Assessing Imaging Data from the Michael J. Fox Foundation's Parkinson's Progression Markers Initiative for use in Future Clinical Trials

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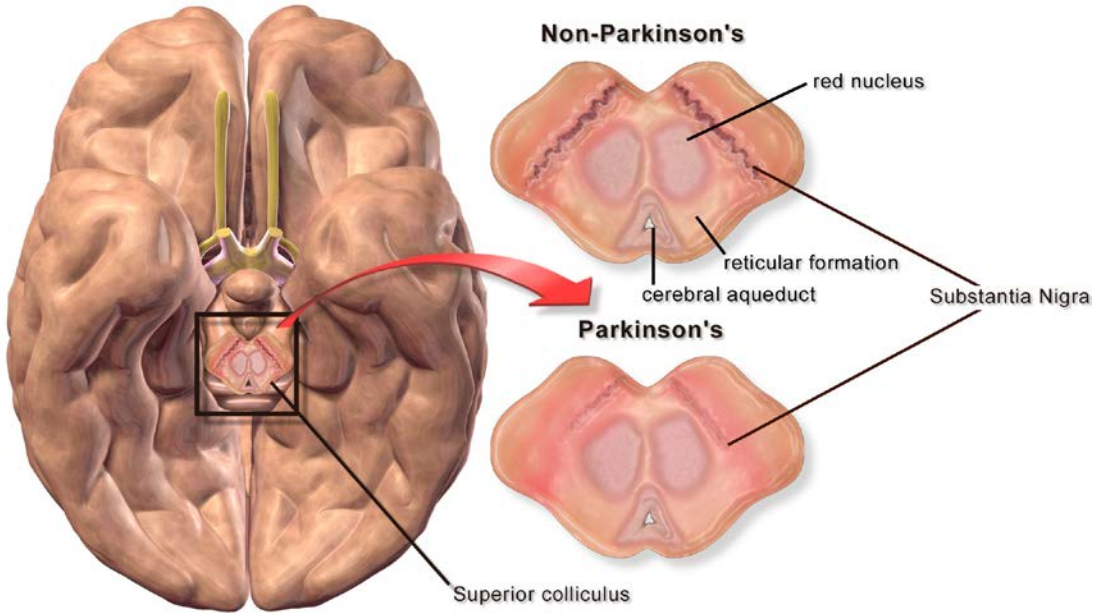
Parkinson's Disease

- A neurodegenerative disease that affects the central nervous system, impairing an individual's motor control



- Occurs in stages:

Minimal symptoms, few unilateral termors (do NOT affect daily routine

Bilateral tremors and rigidity, daily tasks/routine start to become affected

Imbalance of body and slowness of movement

Required personal assisatnace in simple daily tasks

Severe form of all symptoms, inability to rise

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

https://www.michaeljfox.org/page.html?parkinsons-progression-markers-initiative-get-involved

Parkinson's Progression Markers Initiative (PPMI)

- Large-scale study used for tracking Parkinson's Disease Biomarkers
  - Biomarkers: symptoms/signs that indicate medical state or condition of a patient; measured by urinalysis, blood tests, spinal taps, CAT, MRI, and DaTSCANS
- Current treatments for PD only alleviate symptoms temporarily.
- Parkinson's disease studies currently require many subjects to be followed for a long period of time.
- DaTSCANS are one of the potential biomarkers being assessed for PPMI.

