A Longitudinal Analysis of DaTscan Data from Parkinson's Disease Subjects with and without REM Sleep Behavior Disorder

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Jasmine Li, Alena Figueroa, and Stephanie Lewis

Project Mentors: Professor Ryan Cho and

Janel Fedler

Background – Parkinson's Disease and RBD

- **<u>Parkinson's Disease (PD):</u>** a degenerative neurological disorder caused by the loss of dopamine producing neurons in the brain.
  - Main symptoms: rigidity, tremor, bradykinesia
  - Also non-motor symptoms

- **<u>Parkinson's Progressive Markers Initiative (PPMI):</u>** an international, multisite study designed to identify and validate potential biomarkers for PD.

- **<u>Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD):</u>** a condition characterized by abnormal or violent behavior during REM sleep. RBD is accepted as a preclinical symptom of PD.

- **<u>DaTscan imaging:</u>** a brain imaging method used to capture the density of dopamine transporters (DAT) in the striatum.

Regions of the Brain and DAT
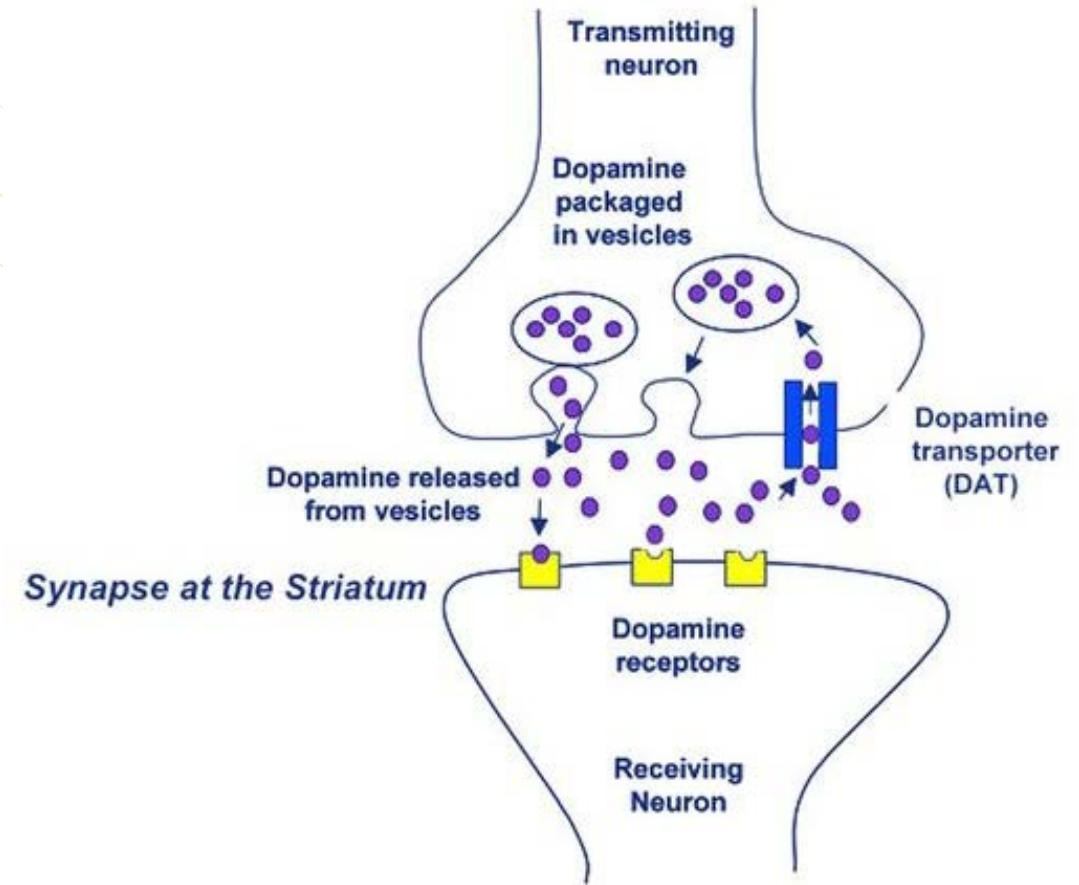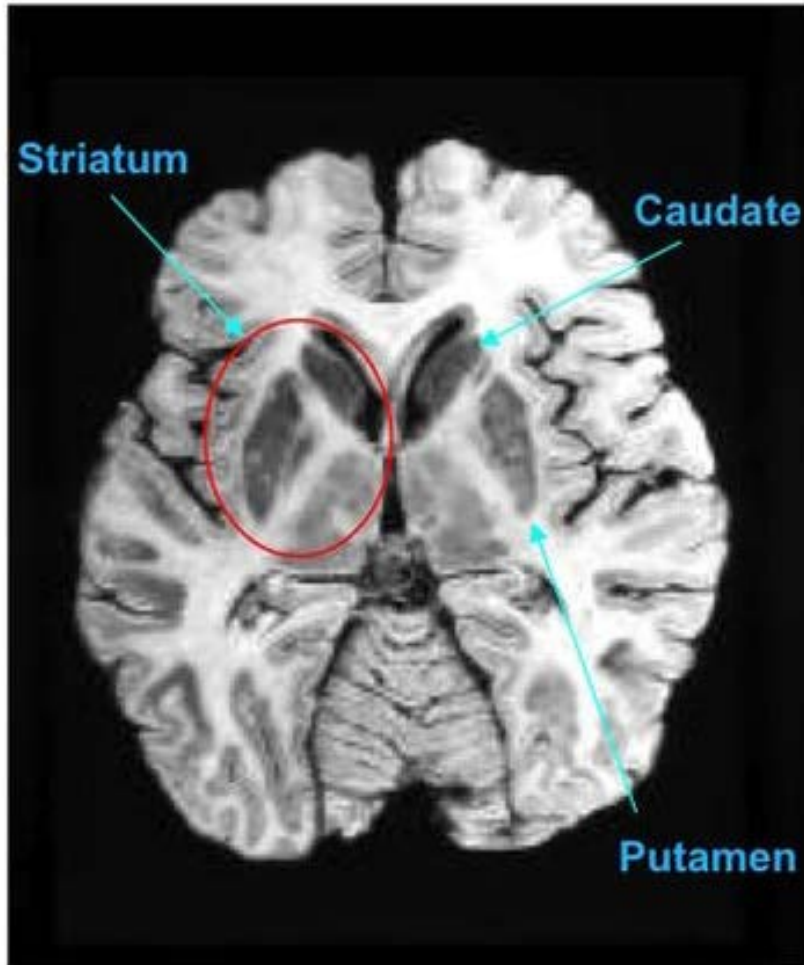
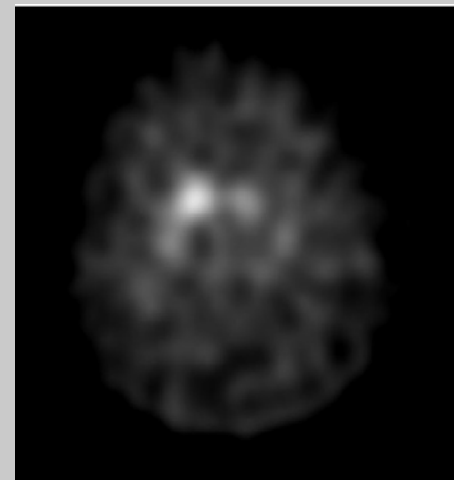| Normal DaTscan Image Results	Abnormal DaTscan Image Results
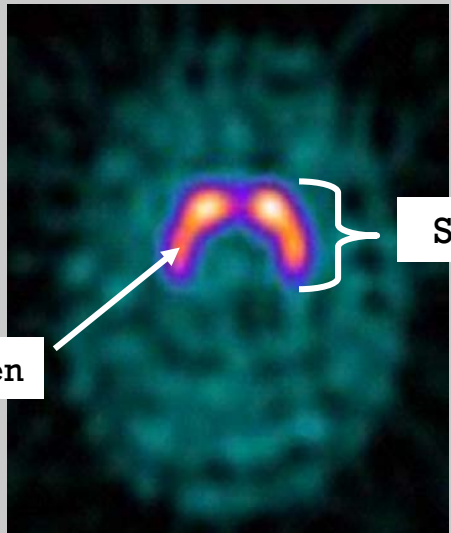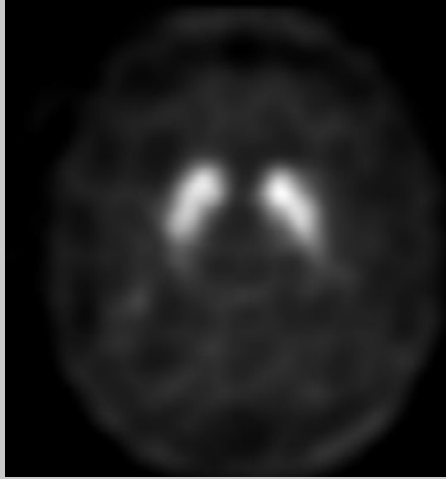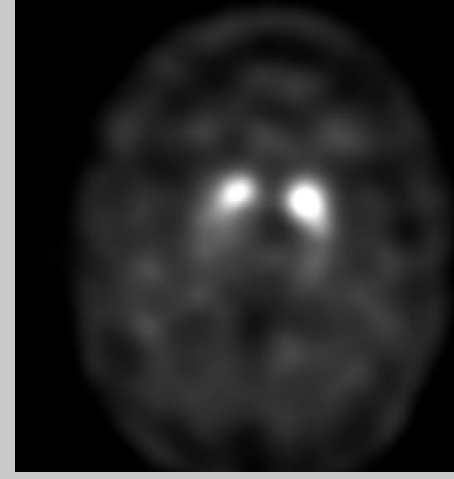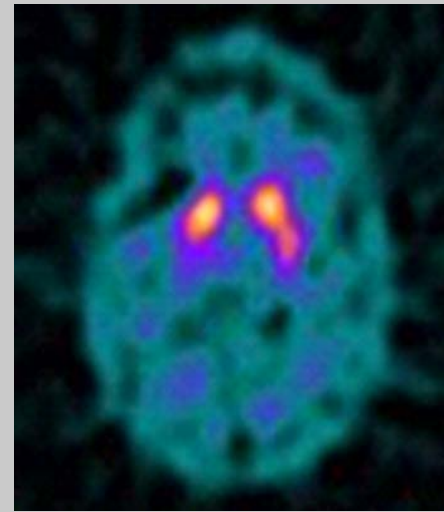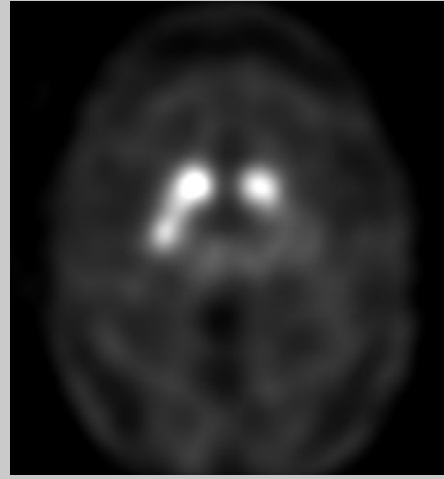
Striatum

