123-I Ioflupane SPECT Measures of Parkinson Disease Progression in the Parkinson Progression Marker Initiative (PPMI) Trial

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Institute for Neurodegenerative Disorders

Disclosure

- Equity interest in Molecular Neuroimaging, LLC
- Consultant: Bayer Healthcare, GE Healthcare, Navidea Biopharmaceuticals, Piramal Imaging

PPMI Overview

- **Observational, five-year, multi-center study to assess progression of clinical features, imaging and biologic biomarkers in *de novo* Parkinson's patients and healthy controls**

- **Subjects are assessed at baseline and every 3-6 months thereafter**
  - **Clinical assessments: motor, neuropsychiatric and cognitive**
  - **Imaging assessments**
  - **Biologics collected: blood, CSF, urine and DNA**

- **Clinical, imaging and biological data and samples collected under standardized protocols and analyzed and stored at core facilities and made available to investigators**

Study synopsis

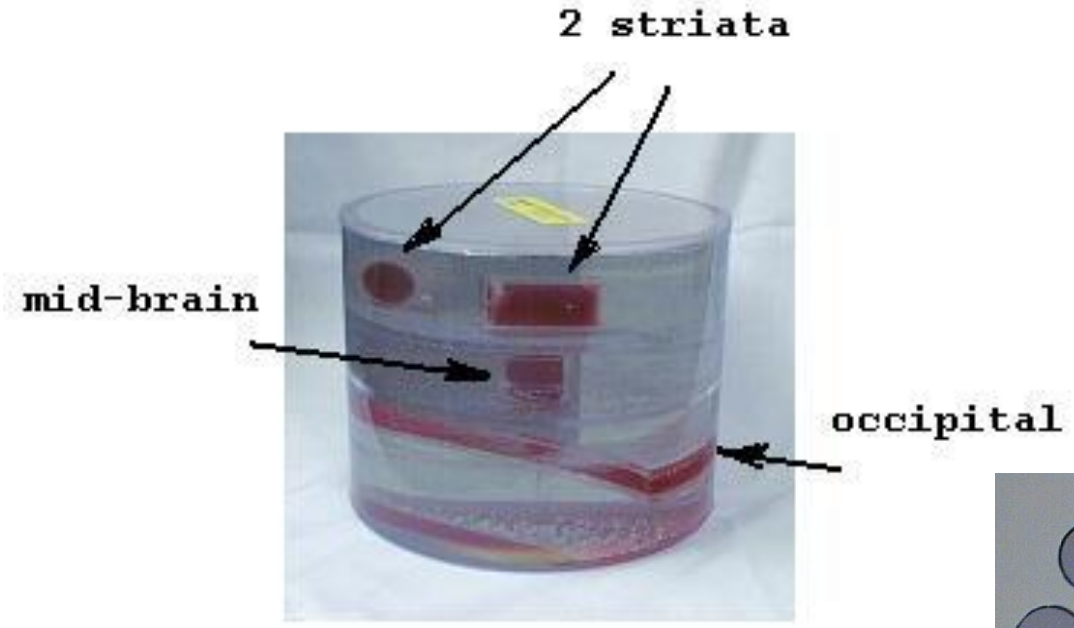
Study population	400 *de novo* PD subjects (newly diagnosed and unmedicated) 200 age- and gender-matched healthy controls Subjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	• Motor assessments • Neuropsychiatric/cognitive testing • Olfaction • DaTSCAN imaging, AV-133 PET, DTI, and resting state MRI
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 potential 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, Oregon
Innsbruck
Marburg
Tübingen
Univ Washington
USF, Tampa
Emory Univ
Macquarie Univ, Sydney

Customized 57-Co Striatal Phantom Acquired Each Day a Subject is Scanned to Provide On-going Camera Calibration



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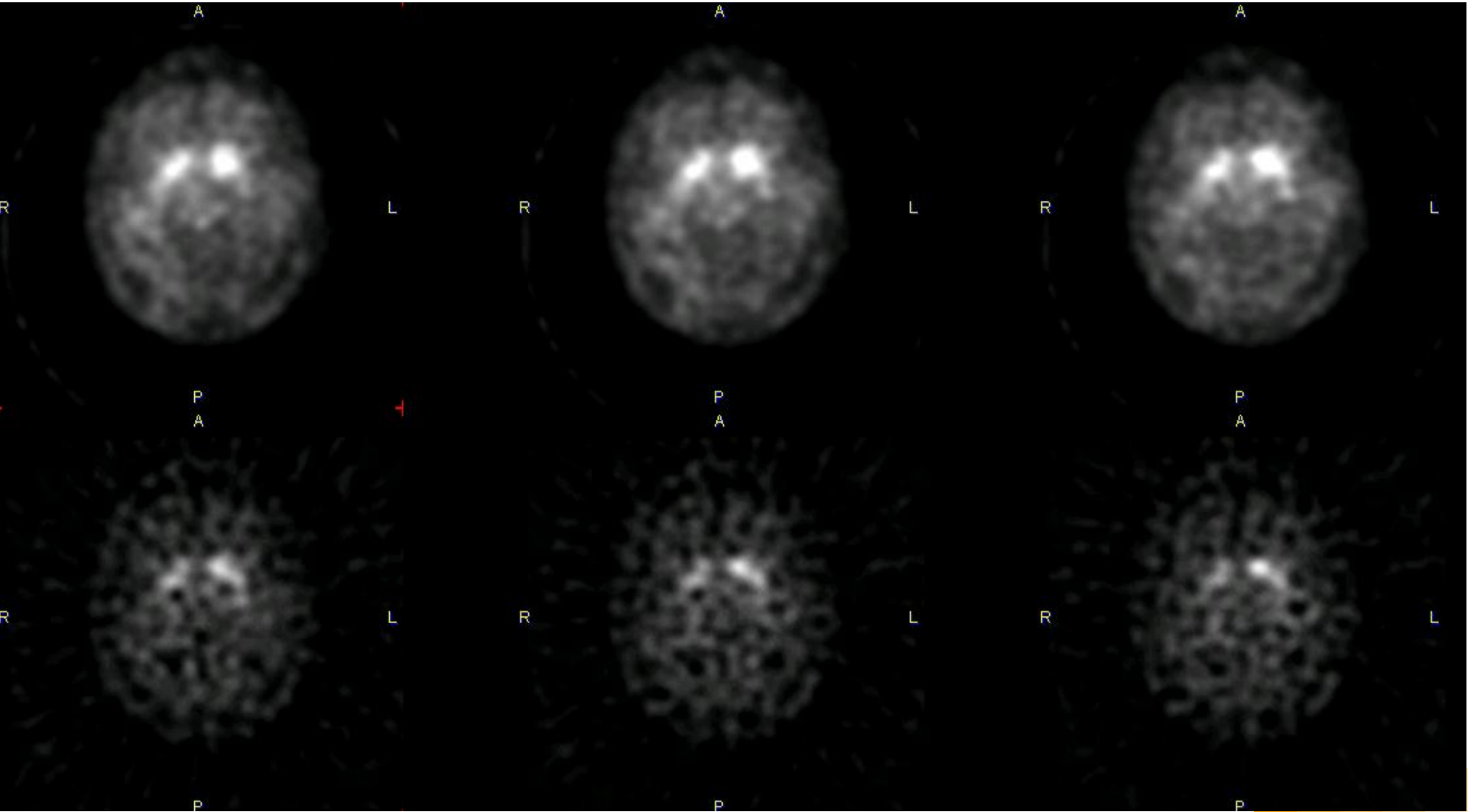
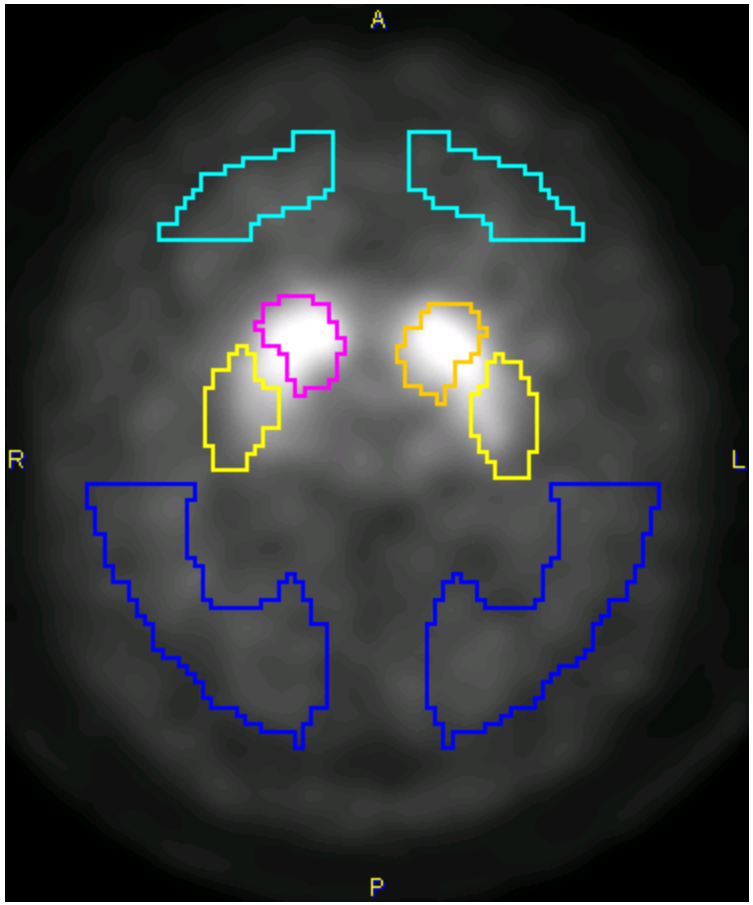
Central Core Lab Reconstructions of Raw Projection Data Improves Quality and Consistency of Quantitative SPECT Data



