QIBA SPECT BIOMARKER COMMITTEE: Literature Review+ Task Force

23 Aug 2016

Agenda

1. Final touches on lit review
2. Review of available PPMI data
3. Profile bits and bobs – reclaiming a claim
4. AOB

Literature Review

ADDED LIT REVIEW TO REFERENCES

REORGANIZED CATEGORIES TO REFLECT TOPIC HEADINGS IN THE PROFILE

ADEQUATE FOR PRESENT

STILL NEEDS SOME ORGANIZATION

WILL REQUIRE CHANGES WITH FURTHER REVISIONS OF PROFILE

Are PPMI Data of Use to QIBA SPECT Committee?

Background: Rationale and Study Synopsis

Recruitment and State of the Data

Data Accessibility and Acquisition Logistics

Parkinson's Progression Marker Initiative (PPMI)

Study synopsis	
Study population	423 *de novo* PD subjects (newly diagnosed and unmedicated) 196 age- and gender-matched healthy controls 64 SWEDDs + Prodromal & Genetic cohorts Subjects are 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- eligibility/serial monitoring •DTI, resting state MRI •AV-133, florbetaben PET substudies
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
Data biosamples sharing	• > 586,000 data downloads • > 70 biosamples shared • www.ppmi-info.org

Goals for PPMI – to inform clinical trials

- Improve diagnostic accuracy (enrich a study population)
- Develop tools to assess disease progression
- Establish outcomes prior to onset of motor symptoms
- Identify PD progression subsets -
  - Develop clinical outcomes (cognition, gait, autonomic)
  - Progression at different rates (fast vs slow)
  - Respond to specific therapy
  - Characterization of Genetic cohorts, Prodromal cohorts

- Phase 2 - provide an efficacy signal to increase confidence for subsequent Phase 3

- Phase 3 studies - enrich the study sample and provide objective outcomes of that reflect clinical benefit

PPMI ENROLLMENT - 2016

GROUP	Consented	Enrolled (n)	Withdrawn	Active	Complete
PD Subjects	488	**423**	45	**371**	**7**
Healthy Controls	241	**196**	20	**170**	**6**
SWEDD Subjects	82	**64**	9	**5**	**50**
Prodromal -Hyposmic	118	**26**	2	**24**	0
Prodromal-RBD	96	**39**	0	**39**	0
LRRK2 PD Cohort	103	**92**	2	**90**	0
LRRK2 UA Cohort	94	**85**	2	**83**	0
SNCA PD Cohort	14	**12**	0	**12**	0
SNCA UA Cohort	4	**4**	0	**4**	0
GBA PD Cohort	18	**17**	0	**17**	0
GBA UA Cohort	26	**21**	0	**21**	0
PD Registry	120	**114**	3	**111**	0
UA Registry	127	**120**	0	**120**	0
TOTAL	**1531**	**1213**	**83**	**1067**	**63**

Research Questions

- In an ongoing multi-center trial, do PD participants demonstrate serial reduction in Ioflupane DAT SPECT with appropriate signal:noise to be used as a progression biomarker?

- Which striatal subregions provide the best signal characteristics for longitudinal assessment of DAT density?

* DAT SPECT LONGITUDINAL STUDY

- In an ongoing study, serial 123-I ioflupane SPECT were acquired at baseline, Year 1 and Year 2 post enrollment of 241 de novo Parkinson's volunteers in the PPMI Trial

- Standardized reconstruction and image processing performed at the PPMI Core Imaging Lab in New Haven

- Regional specific binding ratios (SBR) were measured in ipsilateral and contralateral caudate, anterior putamen, and posterior putamen for each timepoint; baseline, Year 1, and Year 2

