Journal of the Neurological Sciences 351 (2015) 127–132

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Dopaminergic denervation is not necessary to induce gait disorders in atypical parkinsonian syndrome

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ARTICLE INFO

Article history:
Received 24 November 2014
Received in revised form 3 February 2015
Accepted 26 February 2015
Available online 7 March 2015

Keywords:
Gait disorders
Parkinsonian syndromes
Neuroimaging
Nigrostriatal pathways
[123I]FP-CIT SPECT
Dual task

ABSTRACT

Background: Gait impairment is common in parkinsonian syndromes but not specific to striatonigral dysfunction. The relationship between the dopaminergic system and gait parameters is poorly understood. This cross-sectional study aimed to determine if gait measures are related to the striatal dopamine transporters distribution using [123I]FP-CIT SPECT in patients with parkinsonian syndromes.
Materials and methods: Twenty-four patients with gait impairment and parkinsonian syndromes without Parkinson's disease (mean age: 73.6 ± 8.2 years) were included in this study. Gait analysis during single- and dual-task condition (walking and backwards counting) and [123I]FP-CIT SPECT were performed within 3 months of each other. Patients were visually categorized as having normal ($n = 14$) or abnormal ($n = 10$) [123I]FP-CIT SPECT. In addition, a volume-of-interest-based analysis of uptake ratios (caudate and putamen) relative to the occipital cortex and a voxelwise analysis using SPM8 were also performed.
Results: Patients with parkinsonian syndromes and abnormal [123I]FP-CIT SPECT did not significantly differ in terms of spatiotemporal gait parameters from those with normal [123I]FP-CIT SPECT. Moreover, after correction for multiple comparisons, we did not observe any association between regional uptake ratio and spatiotemporal gait parameters for single and dual tasking. Finally, none of these parameters showed a significant association with voxelwise [123I]FP-CIT uptake.
Conclusions: Dopaminergic denervation, as measured by [123I]FP-CIT SPECT, is not necessary to induce alterations of spatiotemporal gait parameters during single and dual task in patients presenting with atypical parkinsonian syndromes.

1. Introduction

Parkinsonism is very prevalent in neurodegenerative diseases and increases markedly with age affecting up to 52 % of people over age 85 years [1]. Gait disorders are common in parkinsonian syndrome (PS) but may be caused by other central or peripheral nervous system disorders [2,3]. Like other axial parkinsonian signs, gait disorders respond poorly to dopaminergic treatments in Parkinson's disease (PD), suggesting the implication of extra-dopaminergic lesions [4]. Positron emission tomography (PET) or single photon emission computerized tomography (SPECT) with ligands that label specific components of the dopaminergic nerve terminal can examine the role of the dopaminergic system in gait disorders. In healthy adults, dopaminergic physiology influences certain aspects of gait independent of age-related changes [5]. While previous data suggest a correlation between gait and 123I labelled -2b-carbomethoxy-3b-(4-iodophenyl)-N-(3-fluoropropyl)nortropane ([123I]FP-CIT) binding in PD [6,7], no study have looked for an association between quantitative gait parameters and [123I]FP-CIT binding in patients with PS without PD. The aim of this study was to search for an association between the striatal dopamine transporters distribution using [123I]FP-CIT SPECT and

Abbreviations: PS, Parkinsonian syndrome; PD, Parkinson's disease; PET, Positron emission tomography; SPECT, Single photon emission computerized tomography; [123I]FP-CIT, 123I labelled-2b-carbomethoxy-3b-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane; CV, Coefficient of variation; VOI, Voxel of interest; SPM, Statistical parametric mapping.

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http://dx.doi.org/10.1016/j.jns.2015.02.051
0022-510X/

quantitative gait parameters during walking at self selected speed and walking while backward counting in patients with PS without PD. We compared spatiotemporal gait parameters in patients with normal and pathological [^{123}I]FP-CIT SPECT, and we determined if there was an association between gait parameters and regional and voxelwise [^{123}I] FP-CIT distribution. We recruited only non-PD patients to be able to study a range of dopamine denervation in a distinct pattern from the classical PD picture.

