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## Brain dysfunction in gait disorders of Caribbean atypical Parkinsonism and progressive supranuclear palsy patients: A comparative study

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### ABSTRACT

**Introduction:** Gait disorders and falls occur early in progressive supranuclear palsy (PSP-RS) and Caribbean atypical parkinsonism (Caribbean AP). However, the link between these signs and brain lesions has never been explored in these patient populations. Here, we investigate and compare the imaging factors that relate to gait and balance disorders in Caribbean AP and PSP-RS patients.

**Methods:** We assessed gait and balance using clinical scales and gait recordings in 16 Caribbean AP and 15 PSP-RS patients and 17 age-matched controls. We measured the grey and white matter brain volumes on 3 T brain MRI images. We performed a principal component analysis (PCA) including all the data to determine differences and similarities between groups, and explore the relationship between gait disorders and brain volumes.

**Results:** Both Caribbean AP patients and PSP-RS have marked gait and balance disorders with similar severity. In both groups, gait and balance disorders were found to be most strongly related to structural changes in the lateral cerebellum, caudate nucleus, and fronto-parietal areas. In Caribbean AP patients, gait disorders were also related to additional changes in the cortex, including frontal, insular, temporal and cuneus lobes, whereas in PSP-RS patients, additional white matter changes involved the mesencephalon and parahippocampal gyrus.

**Conclusion:** Gait and balance disorders in Caribbean AP patients are mainly related to dysfunction of cortical brain areas involved in visuo-sensorimotor processing and self-awareness, whereas these signs mainly result from premotor-brainstem-cerebellar network dysfunction in PSP-RS patients, brain areas involved in initiation and maintenance of locomotor pattern and postural adaptation.

**Abbreviations:** ABC, Activity Balance Confidence scale; APAs, Anticipatory Postural Adjustments; CAP, Caribbean Atypical Parkinsonism; CoG, Centre of Gravity; CoP, Centre of foot Pressure; FAB, Frontal Assessment Battery; FC1, Foot-Contact of the first step; FO1, Foot-Off of the first step; FOG-Q, Freezing of Gait questionnaire; GABS, Gait and Balance Scale; GMV, Grey Matter Volume; MCP, Middle Cerebellar Peduncle; MDRS, Mattis Dementia Rating scale; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MFA, Multiple Factor Analysis; MMS, Mini-Mental Status; MRPI, Magnetic Resonance Parkinsonism Index; PCA, Principal Component Analysis; PPN, Pedunculopontine Nucleus; PSP-RS, Progressive Supranuclear Palsy Richardson's Syndrome; RBD, Rapid-eye movement Behavior Disorders; SCP, Superior Cerebellar Peduncle; SMA, Supplementary Motor Area; VBM, Voxel-Based Morphometry; WMV, White Matter Volume.

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## 1. Introduction

Gait disorders, in particular freezing of gait (FOG) and falls are part of the clinical spectrum of almost all parkinsonian syndromes. In progressive supranuclear palsy (PSP), non-accidental falls during the first three years are considered as a cardinal symptom and mandatory for the diagnosis of Richardson's syndrome (PSP-RS) (Höglinger et al., 2017; Litvan et al., 1997). The physiopathology of falls and postural instability in PSP-RS is not fully understood. Numerous brain areas have been shown to degenerate in PSP-RS patients with tau pathology including the basal ganglia, brainstem, cerebellum, and at the cortical level mainly in the frontal lobes (Cope et al., 2018; Morelli et al., 2011; Neychev et al., 2011; Paviour et al., 2006; Quattrone et al., 2008; Schulz et al., 1999; Warmuth-Metz et al., 2001). Recently, reduced velocity or stride length and postural imbalance of PSP patients were found to be correlated with lesion of these brain regions, and in the parietal cortex (Sintini et al., 2021). Degeneration of cholinergic neurons within the pedunculopontine nucleus (PPN) (Sébillé et al., 2019) with decreased metabolic activity of the centromedian-parafascicular nucleus (CM-Pf) of the thalamus have also been reported and linked to falls and postural instability (Zwergal et al., 2011).

Falls also occur in other atypical parkinsonian (AP) syndromes and Parkinson's disease (PD), but later during the course of the disease (Bloem et al., 2001; Wenning et al., 1999). In the Caribbean islands of Guadeloupe and Martinique, atypical parkinsonism is abnormally frequent. These patients develop levodopa-resistant motor symptoms, with gait disorders and falls occurring early in the course of the disease (with a mean delay of 2.5 years), dementia, and supranuclear-gaze-palsy in about half of the cases (Caparros-Lefebvre and Elbaz, 1999; Lannuzel et al., 2018, Lannuzel et al., 2006, Lannuzel et al., 2007). Unlike the classical forms of PSP, Caribbean AP patients have hallucinations (Lannuzel et al., 2018), rapid eye movement sleep behaviour disorders (RBD) (De Cock et al., 2007), dysautonomia and cortical myoclonus (Apartis et al., 2008). Neuropathological studies have revealed significant differences principally with a cortical distribution of tau pathology (Caparros-Lefebvre et al., 2002), a widespread atrophy of the cerebral cortex, including the frontal and temporal lobes, and a relative mesencephalic sparing compared to PSP-RS patients (Lehéricy et al., 2010). Finally, even though these two groups of patients have postural instability and falls, the specific assessment of gait and postural control in Caribbean AP patients has never been performed and the link between gait and balance disorder severity and brain lesions has not been explored in these patients.

Here, we aim to characterize gait and balance disorders in both Caribbean AP with supranuclear palsy and PSP-RS patients, and to link these signs to brain atrophy using a combined clinical, neurophysiological and neuroimaging approach.

## 2. Materials and methods

### 2.1. Study design

In this explorative study, we recruited patients with Caribbean AP from the Neurology and Rehabilitation Departments of the University Hospitals of Guadeloupe and Martinique, and those with PSP-RS from the Neurology Department of the Paris Pitié-Salpêtrière Hospital (France). Healthy controls were recruited in the three centres. Patients fulfilled the following inclusion criteria: > 40 years old, levodopa-unresponsive progressive parkinsonism, vertical supranuclear downward gaze slowness or palsy. Patients with PSP-RS were selected according to the National Institute of Neurological Disorders and Stroke diagnostic criteria (Litvan et al., 1997; Williams et al., 2005). Caribbean AP were of afro-caribbean descent and may present with additional symptoms such as hallucinations, delusions, RBD, autonomic dysfunction, myoclonus or cortical sensory symptoms (Lannuzel et al., 2018, 2007). Patient presenting actual psychiatric disorders, dementia (Mini-

Mental Status [MMS] < 20 and Frontal Assessment Battery [FAB] < 12), inability to stand upright or walk alone or contraindications to MRI were excluded. This study received approval from the local ethics committee and the French Ministry of Health. All subjects gave informed written consent to participate. The study was performed in accordance with the declaration of Helsinki and Good clinical practice guidelines, sponsored by the Pointe-à-Pitre University Hospital (ClinicalTrials.gov registration: NCT04096651).

### 2.2. Procedures

All clinical, neurophysiological and imaging assessments were performed at the Paris Brain Institute the same day (France). Caribbean AP patients and controls travelled from the west indies to perform the assessments.

