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Atypical brain FDG-PET patterns increase the risk of long-term cognitive and motor progression in Parkinson's disease

Alberto Imarisio [a,1,3], Andrea Pilotto [a,b,c,1,*], Enrico Premi [a,d], Silvia Paola Caminiti [e], Luca Presotto [f,g], Arianna Sala [e], Cinzia Zatti [a,b,c], Alessandro Lupini [a,b,c], Rosanna Turrone [a,b], Barbara Paghera [h], Barbara Borroni [a], Daniela Perani [e,i,2], Alessandro Padovani [a,b,c,2]

[a] Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[b] Neurology Unit, Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia University Hospital, Italy
[c] Laboratory of Digital Neurology and Biosensors, University of Brescia, Italy
[d] Stroke Unit, Department of Neurological and Vision Sciences, ASST Spedali Civili, Brescia, Italy
[e] In Vivo Human Molecular and Structural Neuroimaging Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
[f] Department of Physics "G. Occhialini", University of Milano – Bicocca, Milan, Italy
[g] Milan Centre for Neuroscience, University of Milano - Bicocca, Milan, Italy
[h] Nuclear Medicine Unit, University of Brescia, Brescia, Italy
[i] Nuclear Medicine Unit, San Raffaele Hospital, Milan, Italy

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ABSTRACT

Introduction: Brain hypometabolism patterns have been previously associated with cognitive decline in Parkinson's disease (PD). Our aim is to evaluate the impact of single-subject fluorodeoxyglucose (FDG)-PET brain hypometabolism on long-term cognitive and motor outcomes in PD.
Methods: Forty-nine non-demented PD patients with baseline brain FDG-PET data underwent an extensive clinical follow-up for 8 years. The ability of FDG-PET to predict long-term cognitive and motor progression was evaluated using Cox regression and mixed ANCOVA models.
Results: Participants were classified according to FDG-PET pattern in PD with typical (n = 26) and atypical cortical metabolism (n = 23). Patients with atypical brain hypometabolic patterns showed higher incidence of dementia (60% vs 3%; HR = 18.3), hallucinations (56% vs 7%, HR = 7.3) and faster motor decline compared to typical pattern group.
Conclusion: This study argues for specific patterns of FDG-PET cortical hypometabolism in PD as a prognostic marker for long term cognitive and motor outcomes at single-subject level.

1. Introduction

Clinical presentation and progression rate are heterogeneous in Parkinson's disease (PD). Several longitudinal studies showed that longer disease duration, advanced age and worse non-motor symptoms are associated with an overall poor prognosis [1,2]. Despite the advances in PD clinical subtyping, the identification of patients at higher risk of cognitive and motor progression is still a great challenge at the single-subject level [3]. Recently, we demonstrated the utility of application of brain fluorodeoxyglucose positron emission tomography (FDG-PET) statistical parametric mapping (SPM)-optimized procedure to identify typical and atypical hypometabolic patterns in sporadic PD patients [4]. The typical PD hypometabolic pattern involves very small clusters in anterior cortical regions. The presence of atypical patterns involving large clusters in posterior cortical regions - the so-called "Dementia with Lewy bodies (DLB)-like" and "Alzheimer's disease (AD)-like" FDG-PET patterns - resulted in an accuracy of 85% in predicting conversion to dementia, significantly higher compared with clinical and demographic baseline stratification. The results were in line with several previous studies at group level, indicating

* Corresponding author. Neurology Unit Department of Clinical and Experimental Sciences, University of Brescia, P.zale Spedali Civili, 1, 25123, Brescia, Italy.
E-mail address: andrea.pilotto@unibs.it (A. Pilotto).
[1] Alberto Imarisio and Andrea Pilotto equally contributed to the present work.
[2] Daniela Perani and Alessandro Padovani share senior authorship.
[3] Present address: Department of Molecular Medicine, University of Pavia, Pavia, Italy.

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parieto-temporo-occipital cortical hypometabolism as early marker of future cognitive dysfunction in PD [5–10]. Importantly, despite these FDG-PET patterns resembled those seen in other neurodegenerative diseases, like DLB and AD, the enrolled patients had a confirmed diagnosis of PD (or PD-dementia, PDD) at the last available follow-up both in our previous work [4] and in all the other longitudinal studies assessing the prognostic value of brain FDG-PET hypometabolism [5–7,9]. The relatively short follow-up available, however, did not allow a proper evaluation of the predictive value of atypical FDG-PET patterns on long-term PD progression, including motor, cognitive and functional variables - especially in those subjects who did not convert to dementia. In the present study, a longitudinal cohort of patients with baseline brain FDG-PET data and full cognitive and motor assessment was followed up for eight years. Aim of the study was to address the long-term prognostic value of brain FDG-PET on cognitive (conversion to dementia and hallucinations) and motor outcomes (loss of ambulation and changes in MDS-UPDRS-III total score) at single-subject level in PD patients.

2. Methods

2.1. Participants

Consecutive patients with a clinical diagnosis of PD [11] with disease duration of at least one year and sustained dopaminergic treatment response were consecutively recruited at Neurology Unit of Spedali Civili Hospital, University of Brescia, Italy from January 2006 to December 2010. All patients underwent (i) brain magnetic resonance imaging in order to exclude prominent cortical/subcortical infarcts, cerebral small vessel disease or atypical signs (such as midbrain, cortical or cerebellar atrophy) indicating atypical parkinsonism; (ii) ^{123}I-FP-CIT SPECT imaging to confirm nigrostriatal dopaminergic degeneration. Each patient underwent a standardized neurological examination including the motor assessment with the Movement Disorders Society Unified Parkinson Disease Rating Scale part III (MDS-UPDRS-III) and accepted to undergo follow-up. Patients were divided in tremor-dominant and akinetic-rigid subtypes according to the predominant clinical features [12]. Levo-dopa equivalent daily dose (LEDD) was also calculated at baseline and every two years according to last proposed conversion factors [13]. The neuropsychological evaluation at baseline enabled the stratification of PD patients, in PD with mild cognitive impairment (PD-MCI) or PD with normal cognition (PDNC) according to level II MDS definition, as previously reported [14]. All the patients included in the study had a diagnosis of clinically established PD confirmed after 8-year follow-up according to the last published MDS clinical diagnostic criteria for PD [15]. Both the clinical evaluations and brain FDG-PET scans were performed during “ON” state.

Patients presenting with dementia according to current PDD criteria [16] at baseline were excluded from the study. Specifically, PDD level II MDS diagnostic criteria were applied: i.) Scores 1.5 standard deviation below group norms or previous defined cut-off scores for the MMSE items in at least 2 of the following cognitive domains: attention (Trail Making Test A; Serial 7’s of the MMSE (0–5), at least two incorrect responses [16,17]), executive functions (Clock drawing, inability to insert the correct clock face numbers and/or the clock hands pointing to the correct time: <6/10 score [17,18], Trail Making B), visuospatial function (Rey Complex figure and Drawing of the MMSE pentagons (0–1) [16,17], memory (short story recall and recall of the Rey complex figure), or language abilities (semantic fluency, MMSE language cumulative score for naming (0–2), repetition (0–1) and writing (0–1), at least two incorrect responses [17]); ii.) Self-reported cognitive decline with insidious onset and slow progression; iii.) Self-reported impairment of non-motor activities of daily living (ADL) by the Basic Activities of Daily Living (ADL, cut-off <1 points) and Instrumental Activities of Daily Living (IADL, cut-off <1 points) not depending on motor function.

The following exclusion criteria were also applied at baseline and at follow-up: (1) atypical parkinsonism including corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), according to last MDS clinical diagnostic criteria for PD [15], diagnostic criteria for atypical parkinsonian syndromes [19–22] and frontotemporal dementia (FTD) [23,24]; (2) other neurological disorders or medical conditions potentially responsible for cognitive deficits; (3) prominent cortical or subcortical infarcts, cerebral small vessel disease, brain iron accumulation at MRI; (4) deep brain stimulation; (5) previous diagnosis of major depressive disorder, bipolar disorder, schizophrenia, history of drug or alcohol abuse.

2.2. Standard protocol approvals, registrations, and patient consents

This study was approved by local Ethic Committee and complies with the Helsinki Declaration (grant number NP 1471, DMA). Written informed consent was obtained from all participants.

2.3. FDG-PET image acquisition and pre-processing

All patients underwent FDG-PET scans using GE Discovery 3D PET/CT 690. Image acquisition and preprocessing were performed as recently published [4]. Briefly, images underwent general pre-processing procedures, using the MATLAB (The Mathworks, Inc., Natick, MA) based software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/SPM5/).

Regional hypometabolism was measured in each FDG-PET image by means of a SPM semi-quantitative procedure. Specifically, the optimized procedure started with the normalization of FDG-PET images using an FDG-PET specific template [25]. The normalized images were then smoothed with an isotropic 3D Gaussian kernel (8 mm FWHM) and scaled to the global mean to obtain standardized uptake value ratio (SUVR) images [26,27]. The resulting SUVR images were tested for relative brain hypometabolism by means of a two-sample *t*-test using SPM. In the statistical comparison, the single image was compared with a large normal control FDG-PET dataset, entering age as a nuisance covariate [27]. The normal control dataset belongs to a San Raffaele Hospital dataset that was previously validated [25]. The dataset is made of 112 FDG-PET images acquired from 53 male and 59 female subjects with a mean age of 64.68 ± 9.34 years [min:28-max:83]. The resulting SPM t-map of hypometabolism [HC – single patient], thresholded at $p < 0.05$ with a minimum cluster extent of 100 voxel, was then overlaid to an anatomical template and evaluated by a nuclear medicine physician slice by slice.