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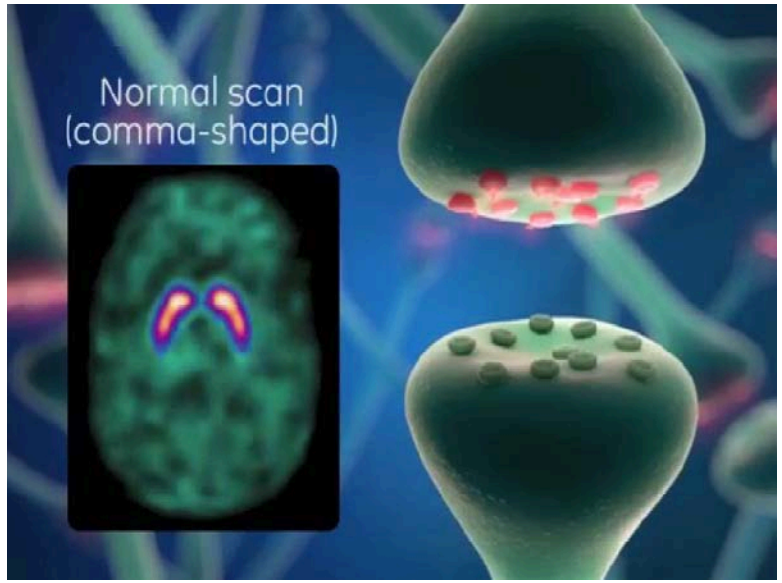
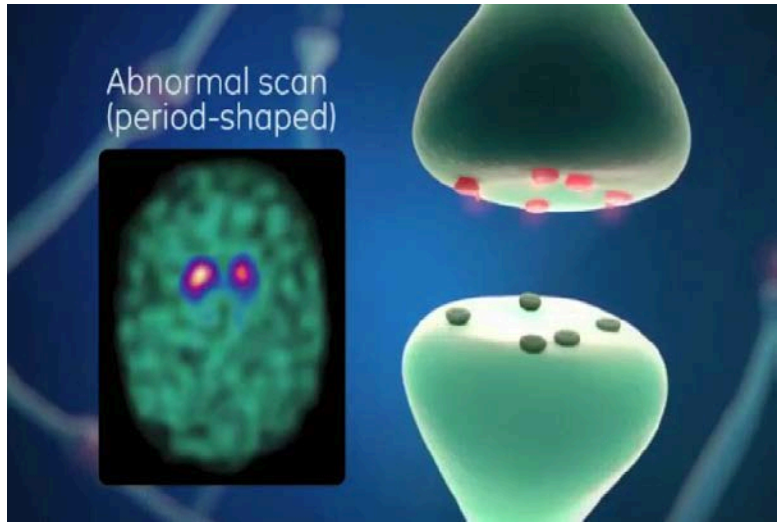




