Parkinsonian oscillations: a computational view

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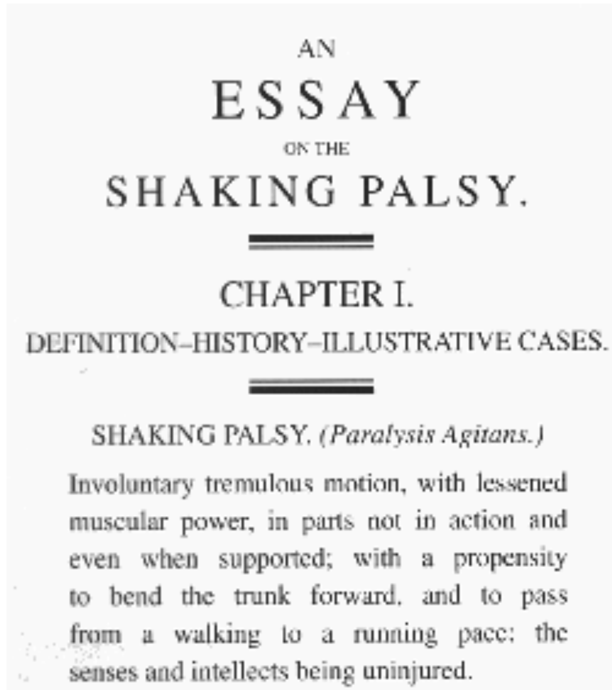
NATIONAL INSTITUTES OF HEALTH

Parkinson’s disease: historical origin in medicine

James Parkinson



AN
ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

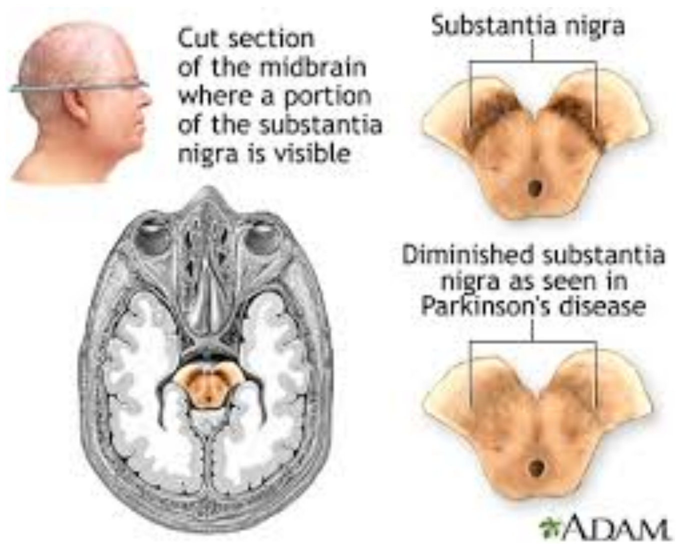
Parkinson, 1817

William Gowers, 1886

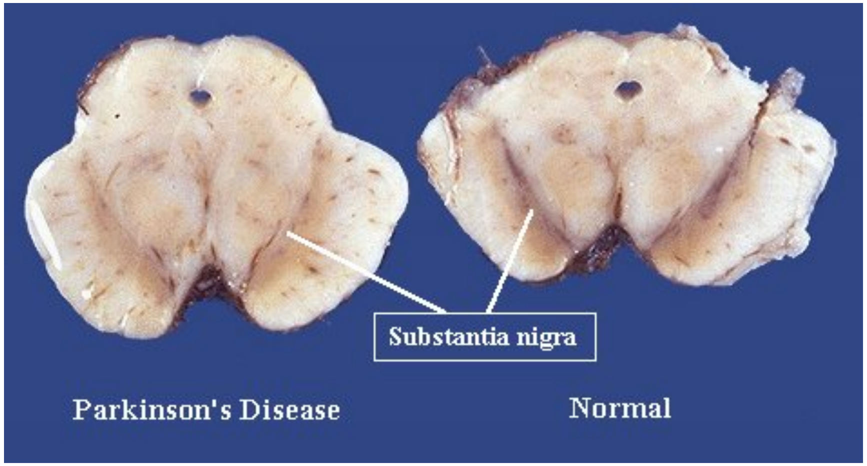
Parkinson's disease: immediate cause

death of dopaminergic neurons in substantia nigra pars compacta:

Hassler et al., pre-1940; Carlsson & Hornykiewicsz, 1950-1970



NIH Medline

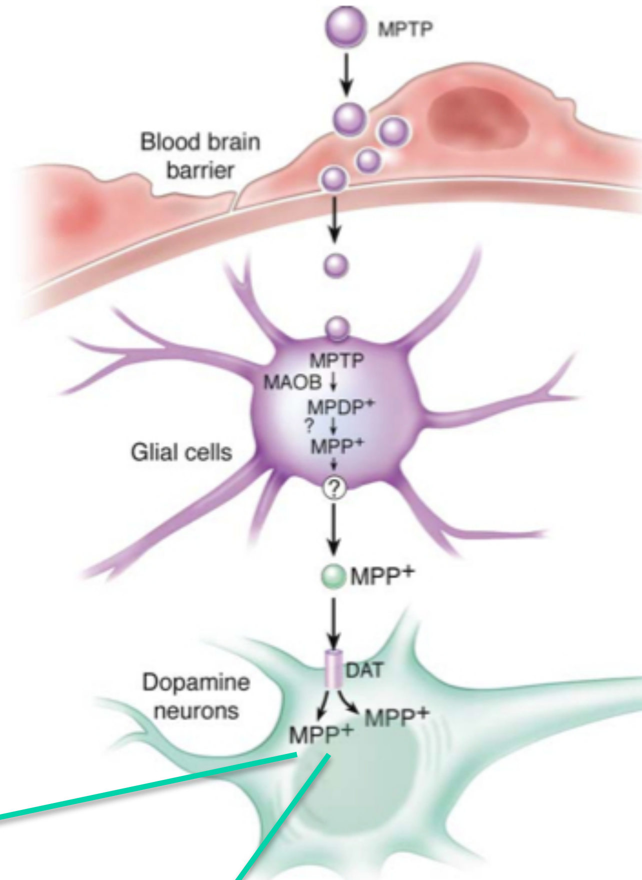


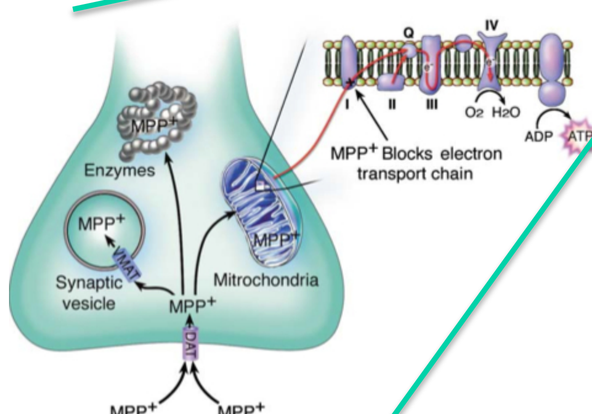
CNS Pathology

OP: Why do these cells die? Why don't other cells die?

The Frozen Addicts

Dr. Bill Langston, *The Case of the Frozen Addicts*



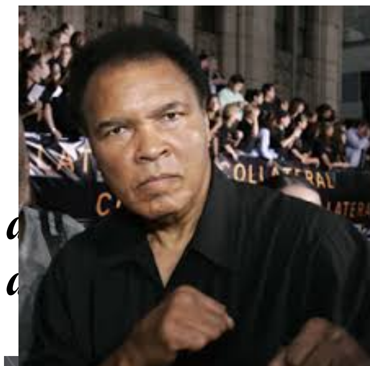


Dauer & Przedborski, *Neuron*, 2003

Parkinson's disease: summary

what: akinesia (difficulty initiating movement), bradykinesia (slowed movement), posture issues, rigidity, tremor

how: dopamine loss: death of dopamine-secreting cells in the substantia nigra pars compacta (SNc) of the *basal ganglia*



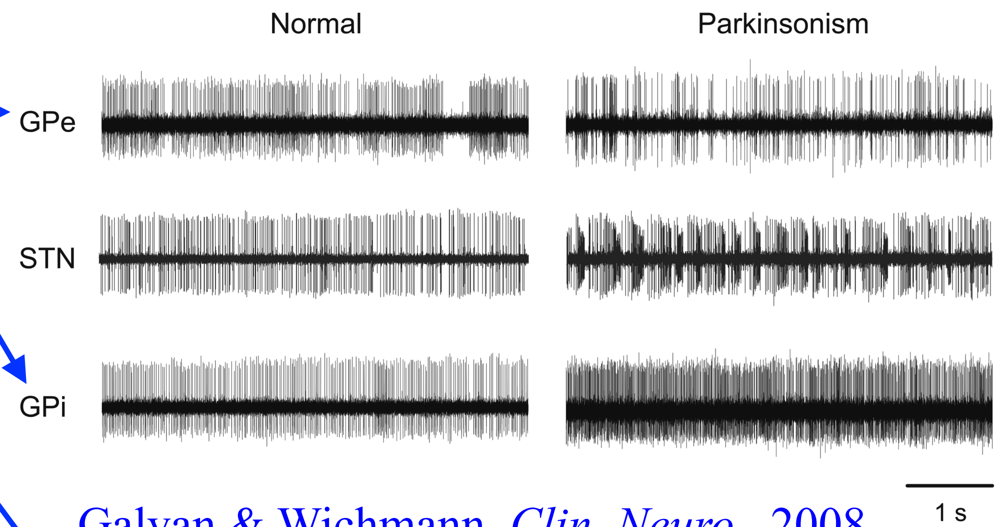
who: "8-18 cases per 100,000 person-years"; 1% of those over 60 and 4% of those over 80; 5-10% of cases are early onset (age 20-50)

why: occasionally but not usually genetic; risks linked to pesticides (e.g., rotenone!), toxins (MPTP -- *The Case of the Frozen Addicts*), heavy metals; possibly protection from caffeine, smoking, anti-inflammatories, estrogens, exercise, (clean) apple skin…

Wikipedia; de Lau et al., *Lancet Neurol.*, 2006; O. Bandmann

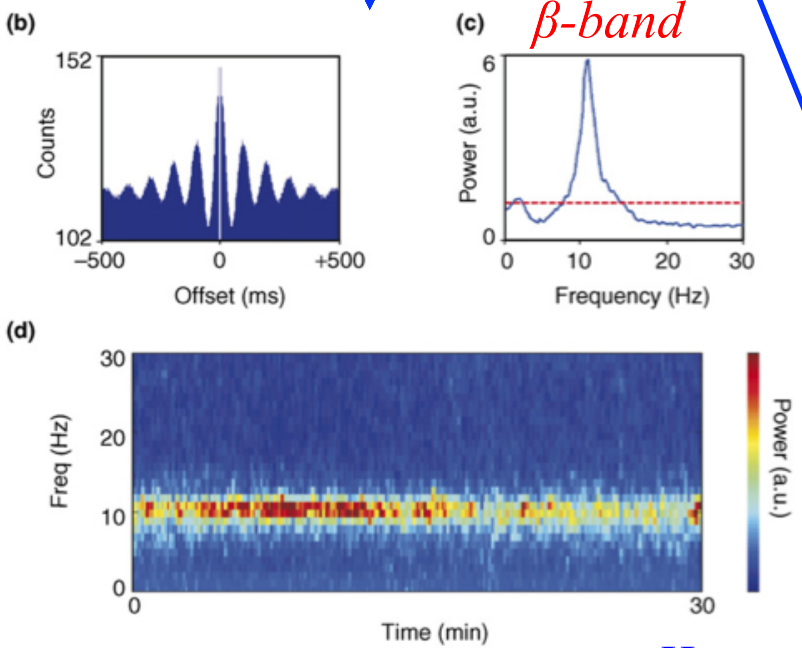
altered basal ganglia neuronal activity patterns in parkinsonism

- *changes in firing rates*
- *increased burstiness*
- *increased oscillations*



Galvan & Wichmann, *Clin. Neuro.*, 2008

Magnin et al., *Neuroscience*, 2000



Hammond et al., *TINS*, 2007; GPi

some past comput. models w/parkinsonian activity

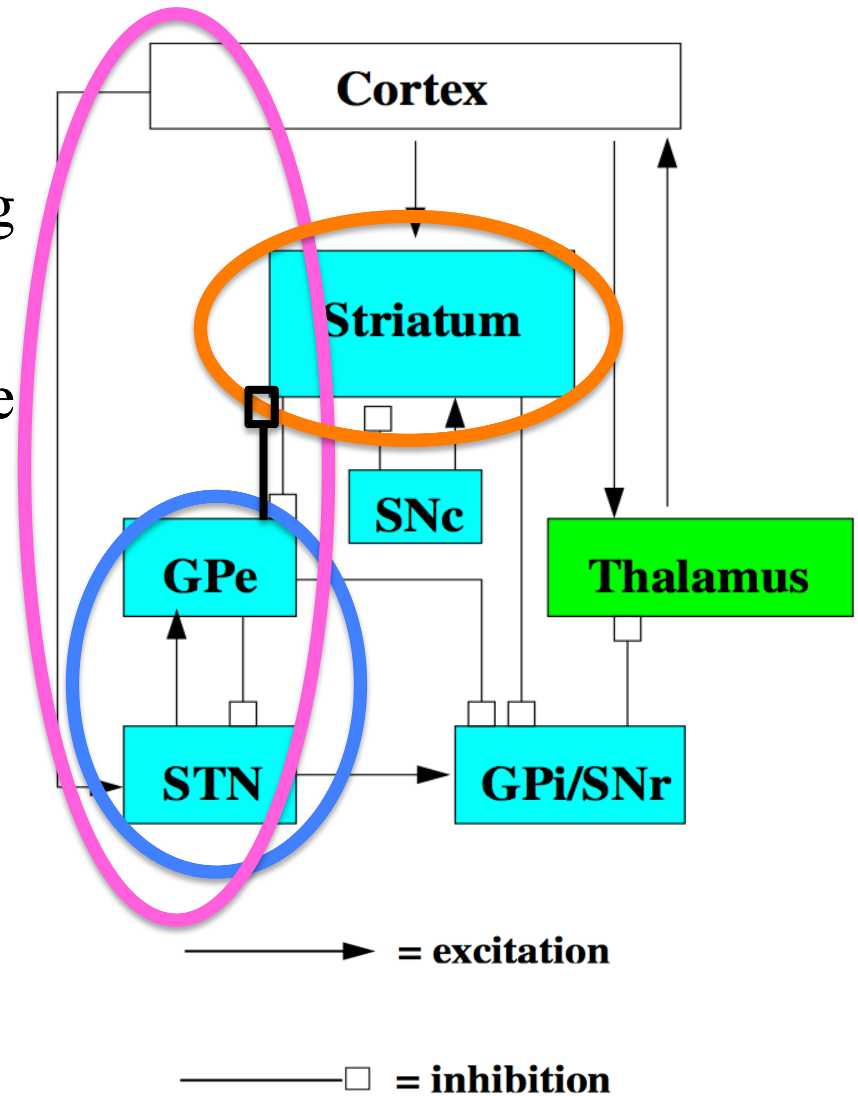
Terman et al., 2002: STN-GPe (E-I loop); cf. Park & Rubchinsky

Leblois et al., 2006: symmetry-breaking in full BG activity-based model

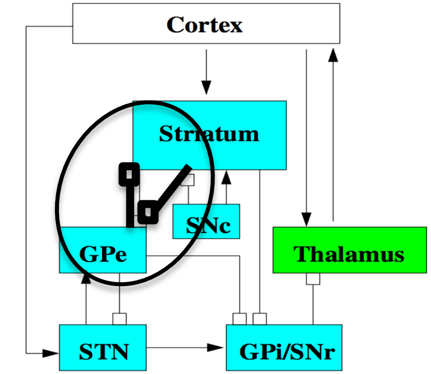
Nevado-Holgado et al., 2010: STN-GPe firing rate model; β oscillations require cortical excitation to STN and synaptic delays

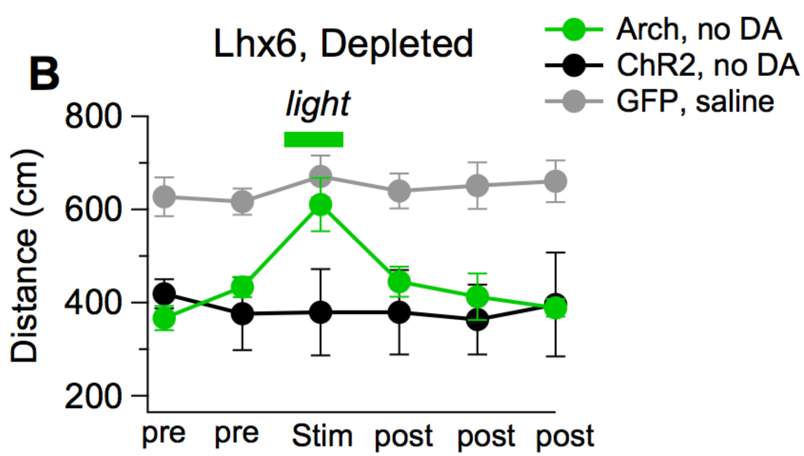
McCarthy et al., 2011: inhibitory interactions in striatal medium spiny neurons (MSNs) sufficient for β

