Neuroimaging of PD Progression

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Primary Endpoint

Biomarker

Surrogate Endpoint

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What is a Primary Endpoint of a clinical study?

clinically important event such as:

-- death, stroke or myocardial infarct
-- disability, quality of life

Bucher, et al: JAMA 1999; 282: 771-777

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A Biomarker

Objectively measured indication of normal biologic process, pathogenic process or drug response

Fleming et al, Ann Intern Med, 1996

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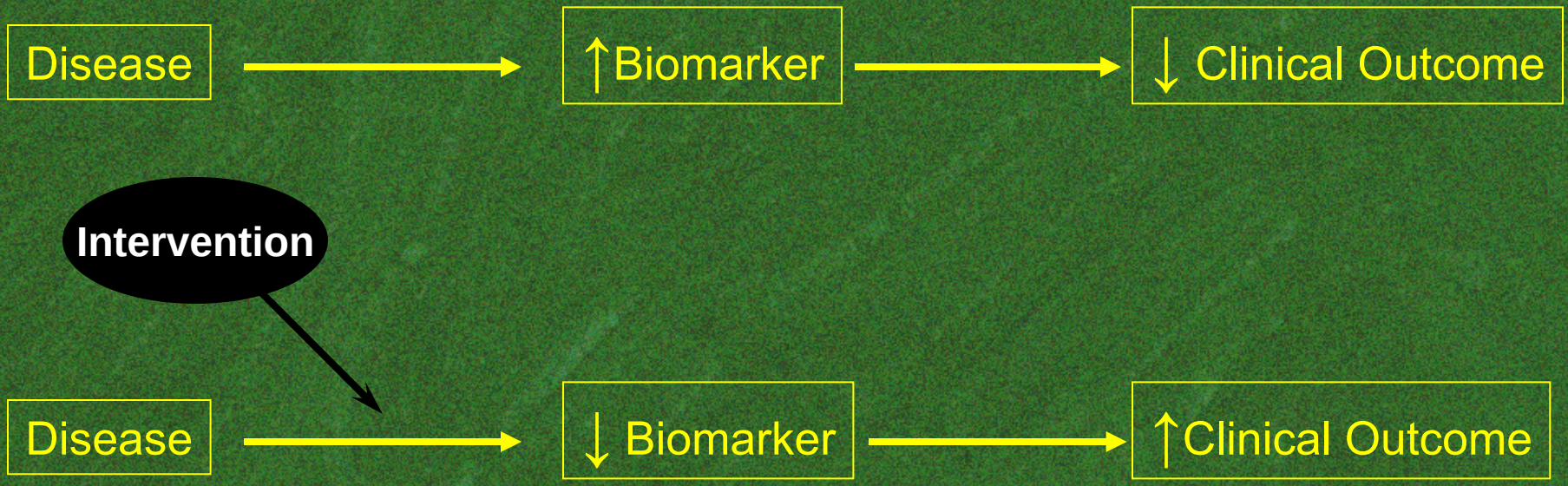
Optimal situation for a biomarker to be a valid surrogate endpoint



Changes in the biomarker mediate all of the effect of the intervention on clinical outcome

Fleming, T. R. et. al. Ann Intern Med 1996;125:605-613

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Failure of a Biomarker as Surrogate Endpoint

Efficacy of encainide after myocardial infarction

(CAPS Am J Cardiol 1988; 61:501-9; CAST NEJM 1991; 324:781-8)

	Encainide	Placebo
VPC Suppression	79%	37%
Mortality	7%	3%

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Validation of a Biomarker as a Surrogate Endpoint

- **Biomarker & clinical outcome:**
  - **Strong, consistent & independent**
  - **Biomarker response must be strong enough to predict**
- **Biomarker predicts efficacy & toxicity**

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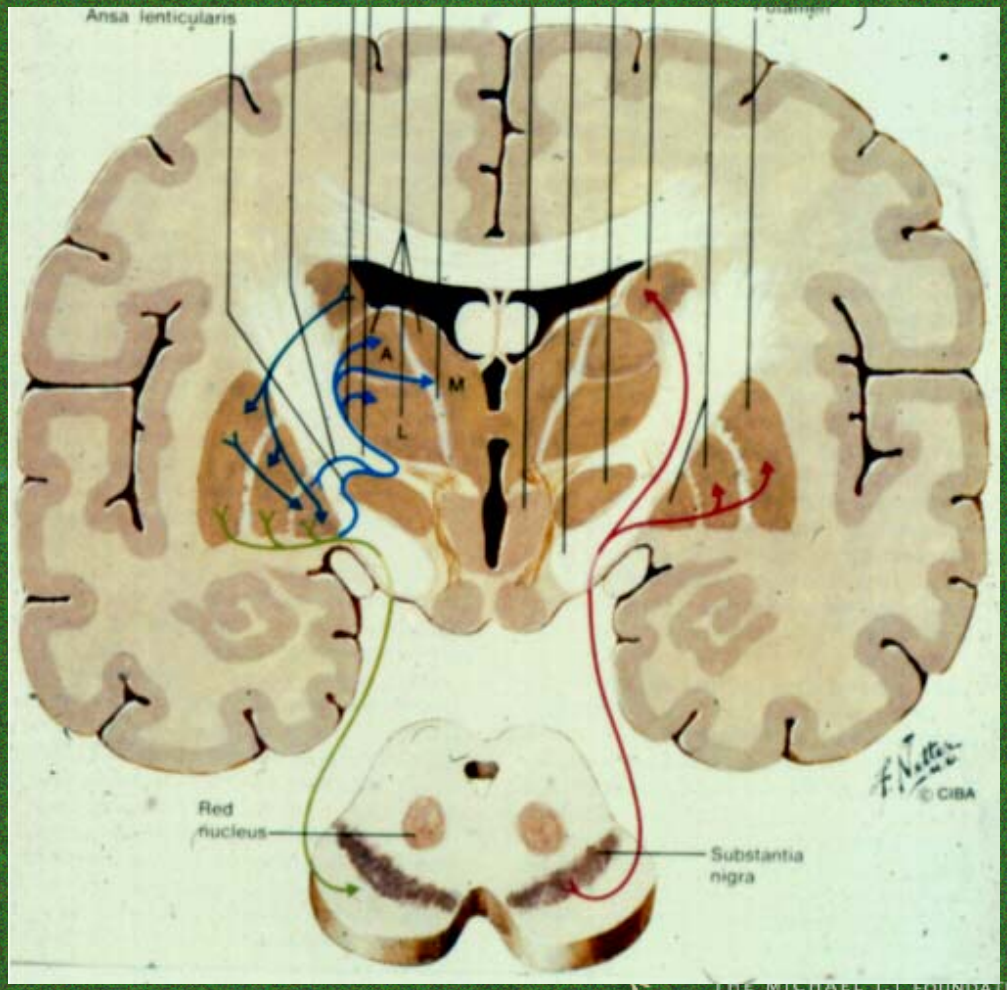
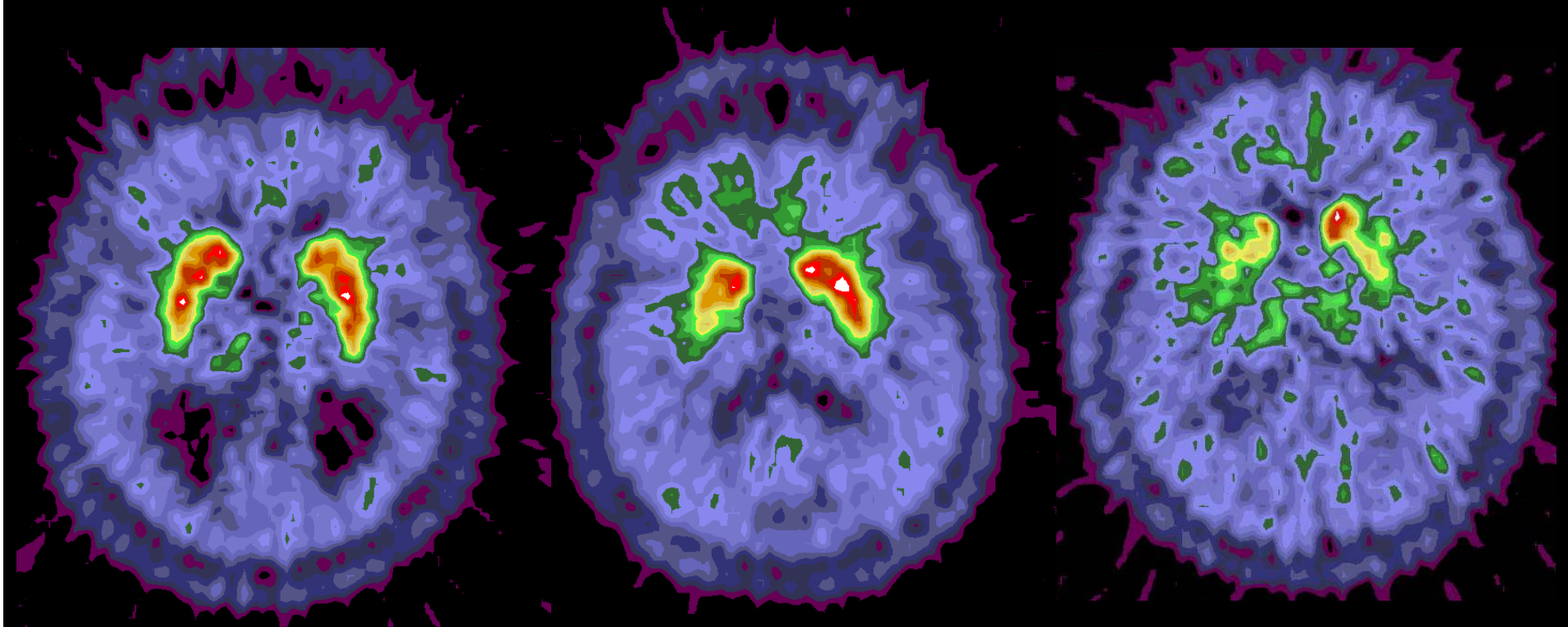
Disease Severity Assumption

