

QIBA SPECT I-123 Biomarker Committee

Nov 16, 2018

Quantitative
Imaging
Biomarkers
Alliance



Agenda

- Roll call 2 min
- Profile 2.0 update, timelines, and strategy 10 min
- Ancillary activities 5 min
- PPMI data relevant to the profile 25 min
- AOB remaining time

Where are we?

Profile: Version 1.0 was released for public comment. Each suggested revision was addressed by the BC and resolved. The committee's new goal is to provide an updated Version 2 by the end of 1Q 2019.

Checklist: Each of the performance requirements in the Profile has been compiled as a set of checklists. These lists have been developed as tools to help actors and imaging sites evaluate their work for conformance with the Profile.

Feasibility Testing: The checklists are being used as quality control tools to assess the ability (or practicality/willingness) of actors to perform each of the Profile's performance specifications. The results of these feasibility tests will then be used to streamline and tighten the Profile performance requirements.

Measuring PD Progression Is Problematic

SLOW, VARIABLE COURSE Clinical measures of Parkinson's disease progression suggest a process which is slow with significant variability both *between* patients and also *within* the individual patient over the course of disease

MEDICATION CONFOUND Assessment of disease progression is confounded by effects of antiparkinson treatments and difficulties achieving complete wash-out of drug effects

PHENOMENOLOGICAL COMPLEXITY Multi-dimensional, complex, and changing clinical picture- what to track; motor scores, ADL's, milestones?



PPMI Study Details: Synopsis

Study population	<ul style="list-style-type: none">▪ 423 de novo PD subjects (newly diagnosed and unmedicated)▪ 196 age- and gender-matched healthy controls▪ 64 SWEDD▪ 67 Prodromal - Olfactory/RBD▪ <i>250 LRRK2 - PD manifest and non-manifesting family members</i>▪ <i>250 GBA- PD manifest and non-manifesting family members</i>▪ <i>100 SNCA - PD manifest and non-manifesting family members</i>▪ <i>Subjects will be followed through 2018</i>
Assessments/ Clinical data collection	<ul style="list-style-type: none">▪ Motor assessments▪ Neurobehavioral/cognitive testing▪ Autonomic, Olfaction, Sleep▪ DaTSCAN, AV133, Amyloid, DTI/RS MRI
Biologic collection/	<ul style="list-style-type: none">▪ DNA, RNA, IPSC▪ Serum and plasma collected at each visit; urine collected annually▪ CSF collected at baseline, 6mo 12 mo and then annually▪ Samples aliquotted and stored in central biorepository
Data and Biosamples shared on website - www.ppmi-info.org	<ul style="list-style-type: none">▪ > 800,000 Data downloads▪ > 100 Sample requests via BRC▪ Ancillary study development



PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson's Research. Other funding partners include a consortium of industry players, non-profit organizations and private individuals.



PPMI IMAGING STUDIES

Nuclear Medicine Techniques

Ioflupane SPECT (DaTScan)- Dopamine transporter

AV133 PET- VMAT2, vesicular transporter

Florbetaben PET- Amyloid deposition

Magnetic Resonance Techniques

MRI- Diffusion Tensor Imaging, DTI maps integrity of brain connections

Resting state MRI- describes functional connections of regions of the brain

MRI T1- provides brain gross anatomy



Two and Four Year Longitudinal Assessment of DAT Imaging Biomarkers in a Progressing Parkinson Disease Cohort: Implications for Clinical Trial Design

John P Seibyl, MD on behalf of the PPMI Investigators

Institute for Neurodegenerative Disorders, and
Invicro, New Haven, United States

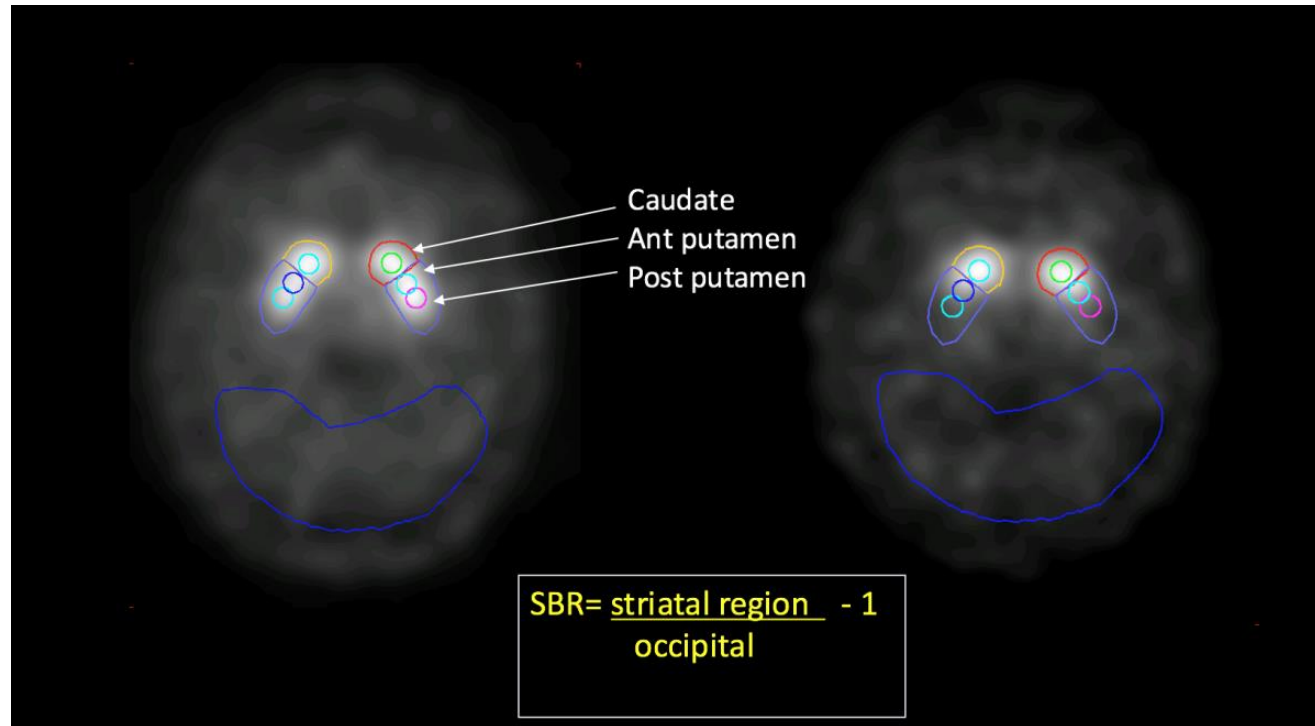


Measuring DAT changes in de novo PD with 123-I Ioflupane SPECT over four years in PPMI

RATIONALE: Prior studies show loss of striatal signal Parkinson's patients studied longitudinally with 123-I Ioflupane SPECT. These studies demonstrate annual loss approximately 7 to 10% of SBR per year, but with significant between subject variance. The purpose of the present investigation was to evaluate different analytic approaches in a large PD cohort studied over four years with serial DAT SPECT.



