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RESEARCH ARTICLE

Multicenter Validation of Metabolic Abnormalities Related to PSP According to the MDS-PSP Criteria

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ABSTRACT: It remains unclear whether the supportive imaging features described in the diagnostic criteria for progressive supranuclear palsy (PSP) are suitable for the full clinical spectrum. The aim of the current study was to define and cross-validate the pattern of glucose metabolism in the brain associated with a diagnosis of different PSP variants. A retrospective multicenter cohort study performed on 73 PSP patients who were referred for a fluorodeoxyglucose positron emission tomography PET scan: PSP–Richardson's syndrome, n = 47; PSP–parkinsonian variant, n = 18; and progressive gait freezing, n = 8. In addition, we included 55 healthy controls and 58 Parkinson's disease (PD) patients. Scans were normalized by global mean activity. We analyzed the regional differences in metabolism between the groups. Moreover, we applied a multivariate analysis to obtain a PSP-related pattern that was cross-validated in independent populations at the individual level. Group analysis showed relative hypometabolism in the midbrain, basal ganglia, thalamus, and frontoinsular cortices and hypermetabolism in the cerebellum and sensorimotor cortices in PSP patients compared with healthy controls and PD patients, the latter with more severe involvement in the basal ganglia and occipital cortices. The PSP-related pattern obtained confirmed the regions described above. At the individual level, the PSP-related pattern showed optimal diagnostic accuracy to distinguish between PSP and healthy controls (sensitivity, 80.4%; specificity, 96.9%)s and between PSP and PD (sensitivity, 80.4%; specificity, 90.7%). Moreover, PSP–Richardson's syndrome and PSP–parkinsonian variant patients showed significantly more PSP-related pattern expression than PD patients and healthy controls. The glucose metabolism assessed by fluorodeoxyglucose PET is a useful and reproducible supportive diagnostic tool for PSP–Richardson's syndrome and PSP–parkinsonian variant. © 2020 International Parkinson and Movement Disorder Society

Key Words: progressive supranuclear palsy; FDG-PET; disease-related metabolic brain pattern; diagnostic biomarker

Progressive supranuclear palsy (PSP) is a primary tauopathy associated with a heterogeneous spectrum of clinical features,[1–4] including a combination of behavioral, cognitive, and motor phenomena. Based on large clinicopathological studies,[1,2] different clinical subgroups of this disease has been described, designated

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as PSP variants. These PSP variants were recently defined in the International Parkinson and Movement Disorder Society criteria for diagnosis of PSP (MDS-PSP).[5] They are thought to be more sensitive than the previous criteria with only a small reduction in specificity,[6,7] especially in the later stages of the disease. Nevertheless, accurate diagnostic biomarkers for early diagnosis of PSP are still needed.

Many neuroimaging studies have proposed different biomarkers for PSP.[8–12] Indeed, MDS-PSP criteria include imaging findings as supportive features. However, the assessment of midbrain atrophy by magnetic resonance imaging (MRI) has weak sensitivity in the early stages,[13] and postsynaptic striatal dopaminergic degeneration fails to differentiate neurodegenerative parkinsonism.[14] Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging as a marker of neuronal damage[15] could be a useful tool to achieve a differential diagnosis of neurodegenerative parkinsonism in relative early stages.[16–19] Because of the limitations of direct visual assessment, a variety of analytical approaches have been applied to analyze FDG-PET images. Univariate voxel-based methods like statistical parametric mapping (SPM) can identify regional differences in mean glucose metabolism between groups. As such, relative hypometabolism has been seen in the midbrain, basal ganglia, thalamus, and frontal lobes of patients with Richardson syndrome variant of PSP (PSP-RS).[16,20–24] However, available studies using this approach show critical limitations, as they are typically small monocentric studies. Multivariate approaches have been applied to not only assess regional abnormalities in metabolism but also changes in brain connectivity. In particular, covariance analysis techniques are designed to detect distinctive interregional correlations in brain glucose metabolism in patients compared with healthy subjects (disease-related pattern) that offer a more profound understanding of the underlying pathophysiological mechanisms.[25] An advantage of this approach is that once a pattern is identified, its expression can be quantified in a single FDG-PET scan. Thus, some studies have used multivariate approaches to obtain a PSP-related pattern (PSPRP) and then assessed its diagnostic value.[17–19,26–28] However, reproducibility with independent cross-validation populations is limited.[22]

Moreover, most studies that have evaluated the utility of neuroimaging as a biomarker have only included PSP-RS. Nevertheless, the diagnostic value of these biomarkers for the full clinical spectrum of PSP remains unclear. Hence, we aimed to identify and validate the metabolic pattern in the brain associated with a diagnosis of PSP according to the MDS-PSP diagnostic criteria at the group and individual levels in a multicenter framework.