PD

Normal

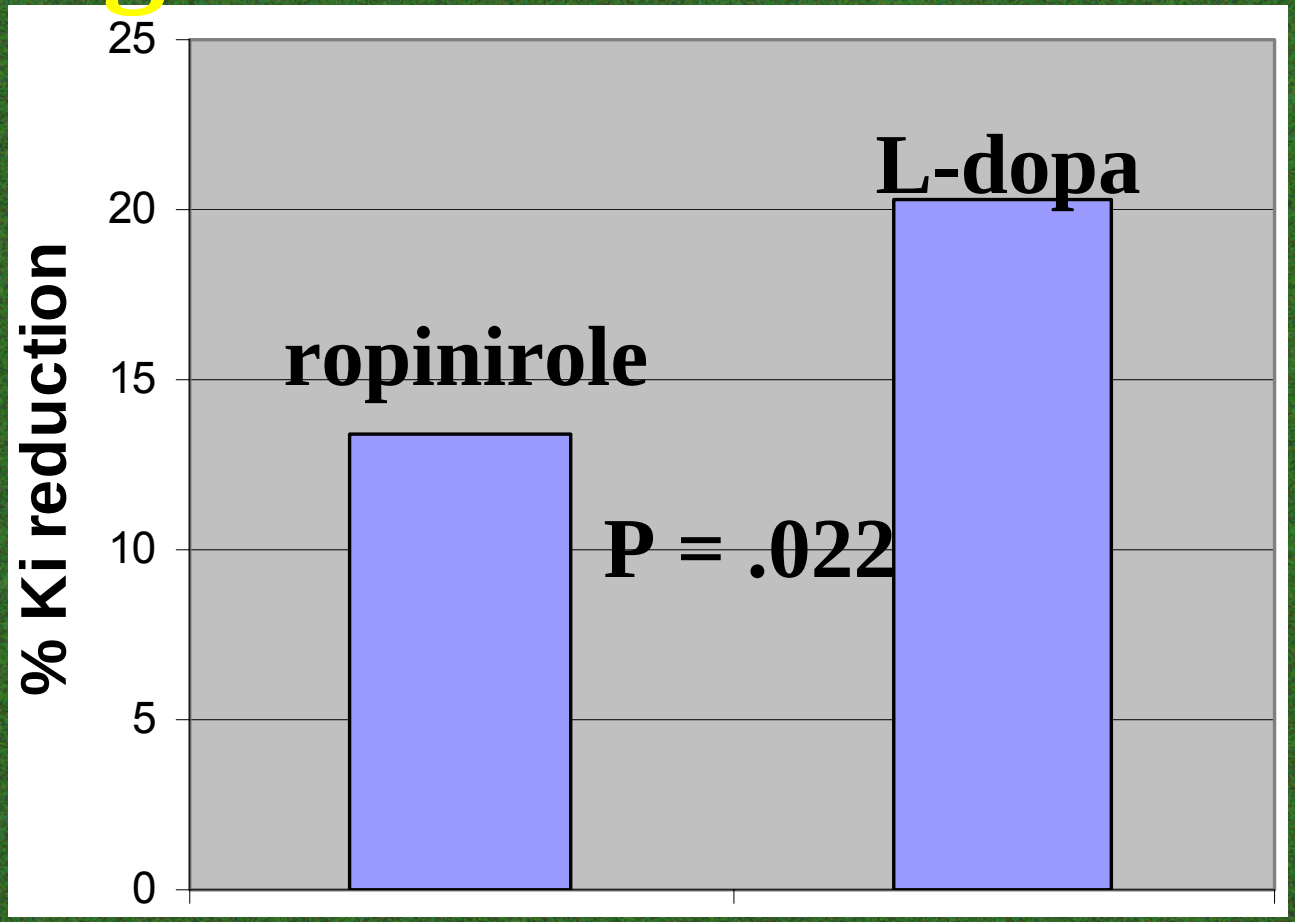


[18F]FDOPA



Normal mild PD moderate PD

L-dopa vs Ropinirole: Change in Putamenal FDOPA



Whone et al, Ann Neurol 2003

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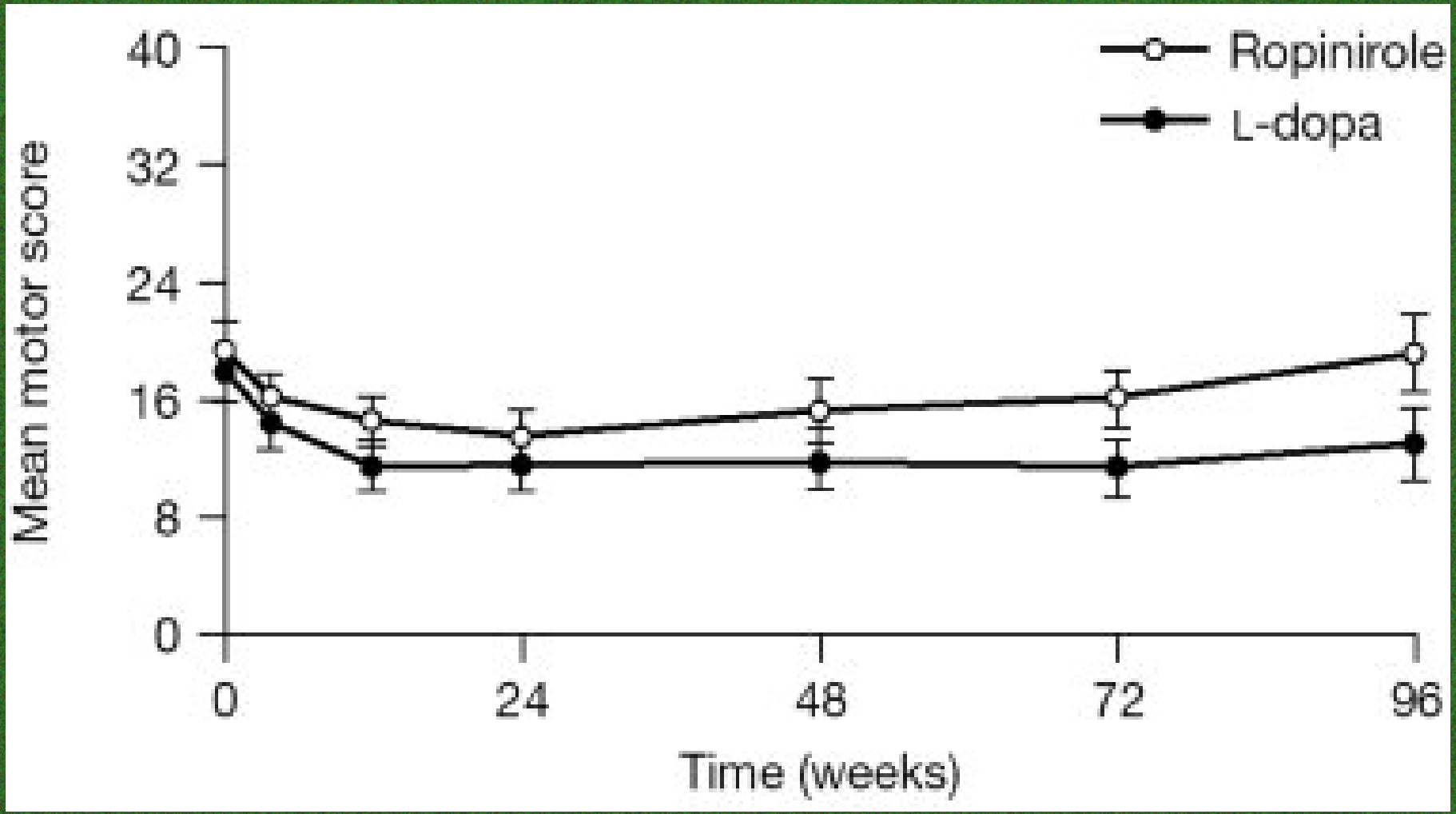
“ON” UPDRS motor score