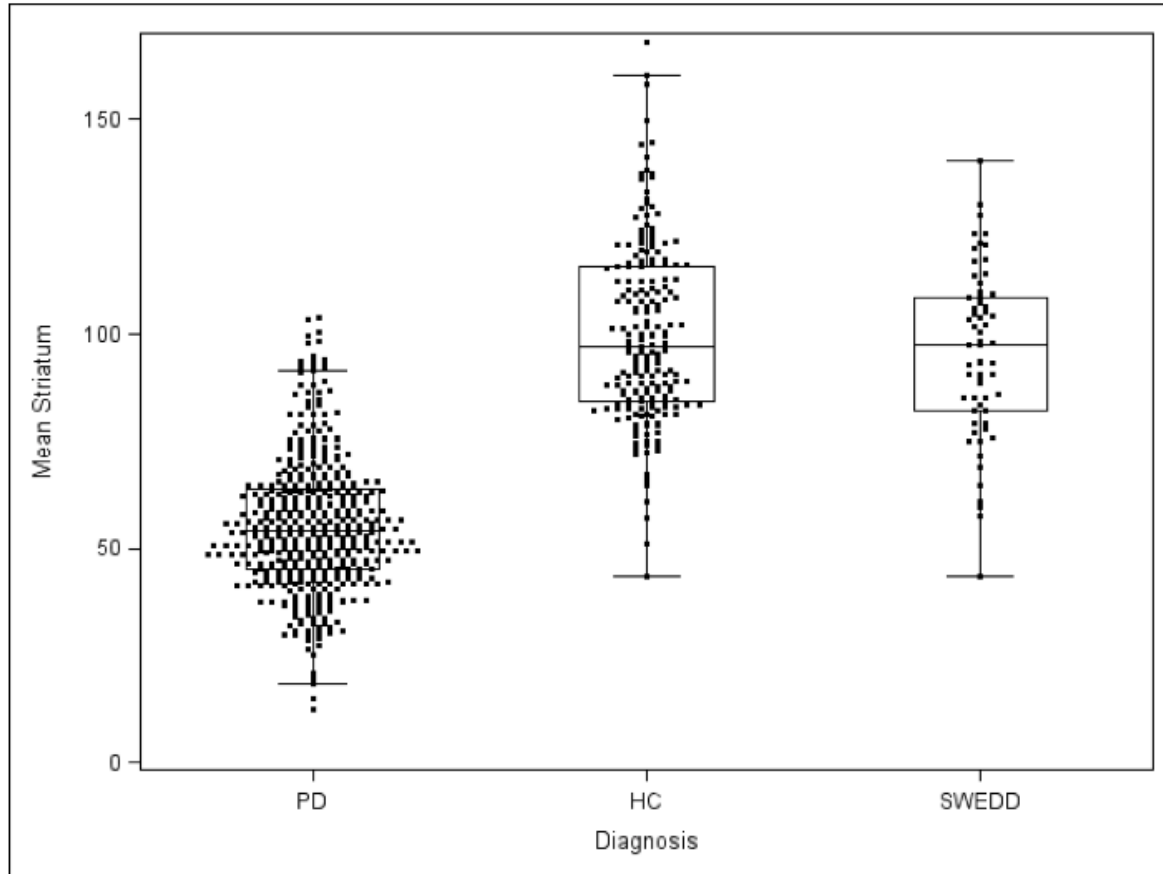
METHODS



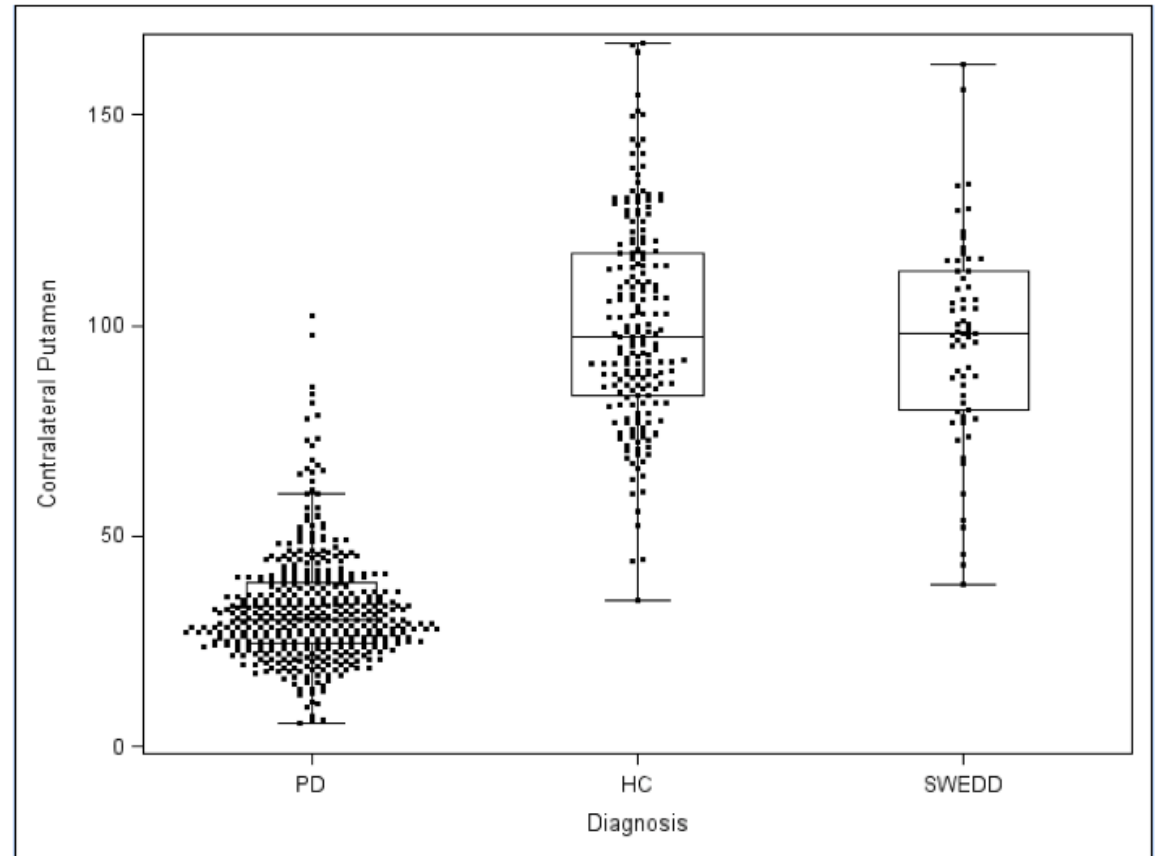
- 343 PD patients in PPMI had serial ioflupane SPECT scans at baseline, 1, and 2 years post enrollment, 282 PD patients had an additional 4 year scan
- Employed small and large region of interest template previously described for developing regional specific binding ratios (SBR).
- Strategies to measure SBR change follows two approaches; delta SBR and % change SBR from baseline.

