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Right posterior hypometabolism in Pisa syndrome of Parkinson's disease: a key to explain body schema perception deficit?

Relatore

Chiar.mo Prof. Matteo Pardini

Candidata

Dott.ssa Erica Biassoni

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SOMMARIO

INTRODUCTION

Parkinson's disease: etiology, epidemiology and risk factors

Parkinson's disease (PD) is the most common parkinsonism and is part of a group of neurological disorders that includes vascular parkinsonism, iatrogenic parkinsonism and other neurodegenerative disorders (such as multiple system atrophy, progressive supranuclear palsy, and dementia with Lewy bodies)[1].

PD is less common in subjects younger than 50 years old and its prevalence increases with age[1]. Also, PD seems more frequent in men than in women[1].

Most cases of PD are idiopathic, but there are also genetic variants[2]. Furthermore, exposure to heavy metals and to herbicides or pesticides have been recognised as possible environmental risk factors. On the contrary, caffeine and cigarette smoke appear to be protective factors[1].

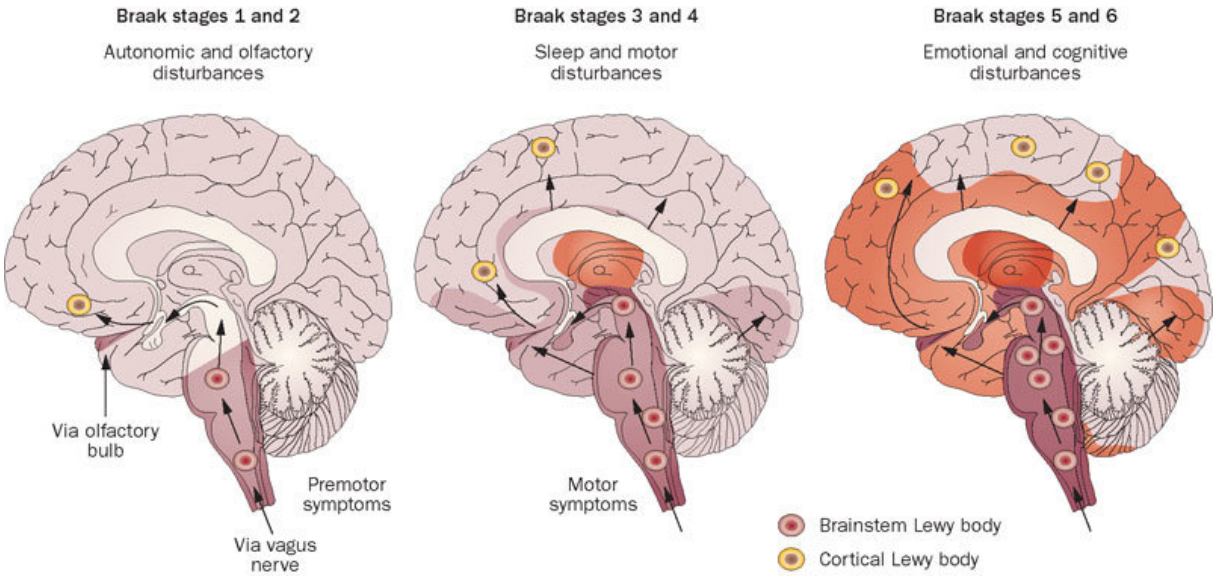
Pathophysiology of Parkinson's disease and models of neuropathological progression

PD pathophysiological hallmark is the death of dopaminergic neurons of the substantia nigra - pars compacta[1,2]. From the histopathological point of view, PD is instead characterized by neuronal inclusions composed largely of protein aggregates of α-synuclein, called Lewy bodies[1,2].

The Braak hypothesis (**Figure 1**) is the most famous model of neuropathological progression to explain PD[3]. According to this hypothesis, PD would originate in medulla and olfactory bulb (stages 1 and 2). In this early and premotor stage non-motor symptoms are prevalent and can consist in Rapid Eye Movement (REM) sleep Behavior Disorders (RBDs)[4] and hyposmia or anosmia[5]. In stages 3 and 4 the pathology would also involve the substantia nigra pars compacta and other midbrain and basal forebrain structures, manifesting at this point with the typical motor symptoms. PD

diagnosis is therefore frequently made at this time. In advanced PD the pathology would spread cranially to cerebral cortex, leading to onset of hallucinations and cognitive impairment.

Figure 1. Braak stages.



Tractography and Neurosurgical Targeting in Deep Brain Stimulation for Parkinson's Disease – Mikkel V. Petersen

More recently, alternative physiopathological models have also been proposed (**Figure 2**)[6,7]. Some examples of these models are the brain first-body first model and the multifocal onset (cortical, limbic, brainstem) hypothesis[6]. In the body-first subtype, the propagation of α-synuclein is in caudocranial direction through the autonomic nervous system, starting from the gut up to the spinal cord and the brainstem. In this case the earliest symptoms are non-motor, such as autonomic dysfunction and RBDs[6].

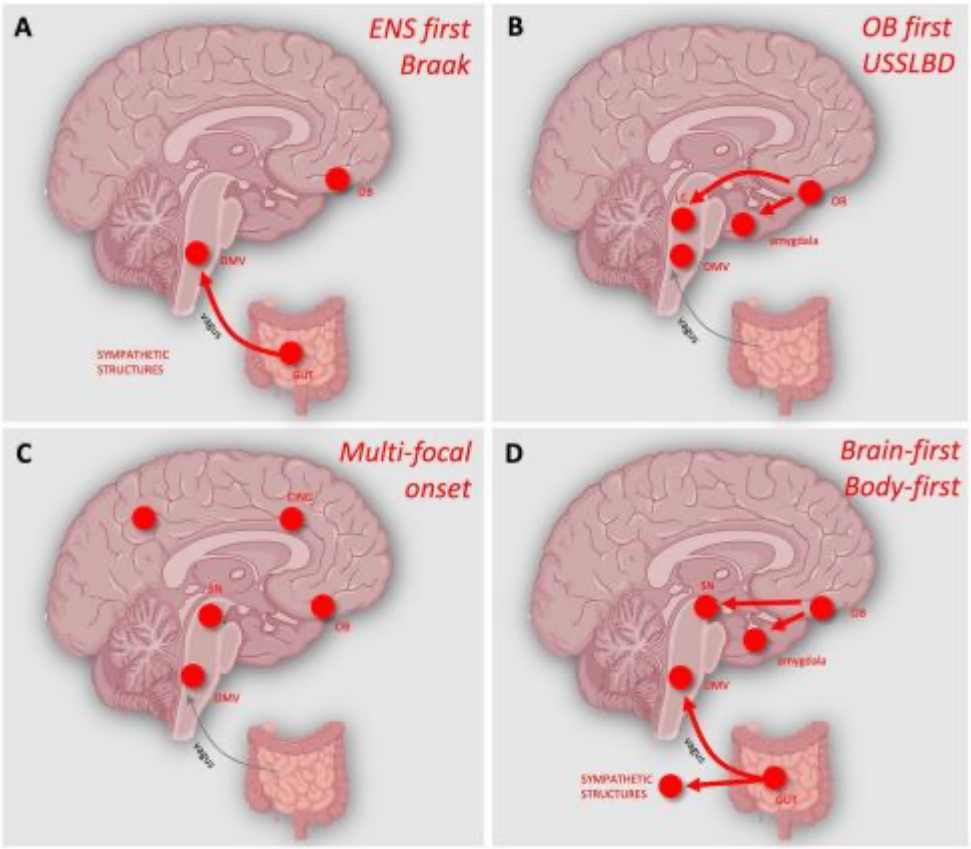
In the brain-first subtype, the initial accumulation of α-synuclein instead begins in the brain, for example in the limbic system, or enters via an olfactory route, and subsequently descends in a cranio-caudal direction at the level of the brainstem[6]. In this second case, therefore, dysautonomia and RBDs develop after the onset of parkinsonism[6].

In the advanced stages of the disease, the two phenotypes tend to converge, as α-synuclein is widespread at this point[6].

However, there are also intermediate phenotypes with mixed characteristics of the two above.

The hypothesis of multifocal onset is instead based on the assumption of a multifocal origin at the level of the central nervous system[7].

Figure 2. Alternative PD physiopathological models.



P. Borghammer, The brain-first vs. body-first model of Parkinson's disease with comparison to alternative models, J Neural Transm. 130 (2023) 737–753

Clinical symptoms and phenotypes

Motor symptoms of PD have been recognized as prominent since its first description and consist of bradykinesia, rigidity, tremor at rest and postural instability with gait impairment[2,8].

However, the motor characteristics of the disease are very heterogeneous and vary from patient to patient[2]. The onset of bradykinesia, rigidity and rest tremor is often unilateral and reflects contralateral basal nuclei degeneration[9]. In particular, the first and most severely affected nucleus is the putamen (especially its posterior part), followed by the caudate nucleus[9].