Images from videos: http://us.datscan.com/professional/video-library/

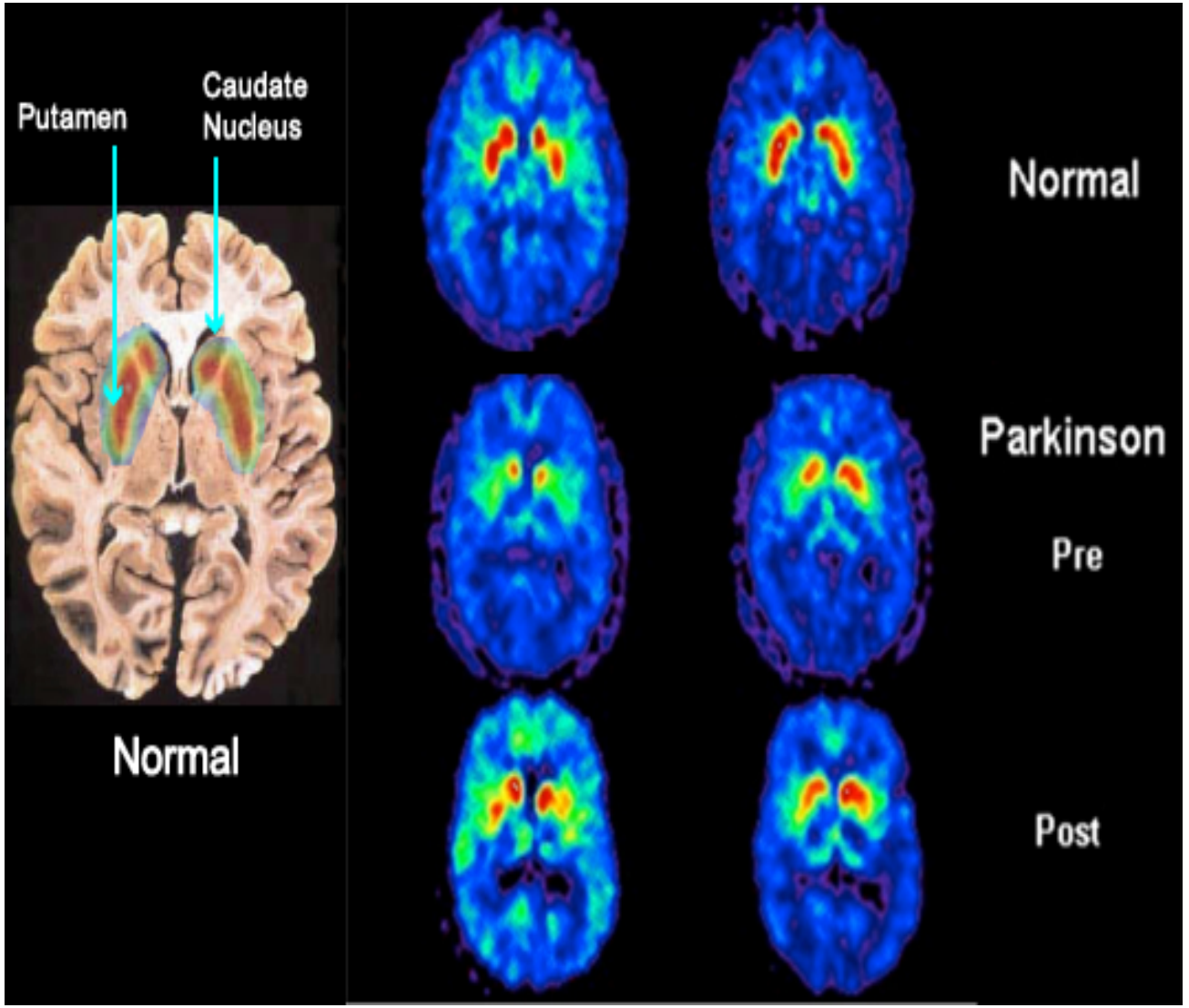
DaTSCAN:
Dopamine Transmitters

- An FDA approved diagnostic test for Parkinson's Disease.
- Intravenous injection of phenyltropane for SPECT imaging.
- Allows for the differentiation of an essential tremor or a tremor due to PD.
- Traditional scans display a linear trend between the structural and physical functional decay of PD motor score.
- As people age, DaTSCAN values naturally decrease.

Brain Regions of DaT

- There are three different regions of the brain being analyzed in this study.
  - Putamen
  - Caudate
  - Striatum

- Ipsilateral: occurring on the same side of the body
- Contralateral: opposite side of body in which condition occurs