2. Materials and methods

2.1. Patients

Twenty-four consecutive patients (7 women and 17 men) referred to the Department of Neurology at the Geneva University Hospitals with gait disorders and PS without PD who underwent a spatiotemporal gait analysis and a [^{123}I]FP-CIT SPECT with a maximum interval of 3 months were retrospectively included in this study. Patients were mobile and walked independently. All underwent a neurological and general examination by board-certified neurologists, confirming the presence of PS and that gait disorders were due solely to a central neurological disturbance (i.e., cerebellar, spinal, peripheral nervous system and systemic causes were excluded). The UK brain bank criteria were applied to define parkinsonian syndrome [8]. Mean age ± SD was 73.6 ± 8.2 years and was not statistically different between women and men (72.0 ± 3.1 and 74.2 ± 9.5 respectively; p = 0.55). Mean duration of gait difficulties was 22.3 ± 28.6 months. At the time of the study, all patients were drug naïve for neuroleptic and anti-parkinsonian medication or other medications affecting the dopaminergic system. Exclusion criteria included acute medical illness in the past 3 months, orthopedic or rheumatologic disorders interfering with gait, patient unable to walk a minimum of 15 m without a walking aid and not able to perform the dual-task evaluation (walking while backward counting). Patients were categorized as having normal ($n = 14$) or abnormal ($n = 10$) [^{123}I]FP-CIT SPECT. The categorization was performed independently by two expert readers (VG and ICM) who were blind to neurological diagnosis. The dichotomization in normal/abnormal imaging was based on visual assessment, supported by BRASS™ automated functional brain analysis software (Hermes BRASS software, Nuclear Diagnostics AB, Sweden). Briefly, BRASS fits and compares patients' images to a 3D reference template [9]. The data of 14 healthy controls are included in the software and provide a normal reference. For all abnormal cases, there was agreement of the visual interpretation by expert readers (V.G; I.C.M.) and of the automated analysis, i.e., [^{123}I]FP-CIT binding was below 2 standard deviation of the normative samples in at least one striatal region. The etiologies of the PS in the normal and the abnormal [^{123}I]FP-CIT SPECT groups are displayed in Table 1 and was performed after completion of clinical work-up, including morphological brain imaging and clinical follow-up. All patients had morphological brain imaging by CT or MR within 6 months from [^{123}I]FP-CIT SPECT data acquisition, which could assess the presence of vascular lesions involving the basal ganglia. In one patient a vascular lesion in the left caudate and putamen was associated with a significantly reduced [^{123}I]FP-CIT uptake on the same side. This retrospective study protocol was approved by the ethics committee of the Geneva University Hospitals.

2.2. [^{123}I]FP-CIT SPECT data acquisition

All patients received about 185 MBq of [^{123}I]FP-CIT by slow intravenous injection. Thyroid uptake was blocked before the scan by administration of Lugol solution (5 drops 5% KI administered before and 4 h after injection). SPECT data acquisition started 4 h after administration of the tracer. The scans were acquired on a triple-head gamma-camera (Toshiba Medical Systems, Tokyo, Japan) equipped with xfan-beam, low-energy, high-resolution collimators. In all cases, the head was fixed in a head-holder to minimize motion artefacts. Acquisition parameters included step-and-shoot mode over 30 min. Sixty projection angles were taken over 360 degrees and a 128 × 128 matrix was used. Reconstruction was performed by filtered backprojection using a Shepp and Logan filter, prefiltered by a fourth order Butterworth filter. The triple-energy window method was used for scatter compensation whereas a uniform Chang attenuation correction was used to compensate for photon attenuation using a uniform attenuation coefficient of 0.15 cm^{-1}.