Non-motor symptoms include instead hyposmia or anosmia, mild cognitive impairment (MCI) or dementia, psychiatric symptoms like apathy or depression, sleep disturbances especially during REM sleep like RBDs, autonomic dysfunctions, excessive daytime sleepiness, fatigue and pain[2]. Non-motor symptoms can frequently precede the onset of motor ones by several years and are associated with both a worse quality of life and a worse prognosis of the disease[2]. The premotor phase of the disease can also be very prolonged, for example the mean latency between the onset of RBDs and the development of motor symptoms can be as long as 12-14 years[5].

Heterogeneity in clinical manifestations led to classify the disease into subtypes, in particular two: tremor-dominant PD (which is characterized by a relative absence of motor disorders other than tremor) and non-tremor-dominant PD - also known as PIGD (Postural Instability and Gait Difficulty, which is characterized by akinetic-rigid syndrome, instability and gait disturbances as well as by the more frequent association with non-motor symptoms)[2,10]. However, there is a spectrum of mixed or indeterminate phenotypes between these two extremes, which also differ from a prognostic point of view[2,10]. Tremor-dominant PD is often associated with a slower progression and less disability than PIGD[2,10]. It has also been hypothesized that the various subtypes may have different pathogenesis and etiologies[2,10].

Considering age as a discriminating factor, we can divide PD into late-onset PD (LOPD: age of onset after 60 years and more frequently with sporadic etiology) and young-onset PD (YOPD: age of onset between 20 and 40 years, frequently associated with dystonic forms and more frequently with genetic etiology)[10].

A different clinical classification instead divides PD into 3 main subtypes: Mainly motor, Intermediate and Diffuse/Malignant, the latter more frequently characterized by a worse prognosis and the presence of non-motor symptoms such as MCI, RBDs and orthostatic hypotension[1,6].

Progression of disease

PD is a neurodegenerative disease which progresses over time with development of treatment-resistant motor and non-motor symptoms[2]. In particular, motor symptoms are only initially managed by symptomatic therapies and worsen during the course of the disease. In the advanced stages of PD complications related to long-term symptomatic treatment like psychosis, motor and non-motor fluctuations and dyskinesias are predominant. Moreover, dysphagia, speech dysfunction, dysautonomic features and axial symptoms like postural instability, freezing of gait, falls are also very disabling for quality of life[2].

Diagnosis

Diagnosis of PD is clinical and based on bradykinesia finding associated with at least one other symptom: either rest tremor or rigidity[8]. Usually motor symptoms onset is asymmetrical with one hemisome more compromised than the other[9].

Diagnosis red flags also exist, namely the absence of non-motor symptoms or the presence of signs or symptoms more suggestive of atypical parkinsonism[1].

However, imaging and instrumental tests are often used to support the diagnosis.

Brain Magnetic Resonance Imaging (MRI) is most useful for ruling out secondary causes of parkinsonism[9]. It results often normal, although it may show occasional diffuse atrophy or abnormalities of the substantia nigra,[9].

18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is also often normal, especially in the early stage of the disease[9]. However, in some cases hypometabolism can be detected in the parieto-occipital and dorsolateral prefrontal cortex while metabolism is usually instead preserved in the cerebellum, putamen and globus pallidus[9].

Dopamine transporter (DaT)-SPECT, on the other hand, can show a reduced uptake of the striatum (more pronounced at the posterior putamen and caudate level)[9]. Reduced uptake is usually asymmetric and controlateral to the more clinically affected hemisome[9]. 18F-Fluoro-

dihydroxyphenylalanine (18F-DOPA) PET is also potentially useful to study dopaminergic system as a radioactive analogue of L-dihydroxyphenilalanine (L-DOPA)[11].

Decreased cardiac 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy uptake is another abnormality possibly found in PD that indicates cardiac denervation by sympathetic fibers[11]. Furthermore, 123I-MIBG can be a useful tool to differentiate PD from atypical parkinsonisms[11].

Electroencephalogram (EEG) has also been studied and proposed as a possible biomarker of disease and as an indicator of longitudinal changes in the functional brain networks in PD[12,13].

Furthermore, the loss of physiological muscle atony in the REM sleep phase can be detected with polysomnography (the so called REM sleep without atonia or RWA)[4]. RWA is typical of RBDs and can suggest a prodromal phase of PD[4,5].

Hyposmia as well can be early diagnosed with a smell test[5].

In the future it is also possible to imagine a role of α-synuclein as a disease biomarker potentially dosable in various body fluids and peripheral tissues (liquor, blood, saliva, intestine, submandibular glands, skin, retina). However, at present, further studies are still needed to establish the best methodology regarding its detection and quantification[14,15].

Therapy

PD is caused by protein aggregations associated with death of dopamine-producing cells[1,2]. Dopamine supplementation is therefore the main therapy of this pathology and response to dopaminergic therapy further reinforces the diagnosis[1,8].

The occurrence of motor fluctuations, end-of-dose wearing off effect and levodopa-induced dyskinesias are related-therapy side effects over time and also constitute supporting criteria of PD diagnosis[2,8].

However, other neurotransmitters such as acetylcholine, serotonin and norepinephrine may be altered in PD and this may both explain the refractoriness of some patients to dopaminergic therapy and be an inspiration for future therapeutic approaches[1].

Despite therapy advances since PD was first described, unfortunately nowadays treatments remain only symptomatic and currently no disease modifying drugs are approved for clinical use to prevent or delay disease development and progression[1,2].

Current treatments for PD increase dopaminergic tone and are mainly focused to alleviate motor symptoms of the disease. However, their effectiveness is greater in the early stages of the disease and in the later stages of PD complications related to long-term symptomatic treatment are not infrequent[2].

Possible other therapeutic targets are currently under study and could target in the future also α-synuclein[16].

Certainly, the prodromal pre-motor phase of disease could be a potential and effective temporal window for future disease-modifying treatments[16].

Postural alterations in PD and Pisa syndrome

As mentioned above, PD is characterized by several motor and non-motor signs and symptoms[2] and abnormal or dystonic postures are especially associated with advanced stages[17]. Abnormal postures of limbs, neck and truck are seen in all parkinsonisms, mostly in multisystem atrophy (68.4%) but also in up to a third of patients with PD, mostly associated with disease severity and levodopa treatment[18]. Challenging to treat by medical, physical, or surgical therapy[17], they represent a critical determinant of the patients' quality of life as they produce pain or discomfort, reduce dexterity, increase falls and need of assistance. Perhaps the most relevant PD-related postural abnormality is the lateral deviation of the trunk, so called 'Pisa syndrome' (PS, also known as trunk dystonia or pleurothotonus) reminding the pendency of the famous tower in Pisa[19]. Differently from

scoliosis, that is the main differential diagnosis of PS, a structural curve with axial vertebral rotation is not evidenced by radiological examination, and trunk deviation resolves when lying supine[20]

If the first cases of PS were described in patients treated with anti-psychotics[21], then PS has been reported in patients with dementia (including Alzheimer disease and dementia with Lewy bodies)[21], PD[21], atypical parkinsonisms[21], normal pressure hydrocephalus[21], subdural hematoma[21] and other neurodegenerative diseases[21]. In PD, PS has been associated with older age, longer disease history and more severe disease stages or aggressive PD phenotype[17,22]. More recently, PS has been identified in patients with PD after dopaminergic therapy modifications[18,21] or following complications of PD surgical treatment procedures[21].

A consensus on the PS diagnostic criteria has recently been published[23] fixing a lateral trunk inclination of at least 10° while standing or walking, that is reducible by passive mobilization and supine position.

Pathophysiology of Pisa syndrome

The pathophysiology of PS is still debated. Two not-mutually exclusive pathophysiological mechanisms are advocated: i) a central mechanism related to a biochemical (dopamine/acetylcholine) and hemispheric unbalance leading to a trunk dystonia; ii) a peripheral mechanism related to pathological changes and fibrosis of paraspinal muscles, ligaments and bones, as well as a possible dystonic hypothesis[22].

A central nervous system (CNS) hypothesis suggests an asymmetric functioning of the basal ganglia circuitry[20,24]. This dopaminergic-nigrostriatal hypothesis seems to be supported by cases of PS onset after exposure to neuroleptics or following changes in the dopaminergic drugs dose[21]. However, although most patients lean towards the less affected side of the body (i.e. towards the more denervated striatum), 30% of patients lean towards the other side and some patients have trunk deviation even without clear striatal functional asymmetry[20]. Those few cases investigated with DaT-SPECT showed conflicting data between the expected reduction of striatal DaT specific-to-non-

displaceable binding ratio (SBR) and the tendency to lean either toward or away from the most affected striatum[25]. Furthermore, Hung et al. described a case with left lateral trunk flexion in which DaT-SPECT revealed predominant SBR reduction in the right putamen while brain perfusion SPECT showed relative hypoperfusion in large cortical areas, mainly in the left hemisphere[26]. These conflicting data therefore suggest that this hypothesis might not consistently explain the pathogenesis of PS in all patients[20].