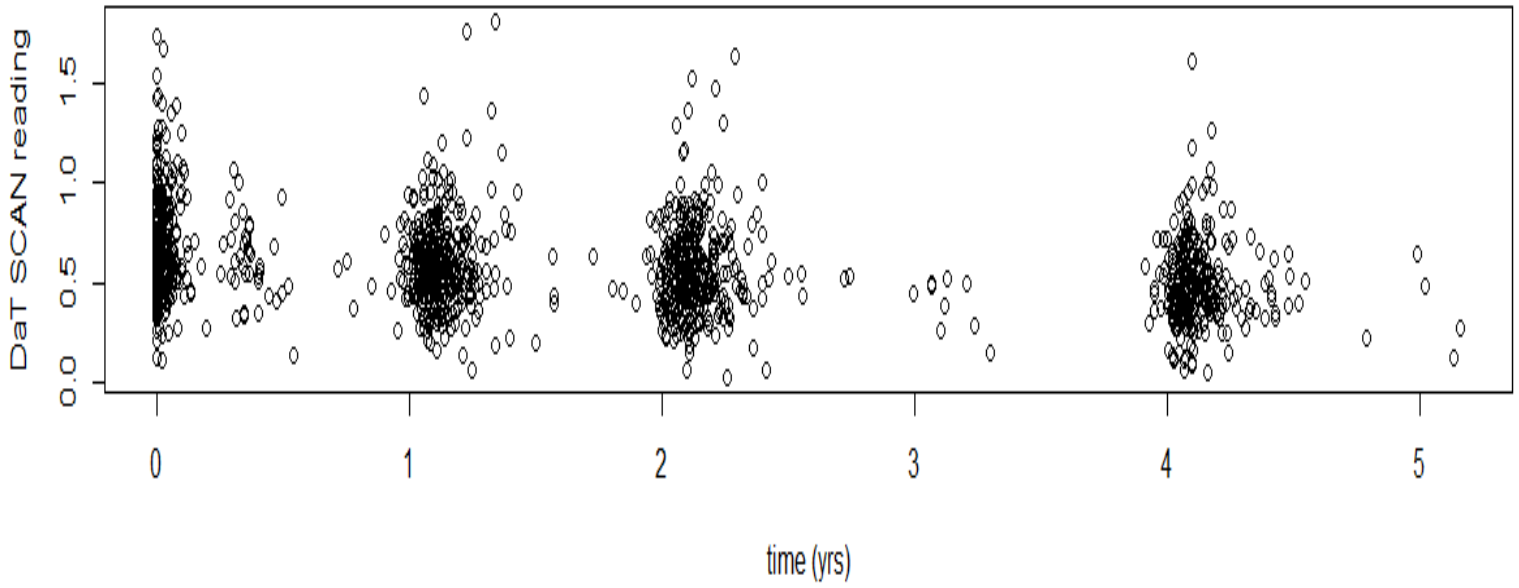
http://www.people.vcu.edu/~mhcrosthwait/clrs%20417web/datzscan.html

PPMI Data

- 351 individuals within study

- 65% male subjects
- 35% female subjects

- Mean age: 61.6
- Standard deviation: 9.716



Model

$$y_{ij} = f(t_{ij}, \Psi_i) + e_{ij}$$

Where

- y_{ij} are the DaTSCAN readings
- $f(t_{ij}, \Psi_i)$ is the nonlinear function
- e_{ij} is the error such that $e_{ij} \sim N(0, \sigma^2)$

$$\Psi_i = \Psi_{pop} + \eta_i$$

Where

- Ψ_{pop} are the fixed effects
- η_i is the random effects such that $\eta_i \sim N(0, \Omega)$

$$f(t_{ij}, \Psi_i) = a_i e^{(-b_i \times t_{ij})}$$

Where

- a_i is the baseline DaTSCAN
- b_i is the rate of decline of DaTSCAN reading
- t_{ij} is the time when the reading was taken

Simulation

$$\Psi_i = \Psi_{pop} + \eta_i$$

Fixed Effects

Parameter	Estimate	SE	p-value
$\beta_{0,a}$	0.68	0.015	-
$\beta_{1\ age,\ a}$	-0.00018	0.0013	0.44
$\beta_{2\ gender,\ a}$	-0.014	0.026	0.29
$\beta_{0,b}$	0.085	0.0059	-
$\beta_{1\ age,\ b}$	0.00041	0.00048	0.20
$\beta_{2\ gender,\ b}$	-0.0023	0.010	0.41
σ^2	0.11	0.003	-

Variance of Random Effects

Parameter	Estimate	SE
Ω^2_a	0.044	0.0038
Ω^2_b	0.0023	0.00054

Rationale of the Simulation

- We want to determine if DaTSCAN data can be used in clinical trials.
- DaTSCAN is a potential biomarker that could make studies faster and require smaller sample sizes.
- With this simulation, we are able to take a preliminary look at hypothetical treatments slowing the rate of decline of DaTSCAN readings in patients with Parkinson's disease and determine the sample size and duration needed for such studies.