Baseline DAT SBR, Age-corrected

Mean Striatal SBR



Contralateral Putamen SBR

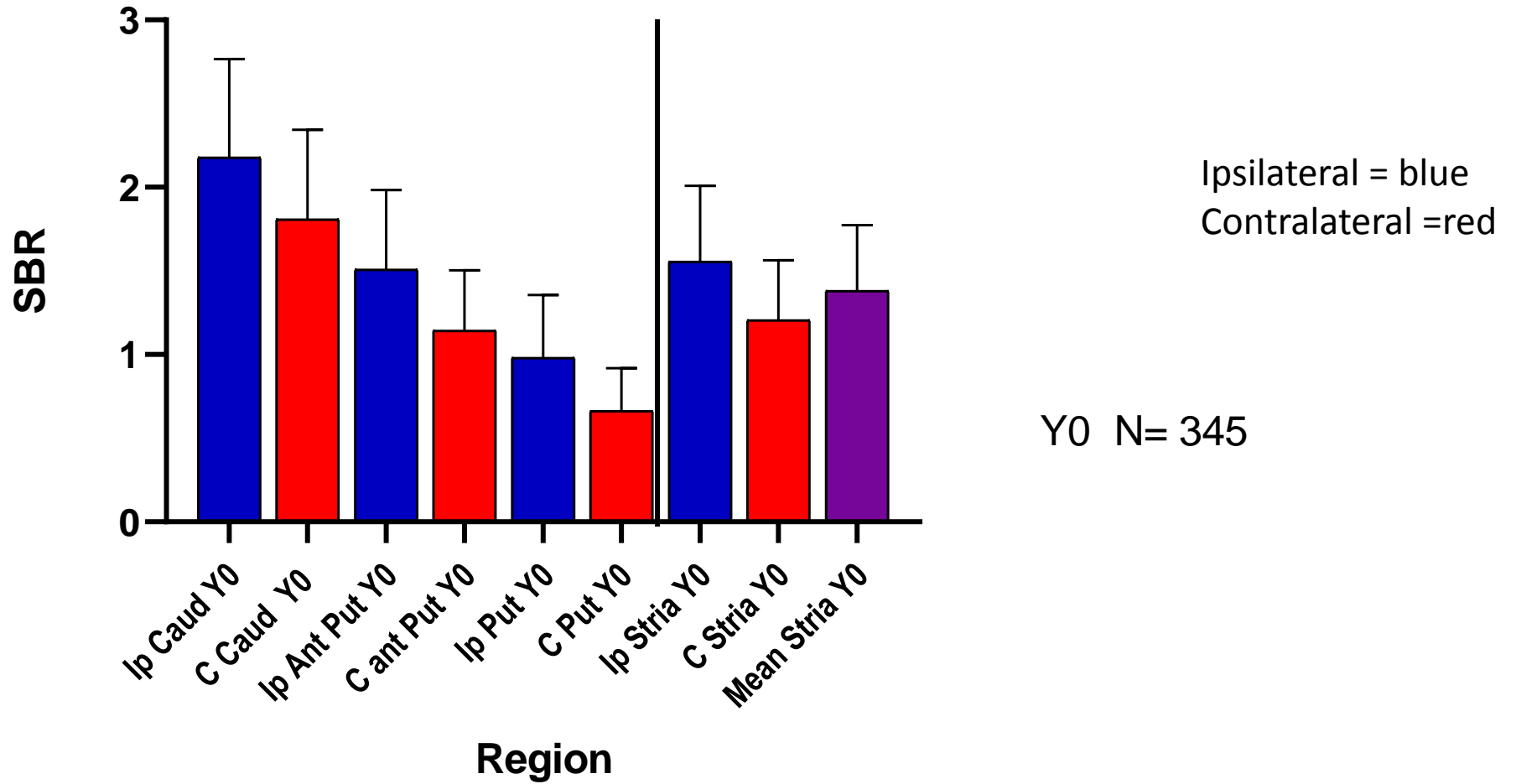


PD n= 423
HC n= 196
SWEDD = 64

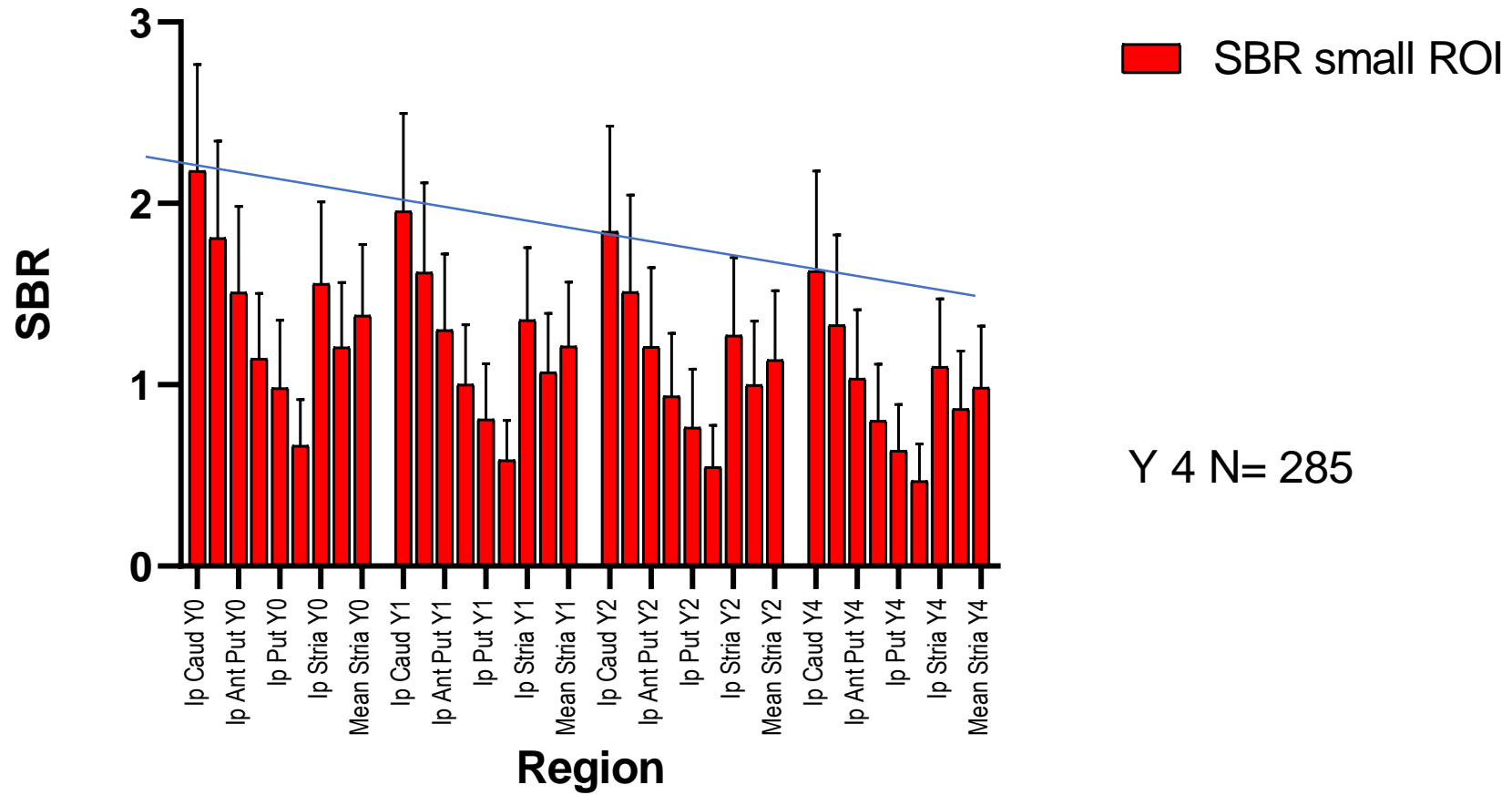
RESEARCH QUESTIONS:

1. What is the better outcome measure of serial DAT change in PD; a delta SBR or a percent change SBR?
2. What is the better striatal sampling strategy; small or large ROIs?
3. Do analytic strategies incorporating curve fitting applied to serial within subject longitudinal SBR data increase the signal size and reduce the variance compared with standard baseline-follow-up SBR change measures?
4. What are the implications of scan analysis method on clinical therapeutic trial design and sample size estimates?