Materials and Methods

Subjects

This retrospective study was carried out at 2 European centers, the Clínica Universidad de Navarra (Spain [SP]) and University Medical Center Groningen (The Netherlands [NL]). We included PSP patients who were referred for FDG-PET imaging between 1997 and 2019 to assist in the differential diagnosis of parkinsonism at a relative early stage of the disease. We included patients who fulfilled MDS-PSP criteria[5] for PSP variants and applied the Multiple Allocations eXtinction (MAX) rules.[29] As reference groups, we included Parkinson's disease (PD) patients and healthy controls (HCs). All PD patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria.[30] For all cases, we used the final clinical diagnosis as the gold standard. See Supplementary Material for further details.

Permission to carry out this study was obtained from the corresponding institutional review board at each institution, and each patient (or caregivers) gave written informed consent.

FDG-PET Acquisition, Reconstruction, and Processing

Both centers used a Siemens ECAT Exact HR+ (Siemens, Knoxville, TN) tomograph and a Siemens Biograph mCT 64 PET (Siemens, Knoxville, TN) tomograph. Based on the PET procedure (PET camera and image reconstruction), we defined four cohorts among the different study groups: cohort A, ECAT Exact HR + $_{NL}$; cohort B, Biograph mCT_{NL}; cohort C, ECAT Exact HR + $_{SP}$; and cohort D, Biograph mCT_{SP}. Hoffman 3D Brain Phantom FDG-PET data were used to correct the differences in the Siemens Biograph mCT reconstruction between both centers and overcome the lack of HCs in cohort D. FDG-PET images were spatially normalized onto a standard Montreal Neurological Institute–based FDG-PET template[31] using SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) implemented in MATLAB R2018a (Mathworks Inc, Natick, MA). The smoothing filter was selected to correct differences in the reconstruction between the centers (Table S1).

FDG-PET Imaging Analysis

Group Analysis

We used both a univariate (SPM) and multivariate (scaled subprofile modeling/principal component analysis [SSM/PCA]) analytical approaches to assess the topographical distribution of brain metabolic abnormalities. In the univariate analysis, the scans were normalized to the global mean activity, and a factorial analysis of variance was used to identify the differences in regional metabolism between the groups (PSP vs HC, PSP vs PD, PD vs HC and each PSP variant vs HC or PD), including

sex, age, and PET procedures as fixed factors. In addition, we performed conjunction analyses to assess which significant voxels were common in the comparisons included.[32] SPM t-maps were created considering clusters with a size of >50 voxels at a defined threshold of $P < 0.05$, with a multiple comparison correction by family-wise error. SPM t-maps were overlaid onto a T1-weighted MRI template and assessed with Hammers' adult atlas.[33]

In the multivariate analysis, we used SSM/PCA to identify a PSPRP among the FDG-PET data from PSP patients and HCs in cohorts A, B, and C. We applied an automated algorithm written in-house, based on the method described by Spetsieris and Eidelberg[34,35] as detailed elsewhere.[36] A final pattern was identified in each cohort ($PSPRP_A$, $PSPRP_B$, $PSPRP_C$).

To determine which regions in the pattern were stable, a bootstrap resampling procedure was performed within each cohort (1000 iterations).[37] Voxels that survived a 1-sided confidence interval threshold of 90% were overlaid on a T1-weighted MRI template. The stable regions in the 3 PSPRPs were visually assessed. In addition, within each cohort we correlated each subject's z scores between any 2 of the patterns ($PSPRP_A$, $PSPRP_B$, and $PSPRP_C$) using a Pearson's correlation test.

Individual Analysis: Validation and Cross-Validation

Once the patterns were identified, we studied their expression at the individual level using multivariate analysis (SSM/topographic profile rating). To address the differences between PET procedures, the raw scores of the subjects in each cohort were z-transformed using the mean and standard deviation of the raw scores from their respective HC group.[34] For the internal validation, a receiver operating characteristic (ROC) analysis was performed based on the PSPRP z scores in each cohort. The cutoff z score that gave optimum sensitivity and specificity was chosen as the threshold. For the cross-validation, we applied each PSPRP to the PSP and HC groups from the remaining cohorts and determined its discrimination power through a ROC analysis. Similarly, we applied the PSPRP on the PD group from each of the cohorts. The pattern that performed best in all data sets was selected as the most reliable PSPRP.

Statistical Analysis

Statistical analyses are described in the Supplementary Material.

Results

Subjects

A total of 73 PSP patients were included in this study: 47 PSP-RS, 18 PSP-P, and 8 PSP with progressive gait freezing (PSP-PGF). A summary of patient enrollment is described in Figure S1, and the demographic and clinical characteristics of the combined Dutch and Spanish cohorts studied are summarized in Table 1. Data from each cohort are presented separately (Table S1).