DAT SPECT Quantitative Analysis

1. Core lab reconstruction from raw projection data, including attenuation correction based on phantoms from site visit
2. Spatial normalization of image creates consistent orientation
3. Apply standard volume of interest template on caudate, putamen, occipital, frontal regions
4. Extract count densities and calculate Striatal Binding Ratios (SBR)

Volume of Interest Sampling



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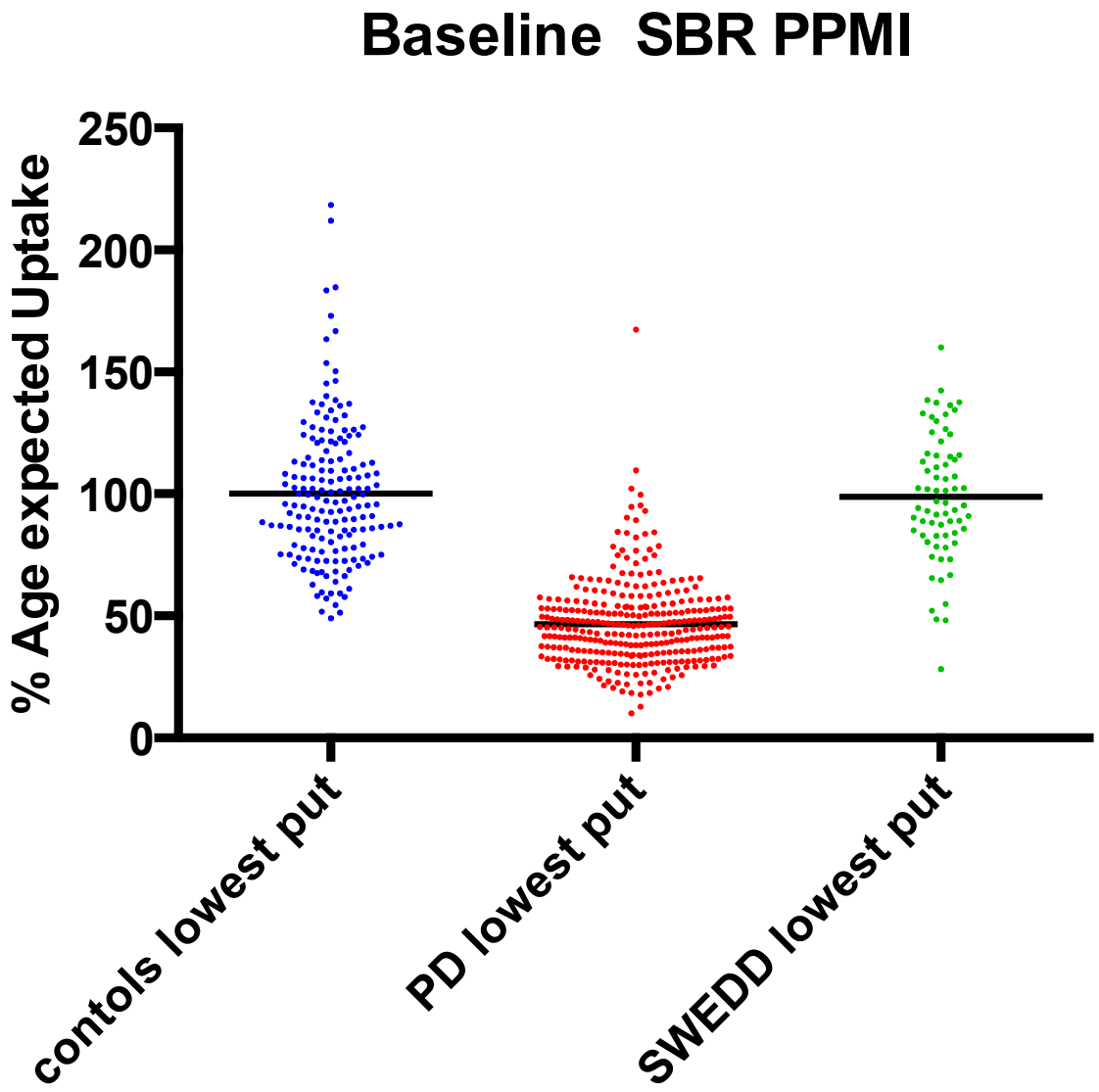
Variable	Enrolled Subjects				
	PD Subjects (N =422) N (%)	Healthy Controls (N =195) N (%)	SWEDD Subjects (N = 63) N (%)	p-value (PD vs. HC)	p-value (PD vs. SWEDD)
Gender				0.79	0.58
Male	276 (65%)	125 (64%)	39 (62%)		
Female	146 (35%)	70 (36%)	24 (38%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Age				0.53	0.22
<56 Years	114 (27%)	55 (28%)	22 (35%)		
56-65 Years	135 (32%)	69 (35%)	14 (22%)		
>65 Years	173 (41%)	71 (36%)	27 (43%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Age				0.27	0.59
Mean	61.7	60.7	60.9		
(Min, Max)	(33, 85)	(31, 84)	(38, 79)		
Missing	0	0	0		
Education				0.55	0.03
<13 Years	77 (18%)	29 (15%)	18 (29%)		
13-23 Years	341 (81%)	165 (85%)	43 (68%)		
>23 Years	4 (1%)	1 (1%)	2 (3%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Ethnicity				0.76	0.64
Hispanic/Latino	9 (2%)	3 (2%)	2 (3%)		
Not Hispanic/Latino	413 (98%)	192 (98%)	61 (97%)		
Missing	0 (0%)	0 (0%)	0 (0%)		
Race				0.87	1.00
White	389 (92%)	181 (93%)	59 (94%)		
Black/African-American	6 (1%)	9 (5%)	1 (2%)		
Asian	8 (2%)	1 (1%)	1 (2%)		
Other	16 (4%)	4 (2%)	1 (2%)		
Missing	3 (1%)	0 (0%)	1 (2%)		

