Striatum as a potential source of exaggerated beta rhythms in Parkinson’s disease

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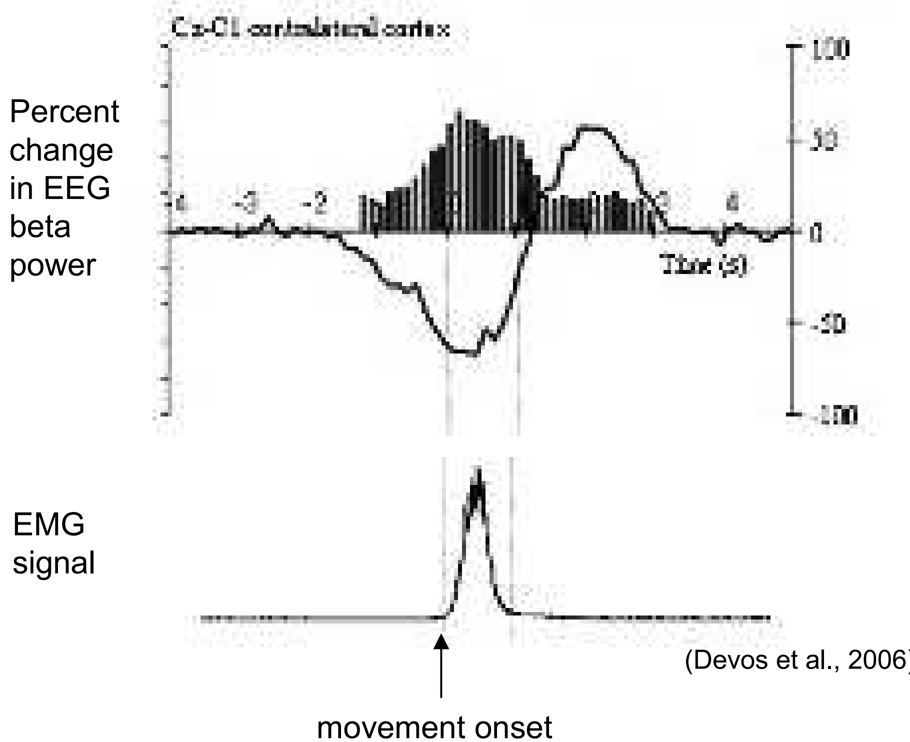
Outline of Talk

- *beta rhythms and movement*
  - *involvement of the cortex and basal ganglia*
- *beta rhythm pathology in Parkinson's disease*
- *the source of the beta rhythms?*
- *striatum as a potential source of beta rhythm generation*
- *biophysical models of striatum*
- *experimental test of our models*
- *mechanism of beta rhythm generation in our model networks*

Beta Rhythms and Movement

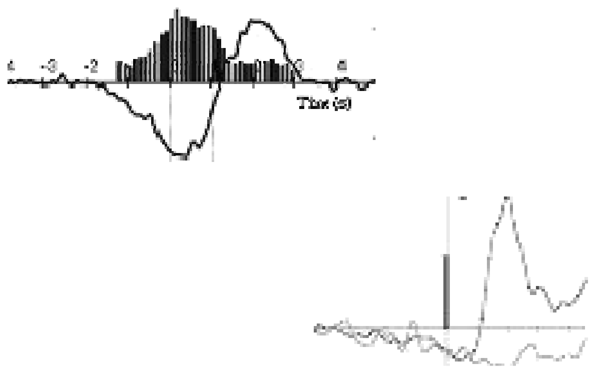
Beta rhythms (12 - 29 Hz)



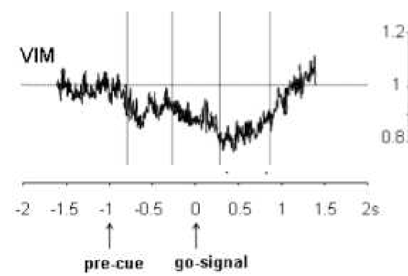
(Devos et al., 2006)

- ↓ *cortical beta during motor preparation and initiation*
- ↑ *cortical beta after movement*

Beta Rhythms and Movement

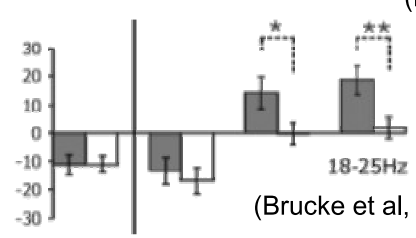


(Sochurkova et al., 2003)