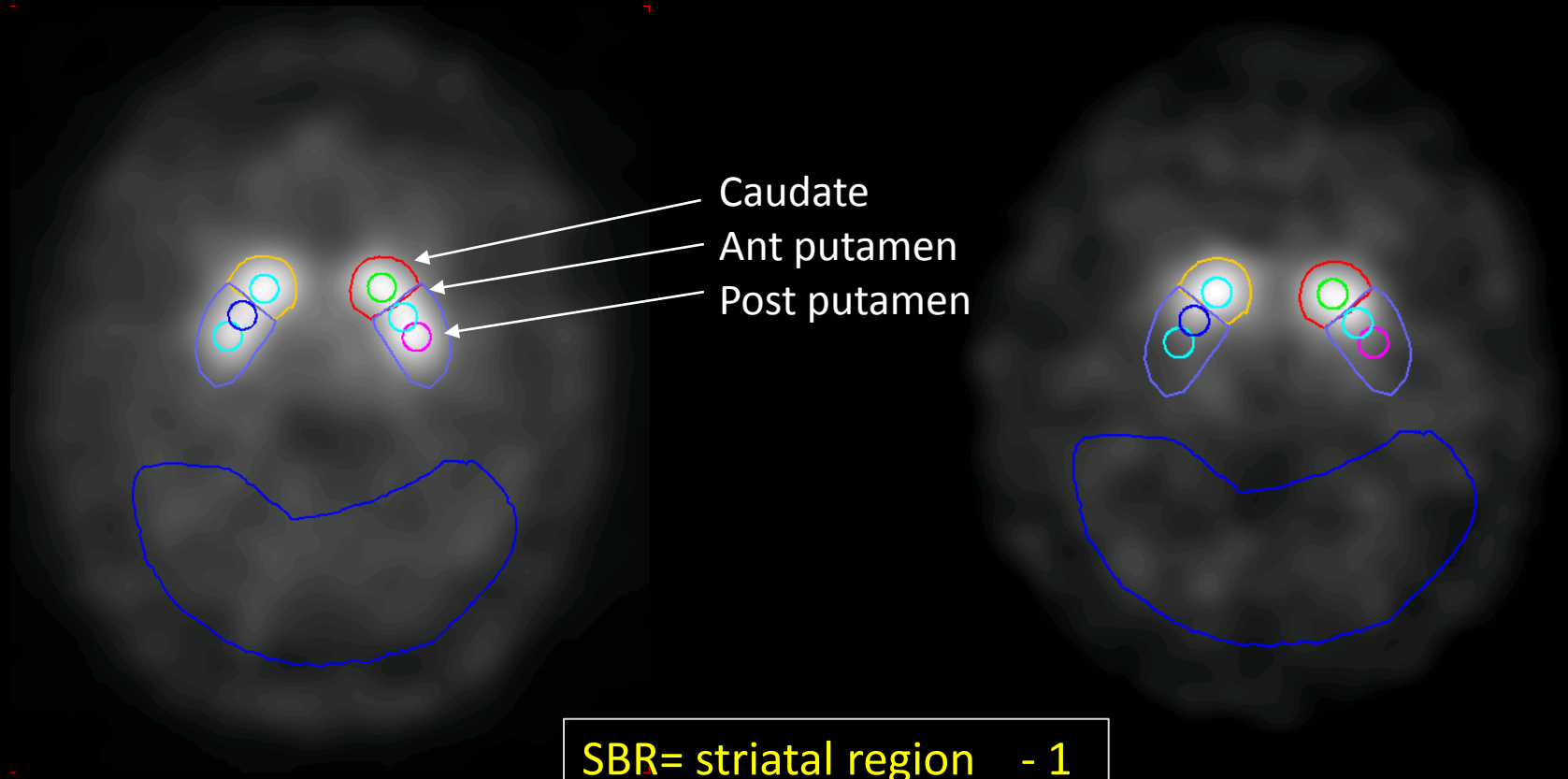
- Percent change from baseline reported for Year 1 and Year 2 as composite SBR and for separate striatal subregions and sides

In Addition…..

- Regional specific binding ratios (SBR) were measured in ipsilateral and contralateral caudate, anterior putamen, and posterior putamen for each timepoint; baseline and Year 4 (N=82)

- Percent change from baseline reported for Year 4 as composite SBR and for separate striatal subregions and sides