#### 2.2.1. Clinical assessment

The following scales were used to assess parkinsonian disability, gait and balance disorders, and cognition: PSP-RS scale (Golbe and Ohman-Strickland, 2007), Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008), Gait and Balance Scale (GABS) (Thomas et al., 2004), Tinetti scale (Tinetti et al., 1988), Freezing of Gait questionnaire (FOG-Q) (Giladi et al., 2009), and Activity Balance Confidence (ABC) scale (Powell and Myers, 1995), MMS (Cockrell and Folstein, 1988), FAB (Dubois et al., 2000), Mattis Dementia Rating scale (MDRS) (Schmidt et al., 1994), Picture Oral naming test (OD-80) (Deloche and Hannequin, 1997), and the Delayed Word Recall test (DWR) (Grober et al., 1988). The educational level was also noted (ranging from 1 to illiterate to 7-graduate studies) (Lannuzel et al., 2018).

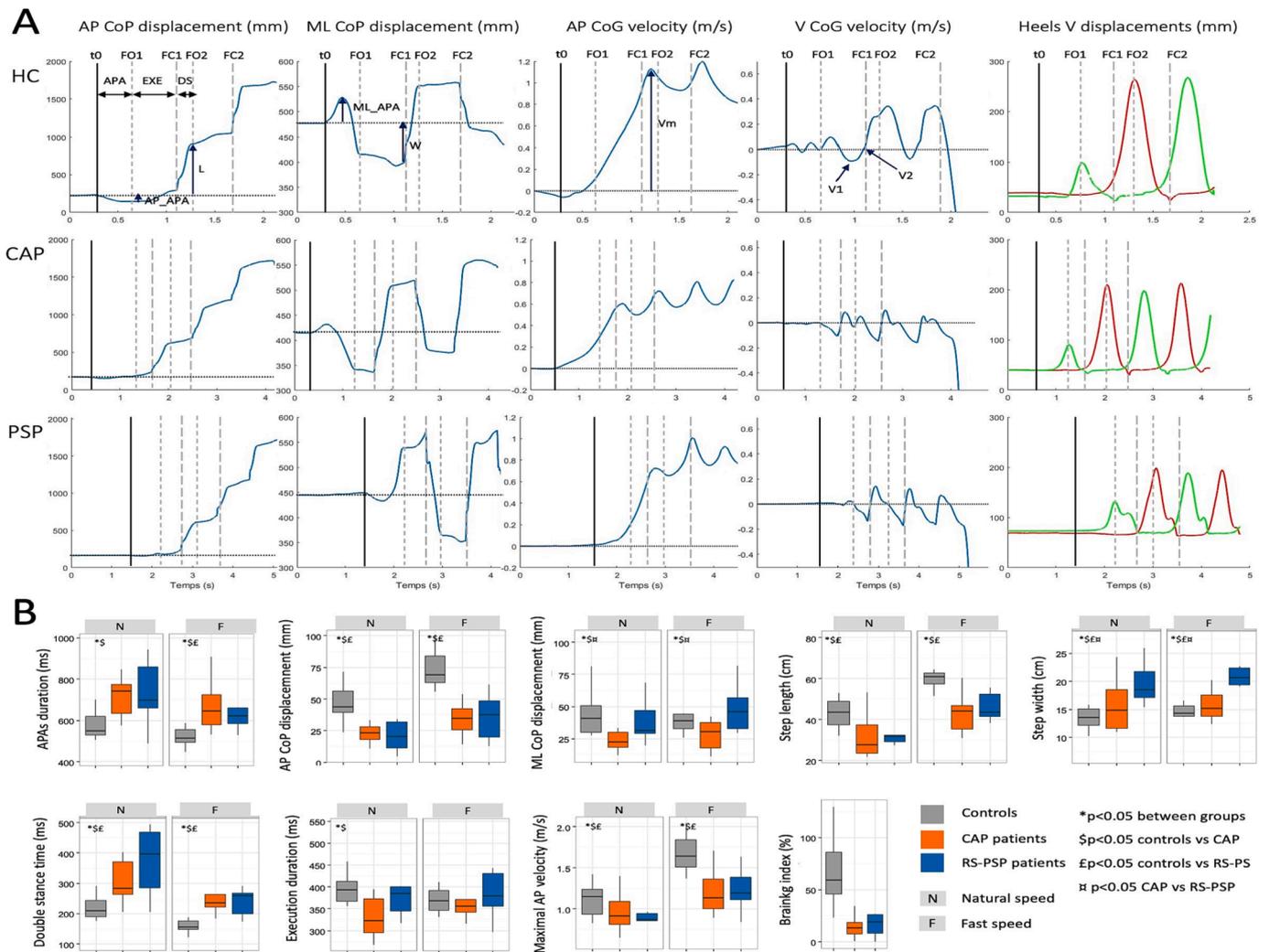
#### 2.2.2. Gait initiation recordings

We assessed gait initiation as it requests simultaneous control of forward, lateral and vertical body movements with specific postural adjustments to trigger locomotion. For this, a force plate (0.9 × 1.8 m. Advanced Mechanical Technology Inc. LG6-4-1. USA) was used to record ground reaction forces and moments, in the three planes to study the biomechanical parameters of gait initiation, and a motion capture system (Vicon® system) to measure displacements of the heels. The activity of soleus (S) and tibialis anterior (TA) muscles were recorded bilaterally using bipolar surface electrodes. Each subject stood motionless and barefoot on the platform and started to walk following an auditory cue for 7–8 m, in self-paced and fast speeds conditions, with 10 to 15 trials for each gait condition.

During gait initiation, two phases can be distinguished: 1) the anticipatory postural adjustments (APAs) phase, corresponding to the period between the first biomechanical event (t0) and foot off of the swing leg (FO1), and 2) the execution of the first step, corresponding to the delay between the foot off (FO1) and the foot contact (FC1, Fig. 1A). We measured: 1) the duration of APAs, execution and double-stance phases, 2) the amplitude of the posterior and lateral displacements of the centre of foot pressure (CoP) during the APAs, 3) the length, width and velocity of the first step and 4) the centre of gravity (CoG) vertical velocity during the first step execution (V1 corresponding to minimum velocity) and at time of foot-contact (V2, Fig. 1A) (Welter et al., 2007).

#### 2.2.3. Oculomotor recording

We recorded eye movements by video-oculography (SMI©, and software E(eye)BRAIN©, sampling frequency: 500 Hz) to better characterize the two patients groups, relative to controls (Pierrot-Deseilligny et al., 1989). Subjects were seated with their heads immobilized, in complete darkness, 61 cm from a screen, and instructed to look as quickly as possible towards a lateral or vertical red target (5°, 8° and 13°) that appeared 200 ms after central green target offset. Saccade accuracy was determined by saccade gain defined by amplitude of the first saccade over final eye position on target. The mean prosaccade



**Fig. 1.** Gait initiation parameters in controls, Caribbean AP and PSP-RS patients. A) Gait initiation parameters recordings using a force platform allowing the calculation of anteroposterior (AP) and mediolateral (ML) centre of foot pressure (CoP) displacements, and anteroposterior and vertical (V) centre of gravity (CoG) velocities, and vertical displacements of right (green line) and left (red line) heels measured with the Vicon system (from left to right traces). Each trace represents the gait initiation parameters obtained during the anticipatory postural adjustments (APAs) phase and execution (EXE) of the first step in an individual control (HC, upper traces), Caribbean AP (CAP middle traces) and PSP-RS (bottom traces) patients. B) Graphs represent the gait initiation parameters obtained in controls (grey), Caribbean AP (orange) and PSP-RS (blue) patients, both in natural (N) and fast (F) gait conditions. Boxplots show the median (dark lines), interquartile (Q1-upper and Q3-bottom parts of the boxes) and range for each gait initiation parameter. t0: time of the first biomechanical event; FO1: time of the foot-off of the swing leg; FC1: foot contact of the swing leg; FO2: time of the foot-off of the stance leg; DS: double-stance phase; L: step length; W: step width; Vm: maximum AP velocity of the CoG; V1: minimum vertical velocity of the CoG and V2: vertical CoG velocity at the time of the foot-contact. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

latency and velocity were calculated by averaging 9 prosaccades in each direction. The antisaccade error rate defined as the percentage of saccades directed toward the lateral target was also measured by instructing the subject to look at a red central fixation point, then to trigger as soon as possible a saccade in the opposite direction to a 13° red right or left target. The frequency of a square wave jerk was also calculated.