In each cohort, there were no differences between the PSP patients and HCs in terms of sex ($P > 0.05$) or age, except for cohort A in which HCs were marginally younger (PSP_A vs HC_A $P = 0.0064$). Within the PSP cohorts, there were no differences in the H&Y scores ($P = 0.112$), in the disease duration at PET or in the functional disability assessed with the SEADL scale ($P = 0.832$ and $P = 0.703$, respectively). The distribution of clinical domains within each variant of PSP is described in Table S2. Most of the PSP patients qualified for more than 1 diagnostic category according to the MDS-PSP criteria, and the mean number of diagnoses for each patient was similar in the PSP_{NL} and PSP_{SP} cohorts ($P = 0.5985$; Table 2). However, this multiple allocation problem was limited when the MAX rules were employed, and the number of diagnoses was noticeably lower in both cohorts ($P < 0.001$ in each group).

Group Analysis

In the univariate analysis (SPM), we compared PSP patients with HCs and PD patients. Compared with the HCs, PSP patients exhibited relative hypometabolism in some subcortical nuclei (mesencephalon, thalamus, right putamen, globus pallidus, and left caudate) and frontoinsular cortices (dorsolateral and dorsomedial prefrontal cortex, precentral and paracentral cortex, including the frontal eye fields and supplementary motor cortex, the anterior cingulate cortex [ACC] and anterior insular cortex [AIC]). Furthermore, they showed relative hypermetabolism in the cerebellum, sensorimotor areas (bilateral precentral, postcentral and precuneus cortex, left inferior-middle occipital gyrus), superior-middle temporal gyrus, left fusiform gyrus, and bilateral posterior insular cortex (Fig. S2A). When compared with PD patients, PSP patients exhibited relative hypometabolism in some subcortical nuclei (mesencephalon, thalamus, putamen, and globus pallidus) and frontoinsular cortex (inferior-middle frontal gyrus, dorsomedial prefrontal cortex, ACC, and AIC), and relative hypermetabolism in the right Rolandic operculum and parietotemporal cortex, the posterior insular cortex (PIC), and the primary and associative visual cortex (Fig. S2B). Regions in which there were significant metabolic differences are described in detail in Table S3. Moreover, we compared each PSP variant with HCs and PD patients (Figures S3–S5). Compared with HCs, PSP-RS patients showed relative hypometabolism in the mesencephalon, caudate, thalamus, and frontoinsular cortex and relative hypermetabolism in cerebellum and sensorimotor cortices. PSP-P patients showed relative

TABLE 1. Demographic and clinical characteristics of the subjects according to the study group

	PSP	PD	HC	*P*
n	73	58	55	
Age at scanning (years)[a]	70.1 (63.2–74.9)	63.7 (58.1–71.6)	67.4 (61.7–69.9)	**0.0036**[b]
Sex, F/M (% female)	35/38 (48%)	20/38 (34.5%)	25/30 (45.5%)	0.2750
H&Y (prior to PET)[a]	3 (3–4)	2 (1.5–2.5)	NA	**< 0.001**[c]
% H&Y ≥ 3, n (%)	64 (87.7%)	9 (15.8%)		**< 0.001**[c]
Disease duration at PET (years)[a]	2.5 (1.6–3.6)	3 (1–4.9)	NA	0. 5264[c]
Disease duration at last follow-up visit (years)[a]	3.7 (2.3–5)	6.8 (2.5–10.5)	NA	**< 0.001**[c]
UPDRS-III[a]	28 (19–38)	16 (12–26)	NA	**< 0.001**[c]
SEADL[a]	60 (50–80)	80 (70–90)	NA	**0.0014**[c]
PSP clinical variant (n)				
PSP-RS	47			
PSP-P	18	—	—	
PSP-PGF	8			
PSP diagnostic certainty (n)				
Probable PSP	67			
Possible PSP	3	—	—	
Suggestive of PSP	3			
Clinical domains (along follow-up), n (%)				
O1–O2	68 (93.1%)			
O3	34 (46.6%)			
P1–P2	53 (72.6%)			
Falls/PI	70 (95.9%)			
A1	8 (10.9%)			
A2	42 (57.5%)			
A3	20 (27.4%)			
C1	3 (4.1%)			
C2	48 (65.7%)			
C2.1	45(61.6%)			
C2.2	46 (63%)			
C2.3	45 (77,5%)[d]			
C2.4	33 (62.3%)[d]			
C2.5	33 (45.2%)			
C3	19 (26%)			

