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Short communication

Impulse control disorder in PD: A lateralized monoaminergic frontostriatal disconnection syndrome?

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ABSTRACT

Background: Impulse Control Disorder symptoms (ICD) in Parkinson's disease (PD) has been recently associated by magnetic Resonance imaging with impaired cortico-striatal connectivity, especially between left putamen and frontal associative areas.
Methods: 84 patients entered the study (21 PD-ICD+ and 64 PD-ICD-) and underwent DATSCAN imaging. The striatal tracer uptake was evaluated using BRASS software (Hermes, Sweden). The whole-brain analysis was performed with Statistical Parametric Mapping (SPM).
Results: PD-ICD+ showed a significant reduction of left putaminal and left inferior frontal gyrus tracer uptake compared to PD-ICD-. Functional covariance analysis using left putamen as the seed point showed that, in contrast to ICD-patients, ICD+ patients had no functional covariance with contralateral basal ganglia and ipsilateral cingulate cortex, as index of an impaired inter- and intra-hemispheric dopamine binding in PD-ICD+.
Discussion: the results support and expand the concept of a functional disconnection syndrome linked to ICD symptoms in PD patients through an asymmetric molecular frontostriatal network breakdown with left basal ganglia as central hub.

1. Introduction

Impulse Control Disorders symptoms (ICDs) are under the label of psychiatric disturbances with loss of voluntary control of impulses and repetitive behaviors to an extent that interferes in major areas of life functioning, like gambling, compulsive eating, compulsive shopping and hypersexuality [1]. In Parkinson's disease (PD) ICD symptoms prevalence is significantly higher in patients who are on dopamine agonists (DAs) treatment. However only a subset of these patients will develop ICD symptoms, suggesting other modulating factors [1,2]. Previous studies pointed out that striatal dopaminergic deficits appeared to be more severe in PD patients presenting with ICD symptoms (PD-ICD+) [3]. Moreover, the pattern of striatal and extrastriatal dopaminergic fibers degeneration might be different in PD patients with and without ICD symptoms [4,5]. Furthermore, the study of Carriere et al. [6] highlighted the role of impaired functional connectivity between striatal and cortical regions in PD-ICD+ and suggested an important contribution of inhibitory cortical regions in ICD symptoms development. These findings prompted the present study, aiming at evaluating the dysregulation of striatal dopaminergic and monoaminergic mesolimbic pathways in PD-ICD+ using single photon emission tomography (SPECT) and ^{123}I-FP-CIT (N-ω -fluoropropyl-2β-carbomethoxy-3β-(4-^{123}I -iodophenyl)nortropane (^{123}I-ioflupane)) (DaTscan®, GE Healthcare). Striatal FP-CIT binding is related to nigrostriatal neurons integrity and could be evaluated with

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different techniques such as BRASS software or SPM. On one hand, BRASS consists in a semi-quantitative analysis of the striatal region compared to a background (occipital) region, normalizing all images to a standardized [123I]FP-CIT template derived from healthy subjects. On the other, SPM analyses are able to directly compared the whole brain binding between different groups of subjects, as well as to perform other type of statistics like multiple regression analysis or second-level analysis like functional covariance analysis. We thus first evaluated the differences in striatal dopaminergic binding with these two methods in a large series of PD patients with and without ICD symptoms.

Extrastriatal FP-CIT binding provides information about monoaminergic afferents (mainly dopaminergic but also serotoninergic) to cortical regions, in particular anterior cingulate and frontal cortex [7]. Thus, by an exploratory approach, we analyze extrastriatal DAT binding and pattern of covariance of related brain regions in the two groups in order to better elucidate the pathophysiology of ICD symptoms.

2. Methods

2.1. Subjects

Consecutive patients with a PD diagnosis according to UK Parkinson's disease Society Brain Bank clinical criteria [8] and supported by at least one-year follow-up were recruited from the Neurology Unit, University of Brescia, Italy. All individuals underwent routine laboratory analyses and brain structural Magnetic Resonance Imaging. A standardized neurological examination was performed, including the Unified Parkinson Disease Rating Scale (UPDRS-III), Mini Mental State Examination (MMSE) and Hoehn and Yahr staging. ICD symptoms were evaluated with Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) [9] considering the published cut-off for each ICD symptom.

Patients with history of alcohol or drug abuse were excluded from the study. All PD patients were receiving regular dopaminergic therapy and levodopa equivalent daily dose (LEDD) was calculated (Table 1). Written informed consent from the subject was obtained for each procedure. The research protocol has been approved by the Ethics Committee of the Brescia Hospital, Brescia, Italy.