Kumar et al., 2011: large scale (LIF) STN-GPe model



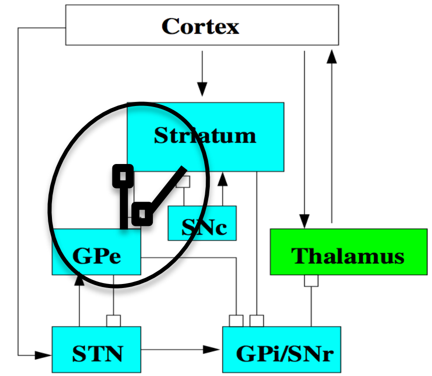
new suspect: pallidostriatal circuit

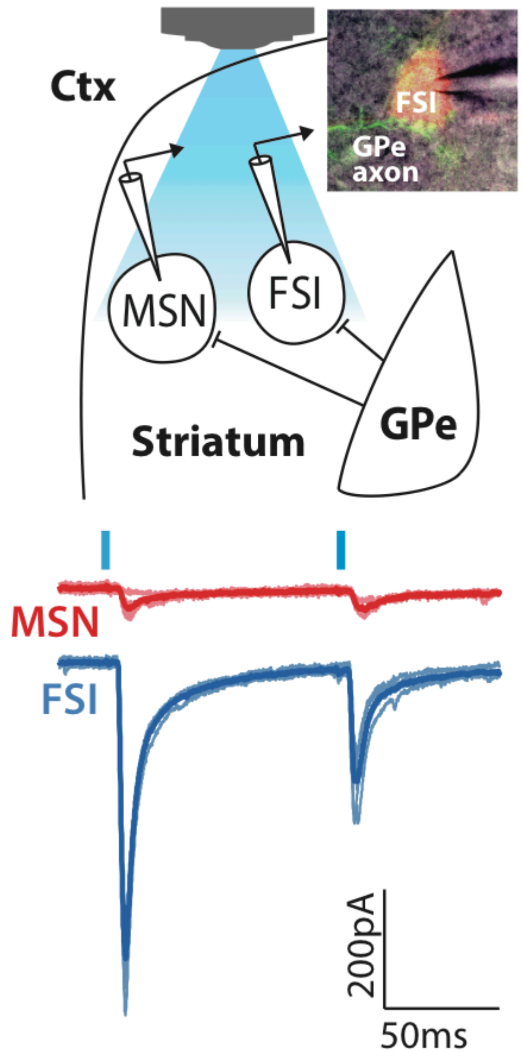


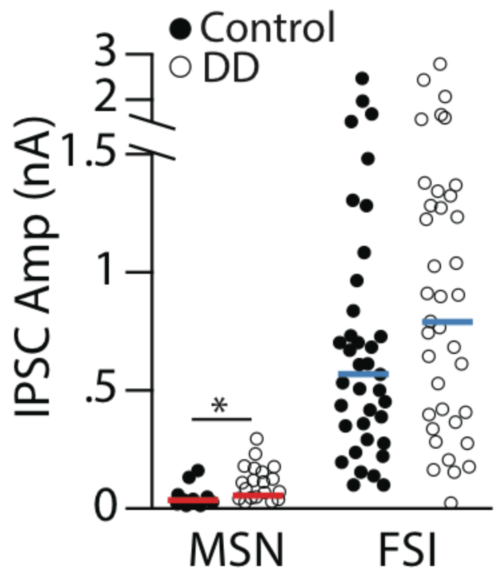


Gittis lab, CMU; unpublished

defining the pallidostriatal circuit

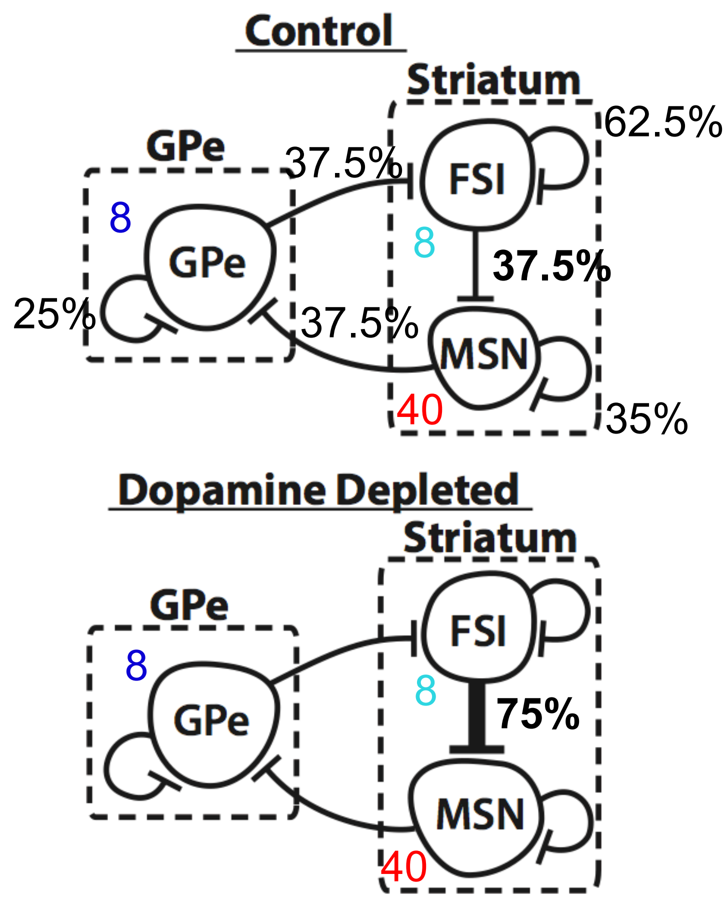


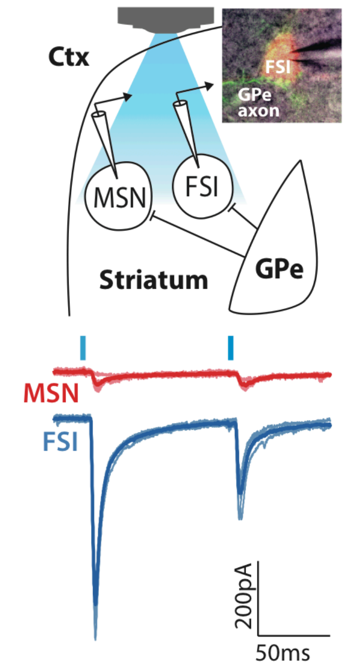




Corbit*, Whalen* et al., *J. Neurosci.*, 2016

pallidostriatal circuit model

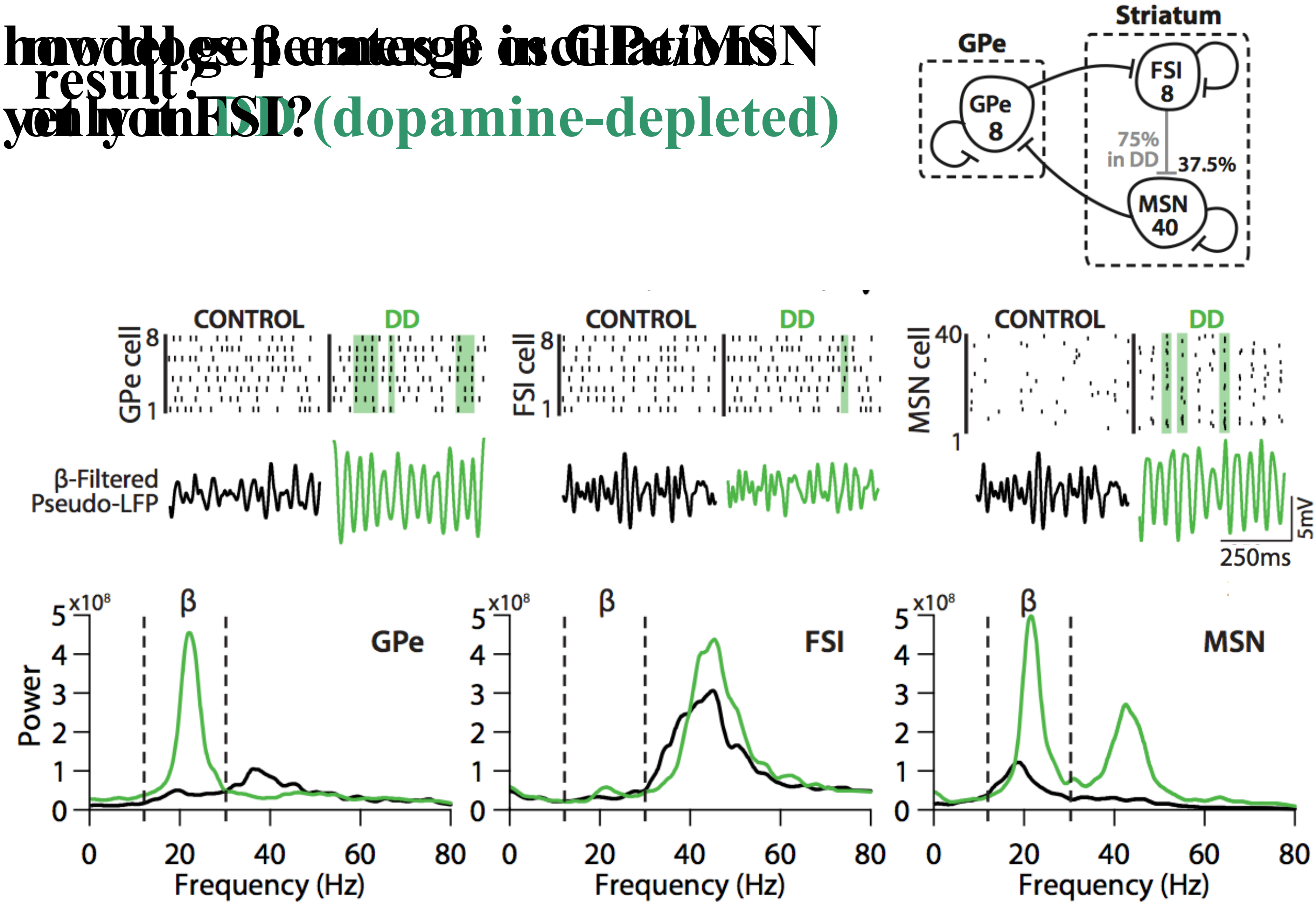




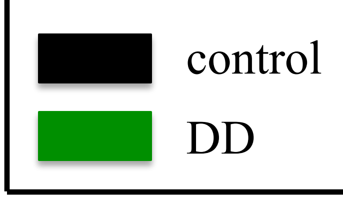
how does β emerge in GPe/MSN yet not in FSI?

model generates β oscillations only in DD (dopamine-depleted)

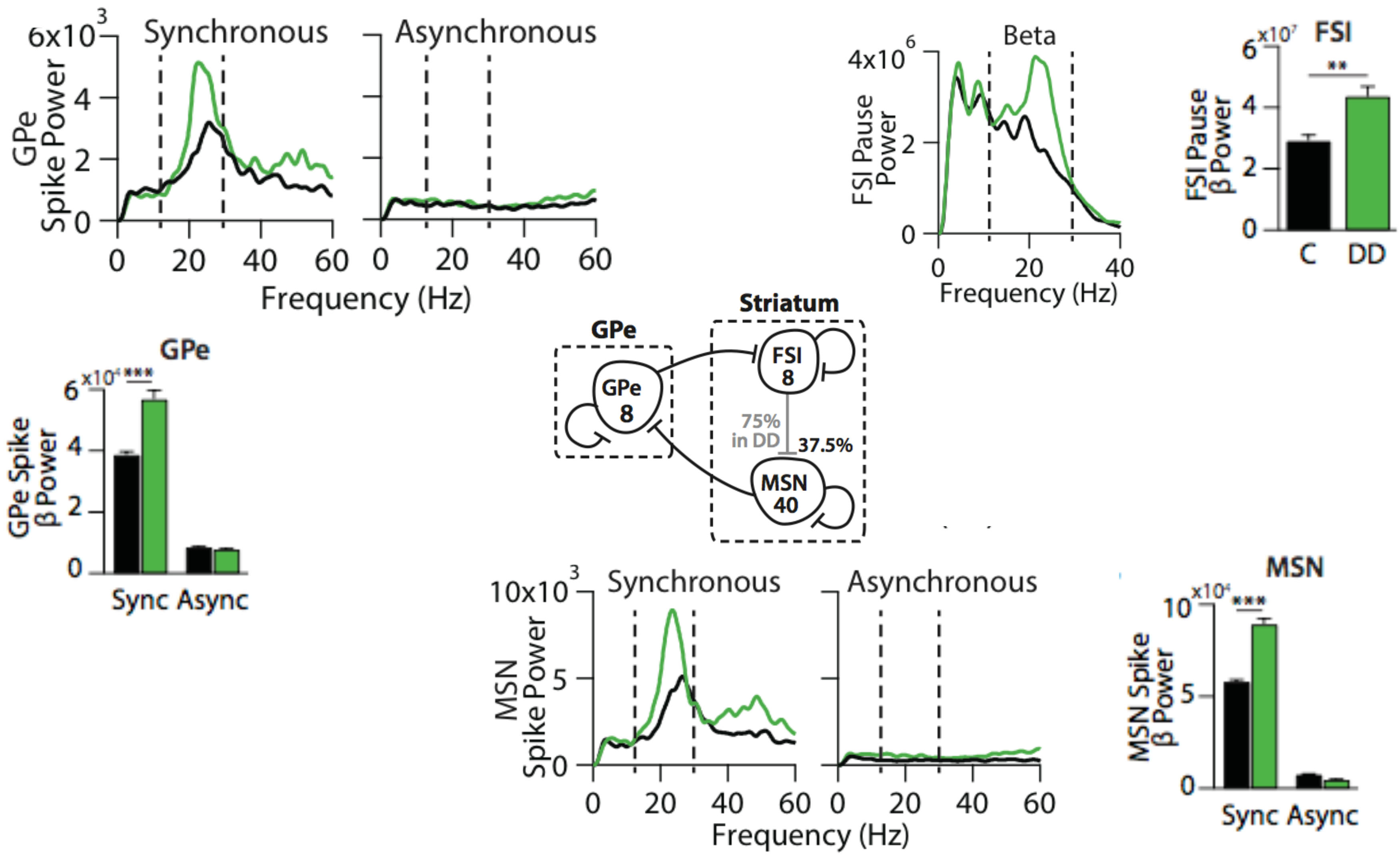
result?



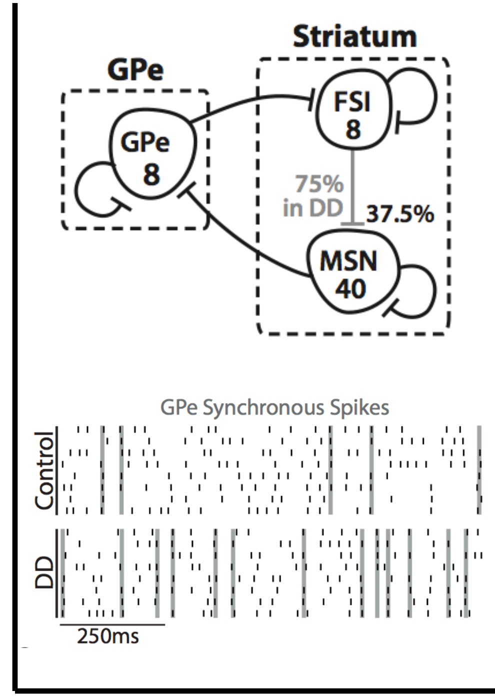
Corbit*, Whalen* et al., *J. Neurosci.*, 2016



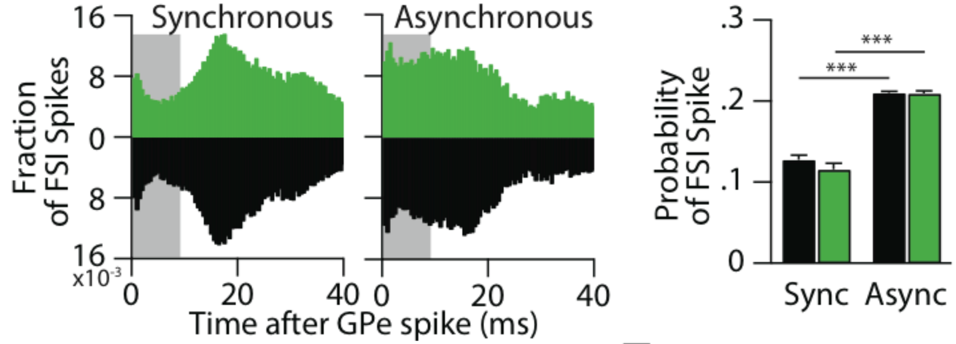
key point: *synchronous events* exhibit β rhythmicity, enhanced in dopamine-depleted



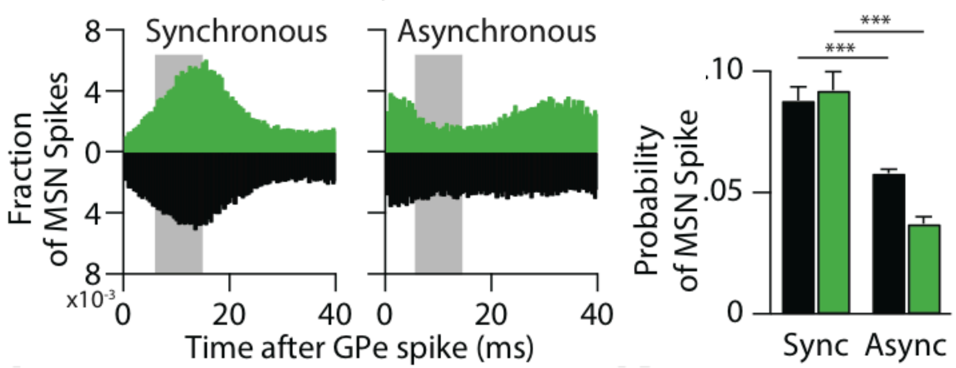
thrown for a loop



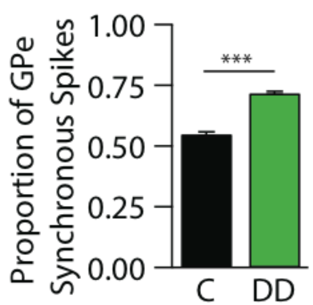
synchronous *spikes in GPe pause FSI…*



…allowing MSN to fire, esp. in DD…

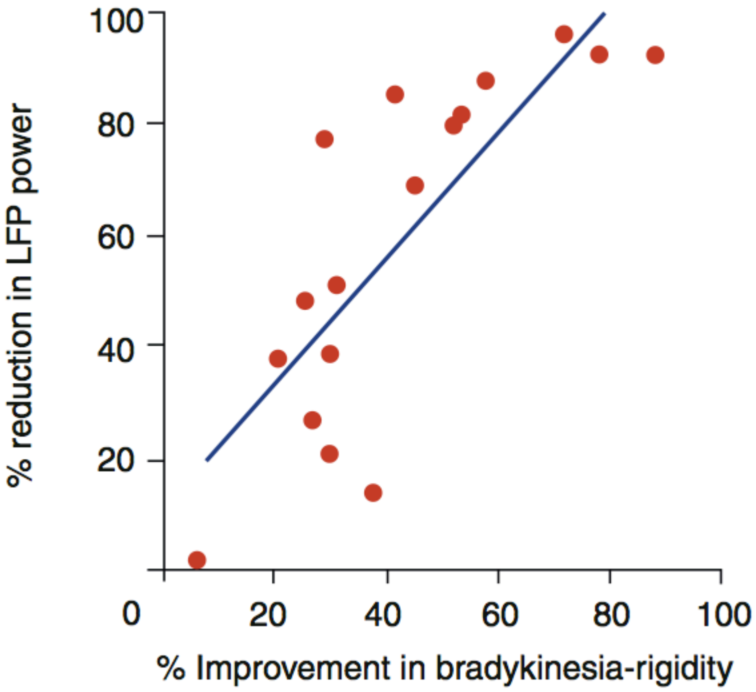


…enhancing GPe synchrony in DD

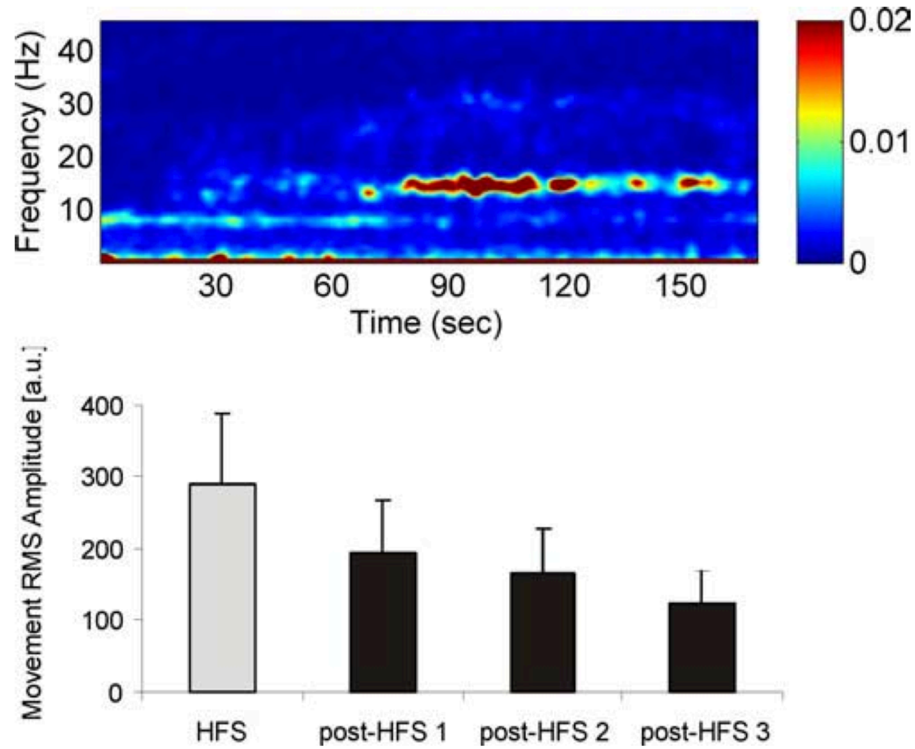


why are β oscillations significant?

β strength correlates with PD severity; re-emergence/ introduction of β can cause PD-like signs



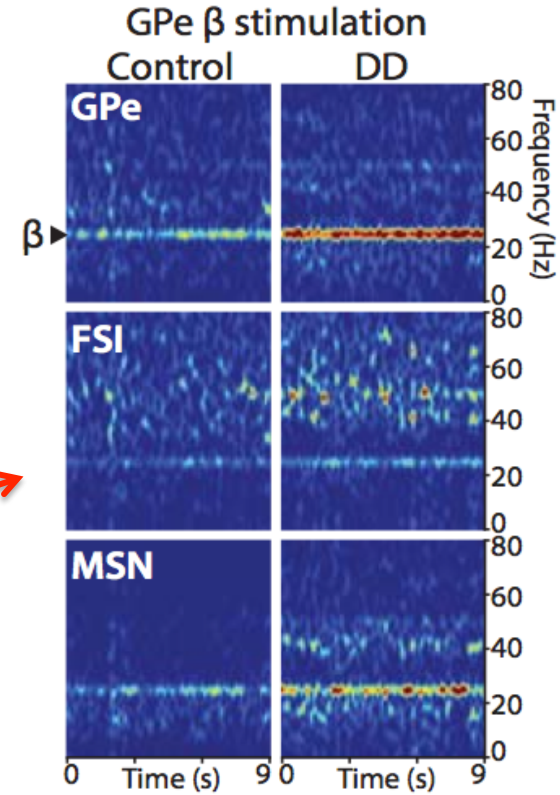
Jenkinson & Brown, TINS, 2011 (cf. Kuhn et al., *EJN, 2006; Exp. Neurol.*, 2009)