n, Number of subjects; PSP, progressive supranuclear palsy; PD, Parkinson's disease; HCs, healthy controls; PSP-RS, Richardson's syndrome variant of PSP; PSP-P, parkinsonian variant of PSP; PSP-PGF, progressive gait-freezing variant of PSP; H&Y, Hoehn and Yahr scale; SEADL, Schwab and England activities of daily living; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; O1, vertical supranuclear gaze palsy; O2, slow velocity of vertical saccades; O3, frequent macro square-wave jerks or "eyelid opening apraxia"; P1, repeated unprovoked falls within 3 years; P2, tendency to fall on the pull test within 3 years; P3, more than 2 steps backward on the pull test within 3 years; Falls/PI, falls or postural instability along the disease; A1, progressive gait freezing within 3 years; A2, parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant; A3, parkinsonism with tremor and/or asymmetric and/or levodopa responsive; C1, speech/language disorder; C2, frontal cognitive/behavioral presentation; C2.1, apathy; C2.2, bradyphrenia; C2.3, dysexecutive syndrome; C2.4, reduced phonemic verbal fluency; C2.5, impulsivity, disinhibition, or perseveration; C3, corticobasal syndrome.
PSP patients were older than PD patients (PSP vs PD, $P < 0.01$; PSP vs HC, $P < 0.05$) with no differences in sex. PSP patients had a higher H&Y score ($P < 0.001$) and UPDRS-III score ($P < 0.001$) and more functional disability measured on the SEADL scale ($P = 0.0014$) than PD patients.
[a]Median (interquartile range).
[b]Kruskal-Wallis and Bonferroni tests.
[c]Wilcoxon rank sum test.
[d]Neuropsychological assessments to evaluate the C2.3 and C2.4 domains were performed in 58 and 53 PSP patients, respectively.

hypometabolism in the mesencephalon, caudate, and thalamus like PSP-RS; however, the abnormalities were more asymmetric, and there was higher hypometabolism in the putamen. PSP-P patients also showed relative hypermetabolism in cerebellum, PIC, and primary motor and somatosensory cortex like PSP-RS; however, occipital regions were spared. PSP-PGF patients showed the least expressive metabolic pattern with relative hypometabolism in the thalamus and relative hypermetabolism in the cerebellum and sensorimotor cortices like PSP-RS. Regarding the conjunction analyses, when we included each variant and HC comparisons (Fig. S5C), we found that the relative hypermetabolism in the left primary motor cortex was the only common and significant region among the 3 comparisons. When we included the PSP-RS-versus-HC and the PSP-P-versus-HC comparisons (Fig. S5A,B), we found that both variants shared relative hypometabolism in the mesencephalon and thalamus and relative hypermetabolism in the PIC and primary motor and somatomotor cortices. Compared with PD patients, PSP-RS patients showed relative hypometabolism in the mesencephalon, thalamus, and frontoinsular cortex and relative hypermetabolism in the occipital cortex. PSP-P patients showed relative hypometabolism in the mesencephalon, thalamus, and right putamen and relative hypermetabolism in the left parieto-occipital cortex. In less restrictive analyses

TABLE 2. MDS-PSP diagnoses with and without Multiple Allocations eXtinction (MAX) rules

PSP_{SP} cohort (n = 40)		
	Without MAX rules	With MAX rules
Total number of patients with >1 MDS-PSP diagnosis	39 (97.5%)	4 (10%)
MDS-PSP diagnoses per patient	5.0 ± 1.8	1.1 ± 0.3
Total number of MDS-PSP diagnoses	198	44
Probable	78	40
Possible	41	2
Suggestive of	78	2
PSP_{NL} cohort (n = 33)		
	Without MAX rules	With MAX rules
Total number of patients with >1 MDS-PSP diagnosis	31 (93.9%)	5 (15.2%)
MDS-PSP diagnoses per patient	4.8 ± 1.3	1.2 ± 0.4
Total number of MDS-PSP diagnoses	152	39
Probable	81	37
Possible	44	1
Suggestive of	27	1

PSP, progressive supranuclear palsy; SP, Spanish cohort; NL, Dutch cohort. MDS-PSP criteria, the International Parkinson Disease and Movement Disorder Society clinical criteria for diagnosis of progressive supranuclear palsy; MAX rules, Multiple Allocations eXtinction rules.
The table shows the final clinical diagnoses using the MDS-PSP criteria with and without the application of the Multiple Allocations eXtinction rules in PSP patients at their last follow-up visit.

($P < 0.001$, uncorrected), PSP-PGF patients showed relative hypometabolism in the primary motor cortex, right mid frontal gyrus, and supplementary motor area, and PSP-RS and PSP-P patients showed relative hypometabolism in the lentiform nucleus.

In the multivariate analysis (SSM/PCA), we first identified the PSPRP from PSP patients and their respective HCs in cohorts A, B, and C. In cohort A, a linear combination of principal components 1, 5, and 10 (explaining 23%, 5%, and 3% of the variance, respectively) best discriminated between HCs and patients in the logistic regression model, and this was referred to as $PSPRP_A$. In cohort B, principal components 1 and 14 were linearly combined to form $PSPRP_B$ (explaining 16% and 2% of the variance, respectively), and in cohort C, principal components 1 and 5 were linearly combined to form $PSPRP_C$ (explaining 19% and 5% of the variance, respectively). The stable regions after the bootstrap resampling procedure are represented in Figure 1. All 3 patterns ($PSPRP_{A–C}$) visually overlapped in abnormal metabolism, which only differed in the cluster sizes of the voxels included. Consistent relative hypometabolism was seen bilaterally in the dorsolateral and dorsomedial prefrontal cortex, AIC, precentral cortex, caudate, putamen, thalamus, mesencephalon, and right globus pallidus. Relative hypermetabolism was seen in the cerebellum and sensorimotor cortex. These patterns were consistent with the univariate approach described above, and moreover, the subject z scores of any 2 PSPRPs were significantly correlated within each data set (Table S4).