Another CNS hypothesis points to an abnormal sensorimotor integration of somatoesthetic stimuli associated with dysfunction of the visual and vestibular system[20,21,27]. Some postural studies[28] demonstrated an alteration of the perception of verticality sense, probably coexisting with visual and vestibular dysfunction and a slower visual processing[29]. These aspects suggest a possible alteration of the body schema representation, supporting a central recognition hypothesis[20]. In fact, some patients perceive themselves as leaning toward the contralateral side once they have been brought back to axis with respect to their original trunk deviation[30]. However, the cause-effect relationship between trunk deviation and an altered sense of verticality remains to be clarified[20]. Also, some authors hypothesized that cognitive impairment may contribute to misperception of the body schema[20], as impairment in specific cognitive domains, e.g., visual-spatial and attention, were reported in PD patients with PS[21].

The peripheral hypothesis is instead based on an alteration of the musculoskeletal system therefore responsible for the postural alteration[20]. Anyway, supporting data to this hypothesis are scarce and often conflicting.

Only a few neuropathological studies about musculoskeletal system have been carried out on patients with camptocornia. These studies have showed several myopathic alterations on muscle biopsy of the paraspinal muscles, although the cause-effect relationship between this type of alterations and chronic postural alteration is not clear[20].

The literature on neuropathology focused to PS is even more scarce. A few studies based on electromyography (EMG) of the paraspinal muscles have in fact shown no signs of denervation or myopathy (except for 2 out of 26 patients in a single study)[20].

Imaging studies of the paraspinal muscles are also rare. However, an early imaging study with Computed Tomography (CT) scan showed fatty degeneration of the lumbar paraspinal muscles, which was more pronounced on the side affected by deviation[20]. Another MRI study showed on the contrary bilateral atrophy of the lumbar paraspinal muscles[20]. Muscle atrophy in this case is not associated with the deviation affected side, but seems more pronounced in the less active muscles on EMG[20]. Nevertheless, muscle atrophy is a process that gradually develops over time and could more easily be a consequence of a chronic postural alteration, rather than its cause[20]. Muscle atrophy is also clearly incompatible as a possible cause of postural alteration in terms of time of onset in cases of rapid onset of PS such as after therapeutic changes or surgical treatment of PD[20].

A dystonic hypothesis also exists[20]. However, EMG data do not seem to be conclusive in this case either, as there are studies with contradictory results and not always comparable from a methodological point of view. Furthermore, semiology of PS is not totally suggestive of dystonia[20]. In PS in fact posture is static and sensory tricks are missing as well as the phenomena of overflow, antagonistic gesture, twisting or twitching. Also, there is no aggravation with movement. Furthermore, unlike typical dystonias, patients are often unaware of their postural deviation and above all they do not feel pain at the onset of trunk deviation[20]. Considering all of this, PS pathophysiology seems to be more easily related both to an altered sensory-motor integration and proprioception[20]. Therefore, according to current knowledge, peripheral alterations do not seem to play a primary causal role in the genesis of PS[20].

Given the uncertainty about the pathophysiology of PS and following the CNS dysregulation hypotheses we analyzed DaT-SPECT and FDG-PET data of a cohort of PD patients developing PS. Our aim was to explore whether a peculiar pattern of nigrostriatal impairment and/or of gray matter metabolism characterize these patients, hence helping clarify the pathogenesis of the PS.

MATERIALS AND METHODS

Patients

We retrospectively selected 34 PD patients who developed PS (PS+ group) during the course of the disease, according to the definition of Doherty et al.[17] and fitting the recently published criteria[23]. There were 16 patients leaning toward the right body side ((r)PS+) and 18 leaning toward the left one ((l)PS+)(**Table 1**).

These patients were selected among a consecutive series of PD patients in the 2004-2020 period if they underwent DaT-SPECT and/or FDG-PET at the time of diagnosis or later and if they were followed-up with regular control visits at least yearly. The diagnosis of PD followed the Gelb criteria[31] for patients enrolled before 2015 and then those of the Movement Disorder Society (MDS)[8]. Patients underwent Magnetic Resonance Imaging (MRI) (or Computed Tomography if MRI was contraindicated) to exclude secondary parkinsonism. The presence of white matter hyperintensities was not an exclusion criterion if the Wahlund scale score was <2 in all regions. Motor impairment was scored with the MDS-UPDRS-III (in older cases assessed with the UPDRS, the correction factor +7 was added to approximate the MDS-UPDRS-III score[32]). Notably, time of PS onset was approximated by computing the time in the middle between the last visit without the PS and the visit when the PS was found. In three instances (*de novo* patients) the PS was already present at baseline. At the time of PS onset, six patients had developed PD dementia (PDD) (CDR >0.5 and MMSE <24/30) and five of them were taking AchEIs.

The main exclusion criteria were illiteracy; dementia according to the Clinical Dementia Rating and the Instrumental Activities of Daily Living (IADL)[33] scales; other neurological disorders; iatrogenic or systemic causes of cognitive impairment; history of major spinal surgery or muscle-skeletal diseases; other postural deformities; psychiatric disorders according to the DSM-V; chronic use of drugs potentially influencing trunk posture such as neuroleptics and AchEIs.

Eighteen patients performed both DaT-SPECT and FDG-PET, twelve patients performed only DaT-SPECT, and four patients only FDG-PET (**Table 2 and Figure 3**). Overall, twenty-six were *de novo*, drug-naïve PD patients and underwent DaT-SPECT and/or FDG-PET within six months from diagnosis for clinical and/or research purposes in the frame of previous studies[34,35]. Five patients performed DaT-SPECT 59.0±47.0 months after diagnosis (range 22-134) and five underwent FDG-PET 91.0±66.0 months after diagnosis (range 20-165) for research purposes, while on anti-parkinsonian treatment. Two of these ten patients performed both DaT-SPECT and FDG-PET. In summary, there were thirty patients in the DaT-SPECT group (16 in the (l)PS+ and 14 in the (r)PS+ subgroup, respectively) and twenty-two patients in the FDG-PET group (13 in the (l)PS+ and 9 in the (r)PS+ subgroup, respectively).

Figure 3. Flowchart of the analysis.