Whone et al, Ann Neurol 2003

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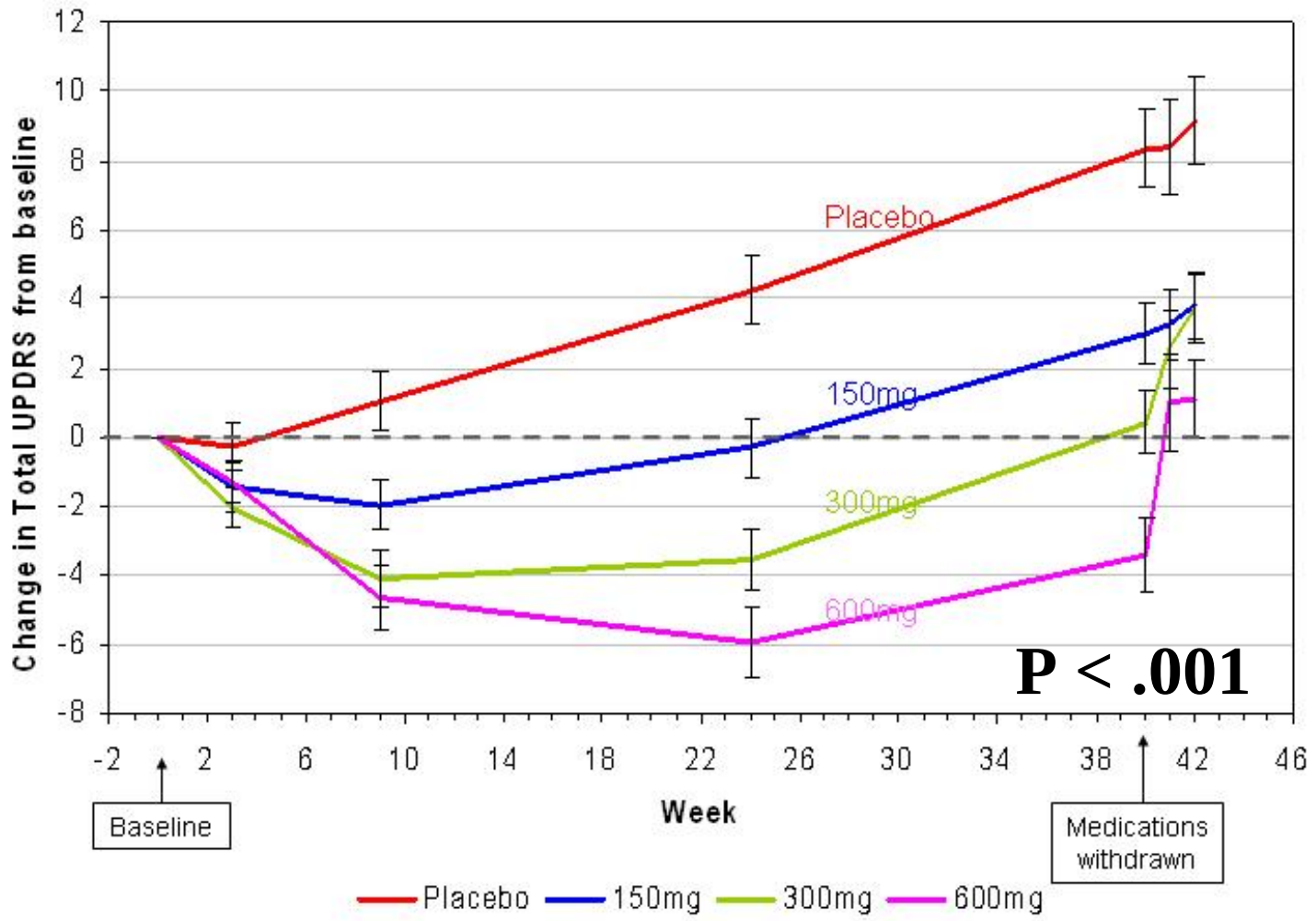
ELLDOPA: PSG, NEJM 2004



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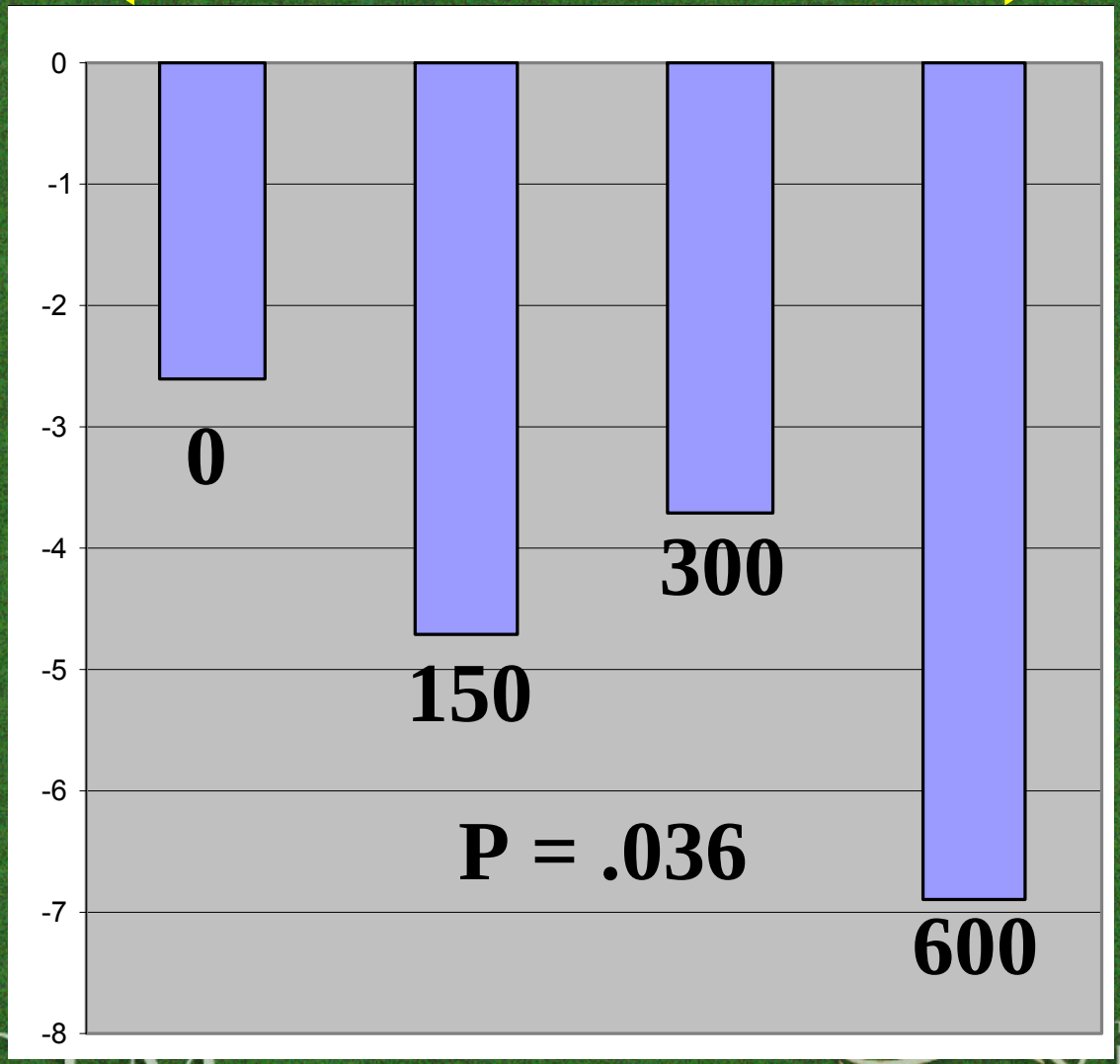
% Reduction of β-CIT Uptake (SWEDDS removed)



Critical Assumptions

Do markers reflect # of DA neurons?

Do Uptake Mechanisms Regulate?

Effects of neuron loss?

Effects of interventions?

Acutely?

Chronically?