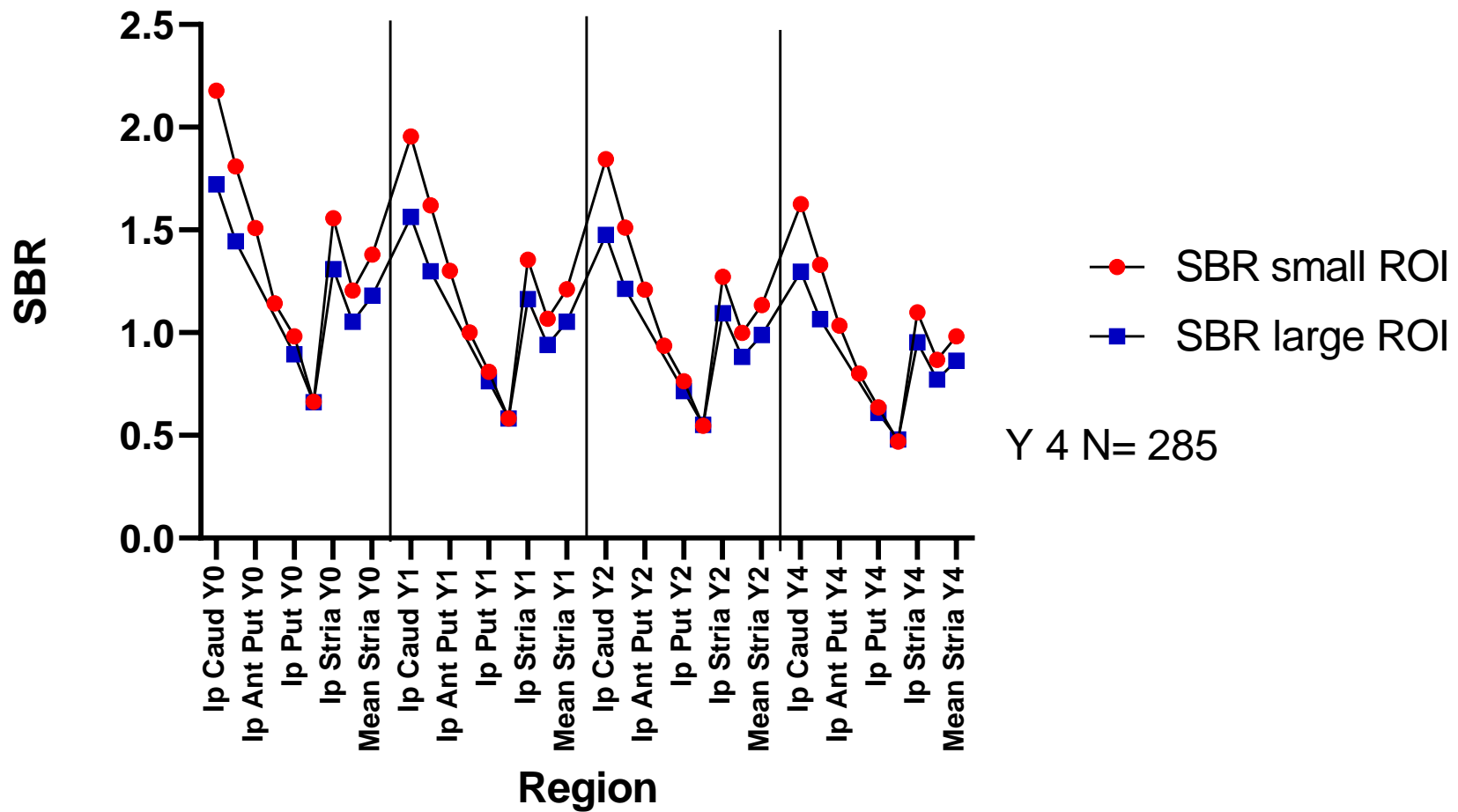
Mean (SD) SBR by REGION



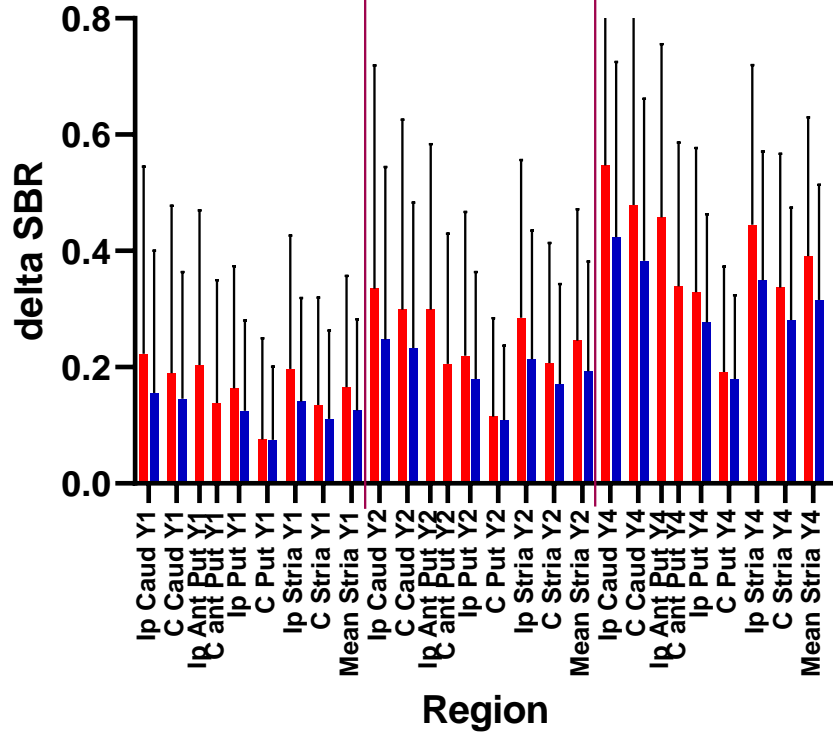
Longitudinal Mean (SD) SBR by REGION



Baseline SBR:Large v Small ROIs



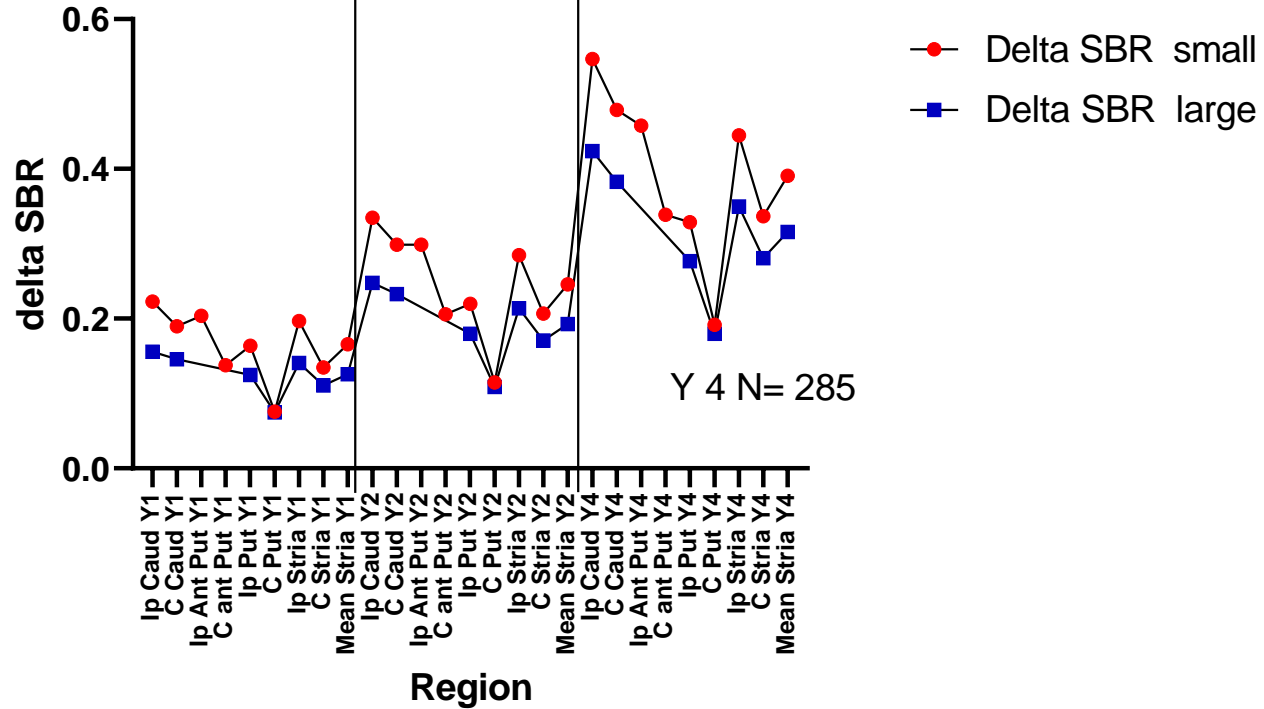
Delta SBR 1, 2 & 4 Yr



- Delta SBR small