DAT Volumes of Interest



SBR= striatal region - 1
occipital

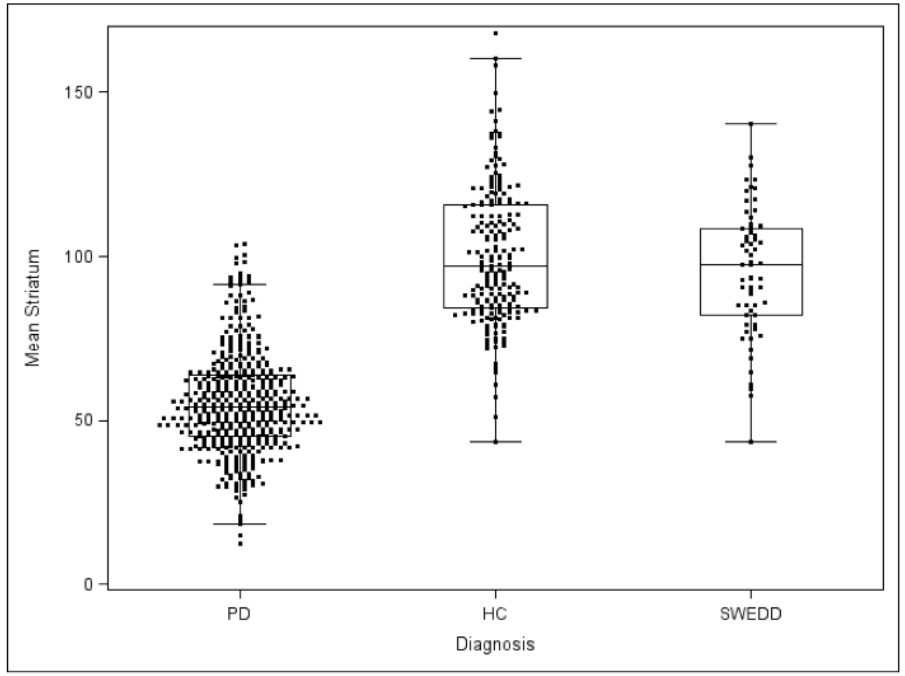
Characteristics of PPMI subjects

Cohort	Gender %M	Age (yrs)	Dz duration (months)	Part III MDS UPDRS baseline
Two Yr PD n=241	**64.3%**	**60.8 ± 6.6**	**6.7 ± 6.8**	**21.5 ± 8.5**

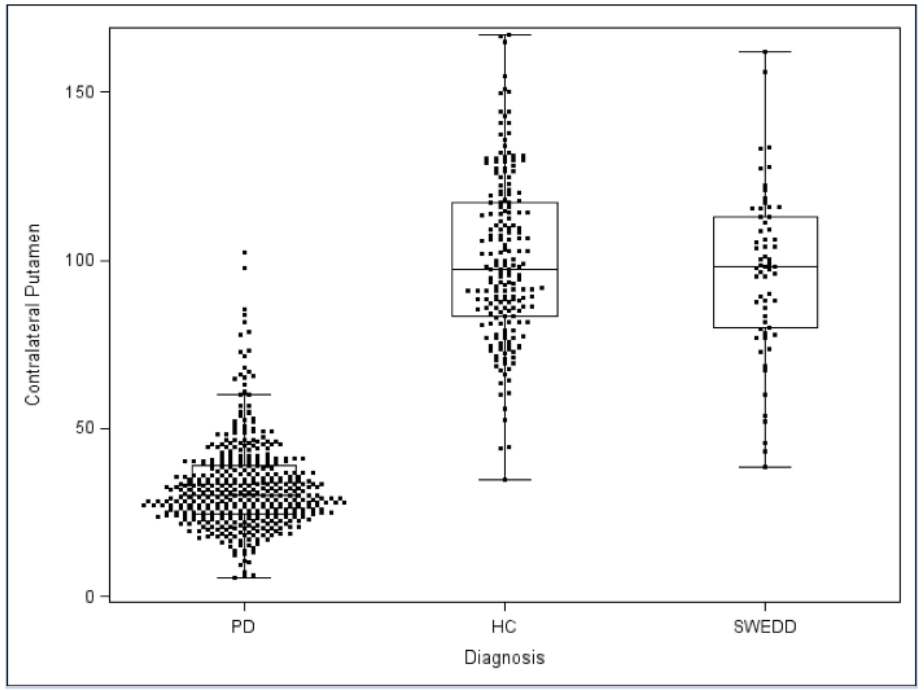
All had an Ioflupane SPECT scan demonstrating presynaptic striatal dopaminergic loss consistent with Parkinsonism prior to enrollment