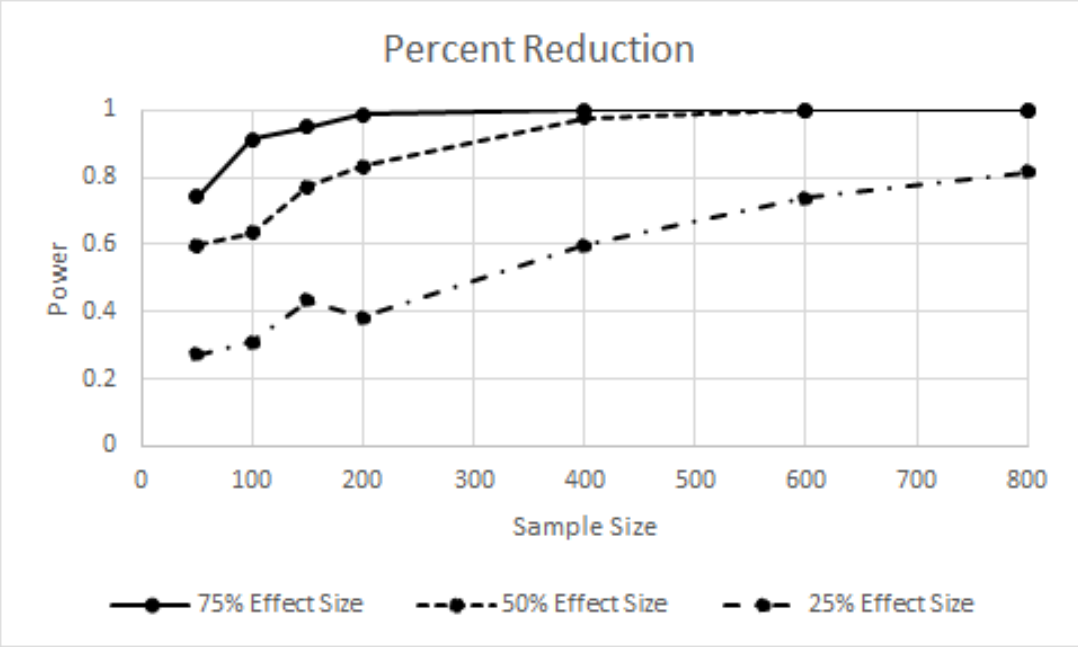
Simulation Setup

Sample Sizes	50, 100, 150, 200, 400, 600, 800
Duration of Study (in years)	2 years
Effect Sizes	0.25, 0.50, 0.75
Regions of the Brain	Contralateral: • Caudate • Putamen • Striatum Ipsilateral: • Caudate • Putamen • Striatum

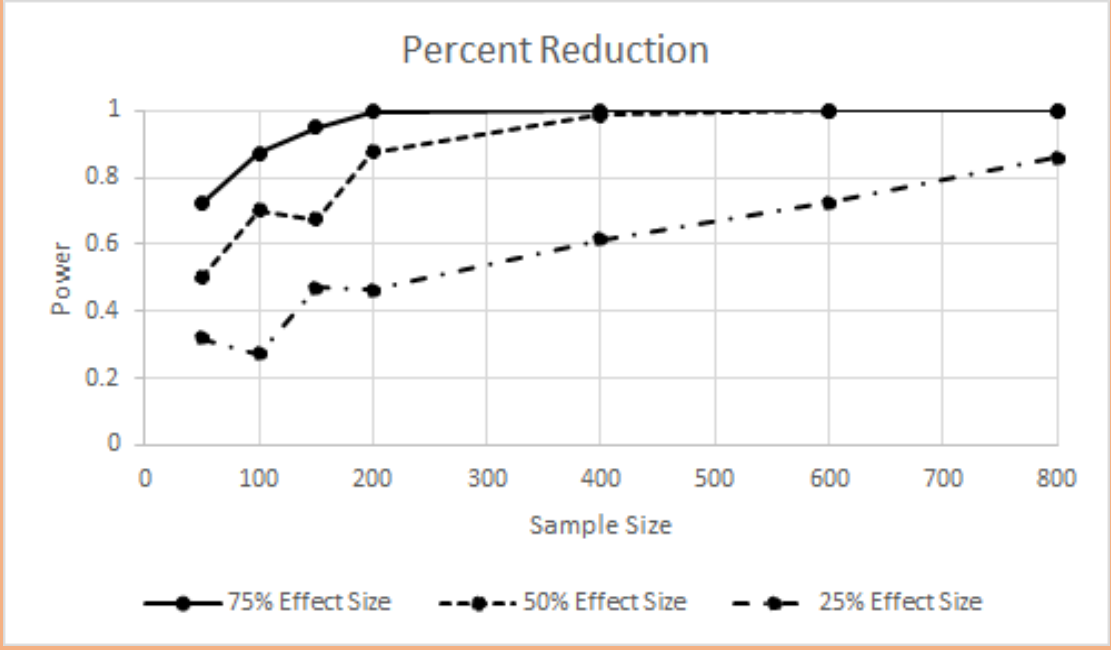
It is noted at every combination of duration, sample size, and effect size shown in this table was simulated.