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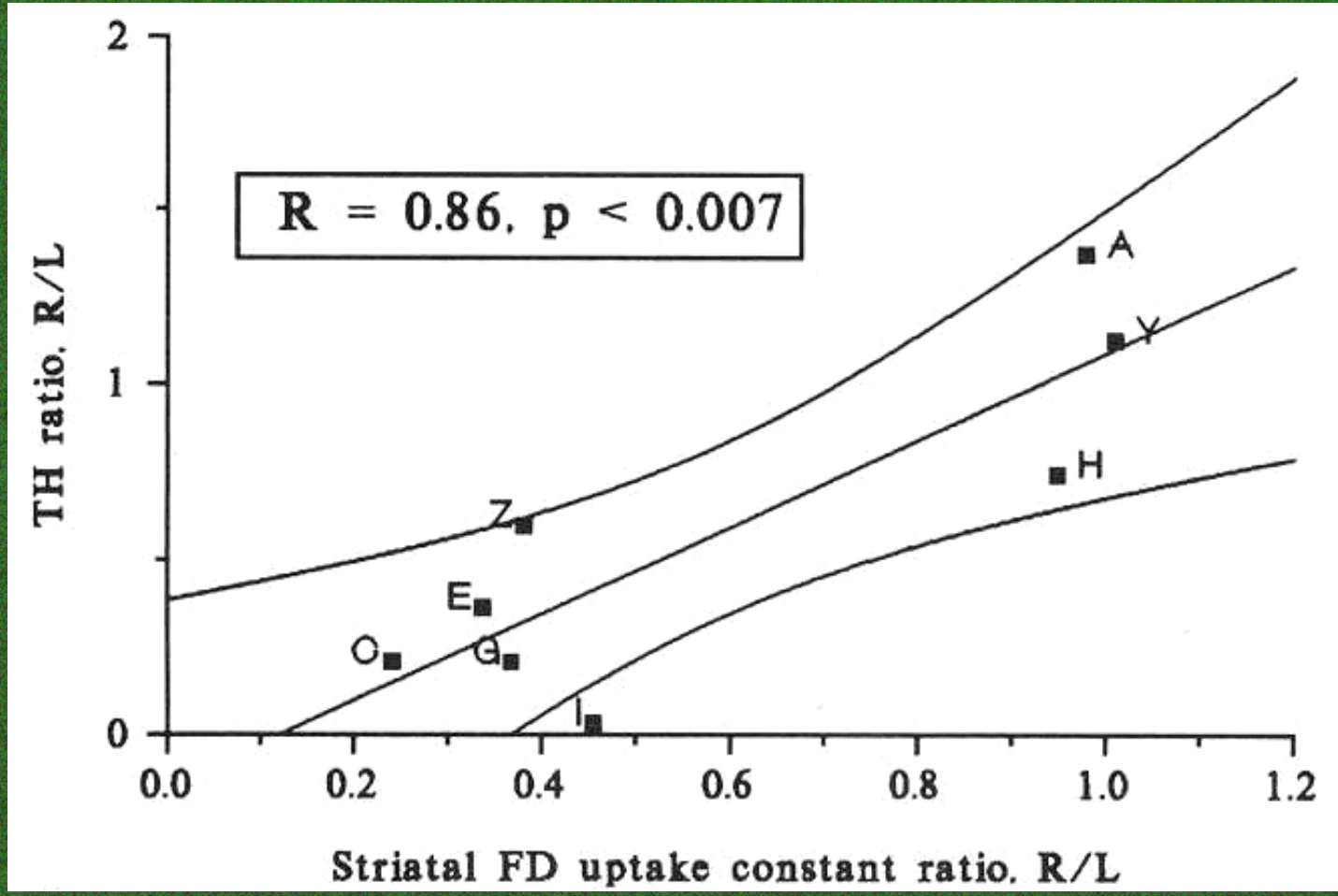
Monkey: FDOPA vs TH ratio

Pate et al, 1993



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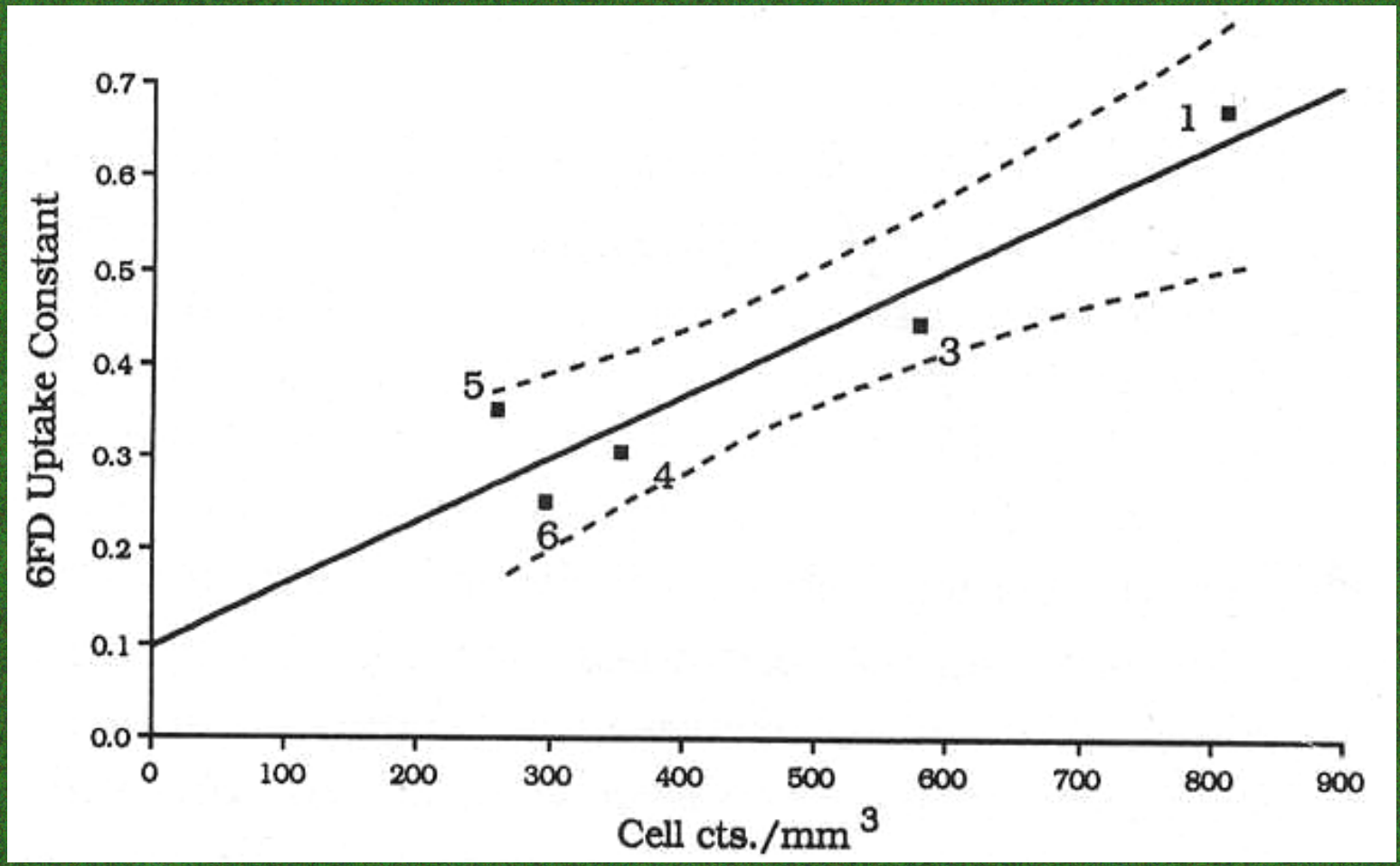
Human: FDOPA vs cell counts

Snow et al, 1993



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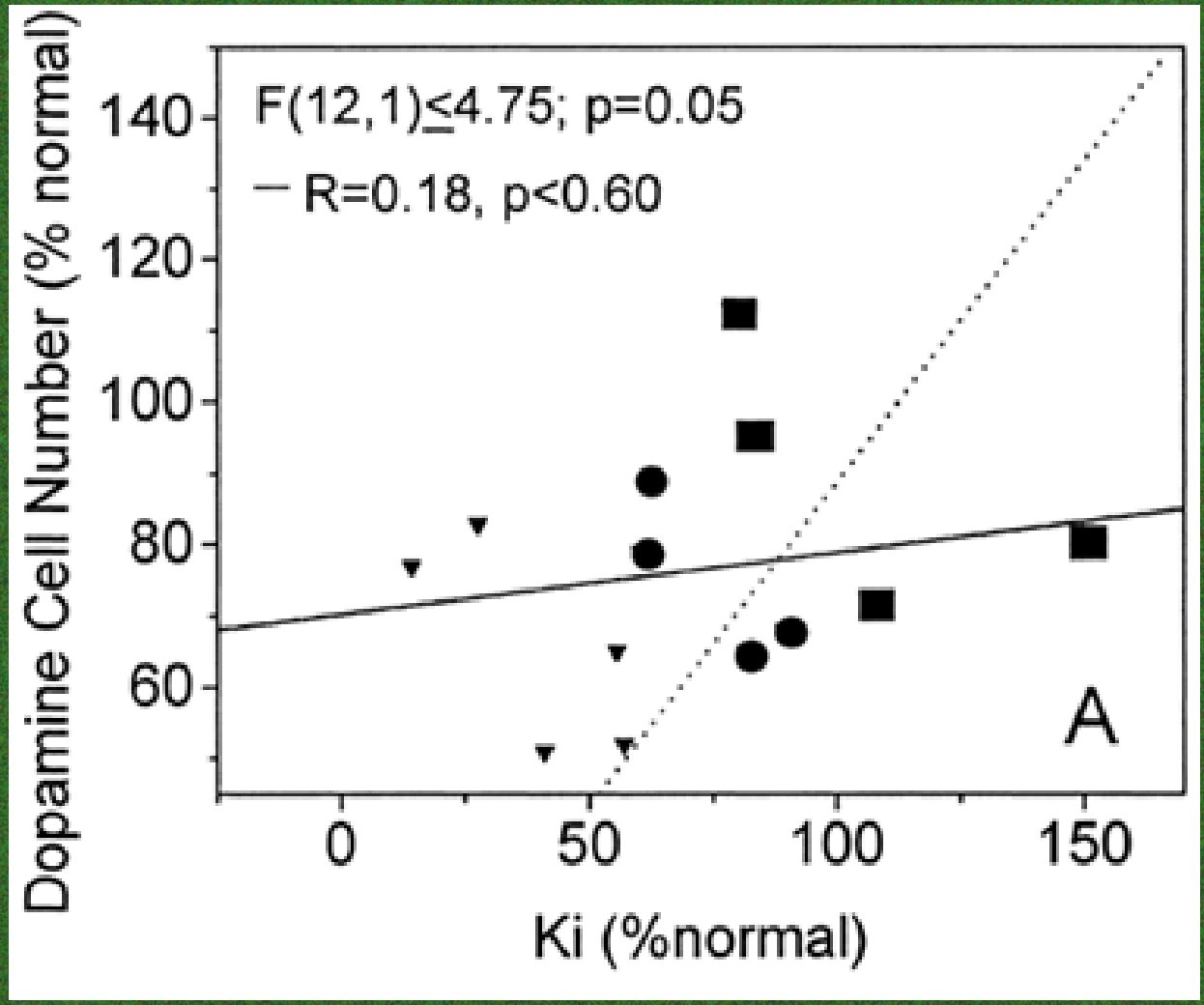
Monkey: FDOPA vs DA neurons