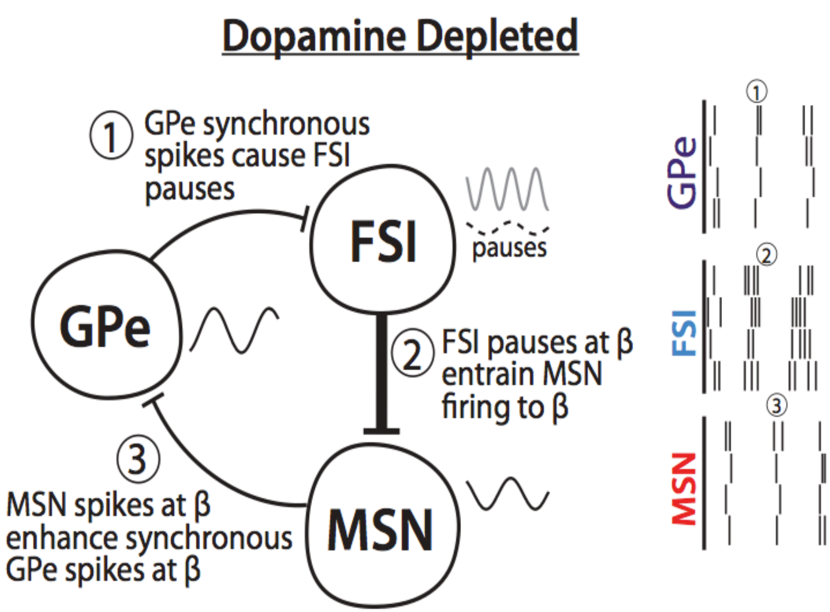


Kuhn et al., *J. Neurosci.*, 2008

Conclusions I

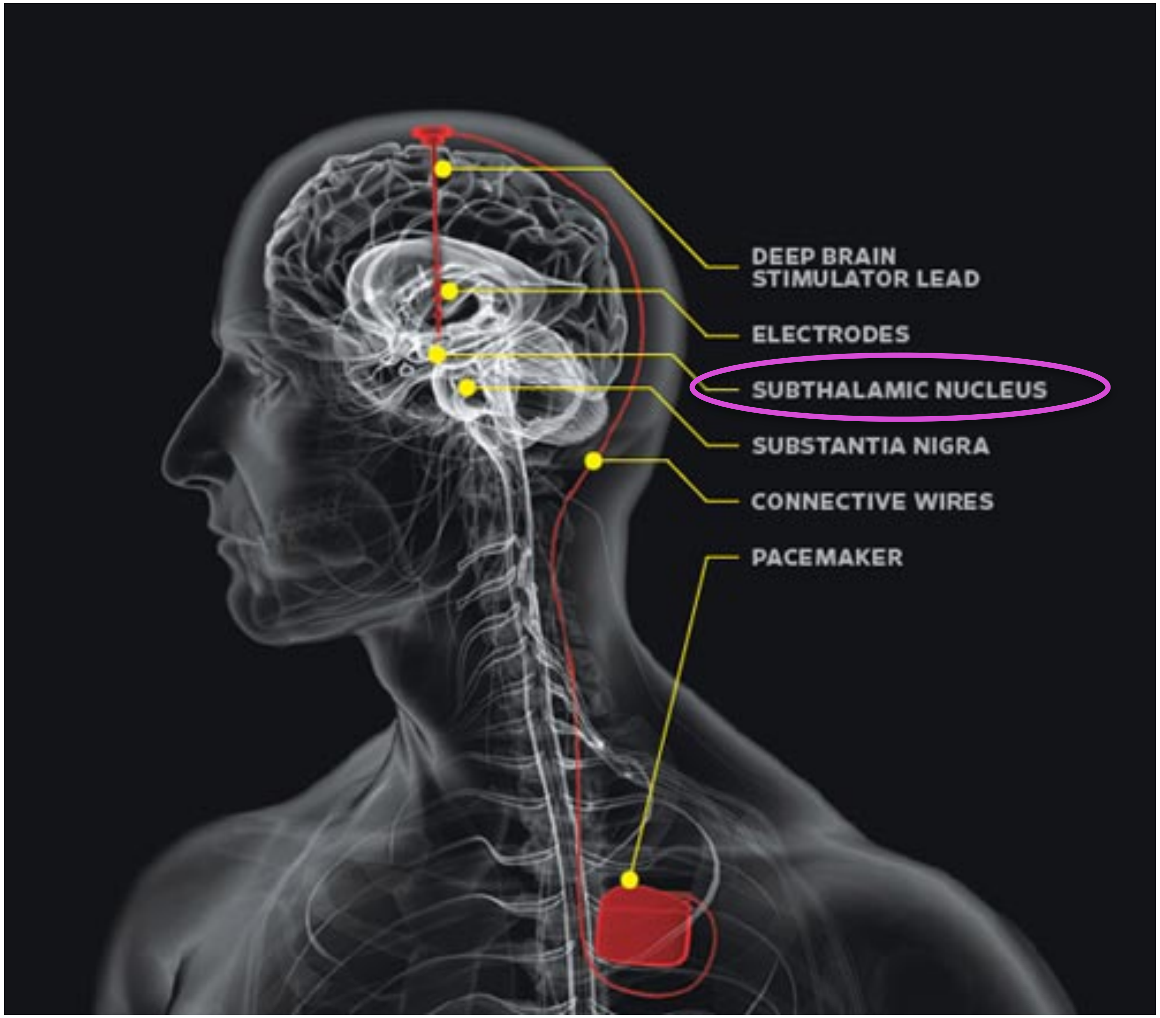
- Parkinson's disease involves pathological activity in the basal ganglia that includes ***enhanced β oscillations***
- these oscillations may originate in ***or be amplified by*** the pallidostriatal circuit
- all circuit elements contribute:





how can motor symptoms be mitigated?

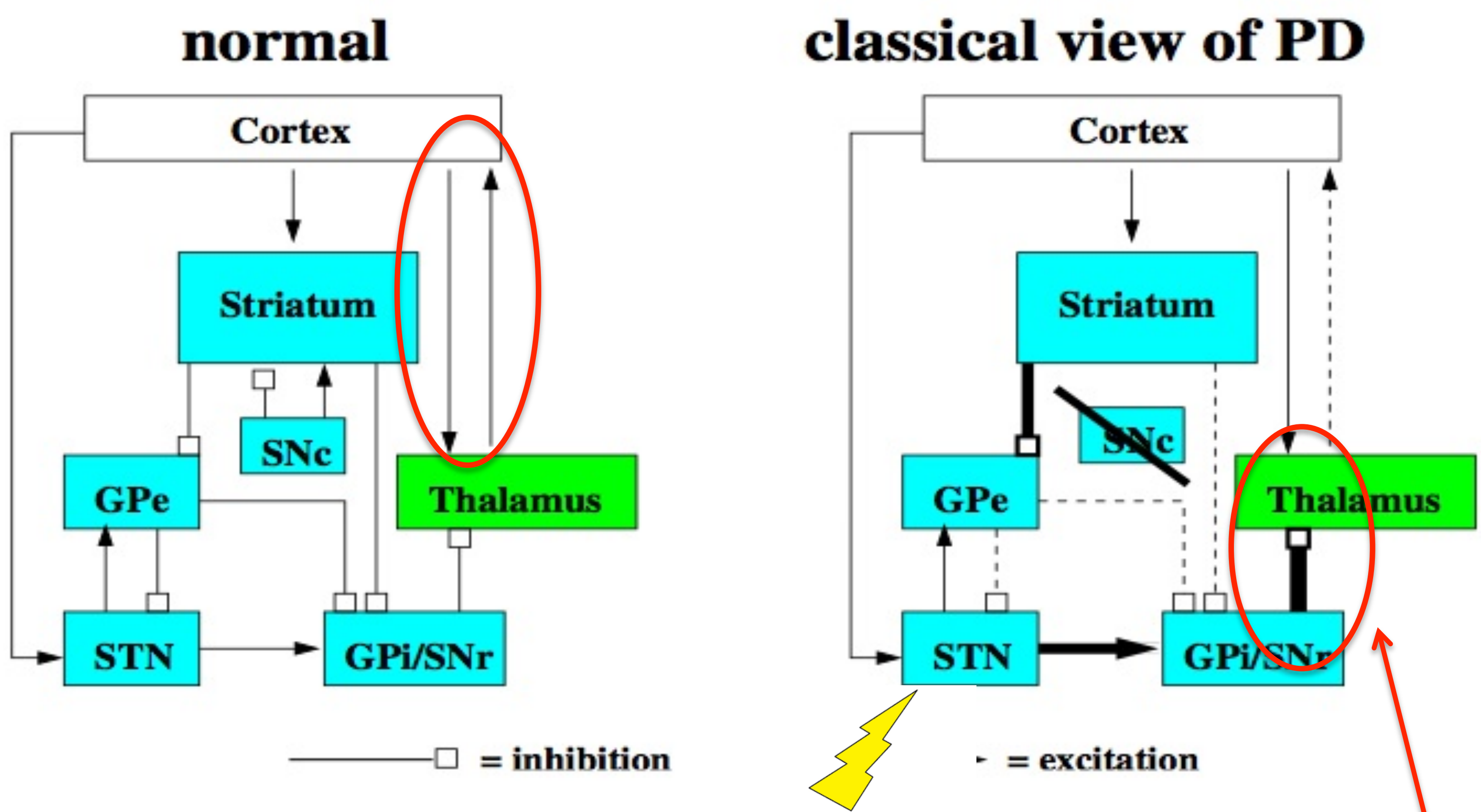
deep brain stimulation (STN-DBS shown here)



The Mayo Clinic

OP: looks great – but how does this work??

idea 1: BG outputs go to thalamic relay station



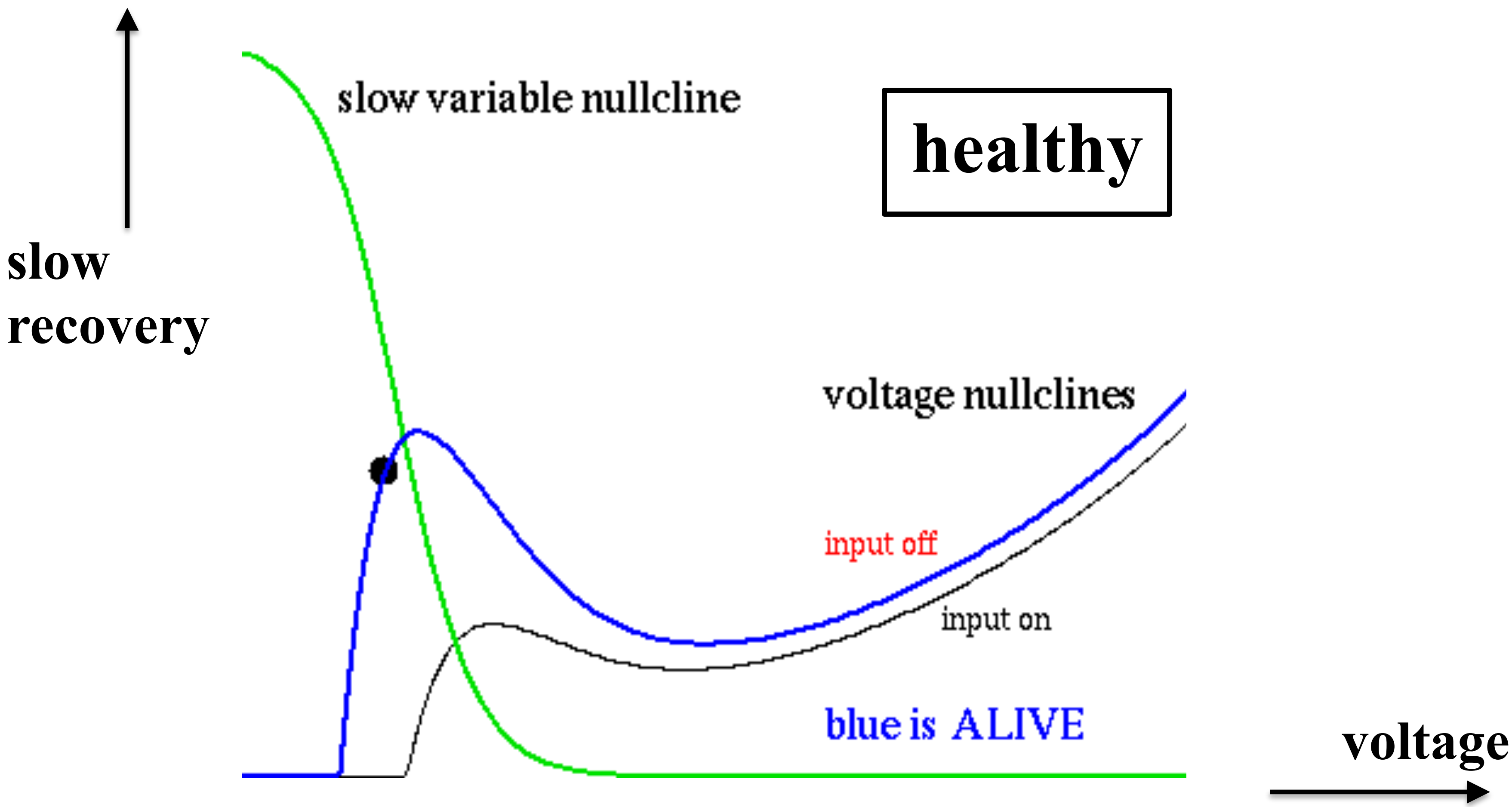
paradox: **how can more inhibition make things better??**

perhaps relay is compromised in PD!

Rubin & Terman, *J. Comp. Neurosci.*, 2004

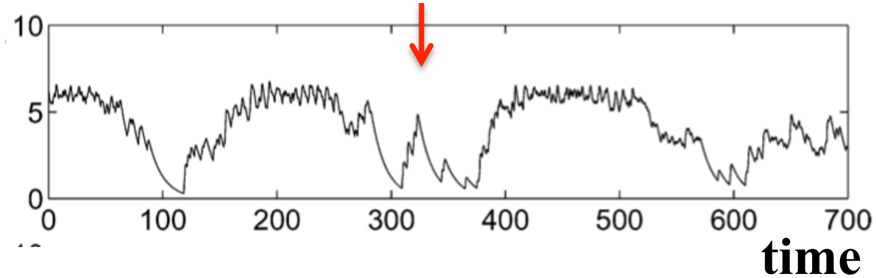
answer: pattern of inhibition trumps amount

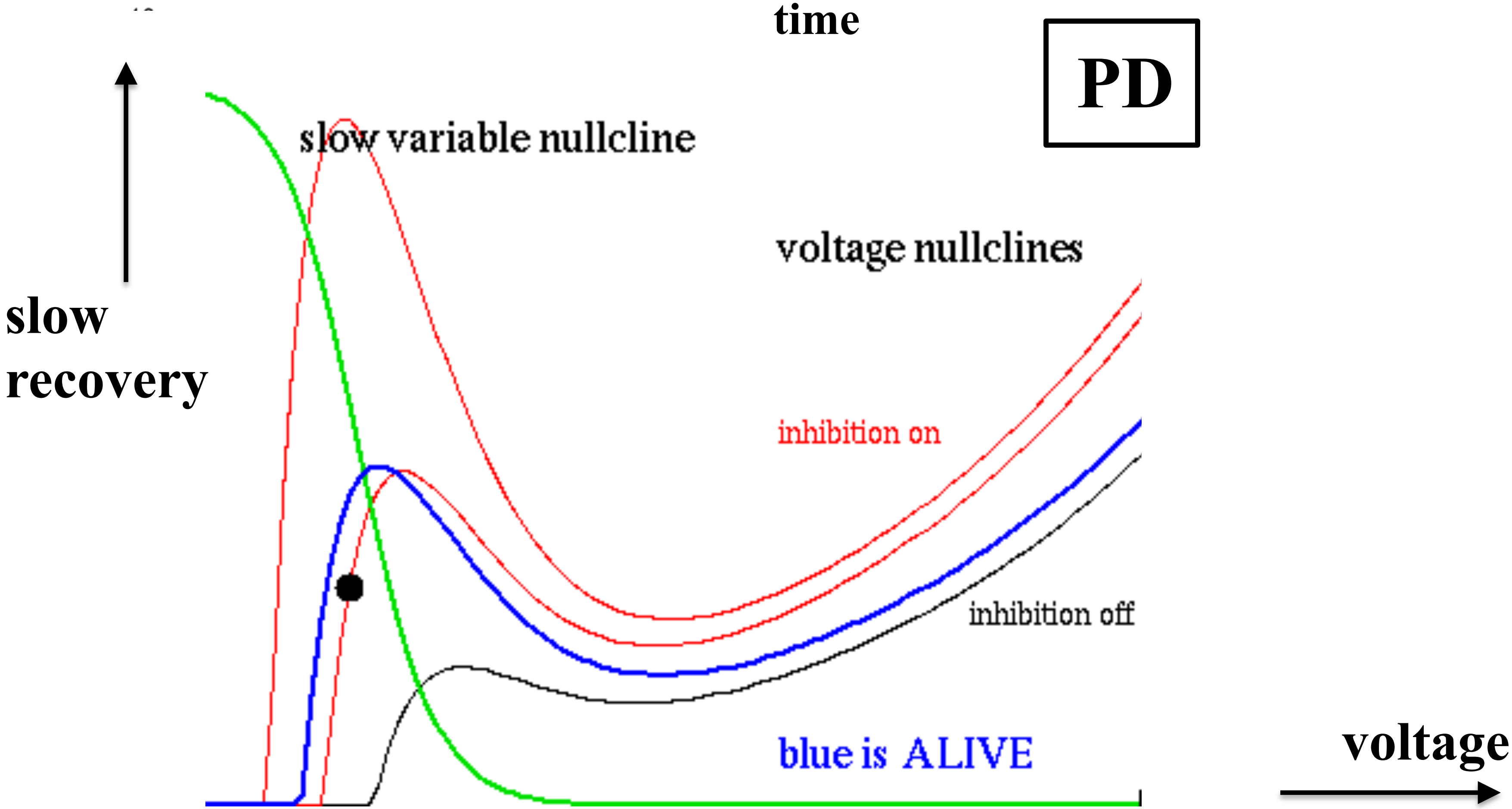
TC (relay) cell should give voltage spike to each input:



answer: pattern of inhibition trumps amount

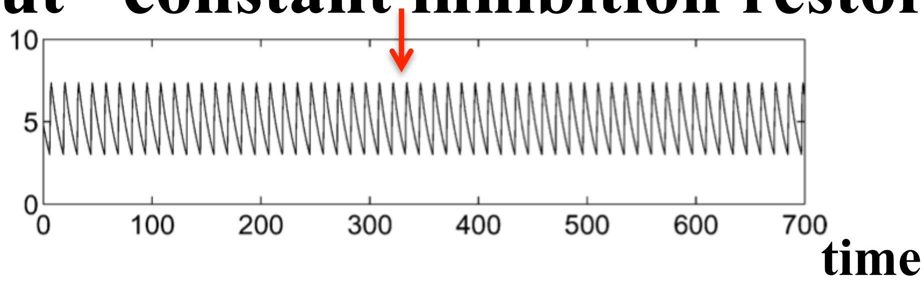
PD – *oscillation* of inhibition throws relay out of whack:

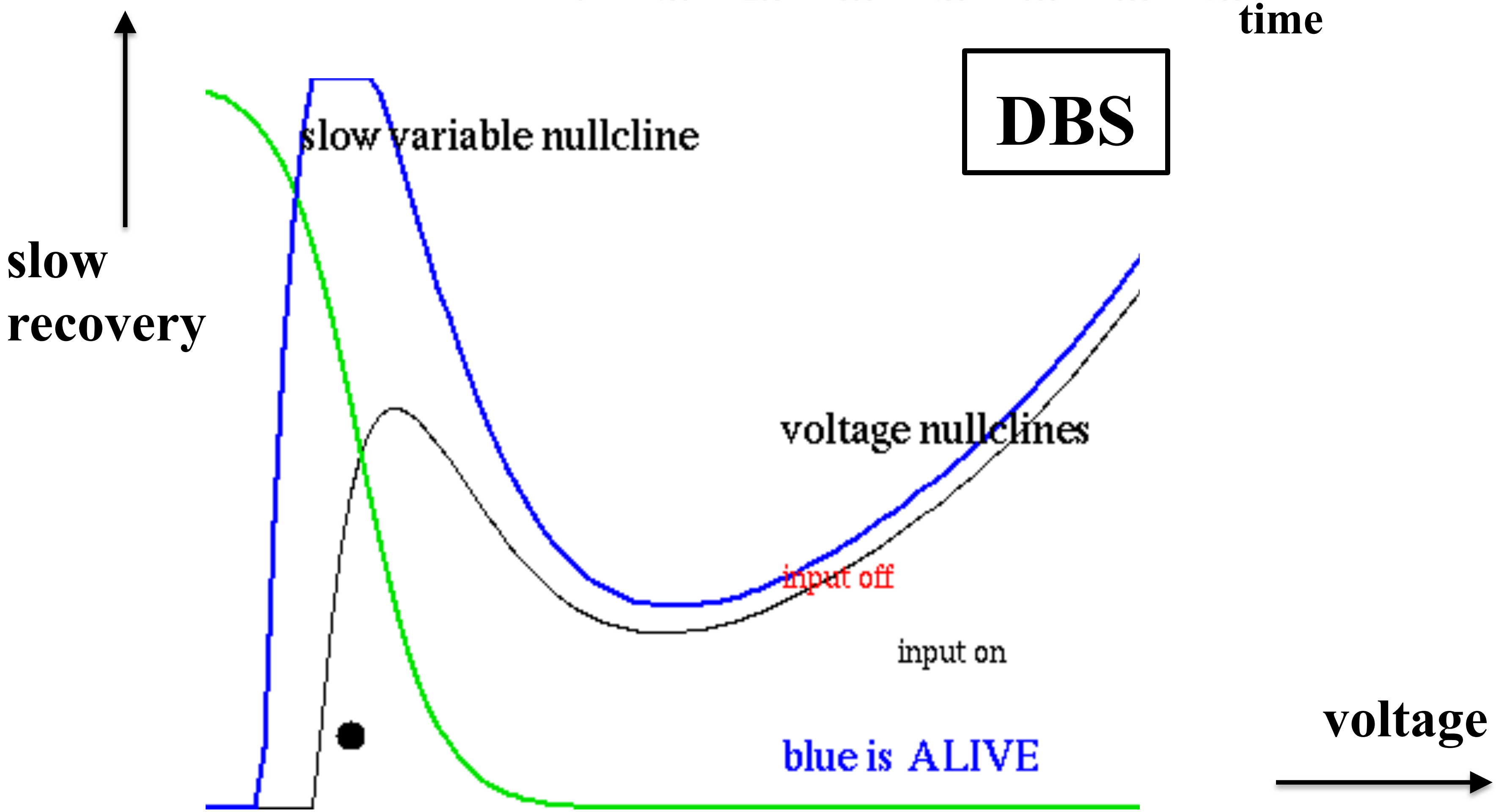




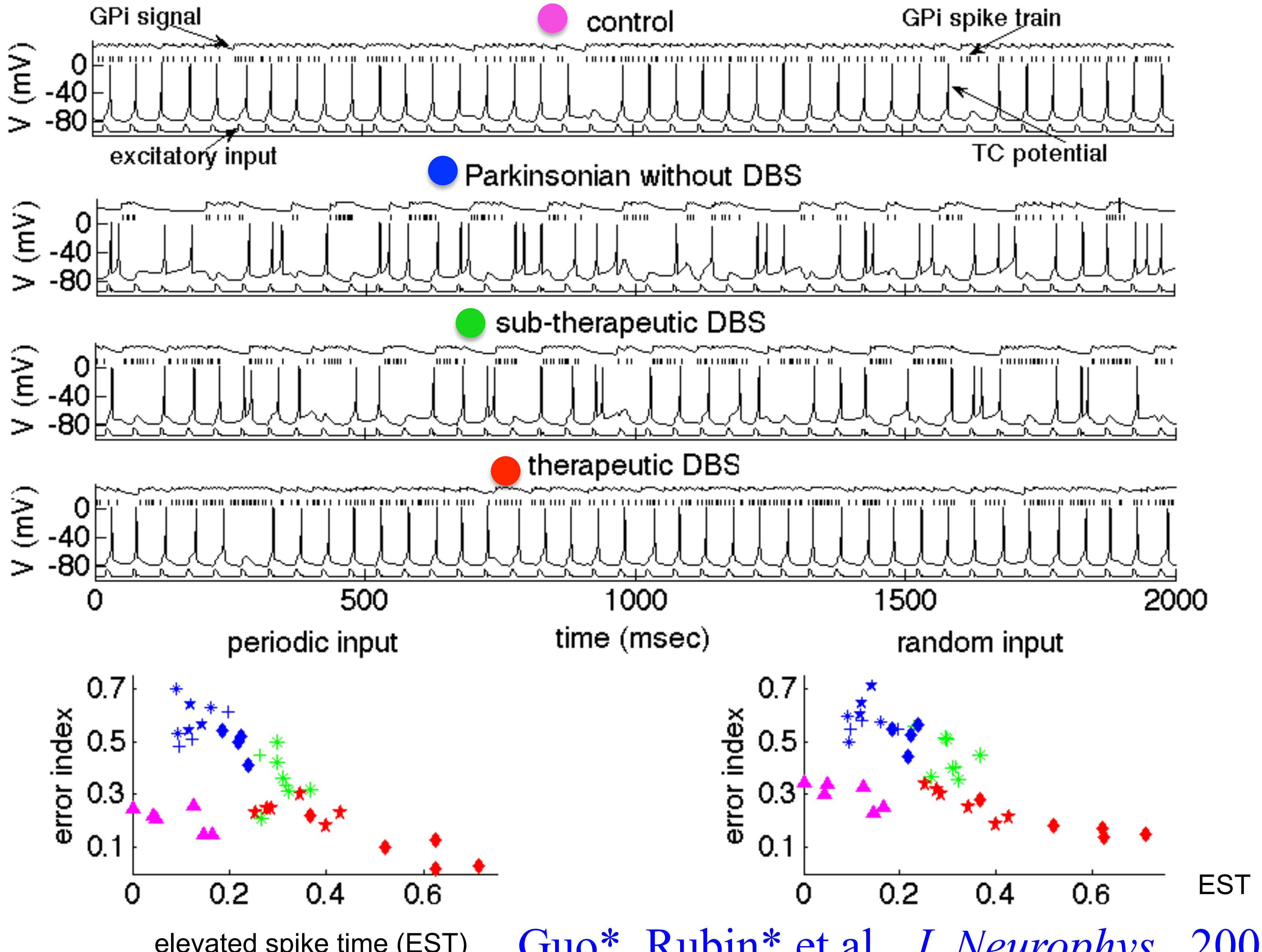
answer: pattern of inhibition trumps amount