2.3. Gait recordings

Gait recordings have been previously described in more details [10, 11]. Briefly, synchronized footswitches (AURION ZeroWire, Milan, Italy, sampling rate of 1000 Hz) and a seven-camera opto-electronic system (VICON Mx3+, Vicon Motion Systems, Oxford, UK, sampling rate of 100 Hz) were used for gait analysis. The 3D position of two reflective markers placed on the foot (on both heels and both 2nd metatarsals) and the temporal data of the footswitches were combined

Table 1
Clinical characteristics of subjects ($n = 24$).

	Normal [^{123}I]FP-CIT SPECT ($n = 14$)	Abnormal [^{123}I]FP-CIT SPECT ($n = 10$)	P-value[a]
Age (years)	75.8 ± 5.5	70.5 ± 10.4	0.46
Female (%)	42.9	10	0.09
Disease duration (months)	17.4 ± 13.3	29.2 ± 41.8	0.72
Comorbidities (n)	3.6 ± 1.3	2.8 ± 2.9	0.27
Treatments (n)	4.5 ± 2.6	3.7 ± 2.2	0.44
Psychoactive drugs (n)	1.0 ± 1.0	0.8 ± 1.0	0.57
Clinical diagnosis (n)			0.52
iNPH	2	3	
AD	1	0	
bvFTD	2	0	
PSP	0	1	
MSA	1	1	
MCI	1	0	
Vascular dementia	2	0	
CBD	1	2	
Progressive gait apraxia	1	1	
AD and iNPH	2	1	
PSP with subcortical leucoencephalopathy	0	1	
Mixed dementia (vascular dementia and AD)	1	0	

iNPH: idiopathic normal pressure hydrocephalus; AD: Alzheimer's disease; bvFTD: behavioral variant of frontotemporal degeneration; PSP: progressive supranuclear palsy; MSA: multiple system atrophy; MCI: mild cognitive impairment; CBD: corticobasal degeneration.
[a] Comparison based on Mann–Whitney test or Fisher exact test as appropriate.

to compute gait parameters including walking speed, stride length, cadence, stride time, step width and step height. These gait parameters were assessed during comfortable speed locomotion on a 10-m walkway in single-task and dual-task (backward counting aloud by subtracting serial 1 from 50) conditions in a random order. Before testing, a trained evaluator gave standardized verbal instructions on the test procedure. For dual-tasking, patients were asked to walk and to count backwards at the best of their capacity without any task prioritization.

2.4. Statistical analysis

Subjects' characteristics were described using means and standard deviations or frequencies and percentages, as appropriate. Comparisons between groups of subjects were performed using the Mann–Whitney test and chi-square test as appropriate. Spearman's correlation coefficients were used to assess relationships between outcomes. After correction for multiple comparisons according to Bonferroni, *P*-values less than 0.0125 were considered statistically significant (each gait parameters were correlated with 4 striatal regions—right/left caudate and right/left putamen). Post hoc power analysis with an alpha set at 0.05 and a power set at 80% were applied to compute the number of patients needed by group to reach a significant *P*-value when comparing the mean of the two groups using an unpaired *t* test. All statistics were performed using the Stata Statistical Software, version 12.1.

2.4.1. Volume-of-interest (VOI) analysis

[^{123}I]FP-CIT SPECT images were quantitatively analyzed using BRASS™, as mentioned earlier. This analysis takes the tomographic data, spatially registers them to a template in a standard space, and finds the count concentration in striatal (Cs) and background occipital (Cb) volumes-of-interest (an example is provided in Fig. 1). Using the activity concentrations in the volumes of interest, striatal uptake ratios defined as [(Cs − Cb)/Cb] of specific tracer binding are calculated. The template VOI sets were predefined in the BRASS software [12,13]. Uptake ratios measured for the caudate and the putamen, for the left and right hemisphere, relative to occipital activity, were taken as input variables.