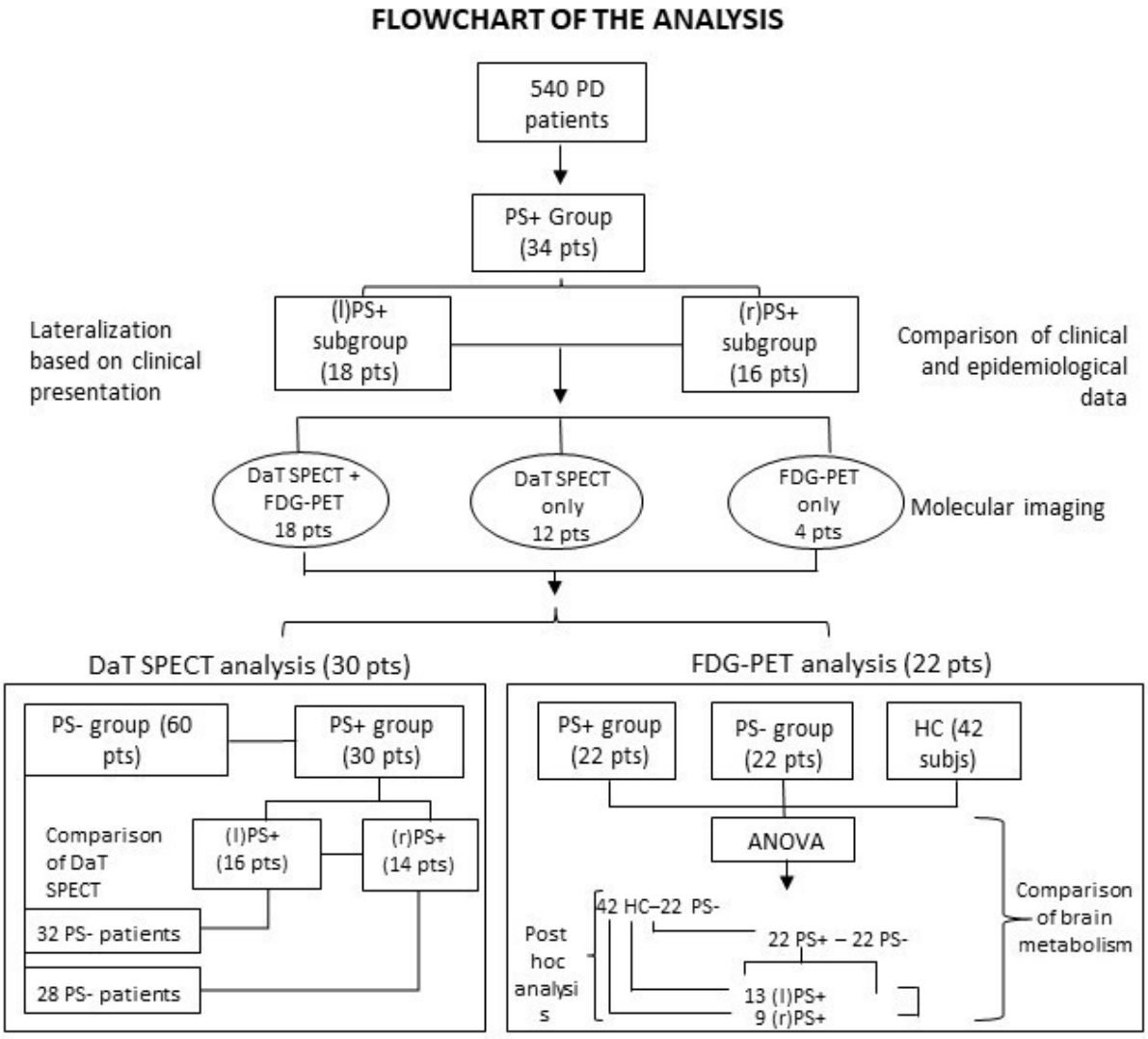


Figure legend: PS+ = patients with PD and the Pisa syndrome. (l)PS+ and (r)PS+ subgroups = PS+ patients leaning toward the left or the right side of the body; PS- DaT ctr = PD patients without PS undergoing DaT-SPECT; PS- PET ctr = PD patients without PS undergoing FDG-PET; HC = healthy control group for FDG-PET comparisons.

Control groups

To compare DaT-SPECT data of the 30 PS+ patients, we selected a group of 60 PD patients that never developed PS during the disease course (PS-, 50 *de novo,* drug-naïve; 38 males; age range 54-86 yrs, mean 71.2±6.7; MMSE score range 20-30, mean 27.8±2.3; education range 2-19 yrs, mean 10.6±3.9; MDS-UPDRS-III score range 8-38, mean 22.8±7.8). They were drawn from our database of PD patients undergoing DaT-SPECT in the same period of PS+ group for clinical and/or research purposes and selected with a case-control criterion (2:1 ratio) matching for age, MDS-UPDRS-III and MMSE scores (±3 for both scores) with PS+ patients and using the same exclusion criteria. Sex and education were matched with PS+ patients when possible and were not significantly different between the two groups (**Table 1**). The choice of using a control group of PD patients for DaT-SPECT comparison with PS+ patients instead a healthy control group derives from the notion that PD patients have an impaired DaT-SPECT by definition.

To compare FDG-PET data of the 22 PS+ patients, we included:

1) a control group (HC) of 42 healthy subjects matched for age, sex, and education with PS+ patients (28 females, age range 49-85 yrs, mean 69.6±8.5; education range 5-17 yers, mean 10.7±3.8; MMSE score range 27-30, mean 29.2±0.8). Their healthy condition was accurately checked in terms of medical history and clinical examination, they were cognitive unimpaired (CDR=0, MMSE score>26) and had a normal FDG-PET that was conducted in the frame of previous studies[36,37]. Exclusion criteria are listed elsewhere[36,37] along with detailed subject information and mainly include neurological or major psychiatric diseases, diabetes, uncontrolled arterial hypertension, anemia and malignancy.

2) A group of 22 PD patients without PS extracted from the sixty PS- patients previously described for DaT-SPECT comparisons, who underwent FDG-PET and who were in the same age, education, MMSE and MDS-UPDRS-III scores range (±3 for both scores) and had similar sex distribution of the 22 PS+ patients (10 females, age range 54-84 yrs, mean 71.9±6.2; education range

5-16, mean 9.5±3.1; MMSE score range 20-30, mean 28.0±2.1; MDS-UPDRS-III score range 10-35, mean 21.9±7.1).

Table 1. Main demographic and clinical data of 34 patients with PD and incident Pisa Syndrome (PS+), in the subgroups leaning to the left (l)PS+ or the right (r)PS+ side of the body, and of the control group of Parkinson Disease patients without incident Pisa Syndrome.

	PS+ all	(l)PS+	(r)PS+	PS-
Number	34	18	16	60
Gender	19 F/15 M	10 F/8 M	9 F/7 M	22 F/38 M
Age at PD diagnosis, years	69.41±8.23 (50-81)	70.44±7.87 (55-81)	68.25±8.73 (50-81)	71.2±6.7 (54-86)
Education, years	10.74±4.44 (2-17)	11.5±3.79 (5-17)	9.88±5.06 (2-17)	10.6±3.9 (2-19)
Duration of motor symptoms at PD diagnosis, months	13.97±13.76 (4-59)	14.0±14.56 (4-59)	13.94±13.27 (4-37)	14.8±10.8 (1-48)
MDS-UPDRS III score at baseline*	25.29±13.28 (7-82)	27.17±16.55 (8-82)	23.19±8.26 (7-35)	22.8±7.8 (8-38)
H&Y scale score at baseline	2.16±0.96 (1-5)	2.03±1.19 (1-5)	2.31±0.6 (1-3)	1.76±0.57 (1-3)
MMSE score at PD baseline	27.35±2.83 (20-30)	26.94±3.17 (20-30)	27.81±2.40 (22-30)	27.8±2.3 (20-30)
Time interval between baseline and PS onset, months	55.58±53.05 (0-182)	61.29±54.88 (0-176)	49.5±52.11 (1-182)	NA
Age at PS onset, years	73.97±5.56 (61-86)	75.22±5.49 (67-86)	72.56±5.46 (61-81)	NA
MMSE score at PS onset	26.56±4.23 (10-30)	26.33±3.69 (18-30)	26.81±4.87 (10-30)	NA
MDS-UPDRS III score at PS onset	26.53±14.27 (7-82)	29.27±18.59 (8-82)	24.50±8.52 (7-35)	NA
LEDD (mg/die) at PS onset	392.41±260.5 (0-1060)	398.56±300.5 (0-1060)	385.5±216.42 (0-860)	NA
Use of AchEIs at PS onset	5	4	1	NA

Table legend: Values are expressed as mean ± standard deviation (range). P value: not significant in all comparisons between left- and right-side PS subgroups or between baseline and the time of onset of PS. Use of AchEIs at PS onset: not significant (chi-square test). MDS-UPDRS= movement disorders society unified Parkinson's disease rating scale, part three; H&Y= Hoehn and Yahr; MMSE= mini-mental state examination; PS= Pisa syndrome; LEDD= levodopa equivalent dose; AchEIs= acetylcholinesterase inhibitors; NA= not applicable. *Baseline is the time of DaT SPECT and/or FDG-PET exam.

Table 2. Main demographic and clinical data in the subgroups of patients with PS (PS+) undergoing DaT-SPECT or FDG-PET divided into subgroups leaning to the left (l)PS+ or the right (r)PS+ side of the body.

DaT SPECT	**Total**	**(l)PS+**	**(r)PS+**
Number	30	16	14
Gender	18 F/12 M	9 F/ 7 M	9 F/5 M
Age at baseline, years	70.4±6.88 (57-81)	71.13±6.67 (57-80)	69.57±7.27 (57-81)
Education, years	10.93±4.56 (2-17)	12.0±3.64 (5-17)	9.9±5.39 (2-17)
MDS-UPDRS III score at baseline	23.17±7.68 (8-36)	22.6±8.18 (8-36)	23.8±7.32 (10-35)
HY score at baseline	2.02±0.79 (1-3)	1.72±0.82 (1-3)*	2.36±0.63 (1-3)
MMSE score at baseline	27.7±2.64 (20-30)	27.56±2.78 (20-30)	27.85±2.57 (24-30)
Duration of symptoms at PD diagnosis, months	14.0±13.58 (4-59)	15.0±14.53 (4-59)	12.0±12.64 (4-37)
Time interval between baseline and PS onset, months	52.47±51.19 (0-182)	52.13±49.38 (0-144)	52.86±55.06 (1-182)

Values are expressed as mean ± standard deviation (range). *$p<0.05$, the other comparisons are not significant between subgroups. Other abbreviations as in Table 1.