PD + DBS – higher but ~constant inhibition restores relay:





test with data-driven computational model



Guo*, Rubin* et al., *J. Neurophys.*, 2008

Conclusions II

• parkinsonian oscillations in basal ganglia will be transmitted to thalamic relay cells

• inhibitory oscillations compromise relay →

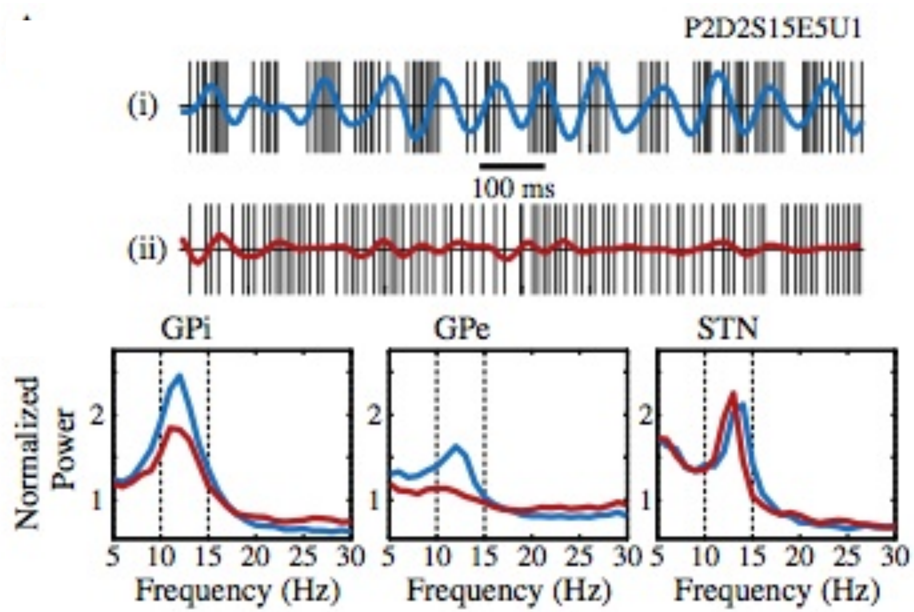
• although DBS drives basal ganglia outputs and may yield larger inhibition, ***inhibition that becomes less variable may restore relay*** →

more experiments on STN-DBS:

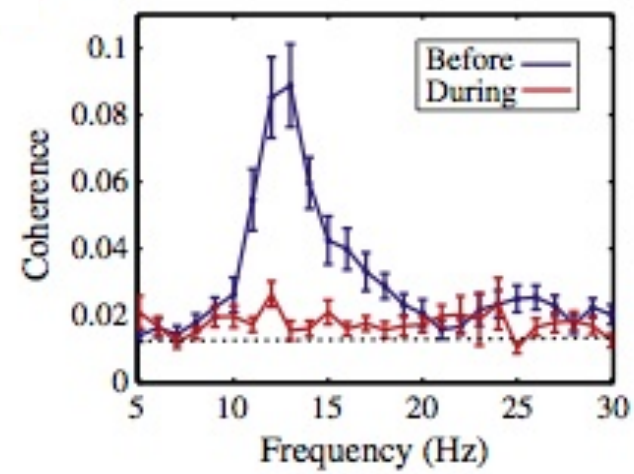
(1) suppresses *β* oscillations in GPi despite ongoing *β* in STN (which drives GPi) and

(2) destroys STN-GPi coherence

(1)



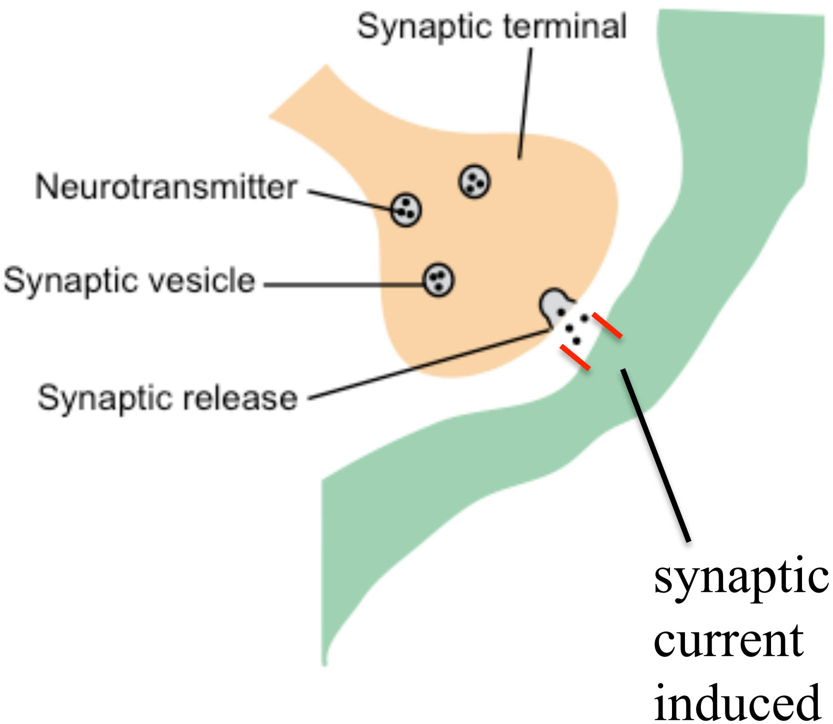
(2)



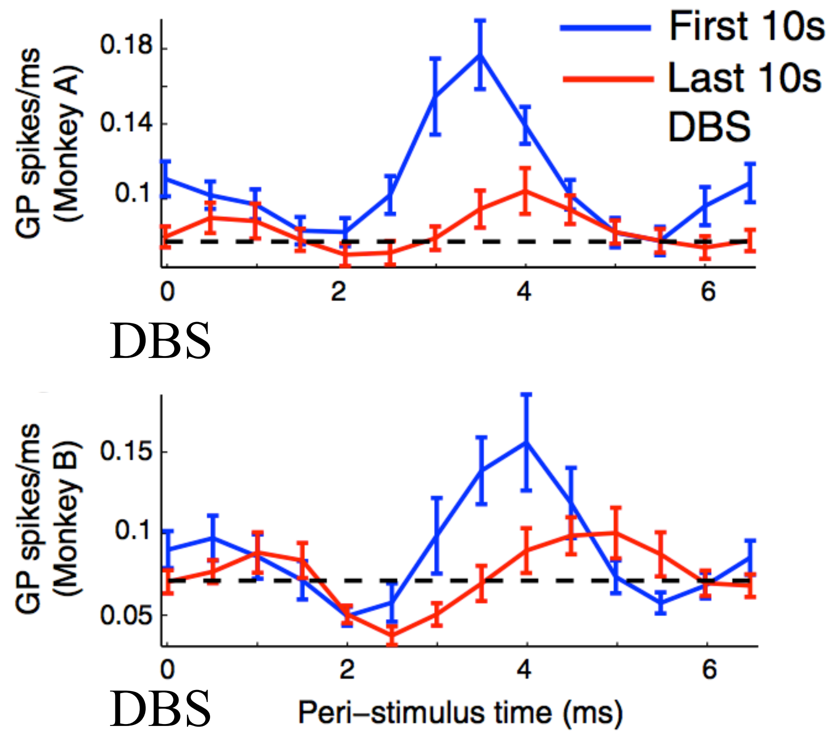
Moran et al., *Front. Syst. Neurosci.; Neurobio. Dis.*, 2011

idea 2: more STN spikes ⇏ proportionally more downstream inhibition: *synaptic depression*

neuronal synapse:



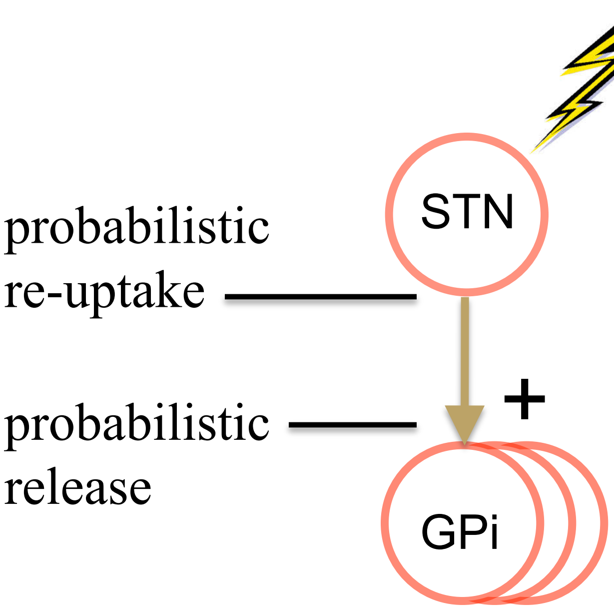
clue:



GPi entrainment gradually reduced

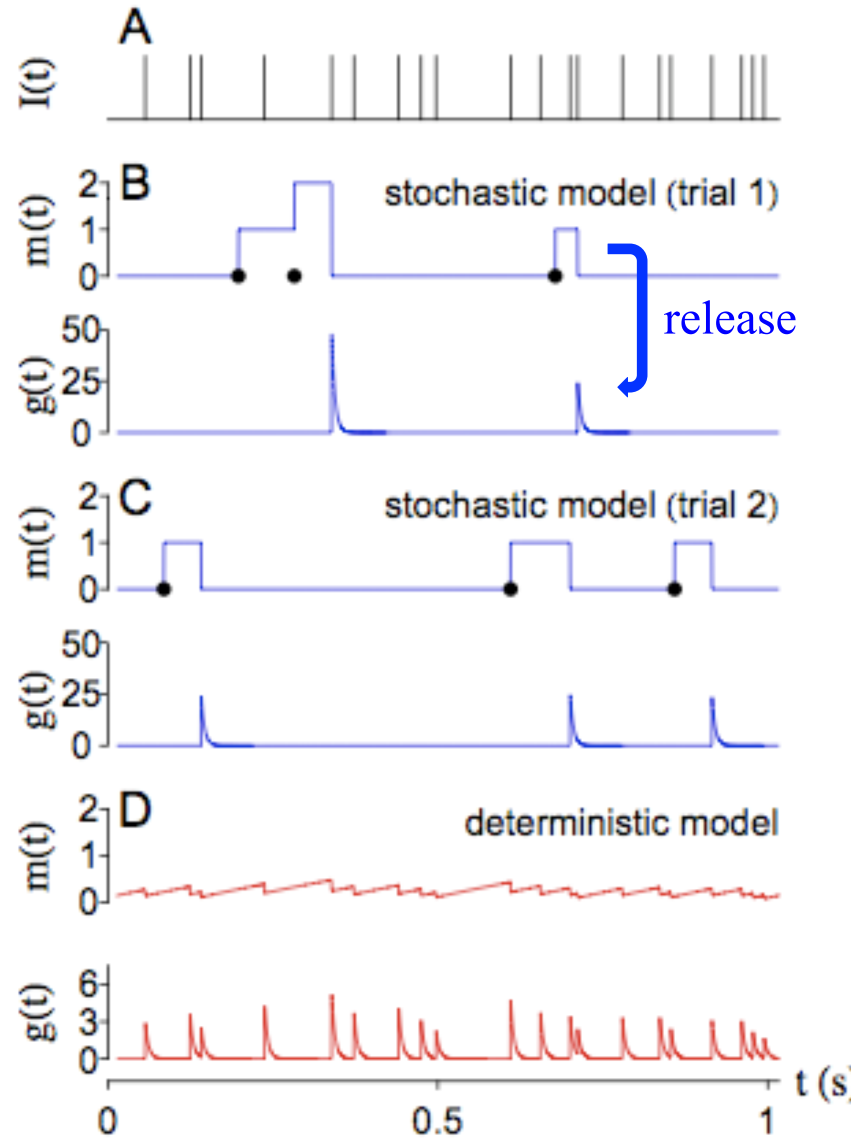
Rosenbaum et al., *Neurobio. Dis.*, 2014

stochastic vesicle dynamics



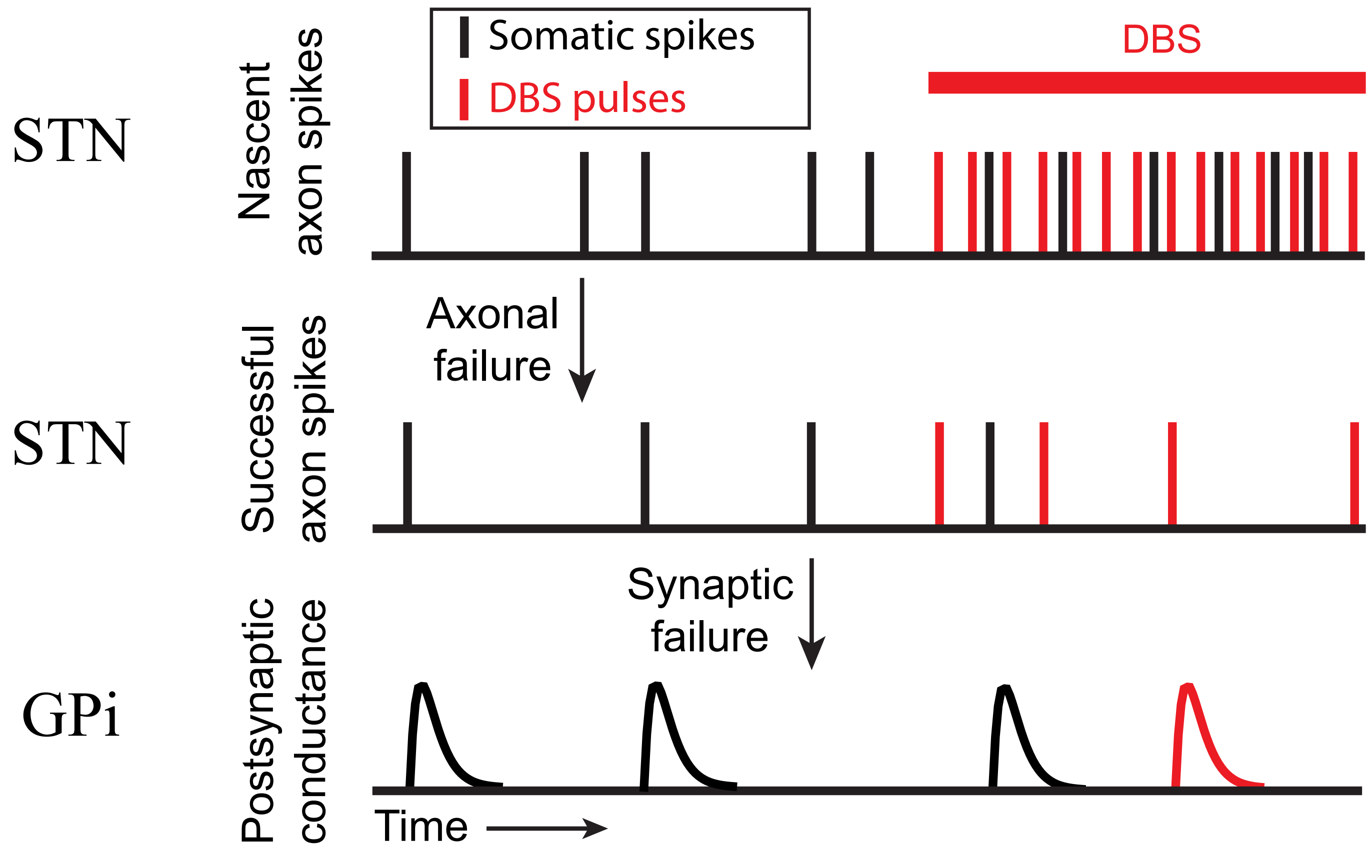
Rosenbaum et al., *PLoS Comp. Biol.*, 2012; *J. Neurophysiol.*, 2013

(see also: Abbott et al., 1997; Goldman et al., 1999; Fuhrmann et al., 2002; **Goldman, 2004**; de la Rocha & Parga, 2005; Grande & Spain, 2005, Lindner et al., 2009, Merkel & Lindner, 2010)