2.4.2. Voxelwise statistical parametric mapping (SPM) analysis

In order to identify possible focal changes of [^{123}I]FP-CIT binding in subregions of the basal ganglia, we also performed a voxelwise SPM analysis. We obtained a customized [^{123}I]FP-CIT template, adopting the method validated by Kas et al. [14]. In brief, we first obtained a customized template on a subgroup of patients for whom a 3D T1 MRI was available. The MR images were spatially normalized to the reference space by the unified segmentation-normalization approach, as implemented in SPM8, which provides better and more reliable matching to a standard template than the commonly used alternatives [15]. Normalization parameters were then applied to the coregistered [^{123}I]FP-CIT images. These images were averaged, as previously described, in order to obtain a customized template, and subsequently all individual [^{123}I]FP-CIT images were spatially normalized to the template and smoothed with a Gaussian kernel of 10 mm full width at half maximum, as previously validated [14]. The spatial normalization was successful also in the cases showing radiological features of normal pressure hydrocephalus, as previously reported [16]. The customized template and exemplary individual normalized images are shown in Fig. 2. In Fig. 3, a normalized image of a patient with normal [^{123}I]FP-CIT SPECT and a patient with pathological [^{123}I]FP-CIT SPECT were illustrated. Linear regression analyses between parametric images and age and spatiotemporal gait parameters, limited to the striata by applying a binary mask, were performed, adopting activity normalization for the mean counts measured in the occipital cortex. *P*-values lower than 0.05 were considered statistically significant.

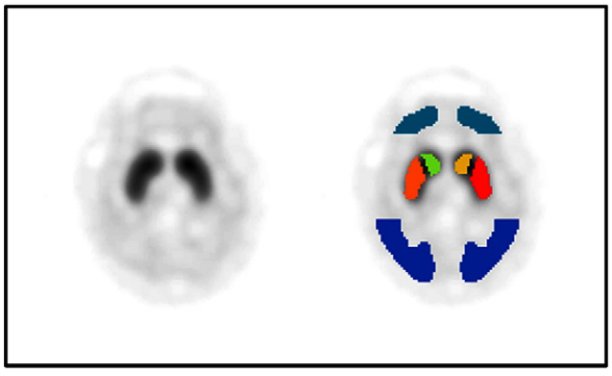

Fig. 1. The figure shows an example of a normal [^{123}I]FP-CIT SPECT study: on the left, the image, spatially normalized, on the right, the volume-of-interest (VOI) map of caudate, putamen, frontal and occipital regions implemented in the BRASS software, overlaid on the normalized image.

3. Results

Demographic and clinical characteristics are summarized in Table 1. Patients with normal and abnormal [^{123}I]FP-CIT SPECT were well matched in terms of demographics and baseline characteristics. Striatal uptake ratio was decreased in the abnormal [^{123}I]FP-CIT SPECT group. The normal and abnormal [^{123}I]FP-CIT SPECT groups showed the same spatiotemporal gait parameters without any differences in term of walking speed, stride and step time, stride and step length, step width and heel height for mean values, coefficients of variation and standard deviations of each parameter (Table 2).

Post hoc power analysis shows the large number of patients that would be needed to reach statistical significance for all gait parameters with the exception of step width for both tasks and step width CV for the dual task.

After correction for multiple comparisons, we did not observe any correlation between striatal uptake ratios and age or spatiotemporal gait parameters for single and dual task (Table 3).

Voxelwise analyses showed an inverse correlation between age and [^{123}I]FP-CIT relative uptake, normalized to the occipital uptake, bilaterally in the medial caudate confirming previous data [17,18]. This was introduced as confounding variable in all linear regression analyses with spatiotemporal gait parameters. No significant association was found between any spatiotemporal gait parameter in single and dual task and [^{123}I]FP-CIT relative uptake in the 24 patients, as well as in each individual group (i.e., patients with normal [^{123}I]FP-CIT SPECT and with abnormal [^{123}I]FP-CIT SPECT).