Yee et al, 2001



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Effects of L-dopa & pramipexole on PET [11C]RTI (DAT)

Contra Post Put	Pramipexole	L-dopa	Placebo
Baseline	1.33 ± 0.14	1.45 ± 0.11	1.13 ± 0.14
Change	-0.13 ± 0.08	-0.28 ± 0.11*	-0.08 ± 0.13
% change	-7	-16	+1.5

*P < .05; n = 10 in each group

Guttman et al, Neurol 2001

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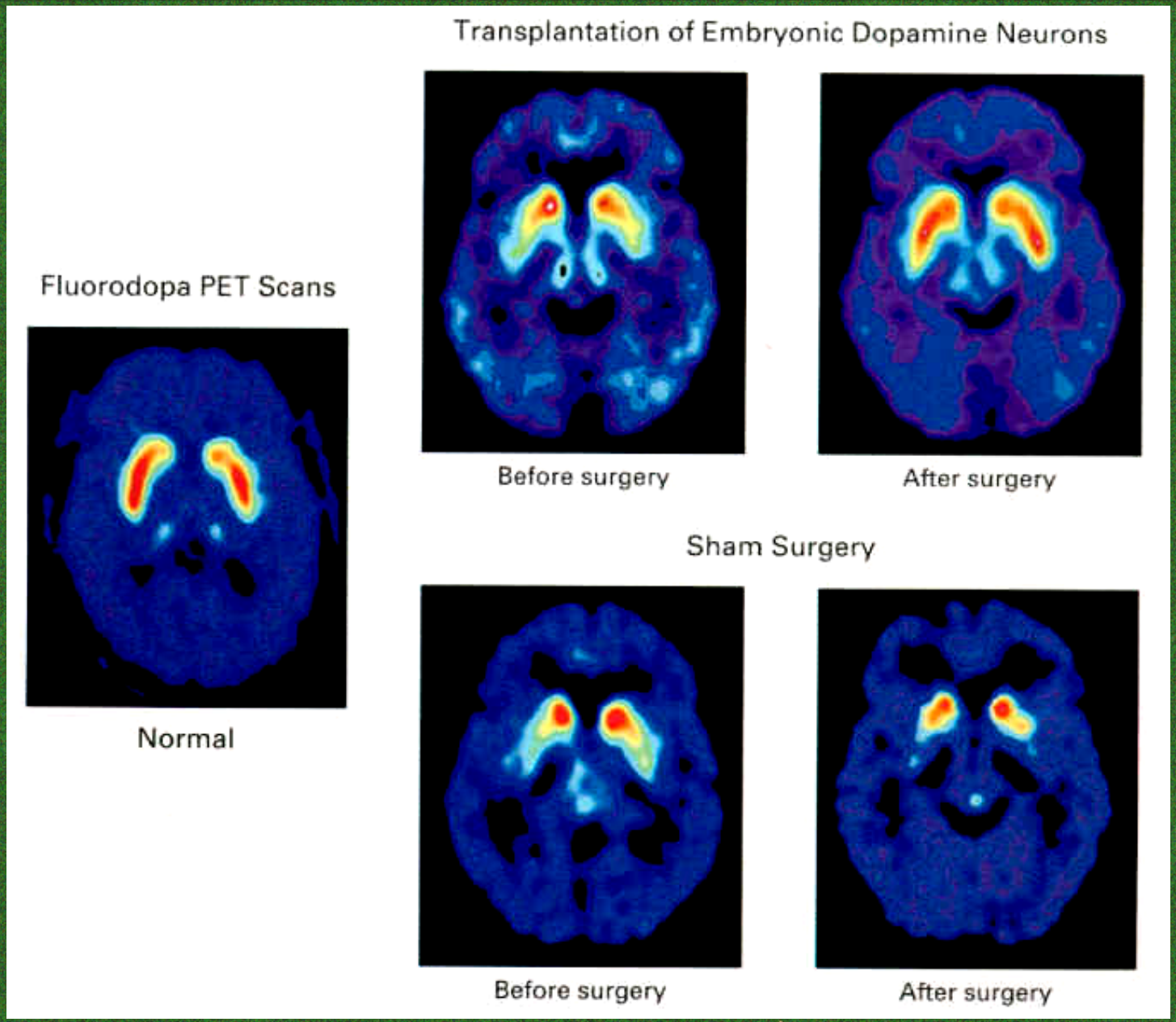

Eidelberg et al
NEJM 2001

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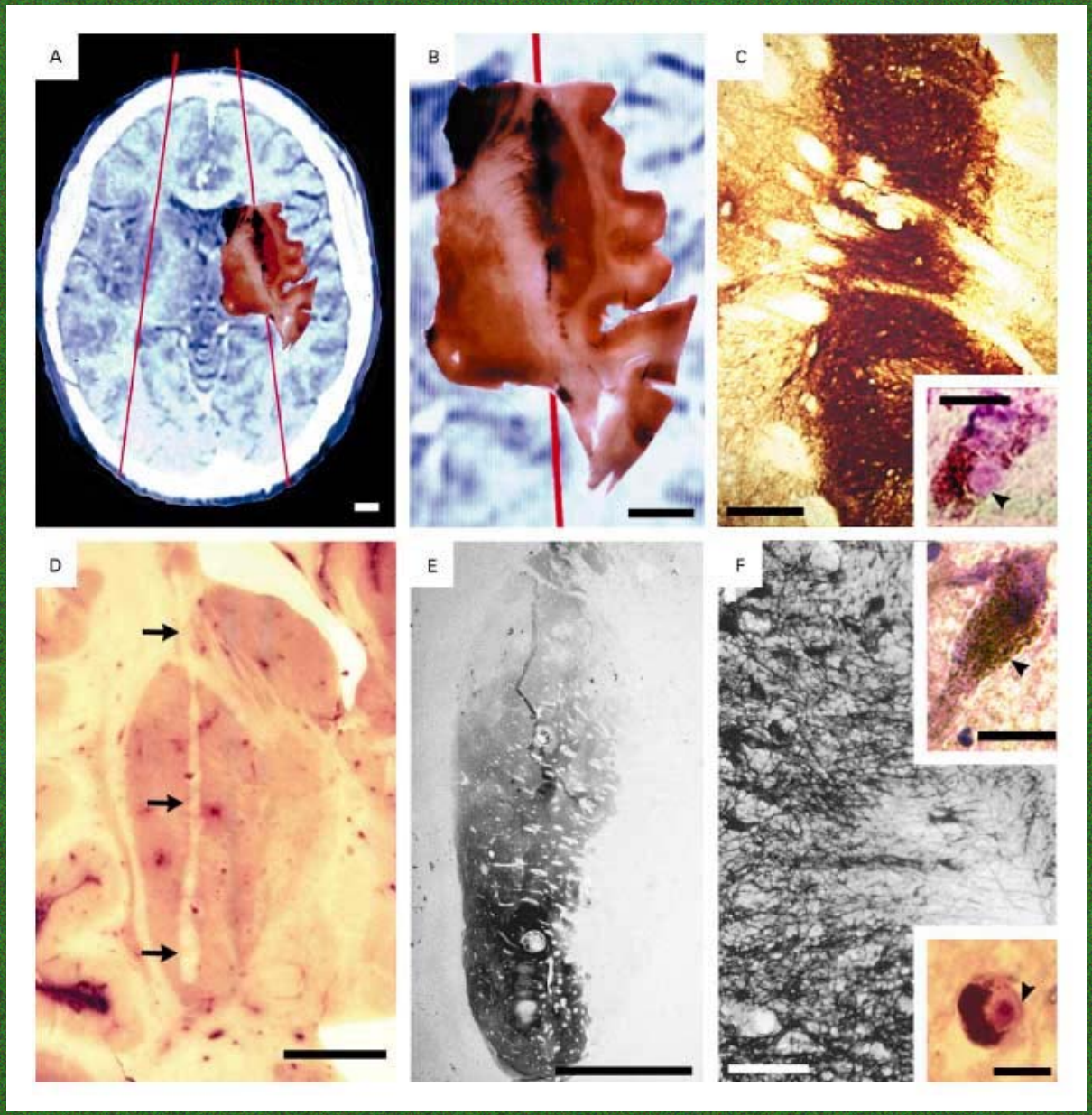

Eidelberg et al
NEJM 2001

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FDOPA PET: ? Specificity
(asymmetry of cell counts vs FDOPA)

1.TH staining cell counts (3 yrs):

Right	Left
22,760 & 14,036	4780 & 2060
18,398	3420

2. FDOPA PET (2 yrs):
symmetric 100 % increase

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Eidelberg et al
NEJM 2001

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Can Biomarkers Measure Neuroprotection?