FDG-PET	**Total**	**(l)PS+**	**(r)PS+**
Number	22	13	9
Gender	13 F / 9 M	8 F/ 5 M	5 F / 4 M
Age at baseline, years	73.05±5.79 (57-81)	72.69±5.36 (57-81)	73.56±4.24 (62-81)
Education, years	10.32±4.58 (2-17)	11.15±4.43 (5-17)	9.11±4.78 (2-17)
MDS-UPDRS III score at baseline	25.73±15.72 (7-82)	27.15±19.10 (8-82)	23.67±9.66 (7-35)

HY score at baseline	2.07 ±1.14 (1-5)	1.88±1.36 (1-5)	2.33±0.71 (1-3)
MMSE at baseline	26.68±2.63 (22-30)	26.69±2.78 (22-30)	26.67±2.55 (22-30)
Duration of symptoms at PD diagnosis, months	15.64±12.01 (4-37)	12.69± 9.30 (4-25)	19.89±4.65 (4-37)
Time interval between baseline and PS onset, months	44.00±55.65 (0-182)	47.77±57.72 (0-176)	38.56±55.45 (1-182)

Values are expressed as mean ± standard deviation (range). *$p<0.05$, the other comparisons are not significant between subgroups. Other abbreviations as in Table 1.

DaT-SPECT image acquisition and reconstruction

Brain DaT-SPECT was acquired according to EANM guidelines[38] using a dual-head Millennium VG camera (GE Healthcare) equipped with low energy, high resolution, parallel-beam collimators. Patients were injected intravenously with about 185 MBq of ^{123}I-FP-CIT (DaTSCAN®, G.E. Healthcare, Little Chalfont, Buckinghamshire, UK) and after 180-240 minutes images were achieved. The exam lasted 40 minutes. We carried out a "step-and-shoot" protocol with a radius rotation lower than 15 cm, and we produced 120 projections evenly spaced over 360°. Total counts were comprised between 1.5 and 2.5 million. We utilized an electronic zoom (zoom factor = 1.8) during data collection to get an acquisition matrix's pixel size of 2.4 mm. Then we used a digital zoom during the reconstruction phase. Obtained images were sampled by cubic voxels (2.33 mm). We processed projections by applying an OSEM algorithm (8 interactions, 10 subsets) that included a proback pair accounting for collimator blur and photon attenuation, and then post-filtering (3-D Gaussian filter with full-width at half maximum 58 mm). Photon attenuation was modified with the approximation of a linear coefficient uniform inside the skull and equal to 0.11 cm^{-1}, and a 2D+1 approximation was put to use in the simulation of the space simulation blur. Scatter compensation was not performed.

Post-processing and quantification was performed with Basal Ganglia V2 software[39]. Background uptake was then subtracted by putamen or caudate uptake as follows: (putamen/caudate uptake—background uptake)/background uptake, to compute SBRs values. SBR values in the Caudate

(C) and the Putamen (P) of each hemisphere, the P/C ratio in each hemisphere, and the right/left asymmetries of both nuclei (right-left)/(right+left)*100[38] were employed in statistical analysis.

FDG-PET image acquisition and reconstruction

Brain FDG-PET was performed according to European Association of Nuclear Medicine's (EANM) guidelines[40]. To get blood glucose level <7.8 mmol/L, patients had to maintain a period of fasting of at least six hours before the exam. After glycemia check, patients were injected intravenously with 185 – 250 MBq of ^{18}F-FDG. Injection was performed after a 10 minute stay in a silent and obscured room in conditions of visual and auditory rest. After 45 minutes, PET scans were acquired, lasting ten minutes. We limited head movements using a policarbonate head holder. We got images using a Biograph Hi-rez PET/CT system (Siemens, Munich, Germany) with a 256×256 matrix in three-dimensional mode, a 16.2 cm axial field and a spatial resolution in plane of 5.8 mm full-width at half-maximum (FWHM). Attenuation correction was based on CT. Dicom image files were exported and transformed into the Analyze format to be preprocessed through MATLAB and the Statistical Parametric Mapping software (SPM 12; Wellcome Trust Center for Neuroimaging, London, UK). PET images were spatially normalized into a specific FDG-PET template in the Montreal Neurological Institute (MNI) stereotaxic space[41], and subsequently spatially smoothed using a 10-mm isotropic Gaussian filter.

Statistical analysis.

The flowchart summarizing analyses is shown in Figure 3.

Clinical and demographic variables were compared among groups and between (l)PS+ and (r)PS+ subgroups with each other using the t-test (or the Wilcoxon test for not normally distributed variables) or the chi-squared test for categorical variables.

DaT-SPECT comparisons.

We compared DaT-SPECT SBRs, P/C ratios and caudate and putamen asymmetries (Wilcoxon test) between: i) PS+ and the PS- groups (**Table 3a**); ii) (l)PS+ (16 patients) subgroup and a double number of patients (in this case 32) extracted from the sample of 60 PS- patients and matched for age, sex, MDS-UPDRS and MMSE scores with the (l)PS+ subgroup (**Table 3b**); iii) (r)PS+ (14 PD patients) subgroup and a double number of patients (in this case 28) extracted from the sample of 60 PS- patients and matched for age, sex, MDS-UPDRS and MMSE scores with the (r)PS+ subgroup (**Table 3c**); iv) (r)PS+ and (l)PS+ subgroups (**Table 3d**)".

Table 3a. DaT SPECT SBR comparison between PS+ group and 60 PS- controls.

	PS+ group	**PS- controls**	**p value**
Left Caudate	2.76±0.88	2.89±1.19	0.52
Left Putamen	1.14±0.61	1.27±0.61	0.3
Right Caudate	2.78±0.89	2.92±1.05	0.49
Right Putamen	1.27±0.59	1.36±0.66	0.5
Left P/C ratio	0.42±0.19	0.46±0.16	0.28
Right P/C ratio	0.47±0.19	0.48±0.19	0.84
Caudate asimmetry (percent; right-left)	-0.04±8.6	1.07±9.57	0.59
Putamen asimmetry (percent; right-left)	6.23±18.74	1.54±22.31	0.32

Table 3b. DaT SPECT SBR comparison between (l)PS+ subgroup (16 patients) and 32 PS- controls

	(l)PS+	PS- controls	p value
Left Caudate	2.88±1.08	2.82±1.06	0.98
Left Putamen	1.18±0.61	1.27±0.63	0.55
Right Caudate	2.88±1.02	2.86±0.99	0.88
Right Putamen	1.23±0.49	1.37±0.63	0.44
Left P/C ratio	0.41±0.16	0.47±0.16	0.26
Right P/C ratio	0.46±0.19	0.49±0.17	0.64
Caudate asimmetry (percent; right-left)	0.2±10.24	1.62±8.67	0.62
Putamen asimmetry (percent; right-left)	4.28±20.26	2.53±18.2	0.76

Table 3c. DaT SPECT SBR comparison between (r)PS+ subgroup (14 patients) and 28 PS- controls

	(r)PS+	PS- controls	p value
Left Caudate	2.63±0.59	2.98±1.33	0.36
Left Putamen	1.10±0.63	1.27±0.61	0.4
Right Caudate	2.66±0.72	2.99±1.14	0.41
Right Putamen	1.31±0.69	1.35±0.69	0.86
Left P/C ratio	0.43±0.24	0.45±0.17	0.68
Right P/C ratio	0.49±0.19	0.46±0.21	0.88
Caudate asimmetry (percent; right-left)	-0.3±6.63	0.45±10.63	0.81
Putamen asimmetry (percent; right-left)	8.46±17.3	0.41±26.54	0.31

Table 3d. DaT SPECT SBR comparison between (l)PS+ and (r)PS+ subgroups

	(l)PS+	(r)PS+	p value
Left Caudate	2.88±1.08	2.63±0.59	0.45
Left Putamen	1.18±0.61	1.10±0.63	0.72
Right Caudate	2.88±1.02	2.66±0.72	0.51
Right Putamen	1.23±0.49	1.31±0.69	0.7
Left P/C ratio	0.41±0.16	0.43±0.24	0.88
Right P/C ratio	0.46±0.19	0.49±0.19	0.66
Caudate asimmetry (percent; right-left)	0.2±10.24	-0.3±6.63	0.88
Putamen asimmetry (percent; right-left)	4.28±20.26	8.46±17.30	0.55

Caudate and Putamen asymmetry are calculated following the formula ((right-left)/(right+left))*100. Values are reported as mean ± SD. P: putamen, C: caudate. No significant difference in all comparisons

Brain FDG-PET comparisons.

In all the analyses (SPM-12), the standard gray matter threshold masking of 0.8 and the default value of 50 for the grand mean scaling were used. Only clusters of at least 50 voxels were considered. Age was used as the nuisance variable in all comparisons. One-way between subject analysis of variance (ANOVA) was used to compare brain metabolic differences among the PS+, PS- and HC groups. Then, post-hoc analyses were performed by direct comparison between couples of these three groups to unveil specific differences. Subsequently, the (r)PS+ (9 patients) and the (l)PS+ (13 patients) subgroups were compared directly one with the other and each of them with the HC group.