(Klostermann et al., 2007)

(Devos et al., 2006)



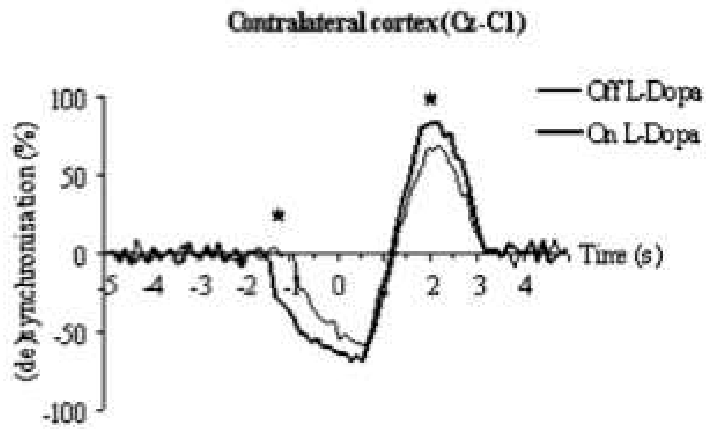
(Brucke et al, 2008)

Beta Rhythm Pathology in Parkinson's Disease

- Parkinson's patients have increased beta oscillations in the cortex and basal ganglia.

- ↑ beta oscillations correlate with bradykinesia-rigidity.

- L-dopa both ameliorates Parkinson's symptoms and decreases beta oscillations.



- Longer latency to decrease in beta prior to movement

- Less change in beta during and after movement

- Deep brain stimulation (DBS) of STN at 130 - 180 Hz alleviates Parkinson's symptoms. DBS at beta frequency worsens symptoms.

Conclusion: beta oscillations appear to be integral to the systems-level pathology of Parkinson's disease.

The source of the abnormal beta oscillations is unknown

Two predominating views on the source of beta in Parkinson's disease:

1. STN-GPe network (STN-GPe pacemaker)
- *-- STN-GPe can oscillate independent of all other input in vitro at 0.8 Hz. (Plenz et al., 1999)*
- *-- Computational modeling suggests GP-STN network can generate rhythmic oscillations.(Terman et al., 2002)*

2. Cortex
- *-- In rat M1 brain slices, high beta arises from the co-application of carbachol and kainate. (Yamawaki et al., 2008)*

3. Another view…striatum

The striatum, beta rhythms and Parkinson's disease

The pathophysiology of Parkinson's disease involves loss of dopaminergic neurons that project predominantly to striatum.

A prominent, waxing and waning beta oscillation exists in the local field potential of normal monkey striatum. (Courtemanche et al., 2003)

The striatum has the cellular and network structure to potentially support both normal and abnormal beta rhythms.

Why is the striatum ignored as a source of beta oscillations?

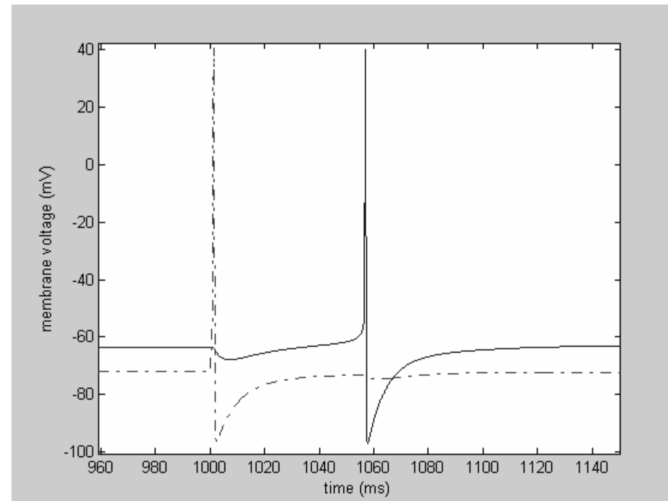
The striatal network is almost entirely inhibitory (99.7% of striatal neurons are GABAergic, 0.3% are cholinergic).