The single-subject hypometabolism patterns were classified by two expert raters (D.P., S.P.C.) blind to any clinical information. The raters had to make a forced decision on whether the hypometabolism SPM patterns were suggestive of a specific disease condition, including AD, DLB, FTD or CBS, according to the disease-specific brain metabolic patterns reported in the literature [27–29]. Specifically, the “PD-typical pattern” was defined by the presence of either no brain hypometabolism or heterogeneity in brain hypometabolism involving motor and premotor regions, somatosensory cortex, anterior cingulate and frontal cortex [4,30]. DLB-like pattern was characterized by temporal-parietal and occipital hypometabolism, variably associated with frontal hypometabolism; AD-like pattern by bilateral temporal-parietal hypometabolism; CBS-like pattern by asymmetric frontal-parietal hypometabolism; FTD-like pattern by frontal-temporal hypometabolism (See Fig. 1 for examples of single-subject typical and atypical FDG-PET patterns). This semi-quantitative approach allows to identify disease-specific topographies, i.e. SPM t-maps of hypometabolism, that might be expressed since early clinical phase, aiding differential diagnosis and exclusion of progression to dementia [31].

Cohen κ coefficient was used to evaluate the interrater agreement. In case of mismatch, the classification performed by D.P. was considered, because of major expertise.

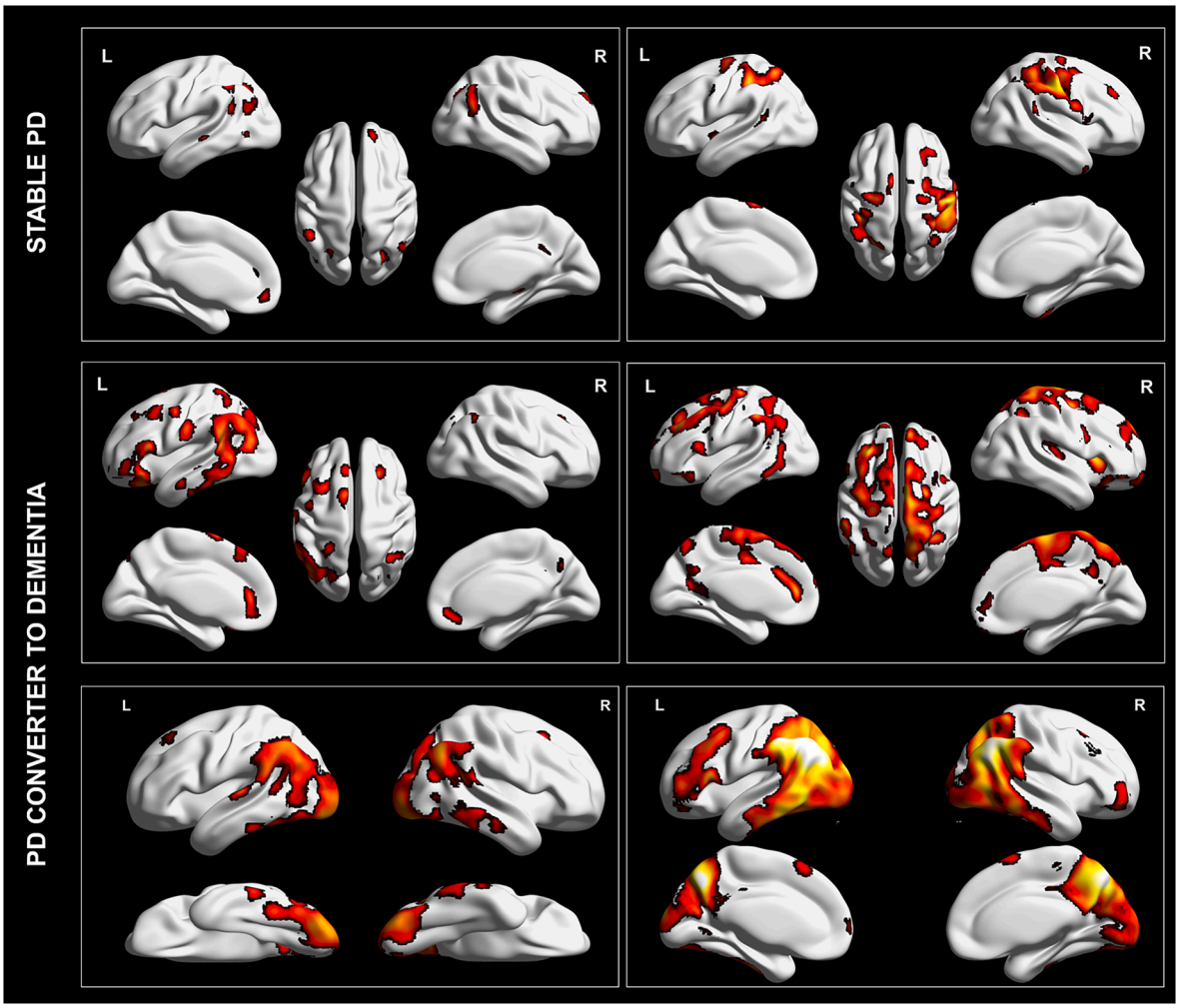

Fig. 1. Examples of typical and atypical statistical parametric mapping of brain FDG-PET patterns at baseline in single PD cases.

2.4. Clinical follow-up

All patients included in the analyses underwent a clinical follow-up every two years up to 8 years. We thus evaluated the onset of the following disability milestones: i) dementia defined by PDD level II Movement Disorder Society diagnostic criteria [16]; ii) hallucinations; iii) inability to walk due to disease progression. MDS-UPDRS-III and levodopa equivalent daily dose (LEDD) changes were evaluated every 2 years for at least 8 years of follow-up.

2.5. Statistical analyses

Comparisons of baseline clinical characteristics of PD patients with "typical" and "atypical" FDG-PET patterns and between converters to dementia at follow-up vs non non-converters were evaluated using Mann Whitney *U* test for continuous variables and Chi-Square for dichotomous variables. Fisher's Exact test was used when at least one expected frequency in a fourfold table was less than five. Further analyses were performed for specific atypical patterns (i.e., AD-like, DLB-like, CBS-like, and FTD-like) contrasted with PD typical FDG-PET group using Kruskal-Wallis test.

The association between FDG-PET patterns and the specific milestones was evaluated using Chi-Square test and then analysed in multivariable analyses using Cox regression model including (i) age, disease duration, sex, years of education and the cognitive status at baseline (PD with normal cognition vs PD-MCI) for dementia and hallucinations risk; (ii) age, sex, disease duration, baseline MDS-UPDRS-III score and ΔLEDD over follow-up ($\Delta LEDD = LEDD_{8years} - LEDD_{baseline}$) for inability to walk. In Chi-Square analyses, the observed frequencies were compared with expected frequencies by means of standardized residuals, considering z critical values corresponding to $\alpha = 0.05$.

The additional value of FDG-PET patterns in predicting conversion to PD disability milestones was also evaluated through multivariable binary logistic regression models including 8-year dementia, hallucinations and inability to walk as dependent variable and the following predictors: (i) baseline clinical-demographic features alone (i.e. age, disease duration, sex, years of education and MCI status at baseline for dementia and hallucinations risk; age, sex, disease duration, baseline MDS-UPDRS-III score and ΔLEDD over follow-up for inability to walk); (ii) clinical-demographic variables and dichotomic brain FDG-PET pattern (PD typical vs PD atypical); (iii) clinical-demographic variables and the specific brain FDG-PET patterns (PD typical, DLB-like, AD-like). PD typical FDG-PET pattern was used as reference category. The fitness of the logit models was measured using Cox and Snell's R^2.

The effect of FDG-PET pattern on MDS-UPDRS-III score progression during follow-up was evaluated using two-way mixed ANCOVA with a between factor "FDG-PET pattern" and a within factor "time", adjusted for the effect of age, disease duration, sex, baseline MDS-UPDRS-III score and ΔLEDD at 8 years. When a significant main effect was reached, *post hoc* tests with Bonferroni correction for multiple comparisons were conducted to analyze group differences. Between-groups differences in progressive LEDD adjustment were evaluated with two-way mixed ANOVA with "FDG-PET pattern" as between factor and "time" as within factor.

Subgroups with n < 5 (i.e. CBS-like and FTD-like patterns) were excluded from all longitudinal analyses comparing the specific brain FDG-PET patterns. Significance was set at $p < 0.05$ for all analyses. Data were analysed by using SPSS 26.0 software (IBM, Armonk, NY, USA).

2.6. Data availability statement

Anonymized data are available upon request to pilottoandreae@gmail.com, andrea.pilotto@unibs.it.

3. Results

3.1. Clinical and brain FDG-PET baseline features

Forty-nine out of original 54 patients which completed the 4-year follow-up [4] were evaluated at six and eight years after baseline brain FDG-PET; five subjects dropped out due to refusal to continue follow-up (n = 3) or death (n = 2) (Suppl. Fig. 1). Both deceased patients had atypical FDG-PET pattern (one CBS-like and one FTD-like) and were excluded from the present analyses. Table 1 shows the baseline and 8-year follow-up clinical characteristics of 49 patients stratified according to FDG-PET pattern. Twenty-six of the 49 patients were classified as PD typical pattern. The remaining 23 patients exhibited an atypical pattern, namely n = 12 DLB-like; n = 6 AD-like; n = 4 CBS-like; n = 1 FTD-like (see Fig. 1 for examples of typical and atypical FDG-PET patterns). Importantly, despite presenting brain hypometabolic patterns resembling other neurodegenerative conditions, all the patients included in the atypical pattern group had a confirmed idiopathic PD clinical diagnosis [11].

The neuroimaging experts (D.P., S.P.C.) had high interrater agreement in the SPM single-subject classification (Cohen $\kappa > 0.98$). Baseline demographics were similar between typical and atypical pattern patients, except for longer disease duration in atypical pattern group (Table 1).