All two-group comparisons were made using two sample T-test. In all analyses, a $p<0.05$ family wise error (FWE)-corrected statistical threshold was applied both at voxel level and at cluster level. An uncorrected $p<0.001$ threshold at voxel level was explored in those comparisons failing to give significant results at $p<0.05$ FWE-corrected threshold. Cluster coordinates were then reported to the MNI space to identify the corresponding cerebral areas in accordance with the Brodmann classification by means of the Automated Anatomical Labeling software[42] implemented in SPM.

RESULTS

Demographic and clinical variables.

Comparison of clinical and demographic variables between (l)PS+ and (r)PS+ subgroups did not show statistically significant differences either in the whole of thirty-four patients (**Table 1**) or in the DaT-SPECT and FDG-PET subgroups (**Table 2**), with the only exception of the HY score in the DaT-SPECT subgroups where the (r)PS+ subgroup showed a higher score than the (l)PS+ one ($p=0.025$). Both the MMSE and the MDS-UPDRS scores slightly worsened when the PS appeared, without significant differences compared to baseline (**Table 1**).

DAT-SPECT comparisons.

No DaT-SPECT comparison yielded a significant difference. See **Tables 3a-d** for details.

Brain FDG-PET comparisons.

ANOVA among PS+, PS- and HC groups demonstrated a progressive metabolism decrease from HC to PS- and to PS+ groups in bilateral parietal and temporal regions predominantly focused in Brodmann areas (BA) 19, 37 and 39 (**Table 4a; Figure 4**). No areas of significant hypometabolism were found in the opposite direction, namely from PS+ to PS- and to HC.

In the post-hoc comparisons, a similar pattern of hypometabolism in bilateral temporo-parietal regions resulted significant in the PS+ group compared to HC (**Table 4b; Figure 5a**). In PS+ compared with PS-, a relative hypometabolism was distributed in bilateral posterior cingulate cortex (PCC) and in right middle temporal gyrus and precuneus, by using a less conservative threshold of uncorrected $p<0.001$ at voxel level (**Table 4e; Figure 6**). In the comparison between PS- and HC

groups we found no significant differences (hypometabolism in bilateral parieto-occipital regions was found only by lowering the height threshold to $p<0.02$; **Table 4f**).

Finally, in both the (r)PS+ and the (l)PS+ subgroup we found a significant relative hypometabolism than HC in the right middle temporal region (BA 39) (**Table 4c and 4d; Figure 5b and 5c**). Conversely, the comparison between these two subgroups yielded no significant result.

Table 4. Cluster's coordinates of significant FDG-PET comparisons. 4a) ANOVA among PS+ group, PS- group and HC (height threshold FWE-corrected p<0.05); **4b,4c,4d)** comparisons between PS+ group and HC, (r)PS+ group and HC and (l)PS+ group and HC, respectively (height threshold: FWE-corrected p<0.05); **4e)** comparison between PS+ group and PS- group (height threshold: uncorrected p<0.001); **4f)** comparison between PS- group and HC (height threshold: uncorrected p<0.02).

Comparison	Cluster level		Voxel level				
	Cluster extent	FWE-corrected p value	Lobe	Max Z score	Talairach coordinates	Cortical region	BA
4a-ANOVA (PS+ group, PS- group and HC)	848	0.000	R Parietal	5.06	50 -63 31	Angular Gy	39
			R Temporal	4.86	56 -59 9	Mid Temporal Gy	39
			R Temporal	4.84	56 -57 -7	Inf Temporal Gy	37
			R Temporal	4.74	41 -74 34	Angular Gy	39
	477	0.000	L Parietal	4.95	-50 -65 33	Angular Gy	39
			L Temporal	4.94	-37 -72 17	Mid Temporal Gy	39
			L Temporal	4.76	-39 -76 31	Angular Gy	39
			L Temporal	4.72	-37 -80 21	Mid Temporal Gy	19
	276	0.000	L Temporal	5.51	-57 -53 -9	Mid Temporal Gy	37
			L Occipital	4.98	-49 -65 -3	Inf Temporal Gy	37
4b-PS+ group compared with HC	943	0.000	R Temporal	5.43	39 -71 18	Mid Temporal Gy	39
			R Temporal	5.34	48 -63 32	Mid Temporal Gy	39
			R Temporal	5.07	56 -59 9	Mid Temporal Gy	39
			R Temporal	5.03	54 -61 12	Mid Temporal Gy	19
			R Temporal	4.76	39 -73 36	Mid Temporal Gy	19
			R Temporal	4.54	54 -50 36	Mid Temporal Gy	40
	342	0.000	L Temporal	5.00	-37 -71 19	Mid Temporal Gy	39
			L Parietal	4.89	-48 -68 29	Angular Gy	39
	51	0.005	L Temporal	4.95	-55 -55 -9	Mid Temporal Gy	37
4c-(r)PS+ group compared with HC	50	0.006	R Temporal	5.05	37 -69 15	Mid Temporal Gys	39
4d-(l)PS+ subgroup compared with HC	75	0.002	R Temporal	4.85	47 -61 32	Mid Temporal Gy	39
4e-PS+ group compared with PS- group	996	0.003	L Limbic	4.28	-13 -67 16	Post Cingulate	31
			R Occipital	4.19	17 -65 18	Precuneus	31
			L Limbic	3.33	-7 -53 6	Post Cingulate	30
			R Limbic	3.25	12 -55 8	Post Cingulate	30
			L Limbic	3.21	-2 -53 26	Cingulate Gyrus	31
	446	0.05	R Temporal	4.26	60 -61 12	Mid Temporal Gy	39
			R Temporal	3.64	45 -57 7	Mid Temporal Gy	39
4f- Relative hypometabolism in PS- group compared to HC	4325	0.006	L Occipital	3.41	-49 -65 -1	Inf Temporal Gy	37
			LOccipital	3.16	-38 -86 6	Mid Occipital Gy	19
			L Parietal	3.09	-33 -75 38	Precuneus	19
			L Temporal	3.06	-55 -53 -5	Mid Temporal Gy	37
			L Temporal	2.98	-47 -54 -18	Fusiform Gy	37
			L Temporal	2.75	-53 -38 -7	Mid Temporal Gy	20
			L Occipital	2.63	-18 -96 2	Cuneus	17
			L Occipital	2.55	-44 -65 14	Mid Temporal Gy	19
			R Occipital	2.51	4 -91 -10	Lingual Gy	18
			L Occipital	2.45	-5 -96 4	Cuneus	17
			R Occipital	2.34	19 -93 -6	Inf Occipital Gy	17
			L Occipital	2.28	-27 -80 12	Mid Occipital Gy	19
			L Temporal	2.17	-47 -37 -22	Fusiform Gyrus	36

Table legend: ANOVA: analysis of variance; BA: Brodmann Area; FWE: family wise error rate; Gy: gyrus; l/L: left; Mid: middle Inf: inferior; PS: Pisa syndrome; Post: posterior; r/R: right. PS+ group: 22 PD patients with Pisa syndrome; PS- group: 22 PD patients without Pisa syndrome; HC: 42 healthy controls.