- Delta SBR large

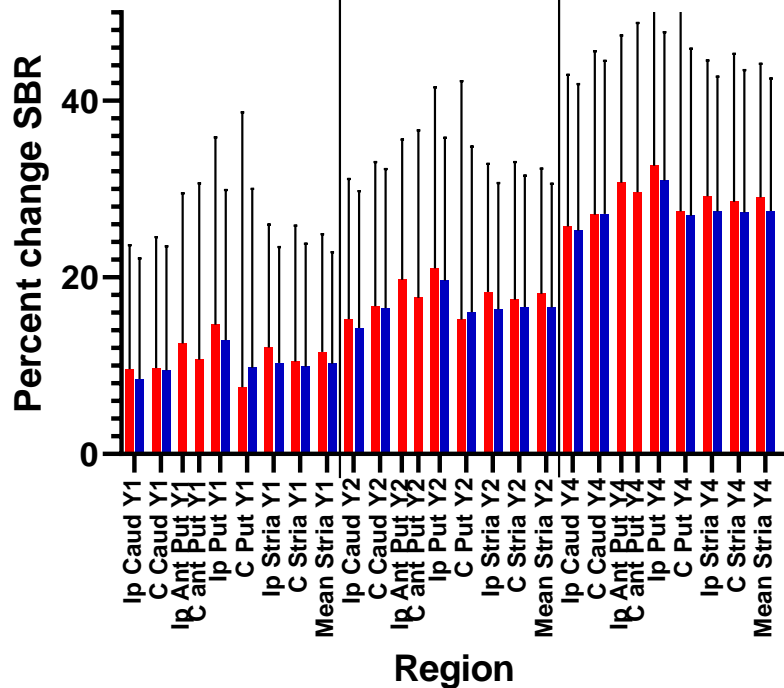
Y 4 N= 285

Delta SBR 1, 2 & 4 Yr



- Delta SBR small
- Delta SBR large

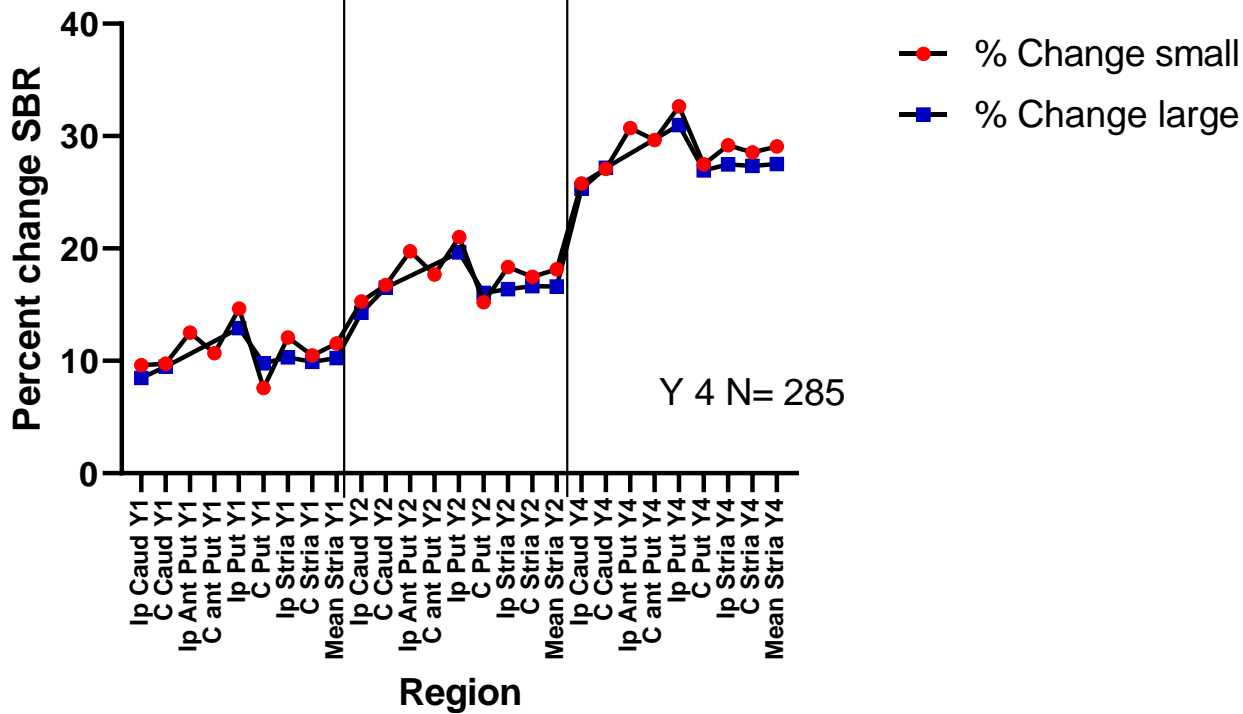
% Change SBR 1, 2 & 4 Yr



% Change small
% Change large

Y 4 N= 285

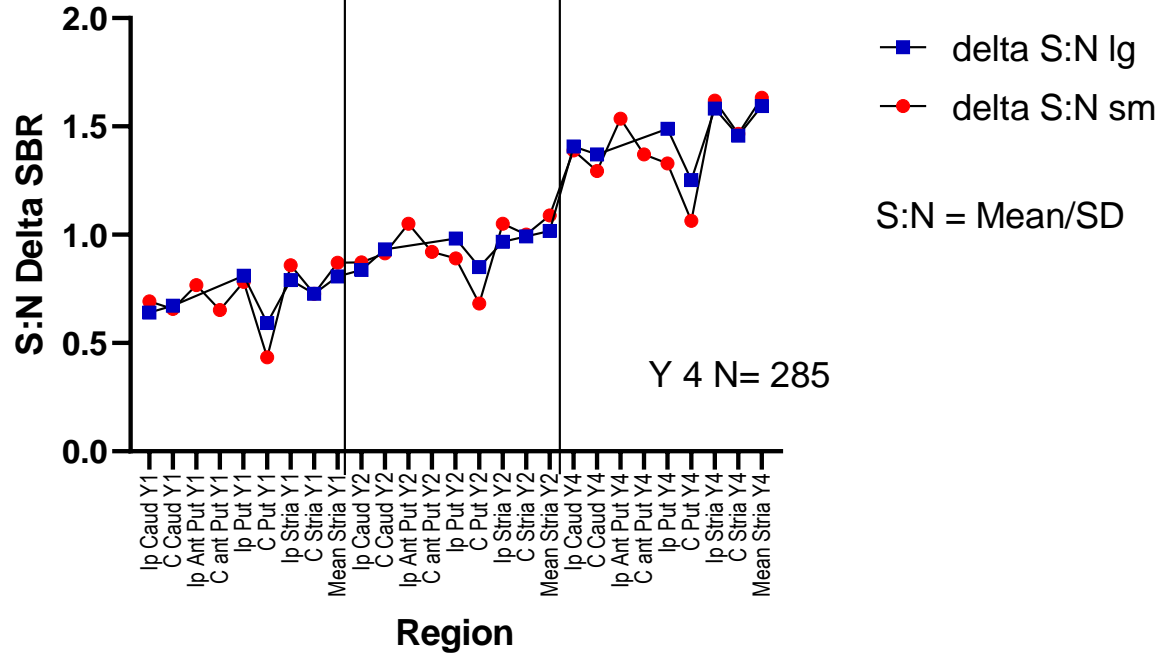