Baseline DAT Data



PD n= 378
HC n= 182
SWEDD = 48

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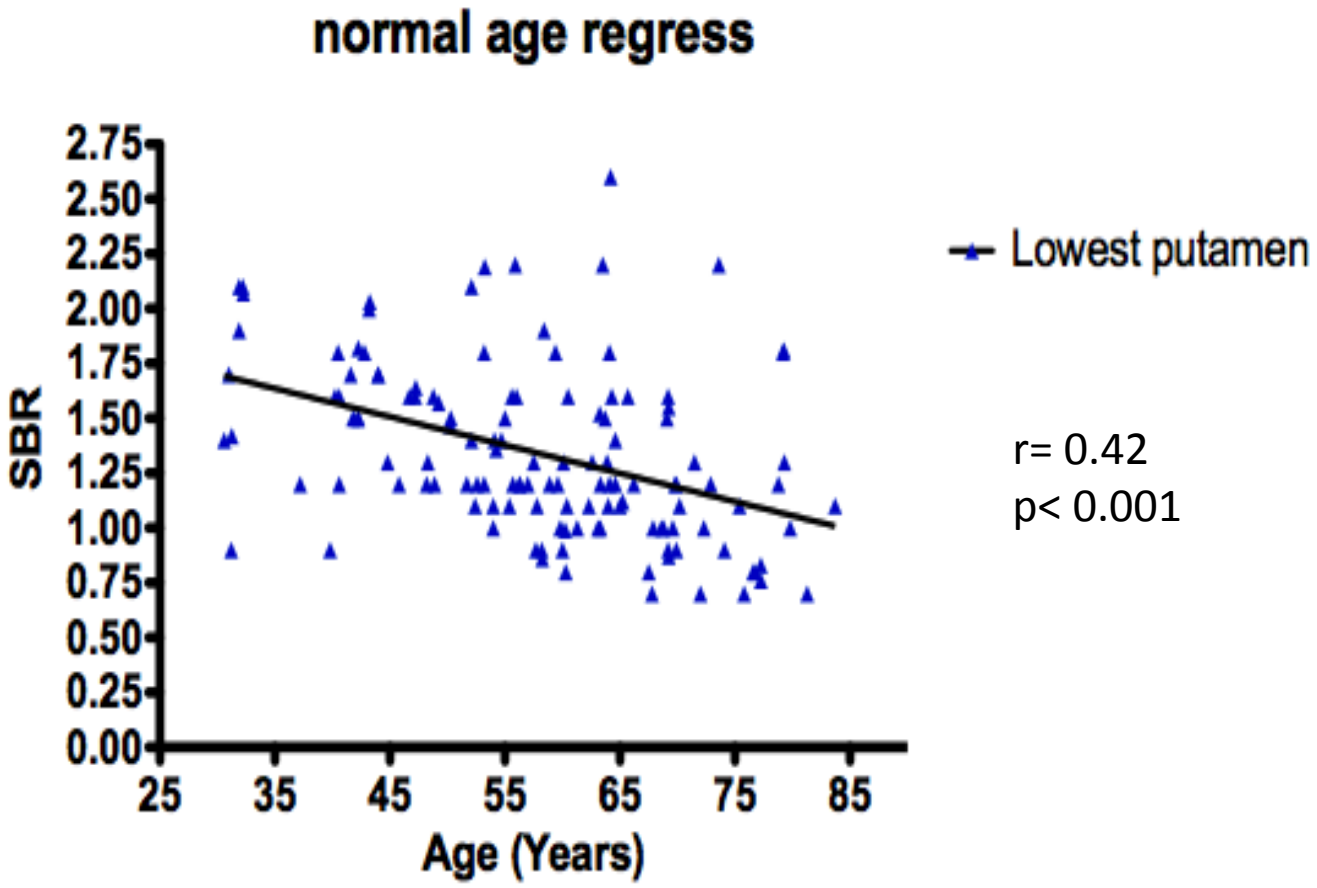
Baseline DAT data

	Enrolled Subjects		
Variable	PD Subjects (N =378)	Healthy Controls (N =182)	p-value (PD vs. HC)
Lowest Caudate	1.21	1.89	<0.001
Lowest Putamen	0.57	1.27	<0.001
Mean Caudate	1.32	1.94	<0.001
Mean Putamen	0.65	1.33	<0.001
Mean Striatum	0.98	1.63	<0.001
Ipsilateral Caudate	1.41	1.89	<0.001
Ipsilateral Putamen	0.73	1.27	<0.001
Contralateral Caudate	1.22	1.99	<0.001
Contralateral Putamen	0.58	1.40	<0.001
Caudate Asymmetry Index	15.96	5.27	<0.001
Putamen Asymmetry Index	26.48	10.20	<0.001
Striatum Asymmetry Index	36.86	8.72	<0.001
Ipsilateral CDR	2.05	1.56	<0.001
Contralateral CDR	2.23	1.47	<0.001

SBR signal loss is 6.2% per Decade in Healthy Volunteers



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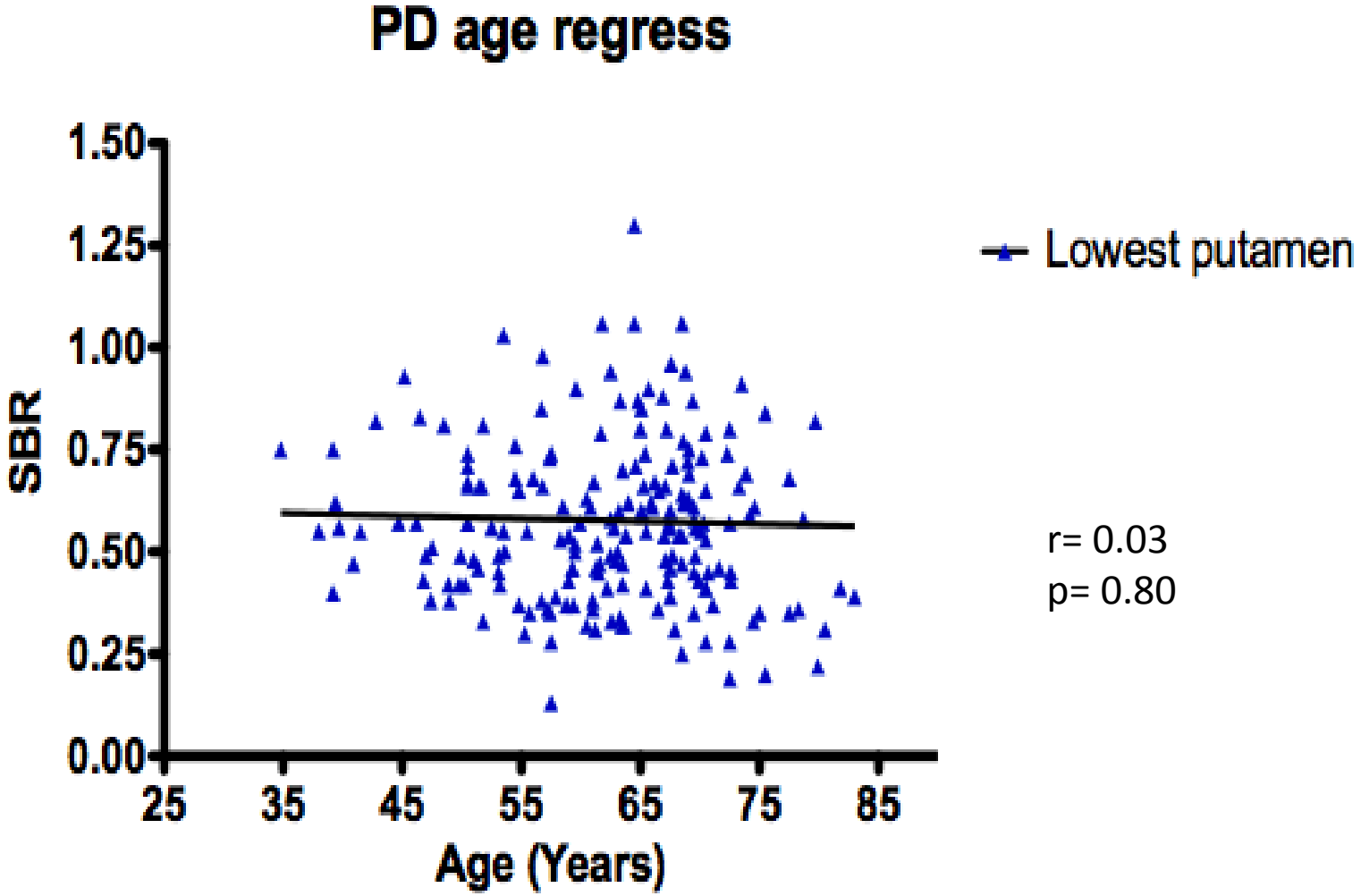
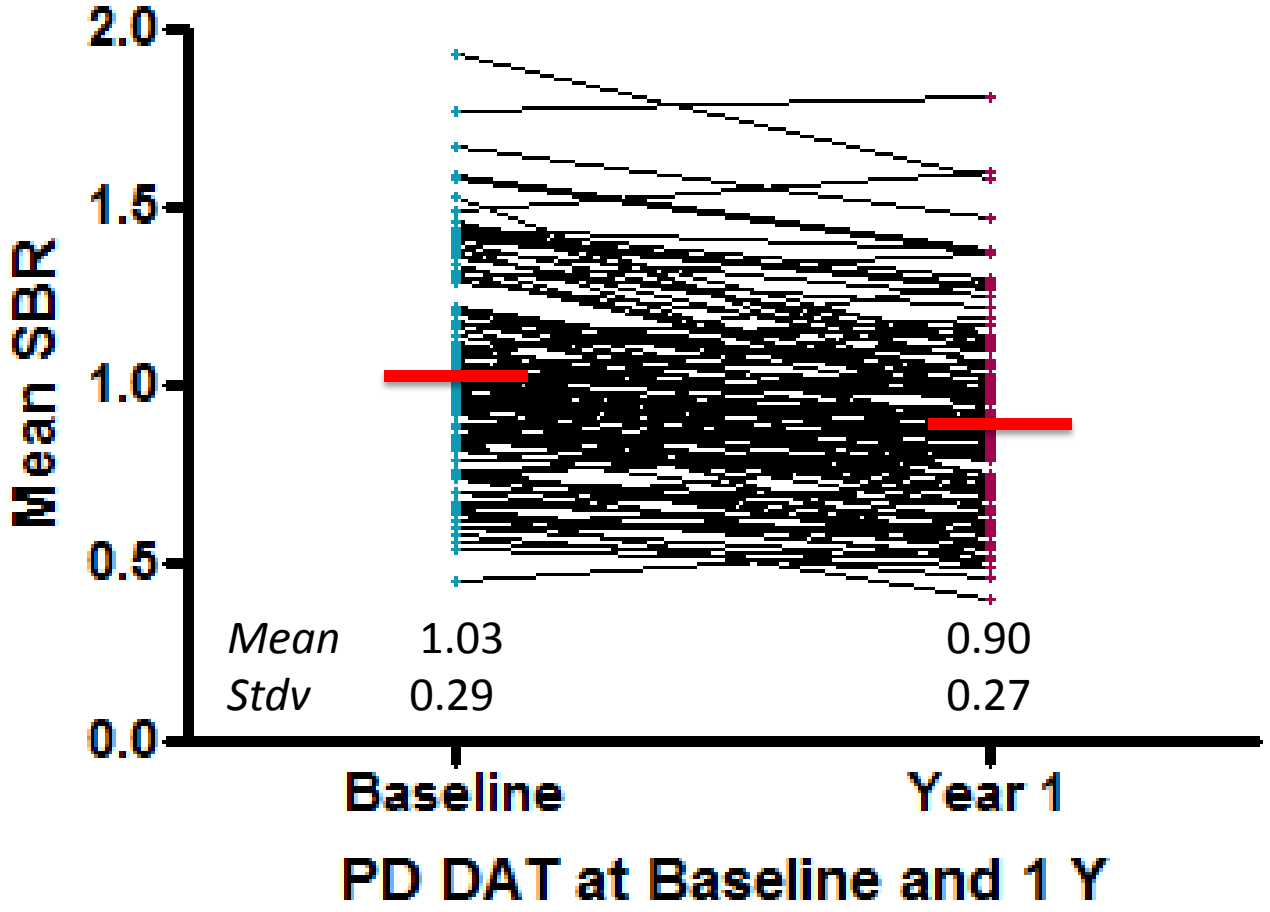
SBR signal in PD is not correlated with age