4. Discussion

In the current study, we evaluated the relationship between the dopaminergic system and spatiotemporal gait parameters in patients with various atypical PS using dopamine transporter distribution and availability with [^{123}I]FP-CIT SPECT. Spatiotemporal gait parameters during single and dual walking task were similar in the patients with normal and abnormal [^{123}I]FP-CIT SPECT. Furthermore, [^{123}I]FP-CIT relative uptakes were not associated with any spatiotemporal gait parameters in single and dual tasking. These data suggest that the dopaminergic denervation is not necessary to alter gait parameters in atypical PS.

Several studies have investigated the relationship between [^{123}I]FP-CIT binding and parkinsonian motor impairment. In normal aging, the nigrostriatal denervation presents an average age-related decline of 5.5% per decade [18]. This physiological denervation may contribute to the common occurrence of subtle parkinsonian motor symptoms with aging [19]. Our study confirms this inverse correlation between age and [123I]FP-CIT striatal uptake. This relationship between [^{123}I]FP-CIT

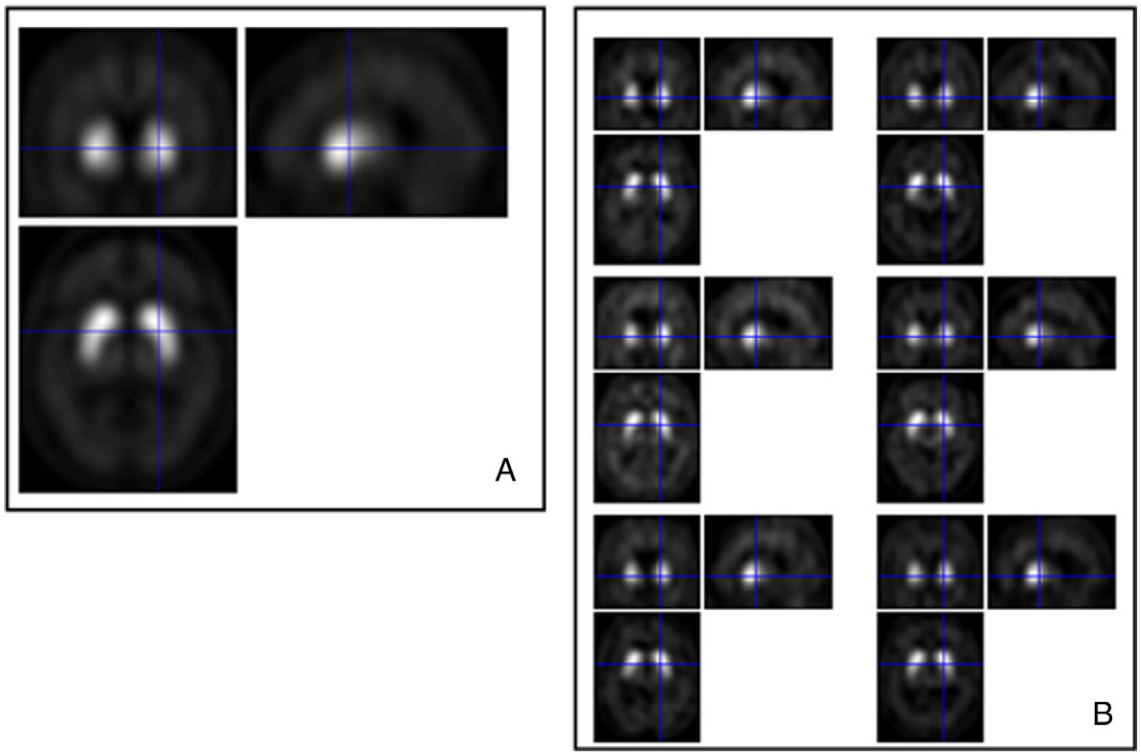

Fig. 2. The figure shows the customized [^{123}I]FP-CIT template obtained (panel A) and 6 examples of individual [^{123}I]FP-CIT SPECT images spatially normalized to the template (panel B).