1. Unclear relationship to DA cell counts
2. Unclear measure with denervation
3. Unclear effects of interventions

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Role of PET Biomarkers

- Research subject selection
- Pathophysiology
- Treatment effects

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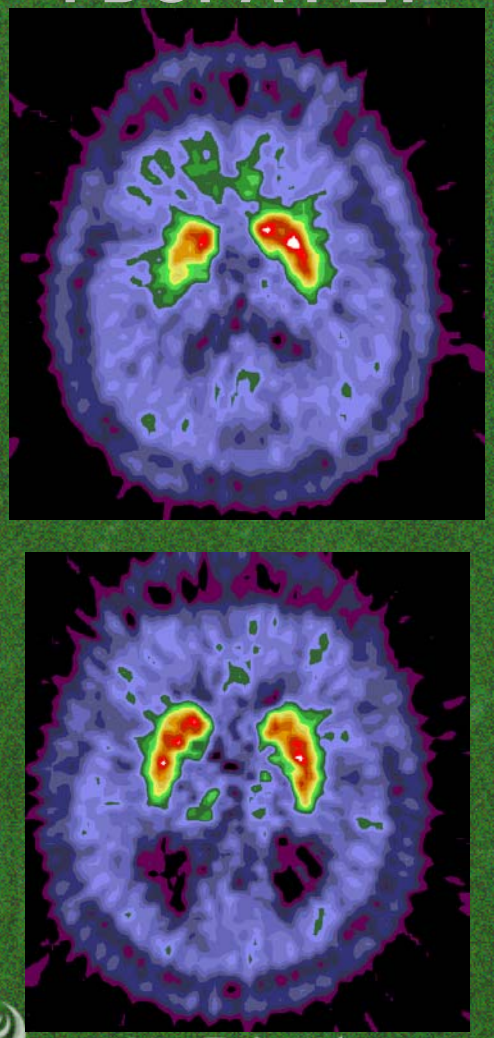
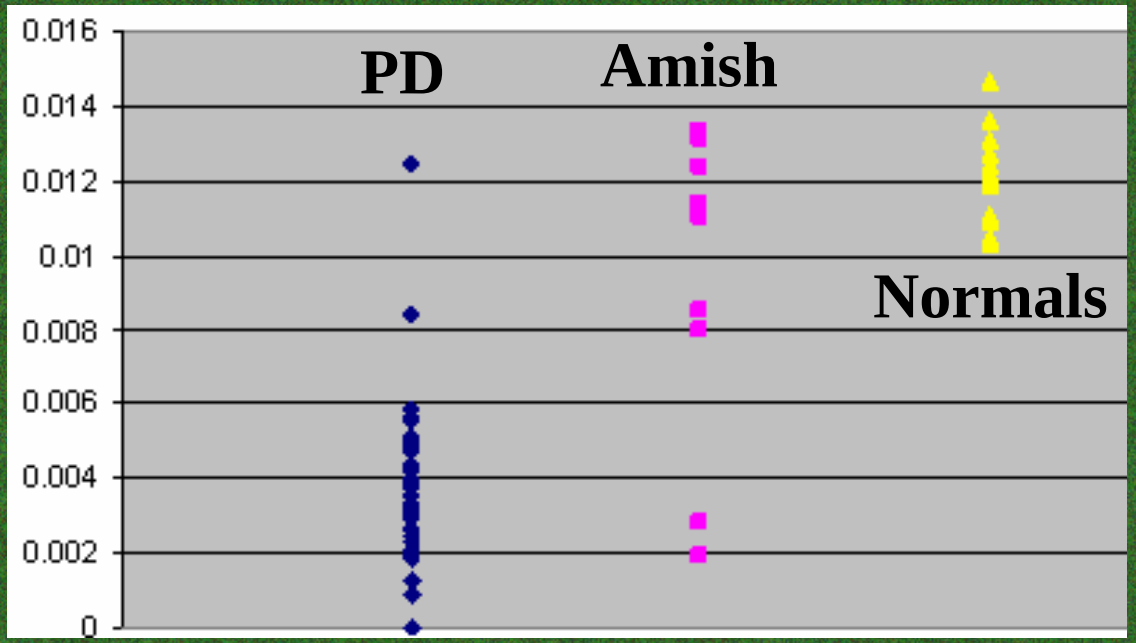
PET Methods

FDOPA PET



Racette et al, Neuropsychiatr Gen 2005

Posterior Putamen Ki



Amish (n=11); normals (n=24) age-matched by ± 2 years; PD (n=56).

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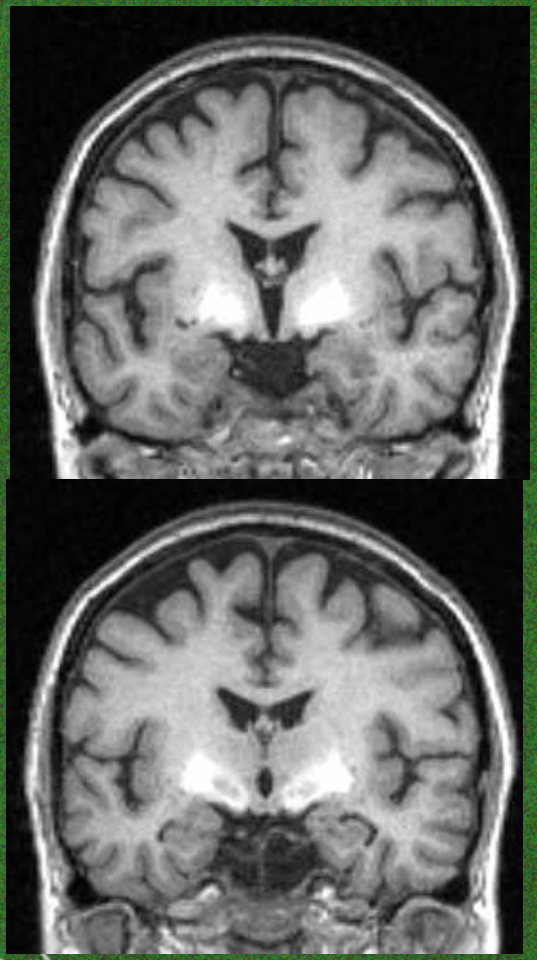
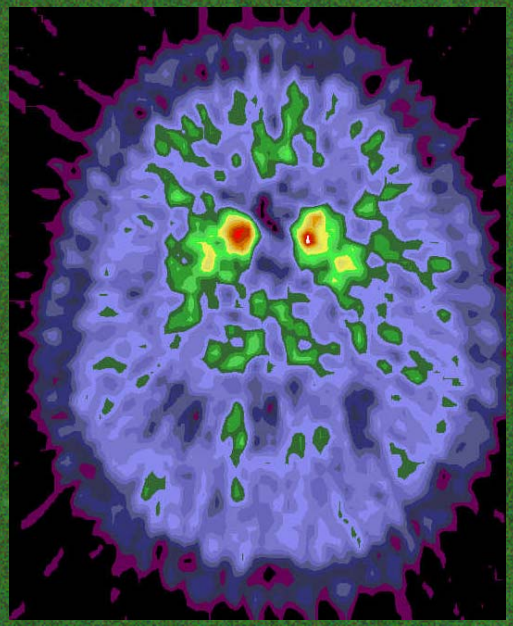
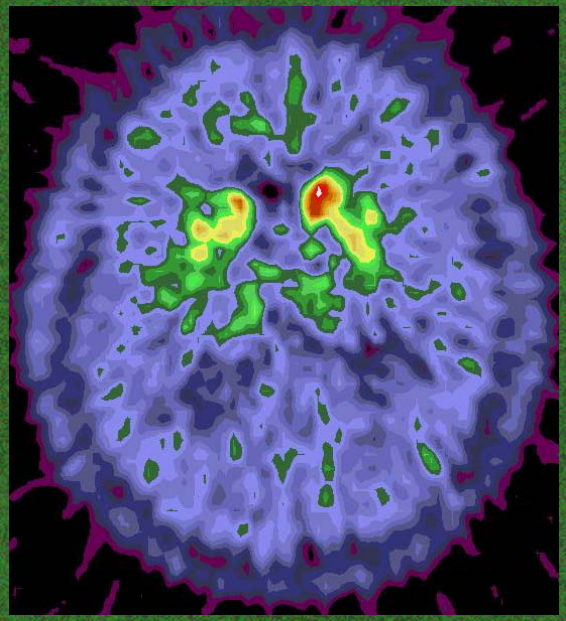
Mn-Induced Parkinsonism