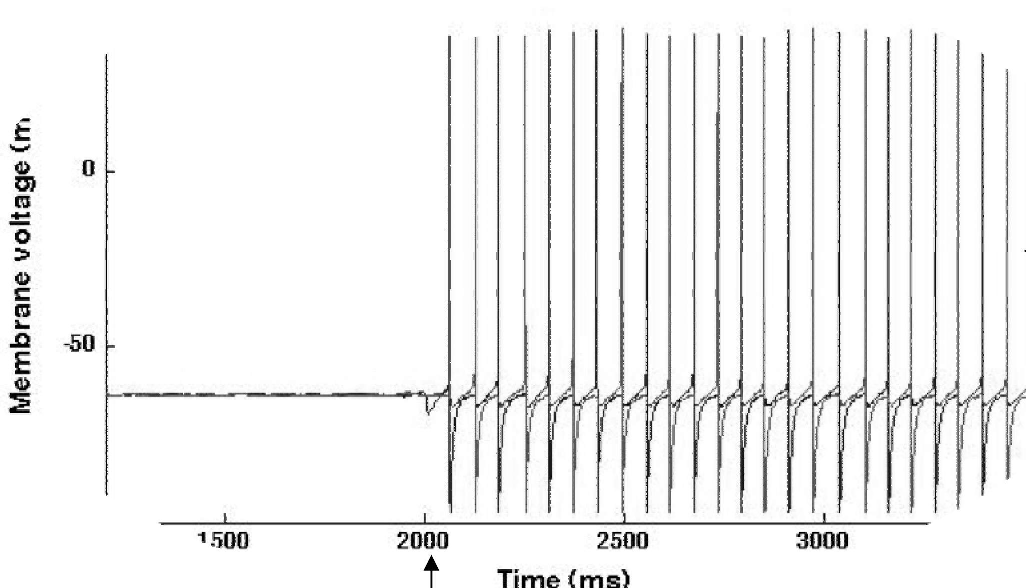
The average spiking rate of the medium spiny neurons (MSNs) (95% of striatal neurons in rodent) is about 1 Hz.

MSNs are the only output neuron of the striatum. If beta originates in striatum and is transmitted to STN, GP and cortex, it must be expressed in the MSNs.

Mathematical models inform us that inhibition can create excitation under certain circumstances

Activation or inactivation of slow currents by hyperpolarization can result in rebound spiking.