binding and motor impairment has been mainly studied in the model of PD. Bradykinesia shows a significant inverse correlation with striatal [^{123}I]FP-CIT binding [4,6,7]. Some studies found also the same inverse correlation for rigidity [6,20]. For gait disorders, some previous reports suggested that in PD, progressive supranuclear palsy and multiple systemic atrophy, gait and posture signs correlate with [^{123}I]FP-CIT binding [7,21]. However, cholinergic but not dopaminergic denervation was associated with the measure of gait speed in non-demented PD patients, suggesting a close relationship between the control of gait and the cholinergic system [22]. These apparent contradictory results may be related to the methods used to assess gait. Except for the Bohnen's study [22], whose the results are in line with our study, the assessment of gait in the previous studies was performed on the items of the Unified Parkinson's Disease Rating Scale (UPDRS), which is a clinical scale designed to follow the longitudinal course of PD. Gait is only assessed using a 5 point scale ranging from normal gait to impaired

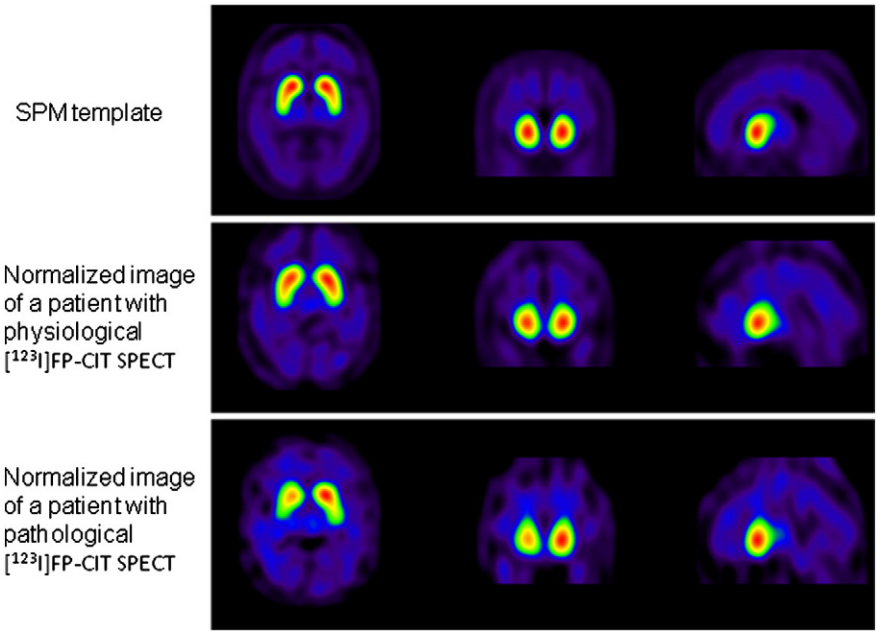

Fig. 3. The figure shows the normalized image of two patients on the SPM template (first raw): one with a physiological [^{123}I]FP-CIT SPECT (second raw) and one with a pathological [^{123}I] FP-CIT SPECT (third raw).

Table 2
Gait performance of subjects ($n = 24$) and comparison between normal and abnormal [^{123}I]FP-CIT SPECT.