Additional clinical data, including timepoints of conversion to PD disability milestones as well as 4- and 6-year follow-up clinical assessments are available in Suppl. Table 1. Full baseline and 8-year cognitive evaluation data are reported as Suppl. Table 2.

3.2. Single-subject brain FDG-PET patterns and milestones of disability

After 8-year follow-up, all the 49 study participants had a confirmed diagnosis of clinically established PD, according to last MDS clinical diagnostic criteria for PD [15], and no patient presented with red flags suggesting a diagnosis of atypical parkinsonism.

At follow-up, 60% of patients with a cortical atypical metabolism converted to dementia compared to 3% in the typical group ($\chi^2(1) = 16.094$; $p < 0.001$) (Table 1). PD typical FDG-PET pattern showed a negative predictive value for conversion to dementia equal to 96.2%. Atypical pattern as a whole had a positive predictive value for 8-year dementia of 60.9%, which strikingly increased in AD-like pattern subgroup (83.3%). Cox regression multivariable model confirmed the higher risk to develop dementia for atypical compared to typical pattern (HR = 31.3; p = 0.005) (Fig. 2). Cox regression model for specific patterns revealed a higher risk of dementia for AD-like (HR = 58.9; p = 0.002) and DLB-like (HR = 21.5; p = 0.009) subgroups compared to subjects with PD typical metabolism (Fig. 2). To further validate the value of atypical brain FDG-PET patterns in predicting dementia conversion we adopted binary logistic regression models with "dementia at 8 years" as dependent variable. In the model including only clinical-demographic variables, advanced age and disease duration increased the odds of dementia conversion (OR = 1.14; p = 0.039 and OR = 1.20; p = 0.029, respectively; $R^2 = 0.188$) (Suppl. Table 3a). The addition of dichotomic FDG-PET pattern resulted in the atypical pattern being the only significant predictor (OR = 64.91; p = 0.004), significantly increasing the fitness of the model ($R^2 = 0.424$). The inclusion of the

Table 1
Patients' demographics and clinical characteristics at baseline and after 8-year follow-up according to their single-subject FDG-PET pattern. Data are presented as mean ± standard deviation and as percentage (sample size) for numeric and categorical variables, respectively.

Variable	PD-all (n = 49)	Typical PD (n = 26)	DLB-like (n = 12)	AD-like (n = 6)	CBS-like (n = 4)	FTD-like (n = 1)	p[c]	All-atypical (n = 23)	p[b]
Sex, M % (n)	67.3 (33)	57.7 (15)	75.0% (9)	83.3 (5)	100.0 (4)	0 (0)	0.191[d]	78.3 (18)	0.130[d]
Age at onset, years	60.1 ± 9.8	59.0 ± 11.0	60.0 ± 9.5	61.5 ± 7.2	63.0 ± 7.8	71.0	0.754[f]	61.4 ± 8.4	0.402[e]
Age at baseline evaluation, years	65.2 + 8.5	63.1 ± 9.8	66.1 ± 6.2	68.8 ± 6.6	68.5 ± 6.5	74.0	0.360[f]	65.2 ± 8.5	0.071
Disease duration, years	5.2 ± 3.3	4.2 ± 2.4	7.3 ± 4.8	7.3 ± 4.8	6.5 ± 1.3	3.0	0.131[f]	6.4 ± 3.8	**0.040**[e]
MDS-UPDRS-III score	22.7 ± 7.3	21.7 ± 7.3	27.2 ± 5.6	18.8 ± 8.7	22.8 ± 6.7	17.0	0.152[f]	23.8 ± 7.3	0.337[e]
LEDD, mg per day	390 ± 330	320 ± 323	434 ± 303	458 ± 344	666 ± 396	160	0.306[f]	469 ± 326	0.062[e]
MMSE baseline score	28.1 ± 1.8	28.5 ± 1.6	28.5 ± 1.3	26.5 ± 2.6	27.3 ± 2.4	27.0	0.102[f]	27.7 ± 2.0	0.155[e]
MCI at baseline, % (n)	51% (25)	46% (12)	50% (6)	67% (4)	50% (2)	100% (1)	0.770[d]	57% (13)	0.660[d]
Education, years	7.5 ± 3.8	7.9 ± 4.1	7.7 ± 3.8	7.7 ± 4.1	5.0 ± 0.0	5.0	0.688[f]	7.1 ± 3.5	0.550[e]
8-year follow-up									
Dementia, % (n)	30.6 (15)[a]	3.8 (1)[a]	58.3 (7)	83.3 (5)[a]	25.0 (1)	100.0 (1)	< **0.001**[d]	60.9 (14)[a]	< **0.001**[d]
Hallucinations, % (n)	30.6 (15)[a]	7.7 (2)[a]	41.7 (5)	83.3 (5)[a]	50.0 (2)	100.0 (1)	**0.001**[d]	56.5 (13)[a]	**0.001**[d]
Inability to walk, % (n)	14.3 (7)	3.8 (1)	16.7 (2)	50.0 (3)[a]	0.0 (0)	100.0 (1)	**0.004**[d]	26.1 (6)	**0.041**[d]
MDS-UPDRS-III score	27.7 ± 14.2	23.1 ± 11.8	31.4 ± 17.2	37.7 ± 13.0	34.3 ± 13.0	15.0	0.077[f]	32.8 ± 15.2	**0.030**[e]
ΔMDS-UPDRS-III score	4.9 ± 14.0	1.4 ± 12.0	4.3 ± 16.4	18.8 ± 9.7	11.5 ± 14.0	−2.0	0.112[g]	9.0 ± 15.1	**0.043**[g]
LEDD, mg per day	696 ± 340	660 ± 369	665 ± 257	756 ± 316	920 ± 468	760	0.807[f]	737 ± 307	0.331[e]
ΔLEDD, mg per day	306 ± 297	340 ± 275	230 ± 368	297 ± 354	253 ± 118	600	0.216[h]	267 ± 322	0.114[h]

Abbreviations and symbols: LEDD, Levodopa Equivalent Daily Dose; $\Delta LEDD = LEDD_{8years} - LEDD_{baseline}$; MCI, Mild Cognitive Impairment; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale; $\Delta MDS\text{-}UPDRS\text{-}III = MDS\text{-}UPDRS\text{-}III_{8years} - MDS\text{-}UPDRS\text{-}III_{baseline}$; MMSE, Mini Mental State Examination.

[a] Observed frequencies significantly different from expected frequencies.
[b] Comparison between patients with typical and atypical single-subject FDG-PET pattern.
[c] Comparison among the five different groups.
[d] Chi-square test.
[e] Mann-Whitney *U* test.
[f] Kruskal-Wallis test.
[g] Two-way mixed ANCOVA adjusted for age, sex, disease duration, baseline MDS-UPDRS-III and ΔLEDD.
[h] Two-way mixed ANOVA.

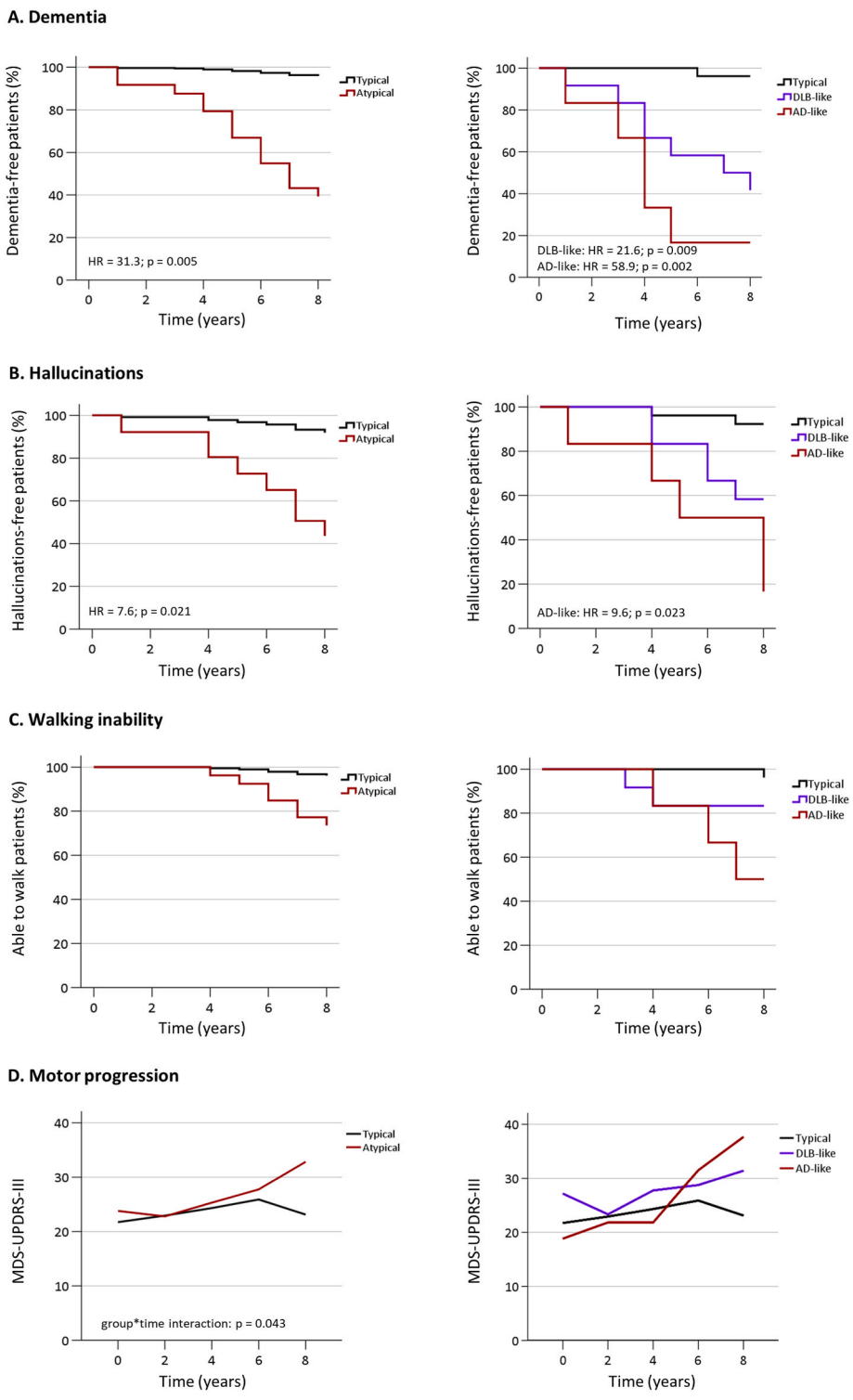

Fig. 2. (A–C) Kaplan-Meier plots for single disability milestones between PD typical and atypical FDG-PET pattern groups. Hazard ratios (HR) and p-values refer to Cox regression models adjusted for clinical-demographic variables using FDG-PET typical pattern as reference category (only statistically significant comparisons are shown). (D) MDS-UPDRS-III total score progression over 8-year follow-up between PD typical and atypical FDG-PET pattern groups. p-value refers to group*time interaction of mixed ANCOVA model. Abbreviations: MDS-UPDRS-III, Movement Disorders Society Unified Parkinson Disease Rating Scale, part III.

