



# Markers of impaired motor and cognitive volition in Parkinson's disease: Correlates of dopamine dysregulation syndrome, impulse control disorder, and dyskinesias

Jared T. Hinkle <sup>a, b</sup>, Kate Perepezko <sup>b</sup>, Liana S. Rosenthal <sup>c, d</sup>, Kelly A. Mills <sup>c, d</sup>, Alexander Pantelyat <sup>c, d</sup>, Zoltan Mari <sup>c, d</sup>, Laura Tochen <sup>e</sup>, Jee Yun Bang <sup>d</sup>, Medha Gudavalli <sup>d</sup>, Nadine Yoritomo <sup>d</sup>, Ankur Butala <sup>d</sup>, Catherine C. Bakker <sup>c</sup>, Vanessa Johnson <sup>d</sup>, Emile Moukheiber <sup>d</sup>, Ted M. Dawson <sup>c, d, f, g, h</sup>, Gregory M. Pontone <sup>b, c, d, \*</sup>

<sup>a</sup> Medical Scientist Training Program, Johns Hopkins University School of Medicine, Baltimore, MD, United States

<sup>b</sup> Dept. of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States

<sup>c</sup> Morris K. Udall Parkinson's Disease Research Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States

<sup>d</sup> Dept. of Neurology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer 6-181, Baltimore, MD, United States

<sup>e</sup> Dept. of Neurology, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC, United States

<sup>f</sup> Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, United States

<sup>g</sup> Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States

<sup>h</sup> Dept. of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States

## ARTICLE INFO

### Article history:

Received 1 June 2017

Received in revised form

16 October 2017

Accepted 18 November 2017

### Keywords:

Parkinson's disease

Dyskinesias

Dopamine Dysregulation Syndrome

DDS

Impulse control disorders

ICD

Hallucinations

Depression

Motor subtypes

## ABSTRACT

**Introduction:** Dopaminergic therapy in Parkinson's disease (PD) can be associated with both motoric (e.g., dyskinesias) and neuropsychiatric adverse effects. Examples of the latter include Dopamine Dysregulation Syndrome (DDS) and impulse control disorder (ICD), which are separate but related behavioral/psychiatric complications of treatment in PD. Dysregulation of volition characterizes both dyskinesias and DDS/ICD; thus, we analyzed potential disease-related correlates in a large PD cohort.

**Methods:** We analyzed cross-sectional data from 654 participants collected through the NINDS Parkinson's Disease Biomarkers Program. DDS/ICD symptoms and dyskinesias were assessed using the Movement Disorders Society (revised) Unified Parkinson's Disease Rating Scale. Potential associated variables were selected from PD-validated or PD-specific scales of neuropsychiatric or motoric status. Multivariable models with DDS/ICD or dyskinesia presence outcomes were produced with backward stepwise regression to identify factors independently associated with DDS/ICD and/or dyskinesias.

**Results:** Fifty-three (8.1%) participants endorsed DDS and/or ICD symptoms and 150 (22.9%) were dyskinetic. In multivariable analysis, psychosis was independently associated with both dyskinesias ( $p = 0.006$ ) and DDS/ICD ( $p < 0.001$ ). Unpredictable motor fluctuations ( $p = 0.026$ ) and depression ( $p = 0.023$ ) were also associated with DDS/ICD; female sex ( $p = 0.025$ ), low tremor score ( $p = 0.001$ ) and high akinesia-rigidity score ( $p < 0.001$ ) were associated with dyskinesias.

**Conclusions:** Our findings suggest that psychosis may be an important marker of impaired volition across motor and cognitive domains. Unpredictable motor fluctuations, psychosis, and depression may together comprise a phenotypic profile of patients at increased risk for DDS/ICD. Similarly, dyskinetic PD patients should be closely monitored for psychotic symptoms and treated appropriately.

© 2017 Elsevier Ltd. All rights reserved.

## 1. Introduction

Parkinson's disease (PD) is characterized by progressive deterioration of both motor and cognitive function. Dopamine (DA)

\* Corresponding author. 600 N. Wolfe Street, Phipps Suite 300, Baltimore, MD 21287, United States.

E-mail address: [gpontone@jhmi.edu](mailto:gpontone@jhmi.edu) (G.M. Pontone).

replacement therapy can alleviate most motor symptoms, but tends to be complicated by a variety of unintended effects. Half of levodopa-treated PD patients develop dyskinesias within 6 years of initiation, although recent evidence demonstrates that duration of levodopa exposure is less relevant to dyskinesia onset than disease duration itself [1]. DA is a key modulator of motivation, impulsivity, and reward-oriented behavior [2]; thus, medications that facilitate DA neurotransmission can modify action selection in PD.

DA medications can engender a range of compulsive abnormalities related to negative reinforcement dysfunction, habit formation, incentive sensitization, and impulsivity, including multiple specific behaviors: (1) abuse of DA medications (DDS); (2) impulse control disorder (ICD) behaviors (excessive gambling or shopping, hypersexuality, hyperphagia, and kleptomania); and (3) punding [2,3]. The pathophysiology of DDS is unclear; potential positive reinforcement mechanisms include increased novelty-seeking and incentive sensitization [3]. Aversion to the “off” state may also predispose to excessive medication usage [4]. The relative preservation of DA neurons in the ventral tegmental area—compared to the substantia nigra—may facilitate DDS and ICD by enabling hyperdopaminergic neurotransmission in the mesolimbic system [5]. Recent evidence has also highlighted the significance of impaired cognitive volition in PD patients with ICDs [6]. Due to commonalities between DDS and ICD more generally, the Movement Disorders Society’s (revised) Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) assesses both using a single item (Part 1, question 6).