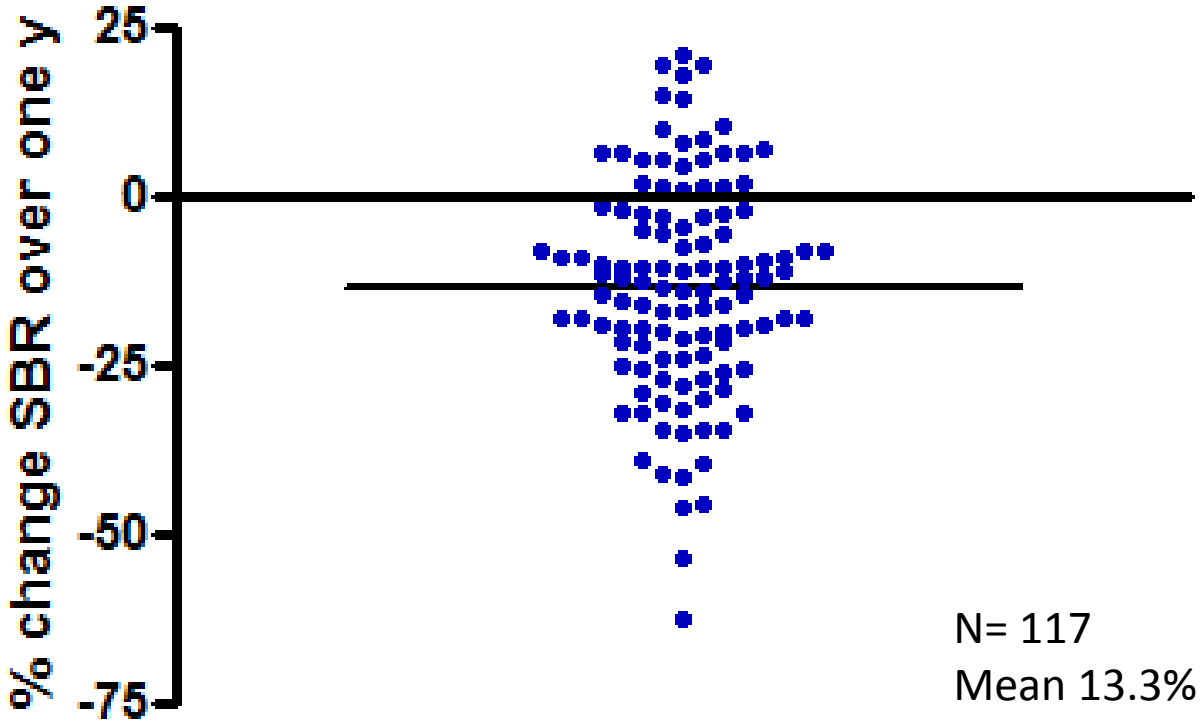


Longitudinal Data DAT



N= 117 PD
p< 0.0001

Longitudinal DAT



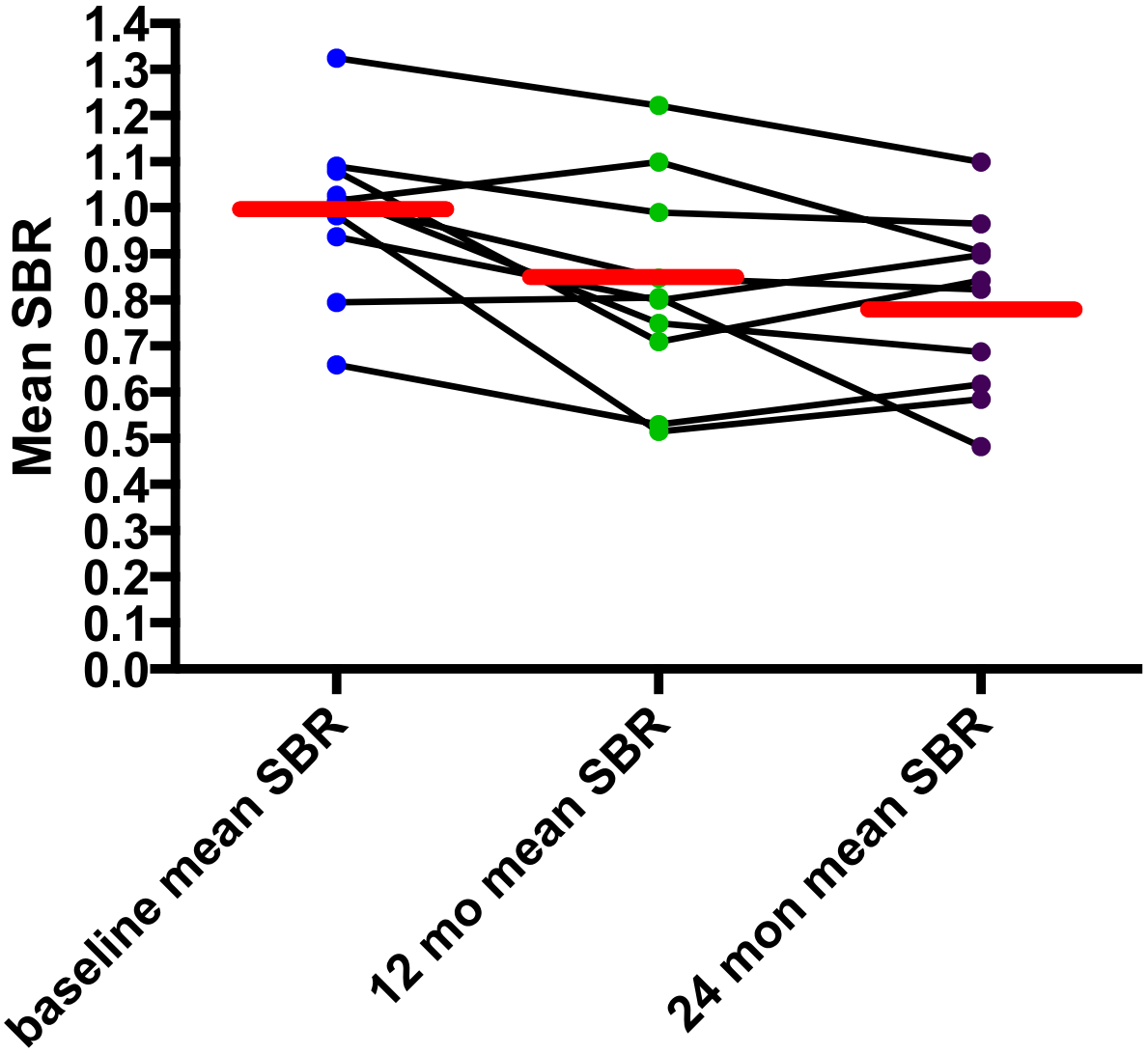
N= 117
Mean 13.3% ± 16.0%
78.6% going down at yr 1