Caudate

Contralateral

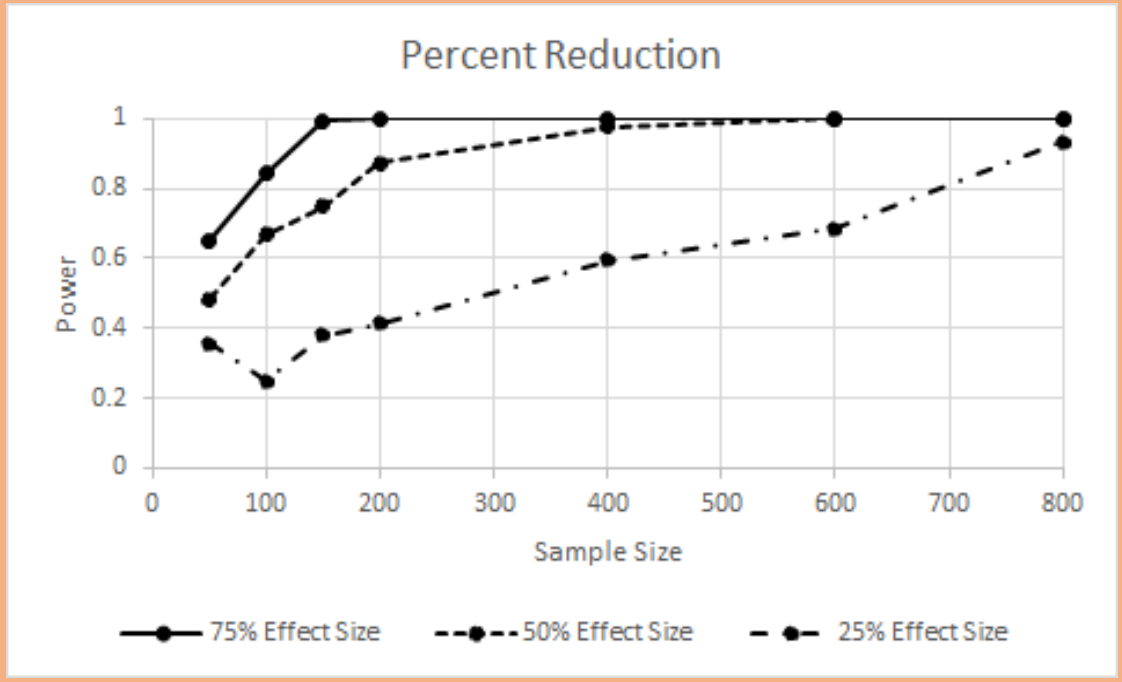


Ipsilateral

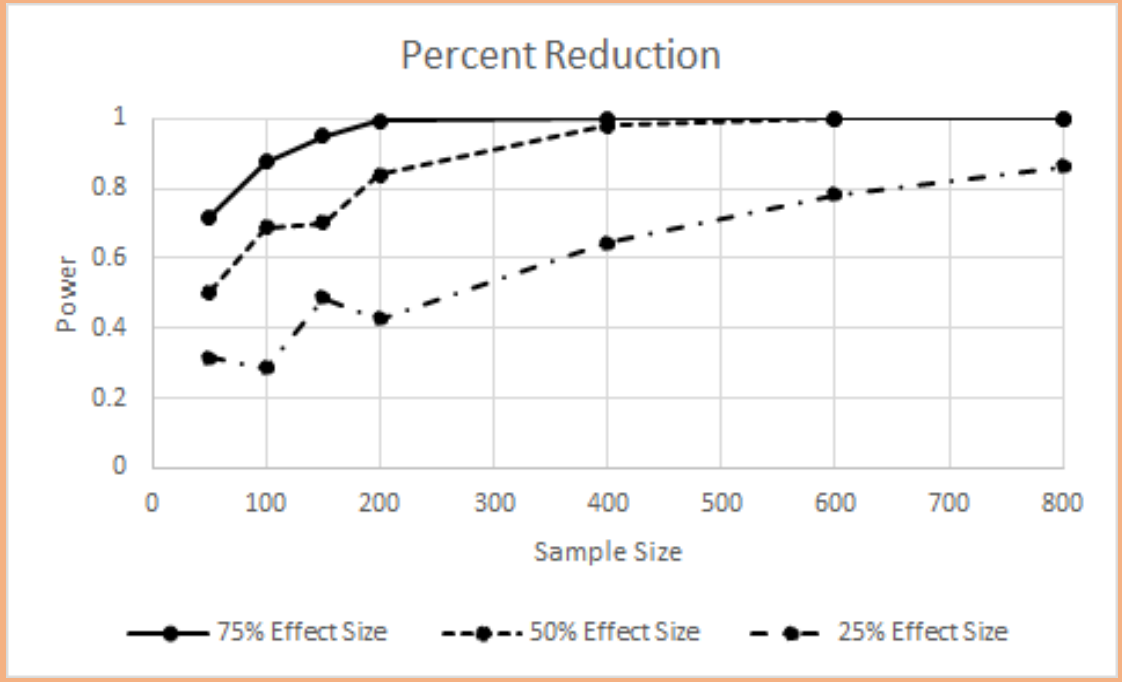


Putamen

Contralateral

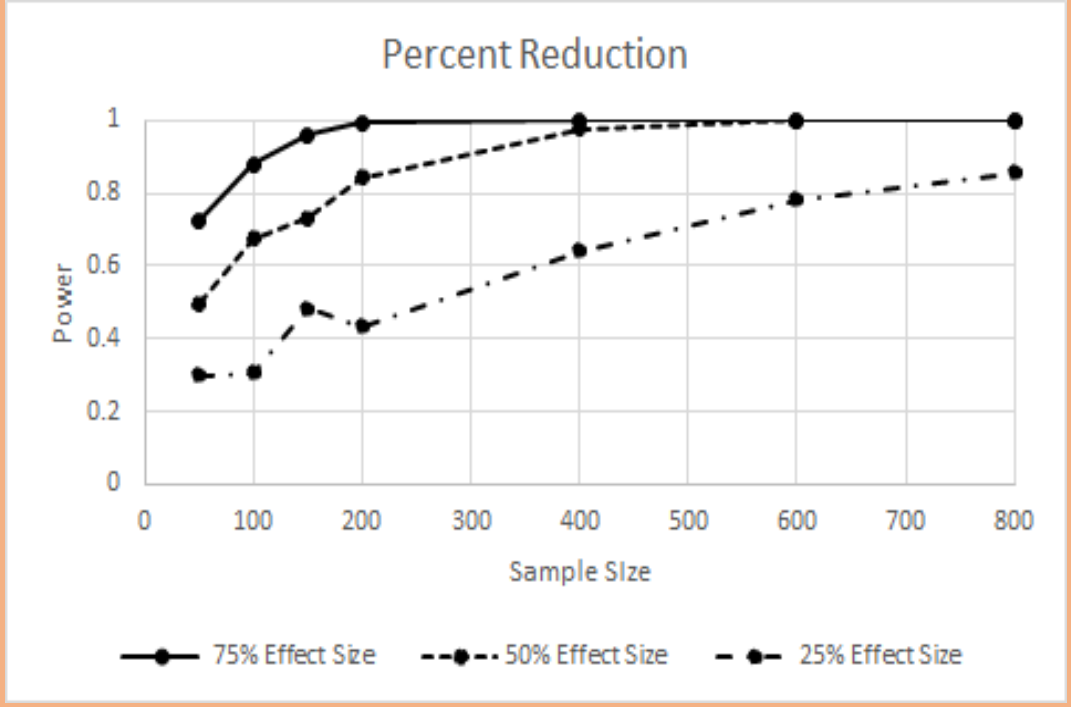


Ipsilateral

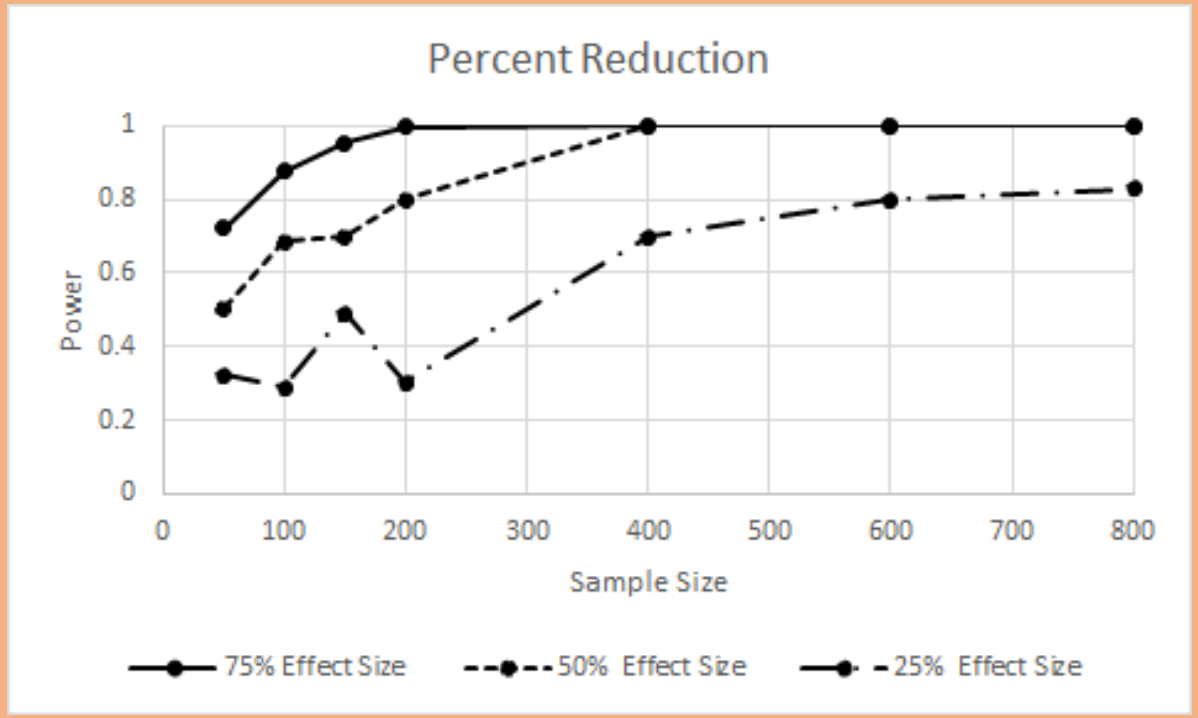


Striatum

Contralateral



Ipsilateral



Conclusion

- We investigated the use of DaTSCAN as a biomarker in Parkinson's Disease.
- Our results show that better trial properties can be obtained as long as the treatment is able to slow the rate of decline of the DaTSCAN reading by more than 50%.
- However, if a 50% slowing is not feasible than it appears that DaTSCAN would not offer much improvement over current Parkinson's Disease trials.

Thank you!

Questions?

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