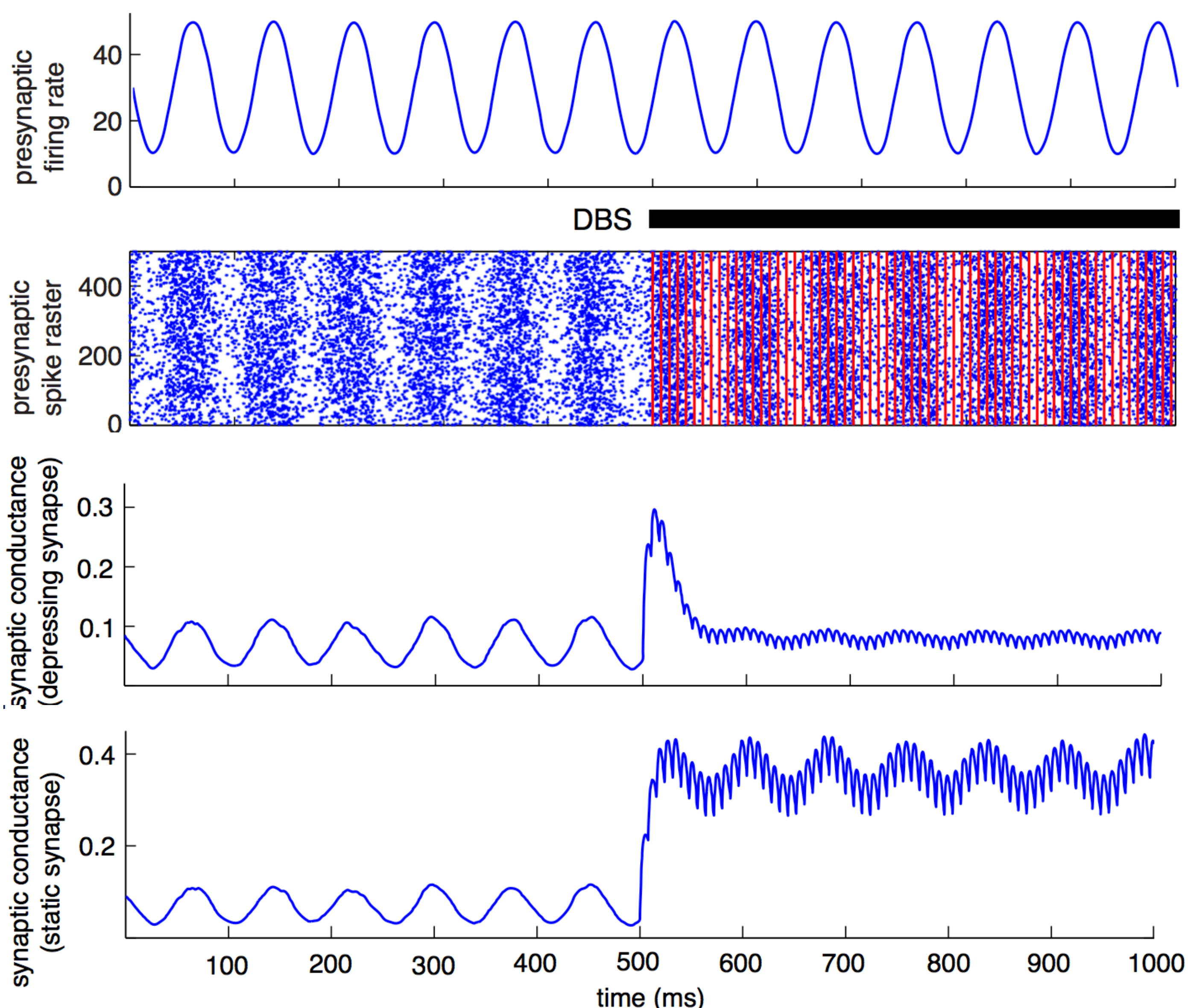
- m(t) = number of available vesicles
- g(t) = synaptic conductance

computational model (1) of short term depression in STN-GPi pathway

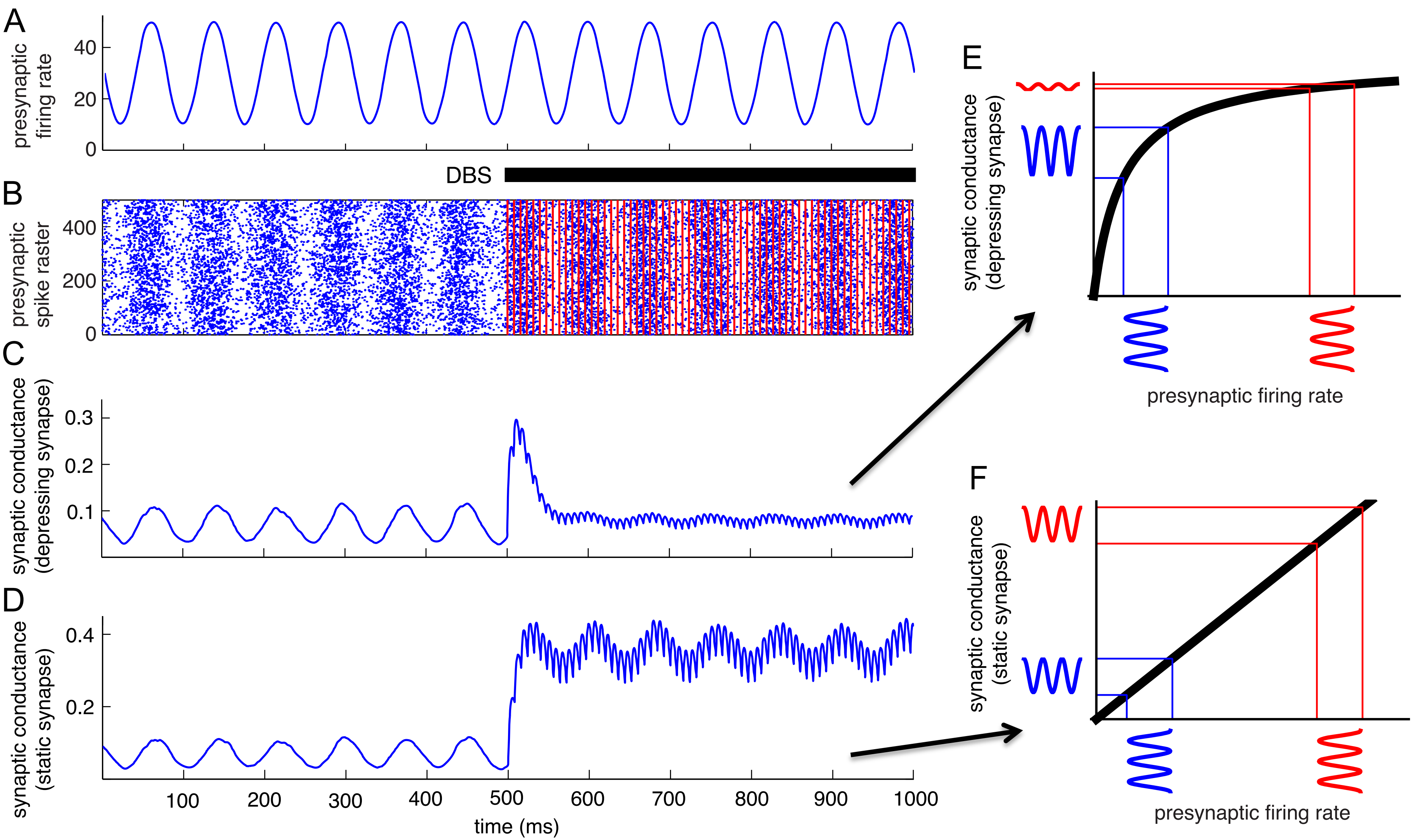


Rosenbaum et al., *Neurobio. Disease*, 2014

DBS-induced synaptic depression suppresses the transfer of low frequency oscillations



DBS-induced synaptic depression suppresses the transfer of low frequency oscillations

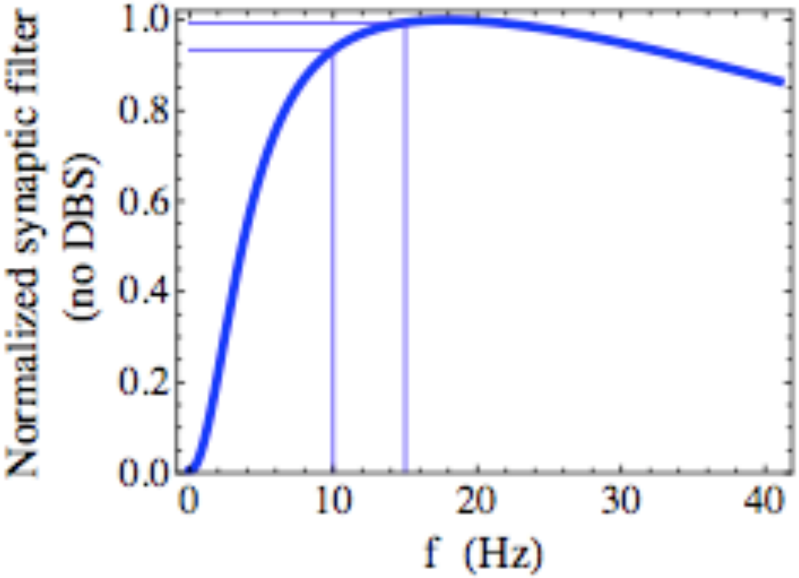


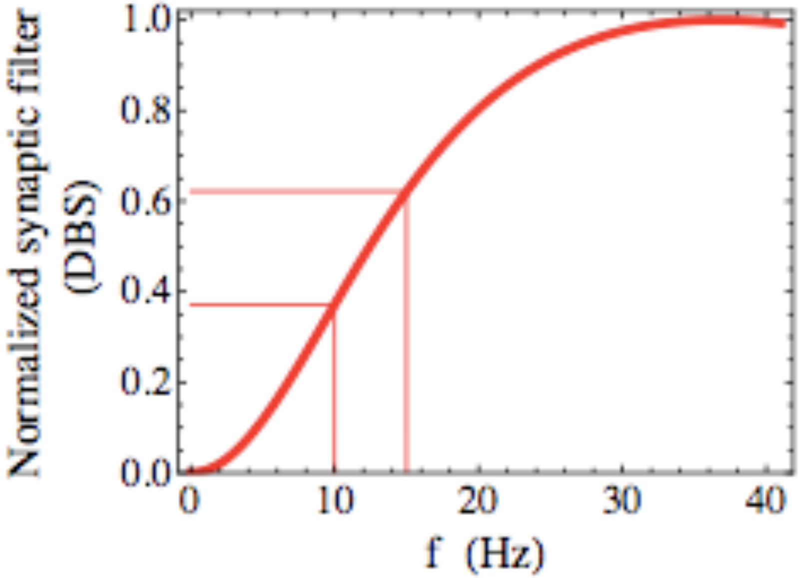
key expression

Poisson re-uptake rate — release probability — firing rate

$$f_0 = (1/\tau_u + U\nu)/(2\pi)$$

effective synaptic cutoff frequency





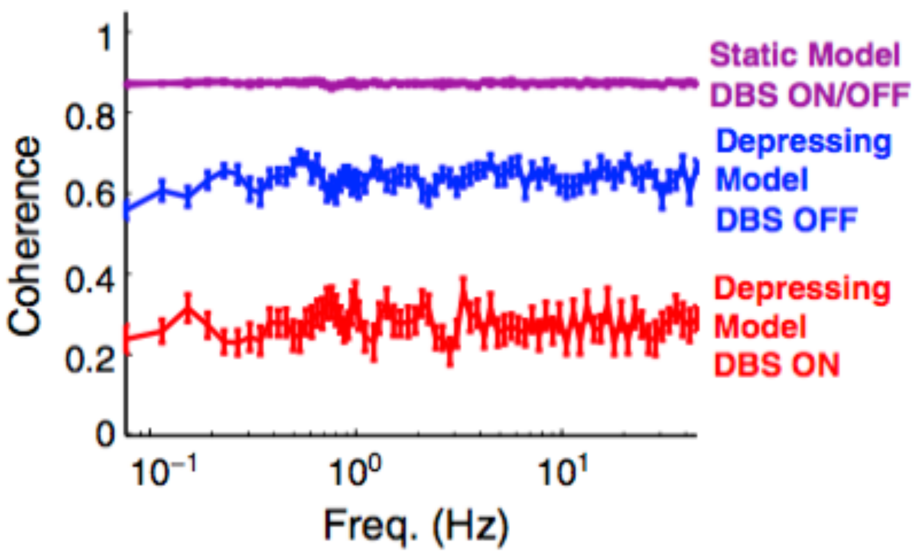
blue: before stimulation

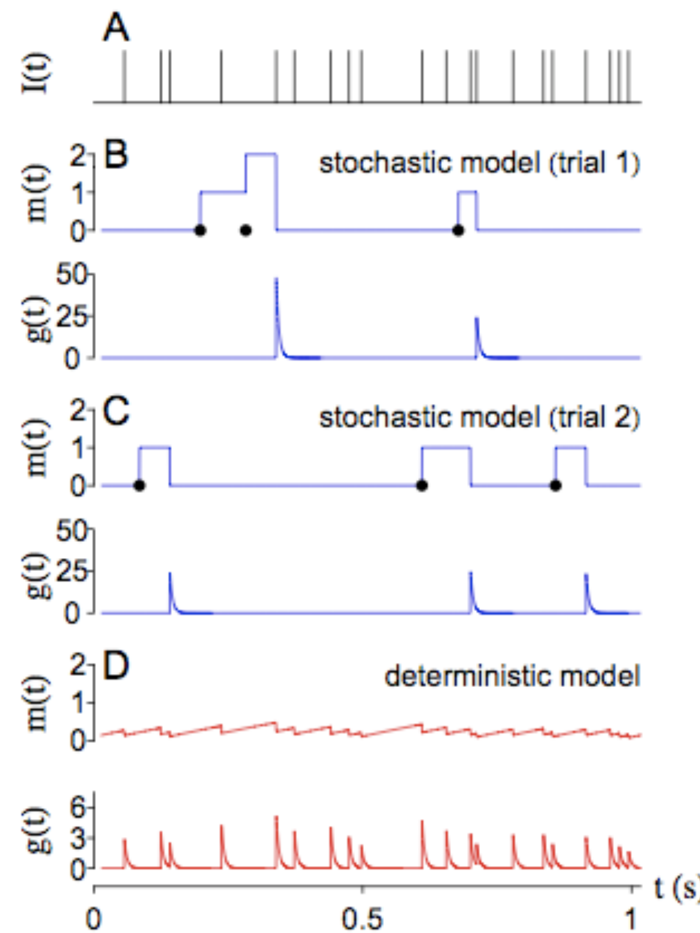
red: during STN-DBS

∴ STN β transmission to GPi suppressed in STN-DBS & GPi output becomes less oscillatory, less tied to STN

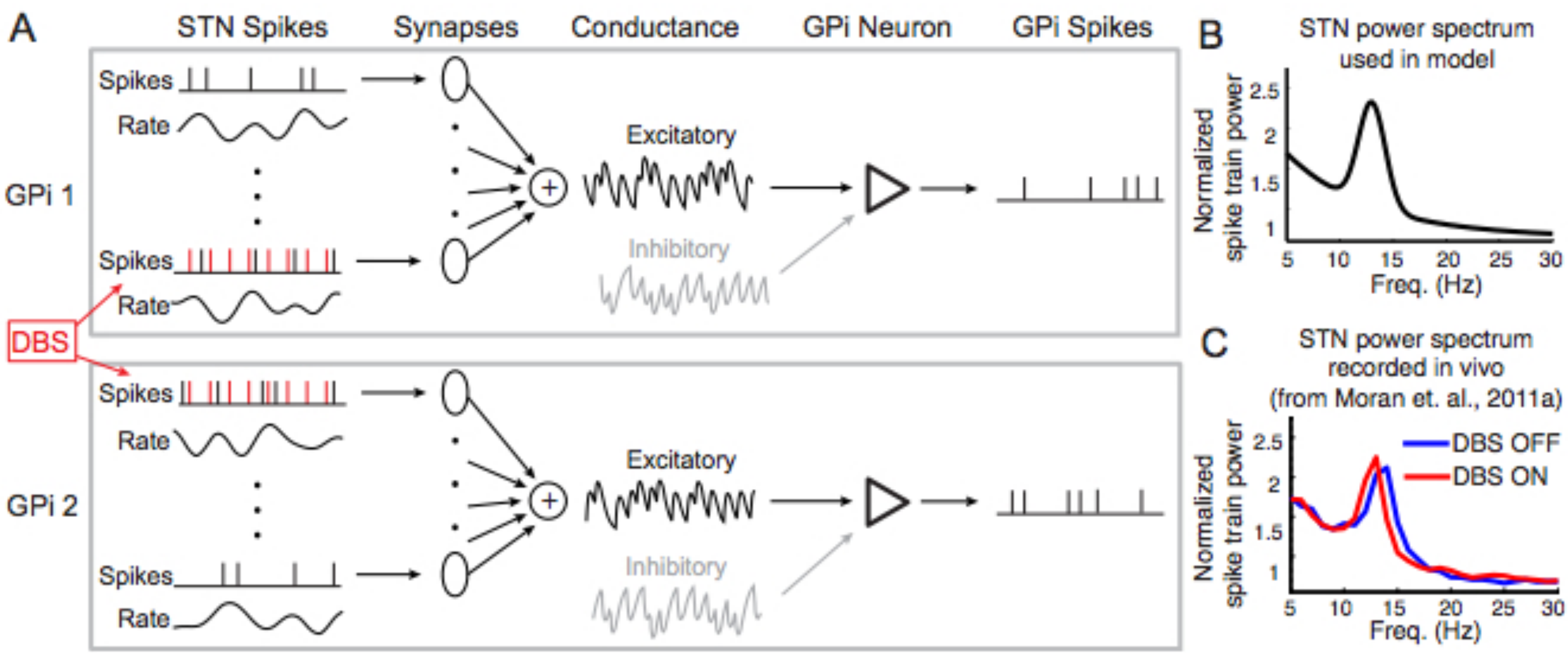
DBS-induced synaptic depression suppresses downstream coherence

for high rate inputs, uptake contributes relatively more to transmission: decorrelate inputs and outputs, ***lower coherence within GPe & with STN***

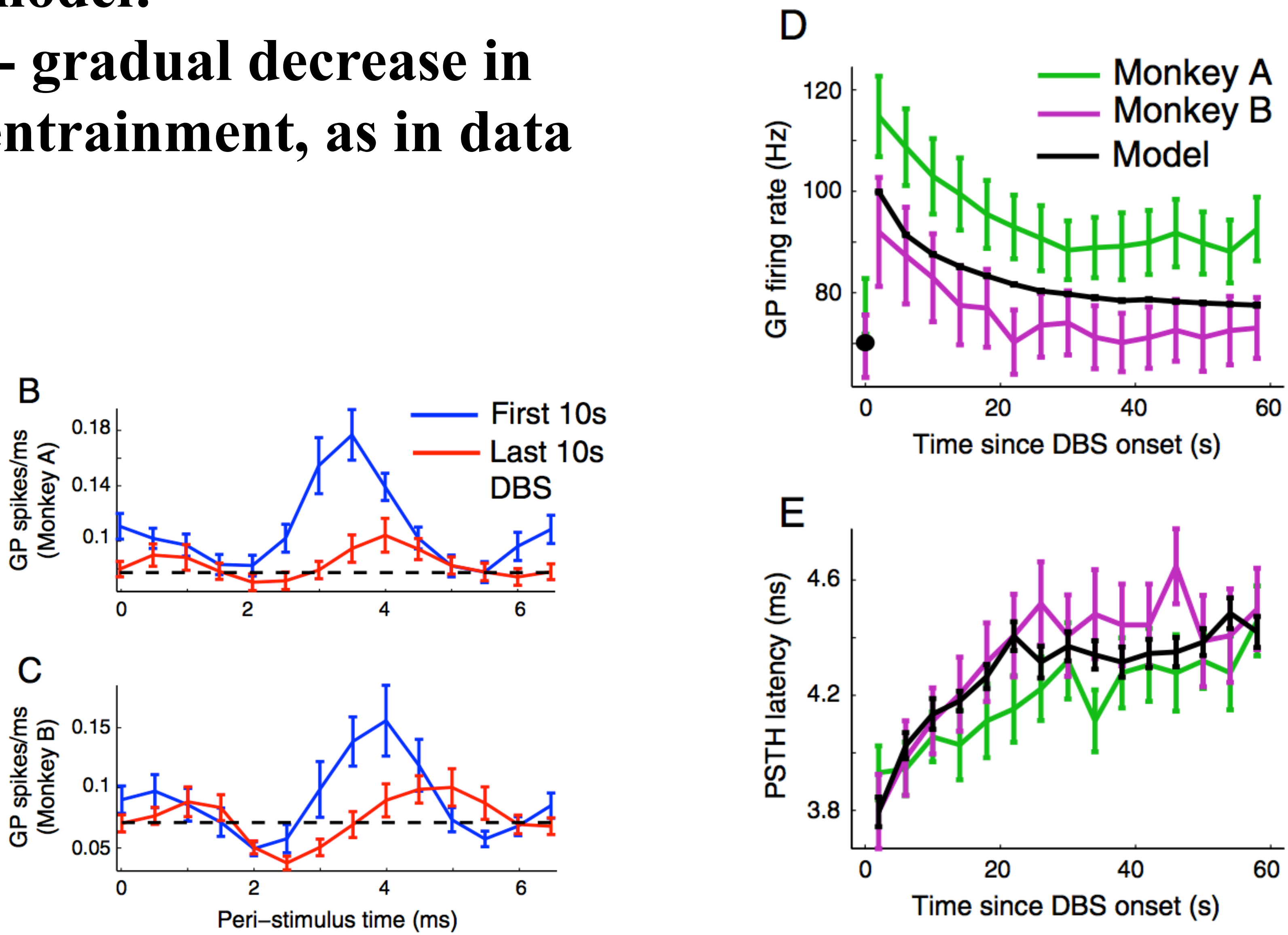




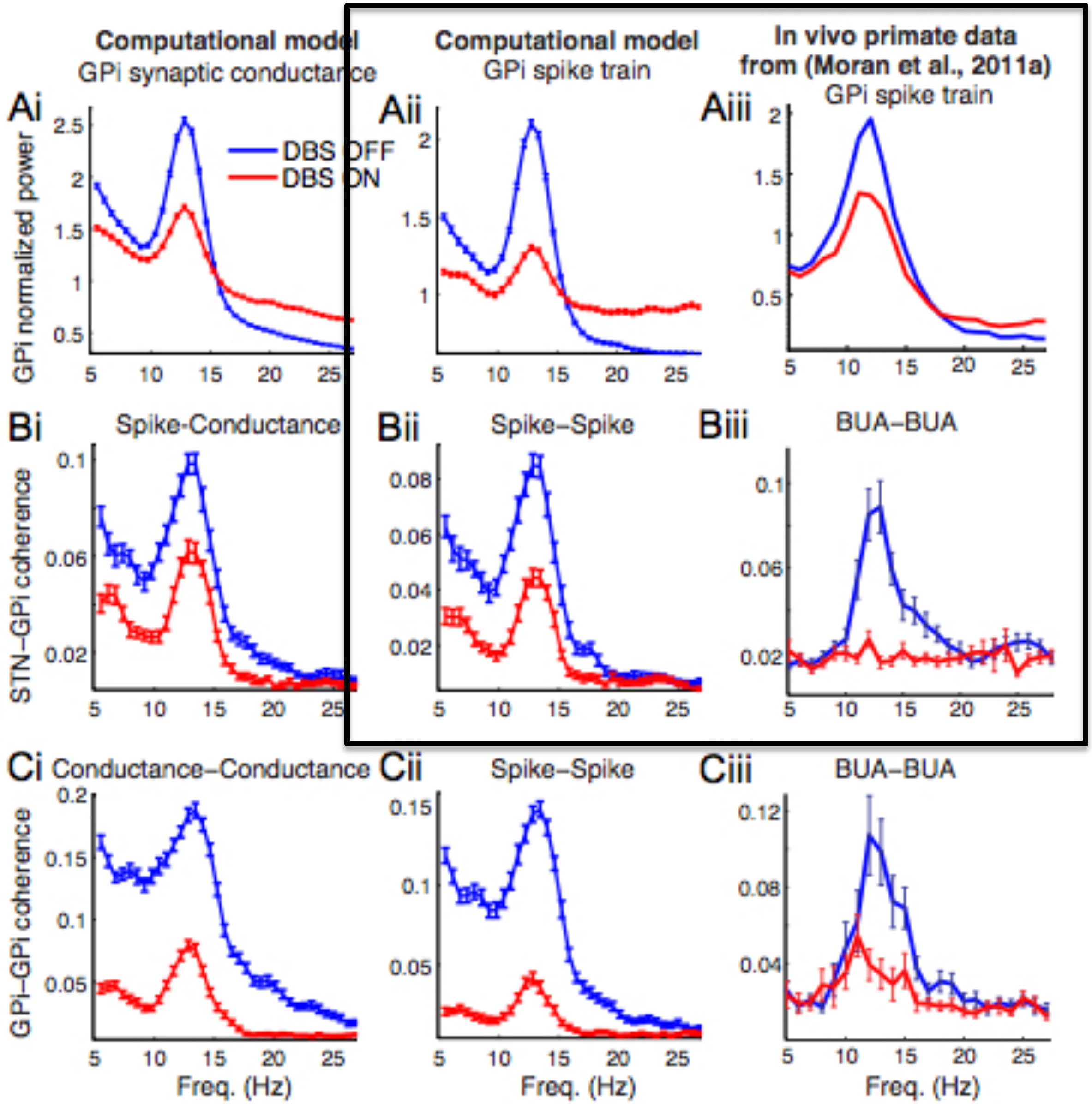
computational model (2) of short term depression in STN-GPi pathway



results from computational model:
-- gradual decrease in entrainment, as in data



results from computational model:
-- reduced beta oscillations and coherence, ~ as in data