**2.2.4. Image acquisition and processing**

All participants underwent Magnetic Resonance Imaging (MRI) on a Siemens VERIO 3 T system (Siemens Healthcare, Germany) with a 32 channel head coil. Three-dimensional (3D) T1-weighted anatomical scans were acquired using a sagittal MPRAGE acquisition (TR/TE/TI = 2300/4.18/900 ms, 1-mm isovoxel size).

We calculated the Magnetic Resonance Parkinsonism Index (MRPI 2.0) (Quattrone et al., 2008), and performed Voxel Based Morphometry (VBM) analysis of T1 images to examine the changes in the grey and white matter concentration (Ashburner and Friston, 2005). The MRPI

index is the product of the ratios of pons to midbrain area (Pa/Ma), the width of middle to superior cerebellar peduncles (MCPd/SCPd), and the average third ventricle diameter (measured at three points) to the maximal frontal horn diameter [(3rd Vd 1 + 2 + 3)/FHD]. MRPI 2.0 = (Pa/Ma) × (MCPd/SCPd) × (average 3rd Vd/FHD) (Quattrone et al., 2008). Vor VBM analyses, data processing and analysis were performed using statistical parametric mapping software (SPM12, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) and the computational anatomy toolbox (CAT12: <https://www.neu.ro.uni-jena.de/cat/>) (Ashburner, 2007; Ashburner and Friston, 2005). Native T1-weighted magnetic resonance volumes were segmented to obtain the grey matter, white matter and cerebrospinal fluid (CSF) images, and non-brain voxels were removed. The T1-weighted magnetic resonance volumes of each subject were spatially normalized with non-linear alignment with the T1 Montreal Neurological Institute template (Talairach and Tournoux, 1988) and resliced to a voxel size of 2x2x2mm<sup>3</sup>. The segmented normalized grey and white matter images

were then smoothed with a 8-mm filter full-width at half maximum isotropic Gaussian kernel. The resulting smoothed and normalized regions contained the average amount of grey or white matter within a region surrounding a voxel.

### 2.3. Statistical analysis

For clinical, oculomotor and gait initiation parameters, median values and 95 % confidence interval were calculated. Non-parametric Kruskal-Wallis (for numerical variables) and Fisher's Exact (for categorical variables) tests were performed to compare data obtained between subject groups. When significant, between group comparisons were made with the Chi-square or Fischer's Exact test, as appropriate for non-parametric variables and with the Student or Mann-Whitney tests for parametric variables.

For VBM data, we used a threshold of  $P < 0.05$  and  $t > 3.8$  with false discovery rate whole brain correction. We used SPM12 factorial design specification to establish the statistical global linear model for the imaging data, that allows us to compare the groups. Multiple factor analysis (MFA) was used as a data-driven exploratory technique to determine the underlying structure of the data. ROI volumes describing the same brain regions in the three groups were grouped together to form a set of blocks. MFA was run on the blocks associated with a brain region. As a first step, individual principal component analyses (PCA) were performed on each block and the result normalized by the corresponding first Eigen value. The obtained matrices were then merged to form a global matrix, and a global PCA was performed. The individual observations were then projected onto the global space to determine the differences/similarities between the individual groups and the relationships between the brain regions. We also performed multi-table Partial Least square correlation analysis to explore the relationship between grey and white matter volumes of each brain region and the severity of gait and balance disorders and cognitive status. Pearson's coefficients were computed, and an approximate multivariate permutation test was performed to adjust for multiple comparisons. Statistical analysis was performed with R (R Core Development Team) and MATLAB version R2017b (The Mathworks. Inc., MA, USA). The level significance was set at  $p < 0.05$  after correction.

## 3. Results

### 3.1. Patients characteristics

Between October 2015 and June 2018, we included 16 patients with Caribbean AP (mean age =  $64.3 \pm 6.8$  years, 9F/7M), 15 patients with PSP-RS (mean age =  $66.2 \pm 5.9$  years, 6F/9M), and 17 age-matched healthy subjects (mean age =  $64.6 \pm 5.1$  years, 12F/5M) (Table 1).

#### 3.1.1. Clinical characteristics

We found no significance differences between groups for age, sex or family history of neurodegenerative diseases (Table 1). The educational level was significantly lower in Caribbean AP compared to both PSP-RS patients and controls.

The mean age at the first symptom, disease duration and the median delay from disease onset to first fall were not significantly different between patient groups (Table 1). In Caribbean AP, the inaugural symptoms in frequency were tremor (6/16 patients), bradykinesia (4/16), rigidity (2/16), postural instability/falls (2/16), hypersialorrhea (1/16) or dystonia (1/16). In PSP-RS patients, the inaugural symptoms were postural instability/falls (9/15 patients), dysarthria (2/15), depression (2/15) or visual blur/diplopia (2/15). PSP-RS patients had more frequently signs of pyramidal dysfunction and none had RBD. In Caribbean AP patients, 6/16 had RBD.

We found no significant difference for the severity of parkinsonism or clinical gait and balance disorders between patient groups (Table 1 and eTable 1). Cognitive status was significantly altered in both patient

**Table 1**

Demographic and clinical features in PSP-RS and Caribbean AP patients, and controls.