Baseline DAT SBR, Age-corrected

Mean Striatal SBR

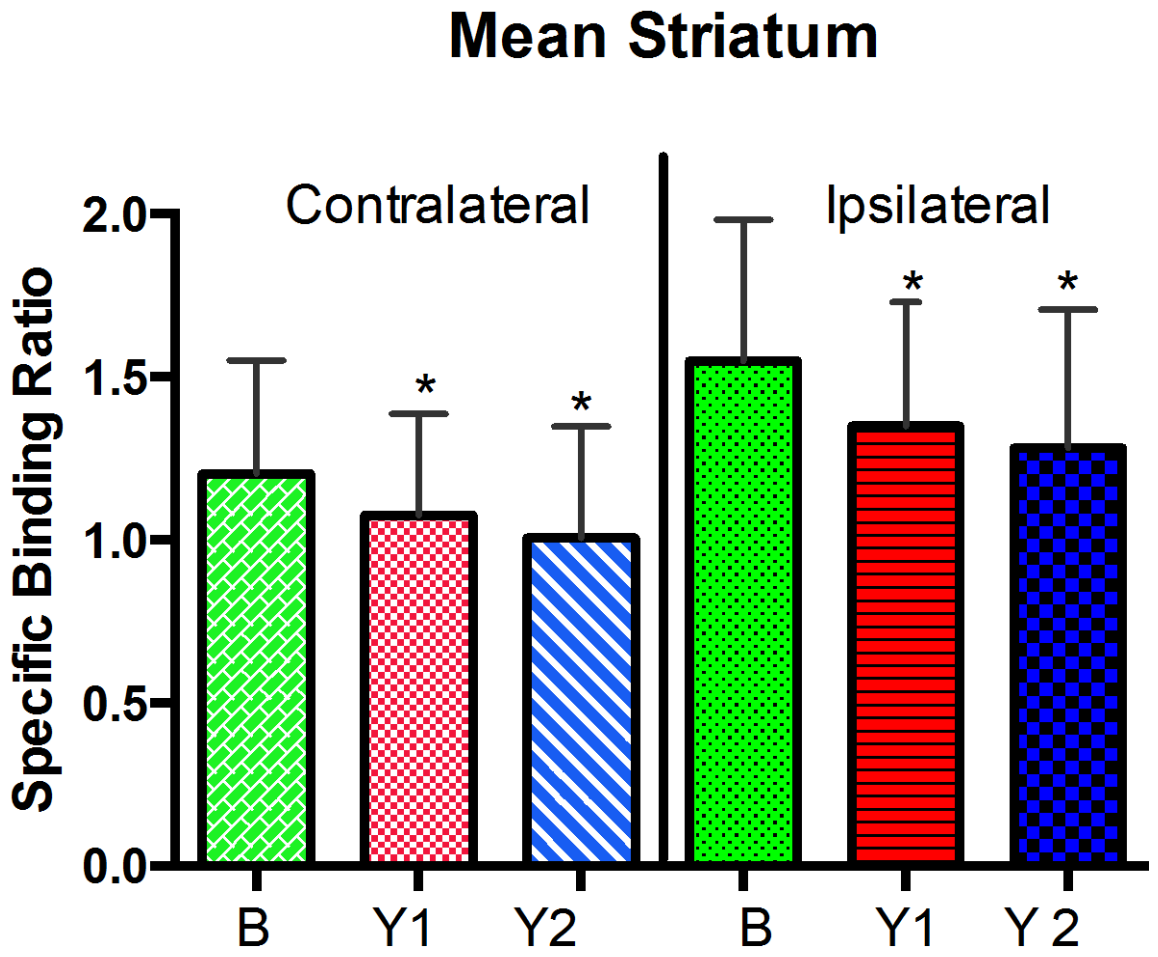


Contralateral Putamen SBR



PD n= 423
HC n= 196
SWEDD = 64

* Results: Composite Striatal SBRs

