Baseline Neuroimaging Characteristics of the Parkinson's Progression Marker Initiative (PPMI) Parkinsons and Healthy Cohorts

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ABSTRACT

Original abstract, additional data in poster

Objectives: The Parkinson's Progression marker initiative (PPMI) is a multicenter, international, longitudinal study evaluating clinical, biochemical, and imaging measures of Parkinson's disease(PD) progression. Features of PPMI include; 1) incorporation of dopamine transporter (DAT) SPECT to confirm the presence or absence of a DAT deficit for enrolled PD and healthy volunteers, respectively, 2) rigorous standardized acquisition protocols, and 3) central core lab reconstruction of raw projection data for subsequent uniform analyses. The objective of this study is to report baseline quantitative SPECT data in PD and healthy volunteers.
Methods: In this on-going study, baseline 123-I Ioflupane SPECT scans from 20 imaging centers included 146 parkinson's subjects, 109 healthy controls, and 8 subjects without evidence of dopaminergic deficit (SWEDD) initially recruited as potential parkinson's subjects. Data were centrally reconstructed, attenuation corrected, and analyzed with a standardized volume of interest template for extraction of regional count densities in the left and right caudate and putamen. Striatal binding ratios (SBR) were calculated using the occipital lobe reference region. Average SBRs, lowest putamenal SBR, left-right percent asymmetry, and caudate:putamen ratios were determined and compared across the three cohorts.
Results: PD, healthy volunteers (HV), and SWEDD subjects had a mean age of 61.7±9.7 y, 58.4 ±12.5 y, and 62.2 ± 12.4 y, respectively. PD subjects had an average disease duration of 8.2 ± 7.8 months and total UPDRS score of 32.7 ± 12.6. Mean average SBR were lower in PD (1.0 ± 0.3) than healthy volunteers (1.7 ± 0.4). Both left-right asymmetry indices and caudate:putamen ratios were higher in PD vs HV. SWEDDs were indistinguishable from HV on all quantitative SBR measures. Linear regression of SBR as function of age in HV showed reduction of 5.0% /decade.
Conclusions: Quantitative DAT SPECT imaging data acquired at baseline in PD and healthy volunteers demonstrate expected cohort differences in this multicenter trial with values consistent with previously reported single center 123-I Ioflupane SPECT studies. Longitudinal data are pending.

INTRODUCTION

- **PPMI is an observational multi-center study to assess progression of clinical features, imaging and biologic biomarkers in Parkinson's patients and healthy controls**
- **PPMI is a five-year natural history study of *de novo* idiopathic PD patients and healthy controls**
- **Subjects are assessed at baseline and every 3-6 months thereafter**
  - **Clinical assessments: motor, neuropsychiatric and cognitive**
  - **Imaging assessment (dopamine transporter imaging, MRI)**
  - **Biologics collected: blood, CSF, urine and DNA**
- **Clinical, imaging and biological data and samples collected under standardized protocols and analyzed, stored at core facilities, and made available to the investigator community**
- **Screening dopamine transporter imaging is required to be abnormal in all PD subjects and normal in controls**
- **Biological samples will be used for verification of promising biomarkers.**

Study synopsis

Study population	400 de novo PD subjects (newly diagnosed and unmedicated) 200 age- and gender-matched healthy controls Subjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	• Motor assessments • Neuropsychiatric/cognitive testing • Olfaction • DaTSCAN imaging, structural MRI,DTI
Biologic collection/ Verification studies	• DNA collected at baseline • Blood collected at each visit; CSF collected at 6mo and then annually • Samples aliquoted and stored in central biorepository • Lead biologic candidates to be tested: alpha-synuclein, DJ-1, urate
PD treatment	• De novo for 6 months • Can participate in clinical trials after 12 months

PPMI Study Sites

Northwestern
IND- New Haven
Johns Hopkins
Federico II - Naples
Parkinson's Institute- Sunnyvale
Univ Pennsylvania
Univ Rochester
APDC- Sun City, AZ
Baylor Univ
Univ Alabama-Birmingham
Boston University
Boca Raton, FL
London
UC San Diego
Cleveland Clinic
Univ Cincinnati
Portland
Innsbruck
Marburg
Tübingen
Univ Washington
USF, Tampa
Emory Univ
Sydney