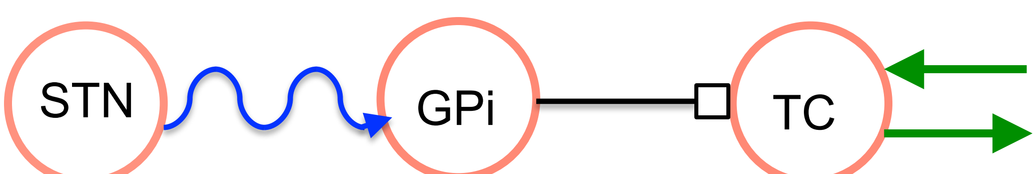


cf. Moran et al., *Neurobiol. Disease*, 2012

FINAL SUMMARY on DBS

- mechanism 1: bursting in GPi can compromise thalamic relay in parkinsonism
- STN-DBS that entrains and regularizes GPi can restore TC relay

- mechanism 2: excessively synchronized β oscillations in GPi can compromise thalamic relay
- STN-DBS weakens GPi β & synchrony and makes GPi output less coherent/more steady – explained based on short term (synaptic and axonal) depression, also restores relay



Collaborators

Pallidostriatal circuit

- **Aryn Gittis, Carnegie Mellon University**
- ***Victoria Corbit,CNUP***
- ***Tim Whalen, PNC***
- *Kevin Zitelli, CNUP*
- *Stephanie Crilly, CMU*

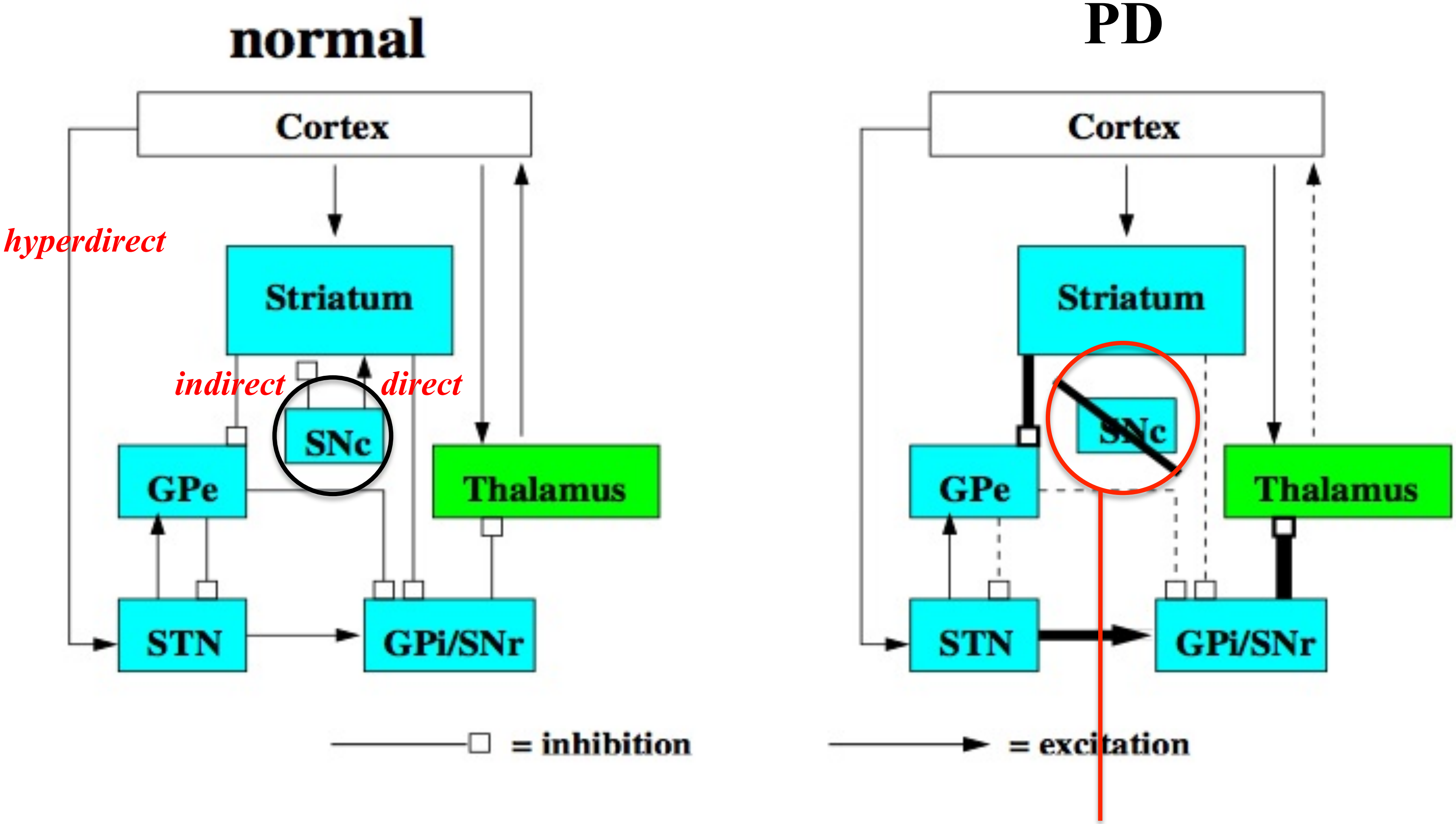
Basal ganglia and DBS modeling

- **David Terman, Ohio State**
- **Yixin Guo, Drexel University**
- Cameron McIntyre, CWRU
- Charles Wilson, UTSA
- Alice Yew, AMS
- Jerry Vitek, U. Minnesota

Short term depression and DBS

- **Robert Rosenbaum, Notre Dame**
- **Robert Turner, Pitt**
- Brent Doiron, Pitt
- Andrew Zimnik, Columbia
- Christian Alzheimer, Nürnberg
- Fang Zheng, Nürnberg

Albus and DeLong: classical (1980's) arithmetical model of the basal ganglia (light blue) and PD



dopamine loss:
imbalance of pathways

fundamental question of parkinsonism (1990's): how can changes in *rates* account for the parkinsonian symptoms?

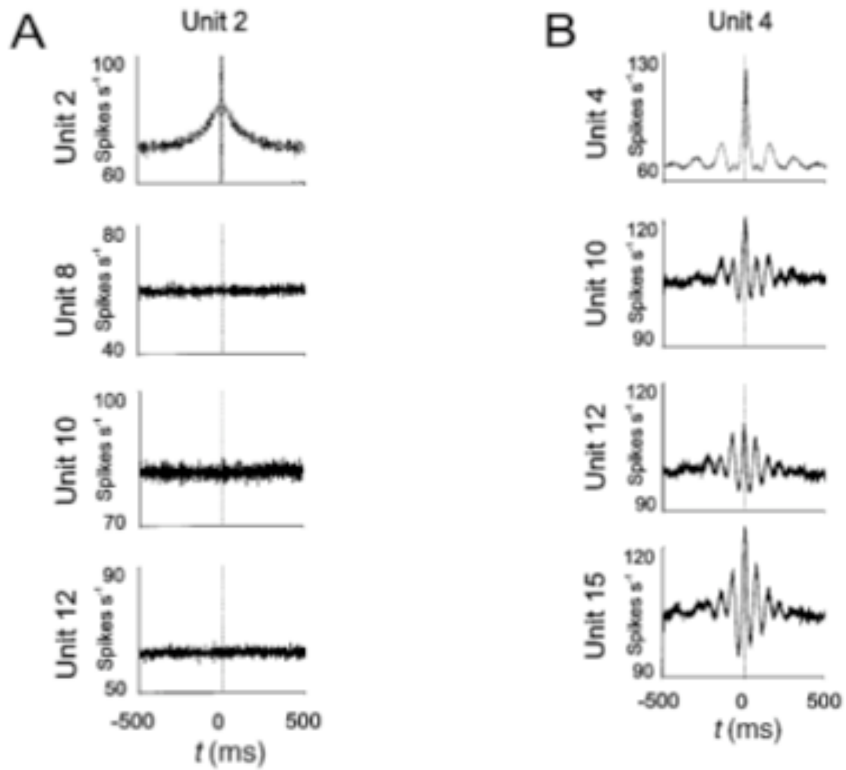
what: akinesia (difficulty initiating movement), bradykinesia (slowed movement), posture issues, rigidity, tremor

A: they can't!

revised Q: (a) what changes in BG activity result from loss of dopamine, (b) how are these changes produced, (c) how do these changes translate into symptoms, and (d) how can these symptoms be mitigated?

altered BG activity patterns in parkinsonism

• *increased synchrony/correlations, loss of specificity*



normal MPTP

Bergman et al., *TINS*, 1998; globus pallidus recordings

(a) changes in BG activity in parkinsonism

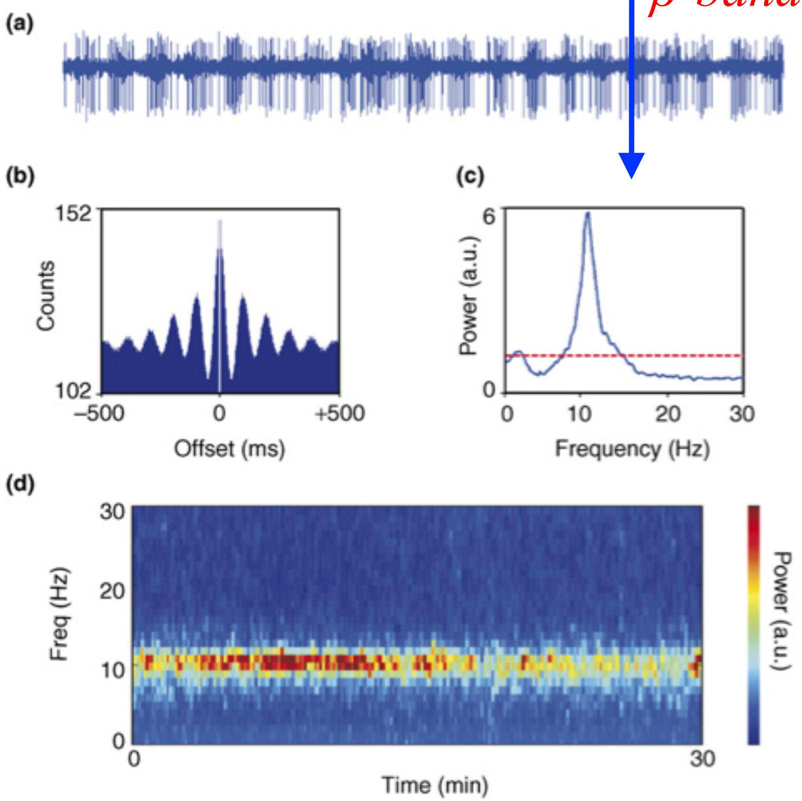
- *changes in firing rates*
- *increased oscillations*
- *increased burstiness*

GPi

Magnin et al., *Neuroscience*, 2000

GPe

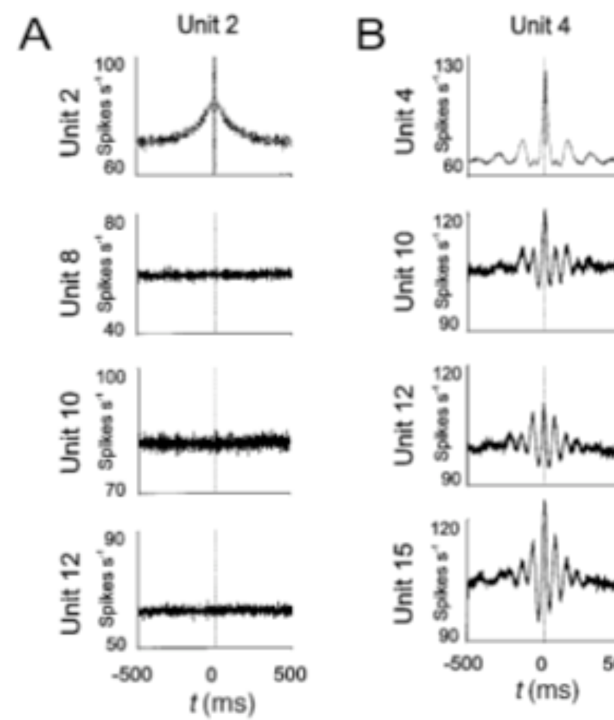
β-band



Hammond et al., *TINS*, 2007; GPi

- *increased correlations*

Bergman et al., *TINS*, 1998; GP



normal

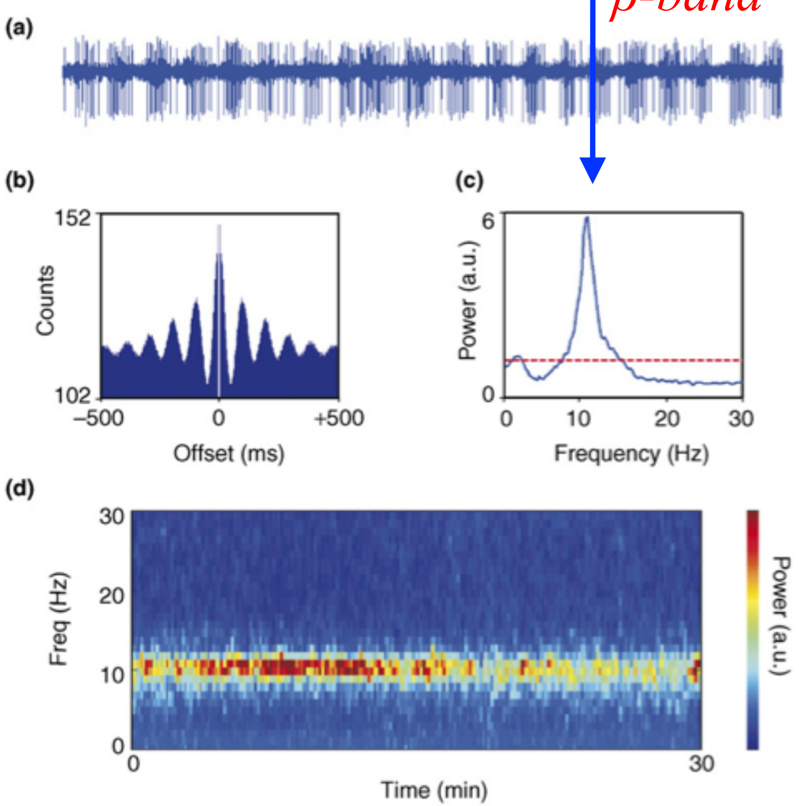
MPTP

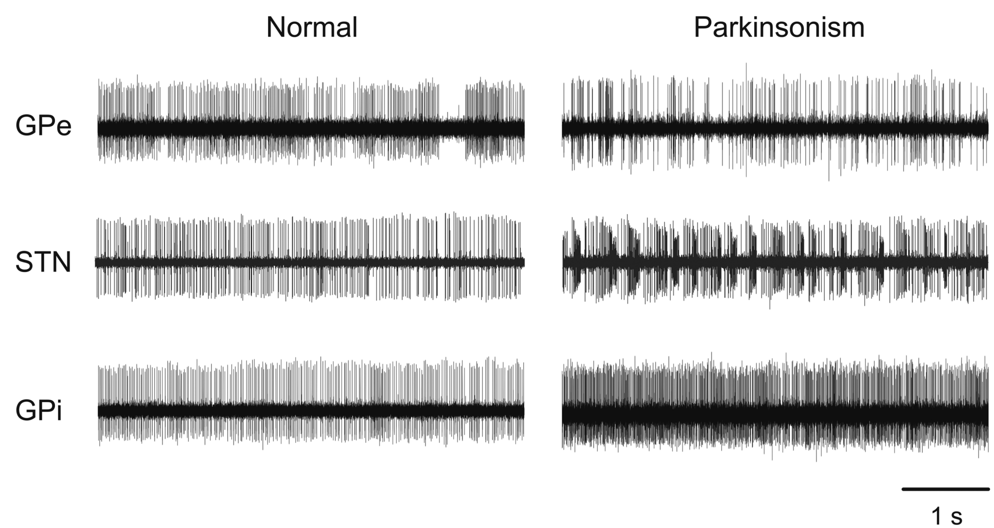
(a) changes in BG activity in parkinsonism

- *changes in firing rates*
- *increased oscillations*
- *increased burstiness*

Magnin et al., *Neuroscience*, 2000

β-band



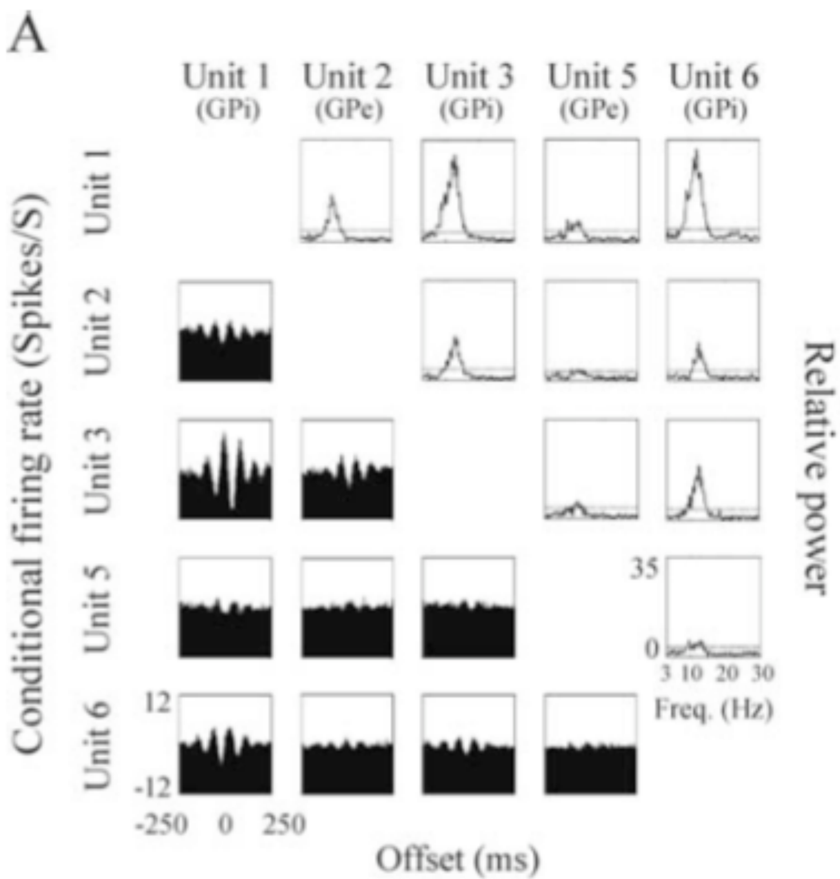


Galvan & Wichmann, *Clin. Neurophysiol.*, 2008

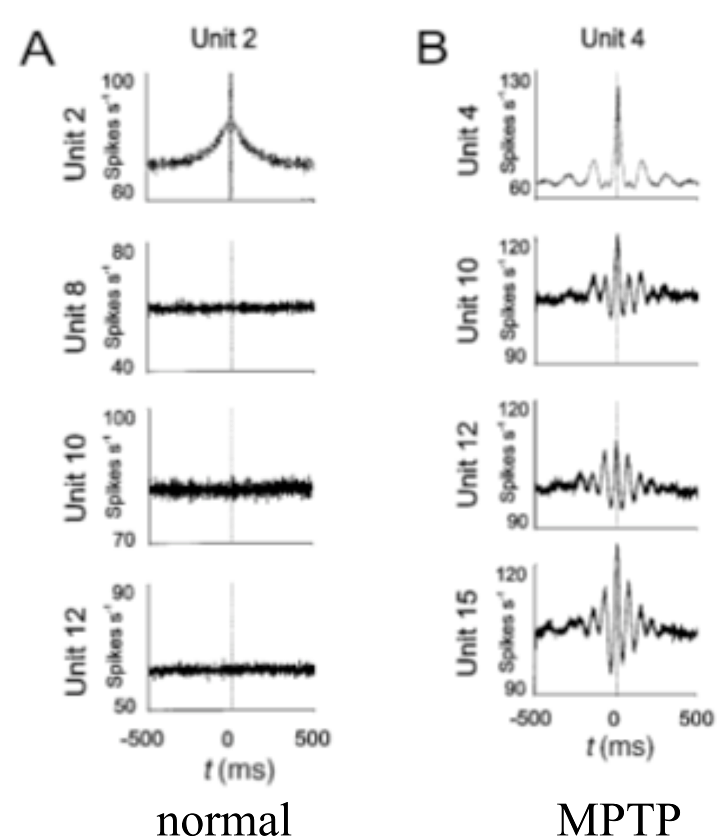
Hammond et al., *TINS*, 2007; GPi

altered basal ganglia activity patterns in parkinsonism

- *loss of specificity/increased correlations*



Heimer et al., *J. Neurosci.*, 2006



Bergman et al., *TINS*, 1998; globus pallidus recordings

some past computational models w/oscillations

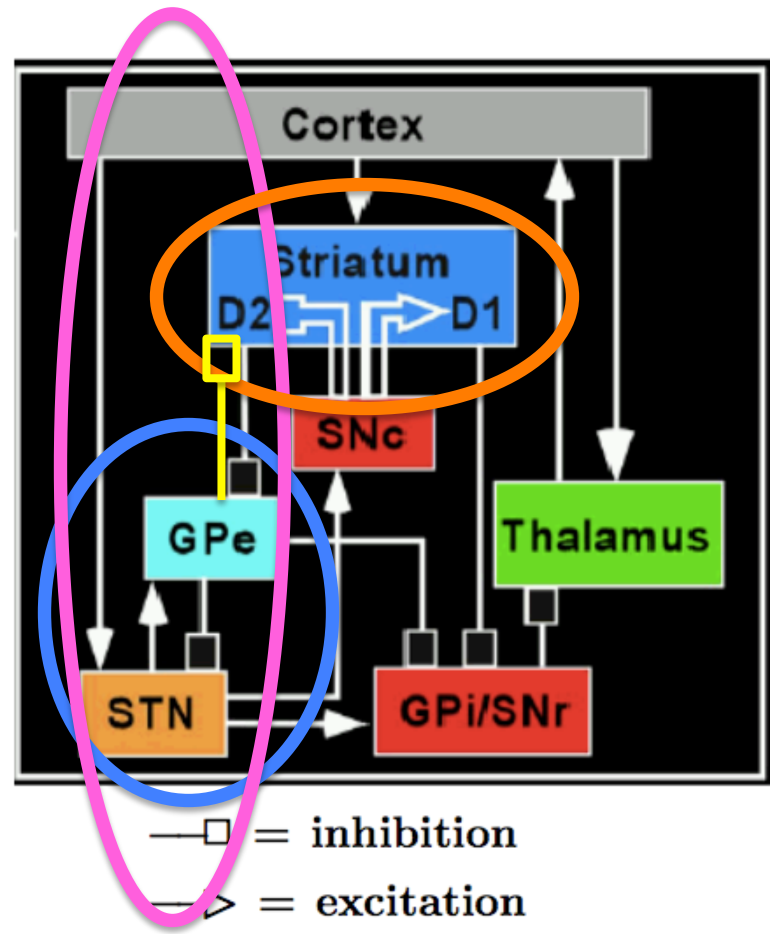
Terman et al., 2002: STN-GPe (E-I loop); cf. Park & Rubchinsky