specific FDG-PET patterns (PD typical vs DLB-like vs AD-like) furtherly improved the model accuracy ($R^2 = 0.512$), with AD-like and DLB-like patterns being highly significant dementia predictors (OR = 246.77; p = 0.009 and OR = 73.18; p = 0.008, respectively) (Suppl. Table 3a). Converters to dementia showed similar baseline clinical-demographic characteristics but higher prevalence of atypical FDG-PET pattern compared to non-converters (93.3% vs 26.5%) (Table 2). Since PD converters showed a slightly increased frequency of MCI at baseline, we evaluated if FDG-PET atypical patterns' predictive value for dementia survived after the exclusion of PD-MCI subgroup from the analyses. Among 24 PD patients with normal cognition (PD-NC) at baseline, 14 presented with PD typical pattern and 10 with an atypical pattern (of which 6 DLB-like, 2 AD-like and 2 CBS-like). At 8-year follow-up, 6 out of 10 atypical pattern PD-NC converted to dementia, while all the PD-NC with PD typical pattern remained non-demented ($\chi^2(1) = 11.200$; p = 0.002; phi = 0.683).

At 8 years, 56% of atypical pattern patients showed hallucinations against 7% in the typical pattern group ($\chi^2(1) = 11.497$; p = 0.001; phi = 0.529). Cox regression model exhibited a higher risk to develop hallucinations for atypical pattern group (HR = 7.6; p = 0.021) and -

Table 2
Baseline and 8-year follow-up demographics, clinical and FDG-PET pattern features between converters and non-converters to dementia at 8-year follow-up. Data are presented as mean ± standard deviation and as percentage (sample size) for numeric and categorical variables, respectively.

	Converters (n = 15)	Non-converters (n = 34)	p-value
Age, years	68.6 ± 6.4	63.8 ± 9.0	0.094[a]
Disease duration, years	6.5 ± 4.3	4.7 ± 2.7	0.226[a]
Sex, M % (n)	66.7 (10)	67.6 (23)	1.000[b]
MCI, % (n)	60.0 (9)	47.1 (16)	0.599[c]
Education, years	7.3 ± 3.9	7.6 ± 3.8	0.720[a]
MDS-UPDRS-III score (baseline)	23.5 ± 7.8	22.3 ± 7.2	0.720[a]
MDS-UPDRS-III score (8 years)	39.1 ± 14.3	22.7 ± 11.1	< **0.001**[a]
ΔMDS-UPDRS-III score	15.5 ± 15.8	0.3 ± 10.2	**0.003**[a]
LEDD, mg per day (baseline)	506.5 ± 347.4	338.2 ± 313.8	0.072[a]
LEDD, mg per day (8 years)	785.9 ± 323.1	656.9 ± 344.3	0.143[a]
ΔLEDD, mg per day	279.5 ± 296.2	318.7 ± 301.9	0.712[a]
Akinetic-rigid subtype, % (n)	66.7 (10)	55.9 (19)	0.695[c]
Tremor-dominant subtype, % (n)	33.3 (5)	44.1 (15)	0.695[c]
Atypical FDG-PET pattern, % (n)	93.3 (14)	26.5 (9)	< **0.001**[c]

Abbreviations and symbols: LEDD, Levodopa Equivalent Daily Dose; ΔLEDD = $LEDD_{8years}$ – $LEDD_{baseline;}$ MCI, Mild Cognitive Impairment; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III; ΔMDS-UPDRS-III = $MDS\text{-}UPDRS\text{-}III_{8years}$ - $MDS\text{-}UPDRS\text{-}III_{baseline.}$
[a] Mann-Whitney *U* test.
[b] Fisher's exact test.
[c] Chi-square test.

specifically - for AD-like pattern compared to typical pattern (HR = 9.6; p = 0.023) (Fig. 2). The binary logistic regression model evaluating only clinical-demographic variables revealed that longer disease duration predicted higher hallucinations risk (OR = 1.30; p = 0.024; R^2 = 0.172). Again, after the inclusion of dichotomic FDG-PET pattern in the model, atypical pattern was the only significant predictor for 8-year hallucinations (OR = 12.98; p = 0.011), improving the proportion of variance explained by the model (R^2 = 0.303). The third logit model confirmed AD-like as the pattern best predicting hallucinations (OR = 33.83; p = 0.015; R^2 = 0.347) (Suppl. Table 3b).

3.3. Single-subject brain FDG-PET pattern and motor function

Six (26.1%) patients with atypical pattern became wheelchair-bound, compared with only 1 (3.8%) with typical pattern ($\chi^2(1)$ = 3.281; p = 0.041; phi = 0.317) (Table 1). Multivariable Cox regression models showed a trend for increased risk of walking inability in atypical pattern group (HR = 15.7; p = 0.105), which was more evident in AD-like pattern subgroup (HR = 38.6; p = 0.051) (Fig. 2). The logit model including only clinical-demographic variables showed a low accuracy in predicting inability to walk (R^2 = 0.083). The inclusion of dichotomic and specific FDG-PET patterns increased the model fitness (R^2 = 0.161 and R^2 = 0.318, respectively), with atypical pattern as a whole and AD-like pattern showing a trend for increased loss of ambulation risk (Suppl. Table 3c).

3.3.1. MDS-UPDRS-III progression

ANCOVA for MDS-UPDRS-III score progression along 8 years between typical and atypical pattern groups revealed a significant interaction FDG-PET pattern*time [F(4,164) = 3.015; p = 0.043)]. Post-hoc analyses revealed a significant progression of MDS-UPDRS-III score in atypical pattern group but not in the typical one (ΔMDS-UPDRS-III = 9.0 ± 15.1 vs 1.4 ± 12.0 points; p = 0.007, Bonferroni corrected) (Fig. 2). Analysing the three PET pattern subgroups, post-hoc comparisons revealed a significant progression of MDS-UPDRS-III score for AD-like group from baseline to 8 years (ΔMDS-UPDRS-III = 18.8 ± 9.7 points; p = 0.011, Bonferroni corrected), not surviving after the correction for baseline clinical-demographic variables (Fig. 2). The LEDD adjustment during follow-up was similar between the two main groups [F(4,188) = 2.135; p = 0.114)] and the specific patterns, thus not impacting on motor progression (Table 1).

3.3.2. Co-linearity of cognitive and motor progression

We examined the interdependency of cognitive and motor progression in our cohort by comparing the change in MDS-UPDRS-III total score over the 8-year follow-up between the PD patients who converted to dementia and the non-converters group. PD converters showed a significant motor progression during the follow-up, while non-converters remained essentially stable (ΔMDS-UPDRS-III = 15.5 ± 15.8 points vs 0.3 ± 10.2 points, respectively). Conversely, LEDD changes during the follow-up were similar between the two groups (Table 2).

4. Discussion

The present findings show that single-subject brain FDG-PET hypometabolism represents a strong risk factor for long-term cognitive and motor progression in PD. AD-like hypometabolism was particularly at risk, followed by DLB-like pattern. In fact, FDG-PET atypical pattern was associated with more than 15-fold increased risk of dementia, 7-fold increased risk of hallucinations and a higher risk of motor progression in term of total MDS-UPDRS-III score at eight years from PET scanning, independently from the adjustments in dopaminergic treatment. These results expand our previous work, where we showed an increased risk for dementia at 4 years in PD patients with AD-like and DLB-like brain hypometabolic patterns [4]. Here, the same PD cohort underwent an additional 4-year follow-up and was longitudinally evaluated for a wider spectrum of clinical measures, including hallucinations, loss of ambulation and motor progression assessed through MDS-UPDRS-III score changes over time – all of which were not reported in our previous study [4]. Moreover, our findings are consistent with other studies reporting (I) worse clinical trajectories in PD patients with temporal atrophy at brain MRI [32,33] and (ii) parieto-temporo-occipital hypometabolism in PD without [5–7,34] and with dementia [5,6,8,35]. Our results are also in line with the so-called "dual syndrome hypothesis", according to which patients with dysfunction in posterior brain regions are associated with worse cognitive progression compared to those with anterior dysfunction [36].