METHODS

123-I Ioflupane SPECT Standardization and Quantitative Analysis

1. **Each imaging center underwent a technical visit to establish a dual energy window (123-I and 57-Co) acquisition protocol, tested on an anthropomorphic 123-I striatal phantom and 57-Co phantom (Fig.1)**
2. **Central SPECT Core lab performed reconstruction from raw projection data, including attenuation correction based on phantoms acquired during the site visit**
3. **Spatial normalization of image performed for consistent orientation**
4. **Apply standard volume of interest template on caudate, putamen, occipital regions**
5. **Extract count densities and calculate Striatal Binding Ratios (SBR) = (striatal region)/(occipital) -1 from 4 h post-injection 123-I Ioflupane image**
6. **57Co Phantom acquired each day a subject is imaged, phantom based correction of SBRs possible**

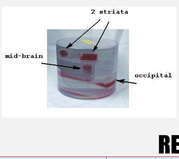


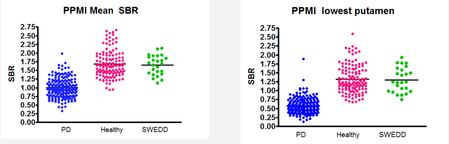
Fig. 1 57Co calibration striatal phantom is acquired each day a PPMI subject is imaged to provide an on-going calibration of the SPECT tomograph and permit correction of SBR data

RESULTS

	Parkinson's	Healthy Volunteers	SWEDDS*
N	146	129	25
Age	62.1 (9.6)	57.9 (12.8)	62.2 (12.4)
Gender (% male)	69%	57%	60%
UPDRS Total	32.7 (12.6)	N/A	27.7 (16.4)
Disease Duration (mo)	8.2 (7.8)	N/A	8.7 (8.8)
Mean SBR	1.00 (0.27)	1.69 (0.38)	1.66 (0.28)
Lowest putamen SBR	0.58 (0.22)	1.33 (0.39)	1.31 (0.34)

* Recruited as PD subject, but scan is without evidence of dopaminergic deficit

Fig. 2 DAT SPECT Striatal Binding Ratios-Baseline Scans



P< 0.0001 for PD vs Healthy and PD vs SWEDD on both SBR measures, no statistical differences between Healthy and SWEDD subjects

Fig. 3 SBR signal loss is 6.2% per Decade in Healthy Volunteers

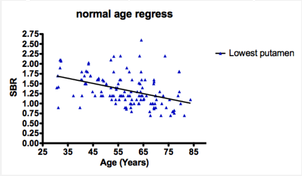


Fig. 4 SBR signal in PD is not correlated with age

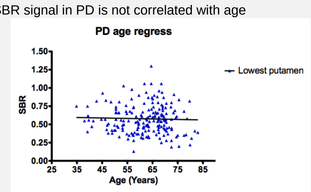


Fig. 5 SBR signal loss is 4.7% per Decade in SWEDDs

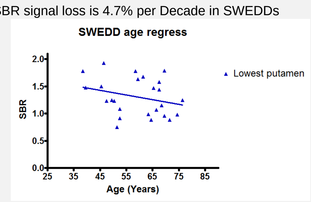


Fig. 6 One Year Longitudinal Assessment of Mean Striatal Binding Ratio in 47 PD Subjects

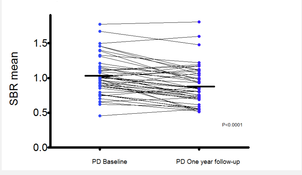
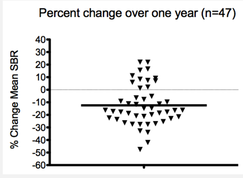


Fig. 7 One Year Percent Change of Mean Striatal Binding Ratio in 47 PD Subjects



DISCUSSION

Creating standardized, poolable, multicenter quantitative measures of 123-I Ioflupane SPECT in PDs and healthy volunteers is feasible, SBR data are similar to single center reports

De novo PD subjects demonstrate on average 50% SBR signal loss relative to controls

SWEDDs rate is about as expected (15%) in de novo PD clinical trials

SWEDDs' SBR values are similar to healthy volunteers, cross-sectional data across an age range show a similar age-associated reduction as healthy volunteers

Normal aging is associated with about 6% signal loss per decade (0.6%/y)

First longitudinal data suggests SBR reductions over one year approximately 20 times the rate of signal loss seen in normal aging

There is significant between subject variability in %SBR reduction over one year, consistent with both prior PD longitudinal imaging and clinical course.

Acknowledgements

The PPMI study is supported by the M.J. Fox Foundation for Parkinson's Research

Additional support is provided by the following corporate partners:

Abbott, Avid, biogen idec, COVANCE, Elan, GE Healthcare, Genentech, GSK, MERCK, Pfizer, Roche

[1]Full author listing available below this poster.

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