Individual Analysis

Validation and Cross-Validation

In each cohort, the mean PSPRP subject score was significantly higher in PSP patients than in HCs (Fig. 2A–C), and the corresponding measures of diagnostic accuracy are shown in Table 3. According to the validation (identification) and cross-validation (independent) cohorts, the most reliable pattern was the

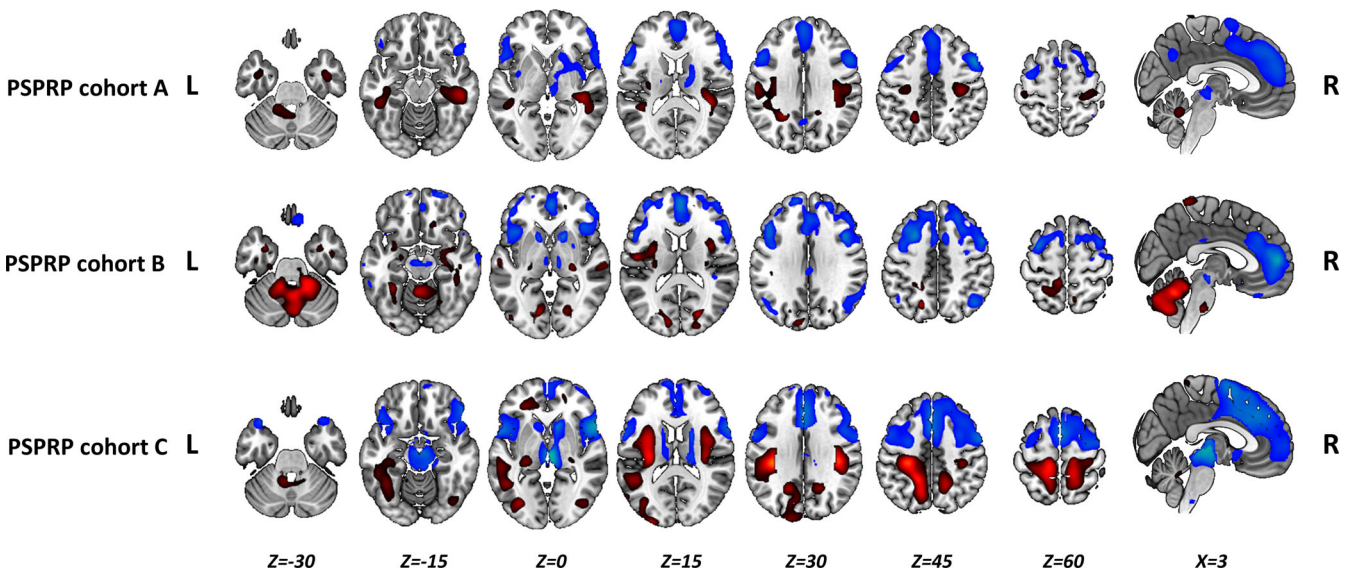

FIG. 1. Pattern maps after the bootstrap procedure (PSPRPA-C). The pattern maps show the voxels that survived a 1-sided confidence interval threshold of 90%. Areas of relative hypometabolism (blue) and hypermetabolism (red) compared with HCs are shown. The patterns share a similar distribution of metabolic changes associated with PSP patients. L, left; R, right; PSPRP, progressive supranuclear palsy–related pattern. [Color figure can be viewed at wileyonlinelibrary.com]