Rate of SBR Signal Change

- Identical to % signal loss in the PROUD* study with DatScan
  - mean change was –15·5% for early (n=57) and –14·2% for delayed (n=58) pramipexole cohorts over 15 months
- Faster than PRECEPT cohort (n=800) using123-I β-CIT

*Mov Disord. 2010 Aug 15;25(11):1627-32.

Longitudinal PD SBR



Conclusions

In this ongoing multicenter PPMI study:

- Baseline cohorts are now fully recruited
- DAT SPECT suggests de novo PD subjects have average SBR reduction about 50% of age matched controls
- Normal aging is associated with about 6% signal loss per decade (0.6%/y) based on cross-sectional data
- First longitudinal data in 117 PD subject suggests SBR reductions over one year is 13.3%, approximately 20 times the rate of signal loss seen in normal aging

Conclusions (cont)

- This rate of change is identical to % signal loss in the PROUD study with 123-I Ioflupane mean change about 15% over 15 months
- Similar to other biomarkers, there is significant between subject variability in %SBR reduction over one year, consistent with both prior PD longitudinal imaging and differences in clinical course between patients
- Correlation of signal loss with medication status, clinical features and other biomarkers are pending

Acknowledgements

Research Support: The Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbott, AVID, Biogen Idec, Covance, Eli Lilly, F. Hoffman-La Roche Ltd., GE Healthcare, Genentech, GSK, Merck, Pfizer Inc, UCB

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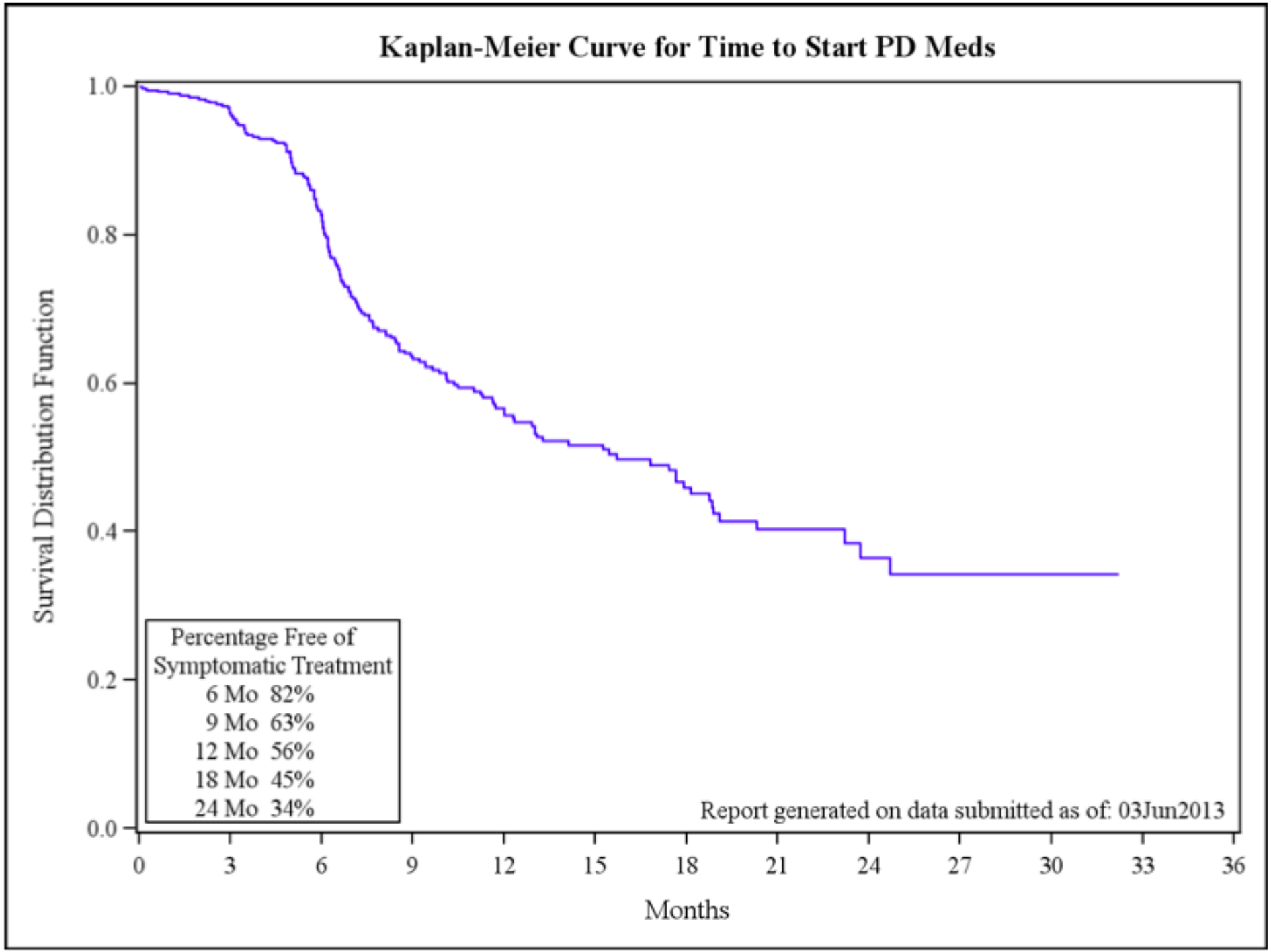
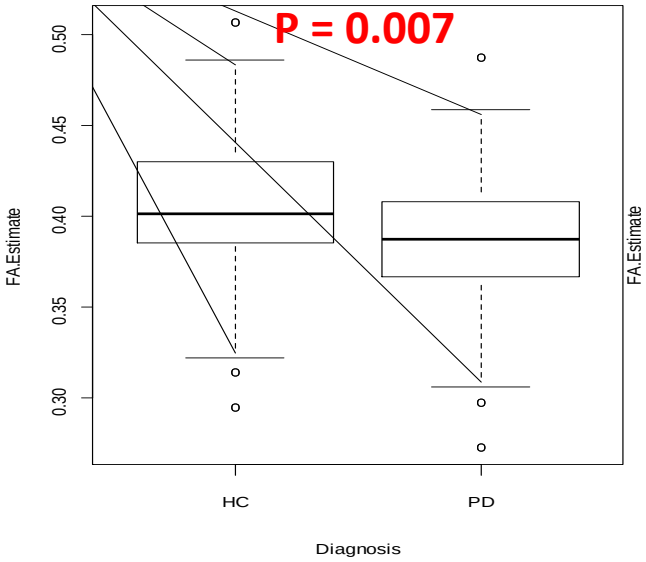
Extra

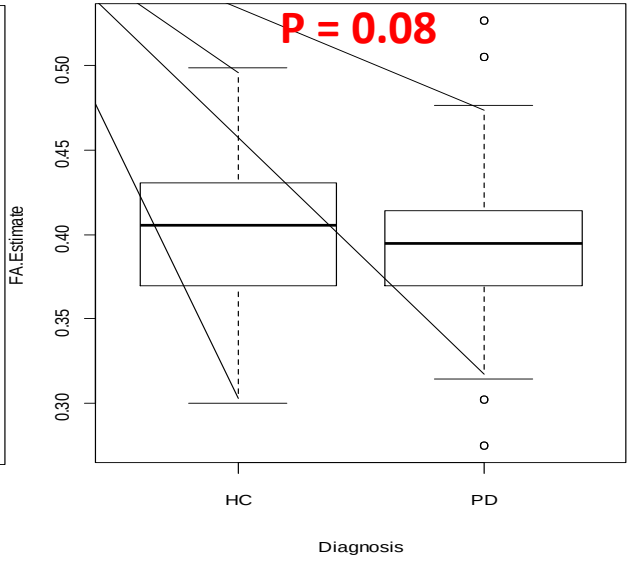

Kaplan-Meier Curve for Time to Start PD Meds
Survival Distribution Function
1.0
0.8
0.6
0.4
0.2
0.0
0
3
6
9
12
15
18
21
24
27
30
33
36
Months
Percentage Free of
Symptomatic Treatment
6 Mo 82%
9 Mo 63%
12 Mo 56%
18 Mo 45%
24 Mo 34%
Report generated on data submitted as of: 03Jun2013