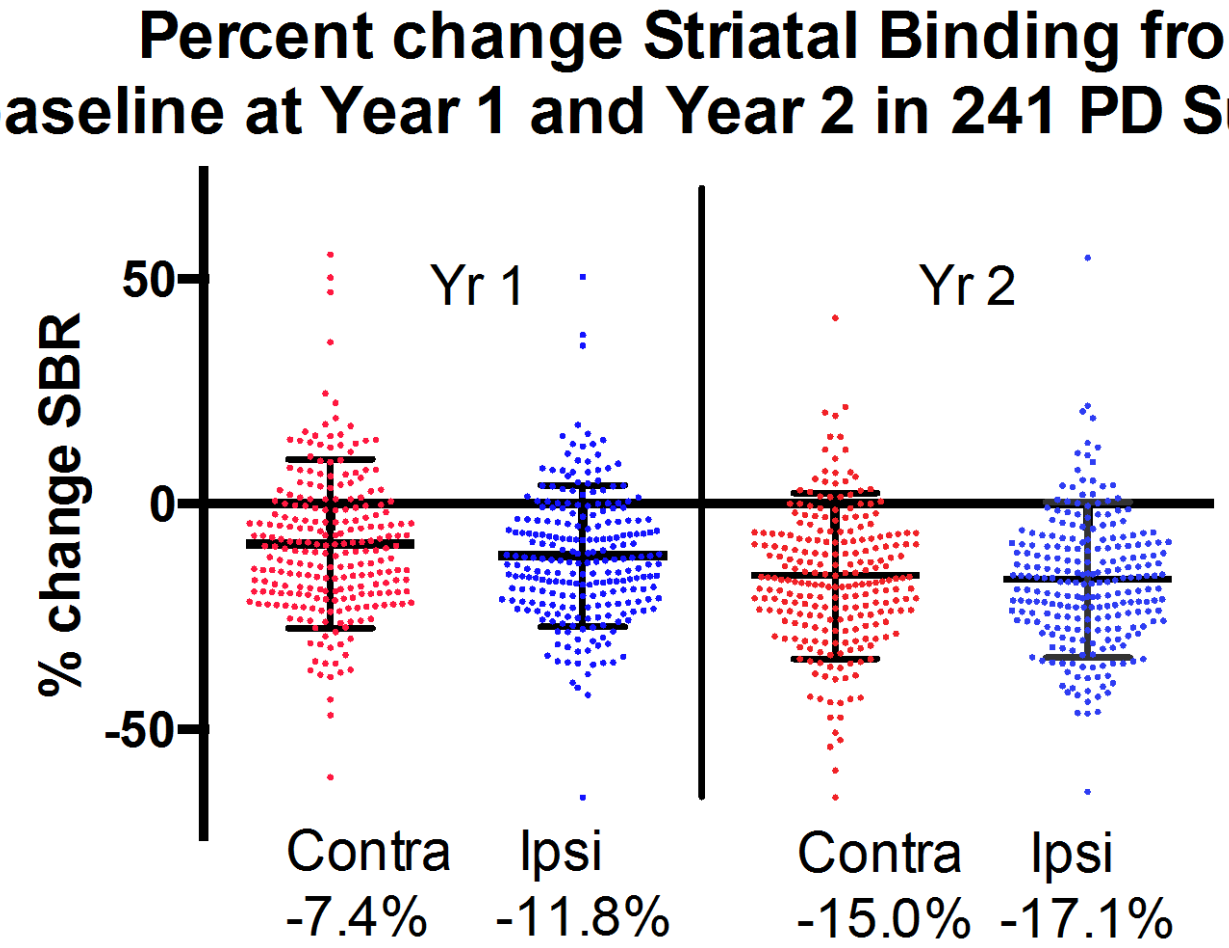


SBR	Contralateral			Ipsilateral		
	Baseline	Y1	Y2	Baseline	Y1	Y2
Mean	**1.20**	**1.08**	**1.01**	**1.55**	**1.35**	**1.28**
Std. Deviation	0.35	0.31	0.34	0.43	0.38	0.42