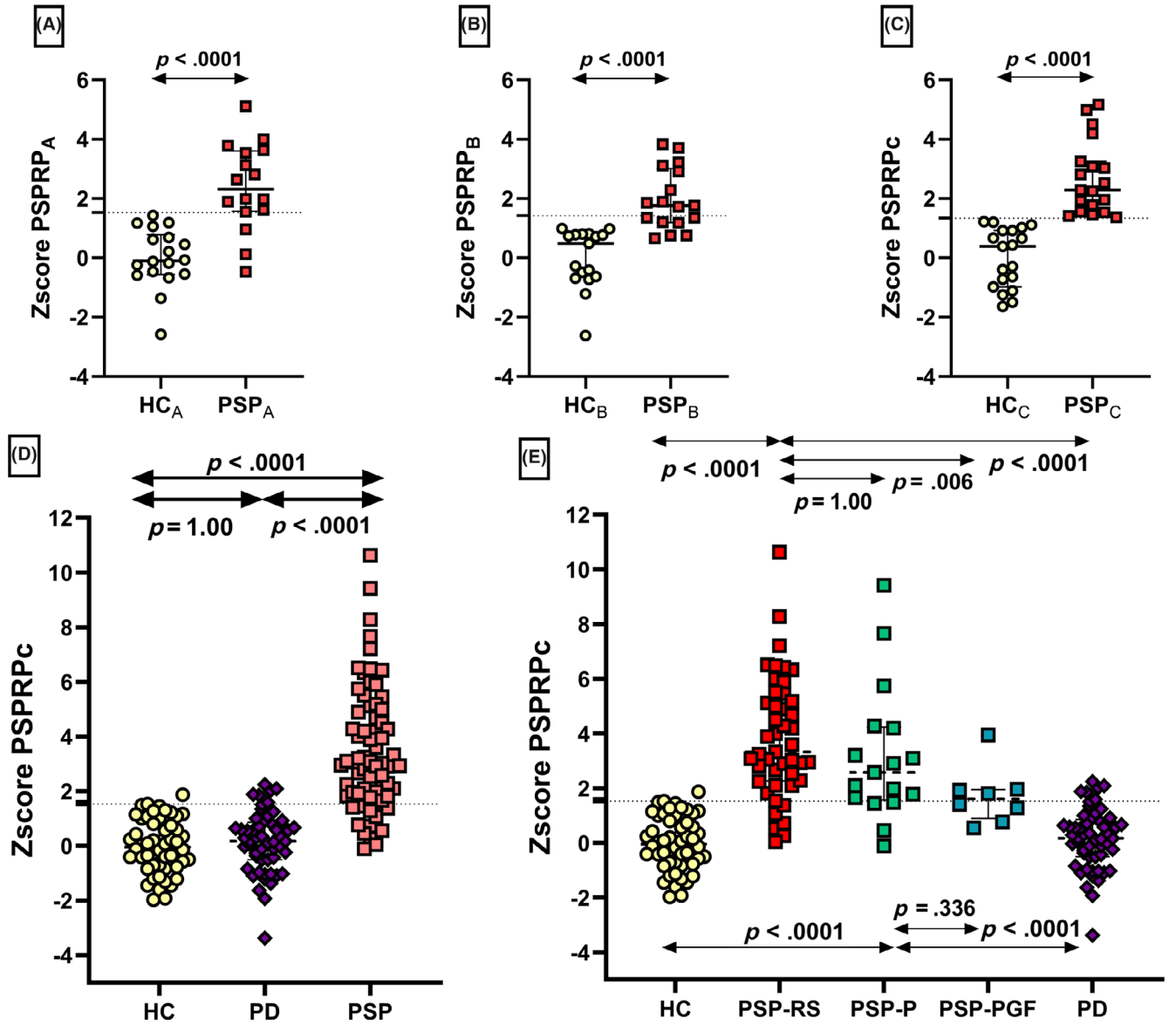

FIG. 2. (A–C) PSPRP expression in the identification population in each cohort In each cohort, the PSPRP subject *Z* scores were significantly higher in the PSP patients than in HCs (2-sample *t* test). (D) Cross-validation of $PSPRP_C$ in independent cohorts. The $PSPRP_C$ subject *Z* scores were significantly higher in the PSP patients than in the PD patients and HCs (Kruskal-Wallis and Bonferroni tests). (E) $PSPRP_C$ expression in PSP variants. $PSPRP_C$ expression discriminated the PSP-RS and PSP-P patients from both PD patients and HCs. PSP-PGF patients were not significantly different despite showing higher $PSPRP_C$ expression than PD patients and HCs (PSP-PGF vs HC, $P = 0.056$; PSP-PGF vs PD, $P = 0.112$; Kruskal-Wallis and Bonferroni tests). PSPRP, progressive supranuclear palsy–related pattern; PSP, progressive supranuclear palsy; PD, Parkinson's disease; HCs, healthy controls; PSP-RS, Richardson's syndrome variant of PSP; PSP-P, parkinsonian variant of PSP; PSP-PGF, progressive gait-freezing variant of PSP. [Color figure can be viewed at wileyonlinelibrary.com]

$PSPRP_C$, as it showed the best diagnostic accuracy to not only distinguish between PSP patients and HCs but also, between the PSP and PD patients (Fig. 2D). In the validation, all the PSP patients and HCs from cohort C were identified correctly. In the cross-validation, 10 PSP patients obtained lower $PSPRP_C$ subject *z* scores than the optimal cutoff when compared with the HCs. Compared with the correctly classified PSP patients, there were no differences in clinical variables with respect to the misclassified PSP patients. Compared with PD patients, the same 10 PSP patients were misclassified, and 5 PD patients displayed slightly higher subject *z* scores than the optimal cutoff. We found no differences in clinical variables between the misclassified PD patients and the rest of the PD patients (Table S5).

Clinical Correlations

No significant correlations between the $PSPRP_C$ subject *z* scores and clinical characteristics were evident.