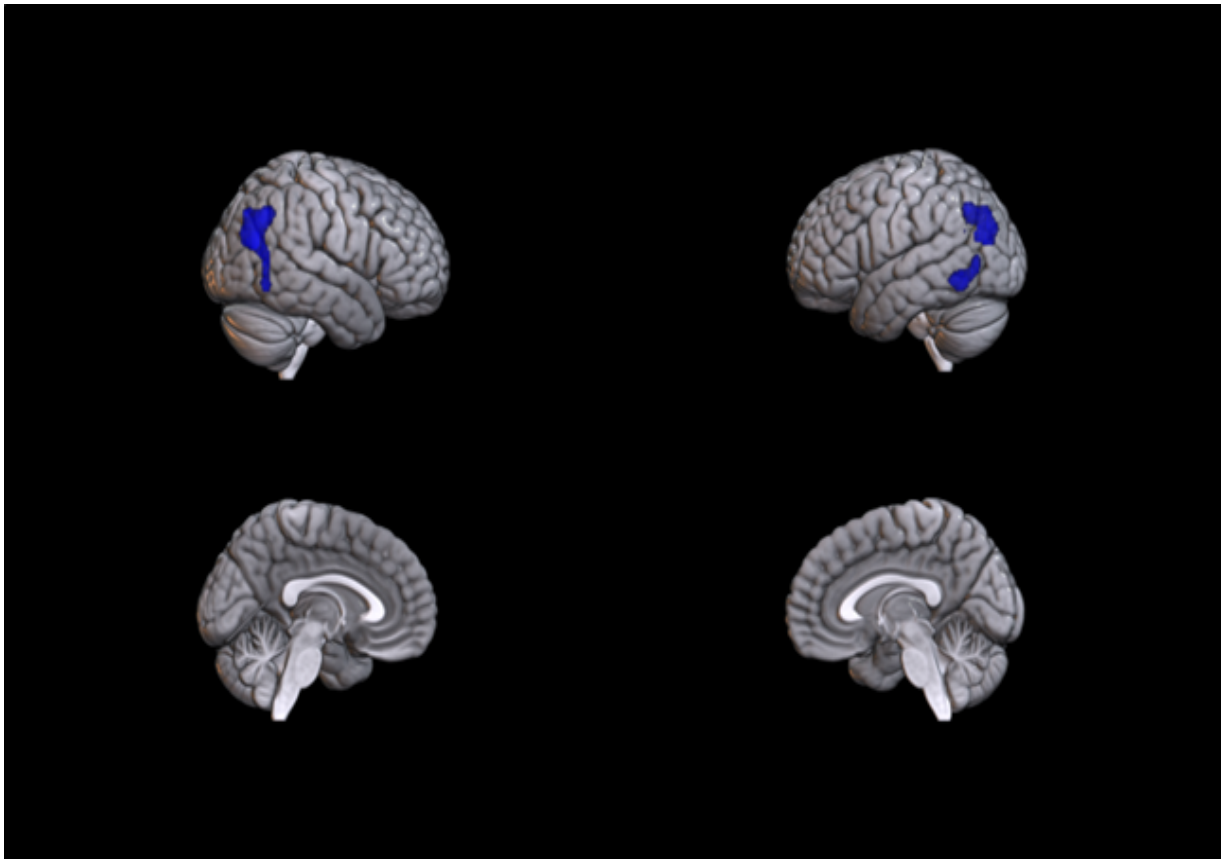


Figure 4. Relative hypometabolism on FDG-PET highlighted by ANOVA among HC, PS- and PS+ PET group. Relative hypometabolic areas are found in right and left parietal and temporal clusters predominantly focused in Brodmann areas 19, 37 and 39 (height threshold: family-wise corrected $p<0.05$). See **Table 4a** for coordinate details.

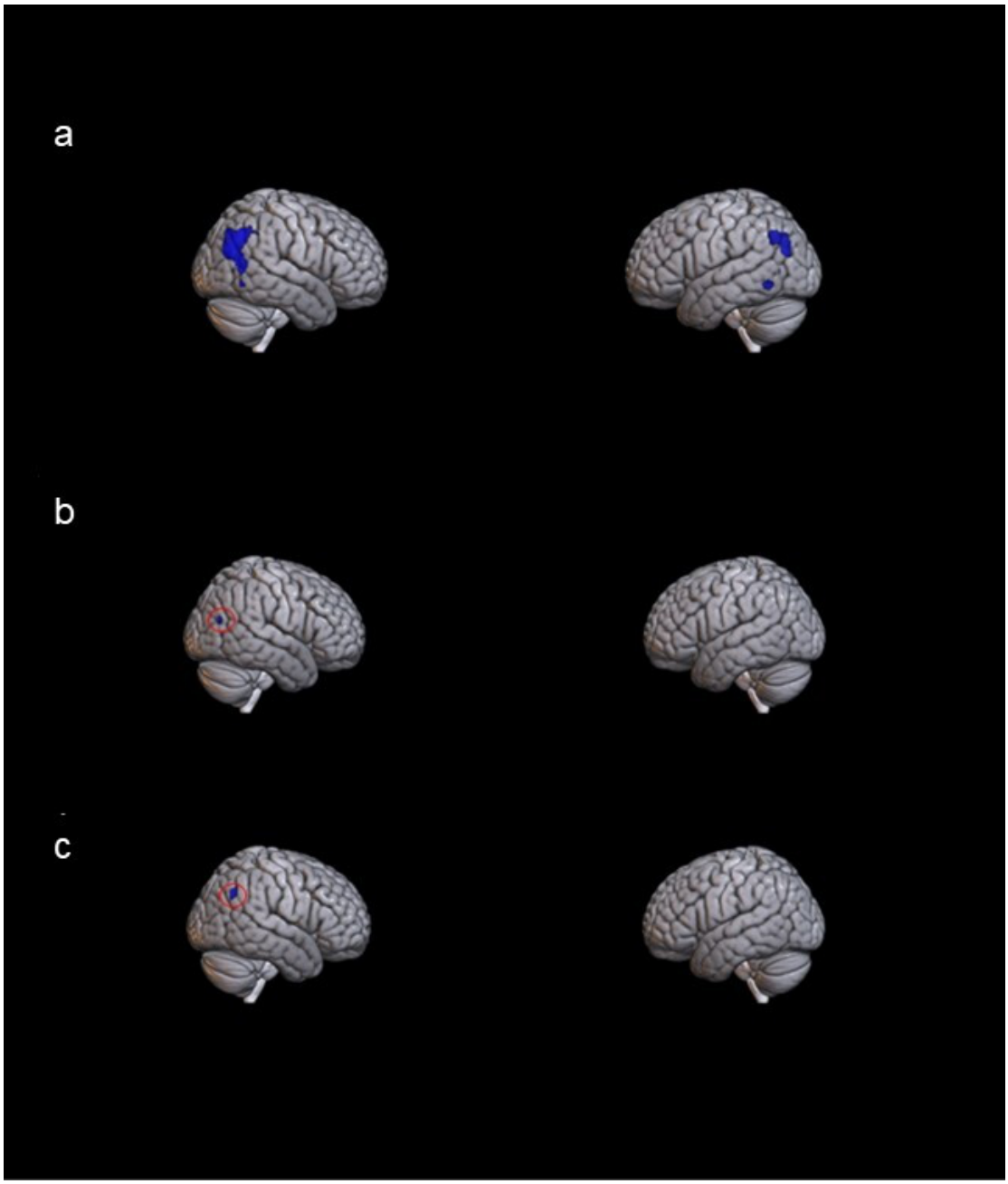


Figure 5. Relative hypometabolism on FDG-PET at post-hoc comparison between either total PS+ (Figure 5a), (r)PS+ (Figure 5b), (l)PS+ (Figure 5c) subgroups, and HC. When comparing the whole PS+ group with HC **(5a)**, relative hypometabolic areas are found in PS+ group in bilateral left and right temporal (more expressed on the right side), predominantly located in Brodmann areas 39, 19, 37 and 40 (height threshold: family-wise corrected $p<0.05$). In lateralized comparisons **(5b, 5c)** a relative hypometabolic area is found in a right hemispheric cluster predominantly located within Brodmann area 39 (height threshold: family-wise corrected $p<0.05$). The red circle highlights the area of significant difference in blue. See **Table 4b-d** for coordinate details.

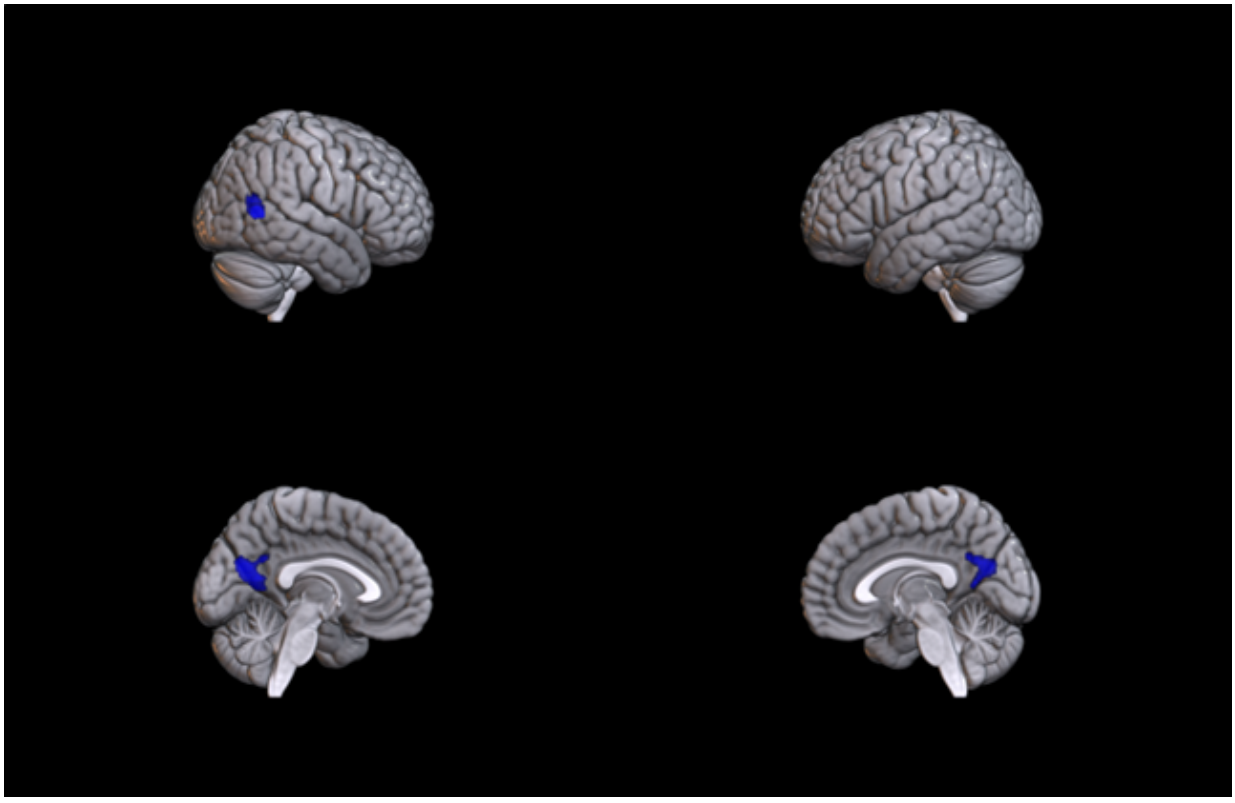


Figure 6. Regions of relative hypometabolism on FDG-PET highlighted by comparison between PS+ group and PS- controls. Relative hypometabolic areas are in left and right posterior cingulate gyri and in right temporal and occipital clusters predominantly located in Brodmann areas 30, 31 and 39 (height threshold: uncorrected $p<0.001$). See **Table 4e** for coordinate details.