Putamen

Background – PPMI

- Observational clinical study

- Goal: identifying progression markers to improve PD treatment

- Establish protocol for imaging data and biological samples

- Project data was from PPMI
  - Studied at baseline as well as over period of 5 years

Methods

PPMI assesses subjects' RBD symptoms through the RBD screening questionnaire (RBDSQ).

- Range: [0, 13]

- RBDSQ score of 6 was determined to be the cutoff point between patients who did or did not have RBD.

  - For example, patients with a RBDSQ ≥ 6 were determined to have RBD

- Separated the PD patients into two groups: "RBD" and "No RBD."

- Using longitudinal PPMI data, we ran models to compare the progression of DaTscan measures between PD patients who have RBD and those who do not.

| Variable	RBD Group (N = 108)	No RBD Group (N = 312)	p-value
Age			
Mean (SD)	61.8 (9.8)	61.6 (9.7)	
Min – Max	34.8 – 82.3	33.5 – 84.9	0.828
Gender			
Female	29 (27%)	116 (37%)	
Male	79 (73%)	196 (63%)	0.068
Race			
White	98 (91%)	290 (93%)	
Black/African-American	3 (3%)	3 (1%)	
Asian	2 (2%)	6 (2%)	0.586
Other	5 (4%)	13 (4%)	
Age at PD diagnosis			
Mean (SD)	59.9 (9.9)	59.6 (10.0)	
Min – Max	32.6 – 81.5	25.4 – 83.0	0.725
Duration of disease (months)			
Mean (SD)	6.1 (6.1)	6.8 (6.7)	
Min – Max	0.4 – 26.1	0.7 – 35.8	0.280
Striatum SBR			
Mean (SD)	1.4 (0.5)	1.4 (0.4)	
Min - Max	0.3 – 2.6	0.5 – 2.5	0.571
Putamen SBR			
Mean (SD)	0.8 (0.3)	0.8 (0.3)	
Min – Max	0.2 – 2.2	0.3 – 2.2	0.700