N= 241
Mean±SD

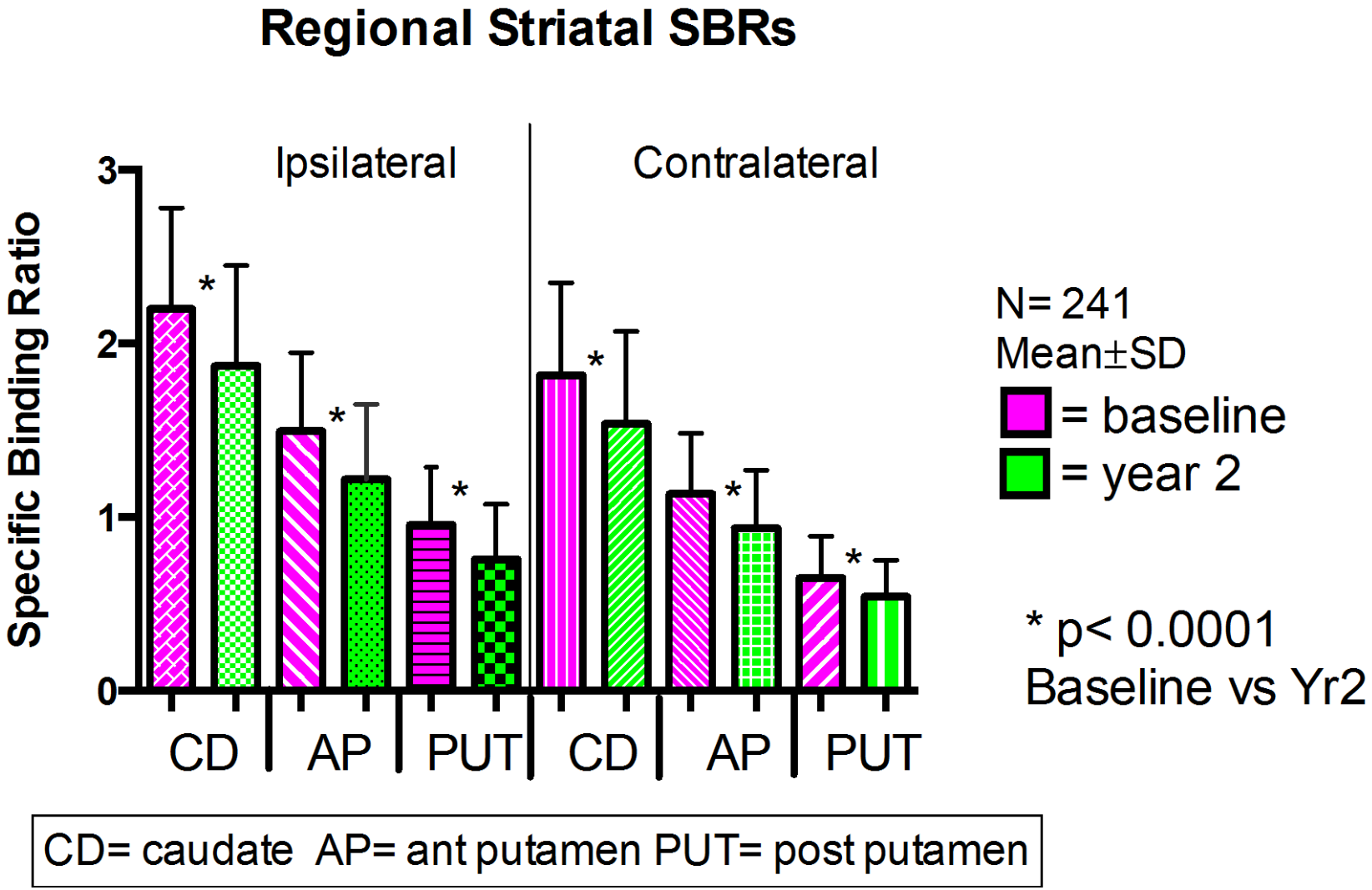
* p<0.0001 v Baseline

* Results: Striatal SBR Rate of Change



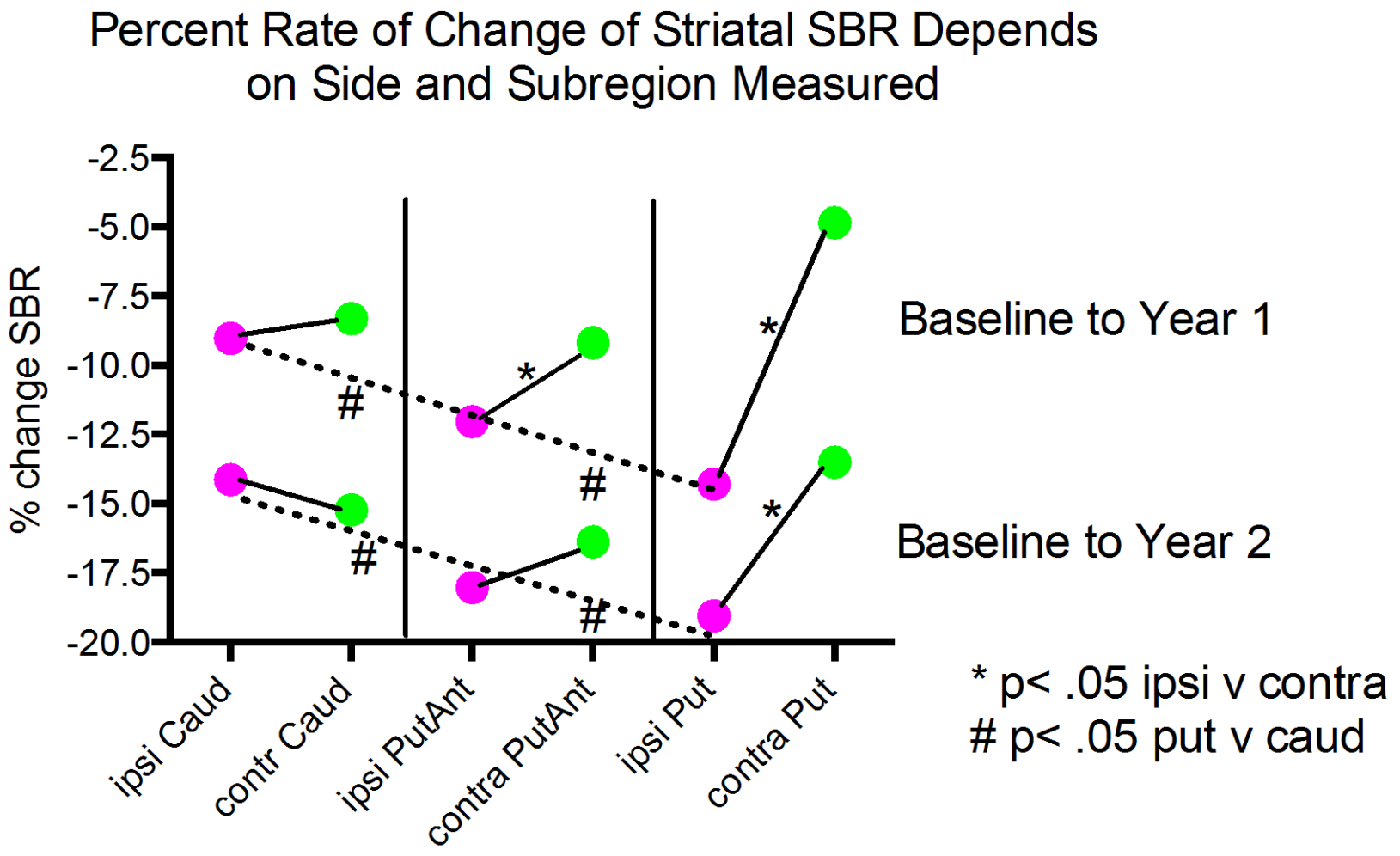