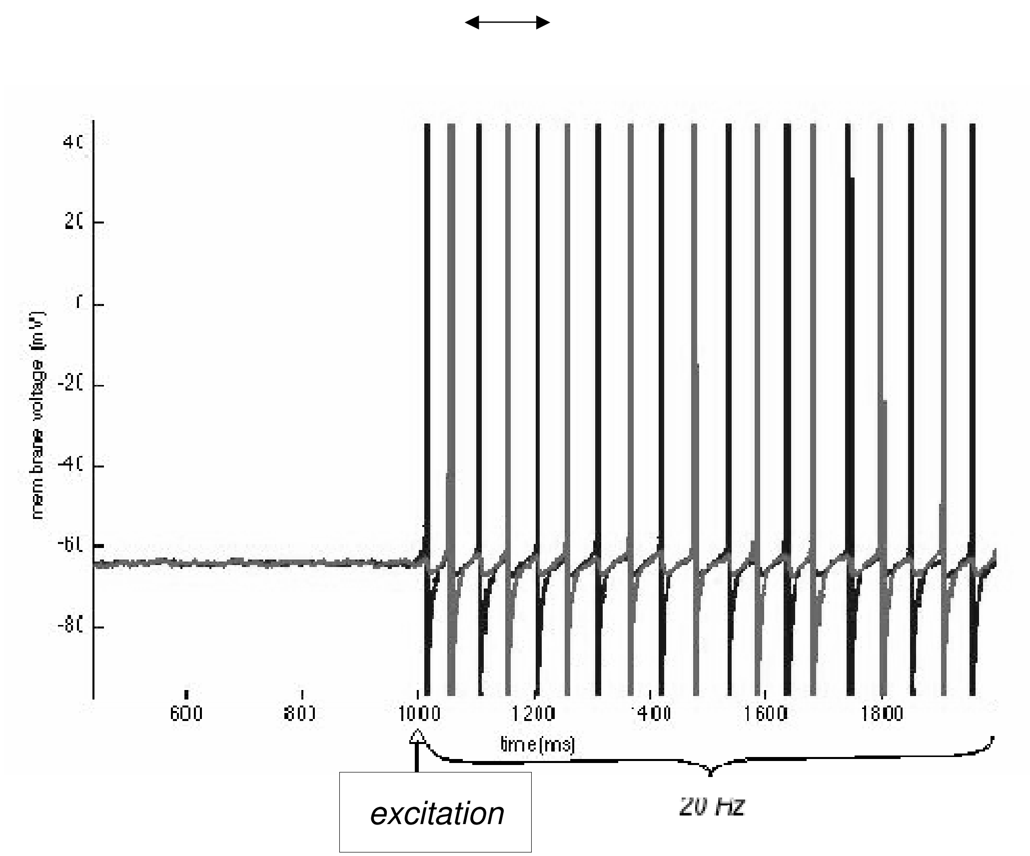


inhibition

Inhibitory networks of such neurons can produce rhythmic activity

The frequency of these inhibition-based rhythms depends on the time constant of the slow current

The M-current has an appropriate time-to-rebound to support beta frequency rhythms



Relationship to Striatal Dynamics

- *The MSNs of the striatum have an M-current.*
- *The MSNs are interconnected by GABAa synapses*

$\Rightarrow$ *Indicate beta rhythm generation is possible in striatum*

Biophysical model of striatum

Medium spiny neurons (MSNs):

Current-balance equation

$$c_m \frac{dV}{dt} + \sum I_{ion} = 0$$

Membrane currents

$$I_{ion} = \bar{g}_{ion} m^j h^k (V - E_{ion})$$

Hodgkin-Huxley-type gating variables

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$

MSN currents:

- *spiking currents (Na^+,K^+,leak)*
- *M-current*
- *background excitation (Iapp)*

  + noise

Networks:

Synaptic current: GABAa (weak)

100 MSNs connected:

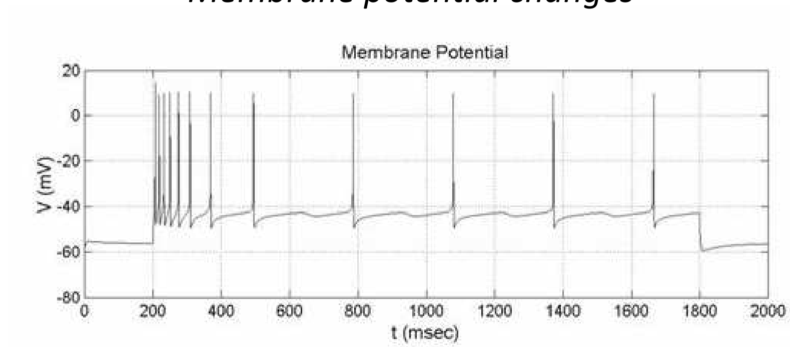
- all-to-all
- 30 nearest neighbors
- 30% random

400 MSNs connected:

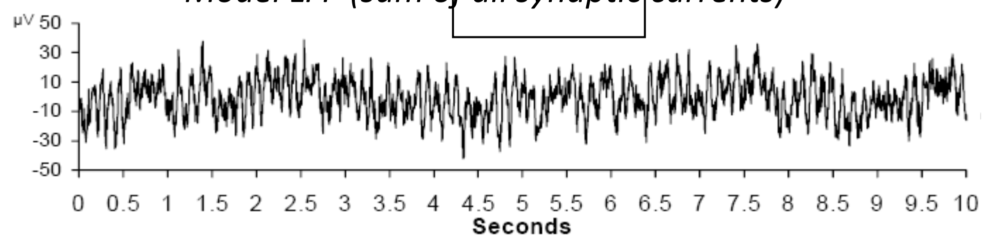
- 30% random
- 7.5% random

Model output:

Membrane potential changes

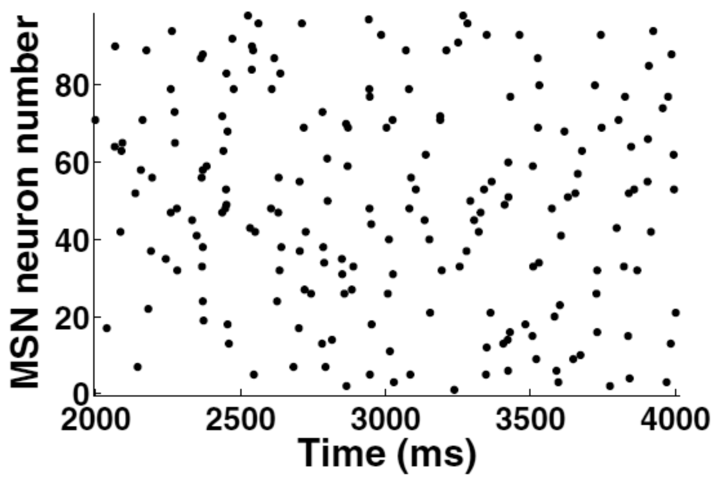


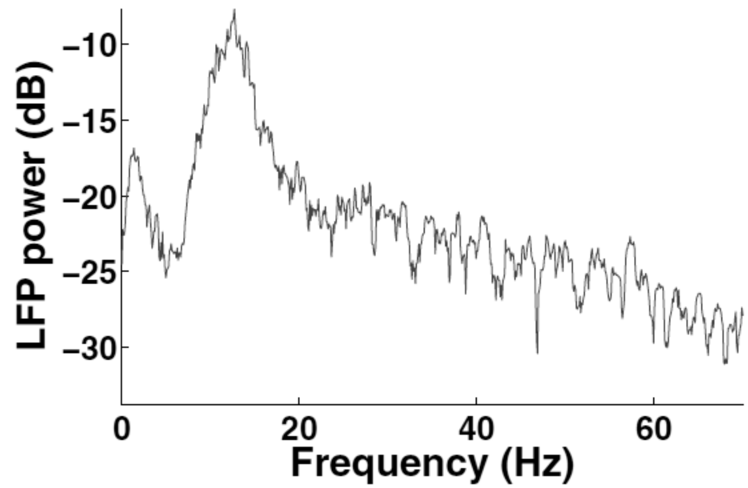
Model LFP (sum of all synaptic currents)



Model reproduces some known features of normal striatal dynamics

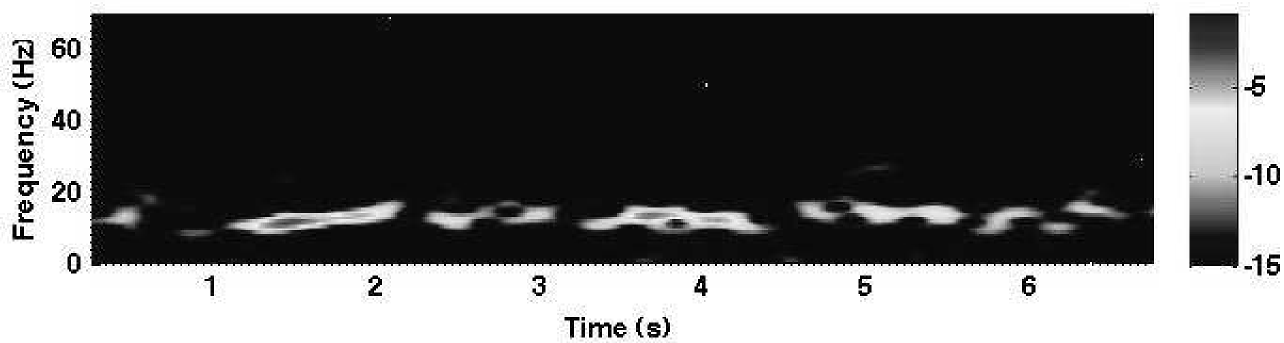
Normal striatum





Average MSN spiking rate ~ 1 Hz

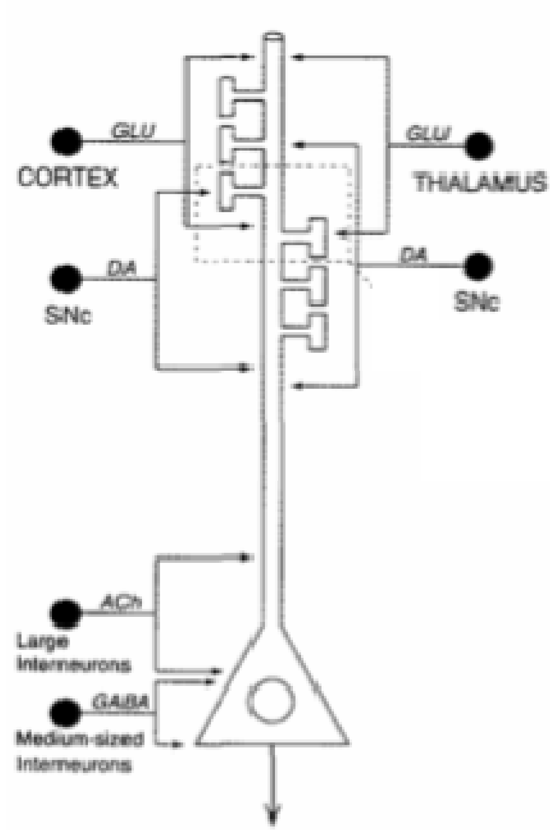
LFP power peaks around 12 Hz (low beta)