In our cohort, the most frequent atypical cortical hypometabolism was the DLB-like pattern, characterized by a prominent parieto-occipital hypometabolism. This might indicate an early cortical spreading of alpha synuclein in this subset of patients resembling DLB at FDG-PET imaging. Importantly, no patients presented with clinical features suggestive of DLB (i.e. dementia, visual hallucinations or fluctuating cognition) at baseline. Given that (i) mean disease duration at baseline was 5.2 years, (ii) mean time from baseline to dementia conversion was 5.0 years (Suppl. Table 1) and (iii) only patients with at least one year from diagnosis were included in the study, we are confident that no DLB patients were misdiagnosed with PD.

Of note, the effect we observed on motor and cognitive progressive disability was even more evident in subjects presenting the AD-like pattern. This hypometabolism with prominent temporal-parietal involvement was relatively rare (12% of the sample) and likely consistent with a possible underlying AD co-pathology. Indeed, several studies reported a strong association between AD-related biomarkers and an increased risk of cognitive and even motor progression in PD [37]. This issue is of high interest for the research community, as PD and DLB with concomitant AD pathology are at higher risk of conversion to dementia and are potentially an interesting target for disease-modifying

treatments acting on amyloid [38]. In addition, neocortical Tau deposition is a common finding in Lewy Body Diseases with cognitive impairment [39,40]. A recent meta-analysis showed that PD patients with cognitive impairment (including 96 PD-MCI and 13 PDD patients) had higher Tau tracer uptake in (i) the inferior temporal lobe than healthy controls and (ii) the entorhinal region compared with PD with normal cognition [41]. Interestingly, these Tau aggregates-enriched brain regions were partially overlapping with the hypometabolic brain areas found in AD-like and DLB-like FDG-PET patterns in our PD cohort. Although no definitive conclusion can be drawn in the absence of neuropathological confirmation or tau imaging, we hypothesize that the posterior brain hypometabolism characterizing atypical FDG-PET patterns could mirror the deposition of hyperphosphorylated Tau or a α-synuclein-β-amyloid-Tau copathology in these PD subgroups with increased risk of conversion to dementia.

A previous work evaluating different machine learning approaches using brain FDG-PET data to predict dementia conversion found a specific AD-like pattern in 12% of PD with normal cognition and 27% of PD-MCI patients [10], which is in line with the percentage of PD patients presenting with the AD-like pattern in our SPM-based study. In addition, a deep learning model trained with brain FDG-PET scans of AD patients included in the Alzheimer's Disease Neuroimaging Initiative database was able to discriminate between PD patients with and without cognitive deficits [42]. Accordingly, in our study the majority (67%) of AD-like pattern patients were PD-MCI at baseline and the 83% converted to dementia at follow-up, revealing a high prognostic value for cognitive decline of this PD atypical hypometabolic brain pattern. Finally, a recent elegant study evaluating a small cohort of early-to-moderate stage non-demented PD patients found a severe temporo-parietal reduction of [^{18}F]FEOBV uptake, a PET tracer used to map regional cholinergic alterations, compared to healthy controls [43]. This study further highlighted the multi-system and multi-neurotransmitter network impairment in PD, beyond the reductionist view of PD as a dopaminergic depletion-driven disease, and creates a link with AD pathophysiology, which is characterized by profound and diffuse brain cholinergic impairment. We thus hypothesize that temporo-parietal hypometabolism characterizing AD-like pattern in PD patients reflects, at least in part, the cholinergic alterations demonstrated by Horsager and colleagues [43].

Independent techniques such as spatial covariance analysis of resting-state metabolic images are emerging and providing highly reproducible, disease-specific metabolic brain patterns in PD (see Ref. [44] for a meta-analysis). The defined scaled subprofile model/principal component analysis (SSM/PCA) is considered independent because it provides a classification of specific pattern expression for each single case. However, this automatic approach tends to misclassify or not classify subjects depending on inter-individual differences, presence of mixed pathologies and different levels of disease severity [45]. Our semi-quantitative approach is defined optimized because it increases the statistical accuracy of the resulting SPM t-maps through a voxel-by-voxel statistical comparison with a large normal dataset and uses a dedicated template for FDG image normalization. This procedure allows the identification of brain hypometabolism patterns at a single-subject level, outperforming both the clinical characterization of patients and the visual qualitative assessment of FDG-PET standard images [27]. While fully quantitative approaches - such as the SSM/PCA - offer an objective value, the visual interpretation of individual T-maps in SPM can be equally informative. By directly inspecting the hypometabolism topography, researchers can gain nuanced insights into the individual variability and distribution of hypometabolism patterns. A recent study conducting a comparative analysis of SPM single-subject and SSM/PCA methodologies in α-synucleinopathies has shed light on this matter [46]. In cases where a subject presents a low pattern score, especially during the initial disease stages when the hypometabolism pattern is not fully expressed, the SSM/PCA classification may fail. In this context the visual inspection of the SPM t-maps gains exceptional significance, because it allows to identify specific hallmarks that are expressed since the prodromal phase of the disease [47]. While this procedure is rater-dependent, it is important to note that substantial to near-perfect inter-rater agreement has been reported for SPM-based classification [27,29,48], as also confirmed in the current study. Future efforts should focus on assessing the translatability of the methodology to different centres and raters.

In line with our previous findings [4], in this study the presence of MCI was slightly more prevalent between PD subgroup converting to dementia, but was not a significant predictor of cognitive decline at the individual level. PD-MCI is a heterogenous condition characterized by different underlying mechanisms, clinical presentations and progression rates, with some patients remaining stable and some even reverting to normal cognition during the disease course [37,49]. Here, we confirm brain FDG-PET voxel-wise analysis as a remarkable risk factor for fast cognitive decline at the single-subject level in PD, independently from baseline cognitive status.

The mean disease duration in the present PD cohort was 5.2 years (Table 1). However, the atypical brain hypometabolic patterns found in our study could reflect distinct pathophysiological processes started in early or even prodromal disease stages, in line with evidence showing that PD-related neurodegeneration precedes clinical symptoms by many years [50]. This would also be in line with previous longitudinal findings in the PPMI cohort showing worse motor and cognitive progression in patients with higher brain atrophy and striatal dopaminergic denervation at baseline [1]. The evaluation of prognostic value of brain FDG-PET patterns in *de novo* PD cohorts is thus warranted.

In addition to cognitive changes, we also observed a significant impact of cortical hypometabolism on motor function assessed during the long-term follow-up. Recent data from MPTP monkey model and PD patients revealed a correlation between nigrostriatal dopaminergic depletion and temporo-parietal glucose hypometabolism [51–54]. By means of a trimodal functional neuroimaging approach, Ruppert and colleagues [52] also found a direct link between putaminal dopaminergic deficit, striatocortical hypoconnectivity and hypometabolism in the inferior parietal cortex (IPC), a brain region implicated in sensorimotor processing, PD-related cognitive impairment and also included between the brain areas defining AD-like FDG-PET pattern in our work [55]. Importantly, they showed a significant correlation between IPC hypometabolism and increasing UPDRS-III score, thus linking low cortical metabolism with worse motor symptoms. Despite nigrostriatal dopaminergic imaging was not performed at the same time of FDG-PET imaging in our sample, the indirect evidence of worse motor progression in patients with atypical FDG-PET pattern allows to speculate that the cortical hypometabolism reflects a widespread nigro-striato-cortical dysfunction, consistent with large prospective data on PPMI dataset [1,54]. Our findings are also in line with a previous report showing that FDG-PET hypometabolism in brain regions considered AD and DLB hallmarks, such as parietal gyrus, precuneus, temporal gyrus, cuneus and occipital gyrus, correlated with worse UPDRS-III total score [56].

PD converters to dementia showed a marked increase in MDS-UPDRS-III total score over the 8-year follow-up, whereas non-converters' motor function remained essentially stable. We thus conclude that dementia converters represent a subpopulation of PD patients with an overall poor prognosis, characterized by faster cognitive and also motor decline. This evidence is in line with previous longitudinal studies showing faster motor progression in PD patients with cognitive impairment [57,58]. Accordingly, the worse cognitive and motor trajectories associated with atypical FDG-PET patterns in our study likely reflect the two sides of the same coin: on the one hand, posterior cortical hypometabolism accounts for the increased risk of dementia; on the other hand, it probably mirrors an extensive nigrostriatal dopaminergic denervation [52,56], which accounts for the higher rate of motor progression in this PD group. In this context, the specific brain hypometabolic patterns identified in our study may represent a valuable tool able to predate malignant PD evolution independently from

clinical-demographic markers.

Despite the hypothesis that atypical FDG-PET patterns described in our work represent the brain metabolic correlate of the recently proposed [1,59] "diffuse malignant" PD subtype is highly intriguing – also considering that the extensive brain posterior hypometabolism of AD-like and DLB-like patterns partially mirrors the temporo-parietal brain atrophy presented by the diffuse malignant PD cluster [1,33] – clinical subtyping was not included in the original study design and we cannot thus draw any definitive conclusion about this possible relationship. Further longitudinal studies addressing this relevant point are warranted.

We recognize some limitations. First, participants were well into the disease course, thus limiting the inference of the results to *de novo* PD patients, a population suitable to receive putative neuroprotective interventions. However, recent studies assessing brain FDG-PET patterns in patients with MCI preceding parkinsonism and in idiopathic REM sleep behavior disorder found an association between hypometabolism in posterior brain regions and higher risk of phenoconversion to overt neurodegeneration [60–62], suggesting FDG-PET as a valuable tool for risk prediction even from prodromal PD stages. Second, the assessment of different prognostic markers (e.g. genetic and biochemical parameters, cerebrospinal fluid or brain amyloid β status, other structural or functional neuroimaging evaluations) were not included in the original study design. Third, disease duration was slightly longer in atypical pattern group, potentially affecting brain FDG-PET outcomes. Fourth, a significant proportion (26%) of non-converters to dementia had an atypical FDG-PET pattern, thus reducing the specificity and positive predictive value of brain glucose hypometabolism. Fifth, despite at follow-up all patients had a confirmed diagnosis of clinically established PD in line with MDS clinical diagnostic criteria [15], which overall accuracy exceeds 90% accordingly to a recent clinical-pathologic study [63], in absence of neuropathological confirmation we cannot totally exclude that a minority of patients actually had another neurodegenerative disease or at least a co-pathology. Finally, sample size was relatively small to consider our results as definitive. Larger, multicentric studies integrating FDG-PET cortical metabolism in a multidimensional approach will ideally enable precision diagnostics and prognostics for PD patients. Strength points of the study are the deep clinical phenotyping performed at baseline and during the long-term follow-up, the SPM standardized procedure, which allowed image analyses at single-subject level, and the conservative multivariable statistical approach applied in longitudinal analyses.