	Controls	PSP-RS	Caribbean AP
Sex ratio (H/F)	5/12	9/6	7/9
Age (years)	68 [57;73]	67 [60;76]	67 [57;77]
Age of disease onset (years)	–	62 [51;72]	56 [39;72]
Disease duration (years)	–	5 [1;8]	4 [2;22]
Falls delay (years)	–	0 [0;3]	0 [0;5]
Family history of degenerative diseases	9/17	11/15	8/16
Educational level	7 [3;7]	7 [4;7]	4 [3;7]\$*
Pyramidal signs	–	12/15	4/16*
Cerebellar signs	–	6/15	5/16
Facial dystonia	–	3/15	0/16
Cervical Dystonia	–	8/15	9/16
Myoclonus	–	1/15	3/16
Hallucinations/Psychosis	–	1/15	4/16
RBD	–	0/15	6/16*
PSP-RS scale	–	37 [20.1;52.9]	28 [7.5;50.5]
MDS-UPDRS scale	–	61 [41.4;100.7]	66.5 [31.2;97.7]
Non motor experiences part A	–	4 [1;10]	7 [0.3;11.2]
Non motor experiences part B	–	7 [3;11.9]	9 [3.7;20.1]
Activities of daily living	–	22 [8;42.9]	22.5 [5.8;37.2]
Motor disability	–	29 [13;48]	21 [12.3;45.2]
Motor complications	–	0 [0;0]	0 [0;3]
Rating Scale for Gait and Equilibrium	–	30 [12.7;46.4]	28.5 [10.5;44.2]
Gait and Balance Scale	–	39 [12.2;61.9]	27.5 [10.1;62.2]
Tinetti scale	–	18 [10.7;26.9]	19.5 [13.3;27.6]
Freezing of Gait Questionnaire	–	12 [4.7;29.3]	13 [2.3;41]
ABC scale	–	58 [14;87]	59 [5.9;90]
MMSE	29 [24;30]	28 [25;30]\$	24 [19;30]\$*
FAB	18 [14;18]	14 [13;17]\$	14 [12;17]\$
MDRS	142 [140;144]	134 [123;143]	131 [121;143]
Forward Span	6 [4;7]	6 [4;8]	5 [4;7]
Backward Span	4 [3;6]	4 [3;5]	3 [2;4]\$*
Frontal Score	58 [48;60]	50 [40;59]\$	50 [20;57]\$
Verbal fluency	25 [14;36]	15 [8;24]	12 [2;28]\$
OD-80	80 [75;80]	80 [61;80]	77 [64;80]\$
Recall test			
Immediate Recall	16 [16;16]	16 [13;16]	16 [13;16]\$
Free recall	35 [30;46]	27 [20;37]	24 [8;36]\$
Total recall	48 [44;48]	47 [43;48]	40 [27;48]\$*
Delayed free recall	15 [11;16]	12 [7;14]	11 [5;15]\$
Delayed total recall	16 [15;16]	16 [15;16]	15 [10;16]\$*
Recognition	16 [15;16]	16 [14;16]	16 [14;16]
Total	146 [134;157]	133 [39;147]	123 [29;144]\$

Values are median and interquartiles.

\*  $p < 0.05$  Caribbean AP compared to PSP-RS patients;

\$  $p < 0.05$  patients compared to controls;

FAB=Frontal Assessment Battery ; MDRS = Mattis Dementia Rating Scale ; MMSE=Mini Mental State Examination ; OD-80 : Oral denomination of 80 images; RSGE: Rating Scale for Gait and Equilibrium.

groups compared to controls, with also lower scores for MMS, backward span and total recall tests in the Caribbean relative to PSP-RS patients (Table 1).

#### 3.1.2. Gait initiation recordings

Both Caribbean AP and PSP-RS patients showed a profound alteration of gait initiation parameters compared to controls, with higher APAs and double stance phases durations and lower APAs posterior CoP displacement, length, velocity of the first step, and braking index (natural and fast gait conditions, Fig. 1B). PSP-RS patients had also a higher double stance duration and mediolateral CoP displacement and step

width relative to Caribbean AP patients (Fig. 1B).

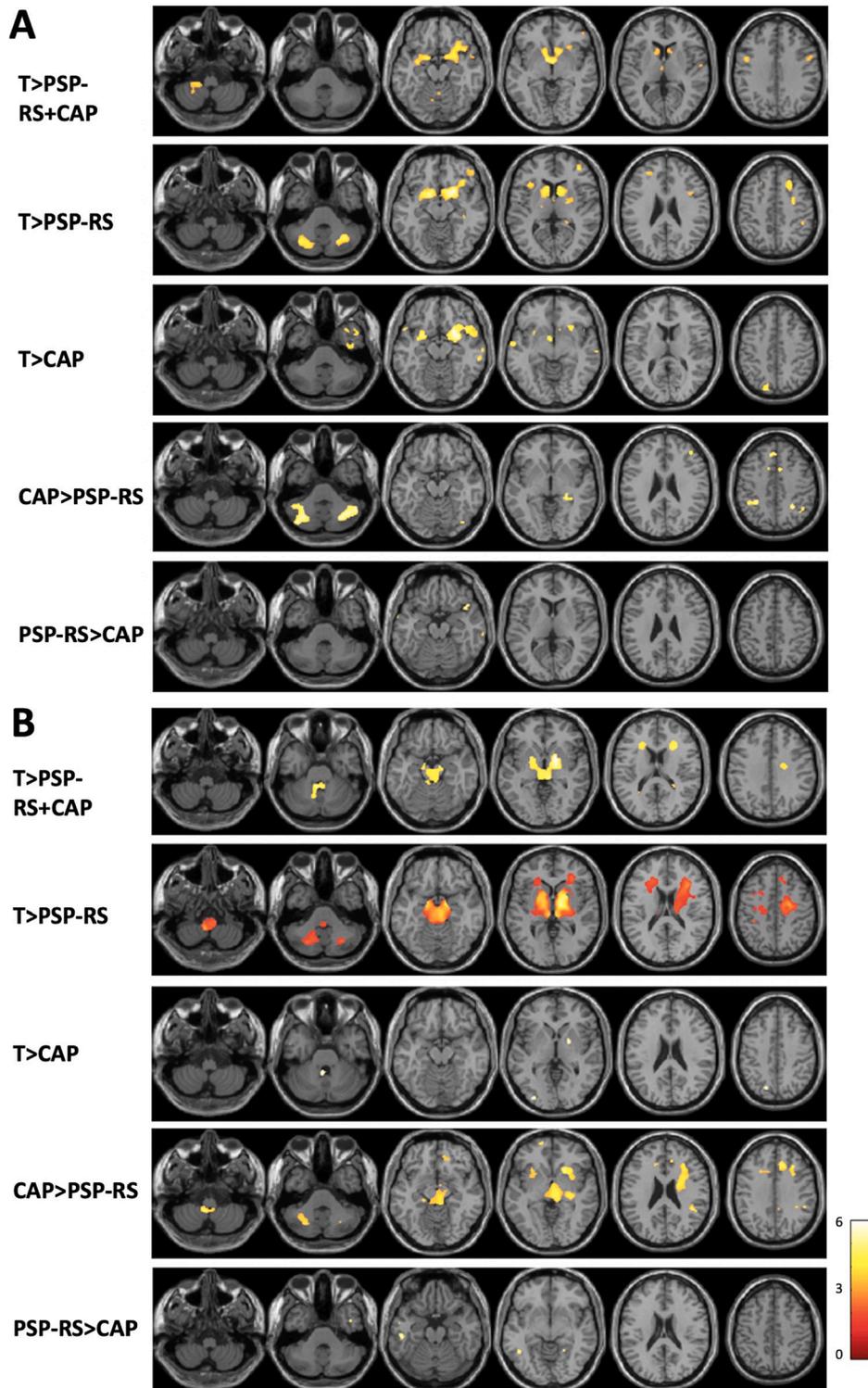
### 3.1.3. Oculomotor recordings

Five patients (4 Caribbean AP and 1 PSP-RS) were not recorded because of complete ophthalmoplegia. In other patients, we found altered oculomotor parameters relative to controls with lower downward and upward saccade velocities, visually guided saccade gain and latency (eTable 2). PSP-RS patients have more severe oculomotor disorders in comparison to Caribbean AP patients, and showed in particular

lower downward prosaccade gain (5°, 8° and 13°) and velocity (8° and 13°) and higher antisaccade error rates (eTable 2).

### 3.2. Differences in grey and white matter brain volumes between Caribbean AP, PSP-RS patients and controls

The MRPI was higher in PSP-RS relative to both Caribbean AP patients and controls (median [interquartiles] values of 10.0 [8.4\_13.2], 15.7 [8.8\_23.2] and 24.1 [14.6\_34.7] for controls, Caribbean AP and



**Fig. 2.** Grey and white matter volume differences in controls, Caribbean AP and PSP-RS patients. Images shows the differences between patients with Caribbean Atypical Parkinsonism (CAP), Progressive Supranuclear Palsy – Richardson’s syndrome (PSP-RS) and control subjects (C) for A) grey and B) white matter volumes. Statistical parametric maps are presented for the averaged normalized T1-wighted image of all control subjects. Voxels were considered significant at  $P < 0.05$  and  $t > 3.8$ , false discovery rate whole brain corrected. Left is right. Scale bar indicates t-score.