DISCUSSION

Many theories on PS pathogenesis have been advanced, however the issue has not been solved yet. In this study, we explored whether some distinct alterations in the nigrostriatal dopaminergic function and/or brain metabolism collected mostly at the time of diagnosis were predictive of subsequent PS development. It appeared that while no significant differences were identified in nigro-striatal pathway function between PS+ and PS- patients, PS+ patients showed a peculiar relative brain hypometabolism in posterior temporal and parietal regions, including the right angular gyrus and the posterior cingulate cortex and the precuneus, mostly already in the early stages and years before PS developed. This alteration in brain metabolism may be one explanation of body schema impairment in Pisa syndrome.

Our results do not fit the nigrostriatal/dopaminergic pathophysiological hypothesis of PS that assumes a possible effect of consensual or non-consensual dopaminergic nigrostriatal deficit on the trunk inclination side. In fact, DaT-SPECT parameters were not significantly different in PS+ than PS- patients, even when considering the two subgroups divided by the trunk inclination side with respect to PS- or one with another. This is in line with the results of a large multicenter clinical study in 143 PD patients with PS where the direction of trunk inclination was unrelated to the clinical PD side[25], thus not confirming previous studies showing that patients with PS lean away from their dominant PD side [25]. Altogether these observations suggest that, in the best hypothesis, basal ganglia functional unbalance is not the only pathophysiologic mechanism to explain PS and points to other mechanisms. Also, from a clinical perspective, an asymmetric nigro-striatal functioning, even after a quantification, does not predict the development of a Pisa syndrome, in agreement with current literature data [5,9].

By exploring the potential predictive role of brain metabolism dysfunction, we found a significant relative hypometabolism in bilateral temporo-parietal regions (BA 19, 37, 39, and 40) in PS+ patients than healthy controls. Even more interestingly, both the subgroups with either left or right trunk inclination were hypometabolic in the right BA39 at temporal-parietal junction as compared to healthy controls. Hypometabolism in right BA39 was also highlighted in PS+ than PS-

patients along with bilateral PCC and right precuneus by lowering the statistical threshold to an uncorrected $p<0.001$.

Therefore, an alteration in the posterior network involving the right BA39 and precuneus, and the bilateral PCC, appears to be central in the Pisa syndrome pathophysiology. To notice, we found a persistence of lateralization of hypometabolism in right BA39 in each comparison involving PS+. Even if it is possible that this result is part of the Parkinson disease related pattern (PDRP), that includes a relative hypometabolism in the posterior brain regions[43], its appearance also when comparing PS+ with PS- (even if with a lower significance), is of interest. In fact, BA39 in the right hemisphere, together with BA40, has essentially gnosis and praxis functions as it is a hub of the network for symbolic recognition of perception by integrating tactile, kinesthetic, vestibular and visual sensations to provide a complete representation of the body in relation to the surrounding space[44]. These areas play a primary role in stereognosis, mental body representation (i.e., somatognosia), exploration and orientation of spatial relationships (gnosis for space), and planning of movements (praxis). Accordingly, functional neuroimaging studies have suggested a strong involvement of BA39 in attention mechanisms[44] , such as reorienting or shifting attention[45]. It is known that lesions of the right parietal association cortex led to relevant impairment of the internal body schema representation, considering that its activity is linked to the localization of the parts of the body[46]. This may explain why PD patients with PS are mostly unaware of their postural disorder, as they perceive themselves to be standing erect and feel as they are leaning on the contralateral side when posture is passively corrected[30]. Furthermore, Formaggio et al.[47] performed an EEG connectivity study and highlighted a critical parietal and occipital disconnection in PD, demonstrating an impaired sensory-motor integration and proprioception reflected by weakened connections between parietal and central areas. Nevertheless, it should be noticed that, when comparing PS+ with PS- patients, a relative hypometabolism also occurred in bilateral PCC, right precuneus and middle temporal gyrus. This finding suggests that a bigger network is involved in Pisa syndrome pathophysiology, that does not include only the right angular gyrus. This circuitry connects the region that is involved in body schema

perception (right angular gyrus)[44–46,48] with posterior regions involved in cognition in alpha-synucleinopathies (PCC and precuneus)[45,46].

Our results are in keeping with the hypothesis that PD patients with PS have an abnormal perception of their body pattern since they already show an impairment in the posterior circuitry that involves the right angular gyrus metabolism (specific area for body schema perception), PCC and precuneus (involved in cognition in alpha-synucleinopathies).

However, it remains unknown why some patients lean to the right and some others to the left side as we did not find any significant difference between the two subgroups and the right BA 39 was equally impaired in both. This may suggest that the pathogenesis of PS is multifactorial and that other factors than body schema disorder play a role at various levels. The role of AchEIs, claimed by some authors[49], does not seem a major player in our series as only 5 out of 34 patients took these drugs. As far as the role of cognitive impairment is concerned, here the topic seems more relevant. In fact, on the one hand only 6 out of our 34 PS patients had PDD at the time of PS onset (compared to 10 out of 60 in the PS- group, p=n.s.) and we selected a large cohort of PD control patients without PS, used for both DaT-SPECT and FDG-PET comparisons, with similar age and MMSE score as patients with PS. On the other hand, compared with PS- we also found hypometabolism of the PCC and precuneus in PS patients, standing for a more severe impairment of cognitive circuitry, not evidenced by the gross estimate of the MMSE and despite we matched the two PD groups for age, MMSE score and MDS-UPDRS score. This latter finding may suggest a trend toward a more severe cognitive impairment already at baseline, besides the specific involvement of gnosis regions in the right hemisphere impairment, since it is known that FDG-PET can unveil brain dysfunction well beyond the clinical appraisal. In fact, the PS- group compared to healthy controls yielded a relative hypometabolism in bilateral parieto-occipital regions only by lowering the statistical threshold to an uncorrected $p<0.02$, in agreement with the finding of milder hypometabolism in de novo PD patients with normal cognition[50].

A strength of our work is that we were able to study both nigrostriatal dopaminergic denervation and cortical metabolism in the same cohort to show peculiar impairment of brain

metabolism, but not of nigrostriatal function, prior of PS onset. The main limitation is that we were unable to repeat DaT-SPECT and FDG-PET measures at the time of PS onset. Although one can expect metabolic findings to be even more expressed as the disease worsen, this hinders to verify whether an unbalanced nigrostriatal function appeared together with the PS onset. Other limitations are the clinical diagnosis of PS without radiological exclusion of scoliosis. In fact, Doherty et al. reported that scoliosis is more common in PD than in the general elderly population, with a prevalence ranging from 8.4% to 90.5% in parkinsonism and from 8.5% to 60% in PD, but also those estimates lacked radiological confirmation[17]. We also lack the electrophysiological assessment of spinal muscles to investigate the dystonic hypothesis, as well as specific scales to evaluate body schema altered perception. Finally, the retrospective nature of the study with the consequence that eight out of 34 patients were not *de novo* drug-naïve PD at baseline, caused an unavoidable inhomogeneity in molecular imaging data in the PS+ group.

In conclusion, the finding of consistent hypometabolism of the right BA39 in the PS+ group, irrespective of trunk deviation lateralization, along with the altered metabolism in the PCC and precuneus area, support the hypothesis of an altered perception of body schema as part of the pathogenetic mechanism of PS. The involvement of PCC and precuneus underpin a role in cognition that probably further modulates this alteration. Such a functional impairment can be unveiled years before the onset of PS by means of FDG-PET while we could not give evidence to support the dopaminergic-nigrostriatal pathophysiological hypothesis.

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