% Subj w/ change SBR <0 :	80.0%	88.1%

* Results- SBR Striatal Subregions



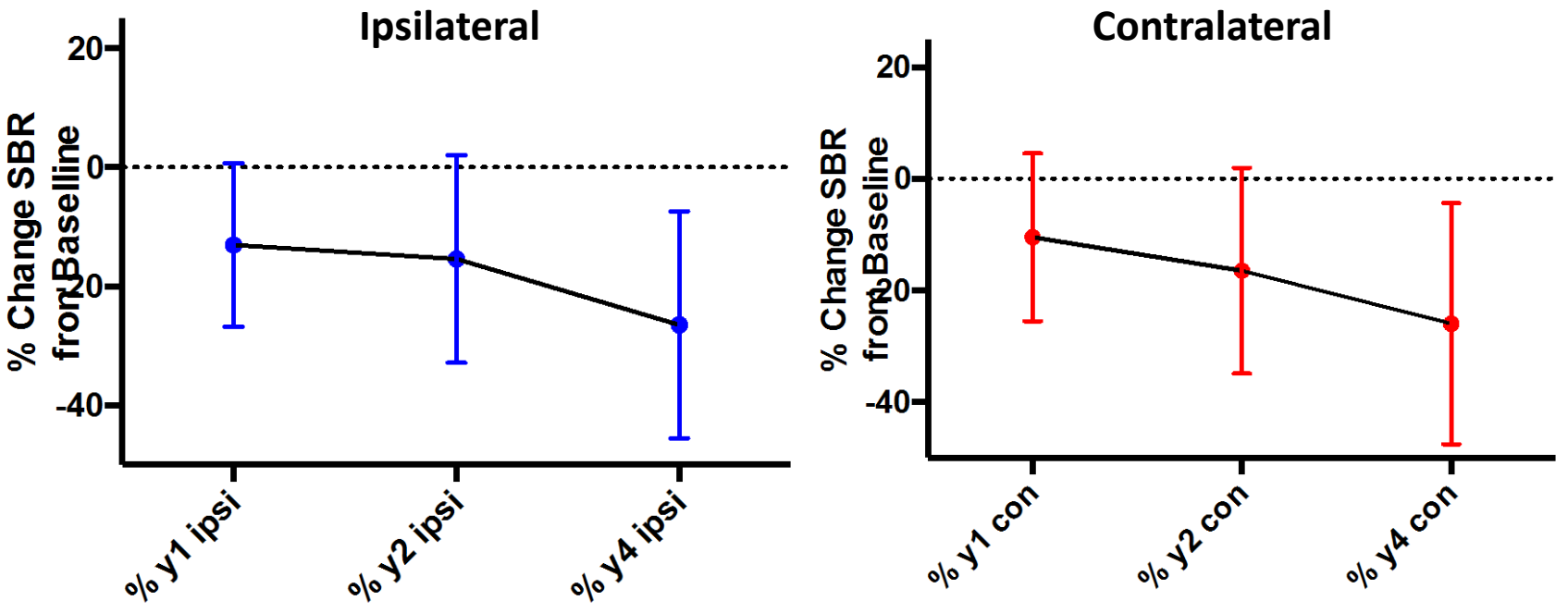
CD= caudate AP= ant putamen PUT= post putamen