On the other hand, we found significant differences in the subject's $PSPRP_C$ pattern expression depending

TABLE 3. PSPRP validation and cross-validation

	Validation			Cross-validation(PSP vs HC)	Cross-validation(PSP vs PD)
	$PSPRP_A$ (PSP_A and HC_A)	$PSPRP_B$ (PSP_B and HC_B)	$PSPRP_C$ (PSP_C and HC_C)	$PSPRP_C$ ($PSP_{A,B,D}$ and $HC_{A,B}$)	$PSPRP_C$ ($PSP_{A,B,D}$ and $PD_{A,B,C}$)
	Discrimination between PSP and HC				Discrimination between PSP and PD
Sensitivity (%)	81.3	82.4	100	80.4	80.4
Specificity (%)	100	100	100	96.9	90.7
Positive predictive value (%)	100	100	100	97.6	89.1
Negative predictive value (%)	85.7	85	100	75.6	83.1
AUC-ROC analysis	0.913	0.931	1	0.945	0.910
Cutoff value (*z* score)	>1.43	> 0.99	>1.3	>1.53	>1.59
Positive likelihood ratio	-	-	-	25.70	8.68
Negative likelihood ratio	0.19	0.18	0	0.20	0.22

AUC, area under the curve; HC, healthy controls; PD, Parkinson's disease; PSP, progressive supranuclear palsy; PSPRP, PSP-related pattern; ROC, eeceiver operating characteristic.
$PSPRP_C$ performed best in both the validation and cross-validations. The first 3 columns show the diagnostic accuracy scores for each PSPRP, whereas the following columns show the $PSPRP_C$ cross-validation scores (data from $PSPRP_A$ and $PSPRP_B$ are not shown).

on the PSP variant. In particular, $PSPRP_C$ expression clearly discriminated PSP-RS and PSP-P patients from both PD patients and HCs. PSP-PGF patients also showed stronger $PSPRP_C$ expression relative to PD and HC subjects, although these differences did not reach statistical significance (Fig. 2E).

Discussion

In this study, we report the PSP-related metabolic abnormalities found in the brains of the largest cohort ever reported and our analysis of their potential as diagnostic biomarkers using a longitudinal clinical diagnosis as the gold standard. To our knowledge, this is the first study to address this issue taking into account the MDS-PSP criteria that define a more realistic and heterogeneous PSP cohort. We included patients with final diagnoses of PSP variants in whom the application of the MAX rules successfully overcame the multiple allocation problem, simplifying and standardizing the use of the MDS-PSP criteria.

In terms of the FDG-PET imaging data, both methods used in the group-level analysis identified a consistent topographical distribution of brain metabolic abnormalities in multicenter populations of PSP patients. The results of the univariate analysis (SPM) are consistent with previous studies,[16,17,19–22,24] which described relative hypometabolism in some subcortical nuclei and frontal cortices and relative hypermetabolism in the cerebellum and sensorimotor cortices. Unfortunately, most of these publications were small single-center studies and partially addressed the problem of massive multiple comparisons. Thus, the conservative analyses carried out in this study highlight the robustness of these metabolic abnormalities. Furthermore, the 3 PSP variants shared metabolic abnormalities in the subcortical nuclei, cerebellum, and sensorimotor cortex and differed in the degree and the spread of the metabolic abnormalities. These abnormalities were more asymmetric with higher involvement of the putamen in PSP-P patients. These findings support previous descriptions of the metabolic abnormalities in PSP-P and PSP-PGF.[21,38] Regarding the multivariate analysis (SSM/PCA), we found a significant correlation between the expression of the different patterns in each cohort ($PSPRP_A$, $PSPRP_B$, $PSPRP_C$), suggesting similarities between these patterns in terms of topography and network expression in independent cohorts. The concordance between the patterns could be explained by the clinical characteristics of each cohort. In our study, cohort A had a higher proportion of patients with PSP-P than the rest of the cohorts, which could justify the asymmetrical involvement of the basal ganglia in $PSPRP_A$, and the weaker correlation between this and the rest of the patterns. By contrast, cohorts B and C showed closer clinical similarities and the strongest correlation between the patterns.

Interestingly, both analyses identified dysfunction in the supraspinal locomotor network, a network involved in the gait disturbances of PSP patients.[39,40] In fact, most of the PSP patients included in this study suffered falls and/or postural instability, supporting this clinical correlation. We observed relative hypometabolism in critical elements of the indirect locomotor pathway and relative hypermetabolism in the direct pathway. These changes are considered to compensate basal ganglia-thalamus-cortical loop dysfunction,[39,41,42] leading to hyperactivity of the corticospinal pathway.[42] This somatomotor network also connects to sensory networks. Sensory signals arising from external stimuli can detect and correct postural instability by acting on the cerebral cortex,

cerebellum, thalamus, and mesencephalon in HCs.[43] Consistent with previous studies,[16,19,22] our PSP patients showed relative hypermetabolism in sensory network that might be because of a compensatory mechanism to control postural imbalance. However, prominent network disruptions in sensorimotor systems have been described in PD patients,[44] which may also contribute to these regional differences in metabolism relative to PD patients. Remarkably, we also found relative hypometabolism in the AIC and hypermetabolism in the PIC in PSP patients, alterations that have not been described previously. The AIC is related to both high-level cognitive control and affective processes, and the PIC is involved in sensorimotor processing. The AIC establishes connections with the ACC, and both are part of the salience network. Abnormal salience network connectivity has been described in PSP patients, which is thought to be secondary to its disconnection from subcortical nodes[45–47] and that has been associated with decreased socioemotional sensitivity.[45] In PSP, apathy has also been related to atrophy in the ACC and insular cortex.[48] We found relative hypometabolism in both the AIC and ACC, which may account for the affective and cognitive features in our PSP patients. By contrast, the PIC relative hypermetabolism observed may be because of increased input from sensory regions and the cerebellum, yet it may also compensate AIC dysfunction.[49]