2.2. SPECT imaging

Intravenous administration of 110–185 MBq of ^{123}I-FP-CIT was performed 30 min after thyroid blockade (800 mg of KClO4) in all subjects. Taking into account that SERT blockers (like Selective Serotonine Reuptake Inhibitors, SSRI) may influence [123I]FP-CIT binding ratios (especially for sertraline) leading to increases of striatal to occipital ratios of approximately 10%, antidepressant therapy, if present, was suspended three weeks before the assessment. Brain SPECT was performed using a dual-head gamma-camera (Infinia Hawkey, GE Healthcare Ltd) calibrated with 159 KeV photopeak and ±10% energy window. Rotational radius was minimized (<16 cm). 120 projections over 360° (40 s/view) were acquired using a step-and-shoot protocol at 3° interval with the camera heads following a circular orbit (matrix size 128 × 128; zoom 1.1) resulting in 43 min of total scan time (Total counts 1.8–3 x10^6). Data were reconstructed by filtered backprojection, with a Butterworth 3-dimensional (3D) post-filter (order = 10.0; cut-off 0.50 cycle/cm) and corrected for attenuation (Chang's method, 0.12/cm^{-1}). BRASS™ software (BRASS, Brain Registration & Analysis Software Suite, Hermes Medical Solutions, Stockholm, Sweden; http://www.hermesmedical.com/products/hybrid-nm-processing/brass.html) was used for region-of–interest (ROI) analysis of striatal regions. A single ROI over the occipital lobe provides the background uptake area, and specific ratios for each caudate/putamen were calculated. Whole-brain voxelwise analysis was performed using Statistical Parametric Mapping (SPM8 Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/), using a ^{123}I-FP-CIT template from 30 healthy controls [10]. Individual ^{123}I-FP-CIT data were realigned, spatially transformed to template in Montreal Neurological Institute space and smoothed (3D Gaussian filter with 8 mm Full Width at Half Maximum). Each voxel value of each scan was normalized to the mean value within the occipital cortex. The statistical threshold was $p < 0.005$ uncorrected for multiple comparisons, cluster threshold = 60 voxels. PD-ICD+ versus PD-ICD- for both approaches (BRASS and whole-brain SPM) was performed using covariance analysis adjusted for age, gender, disease duration and clinical phenotype (tremor vs akinetic-rigid type). In order to assess inter- and intra-hemispheric connectivity according to the presence of ICD symptoms, analysis of functional covariance was finally performed. Significant clusters from SPM analysis (PD-ICD+<PD-ICD-) were used as ROI, calculating mean DAT binding in each subject. Correlation analyses for each ROI with whole-brain voxelwise DAT binding were performed in both groups.

2.3. Statistical analysis

Demographic and clinical characteristics comparison between groups (PD-ICD+ vs PD-ICD-) were assessed by Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables, significance level was set at $p < 0.05$. The data were analyzed using IBM SPSS Statistics 22.0 for Windows.

3. Results

Table 1 showed demographic and clinical characteristics of patients according to the presence of ICD symptoms. PD-ICD- and PD-ICD+ did not differ for age, gender, disease duration, motor and cognitive impairment. PD-ICD+ presented a significant higher use of dopamine agonist and total LEDD without a significantly different dopamine-agonist dosage. The more frequent types of ICD symptoms were compulsive eating (n = 12), pathological gambling (n = 7), hypersexuality (n = 6); punding/hobbyism (n = 2), overlapping in seven patients. Dopamine Dysregulation Syndrome (DDS) was presented by three patients in combination with other ICD symptom and isolated in one subject. No gender effect has been observed in ICD symptoms prevalence.

BRASS analysis adjusted for age, gender, disease duration and clinical phenotype showed a significant reduction in left putaminal binding in PD-ICD+ versus PD-ICD- (1.20 ± 0.50 vs 0.95 ± 0.48; p 0.046, corrected for age at onset, gender, disease duration and clinical phenotype). SPM analysis (Fig. 1A-B) confirmed the left putamen involvement (x,y,z: −30, −4, 10; T = 3.03, 138 voxels), with further reduced binding in the left inferior frontal gyrus (x,y,z: −22, 10, −14; T = 3.32, 69 voxels) in PD-ICD+.

Considering left putamen as seed point (Fig. 1C–D), PD-ICD- showed a positive functional association with the contralateral basal ganglia (x,y,z: 30, −6, 10; T = 4.59, 1563 voxels) and cingulate gyrus (x,y,z: −12, 6, 44; T = 4.73, 507 voxels) whereas in PD-ICD+ local correlation with left putamen (x,y,z: −30, 4, 4; T = 4.51, 1592 voxels) and cingulate gyrus (x,y,z: −2, 26, 28; T = 3.77, 128 voxels) were evident.

4. Discussion

In the present work we confirmed the involvement of striatal