PSP-RS patients, respectively, eTable 3). Midbrain surface and diameters of the superior (SCP) and middle (MCP) cerebellar peduncles were also significantly lower in PSP-RS patients compared to both Caribbean AP patients and controls (eTable 3).

VBM analysis showed significant decreases in grey (GMV) and white (WMV) matter volumes for both patient groups relative to controls in the striatum, the insula, temporal, parietal and frontal cortices (Fig. 2, Tables 2 and 3). Compared to controls, we found additional decreases in WMV in the occipital lobe and the vermis of the cerebellum in Caribbean AP patients; and in the thalamus, mesencephalon, and cerebellar hemispheres bilaterally in PSP-RS (Fig. 2, Tables 2 and 3). Comparing Caribbean AP and PSP-RS patients, we found significantly lower GMV and WMV mainly in the right temporal pole and parietal superior lobule in Caribbean AP relative to PSP-RS patients; and in the thalamus, mesencephalon, striatum, cerebellar hemispheres, frontal and parietal areas, and the right temporal lobe in PSP-RS relative to Caribbean AP patients (Fig. 2, Tables 2 and 3).

### 3.3. Clinical signs, gait parameters, and imaging data that discriminate between controls, Caribbean AP and PSP-RS patients

We performed a multifactor analysis to examine the link between clinical, neurophysiological and imaging parameters. We found two components that had eigenvalues greater than one, explaining respectively 32% and 11% of the total variance for the three groups (controls, Caribbean AP patients, PSP-RS patients). The first component separated healthy controls from patients, and the second component Caribbean AP from PSP-RS patients (Fig. 3).

The first component has stronger loading on clinical characteristics, gait and oculomotor parameters than the VBM data component (Fig. 3). Almost all clinical variables reflecting cognitive status and gait and oculomotor parameters included in the analysis discriminated patients from controls. For the first component, brain VBM data were the cerebellum (external and white matter), brainstem, parahippocampal gyrus, mid, inferior, superior and inferior orbital frontal gyri, posterior cingulate and supramarginalis gyri (Fig. 3). The second component has stronger loading on VBM data, including the cerebellum (lateral and white matter), brainstem, subcallosal area, posterior and mid cingulate gyri, parahippocampal gyrus, anterior insula, mid, inferior and superior frontal and posterior orbital gyri, the frontal pole, medial premotor and primary motor cortices, left angular and supramarginalis gyri and the cuneus.

For the second component, clinical variables that distinguished Caribbean AP and PSP-RS patients were clinical scores that reflect cognitive status (total and delayed total recall, backward span and MMS scores), gait parameters that mainly reflect postural control (APAs mediolateral displacement, APAs, double-stance and step durations, step width and length, and vertical velocities), and oculomotor parameters were upward and downward gains (Fig. 3).

### 3.4. Correlation analysis between the severity of gait and balance disorders, cognitive deficit and brain volumes in Caribbean AP and PSP-RS patients

Fig. 4 shows the relationship between brain volume areas extracted from the PCA analysis and some clinical scores and gait parameters for Caribbean AP and PSP-RS patients.

In both patient groups, the severity of gait and balance disorders correlated with lateral cerebellum, caudate nucleus, inferior frontal gyrus and operculum, posterior cingulum, angular, postcentral and supramarginalis gyri GMV (Fig. 4). Additionally, in Caribbean AP patients, the severity of gait and balance disorders also correlated with frontal areas (frontal pole, midfrontal, medial precentral gyrus), temporal tractus, anterior insula and cuneus GMV. In PSP-RS patients, the severity of gait and balance disorders also correlated with cerebral, cerebellar, and midbrain WMV, the MRPI, and the frontal (superior

**Table 2**  
Grey matter volume differences in controls, PSP-RS and Caribbean AP patients.

	Side	MNI Coordinates			t-score
		X	Y	Z	
<b>Controls &gt; Caribbean AP patients</b>					
Frontal lobe					
Superior frontal gyrus	Right	10	-9	78	5.22
Temporal lobe					
Temporal pole	Left	-45	14	-27	4.55
	Right	48	10	-21	5.12
Superior Temporal gyrus	Left	-62	-8	-3	4.39
	Right	58	6	-2	3.96
Mid-Inferior temporal gyrus	Right	54	-15	-30	3.97
Fusiform gyrus	Right	36	-10	-45	4.19
Hippocampus/Amygdala	Left	-32	-2	-16	4.47
Parietal lobe					
Superior parietal lobule	Left	-16	-81	46	3.99
Insula					
	Left	-26	6	-14	4.87
	Right	32	4	-14	5.53
Pallidum/Putamen	Left	-26	6	-14	4.87
	Right	26	12	-12	5.71
Thalamus/Diencephalon	Left	-6	-2	-4	4.50
	Right	4	-2	-2	3.80
<b>Controls &gt; PSP-RS patients</b>					
Frontal lobe					
Superior frontal gyrus	Left	-24	44	28	4.20
	Right	24	22	46	4.66
Mid frontal gyrus	Right	30	0	48	4.03
Inferior frontal gyrus	Right	48	44	-6	4.42
Precentral gyrus	Left	-46	-3	34	4.23
Temporal lobe					
Mid temporal gyrus	Right	48	-48	14	3.81
Hippocampus	Right	24	-40	4	4.82
Parietal lobe					
Supramarginalis / Angular gyrus	Right	46	-39	46	4.07
Parietal superior lobule	Left	-39	-56	57	4.30
	Right	22	-63	60	3.84
Caudate/Putamen	Left	-9	10	-3	4.97
	Right	22	12	-12	4.83
Thalamus (posterolateral)	Left	-18	-36	3	3.94
Cerebellum hemispheres	Left	-27	-64	-40	4.19
	Right	33	-58	-39	4.36
<b>Caribbean AP patients &gt; PSP-RS patients</b>					
Frontal lobe					
Supplementary motor area	Right	8	10	44	4.02
Mid frontal gyrus	Left	-45	20	48	4.23
Superior frontal gyrus	Left	-8	33	42	4.14
Temporal lobe					
Superior and mid temporal gyrus	Right	48	-48	12	4.31
Hippocampus	Right	34	-34	-6	4.29
Parietal lobe					
Supramarginalis / Angular gyrus	Left	-39	-51	52	4.06
	Right	45	-56	39	4.88
Superior parietal lobule	Left	-30	-42	45	4.85
	Right	30	-52	46	5.06
Occipital lobe					
Inferior occipital gyrus	Right	27	-84	0	3.94
Superior occipital gyrus	Left	-10	-87	18	3.88
Cerebellum hemispheres	Left	-40	-75	-39	4.54
	Right	51	-54	-44	5.03
<b>PSP-RS patients &gt; Caribbean AP patients</b>					
Temporal lobe					
Temporal pole	Right	44	16	-15	4.73
	Right	69	-20	-10	4.59
Parietal lobe					
Parietal superior lobule	Right	30	-50	70	3.86
<b>PSP-RS patients &gt; Controls</b>					
Anterior cingulate gyrus					
	Right	6	30	18	4.59
<b>Caribbean AP patients &gt; Controls</b>					
Frontal lobe					
Rectus gyrus	Left	-4	28	-28	5.03
Occipital lobe					
Mid-Inferior occipital gyrus	Right	39	-70	27	3.99

AP: Atypical Parkinsonism; PSP-RS: Progressive Supranuclear Palsy-Richardson's syndrome.