Features at Baseline

- T-tests for continuous variables
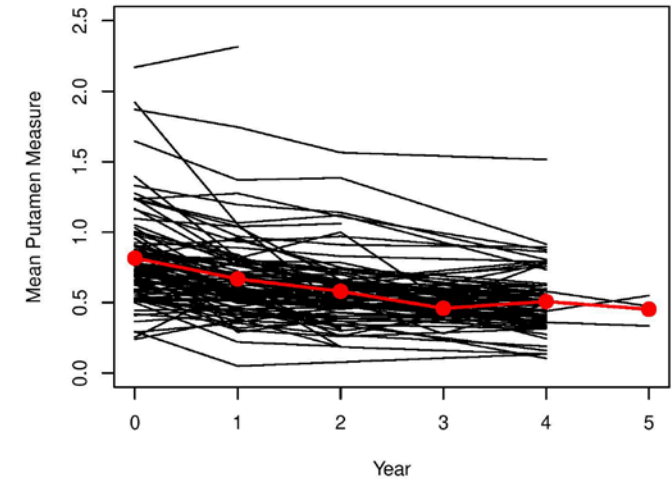- Chi-squared tests for categorical variables

Spaghetti Plots and Sample Mean Trajectories

- Measures were taken at baseline and at years 1, 2, and 4
- Measures at years 3 and 5 were taken out of the scheduled window
  - However, they did not noticeably change the sample mean trajectories, so they were included
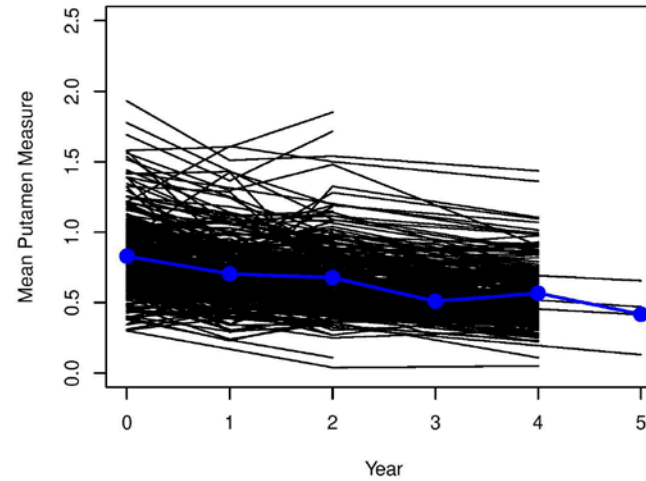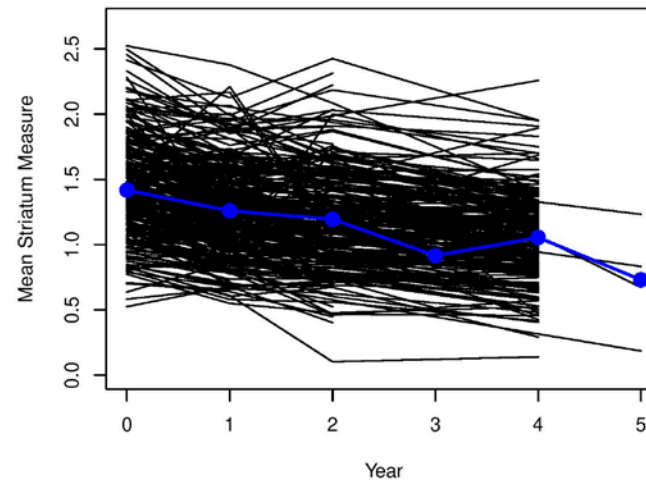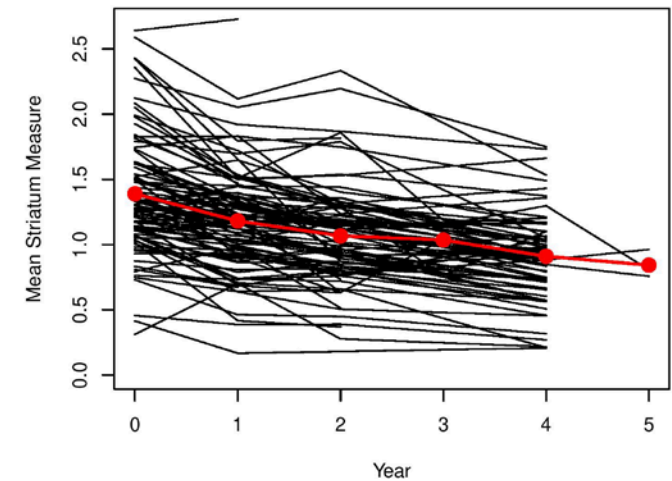
Initial Model for Change in Mean DaT Measures Over Time

Assumption: Outcomes will change linearly over time

Goal: To compare the slopes for each group and test H_0: $\beta_3 = 0$ versus H_A: $\beta_3 \neq 0$.