MRI



FDOPA PET





Mn Exposure **Idiopathic PD**

Racette et al, 2004

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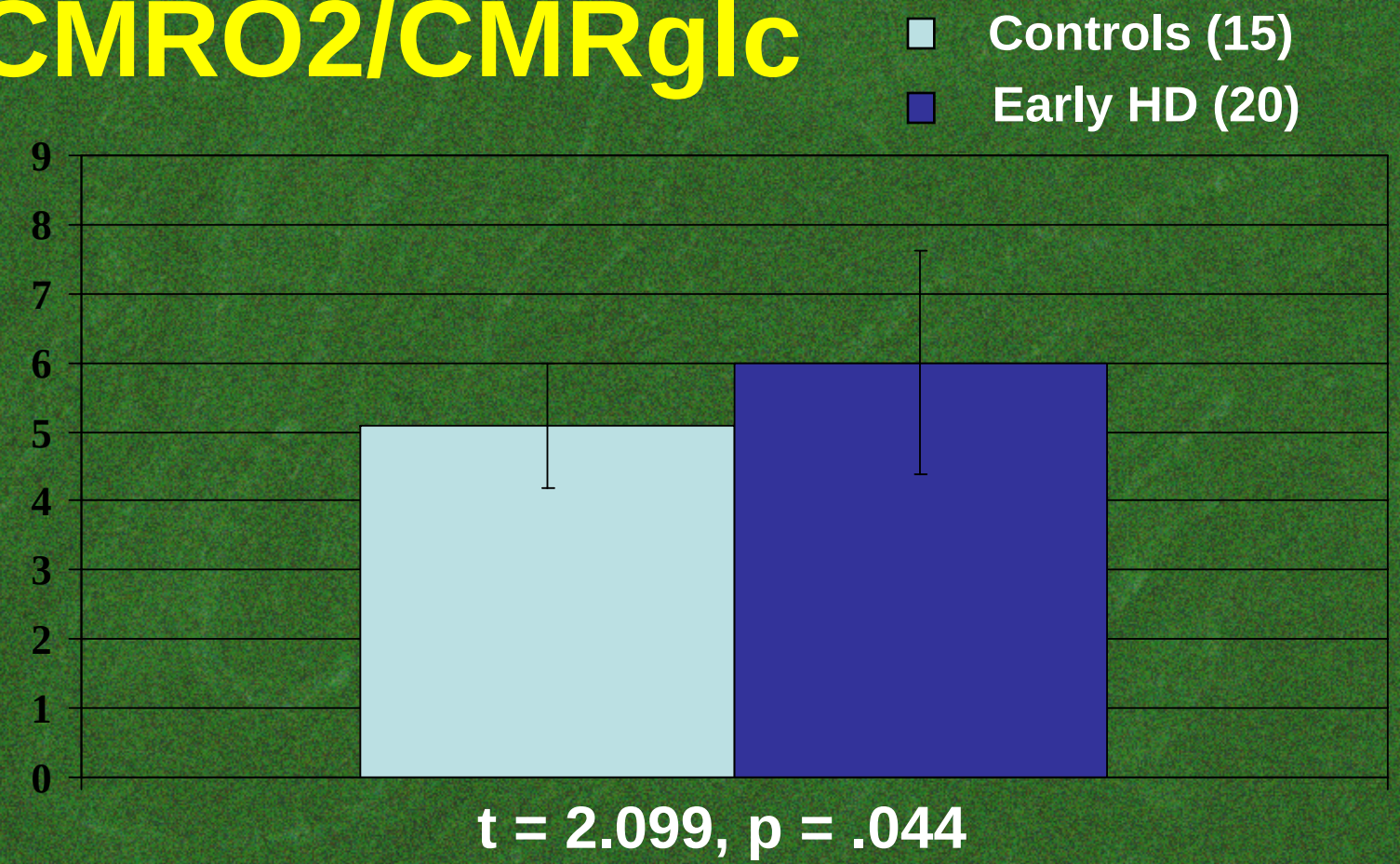
HD Striatal CMRO2/CMRglc



t = 2.099, p = .044

Powers et al, PNAS, in press

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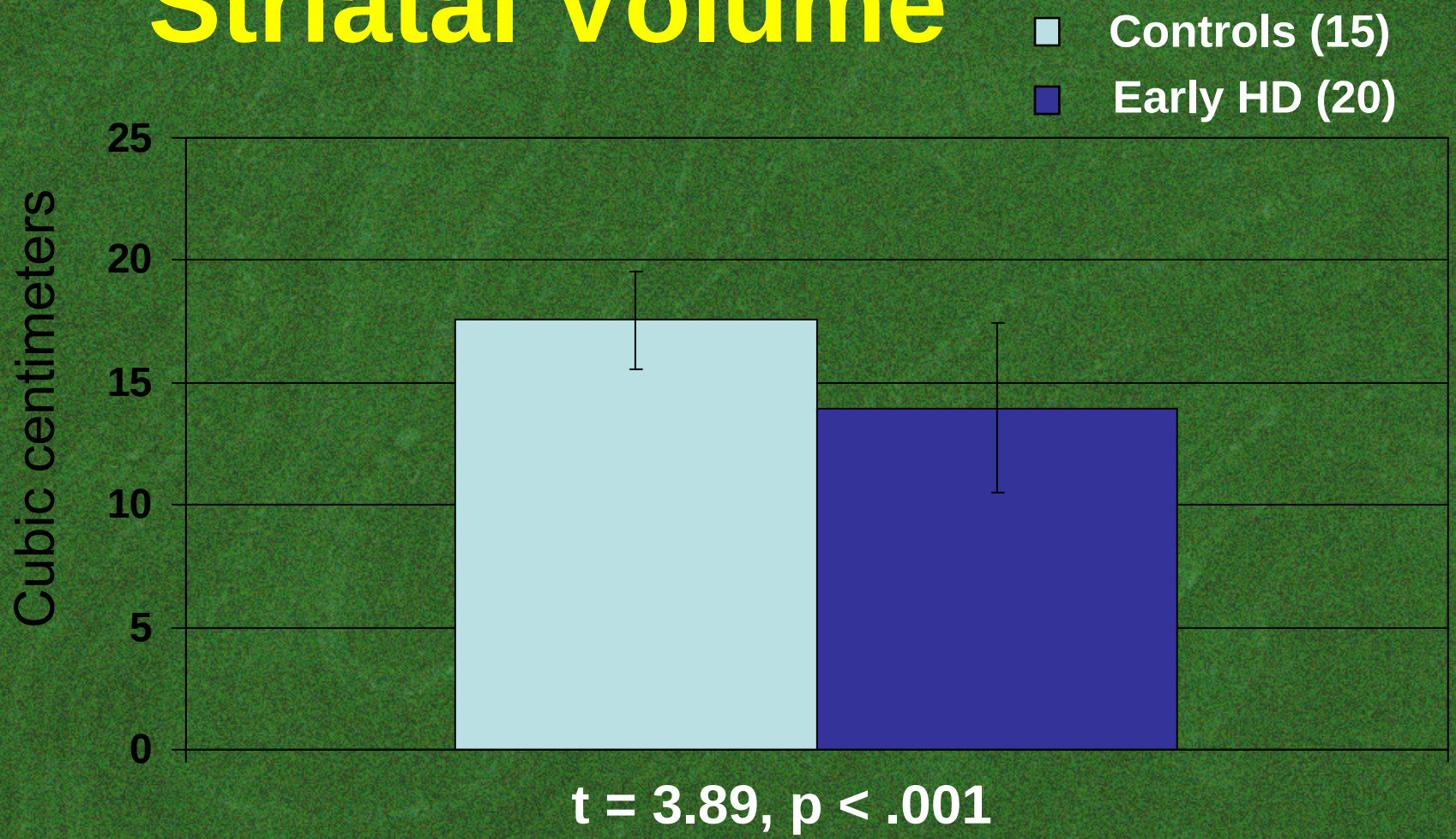
Striatal Volume