In summary, we demonstrated that atypical cortical FDG-PET patterns at baseline constitute a strong risk factor for long-term cognitive and motor impairment in PD at single-subject level. If confirmed in independent longitudinal cohorts of prodromal and early-stage PD, our findings will contribute to enable risk stratification in future clinical trials.

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Authors' roles

Alberto Imarisio: study concept and design, acquisition of data, analyses and interpretation of data, revising the manuscript for content.

Andrea Pilotto: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content.

Enrico Premi: study concept and design, acquisition of data, revising the manuscript for content.

Silvia Paola Caminiti: analysis and interpretation of data, revising the manuscript for content.

Luca Presotto: analysis and interpretation of data, revising the manuscript for content.

Arianna Sala: analysis and interpretation of data, revising the manuscript for content.

Cinzia Zatti: acquisition of data.

Alessandro Lupini: acquisition of data.

Rosanna Turrone: acquisition of data.

Barbara Paghera: acquisition of data.

Barbara Borroni: revising the manuscript for content.

Daniela Perani: study concept and design, analysis and interpretation of data, revising the manuscript for content.

Alessandro Padovani: study concept and design, revising the manuscript for content.

All Authors have approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] S.M. Fereshtehnejad, Y. Zeighami, A. Dagher, R.B. Postuma, Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression, Brain 140 (2017) 1959–1976, https://doi.org/10.1093/brain/awx118.

[2] A. Pilotto, A. Romagnolo, J.A. Tuazon, J.A. Vizcarra, L. Marsili, M. Zibetti, M. Rosso, F. Rodriguez-Porcel, B. Borroni, M.C. Rizzetti, C. Rossi, D. Vizcarra-Escobar, J.R. Molano, L. Lopiano, R. Ceravolo, M. Masellis, A.J. Espay, A. Padovani, A. Merola, Orthostatic hypotension and REM sleep behaviour disorder: impact on clinical outcomes in α-synucleinopathies, J. Neurol. Neurosurg. Psychiatry 90 (2019) 1257–1263, https://doi.org/10.1136/jnnp-2019-320846.

[3] A.J. Espay, P. Brundin, A.E. Lang, Precision medicine for disease modification in Parkinson disease, Nat. Rev. Neurol. 13 (2017) 119–126, https://doi.org/10.1038/nrneurol.2016.196.

[4] A. Pilotto, E. Premi, S.P. Caminiti, L. Presotto, R. Turrone, A. Alberici, B. Paghera, B. Borroni, A. Padovani, D. Perani, Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease, Neurology 90 (2018) e1029–e1037, https://doi.org/10.1212/WNL.0000000000005161.

[5] N.I. Bohnen, R.A. Koeppe, S. Minoshima, B. Giordani, R.L. Albin, K.A. Frey, D. E. Kuhl, Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study, J. Nucl. Med. 52 (2011) 848–855, https://doi.org/10.2967/jnumed.111.089946.

[6] T. Baba, Y. Hosokai, Y. Nishio, A. Kikuchi, K. Hirayama, K. Suzuki, T. Hasegawa, M. Aoki, A. Takeda, E. Mori, Longitudinal study of cognitive and cerebral metabolic changes in Parkinson's disease, J. Neurol. Sci. 372 (2017) 288–293, https://doi.org/10.1016/j.jns.2016.11.068.

[7] M.J. Firbank, A.J. Yarnall, R.A. Lawson, G.W. Duncan, T.K. Khoo, G.S. Petrides, J. T. O'Brien, R.A. Barker, R.J. Maxwell, D.J. Brooks, D.J. Burn, Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study, J. Neurol. Neurosurg. Psychiatry 88 (2017) 310–316, https://doi.org/10.1136/JNNP-2016-313918.

[8] D. Blum, C. la Fougère, A. Pilotto, W. Maetzler, D. Berg, M. Reimold, I. Liepelt-Scarfone, Hypermetabolism in the cerebellum and brainstem and cortical hypometabolism are independently associated with cognitive impairment in Parkinson's disease, Eur. J. Nucl. Med. Mol. Imag. 45 (2018) 2387–2395, https://doi.org/10.1007/s00259-018-4085-1.

[9] S. Booth, K.W. Park, C.S. Lee, J.H. Ko, Predicting cognitive decline in Parkinson's disease using FDG-PET–based supervised learning, J. Clin. Invest. 132 (2022), https://doi.org/10.1172/JCI157074.

[10] A. Katako, P. Shelton, A.L. Goertzen, D. Levin, B. Bybel, M. Aljuaid, H.J. Yoon, D. Y. Kang, S.M. Kim, C.S. Lee, J.H. Ko, Machine learning identified an Alzheimer's disease-related FDG-PET pattern which is also expressed in Lewy body dementia and Parkinson's disease dementia, Sci. Rep. 8 (2018), 13236, https://doi.org/10.1038/s41598-018-31653-6.

[11] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184, https://doi.org/10.1136/jnnp.55.3.181.

[12] G.A. Kang, J.M. Bronstein, D.L. Masterman, M. Redelings, J.A. Crum, B. Ritz, Clinical characteristics in early Parkinson's disease in a central California population-based study, Mov. Disord. 20 (2005) 1133–1142, https://doi.org/10.1002/mds.20513.

[13] S. Schade, B. Mollenhauer, C. Trenkwalder, Levodopa equivalent dose conversion factors: an updated proposal including opicapone and safinamide, Mov. Disord. Clin. Pract. 7 (2020) 343–345, https://doi.org/10.1002/mdc3.12921.

[14] A. Pilotto, R. Turrone, I. Liepelt-Scarfone, M. Bianchi, L. Poli, B. Borroni, A. Alberici, E. Premi, A. Formenti, B. Bigni, M. Cosseddu, E. Cottini, D. Berg, A. Padovani, Vascular risk factors and cognition in Parkinson's disease, J. Alzheim. Dis. 51 (2016) 563–570, https://doi.org/10.3233/JAD-150610.

[15] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601, https://doi.org/10.1002/mds.26424.

[16] M. Emre, D. Aarsland, R. Brown, D.J. Burn, C. Duyckaerts, Y. Mizuno, G.A. Broe, J. Cummings, D.W. Dickson, S. Gauthier, J. Goldman, C. Goetz, A. Korczyn, A. Lees, R. Levy, I. Litvan, I. McKeith, W. Olanow, W. Poewe, N. Quinn, C. Sampaio, E. Tolosa, B. Dubois, Clinical diagnostic criteria for dementia associated with Parkinson's disease, Mov. Disord. 22 (2007) 1689–1707, https://doi.org/10.1002/mds.21507.

[17] B. Dubois, D. Burn, C. Goetz, D. Aarsland, R.G. Brown, G.A. Broe, D. Dickson, C. Duyckaerts, J. Cummings, S. Gauthier, A. Korczyn, A. Lees, R. Levy, I. Litvan, Y. Mizuno, I.G. McKeith, C.W. Olanow, W. Poewe, C. Sampaio, E. Tolosa, M. Emre, Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force, Mov. Disord. 22 (2007) 2314–2324, https://doi.org/10.1002/mds.21844.

[18] G. Santangelo, C. Vitale, M. Picillo, M. Moccia, S. Cuoco, K. Longo, D. Pezzella, A. di Grazia, R. Erro, M.T. Pellecchia, M. Amboni, L. Trojano, P. Barone, Mild Cognitive Impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study, Parkinsonism Relat. Disorders 21 (2015) 1219–1226, https://doi.org/10.1016/j.parkreldis.2015.08.024.

[19] M.J. Armstrong, I. Litvan, A.E. Lang, T.H. Bak, K.P. Bhatia, B. Borroni, A.L. Boxer, D.W. Dickson, M. Grossman, M. Hallett, K.A. Josephs, A. Kertesz, S.E. Lee, B. L. Miller, S.G. Reich, D.E. Riley, E. Tolosa, A.I. Tröster, M. Vidailhet, W.J. Weiner, Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (2013) 496–503, https://doi.org/10.1212/WNL.0b013e31827f0fd1.

[20] G.U. Höglinger, G. Respondek, M. Stamelou, C. Kurz, K.A. Josephs, A.E. Lang, B. Mollenhauer, U. Müller, C. Nilsson, J.L. Whitwell, T. Arzberger, E. Englund, E. Gelpi, A. Giese, D.J. Irwin, W.G. Meissner, A. Pantelyat, A. Rajput, J.C. van Swieten, C. Troakes, A. Antonini, K.P. Bhatia, Y. Bordelon, Y. Compta, J.C. Corvol, C. Colosimo, D.W. Dickson, R. Dodel, L. Ferguson, M. Grossman, J. Kassubek, F. Krismer, J. Levin, S. Lorenzl, H.R. Morris, P. Nestor, W.H. Oertel, W. Poewe, G. Rabinovici, J.B. Rowe, G.D. Schellenberg, K. Seppi, T. van Eimeren, G. K. Wenning, A.L. Boxer, L.I. Golbe, I. Litvan, A.L. Boxer, A. Rajput, A. Pantelyat, A. E. Lang, A. Giese, B. Mollenhauer, C. Colosimo, C. Kurz, C. Nilsson, C. Troakes, D. J. Irwin, D.W. Dickson, E. Gelpi, F. Krismer, G.D. Schellenberg, G. Respondek, G. Rabinovici, G.K. Wenning, G.U. Höglinger, H.R. Morris, I. Litvan, J. Kassubek, J. C. Corvol, J.L. Whitwell, J. Levin, J. van Swieten, K.P. Bhatia, K.A. Josephs, K. Seppi, L.I. Golbe, M. Grossman, P. Nestor, R. Dodel, S. Lorenzl, T. van Eimeren, T. Arzberger, U. Müller, W.G. Meissner, W. Poewe, W.H. Oertel, Y. Compta, Y. Bordelon, Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria, Mov, Disord 32 (2017) 853–864, https://doi.org/10.1002/mds.26987.