	Normal ($n = 14$)	Abnormal ($n = 10$)	*P*-value[a]	Power *N*[b]
Single task				
Gait speed (m/s)	0.68 ± 0.29	0.73 ± 0.38	0.81	583
Stride time (s)	1.28 ± 0.21	1.27 ± 0.28	0.60	23478
CV (%)	3.73 ± 1.96	3.57 ± 2.44	0.60	3120
Stride length (m)	0.82 ± 0.31	0.85 ± 0.37	0.86	1900
CV (%)	7.25 ± 6.52	5.21 ± 4.91	0.24	126
Step width (m)	0.09 ± 0.04	0.12 ± 0.05	0.27	51
CV (%)	31.2 ± 23.6	18.5 ± 12.1	0.20	35
Step height (m)	0.16 ± 0.05	0.18 ± 0.06	0.38	108
CV (%)	6.42 ± 4.63	6.96 ± 6.60	0.91	1785
Dual task[c]				
Gait speed (m/s)	0.53 ± 0.26	0.57 ± 0.32	0.81	877
Stride time (s)	1.47 ± 0.30	1.41 ± 0.38	0.73	494
CV (%)	6.80 ± 3.60	6.30 ± 3.93	0.56	889
Stride length (m)	0.73 ± 0.32	0.72 ± 0.35	0.95	16410
CV (%)	9.32 ± 7.88	9.54 ± 6.64	0.68	17792
Step width (m)	0.11 ± 0.04	0.11 ± 0.05	0.81	3319
CV (%)	24.4 ± 16.5	16.7 ± 8.23	0.32	46
Step height (m)	0.15 ± 0.05	0.16 ± 0.06	0.64	234
CV (%)	9.16 ± 6.65	7.95 ± 7.59	0.52	547

CV: coefficient of variation (= 100 x standard deviation/mean).
[a] Comparison based on Mann–Whitney test.
[b] Power *N* indicates the number of patients needed by group to reach a significant *P*-value with an alpha set at 0.05 and a power set at 80%.
[c] Gait while backward counting,

mobility. In the present study, we compared quantitative spatiotemporal gait parameters with [^{123}I]FP-CIT binding.

Positron emission tomography has been used to determine the cerebral regions involving during mental imagery of walking. Malouin et al. [23] showed that the involvement of multiple cortical regions involving supplementary motor area was required during the imagination of gait. Recently, brain networks activated during mental imagery of gait were studied using functional MRI (fMRI). Converging results showed that networks involving bilateral primary motor cortex, supplemental motor area, prefrontal regions and cerebellum are recruited during mental imagery of gait [24–27]. Others functional imaging techniques, such as near-infrared spectroscopy, were also used to highlight the role of the prefrontal regions in the preparation and execution of actual walking [28,29]. These converging results suggest that a cortical network is implicated in the imagery of walking and not the basal ganglia. This cortical network involved in mental imagery of gait could in part explain this absence of association between gait parameters and [^{123}I]FP-CIT binding. Cortical pathology occurs in all parkinsonian disorders, including PD and likely contributes to gait impairment [30].

With these results, we cannot exclude that [^{123}I]FP-CIT binding plays a role in motor impairment when the nigrostriatal pathway is involved, given that our population includes patients with mixed etiologies: however, our data are in line with previous evidence showing that gait is modulated by an extended network and that the basal ganglia dopaminergic dysfunction is not associated with distinctive features. The strength of our study was that we used a transnosological and not a diagnostic-based approach in patients with gait impairment and various atypical PS affecting the nigrostriatal pathways and the cerebral cortex.

The main limitation of our study was that our patients did not have autopsy-confirmed diagnoses. Our relatively small sample size also necessitates caution, but the study is relatively underpowered only for step width for both tasks and step width CV for the dual task. Our data provide information to plan future studies. However, to the best of our knowledge, there are no previous published data showing a relationship between spatiotemporal gait parameters and [^{123}I]FP-CIT uptake.

5. Conclusion

In patients with atypical PS, dopaminergic denervation, assessed by [^{123}I]FP-CIT binding, was not necessary to alter spatiotemporal gait

Table 3
Correlations[a] between gait parameters and [^{123}I]FP-CIT SPECT normalized striatal binding in all participants ($n = 24$), in abnormal [^{123}I]FP-CIT SPECT ($n = 10$), and normal [^{123}I]FP-CIT SPECT ($n = 14$).