FA Of Substantia Nigra (Manual ROI)

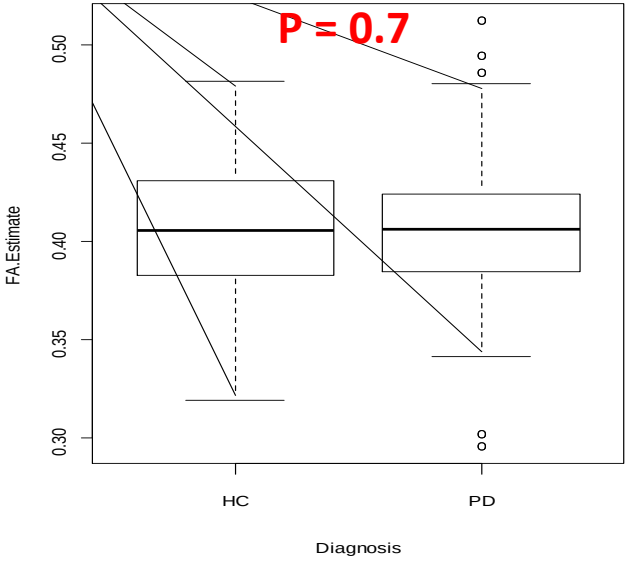
Rostral



Middle



Caudal



PD=100, Control= 52

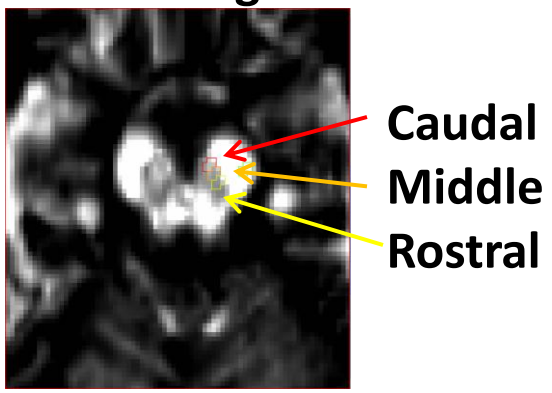
100Analysis:

By diagnosis and side of symptom onset.

Statistics:

Using permutations to approximate a t-distribution

Markings



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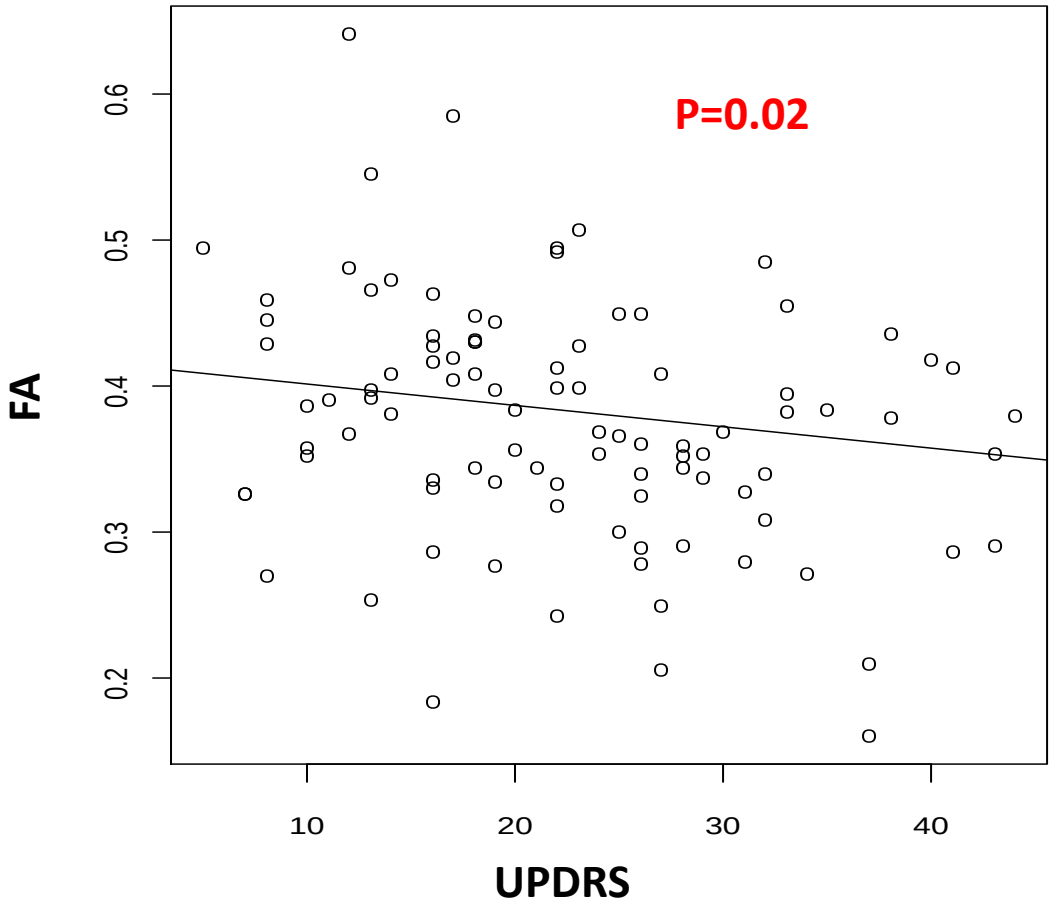
FA Of Substantia Niagra vs UPDRS.III



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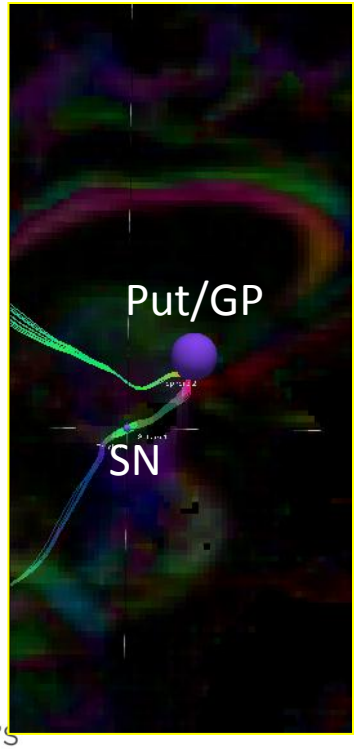
New Analysis: Tractography Of Striato-Nigral Tract