Beta oscillations wax and wane over time

Modeling the Parkinsonian MSN Network

medium spiny neuron



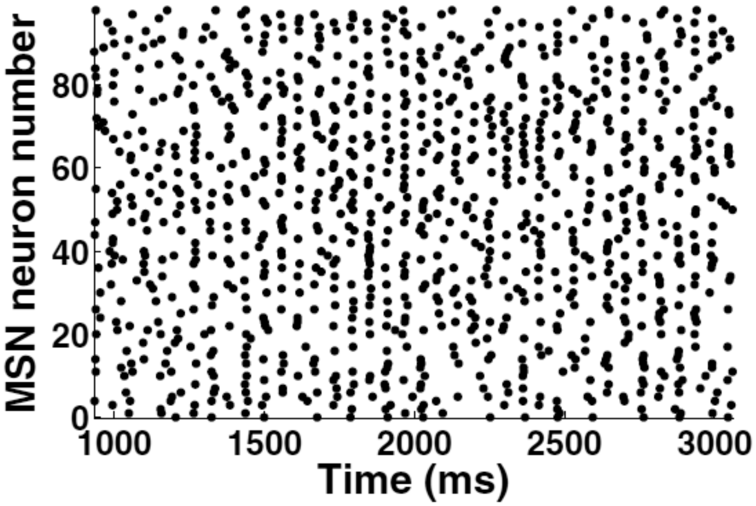
Relationship between Dopamine and Acetylcholine in Striatum

- *Dopamine tonically inhibits ACh release in the striatum.*
- $\downarrow$ *dopamine* $\rightarrow$ $\uparrow$ *ACh*
- *The M-current in MSNs is reduced by ACh.*
- *Reduction of the M-current produces excitation.*