% Change SBR 1, 2 & 4 Yr



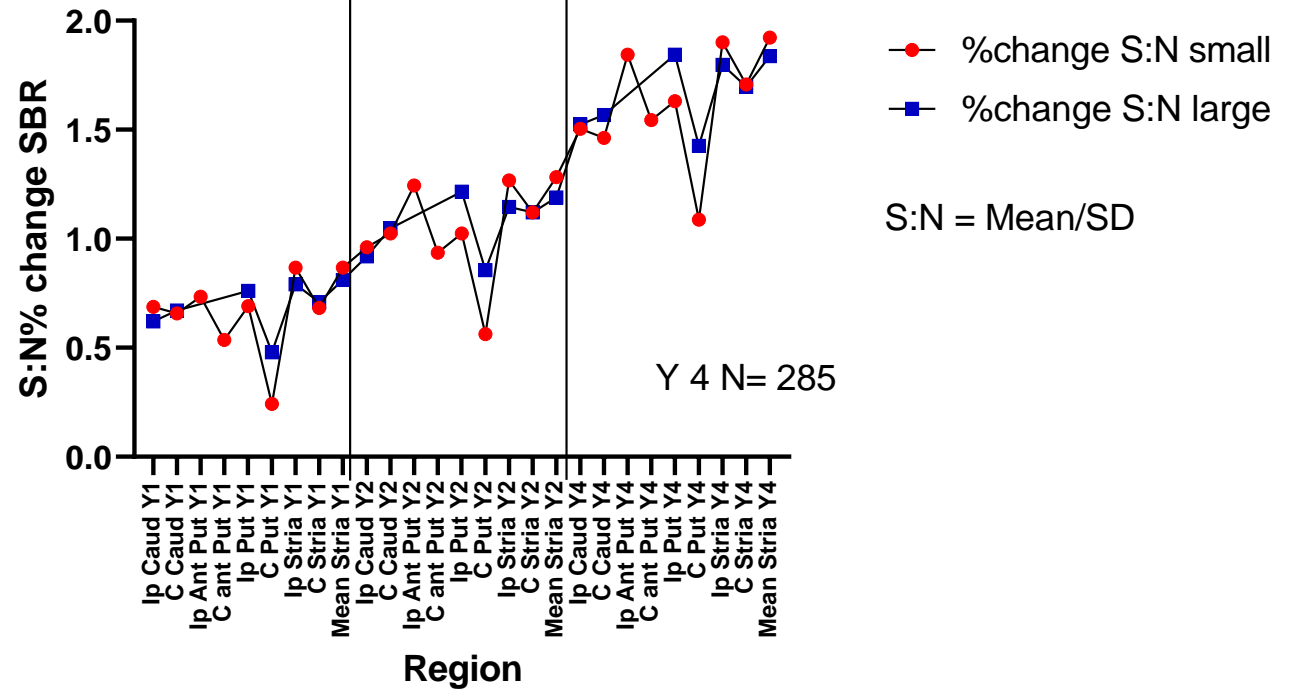
% Change small
% Change large

Y 4 N= 285

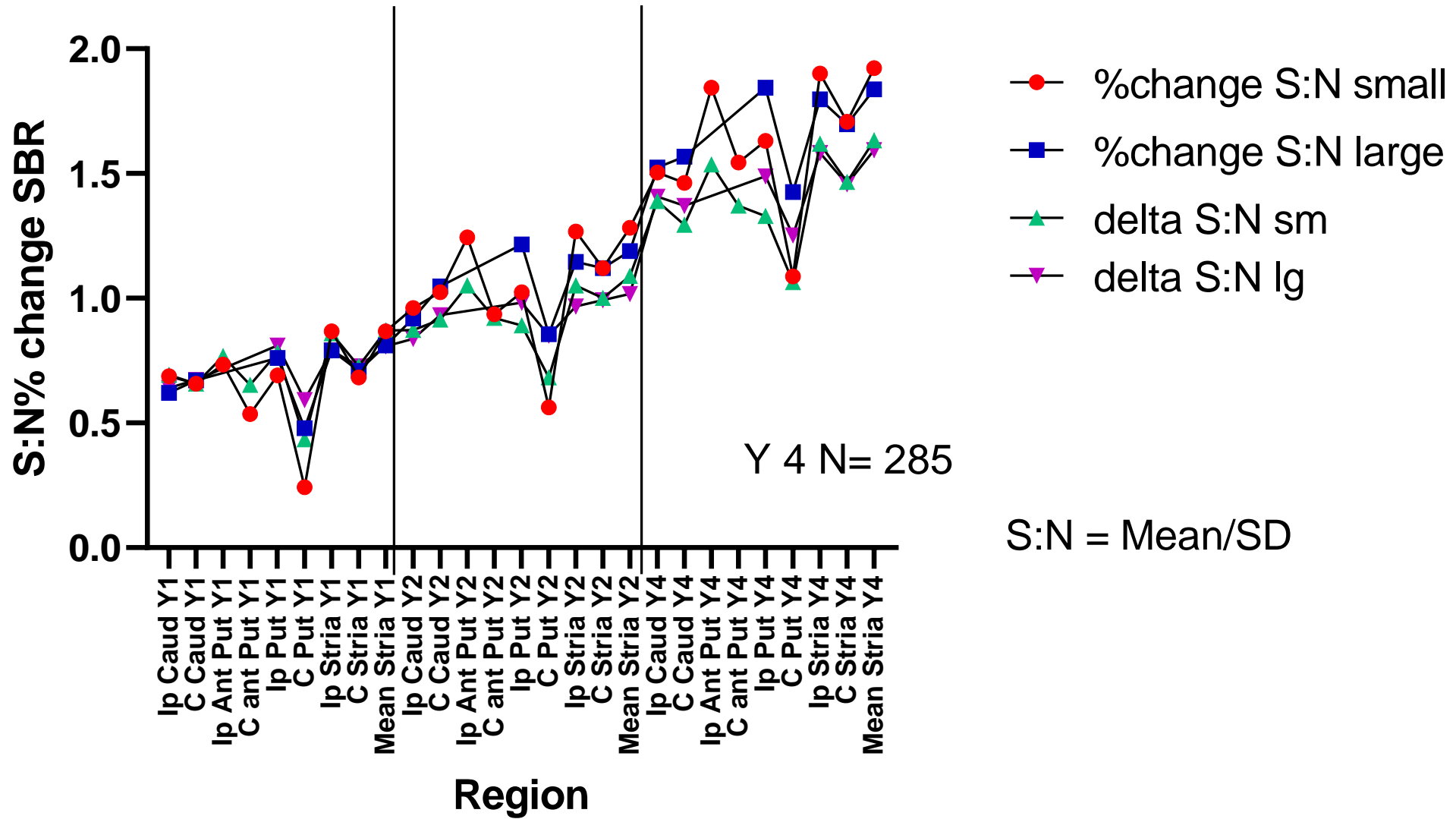
S:N Delta SBR 1, 2 & 4 Yr



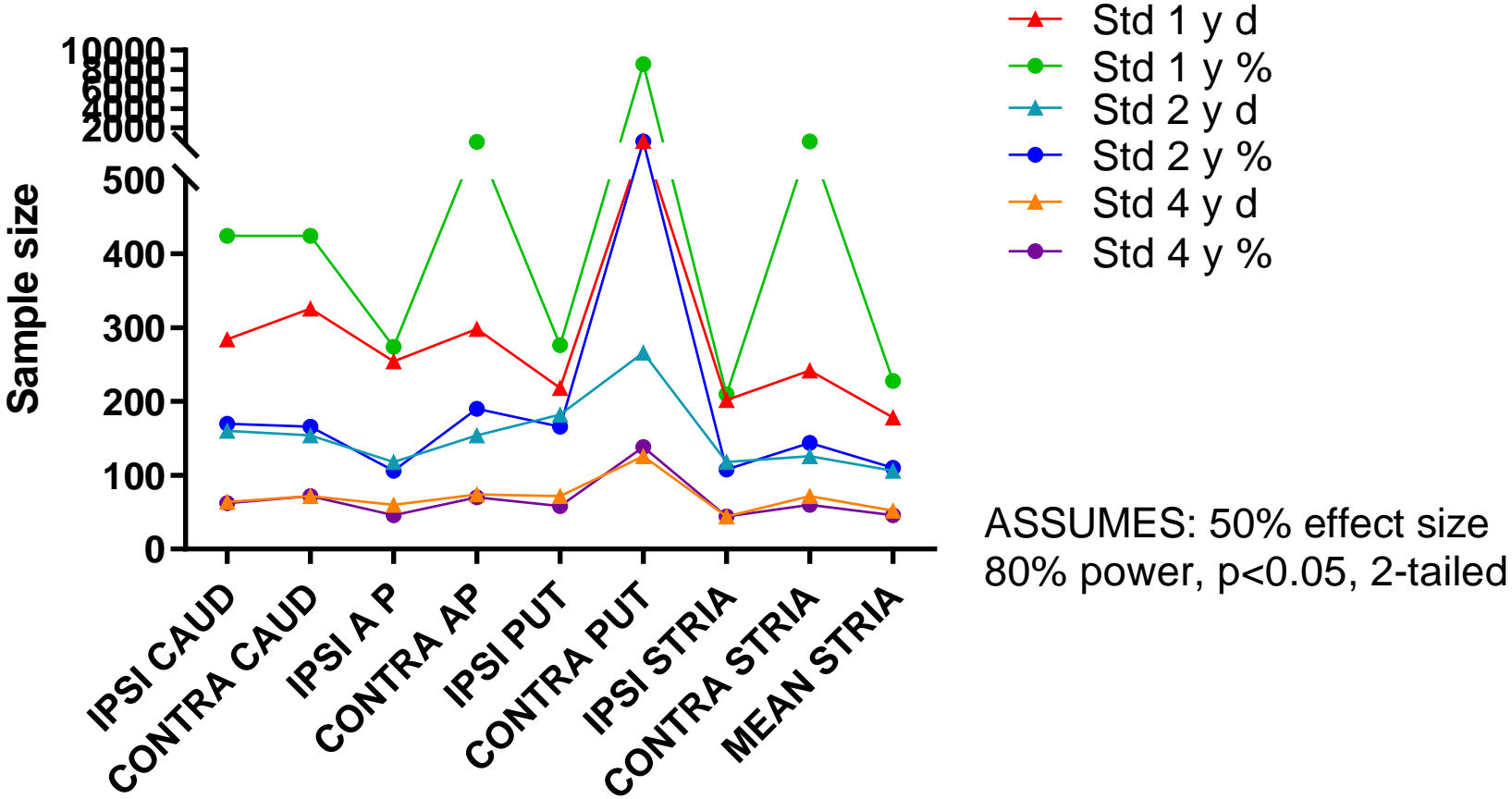
S:N % Change SBR 1, 2 & 4 Yr