	All participants ($n = 24$)				Abnormal [^{123}I]FP-CIT SPECT ($n = 10$)				Normal [^{123}I]FP-CIT SPECT ($n = 14$)			
	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen
Single task												
Gait speed	−0.22	−0.07	−0.32	−0.30	−0.44	−0.15	−0.62	−0.48	−0.07	0.09	0.03	−0.15
Stride time	0.10	0.08	0.24	0.28	−0.08	−0.03	0.22	0.19	0.14	0.05	0.03	0.14
CV	0.13	−0.16	0.12	0.09	0.10	−0.12	0.30	0.19	0.20	−0.16	0.09	0.10
Stride length	−0.23	−0.06	−0.26	−0.24	−0.59	−0.31	−0.62	−0.52	−0.09	0.14	0.10	−0.09
CV	0.33	0.10	0.15	0.20	0.59	0.20	0.46	0.24	0.12	−0.09	−0.20	−0.01
Step width	−0.25	−0.35	−0.26	−0.13	−0.26	−0.25	−0.18	−0.21	−0.08	−0.24	−0.23	0.07
CV	0.14	0.22	0.15	0.09	0.21	0.33	−0.09	0.27	−0.05	0.06	0.18	−0.16
Step height	−0.31	−0.18	−0.41**	−0.38	−0.46	−0.21	−0.59	−0.48	−0.19	0.00	−0.08	−0.22
CV	0.11	0.03	0.13	0.17	−0.03	−0.07	0.19	0.12	0.24	0.02	0.06	0.23
Dual task[b]												
Gait speed	−0.10	0.03	−0.17	−0.22	−0.30	−0.07	−0.69**	−0.36	0.13	0.30	0.29	−0.02
Stride time	−0.24	−0.15	−0.02	0.01	−0.25	−0.13	0.15	−0.07	−0.56**	−0.42	−0.29	0.01
CV	−0.03	−0.19	−0.06	0.01	−0.12	−0.29	−0.03	−0.29	−0.34	−0.41	−0.27	−0.12
Stride length	−0.15	0.01	−0.21	−0.21	−0.50	−0.24	−0.69**	−0.47	0.01	0.15	0.08	−0.15
CV	−0.04	−0.11	0.02	0.10	0.07	−0.19	0.14	0.07	0.00	−0.02	0.05	0.31
Step width	−0.07	−0.27	−0.08	0.01	0.03	−0.03	−0.02	−0.06	−0.28	−0.53	−0.40	−0.17
CV	0.11	0.31	0.13	0.07	−0.67**	−0.29	−0.66**	−0.62	0.31	0.49	0.53	0.31
Step height	−0.26	−0.11	−0.33	−0.31	−0.42	−0.12	−0.72**	−0.39	−0.10	0.06	0.02	−0.21
CV	0.10	−0.05	0.27	0.25	0.38	0.02	0.67**	0.31	−0.26	−0.32	−0.11	0.04

[a] Spearman correlation coefficient.
[b] Gait while backward counting.
* Significant correlation after correction for multiple comparisons ($p < 0.0125$).
** Significant correlation without correction for multiple comparisons ($p < 0.05$).
CV: coefficient of variation (= 100 x standard deviation/mean).

parameters in single and in dual tasking. In addition to the understanding of the neural basis of gait disorders, these findings suggest a non-dopaminergic approach to improve gait disorders in patients with atypical parkinsonian syndromes. A further approach needs to examine the role of the dopaminergic system with spatiotemporal gait parameters in patients with de novo PD naive for anti-parkinsonian therapy.

Funding

Gilles Allali was supported by the Geneva University Hospitals (PRD 11-I-3 and PRD 12-2013-I) and the Baasch-Medicus Foundation. Frédéric Assal was supported by the Société Académique de Genève (Fonds Cognitive Memory NAC 08-025) and the Swiss National Science Foundation (grant no. 320030-138163/1). The sponsors have no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest

None.

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