* Results- Rate of Change in Striatal Subregions



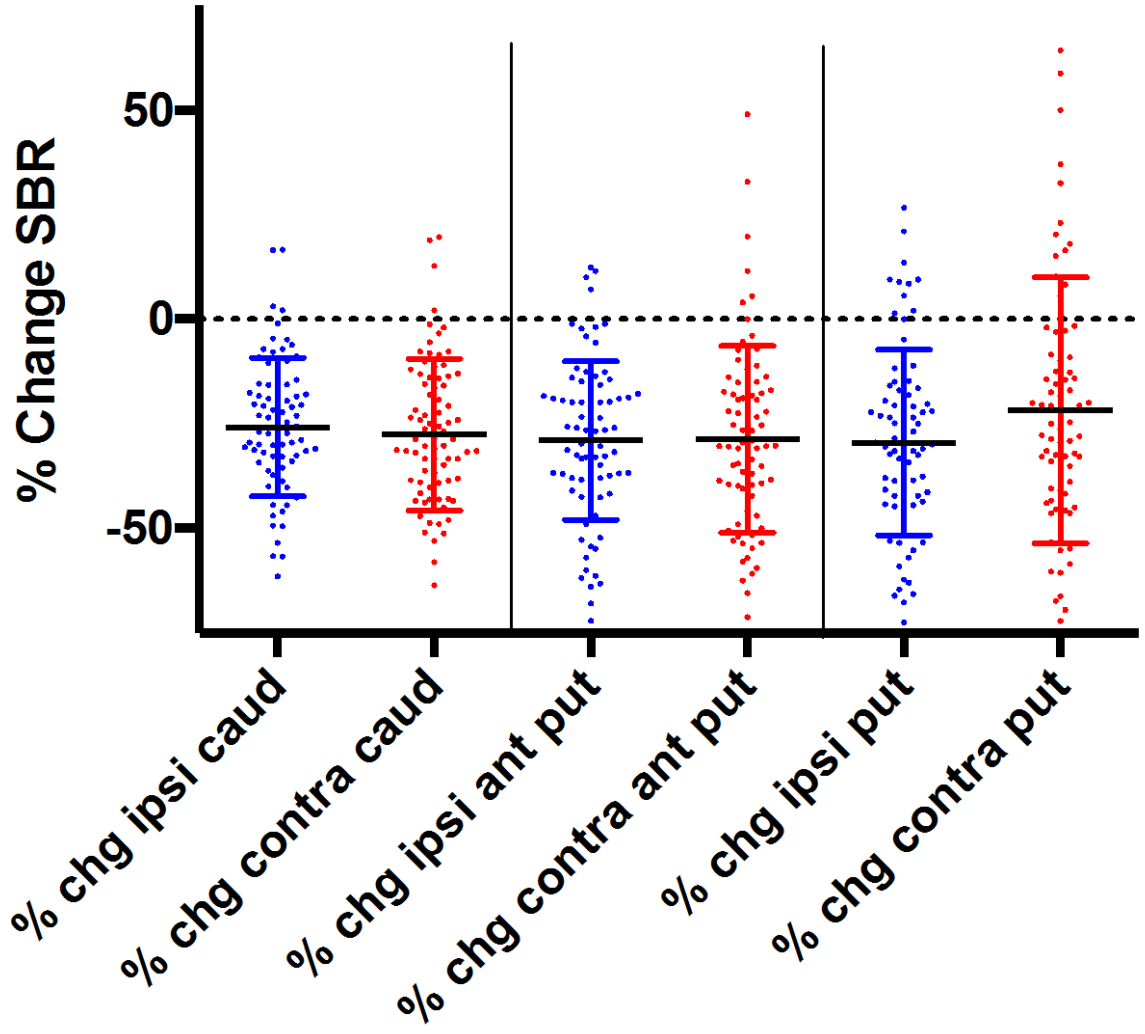
Ipsi = ipsilateral, contra= contralateral, caud=caudate
Put= putamen, PutAnt= anterior putamen

Ipsilateral and Contralateral Mean % Change Striatal SBR over Four Years



Each timepoint is change from original baseline

Baseline to Y4 Mean % Change SBR are Similar Across all Striatal Subregions



Mean % change SBR in Striatal Subregions over 4 years

	ipsi caud	contra caud	ipsi ant put	contra ant put	ipsi put	contra put	ipsi stria	contra stria
Mean	**-25.8**	**-27.5**	**-29.0**	**-28.7**	**-29.4**	**-21.8**	**-28.2**	**-27.8**
Std. Deviation	16.6	18.1	18.9	22.4	22.3	31.8	16.1	18.5
% COV	***64.2***	***65.8***	***65.3***	***78.0***	***75.8***	***146.2***	57.0	66.6
Mean baseline SBR	2.23	1.86	1.53	1.16	0.98	0.65	1.58	1.22

N= 82

%COV variability between regions may be inversely related to baseline SBR

Are PPMI Data of Use to QIBA SPECT Committee?

Data Accessibility and Acquisition Logistics

- Web-based provision of DAT images;PD and age-matched controls
- Create normative templates
- Support claims (longitudinal, discriminatory)
- Standardize test datasets for processing validation

Profile bits and bobs

Reclaiming the discriminatory claim?

Claim 1: **Cross sectional discrimination.**
During the initial presentation of newly symptomatic patients, a diagnosis of Parkinson's disease (PD) is consistent with a finding of a SBR in the posterior putamen that is 50% or less than the value in aged-matched controls, or 80% or less than the value in the whole striatum.

Wrap-up

Review action Items

Any other business