S:N % Change & Delta SBR 1, 2 & 4 Yr



Sample size by region



ANALYSIS METHODS

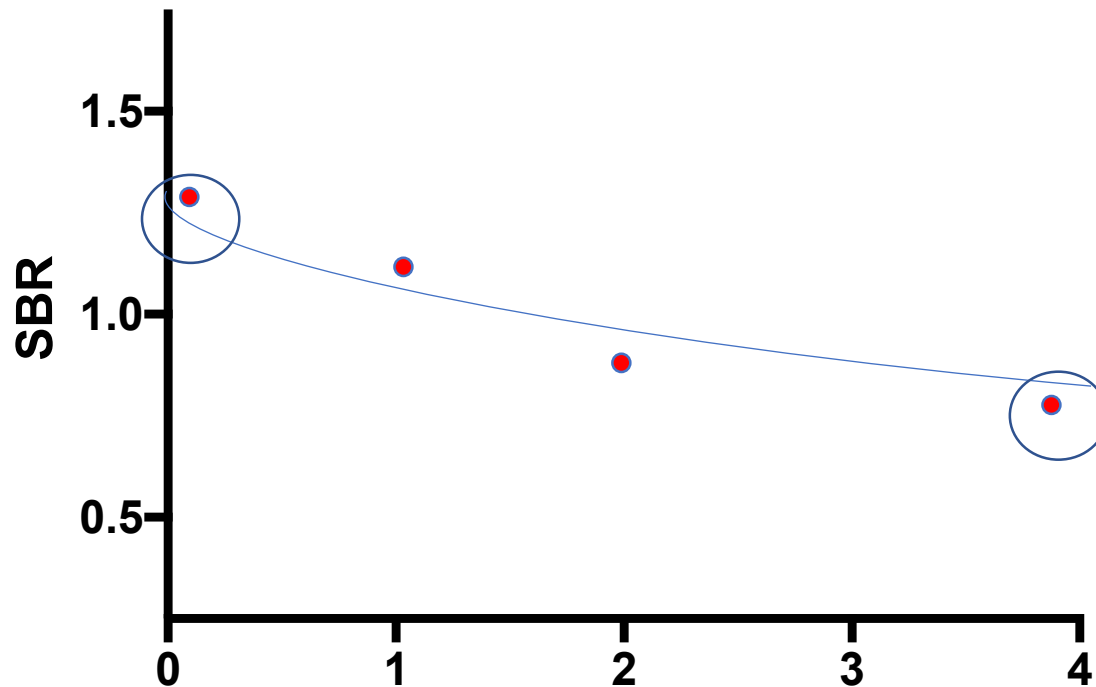
Method 2 Exponential fit

Delta and % change from equation

Method 1

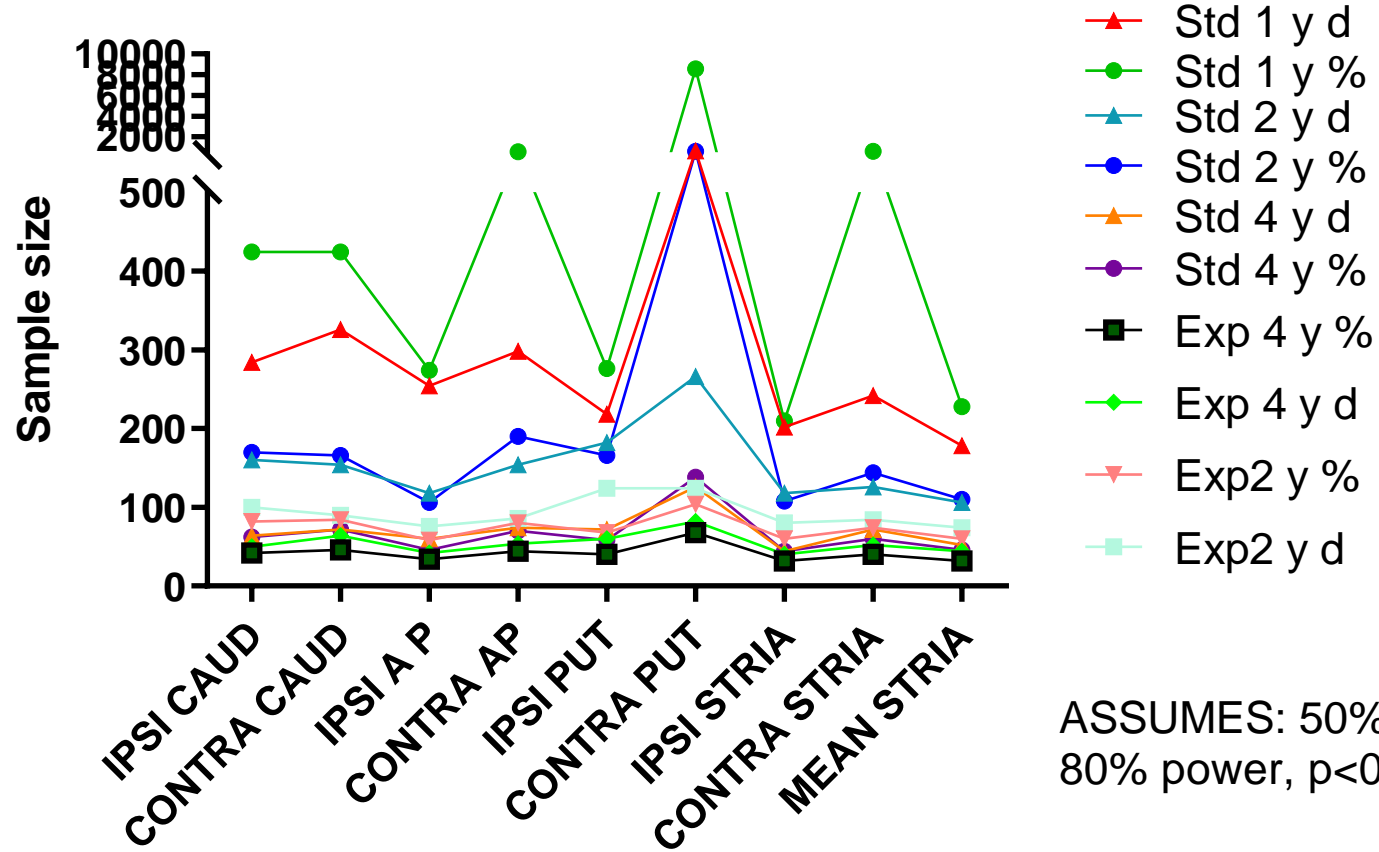
Delta SBR = - SBR(y0) - SBR(y4)