**Table 3**  
White matter volume differences in controls, PSP-RS and Caribbean AP patients.

	Side	MNI Coordinates			t-score
		X	Y	Z	
<b>Controls &gt; Caribbean AP patients</b>					
Parietal lobe					
Superior parietal lobule	Left	-16	-74	45	4.12
Occipital lobe					
Mid-inferior occipital lobule	Left	-32	-87	2	4.01
Pallidum/Putamen	Right	20	3	-2	3.81
Vermis of the cerebellum (lobule I-V)		-3	-45	-27	4.04
<b>Controls &gt; PSP-RS patients</b>					
Frontal lobe					
Superior-Mid frontal gyrus	Right	10	32	44	3.82
Supplementary motor area	Right	8	3	54	3.97
Precentral gyrus	Left	-21	-18	48	4.04
Parietal lobe					
Post-central gyrus	Left	-36	-34	45	4.11
Caudate/Putamen	Right	18	6	-2	6.44
Thalamus/Diencephalon	Left	-6	-15	-4	7.11
	Right	10	-12	-4	6.00
Cerebellum hemispheres					
	Left	-27	-60	-40	4.25
	Right	30	-66	-39	4.30
<b>Caribbean AP patients &gt; PSP-RS patients</b>					
Frontal lobe					
Supplementary motor area	Right	10	4	54	4.72
Frontal pole	Left	-15	63	-4	4.53
Mid-Superior frontal gyrus	Left	-21	15	44	4.34
Medial-anterior orbital gyrus	Right	18	40	-14	3.84
Parietal lobe					
Angular gyrus	Left	-34	-60	46	4.57
	Right	45	-44	21	5.83
Supramarginalis gyrus	Right	52	-42	36	5.02
Superior parietal lobule	Right	39	-42	39	4.65
Posterior cingulate gyrus	Right	8	-45	34	3.81
Caudate/Putamen	Left	-22	10	14	3.80
	Right	22	10	16	6.30
Thalamus	Right	22	-2	-14	6.12
Mesencephalon		18	-18	-18	3.67
Cerebellum hemispheres	Left	-27	-64	-39	4.04
<b>PSP-RS patients &gt; Caribbean AP patients</b>					
Temporal lobe					
Mid temporal gyrus	Left	-50	-26	-20	4.25
Inferior temporal gyrus	Left	-45	-52	-10	4.76
	Right	44	2	-39	4.18
Fusiform gyrus	Right	24	-50	-4	3.96
<b>Caribbean AP patients &gt; Controls</b>					
Occipital gyrus	Right	44	-74	16	4.09

AP: Atypical Parkinsonism; PSP-RS: Progressive Supranuclear Palsy-Richardson's syndrome.

frontal, posterior orbital) and parahippocampal gyri GMV (Fig. 4).

In Caribbean AP patients, the cognitive deficit correlated with decreased GMV in the lateral cerebellum, caudate nucleus, frontal pole, midfrontal and inferior frontal gyrus, and supramarginalis gyrus (Fig. 4). For PSP-RS patients, we found significant correlations between total recall and OD-80 scores with cerebral white matter, midbrain, caudate nucleus, superior medial frontal, inferior frontal, inferior frontal pars orbicularis gyri and frontal operculum; postcentral, supramarginalis, angular and parahippocampal gyri GMV (Fig. 4).

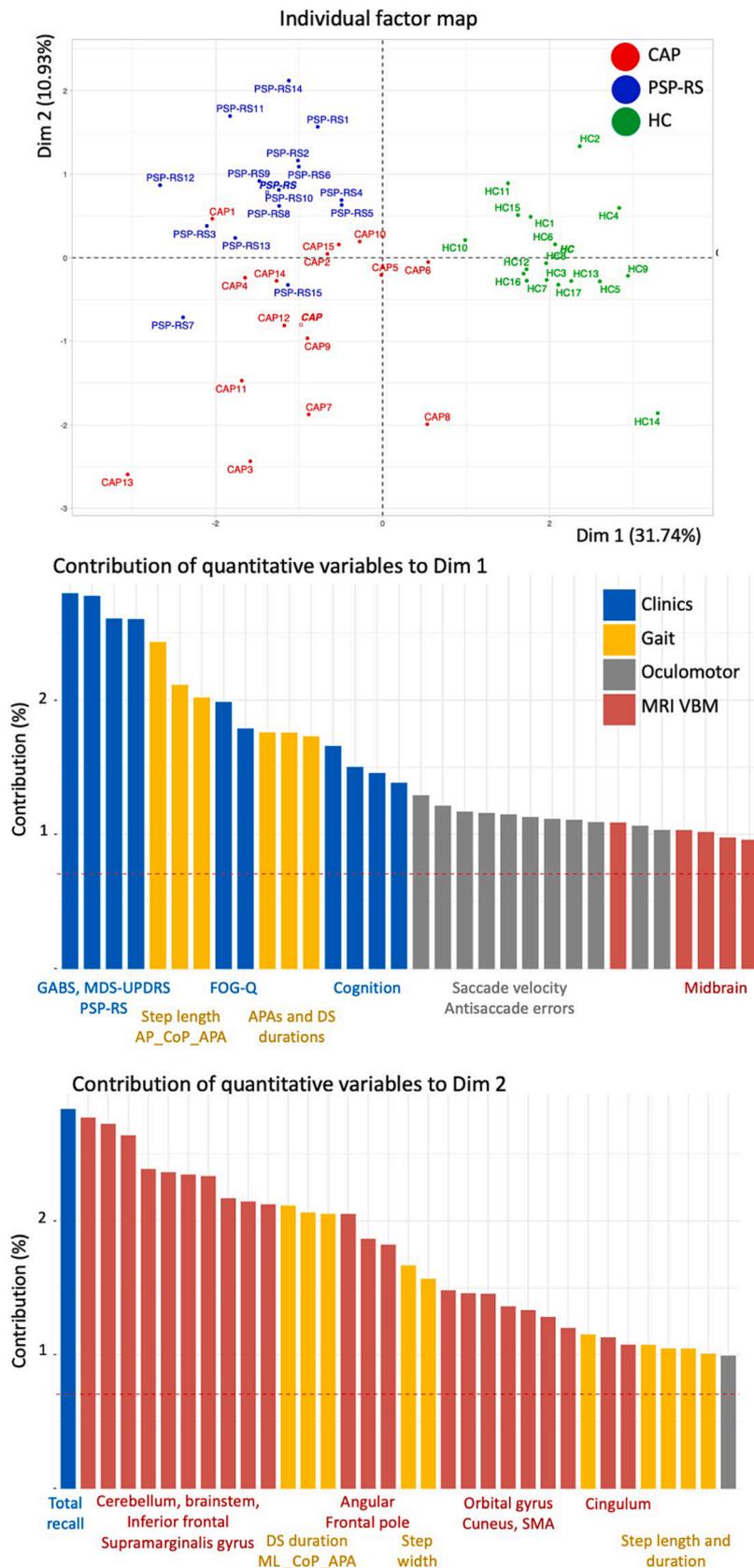
#### 4. Discussion

In this study combining clinical, neurophysiological, and imaging approaches, we found that Caribbean AP patients have marked gait and