t = 3.89, p < .001

Powers et al, PNAS, in press

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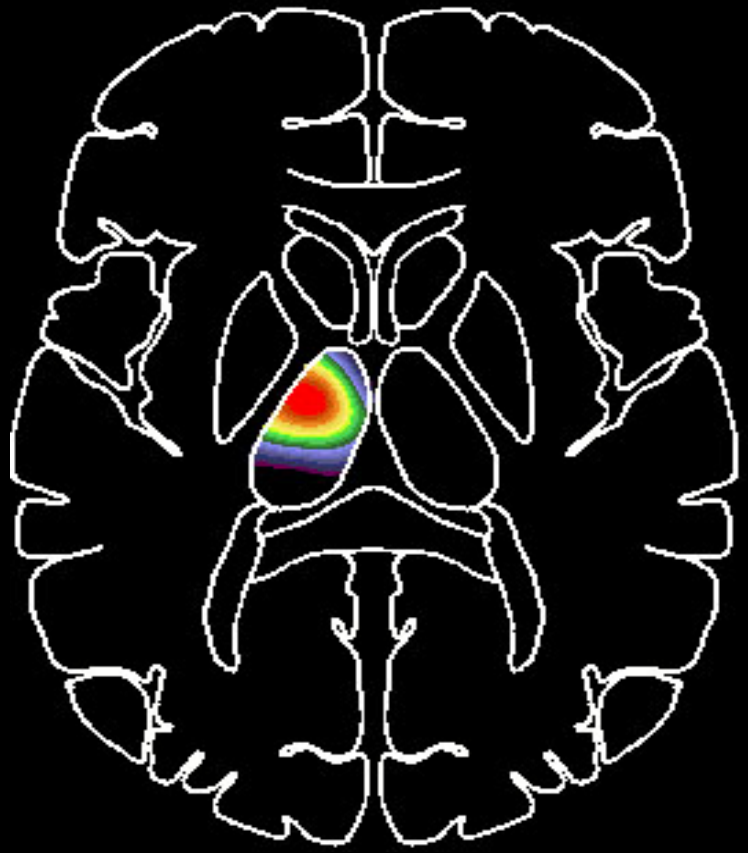
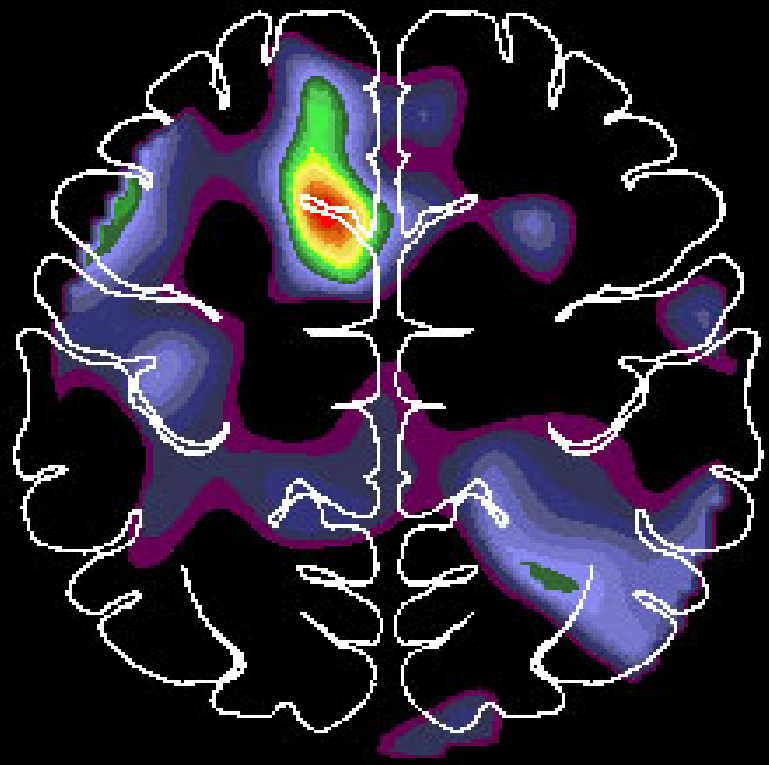
Responses to Thalamic Stimulation



Thalamus

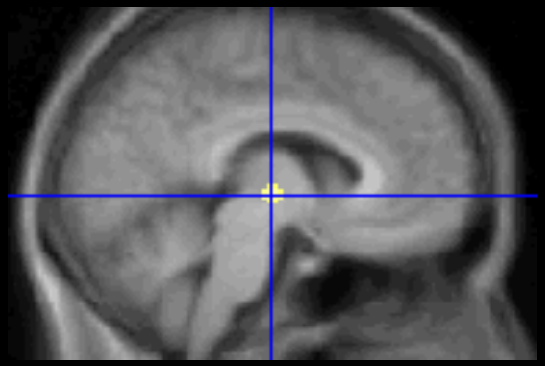


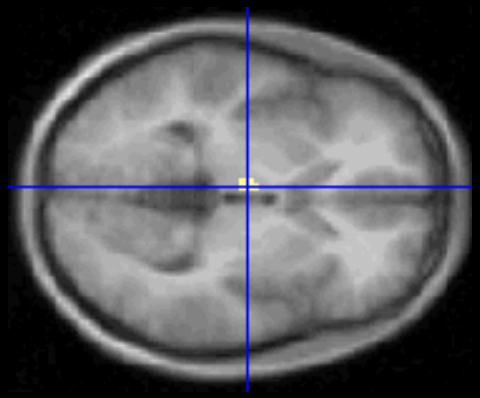
Cortex

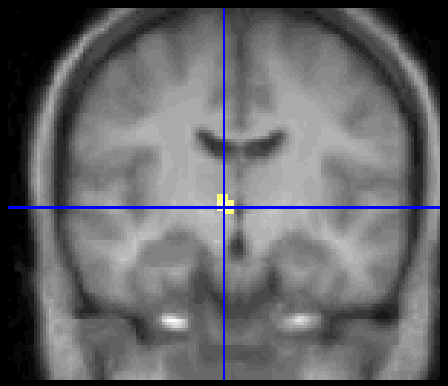
Perlmutter et al, Neurology 2002

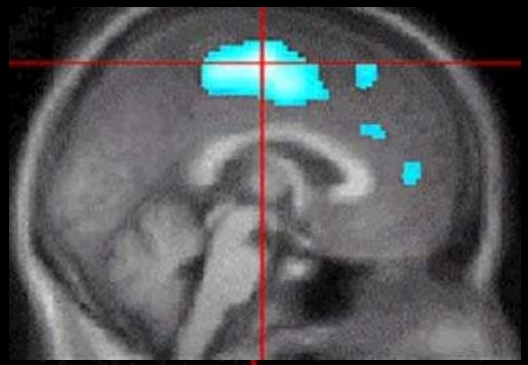
Increases

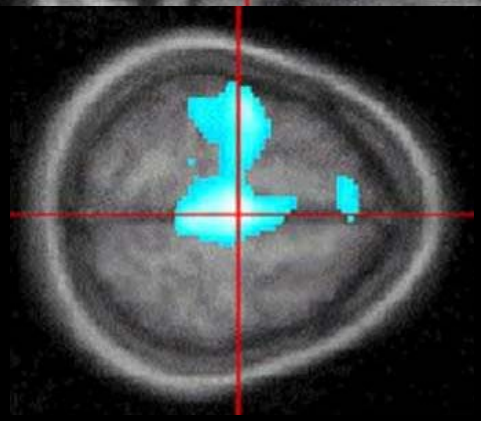
Decreases

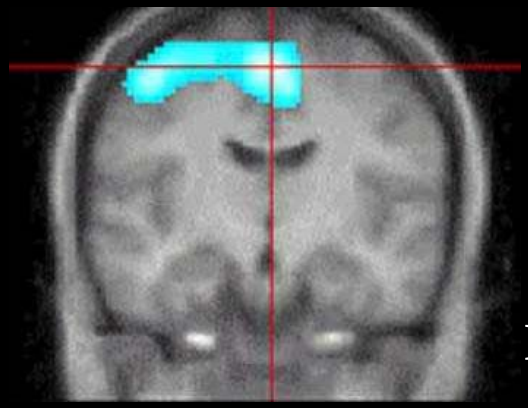




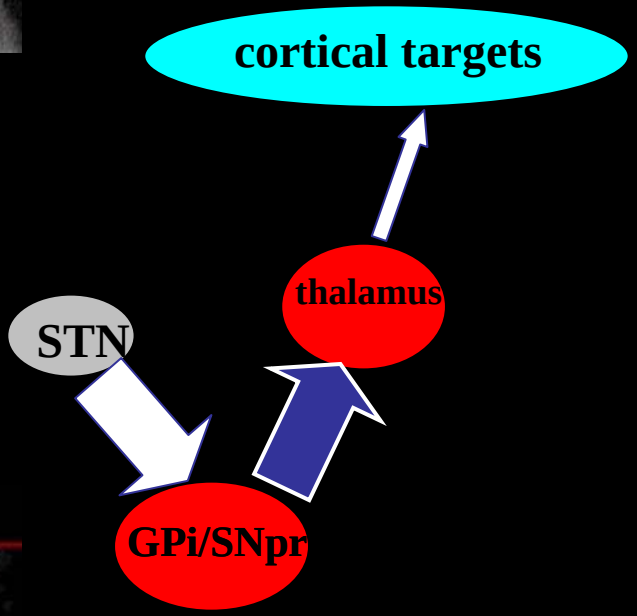








STN output: increased



Hershey et al, Neurol 2003

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