- Population:

$$E(SBR) = \beta_0 + \beta_1 \cdot year + \beta_2 \cdot RBD + \beta_3 \cdot year \cdot RBD$$

- Estimate:

$$\widehat{E(SBR)} = \widehat{\beta_0} + \underbrace{\widehat{\beta_1} \cdot year}_{\text{Time Effect}} + \underbrace{\widehat{\beta_2} \cdot RBD}_{\text{RBD Effect}} + \underbrace{\widehat{\beta_3} \cdot year \cdot RBD}_{\text{Interaction Effect}}$$

The RBD indicator equals 1 if the PD subject has RBD and 0 if the PD subject does not have RBD.

- No RBD Group:

$$\widehat{E(SBR)} = \widehat{\beta_0} + \widehat{\beta_1} \cdot year$$

- RBD Group:

$$\widehat{E(SBR)} = (\widehat{\beta_0} + \widehat{\beta_2}) + (\widehat{\beta_1} + \widehat{\beta_3}) \cdot year$$

GEE Results

- We used an autoregressive correlation structure (ar1) to account for within-subject correlation.

Region: Putamen

Coefficient	Estimate	SE	p-value
Intercept	0.821	0.0156	< 0.001
Year	-0.067	0.003	< 0.001
RBD	-0.027	0.036	0.460
RBD:year	-0.003	0.007	0.650

$$E(\widehat{SBR_P}) = 0.821 - 0.067 \cdot year - 0.027 \cdot RBD - 0.003 \cdot year \cdot RBD$$

Region: Striatum

Coefficients	Estimate	SE	p-value
Intercept	1.405	0.021	< 0.001
Year	-0.094	0.004	< 0.001
RBD	-0.037	0.048	0.447
RBD:year	-0.020	0.008	0.017

$$E(\widehat{SBR_S}) = 1.405 - 0.094 \cdot year - 0.037 \cdot RBD - 0.020 \cdot year \cdot RBD$$

Linear Trends for No RBD and RBD Groups

Mean Putamen Measures Over Time

Mean Striatum Measures Over Time
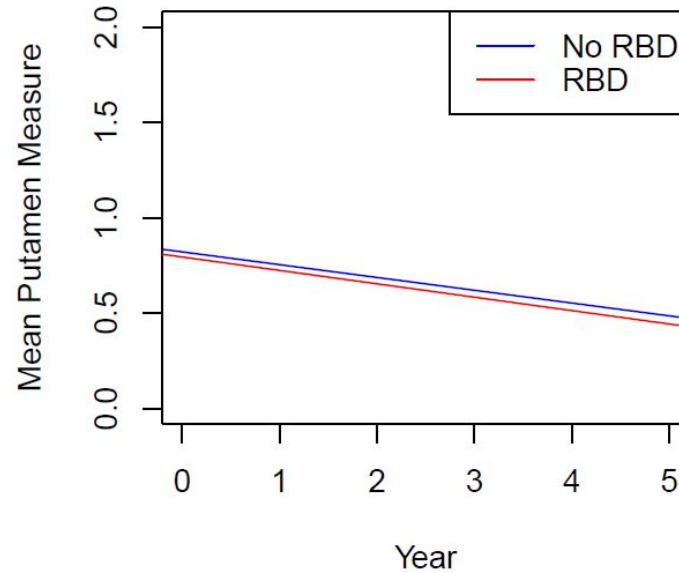
Region: Putamen

- No RBD:

$$E(\widehat{SBR_P}) = 0.821 - 0.067 \cdot year$$

- RBD:

$$E(\widehat{SBR_P}) = 0.794 - 0.070 \cdot year$$
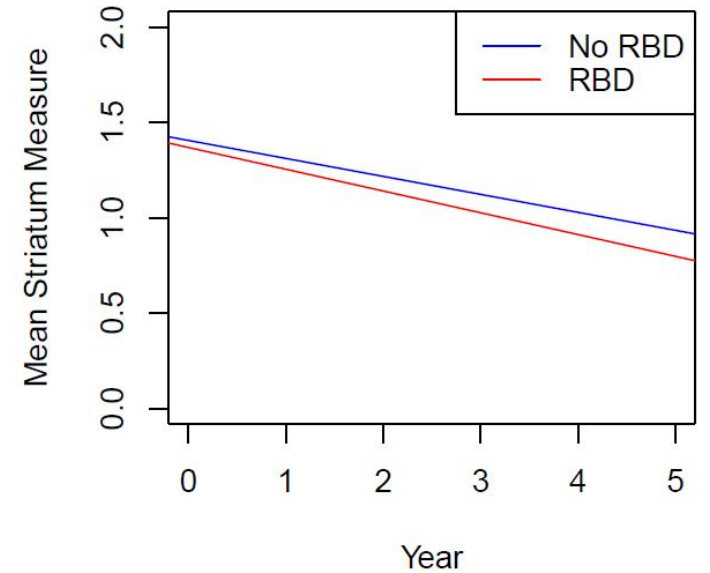
Region: Striatum

- No RBD:

$$E(\widehat{SBR_S}) = 1.405 - 0.094 \cdot year$$

- RBD:

$$E(\widehat{SBR_S}) = 1.368 - 0.114 \cdot year$$

Adjusting the Model for Covariates

$$\widehat{E(SBR)} = \widehat{\beta}_0 + \underbrace{\widehat{\beta}_1 \cdot year}_{\text{Time Effect}} + \underbrace{\widehat{\beta}_2 \cdot RBD}_{\text{RBD Effect}} + \underbrace{\widehat{\beta}_3 \cdot year \cdot RBD}_{\text{Interaction Effect}} + \beta_4 \cdot age + \beta_5 \cdot gender + \beta_6 \cdot duration,$$

where the age of the subject and the duration of PD since diagnosis are the values at baseline.

GEE Results

Region: Putamen

Coefficients	Estimate	SE	p-value
Intercept	0.983	0.092	<0.001
Year	-0.067	0.003	<0.001
RBD	-0.027	0.037	0.458
RBD:year	-0.003	0.007	0.616
Age	-0.003	0.001	0.033
Gender	0.013	0.027	0.628
Duration	-0.034	0.019	0.076

Region: Striatum

Coefficients	Estimate	SE	p-value
Intercept	1.731	0.129	<0.001
Year	-0.094	0.004	<0.001
RBD	-0.033	0.049	0.496
RBD:year	-0.020	0.008	0.015
Age	-0.006	0.002	0.001
Gender	0.030	0.037	0.420
Duration	-0.007	0.031	0.824

$$E(\widehat{SBR}_P) = 0.983 - 0.067 \cdot year - 0.027 \cdot RBD - 0.003 \cdot year \cdot RBD - 0.003 \cdot age + 0.013 \cdot gender - 0.034 \cdot duration$$

$$E(\widehat{SBR}_S) = 1.731 - 0.094 \cdot year - 0.033 \cdot RBD - 0.020 \cdot year \cdot RBD - 0.006 \cdot age + 0.030 \cdot gender - 0.007 \cdot duration$$

Conclusion

- Significant interaction between yearly progression and RBD status for <u>mean striatum measure</u>
  - NOT for mean putamen measure
- Additional 0.020 reduction in striatum measure per year for RBD patients
- Statistical significance ≠ Clinical significance
- Underlying cause for this difference between RBD / RBD no is unknown

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Variable	RBD Group (N = 108)	No RBD Group (N = 312)	p-value
MDS-UPDRS part III			
Mean (SD)	22.0 (8.8)	20.4 (8.8)	0.109
Min - Max	6.0 – 41.0	4.0 – 51.0	
Missing	0	0	
MDS-UPDRS total			
Mean (SD)	37.5 (14.1)	30.4 (12.3)	< 0.001
Min - Max	10.0 – 70.0	7.0 – 72.0	
Missing	0	1	
Epworth Sleepiness Scale Score			
Mean (SD)	6.5 (4.2)	5.5 (3.1)	0.025
Min - Max	0.0 – 20.0	0.0 – 15.0	
Missing	0	0	
Geriatric Depression Scale Score			
Mean (SD)	3.0 (2.8)	2.1 (2.3)	0.002
Min - Max	0.0 – 12.0	0.0 – 14.0	
Missing	0	0	

The Brain and Parkinson's Disease

Basal ganglia

Cerebral cortex

Caudate nucleus
Putamen — Striatum

Thalamus

Globus pallidus

Subthalamic nucleus

Substantia nigra

Front — Back

A. Normal

Caudate

Putamen

B. Parkinson's Disease

Nigrostriatal pathway

SNpc