancet Neurol 2004;3:736-743
Oh et al 2012	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), MSA: Gilman et al. Neurology 2008;71:670-676
Nocker et al 2012	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, MSA: Gilman et al. Neurology 2008;71:670-676
Jacobson Mo et al 2013	MSA: Gilman et al. J Neurol Sci 1999;163:94-98, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), clinically uncertain parkinsonian syndromes (CUPS) at the time of imaging
Hammesfahr et al 2016	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, CBS: Mathew et al J Neurol Neurosurg Psychiatry 2012;83:405-410 and Armstrong et al. Neurology 2013;80:496-503
Kim et al 2016	MSA: Gilman et al. Neurology 2008;71:670-676
Joling et al 2017	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9), MSA: Gilman et al. Neurology 2008;71:670-676
Ohta et al 2017	PSP: NINDS-SPSP International workshop criteria (Litvan et al. Neurology 1996;47:1-9)
Saari et al 2017	Neuropathological diagnoses
Nicastro et al 2018	MSA: Gilman et al. Neurology 2008;71:670-676
Brooks et al 1990a	Individual clinical details reported
Brooks et al 1990b	Individual clinical details reported
Burn et al 1994	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184

Otsuka et al 1995	Individual clinical details reported
Otsuka et al 1997	MSA-P: Fearnley & Lees, Brain 1990;113:1823-1842, individual clinical details reported
Antonini et al 1997	PD: Hughes et al. J Neurol Neurosurg Psychiatry 1992;55:181-184, individual clinical details reported.

Supplemental Table 6. Summary of DAT results (hemispheric values and ratios). *g* = Hedges' *g*, CI = 95% confidence interval for *g,* n = number of studies/number of patients, I^2 = heterogeneity index. AI = asymmetry index. There were no available studies that have compared MSA-C patients to PSP or CBS patients. Data were insufficient also for MSA-P vs. CBS comparison. Statistically significant comparisons are highlighted with bold text.

	PD vs MSA-P	**PD vs PSP**	**PD vs MSA-C**	**PD vs CBS**	**MSA-P vs PSP**	**MSA-P vs MSA-C**	**PSP vs CBS**
Caudate Contralateral	*g*=-0.61 CI=-2.35 to 1.13 n=3/268, I^2=74.9%	***g*=-1.05** **CI=-2.09 to -0.01** **n=6/181, I^2=78.5%**	Insufficient data n=1/55	*g*=-0.36 CI=-1.63 to 0.91 n=3/122, I^2=49.4%	Insufficient data n=1/13	Insufficient data n=1/49	Insufficient data n=1/17
Caudate Ipsilateral	*g*=-0.76 CI=-2.52 to 1.01 n=3/268, I^2=77.6%	***g*=-1.35** **CI=-2.45 to -0.25** **n=6/181, I^2=79.0%**	Insufficient data n=1/55	*g*=-0.24 CI=-0.85 to 0.37 n=3/122, I^2=0.0%	Insufficient data n=1/13	Insufficient data n=1/49	Insufficient data n=1/17
Putamen Anterior	*g*=-0.40 CI=-3.11 to 2.32 n=3/247, I^2=90.2%	***g*=-0.66** **CI=-1.25 to -0.07** **n=4/133, I^2=0.0%**	Insufficient data n=0	Insufficient data n=0	*g*=-0.05 CI=-8.74 to 8.65 n=2/56, I^2=79.8%	Insufficient data n=1/34	Insufficient data n=0
Putamen Posterior	*g*=-0.12 CI=-1.57 to 1.34 n=4/266, I^2=85.4%	*g*=-0.23 CI=-1.30 to 0.83 n=4/133, I^2=63.6%	Insufficient data n=0	Insufficient data n=0	*g*=0.19 CI=-11.29 to 11.66 n=2/56, I^2=87.4%	Insufficient data n=1/34	Insufficient data n=0
Putamen Contralateral	*g*=-0.10 CI=-4.71 to 4.50 n=2/249, I^2=80.0%	*g*=-0.63 CI=-2.04 to 0.77 n=4/145, I^2=82.3%	Insufficient data n=1/55	*g*=0.48 CI=-0.48 to 1.44 n=3/122, I^2=24.8%	Insufficient data n=0	Insufficient data n=1/49	Insufficient data n=1/17
Putamen Ipsilateral	*g*=-0.58 CI=-3.20 to 2.05 n=2/249, I^2=38.0%	*g*=-1.40 CI=-3.63 to 0.82 n=4/145, I^2=89.9%	Insufficient data n=1/55	*g*=0.57 CI=-0.53 to 1.67 n=3/122, I^2=41.1%	Insufficient data n=0	Insufficient data n=1/49	Insufficient data n=1/17
Putamen AI	*g*=0.02 CI=-0.89 to 0.93 n=4/264, I^2=74.9%	Insufficient data n=1/31	Insufficient data n=0	Insufficient data n=1/73	Insufficient data n=1/29	Insufficient data n=0	Insufficient data n=0
Putamen / Caudate ratio	*g*=0.36 CI=-4.70 to 5.42 n=2/263, I^2=75.0%	*g*=1.08 CI=-0.85 to 3.01 n=4/185, I^2=88.8%	Insufficient data n=0	*g*=1.08 CI=-0.88 to 3.03 n=3/101, I^2=62.0%	Insufficient data n=1/20	Insufficient data n=0	Insufficient data n=1/17

Supplemental Table 7. Summary of AADC results. *g* = Hedges' *g*, CI = 95% confidence interval for *g,* n = number of studies/number of patients. All other AADC comparisons had insufficient data.

	PD vs MSA-P	**PD vs PSP**	**MSA-P vs PSP**
Caudate	*g*=-0.54 CI=-1.23 to 0.14 n=5/148	*g*=-1.50 CI=-5.79 to 2.79 n=2/64	*g*=-0.91 CI=-2.77 to 0.96 n=2/63
Putamen	*g*=-0.01 CI=-0.62 to 0.60 n=5/148	*g*=-0.41 CI=-4.10 to 3.28 n=2/64	*g*=-0.07 CI=-1.83 to 1.69 n=2/63

Supplemental Table 8. Associations of moderators with Hedges' g (the difference between PD and MSA-P/PSP) in meta-regression analyses. The only significant association in meta-regressions was detected using HY stage as the moderator in PD vs. MSA-P caudate comparison (highlighted).

Comparison	Region	Moderator	β (95% CI)	n (studies)
PD vs MSA-P	Caudate	Disease duration	0.12 (0.0 to 0.24)	12
		HY stage	**0.74 (0.19 to 1.29)**	**7**
		Motor UPDRS	0.03 (-0.01 to 0.07)	9
	Putamen	Disease duration	-0.35 (-1.75 to 1.06)	10
		HY stage	0.90 (-1.95 to 3.76)	5
		Motor UPDRS	0.027 (-0.03 to 0.08)	8
PD vs PSP	Caudate	Disease duration	0.23 (-0.28 to 0.73)	10
		HY stage	0.96 (-4.0 to 5.9)	4
		Motor UPDRS	0.089 (-0.02 to 0.19)	6
	Putamen	Disease duration	0.060 (-0.84 to 0.96)	7
		HY stage	1.58 (-10.1 to 13.2)	2
		Motor UPDRS	0.059 (-0.03 to 0.14)	5