At a broader level, there is conceptual similarity between behavioral disorders marked by impaired cognitive volition (such as ICD and likely DDS) and involuntary bodily movements like dyskinesias. It has been proposed that these phenomena occupy a continuum of pathophysiologically similar mechanisms relating to topographically distinct basal ganglia circuits [7]. Hypersensitization of dorsal striatum neurons receiving coincident input from glutamatergic and nigrostriatal DA projections—in the context of pulsatile DA receptor stimulation—remains the current paradigm for dyskinesia etiology [8]. For DDS and ICD, the focus is shifted to mesocorticolimbic projections and the ventral striatum as the site of hyperdopaminergic dysregulation. Activity in signaling cascades that are implicated in substance use disorders—such as the ERK and DARPP-32/PPP1R1B pathways—are also altered in dyskinetic patients, suggesting molecular overlap between altered reward-processing and dyskinesias [7]. Similar considerations inspired a recent study demonstrating that PD patients with moderate to severe dyskinesias—assessed by the Unified Dyskinesia Rating Scale—more frequently had ICDs or related behaviors (such as DDS, hobbyism, and punding) than patients with only mild dyskinesias [9].

We hypothesized that dyskinesias may share similar markers with DDS and ICD given the analogous impairment of volition and similarities in theoretical origins (hyperdopaminergic dysregulation). Shared clinical associations would strengthen the hypothesis of shared or parallel etiologies. To test this hypothesis, we performed a risk-factor analysis for potential neuropsychiatric and/or motoric markers of dyskinesias and DDS/ICD.

## 2. Methods

**Database and Participants:** Data were extracted from the NINDS Parkinson’s Disease Biomarker Program (PDBP) dataset on December 28, 2016. Baseline data from participants enrolled in the PDBP study at seven academic centers in the United States were used in the present study. Each participating center’s local IRB has approved the PDBP protocol and all participants provided informed consent.

Participant data were extracted for analysis only if a diagnosis of “probable or possible idiopathic Parkinson’s disease” was made per UK Brain Bank criteria [10]. Other inclusion criteria were complete demographic and medication information and complete data for the following PD-validated or PD-specific scales: MDS-UPDRS; the 17 item Hamilton Depression Rating Scale (HAM-D); the 14 item Hamilton Anxiety Rating Scale (HAM-A); and the Montreal Cognitive Assessment (MoCA). Additionally, patients with a MoCA score  $\leq 17$  were excluded to remove participants with probable dementia [11].

**Measures:** **Supplementary Table 1** provides an overview of components from the MDS-UPDRS utilized in the present study. The primary outcome variables of interest were MDS-UPDRS question 1.6—which assesses the impact of DDS and/or ICD symptoms on patient and caregiver/family life, scored using a Likert scale of 0–4—and the presence of dyskinesias, assessed using Part-IV (complications of therapy) of the MDS-UPDRS. Dyskinesias were deemed present if a patient reported a score of  $\geq 1$  on Q4.1, which assesses the daily duration of dyskinesias.

To determine the presence of clinically significant anxiety and depression, we used PD-validated cutoffs for the HAM-A ( $>11$ ) and HAM-D ( $>9$ ) [12,13]. Medication data were used to calculate Levodopa Equivalent Daily Dosage (LEDD, mg/day) per convention [14]. LEDD from DA agonists was recorded separately (“DA-LEDD”) and not included in the total LEDD; these were independent measures. Akinesia-rigidity (AR) and tremor motor impairment scores were calculated based on updated methodology for the MDS-UPDRS Motor Examination; however, rather than dividing mean AR score by mean tremor score to derive subtype classification, we utilized these mean scores separately for regression analysis to standardize and facilitate interpretation of odds ratios [15].

**Statistics:** We used univariable methods to characterize differences among participants grouped by DDS/ICD and dyskinesia presence, including Kruskal-Wallis (nonparametric ANOVA) tests for continuous or ordinal data and Fisher’s exact tests for nominal data (Table 2). For regression, the distributions of the primary outcome variables (MDS-UPDRS questions 1.6 for DDS/ICD, 4.1 for dyskinesias) were first evaluated. As they did not follow either a Poisson or a normal distribution, we dichotomized them as binary variables, such that any response  $\geq 1$  was scored as 1. LEDD values (mg/day) were divided by 100 in regression to improve interpretation of odds ratios. For all regression analyses, the MDS-UPDRS items assessing DDS/ICD and psychotic symptoms were treated as binary variables ( $\geq 1$  scored as 1) due to the low prevalence of scores over 1.

We used backward stepwise logistic regression to identify independent variables for multivariable modeling. Sixteen of the variables in Table 2—all except age to avoid collinearity—were included for the DDS/ICD outcome model, plus a variable measuring the sum of the two dyskinesia items of the MDS-UPDRS IV (daily duration and functional impact of dyskinesias; q4.1 and 4.2 respectively). These seventeen variables were included in a logistic regression (with binary DDS/ICD scores as the outcome variable), which was then subjected to backward stepwise variable removal guided by corrected Akaike’s information criterion (AICc). In parallel, a model for stepwise input with dyskinesia presence as the outcome variable was constructed, using the same variables, except with the DDS/ICD item substituting for the dyskinesia predictor. No measures of motor fluctuations were included, as fluctuations are intrinsic to certain classes of dyskinesias that are not differentiated by the MDS-UPDRS [16]. Each model also included an interaction term between AR motor score and disease duration to account for the observation that conversion to the AR phenotype over time is typical in PD [17]. An interaction term between LEDD and disease

Download English Version:

<https://daneshyari.com/en/article/8285543>

Download Persian Version:

<https://daneshyari.com/article/8285543>

[Daneshyari.com](https://daneshyari.com)