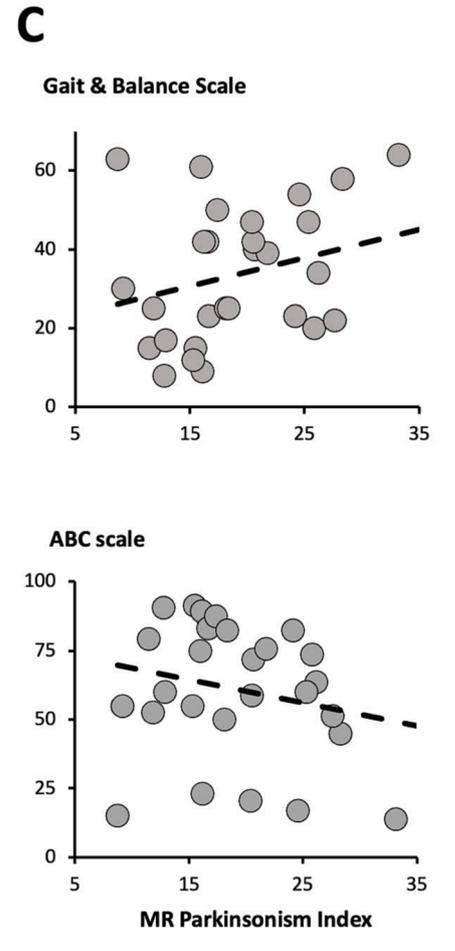
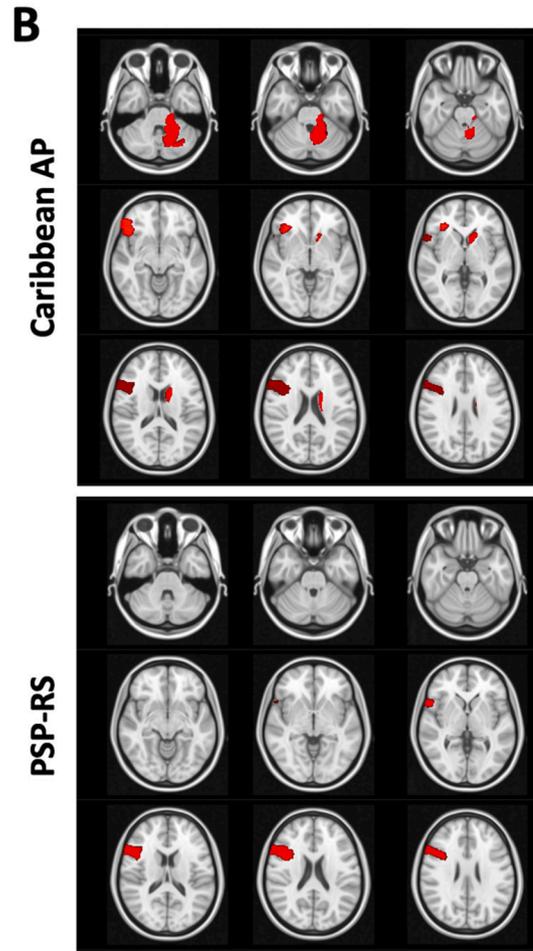
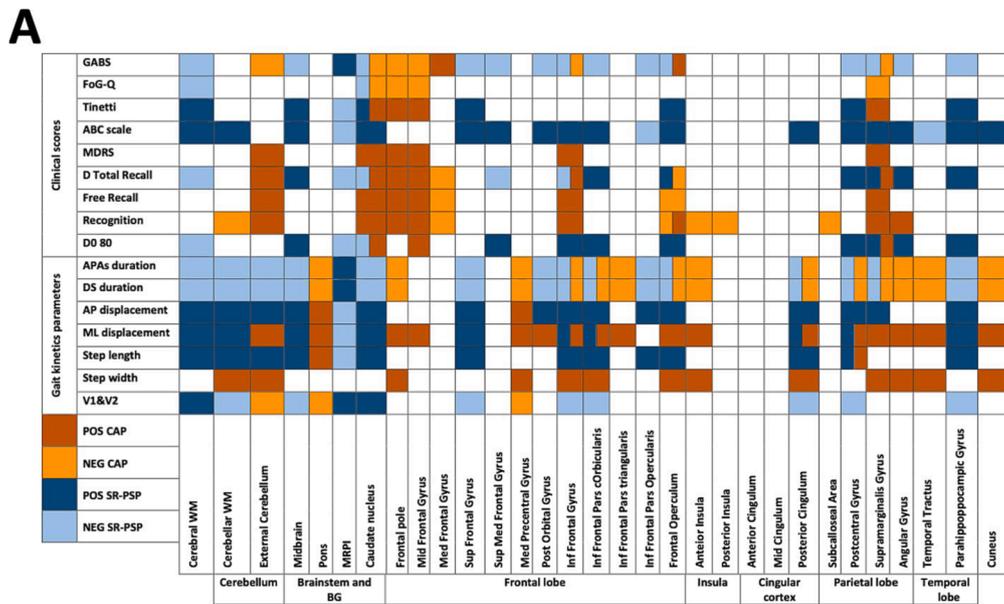
balance disorders with similar clinical severity to PSP-RS patients but, in addition, more severe cognitive deficits. Both patient groups showed modified gait initiation performance relative to controls, with an additional mediolateral deficit in PSP-RS patients. In both groups, gait and balance disorders were related to structural changes in the lateral cerebellum, basal ganglia, and fronto-parietal cortical areas. The pattern also differed between the two groups, with involvement of larger cortical areas (frontal, temporal, insula, and cuneus) in Caribbean AP patients, and of the midbrain in PSP-RS patients.

To our knowledge, this is the first study reporting gait and balance performances in patients with Caribbean AP in relation to brain areas volumes, and in comparison to PSP-RS patients and controls. Both Caribbean AP and PSP-RS patients had severe clinical gait and balance disorders, with precocious falls and profound alterations of gait and postural controls, including very low step length and velocity, increased stance durations and absence of vertical postural control (reflected by a braking index near zero) (Welter et al., 2007). This result is in line with the recent report of severe clinical gait and balance disorders with precocious falls in a larger cohort of Caribbean AP patients (Lannuzel et al., 2018), suggesting that these axial motor signs could not formally distinguish these two diseases. Our results are also in line with the reports of decreased anteroposterior APAs (Amano et al., 2015), gait speed and step length (Hatanaka et al., 2016; Raccagni et al., 2018; Welter et al., 2007) and altered static and dynamic postural control in PSP-RS patients (Ali et al., 2021; Amboni et al., 2021; Hatanaka et al., 2016; Kammermeier et al., 2018; Song et al., 2022; Welter et al., 2007; Zwergal et al., 2011). In both Caribbean AP and PSP-RS patients, we found that gait and postural deficits correlated with GMV in the caudate nucleus, inferior frontal and pars orbicularis gyri, frontal operculum, posterior cingulate, postcentral and supramarginalis gyri, with some of these brain region volumes discriminating patients from controls (Lehéricy et al., 2010; Paviour et al., 2006; Pyatigorskaya et al., 2020; Sintini et al., 2021; Whitwell et al., 2011). These brain areas are implicated in processing and integration of vestibular, visual and somatosensory information, and changes in the activity in the postcentral and supramarginal gyrus activity have been found during real or mental imagery of walking in healthy subjects (Jahn et al., 2004; la Fougere et al., 2010). Reduced grey matter volumes and dysfunction in these deep and cortical brain areas have also been previously associated with lower gait speed and/or longer double support time in PSP patients (Sintini et al., 2021; Zwergal et al., 2013) and in large cohorts of community-dwelling adults (Callisaya et al., 2014; DiSalvio et al., 2020; Dumurgier et al., 2012; Ogama et al., 2014; Rosano et al., 2008).