[21] G.K. Wenning, I. Stankovic, L. Vignatelli, A. Fanciulli, G. Calandra-Buonaura, K. Seppi, J. Palma, W.G. Meissner, F. Krismer, D. Berg, P. Cortelli, R. Freeman, G. Halliday, G. Höglinger, A. Lang, H. Ling, I. Litvan, P. Low, Y. Miki, J. Panicker, M.T. Pellecchia, N. Quinn, R. Sakakibara, M. Stamelou, E. Tolosa, S. Tsuji, T. Warner, W. Poewe, H. Kaufmann, The movement disorder society criteria for the diagnosis of multiple system atrophy, Mov. Disord. 37 (2022) 1131–1148, https://doi.org/10.1002/mds.29005.

[22] I.G. McKeith, B.F. Boeve, D.W. Dickson, G. Halliday, J.P. Taylor, D. Weintraub, D. Aarsland, J. Galvin, J. Attems, C.G. Ballard, A. Bayston, T.G. Beach, F. Blanc, N. Bohnen, L. Bonanni, J. Bras, P. Brundin, D. Burn, A. Chen-Plotkin, J.E. Duda, O. El-Agnaf, H. Feldman, T.J. Ferman, D. Ffytche, H. Fujishiro, D. Galasko, J. G. Goldman, S.N. Gomperts, N.R. Graff-Radford, L.S. Honig, A. Iranzo, K. Kantarci, D. Kaufer, W. Kukull, V.M.Y. Lee, J.B. Leverenz, S. Lewis, C. Lippa, A. Lunde, M. Masellis, E. Masliah, P. McLean, B. Mollenhauer, T.J. Montine, E. Moreno, E. Mori, M. Murray, J.T. O'Brien, S. Orimo, R.B. Postuma, S. Ramaswamy, O. A. Ross, D.P. Salmon, A. Singleton, A. Taylor, A. Thomas, P. Tiraboschi, J. B. Toledo, J.Q. Trojanowski, D. Tsuang, Z. Walker, M. Yamada, K. Kosaka, Diagnosis and management of dementia with Lewy bodies, Neurology 89 (2017) 88–100, https://doi.org/10.1212/WNL.0000000000004058.

[23] K. Rascovsky, J.R. Hodges, D. Knopman, M.F. Mendez, J.H. Kramer, J. Neuhaus, J. C. van Swieten, H. Seelaar, E.G.P. Dopper, C.U. Onyike, A.E. Hillis, K.A. Josephs, B. F. Boeve, A. Kertesz, W.W. Seeley, K.P. Rankin, J.K. Johnson, M.-L. Gorno-Tempini, H. Rosen, C.E. Prioleau-Latham, A. Lee, C.M. Kipps, P. Lillo, O. Piguet, J.D. Rohrer, M.N. Rossor, J.D. Warren, N.C. Fox, D. Galasko, D.P. Salmon, S.E. Black, M. Mesulam, S. Weintraub, B.C. Dickerson, J. Diehl-Schmid, F. Pasquier, V. Deramecourt, F. Lebert, Y. Pijnenburg, T.W. Chow, F. Manes, J. Grafman, S. F. Cappa, M. Freedman, M. Grossman, B.L. Miller, Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, Brain 134 (2011) 2456–2477, https://doi.org/10.1093/brain/awr179.

[24] M.L. Gorno-Tempini, A.E. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S.F. Cappa, J.M. Ogar, J.D. Rohrer, S. Black, B.F. Boeve, F. Manes, N.F. Dronkers, R. Vandenberghe, K. Rascovsky, K. Patterson, B.L. Miller, D.S. Knopman, J. R. Hodges, M.M. Mesulam, M. Grossman, Classification of primary progressive aphasia and its variants, Neurology 76 (2011) 1006–1014, https://doi.org/10.1212/WNL.0b013e31821103e6.

[25] P.A. Della Rosa, C. Cerami, F. Gallivanone, A. Prestia, A. Caroli, I. Castiglioni, M. C. Gilardi, G. Frisoni, K. Friston, J. Ashburner, D. Perani, A standardized [18F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia, Neuroinformatics 12 (2014) 575–593, https://doi.org/10.1007/s12021-014-9235-4.

[26] M. Signorini, E. Paulesu, K. Friston, D. Perani, A. Colleluori, G. Lucignani, F. Grassi, V. Bettinardi, R.S. Frackowiak, F. Fazio, Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and nonquantitative [18F]FDG PET: a clinical validation of statistical parametric mapping, Neuroimage 9 (1999) 63–80, https://doi.org/10.1006/nimg.1998.0381.

[27] D. Perani, P.A. Della Rosa, C. Cerami, F. Gallivanone, F. Fallanca, E.G. Vanoli, A. Panzacchi, F. Nobili, S. Pappatà, A. Marcone, V. Garibotto, I. Castiglioni, G. Magnani, S.F. Cappa, L. Gianolli, A. Drzezga, R. Perneczky, M. Didic, E. Guedj, B.N. Van Berckel, R. Ossenkoppele, S. Morbelli, G. Frisoni, A. Caroli, Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting 6 (2014) 445–454, https://doi.org/10.1016/j.nicl.2014.10.009.

[28] L.K. Teune, A.L. Bartels, B.M. de Jong, A.T.M. Willemsen, S.A. Eshuis, J.J. de Vries, J.C.H. van Oostrom, K.L. Leenders, Typical cerebral metabolic patterns in neurodegenerative brain diseases, Mov. Disord. 25 (2010) 2395–2404, https://doi.org/10.1002/mds.23291.

[29] S.P. Caminiti, P. Alongi, L. Majno, M.A. Volontè, C. Cerami, L. Gianolli, G. Comi, D. Perani, Evaluation of an optimized [18 F]fluoro-deoxy-glucose positron emission tomography voxel-wise method to early support differential diagnosis in atypical Parkinsonian disorders, Eur. J. Neurol. 24 (2017), https://doi.org/10.1111/ene.13269, 687-e26.

[30] Y. Hosokai, Y. Nishio, K. Hirayama, A. Takeda, T. Ishioka, Y. Sawada, K. Suzuki, Y. Itoyama, S. Takahashi, H. Fukuda, E. Mori, Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment, Mov. Disord. 24 (2009) 854–862, https://doi.org/10.1002/mds.22444.

[31] S.P. Caminiti, T. Ballarini, A. Sala, C. Cerami, L. Presotto, R. Santangelo, F. Fallanca, E.G. Vanoli, L. Gianolli, S. Iannaccone, G. Magnani, D. Perani, L. Parnetti, P. Eusebi, G. Frisoni, F. Nobili, A. Picco, E. Scarpini, FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort 18 (2018) 167–177, https://doi.org/10.1016/j.nicl.2018.01.019.

[32] S. Aybek, F. Lazeyras, A. Gronchi-Perrin, P.R. Burkhard, J.G. Villemure, F.J. G. Vingerhoets, Hippocampal atrophy predicts conversion to dementia after STN-