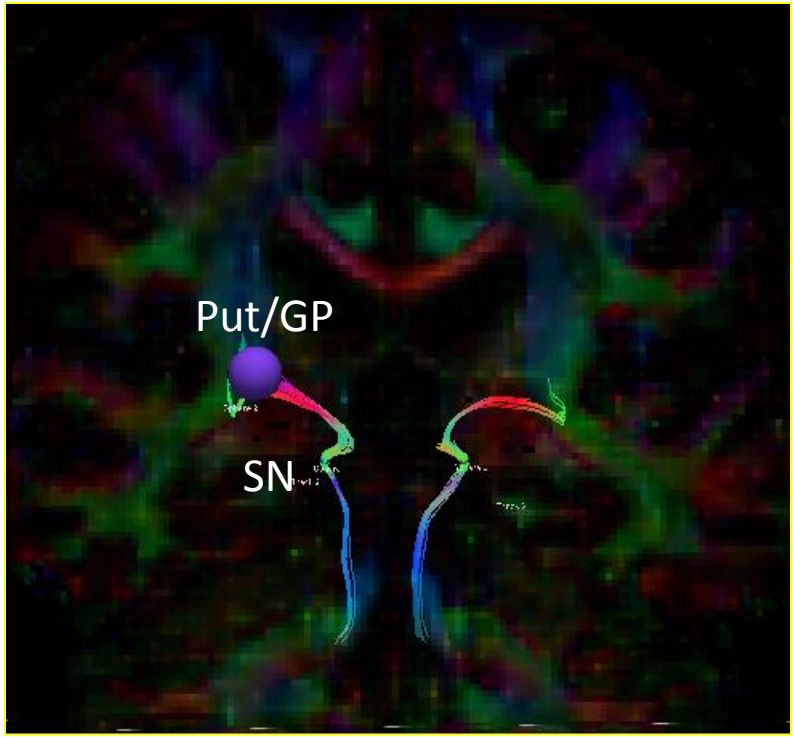
Tracing the nigro-striatal fibers

Seeding in post Putamen

Automated fiber tracking ends in SN pars compacta

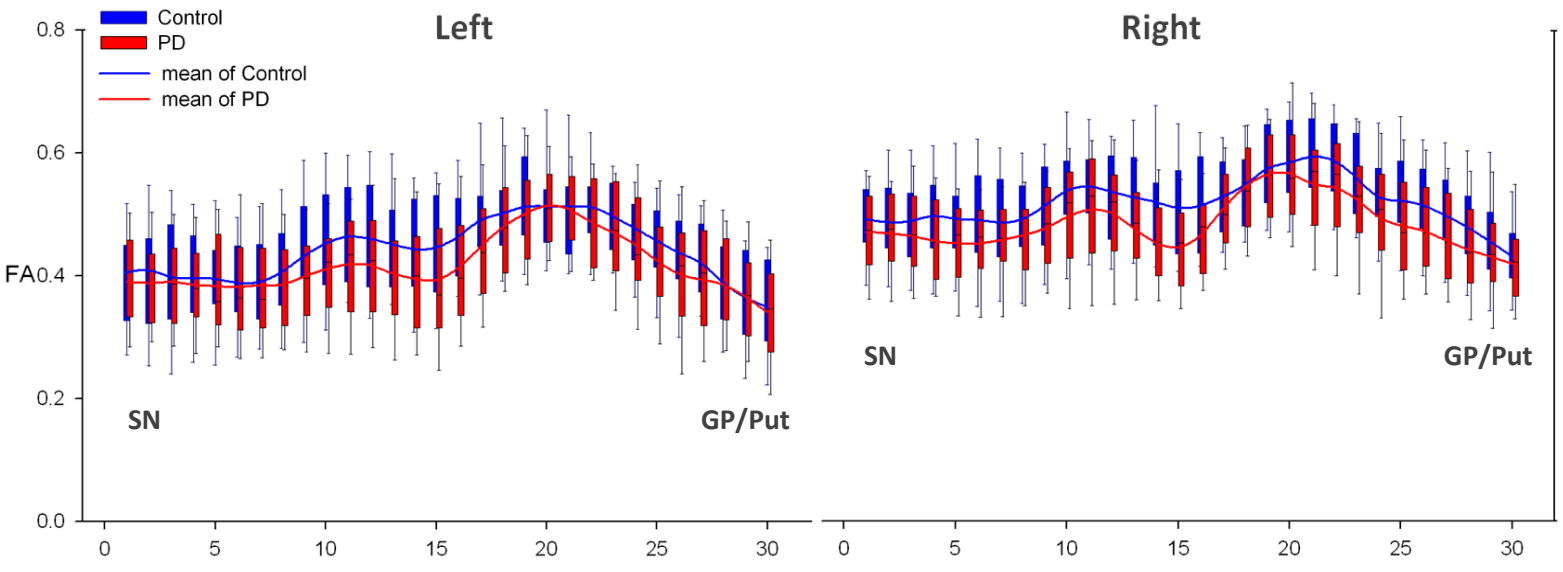


Sagittal View



coronal

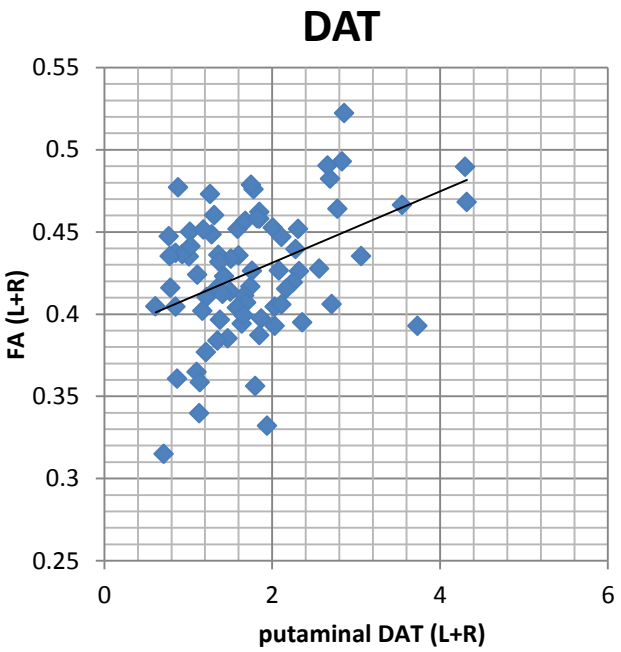
FA Profile Along Striato-Nigral Tract

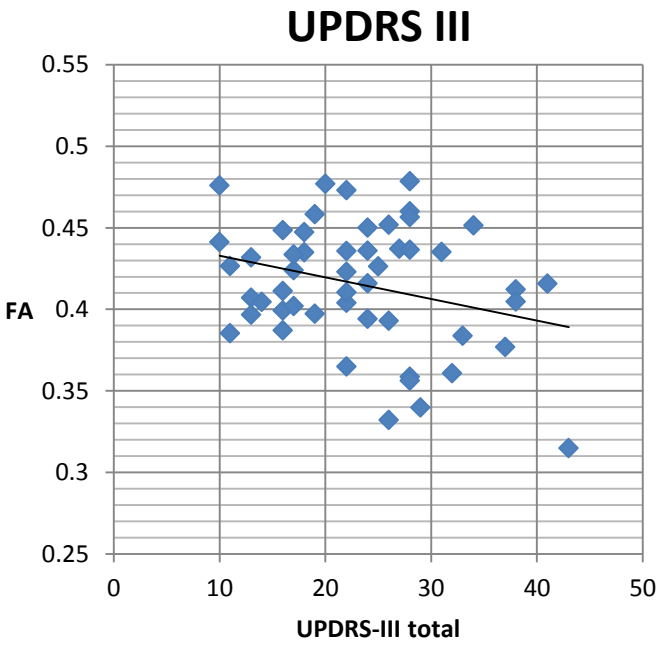


27 control 51 PD)

	Control	PD	*p* value
Fractional Anisotropy	0.45 ± 0.04	0.42 ± 0.04	**0.002**
Axial Diffusivity [$10^{-3}mm^2/s$]	1.21 ± 0.09	1.26 ± 0.10	0.05
Radial Diffusivity [$10^{-3}mm^2/s$]	0.58 ± 0.08	0.63 ±0.10	**0.02**
Mean diffusivity [$10^{-3}mm^2/s$]	0.79 ± 0.08	0.84 ± 0.09	**0.02**