The only significant difference in gait parameters between patients was higher mediolateral APAs (Amano et al., 2015), step width and double-stance duration in PSP-RS patients relative to Caribbean AP patients. This suggests that PSP-RS patients had too large a step width relative to their step length with an enlarged base of support during walking reflecting higher postural instability and ataxia. This could be due to the cerebellar atrophy found in PSP-RS relative to both Caribbean AP and controls (Sintini et al., 2021), but also in relation to atrophy of the basal ganglia and mesencephalon with higher MRPI index, as previously reported (Lehéricy et al., 2010). A significant loss of PPN cholinergic neurons with decreased thalamic cholinergic activity has previously been demonstrated in PSP-RS patients, and related to postural instability and falls (Sébillé et al., 2019). The PPN is also highly connected with the SMA and the SMA-PPN network has been shown to be dysfunctional in PD patients with freezing of gait (Peterson et al., 2014; Snijders et al., 2011) and/or falls (Sébillé et al., 2019). In our study, we found that premotor and sensorimotor areas volumes also distinguished PSP-RS from Caribbean AP patients, suggesting that lesions of this SMA-PPN network, in addition with the cerebellar damage, are the main contributors to gait and balance deficit in PSP-RS patients (Sintini et al., 2021). In Caribbean AP patients relative to PSP-RS patients, gait and balance deficits were also related to atrophy of the medial precentral gyrus, anterior insula, angular and supramarginalis



**Fig. 3.** Multifactor analysis including clinical, gait, oculomotor and MRI data for controls, PSP-RS and Caribbean AP patients. The graphs represent the principal component analysis results for all the clinical, neurophysiological and imaging data obtained in the controls, PSP-RS and Caribbean AP patients. This analysis discriminated the 3 groups of subjects (upper panel). Controls (blue dots) and patients are discriminated along axis 1, and Caribbean AP (red dots) and PSP-RS (green dots) patients along axis 2. The first component is mainly composed of clinical, gait and oculomotor parameters (middle panel), and the second component mainly composed of imaging, cognitive scores and gait recording parameters (bottom panel). APA = anticipatory postural adjustment, AP = anteroposterior, CoP = centre of foot pressure, DS = double-stance, ML = mediolateral, SMA = supplementary motor area, VBM = voxel-based morphometry. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 4.** Correlation analysis between brain MRI grey and white matter volumes and severity of gait and balance disorders in CAP and PSP-RS patients. A) Significant correlations found between gait and balance disorders with both clinical scales and gait recording parameters in Caribbean AP (brown and orange squares for positive and negative correlations, respectively) and PSP-RS patients (dark blue and light blue squares for positive and negative correlations, respectively). B) Visualisation of brain areas correlating with mediolateral displacement during gait initiation in Caribbean AP (upper panel) and PSP-RS (lower panel) patients. C) Graphs show the linear correlation between the GABS (upper panel) and ABC (lower panel) scales and the Magnetic Resonance Parkinsonism Index (MRPI), in both Caribbean AP and PSP-RS patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

gyrus, and cuneus. Reduced grey matter volumes in these brain areas have, in part, been previously reported in Caribbean AP patients (Lehéricy et al., 2010). The medial precentral gyrus is part of the primary motor cortex controlling leg muscle activity and has been shown to be activated during mental imagery of walking (Jahn et al., 2004; Karachi et al., 2012). The anterior insula cortex has been involved in awareness and interoception, and the supramarginalis and angular gyrus and cuneus are interconnected structures involved in sensory processing and spatio-temporal self-location ability (de Boer et al., 2020). This could indicate that gait disorders in Caribbean AP patients are more related to changes in sensory processing and self-perception.

Additionally, our study revealed a more pronounced cognitive deficit in Caribbean AP patients and we observed a correlation between both cognitive deficit and gait disorders with reduced volumes in specific brain regions, namely the caudate nucleus, frontal pole, mid and inferior frontal gyrus. These areas have been implicated in executive functions such as attentional switching, action execution, and response inhibition (Alvarez and Emory, 2006). This finding suggests that the severity of the dysexecutive syndrome largely contributes to the occurrence of gait disorders in Caribbean AP patients. Previous research has also reported a similar association between gait disorders and dysexecutive syndrome in patients with Parkinson's disease (PD), particularly in relation to the severity of freezing of gait (Teramoto et al., 2014), as well as in individuals with frontotemporal dementia (Allali et al., 2010). Furthermore, it is worth noting that Caribbean AP patients in our study exhibited a lower level of education, which has recently been identified as a risk factor for dementia (Lannuzel et al., 2018). This finding suggests a potential decrease in cognitive reserve within this patient's population. These patients also displayed lower GMV and WMV in the temporal lobe, including regions such as the temporal pole, hippocampus, fusiform gyrus, and inferior temporal gyrus (Lehéricy et al., 2010). These findings indicate the presence of additional brain lesions in these specific areas known to be involved in various cognitive processes, including visual processing, memory, naming, and word-object labeling (Herlin et al., 2021).

Lastly, our study found a higher frequency of visual hallucinations in Caribbean AP patients, along with lower white matter volumes in the occipital lobe, encompassing the occipital pole and calcarine cortex, previously incriminated in the occurrence of visual hallucinations in patients with PD or Lewy body disease (Mehararam et al., 2022).

This study has some limitations. First, the sample size for each group was relatively low. However, these two disorders are rare, and we used strict inclusion criteria to select patients with actual gait and/or balance disorders without dementia, to limit the influence of cognitive deficit on gait ability. Another limitation is the fact that diagnoses of Caribbean AP and PSP-RS were based on clinical features and disease history, and not pathologically confirmed. However, the fact that both groups could be accurately distinguished using PCA with brain imaging data and clinical features previously reported to be different between these two patient populations, such as cognition, RBD or midbrain atrophy (Lannuzel et al., 2018; Lehéricy et al., 2010), confirmed the accurate baseline classification of patients. Lastly, we included patients with severe disease with ongoing postural instability and/or falls to find brain anatomical factors that could contribute to these signs, with a mean disease duration of 4 years, and no longitudinal follow-up. This prevented us from examining the precise relationship between brain areas change and the appearance and/or aggravation of gait disorders and postural instability over time.

## 5. Conclusions

Our results indicate that gait and balance disorders observed in Caribbean AP patients are mainly related to dysfunction of cortical brain areas involved in visuo-sensorimotor processing and self-awareness, whereas these signs mainly result from premotor-brainstem-cerebellar network dysfunction in PSP-RS patients, brain areas involved in

initiation and maintenance of locomotor pattern and postural adaptation. Further studies are needed to examine the changes in brain imagery and gait and postural control in longitudinal cohort studies. Therapeutic interventions, such as non-invasive brain stimulation, could also be tested to modulate these brain areas, and to try to improve gait and balance for which no curative or symptomatic treatment exists up to now (Mi et al., 2020; Wong et al., 2022).

## 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.

## Data availability

All relevant data are within the article. Requests for anonymized data should be sent to M.L. Welter at the Paris Brain Institute, 75013 Paris, France.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2023.103443>.

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