Leblois et al., 2006: symmetry-breaking in full BG activity-based model

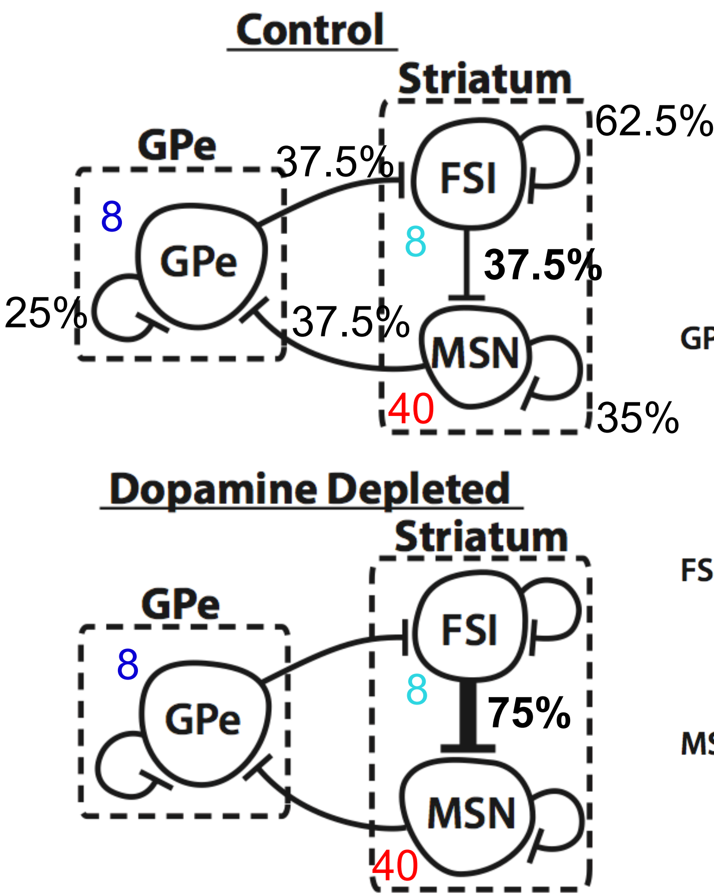
Nevado-Holgado et al., 2010: STN-GPe firing rate model; β oscillations require cortical excitation to STN and synaptic delays

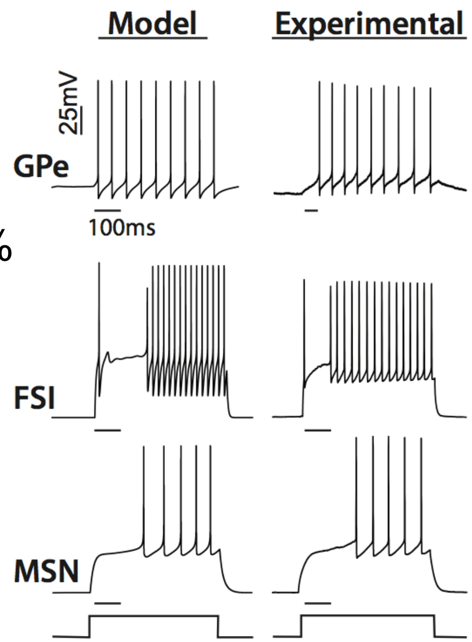
McCarthy et al., 2011: inhibitory interactions in striatal medium spiny neurons (MSNs) sufficient for β

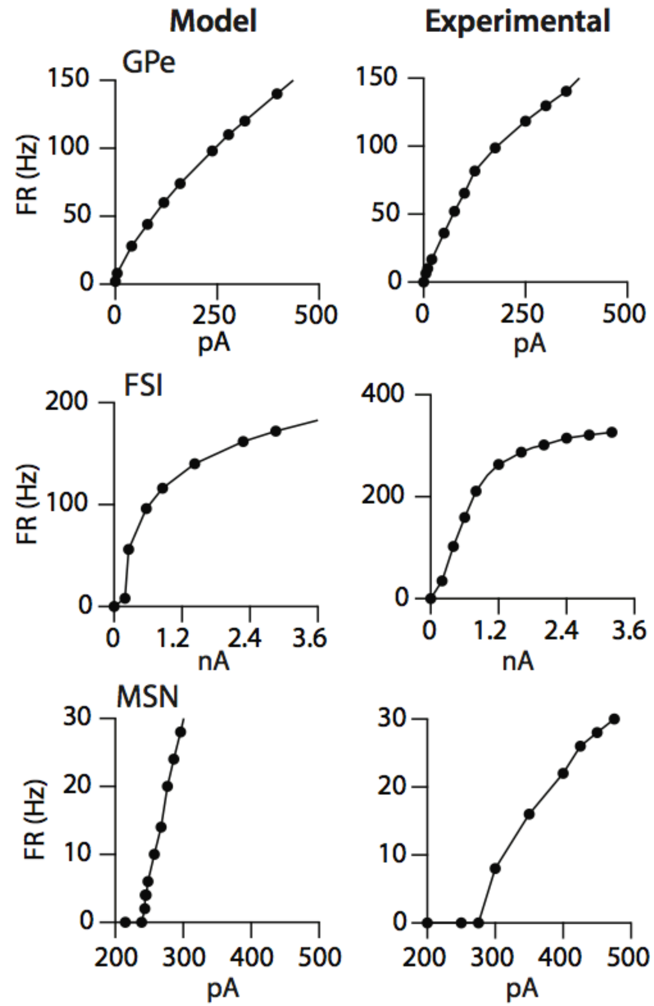
Kumar et al., 2011: large scale (LIF) STN-GPe model



pallidostriatal circuit model



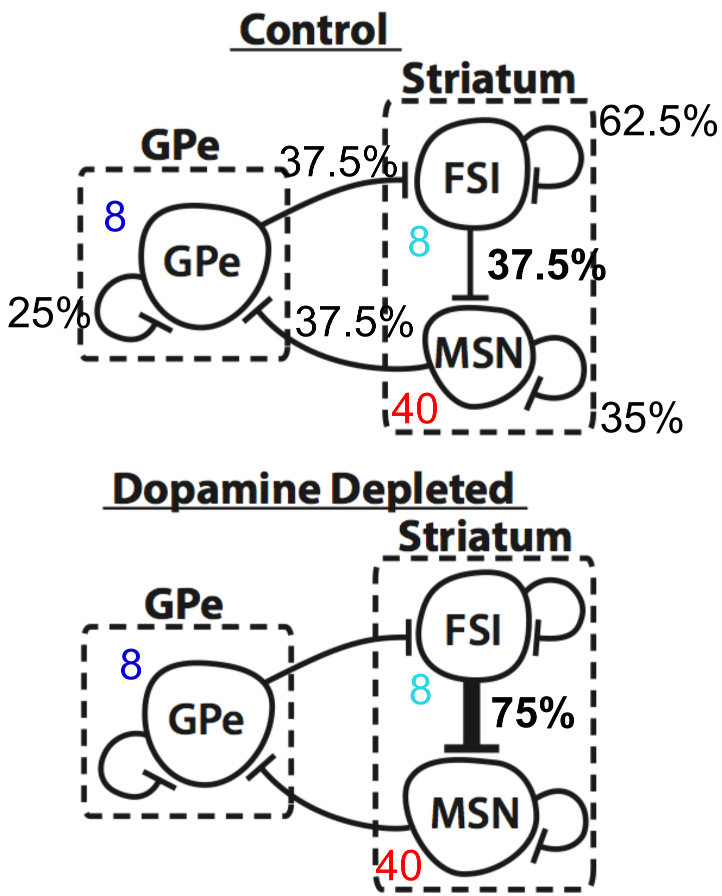


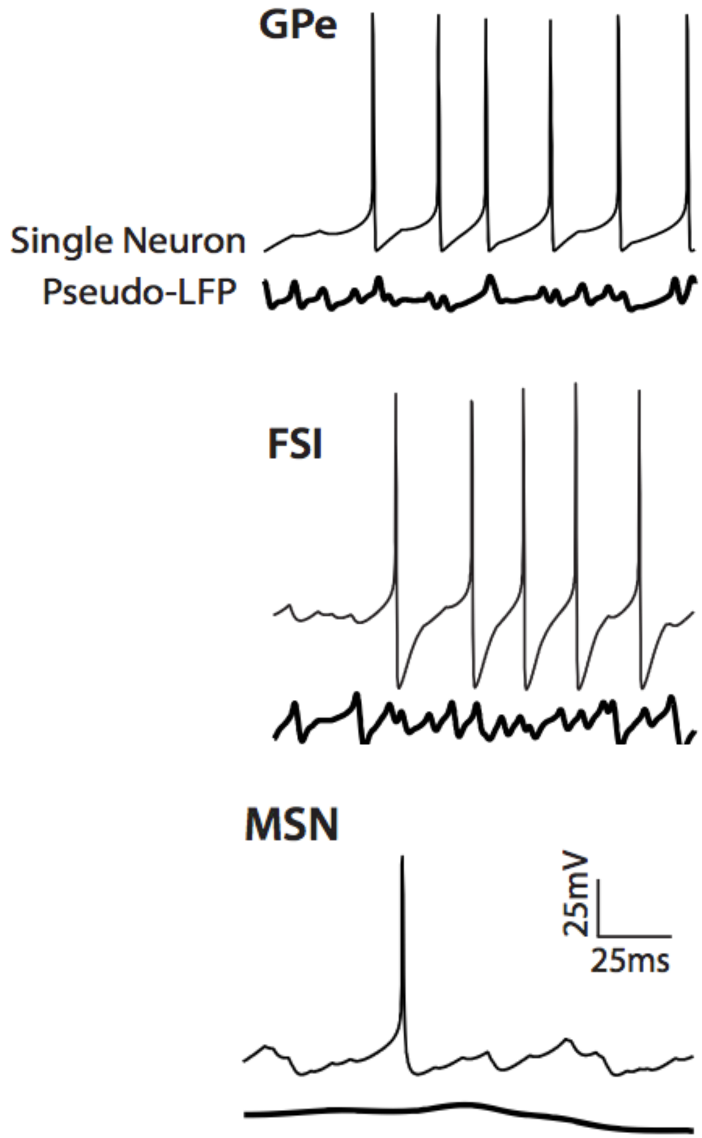


single cell responses

Corbit*, Whalen* et al., *J. Neurosci.*, 2016

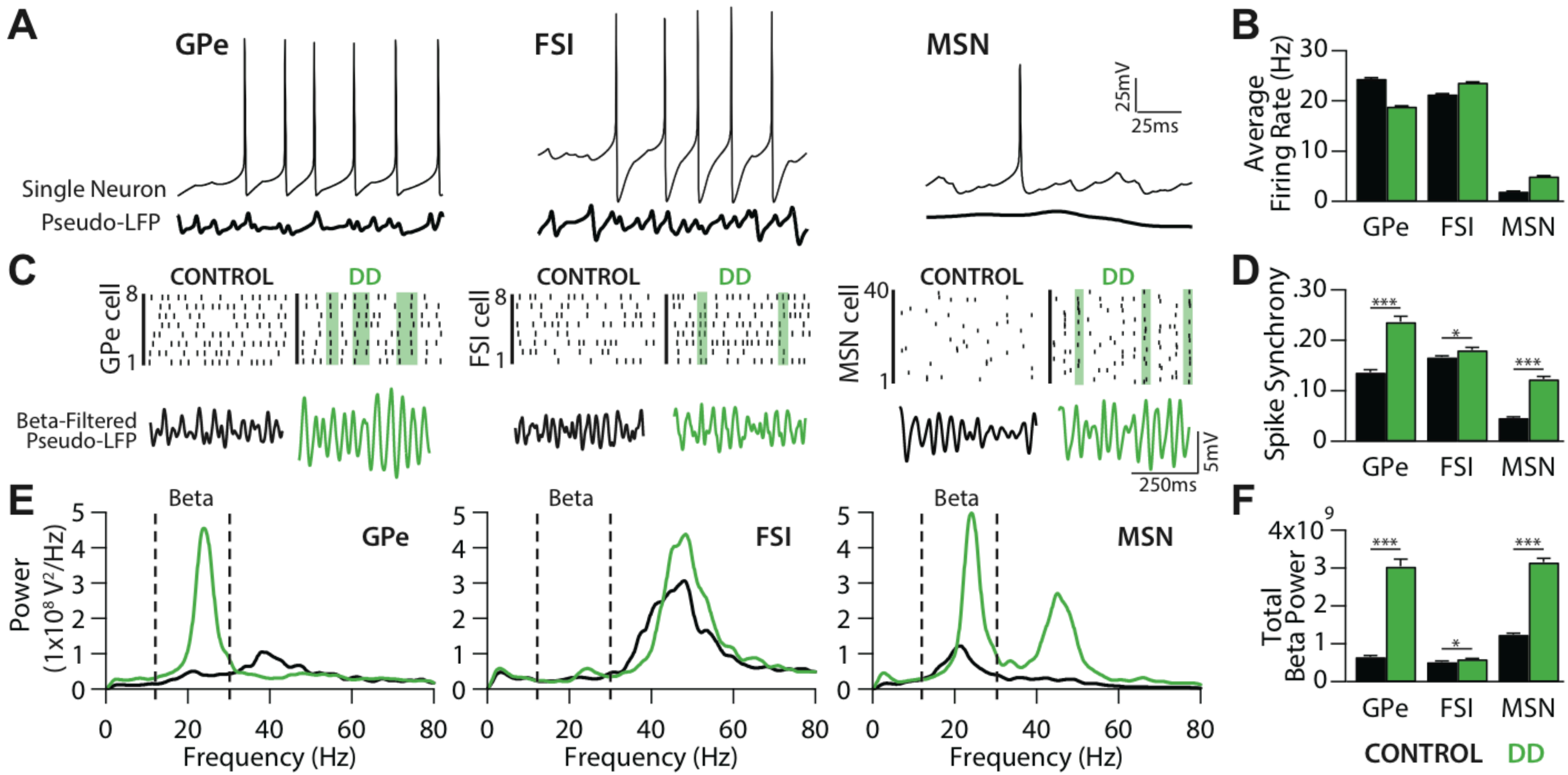
pallidostriatal circuit model





Corbit*, Whalen* et al., *J. Neurosci.*, 2016

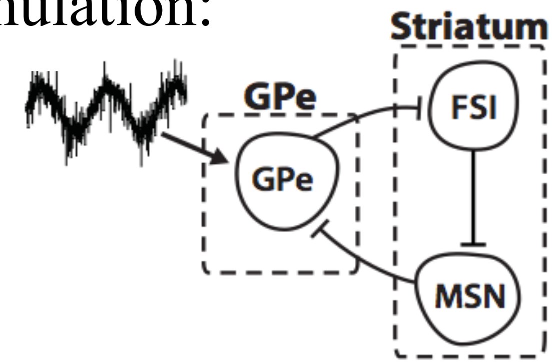
model generates β oscillations only in DD



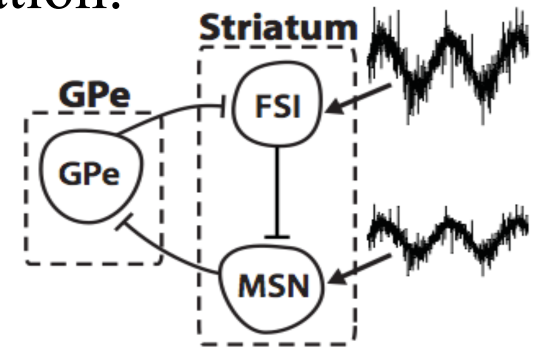
Corbit*, Whalen* et al., *J. Neurosci.*, 2016

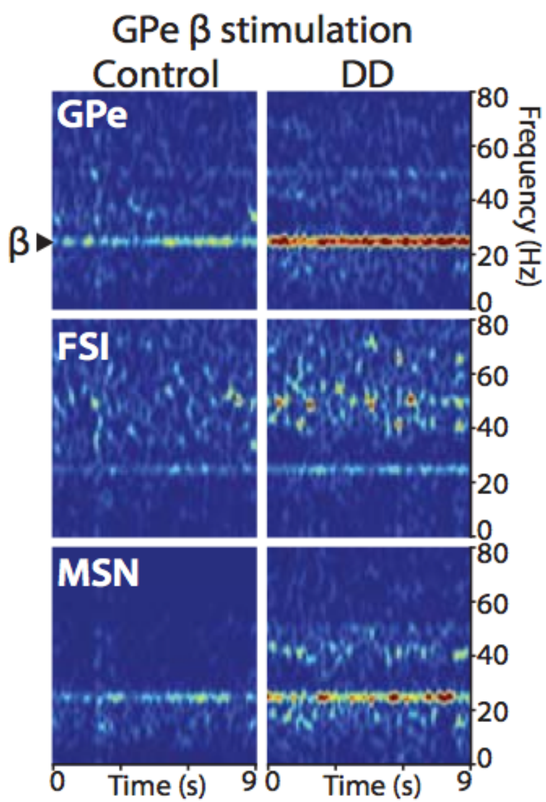
pallidostriatal circuit could amplify β

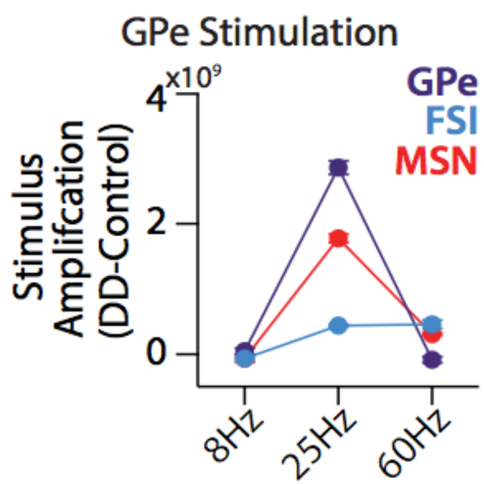
GPe stimulation:

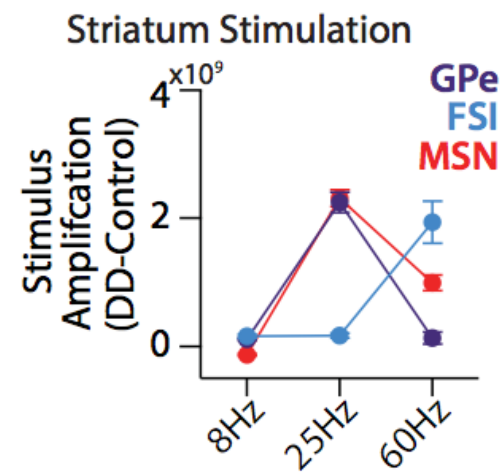


striatal stimulation:

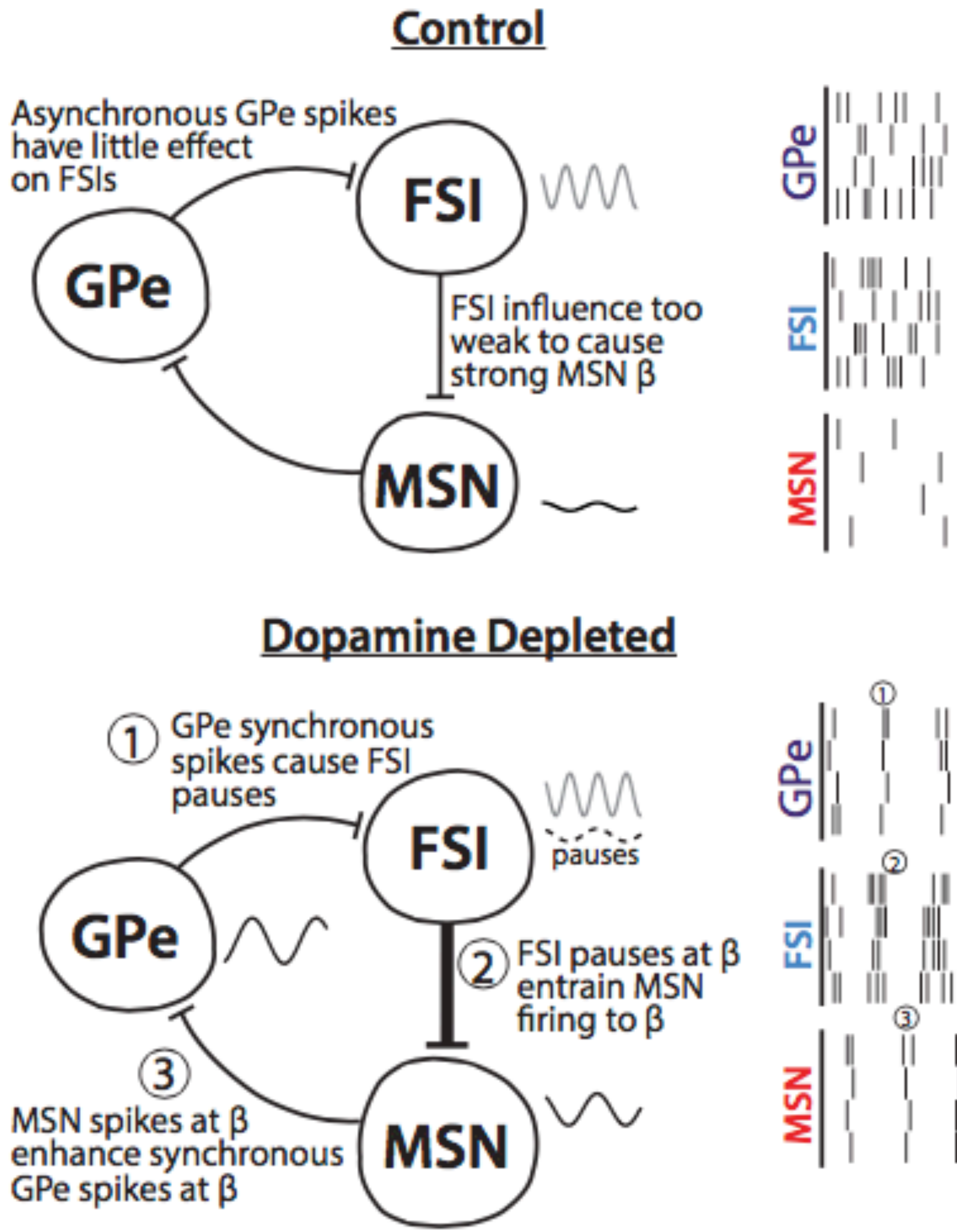




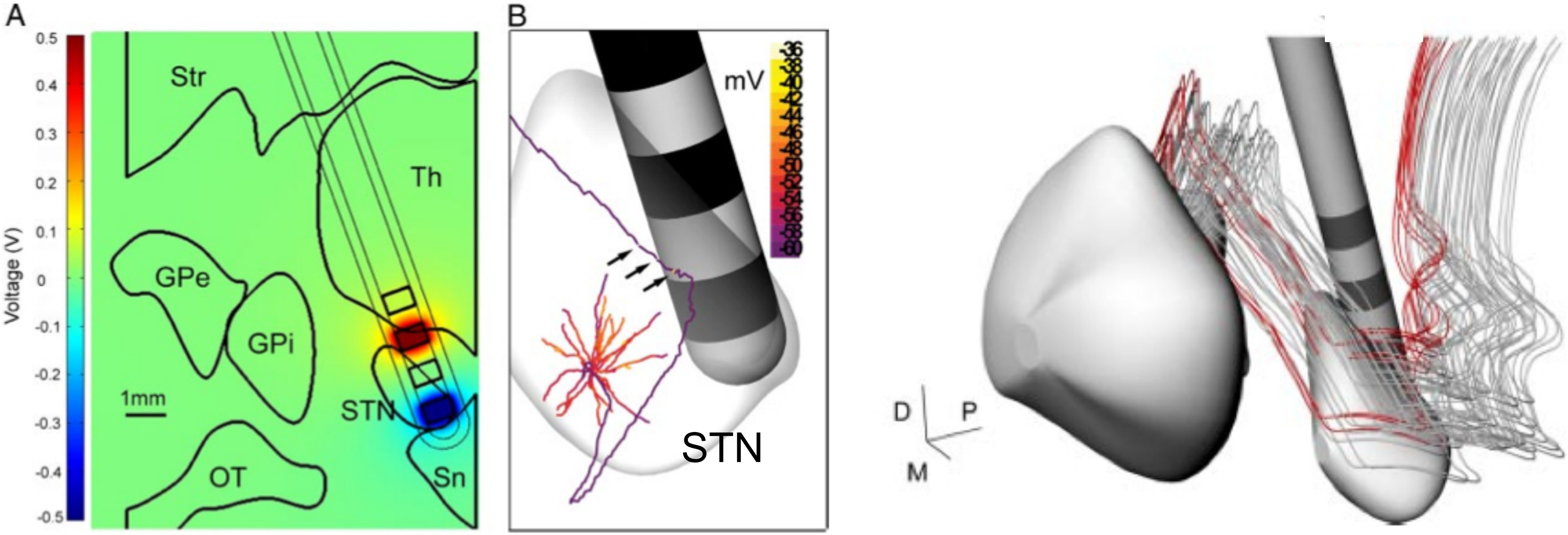




thrown for a loop



zooming in

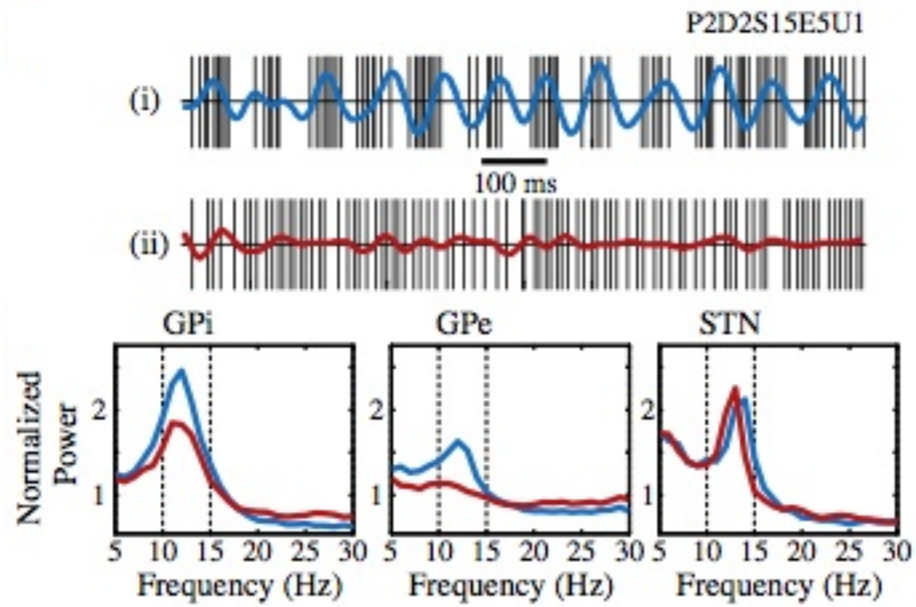


Miocinović et al., *J. Neurophysiol.*, 2006

OP: **looks great – but how does this work??**

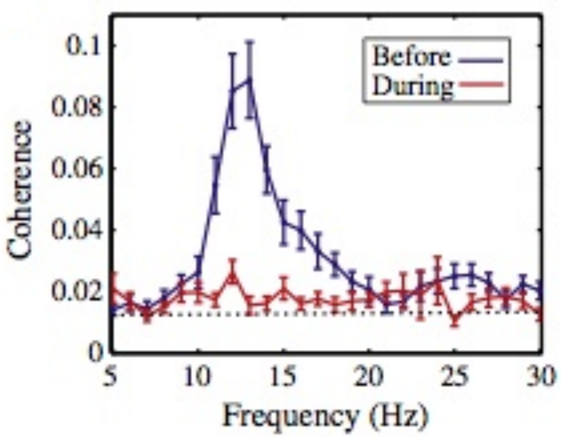
more experiments: STN-DBS (1) suppresses beta oscillations in GPi despite ongoing beta in STN (which drives GPi) and (2) destroys GPi-STN coherence despite (3) GPi entrainment to STN in DBS

(1)

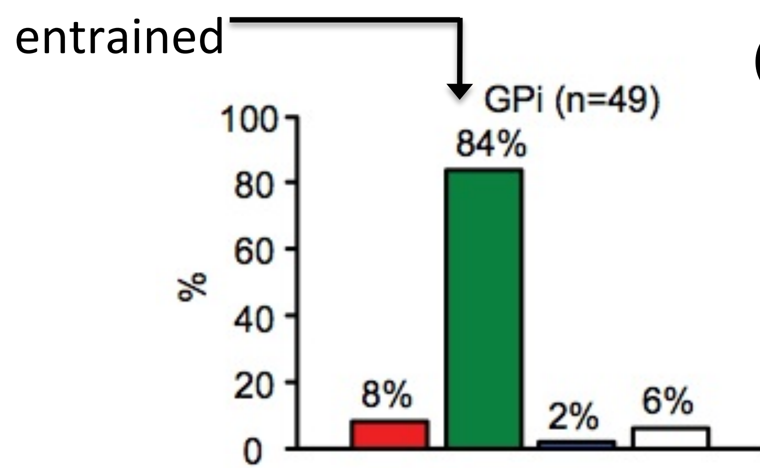


Moran et al., 2011 & 2012

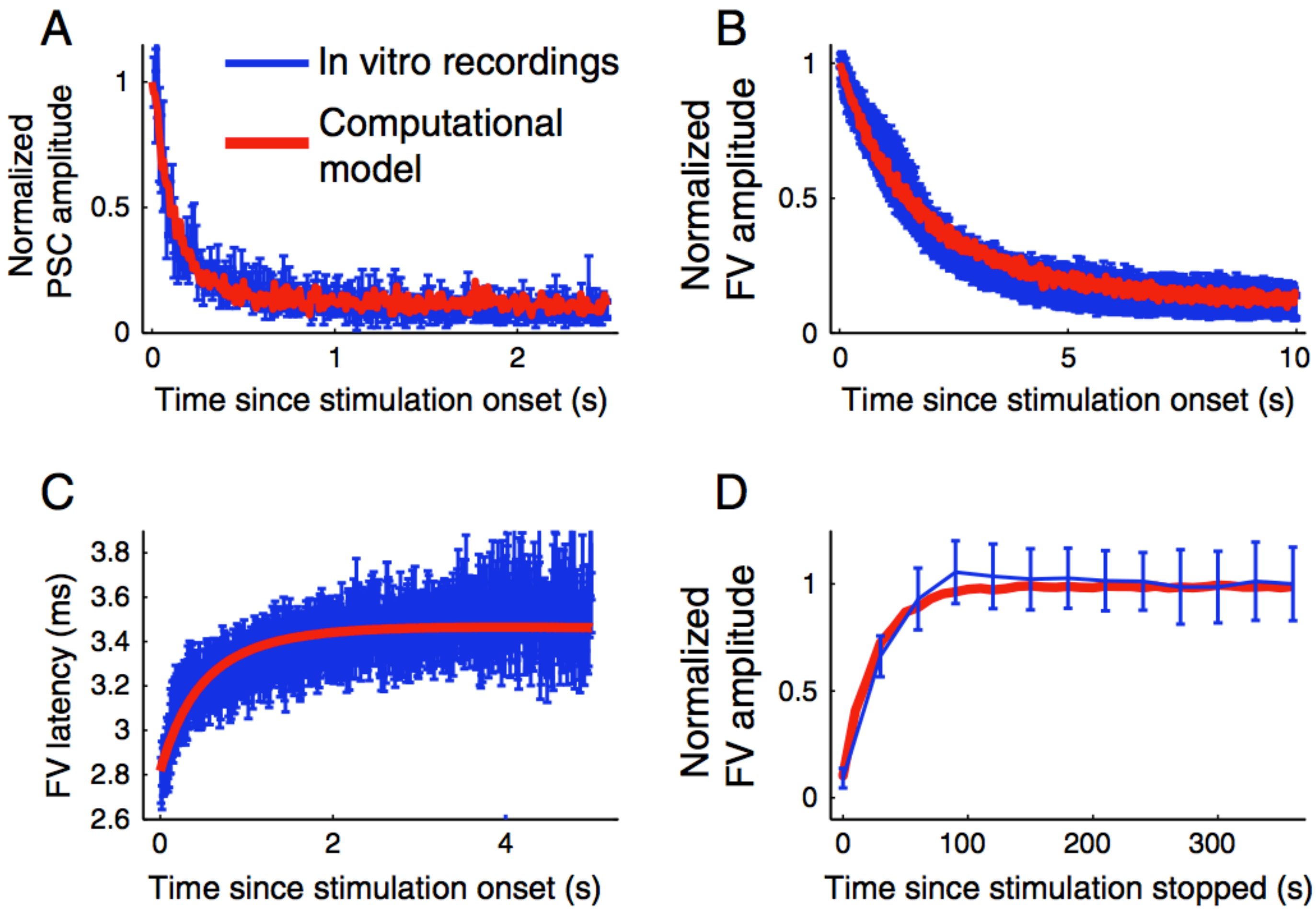
(2)



(3)

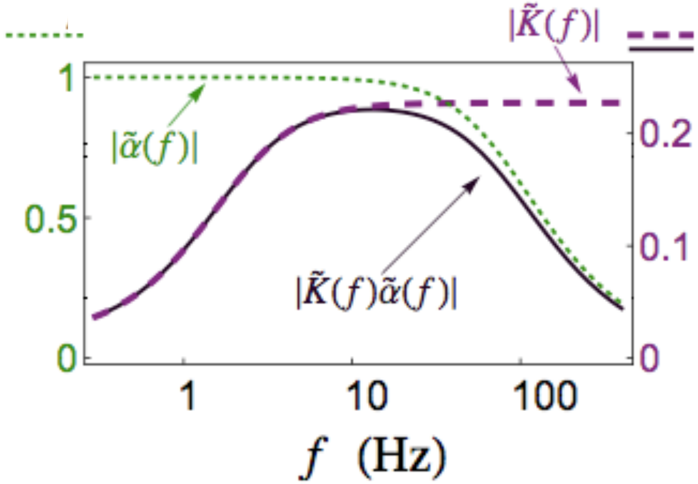


DBS also induces axonal failure, another form of depression



implications of depression: deterministic & stochastic

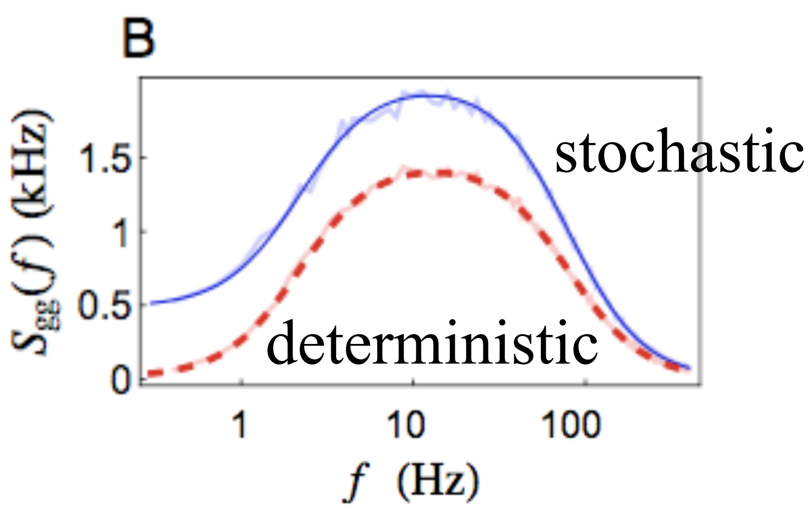
(a) band-pass synaptic filter yields peaked cross-spectrum of input/conductance



$$R_{Ig}(\tau) = \mathrm{cov}(I(t), g(t+\tau))$$

$$\begin{aligned} S_{Ig}(f) &= \int_{-\infty}^{\infty} R_{Ig}(\tau) e^{-2\pi I f \tau} d\tau \\ &= \widetilde{\alpha}(f)\widetilde{K}(f)\nu \end{aligned}$$

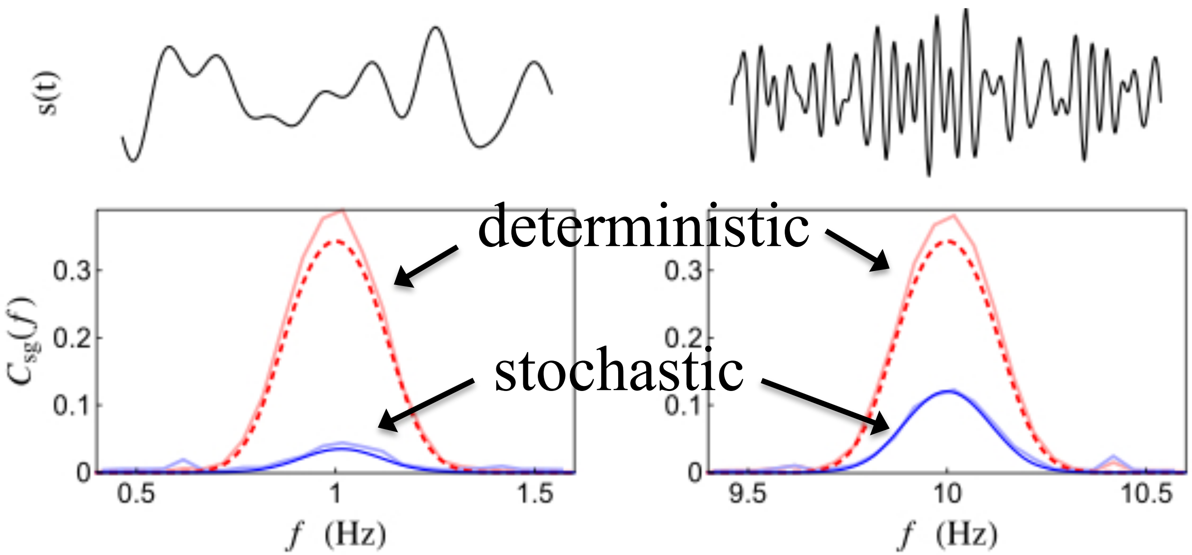
(b) at population level, power spectrum of total conductance is peaked



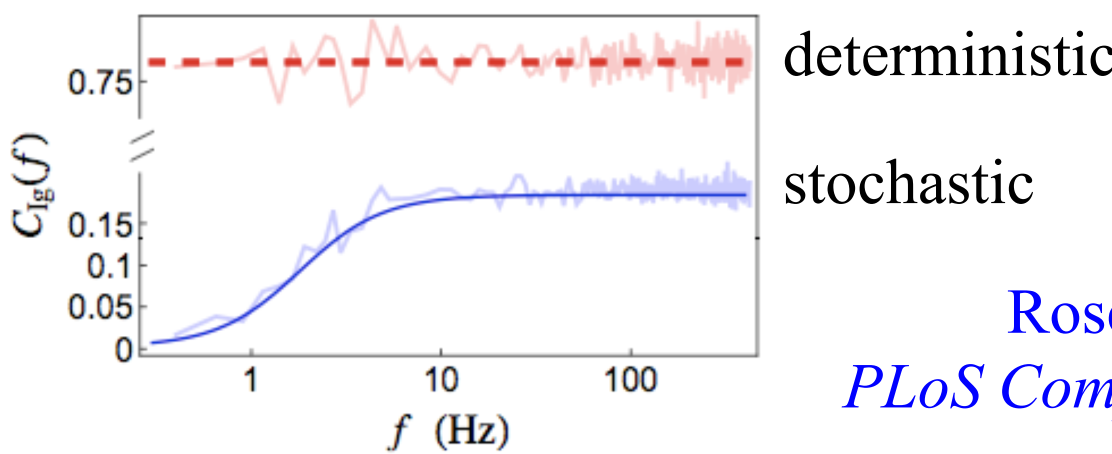
Rosenbaum et al.,
PLoS Comp. Biol., 2012

implications: stochastic

(c) transmit high frequency signal more reliably than low frequency



(d) for high rate inputs, uptake contributes relatively more to transmission ➡ decorrelate inputs and outputs, lower coherence



Rosenbaum et al., *PLoS Comp. Biol.*, 2012