A multivariate approach was also used to assess the diagnostic utility of PSPRP in single FDG-PET scans across different populations. Studies of pattern validation that used cross-validation statistical tools[19,26] or single-center independent cohorts[17,18,28] showed excellent diagnostic accuracy. However, it is known that scanner and reconstruction protocols can influence raw scores,[50,51] and hence, they might have an impact on the diagnostic accuracy of the pattern. The common way to address this problem is by calibrating with HCs. PSPRP reproducibility across 2 truly independent cohorts has been assessed previously in a cross-validation study,[22] producing a topography and disease discrimination power between cohorts in line with our results. Nevertheless, no previous study assessed the usefulness of PSPRP as a diagnostic tool for different PSP variants defined by the MDS-PSP criteria. Our data showed a PSPRP with optimal validation outcomes to differentiate PSP from PD and HCs in both the identification and cross-validation populations.

We further studied the relationship between the patterns and clinical variables. In agreement with previous studies, we found no correlation between the pattern and the Unified Parkinson's Disease Rating Scale part III, Hoehn & Yahr, and Schwab and England Activities of Daily Living scores,[22] which might reflect the inherent limitations of these scales to assess PSP patients.[52] It is important to note that we found a gradual expression of PSPRP in PSP variants (PSP-RS > PSP-P > PSP-PGF). Moreover, PSP-RS and PSP-P patients showed discriminatory and higher expression of the PSPRP than PD patients and HCs. PSPRP expression by PSP-PGF patients was not significantly different despite its higher expression than in PD patients and HCs. These findings are consistent with the common metabolic abnormalities found in PSP variants, with PSP-PGF patients showing the least expressive metabolic abnormalities and PSP-RS and PSP-P patients sharing involvement of midbrain and subcortical nuclei and differing in the degree of cortical involvement. Moreover, these results are in line with some neuropathological studies that described similar networks implied and differences in the global distribution and severity of tau pathology between PSP variants.[3,4,53,54] In fact, a recent neuropathological study observed common early vulnerability patterns that characterize all PSP clinical subtypes jointly (pallido-nigro-luysian axis), but different dynamics of propagation.[54] In other words, our findings suggest that despite the existence of probable neuropathological and functional differences between PSP variants, they may also share a common pattern that can serve as a PSP biomarker to discriminate PSP variants from PD patients and HCs.

The major limitations of this study are the lack of neuropathological confirmation and its retrospective nature, which may have introduced selection bias and limited the number of clinical-imaging correlations assessed. Nevertheless, we mainly selected PSP patients with a probable level of diagnostic certainty and/or PSP-specific clinical syndromes to increase the accuracy of clinical diagnosis. Furthermore, we only included part of the syndromic variants described, and the generalizability of the findings to the rest of variants should be addressed in further studies. An additional limitation could be the heterogeneity inherent in multicenter studies. The PSP cohorts were clinically followed by different movement disorders specialists, and the FDG-PET images differed in terms of the PET cameras and reconstruction protocols, conditions that may have introduced some center-dependent variability. However, 2 neurologists performed a systematic chart review of the medical reports, focusing on predefined clinical domains, and they ruled out the patients with poor-quality medical reports. The final diagnosis was defined according the MDS-PSP criteria, and we applied the MAX rules to reduce the multiple allocations problem. Moreover, the differences between PET procedures were adjusted by additional smoothing during image processing by including the PET procedure as a factor in the SPM analysis and by *z*-transforming the raw individual scores in the SSM/PCA analysis. Nevertheless, despite the apparent heterogeneity, the topography of brain glucose metabolism observed was very similar between cohorts, showing optimal diagnostic accuracy in the cross-validation analysis.

In conclusion, this is the first multicenter study that includes different PSP variants according the MDS-PSP criteria, and it defines regional and network abnormalities in PSP. Our findings confirm the existence of an accurate and highly reproducible PSPRP across different populations and PSP variants. These results reinforce the consideration of the FDG-PET PSPRP as a supportive diagnostic biomarker for PSP-RS and PSP-P.

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G.M.A.: conception, organization, and execution of the research project; design and execution of the statistical analysis; writing of the first draft of the manuscript.

L.v.B.: conception, organization, and execution of the research project; design and execution of the statistical analysis.

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