% change = delta SBR / SBR(y0)



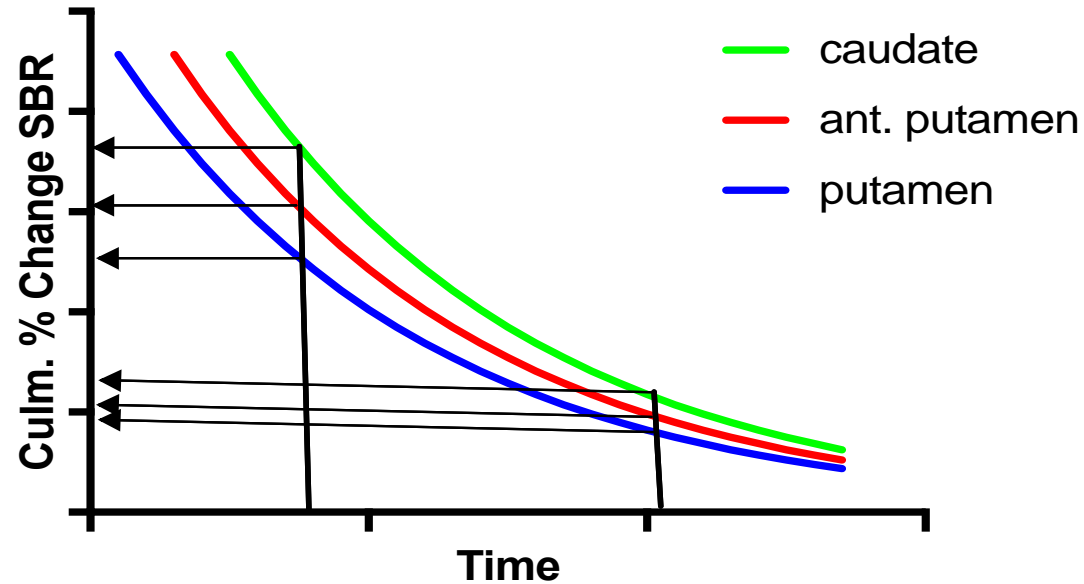
Compare variance and signal:noise for each measure as well as strength of correlation with motor symptoms and power analyses for detecting change in clinical trials.

Sample size by region



ASSUMES: 50% effect size
80% power, p<0.05, 2-tailed

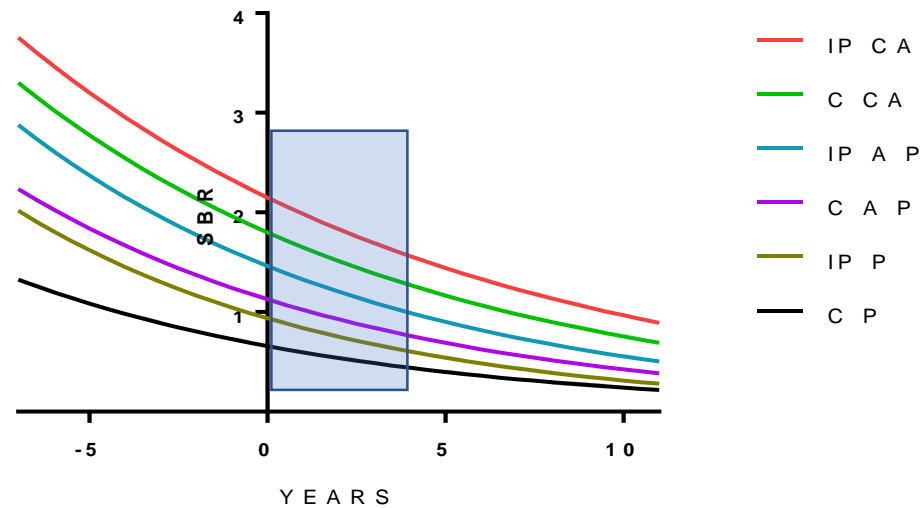
A Model for Non-linear Reductions in Regional Striatal SBR Change Predicts Convergence of % SBRs Over Time



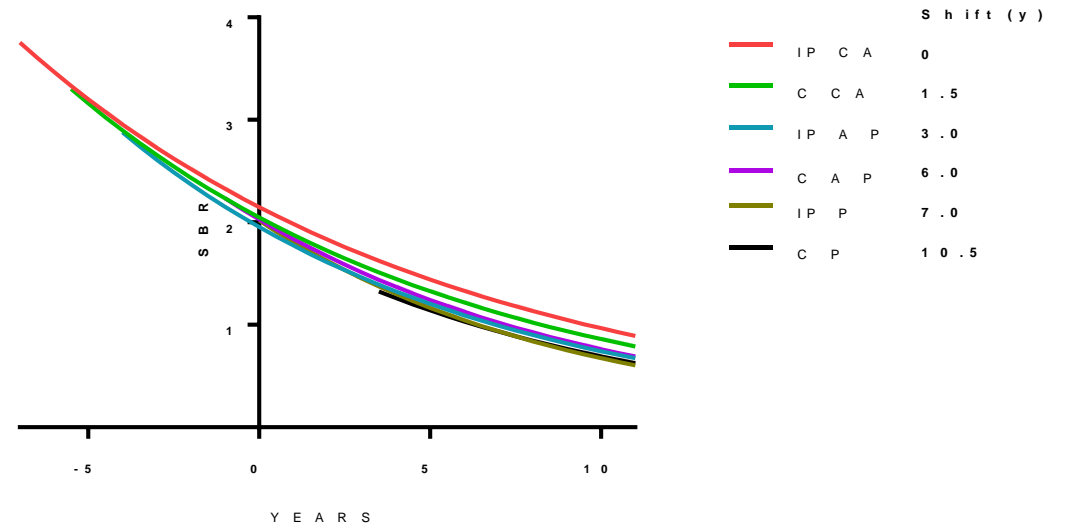
A non-linear pattern of DAT loss, such as in the simple exponential curves depicted above, identical across all striatal subregions, but with a phase shift to the right from posterior putamen to anterior putamen to caudate can explain the regional differences in the rates of specific binding loss seen in this study and their subsequent equalization. When assayed at time 1, there are regional differences in the absolute SBR, and those regions with highest SBRs are also on the fastest portion of the elimination curve. At time 2, the absolute differences in regional SBRs and the percent change per year are diminishing and converging.

Regional striatal SBR based on based on monexponential curve fits of 4 year, 4 scan data extrapolating 6 y prior and 11 y post baseline shows similar curves apparently phase shifted

Mean curves (n=271, 4 Y data)



Mean curves (n=271, 4 Y data)



Shifting the curves back to right such that they overlap results in an estimate of the years that region is ahead in the neurodegenerative process relative to ipsilateral caudate.

Conclusions

- These multicenter, multicamera data are consistent with other smaller studies indicating a 6-10% SBR loss/yr and exponential patterns of DAT signal reduction.
- Striatal sub-regions have different signal:noise characteristics for measures of SBR change over four years with contralateral putamen the lowest and mean striatum and ipsilateral putamen the highest and better for tracking treatment-induced slowing of DaT loss.
- Large and small ROI strategies are generally equivalent with regard to signal to noise, but smaller ROIs provide additional, relevant striatal subregion information.
- Percent change SBR is superior to delta SBR in tracking DaT signal loss.
- Correlation with motor UPDRS (data not shown) is moderate but significant and highest for methods using nonlinear fits.
- Power analyses are most robust for data analyzed with exponential fitting.

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