Relation Between Radial Diffusivity Along The Tract And DAT/UPDRS





r = -0.42, p = 0.0001

r = -0.29, p = 0.04

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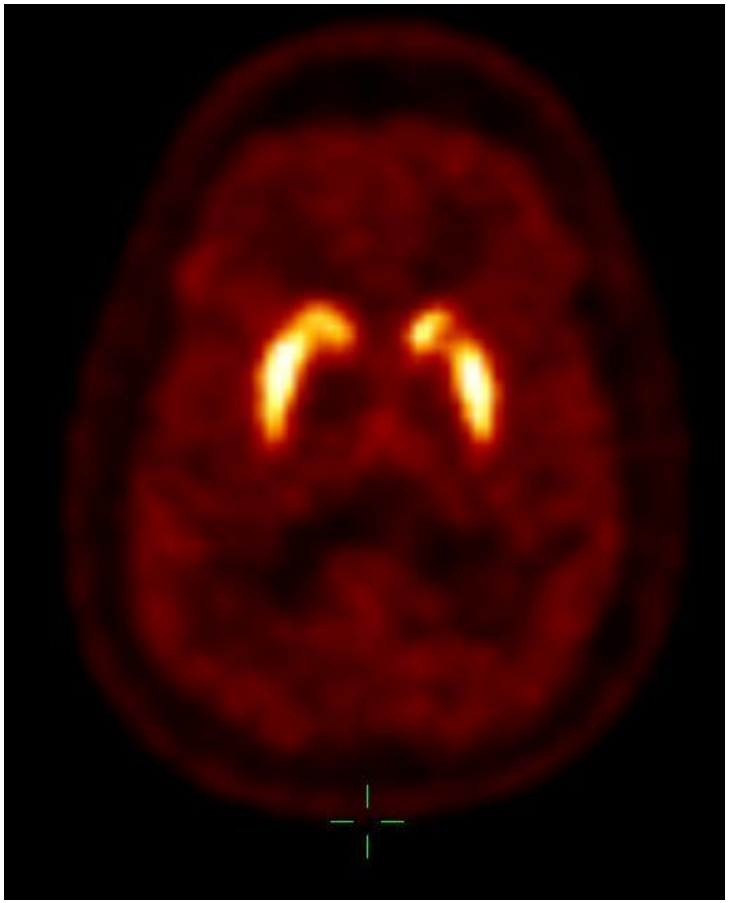
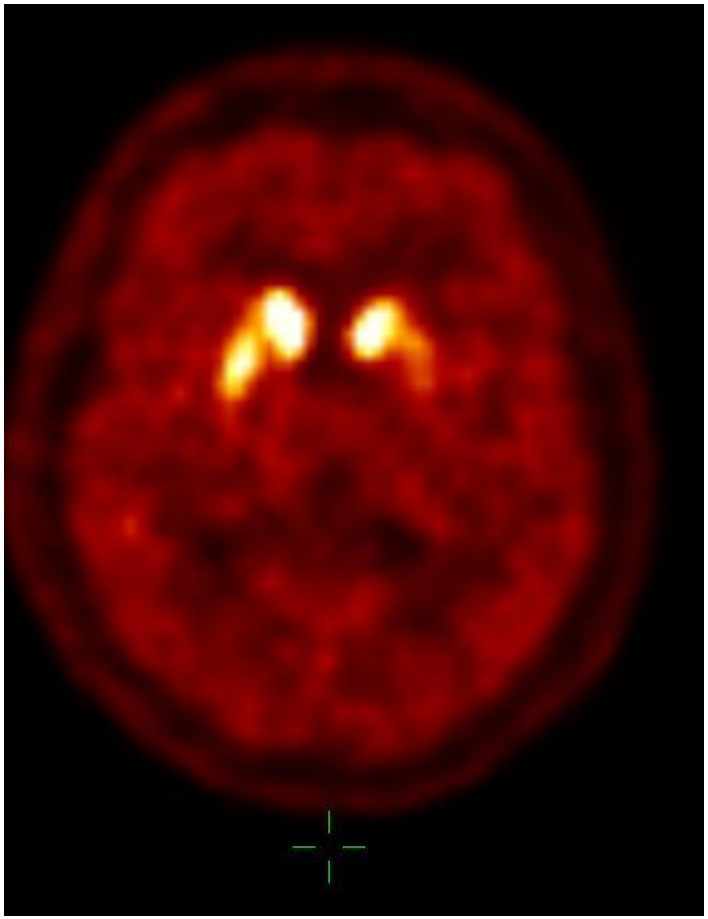
18F-AV-133: Targets VMAT2



Healthy Subject

Mean putamen binding ratio = 3.52

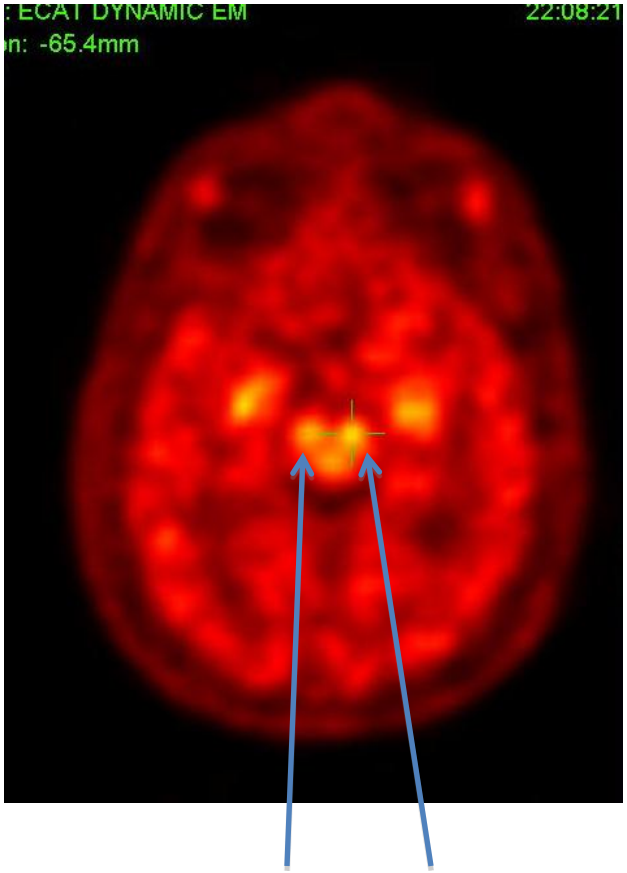


Parkinson's Subject

Mean putamen binding ratio = 1.36

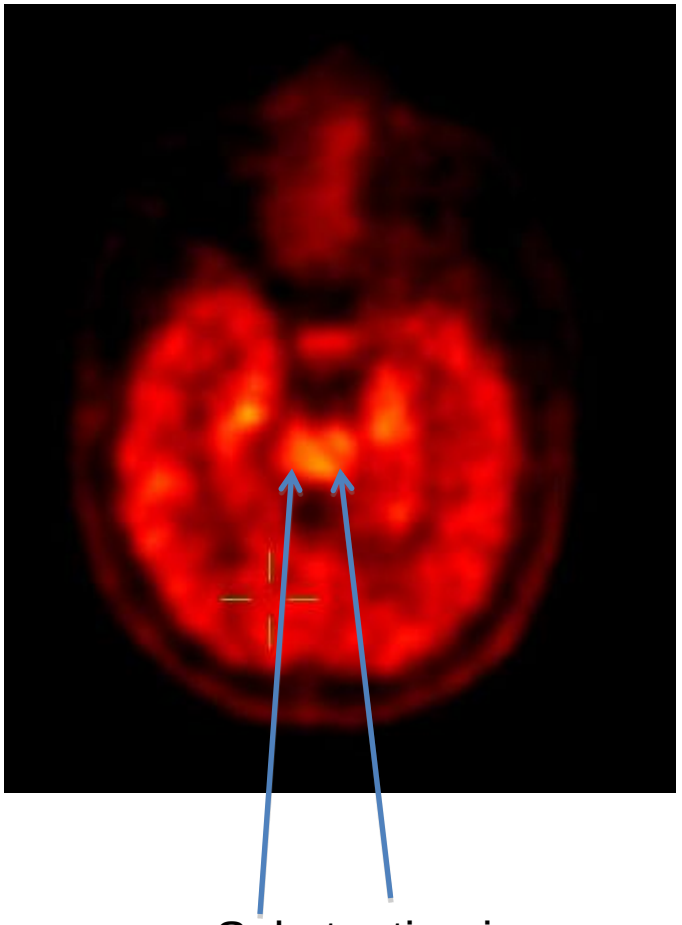
18F-AV133 PET: possible to image the substantia nigra directly

Healthy Subject



Substantia nigra
SN ratio = 1.59

PD Subject



Substantia nigra
SN ratio = 0.91

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Enrollment

Active PD	Active Healthy	Active SWEDD	Total Active Subjects
390	184	58	632

As of 8 April 2013

SBR phantom correction

Approach #1 (Scaling) Normalize each DAT study (mean SBR) to the phantom (mean SBR) acquired on the imaging day, e.g., set the 57Co SBR at 100% and multiply through the subject scan using the phantom normalizing factor then calculate percent change on the phantom-normalized subject SBRs

Approach #2 For longitudinal change, calculate the % change for 57Co mean SBR and subtract this change as the "technical" component of the change from baseline to follow-up

		Baseline mean SBR	Y1 mean SBR	% change
No Correction	Mean	1.02	0.90	-13.26
	SD	0.29	0.27	15.96
	%COV	28.0	29.8	-120.3

		Baseline mean SBR	Y1 mean SBR	% change
Scaling Correction	Mean	22.33	19.50	-14.90
	SD	6.71	6.13	20.04
	%COV	30.1	31.5	-134.5

		Baseline mean SBR	Y1 mean SBR	% change
Subtractive Correction	Mean	1.03	0.90	-15.78
	SD	0.29	0.28	22.35
	%COV	27.9	31.4	-141.7

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N= 117 Baseline and Year 1 scans