DBS in Parkinson's disease, Park. Relat. Disord. 15 (2009) 521–524, https://doi.org/10.1016/j.parkreldis.2009.01.003.
[33] Y. Zeighami, S.-M. Fereshtehnejad, M. Dadar, D.L. Collins, R.B. Postuma, B. Mišić, A. Dagher, A clinical-anatomical signature of Parkinson's disease identified with partial least squares and magnetic resonance imaging, Neuroimage 190 (2019) 69–78, https://doi.org/10.1016/j.neuroimage.2017.12.050.
[34] C. Tard, F. Demailly, A. Delval, F. Semah, L. Defebvre, K. Dujardin, C. Moreau, Hypometabolism in posterior and temporal areas of the brain is associated with cognitive decline in Parkinson's disease, J. Parkinsons Dis. 5 (2015) 569–574, https://doi.org/10.3233/JPD-150583.
[35] L. Wu, F. Liu, J. Ge, J. Zhao, Y. Tang, W. Yu, H. Yu, T. Anderson, C. Zuo, L. Chen, J. Wang, Clinical characteristics of cognitive impairment in patients with Parkinson's disease and its related pattern in 18 F-FDG PET imaging, Hum. Brain Mapp. 39 (2018) 4652–4662, https://doi.org/10.1002/hbm.24311.
[36] C.H. Williams-Gray, J.R. Evans, A. Goris, T. Foltynie, M. Ban, T.W. Robbins, C. Brayne, B.S. Kolachana, D.R. Weinberger, S.J. Sawcer, R.A. Barker, The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort, Brain 132 (2009) 2958–2969, https://doi.org/10.1093/brain/awp245.
[37] D. Aarsland, L. Batzu, G.M. Halliday, G.J. Geurtsen, C. Ballard, K. Ray Chaudhuri, D. Weintraub, Parkinson disease-associated cognitive impairment, Nat. Rev. Dis. Prim. 7 (2021) 47, https://doi.org/10.1038/s41572-021-00280-3.
[38] J.B. Toledo, C. Abdelnour, R.S. Weil, D. Ferreira, F. Rodriguez-Porcel, A. Pilotto, K. A. Wyman-Chick, M.J. Grothe, J.P.M. Kane, A. Taylor, A. Rongve, S. Scholz, J. B. Leverenz, B.F. Boeve, D. Aarsland, I.G. McKeith, S. Lewis, I. Leroi, J.P. Taylor, Dementia with Lewy bodies: impact of co-pathologies and implications for clinical trial design, Alzheimer's Dementia (2022) 1–15, https://doi.org/10.1002/alz.12814.
[39] S.N. Gomperts, J.J. Locascio, S.J. Makaretz, A. Schultz, C. Caso, N. Vasdev, R. Sperling, J.H. Growdon, B.C. Dickerson, K. Johnson, Tau positron emission tomographic imaging in the Lewy body diseases, JAMA Neurol. 73 (2016) 1334, https://doi.org/10.1001/jamaneurol.2016.3338.
[40] R. Smith, M. Schöll, E. Londos, T. Ohlsson, O. Hansson, 18F-AV-1451 in Parkinson's disease with and without dementia and in dementia with Lewy bodies, Sci. Rep. 8 (2018) 4717, https://doi.org/10.1038/s41598-018-23041-x.
[41] J. Zhang, J. Jin, D. Su, T. Feng, H. Zhao, Tau-PET imaging in Parkinson's disease: a systematic review and meta-analysis, Front. Neurol. 14 (2023), https://doi.org/10.3389/fneur.2023.1145939.
[42] H. Choi, Y.K. Kim, E.J. Yoon, J.-Y. Lee, D.S. Lee, Cognitive signature of brain FDG PET based on deep learning: domain transfer from Alzheimer's disease to Parkinson's disease, Eur. J. Nucl. Med. Mol. Imag. 47 (2020) 403–412, https://doi.org/10.1007/s00259-019-04538-7.
[43] J. Horsager, N. Okkels, A.K. Hansen, M.F. Damholdt, K.H. Andersen, T. D. Fedorova, O.L. Munk, E.H. Danielsen, N. Pavese, D.J. Brooks, P. Borghammer, Mapping cholinergic synaptic loss in Parkinson's disease: an [18F]FEOBV PET case-control study, J. Parkinsons Dis. 12 (2022) 2493–2506, https://doi.org/10.3233/JPD-223489.
[44] P.-E. Papathoma, I. Markaki, C. Tang, M. Lilja Lindström, I. Savitcheva, D. Eidelberg, P. Svenningsson, A replication study, systematic review and meta-analysis of automated image-based diagnosis in parkinsonism, Sci. Rep. 12 (2022) 2763, https://doi.org/10.1038/s41598-022-06663-0.
[45] K.A. Schindlbeck, D.K. Gupta, C.C. Tang, S.A. O'Shea, K.L. Poston, Y.Y. Choi, V. Dhawan, J.-P. Vonsattel, S. Fahn, D. Eidelberg, Neuropathological correlation supports automated image-based differential diagnosis in parkinsonism, Eur. J. Nucl. Med. Mol. Imag. 48 (2021) 3522–3529, https://doi.org/10.1007/s00259-021-05302-6.
[46] G. Carli, S.K. Meles, F.E. Reesink, B.M. de Jong, A. Pilotto, A. Padovani, A. Galbiati, L. Ferini-Strambi, K.L. Leenders, D. Perani, Comparison of univariate and multivariate analyses for brain [18F]FDG PET data in α-synucleinopathies, NeuroImage. Clin. 39 (2023), 103475, https://doi.org/10.1016/j.nicl.2023.103475.
[47] S.P. Caminiti, S. De Francesco, G. Tondo, A. Galli, A. Redolfi, D. Perani, Alzheimer's Disease Neuroimaging Initiative, Interceptor Project, FDG-PET markers of heterogeneity and different risk of progression in amnestic MCI, Alzheimers. Dement. (2023), https://doi.org/10.1002/alz.13385.
[48] S.P. Caminiti, A. Sala, L. Iaccarino, L. Beretta, A. Pilotto, L. Gianolli, S. Iannaccone, G. Magnani, A. Padovani, L. Ferini-Strambi, D. Perani, Brain glucose metabolism in Lewy body dementia: implications for diagnostic criteria, Alzheimers, Respir. Ther. 11 (2019) 20, https://doi.org/10.1186/s13195-019-0473-4.
[49] K.F. Pedersen, J.P. Larsen, O.-B. Tysnes, G. Alves, Natural course of mild cognitive impairment in Parkinson disease, Neurology 88 (2017) 767–774, https://doi.org/10.1212/WNL.0000000000003634.
[50] B.R. Bloem, M.S. Okun, C. Klein, Parkinson's disease, Lancet 397 (2021) 2284–2303, https://doi.org/10.1016/S0140-6736(21)00218-X.
[51] F. Molinet-Dronda, J. Blesa, N.L.-G. del Rey, C. Juri, M. Collantes, J.A. Pineda-Pardo, I. Trigo-Damas, E. Iglesias, L.F. Hernández, R. Rodríguez-Rojas, B. Gago, M. Ecay, E. Prieto, M.Á. García-Cabezas, C. Cavada, M.C. Rodríguez-Oroz, I. Peñuelas, J.A. Obeso, Cerebral metabolic pattern associated with progressive parkinsonism in non-human primates reveals early cortical hypometabolism, Neurobiol. Dis. 167 (2022), 105669, https://doi.org/10.1016/j.nbd.2022.105669.
[52] M.C. Ruppert, A. Greuel, M. Tahmasian, F. Schwartz, S. Stürmer, F. Maier, J. Hammes, M. Tittgemeyer, L. Timmermann, T. van Eimeren, A. Drzezga, C. Eggers, Network degeneration in Parkinson's disease: multimodal imaging of nigro-striato-cortical dysfunction, Brain 143 (2020) 944–959, https://doi.org/10.1093/brain/awaa019.
[53] B. Orso, D. Arnaldi, N. Girtler, A. Brugnolo, E. Doglione, P. Mattioli, E. Biassoni, R. Fancellu, F. Massa, M. Bauckneht, S. Chiola, S. Morbelli, F. Nobili, M. Pardini, Dopaminergic and serotonergic degeneration and cortical [18 F] fluorodeoxyglucose positron emission tomography in de novo Parkinson's disease, Mov. Disord. 36 (2021) 2293–2302, https://doi.org/10.1002/mds.28654.
[54] A. Schrag, U.F. Siddiqui, Z. Anastasiou, D. Weintraub, J.M. Schott, Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study, Lancet Neurol. 16 (2017) 66–75, https://doi.org/10.1016/S1474-4422(16)30328-3.
[55] F. Albrecht, T. Ballarini, J. Neumann, M.L. Schroeter, FDG-PET hypometabolism is more sensitive than MRI atrophy in Parkinson's disease: a whole-brain multimodal imaging meta-analysis 21 (2019), 101594, https://doi.org/10.1016/j.nicl.2018.11.004.
[56] F.-T. Liu, J.-J. Ge, J.-J. Wu, P. Wu, Y. Ma, C.-T. Zuo, J. Wang, Clinical, dopaminergic, and metabolic correlations in Parkinson disease, Clin. Nucl. Med. 43 (2018) 562–571, https://doi.org/10.1097/RLU.0000000000002148.
[57] C. Marras, P. Rochon, A.E. Lang, Predicting motor decline and disability in Parkinson disease, Arch. Neurol. 59 (2002) 1724, https://doi.org/10.1001/archneur.59.11.1724.
[58] G. Reinoso, J.C. Allen, W.-L. Au, S.-H. Seah, K.-Y. Tay, L.C.S. Tan, Clinical evolution of Parkinson's disease and prognostic factors affecting motor progression: 9-year follow-up study, Eur. J. Neurol. 22 (2015) 457–463, https://doi.org/10.1111/ene.12476.
[59] S.M. Fereshtehnejad, S.R. Romenets, J.B.M. Anang, V. Latreille, J.F. Gagnon, R. B. Postuma, New clinical subtypes of Parkinson disease and their longitudinal progression a prospective cohort comparison with other phenotypes, JAMA Neurol. 72 (2015) 863–873, https://doi.org/10.1001/jamaneurol.2015.0703.
[60] F. Massa, D. Arnaldi, F. De Cesari, N. Girtler, A. Brugnolo, M. Grazzini, M. Bauckneht, R. Meli, S. Morbelli, M. Pardini, G. Sambuceti, F. De Carli, P. Tiraboschi, F. Nobili, Neuroimaging findings and clinical trajectories of Lewy body disease in patients with MCI, Neurobiol. Aging 76 (2019) 9–17, https://doi.org/10.1016/j.neurobiolaging.2018.12.001.
[61] J.H. Shin, J.-Y. Lee, Y.-K. Kim, E.J. Yoon, H. Kim, H. Nam, B. Jeon, Parkinson disease-related brain metabolic patterns and neurodegeneration in isolated REM sleep behavior disorder, Neurology 97 (2021) e378–e388, https://doi.org/10.1212/WNL.0000000000012228.
[62] G. Carli, S.P. Caminiti, A. Galbiati, S. Marelli, F. Casoni, A. Padovani, L. Ferini-Strambi, D. Perani, In-vivo signatures of neurodegeneration in isolated rapid eye movement sleep behaviour disorder, Eur. J. Neurol. 27 (2020) 1285–1295, https://doi.org/10.1111/ene.14215.
[63] S. Virameteekul, T. Revesz, Z. Jaunmuktane, T.T. Warner, E. De Pablo-Fernández, Clinical diagnostic accuracy of Parkinson's disease: where do we stand? Mov. Disord. 38 (2023) 558–566, https://doi.org/10.1002/mds.29317.