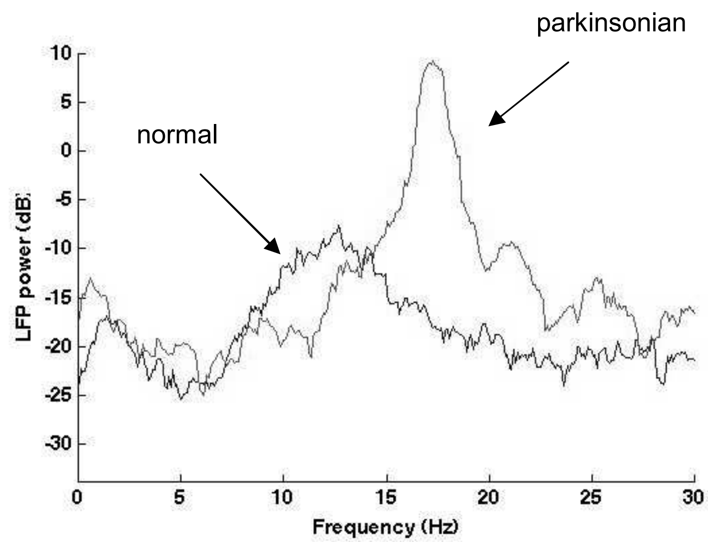
$\downarrow$

Model of parkinsonian MSN network:
$\downarrow$ *M-current maximal conductance*

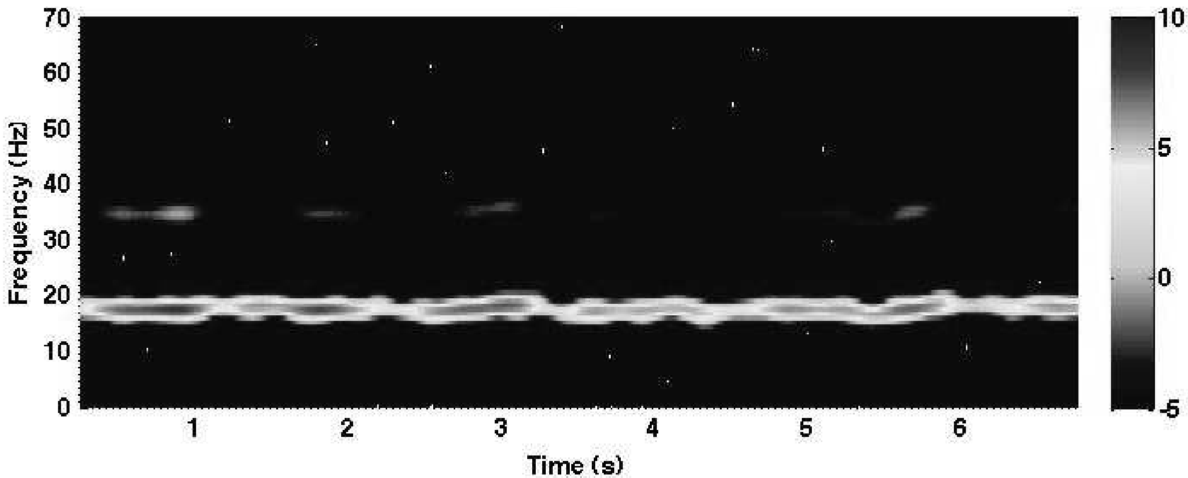
Beta power increases in model of parkinsonian striatum



Obvious patterning of MSNs
Average spiking rate ~ 4 Hz



Increase in beta power and beta frequency. Power peaks at 17 Hz.



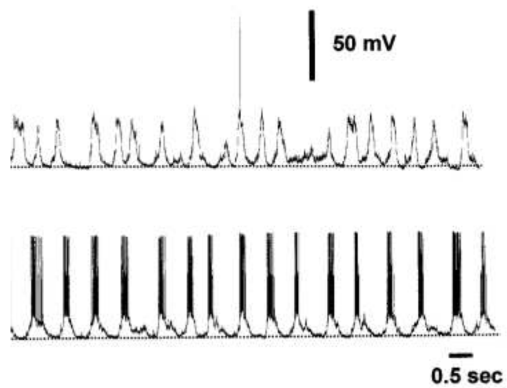
Beta oscillation more persistent than in the normal network

Evidence for both increased MSN spiking and increased frequency of beta in PD

Anesthetized rat

normal

6-OHDA



(Tseng et al., 2001)

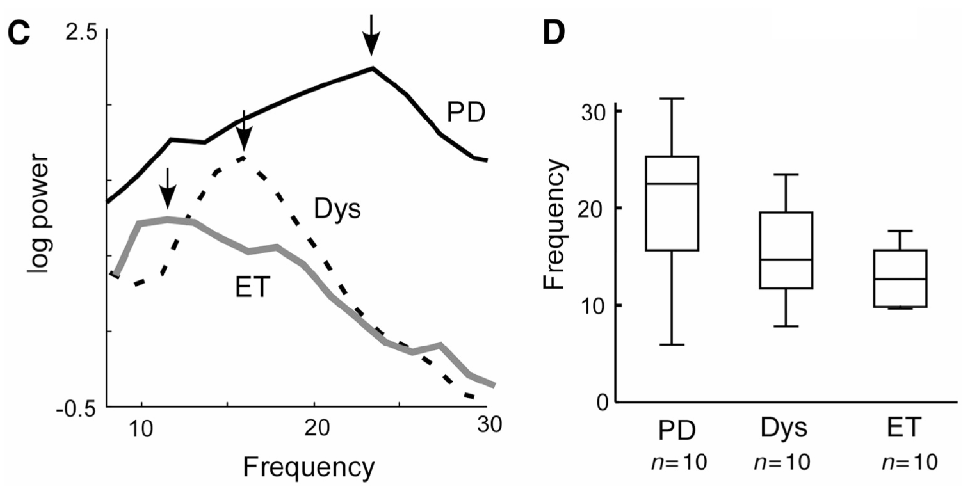
MPTP monkey (in vivo)

Increased spiking of MSNS:

Normal: 0.5 - 2 Hz
MPTP: 28.2±1.5 Hz

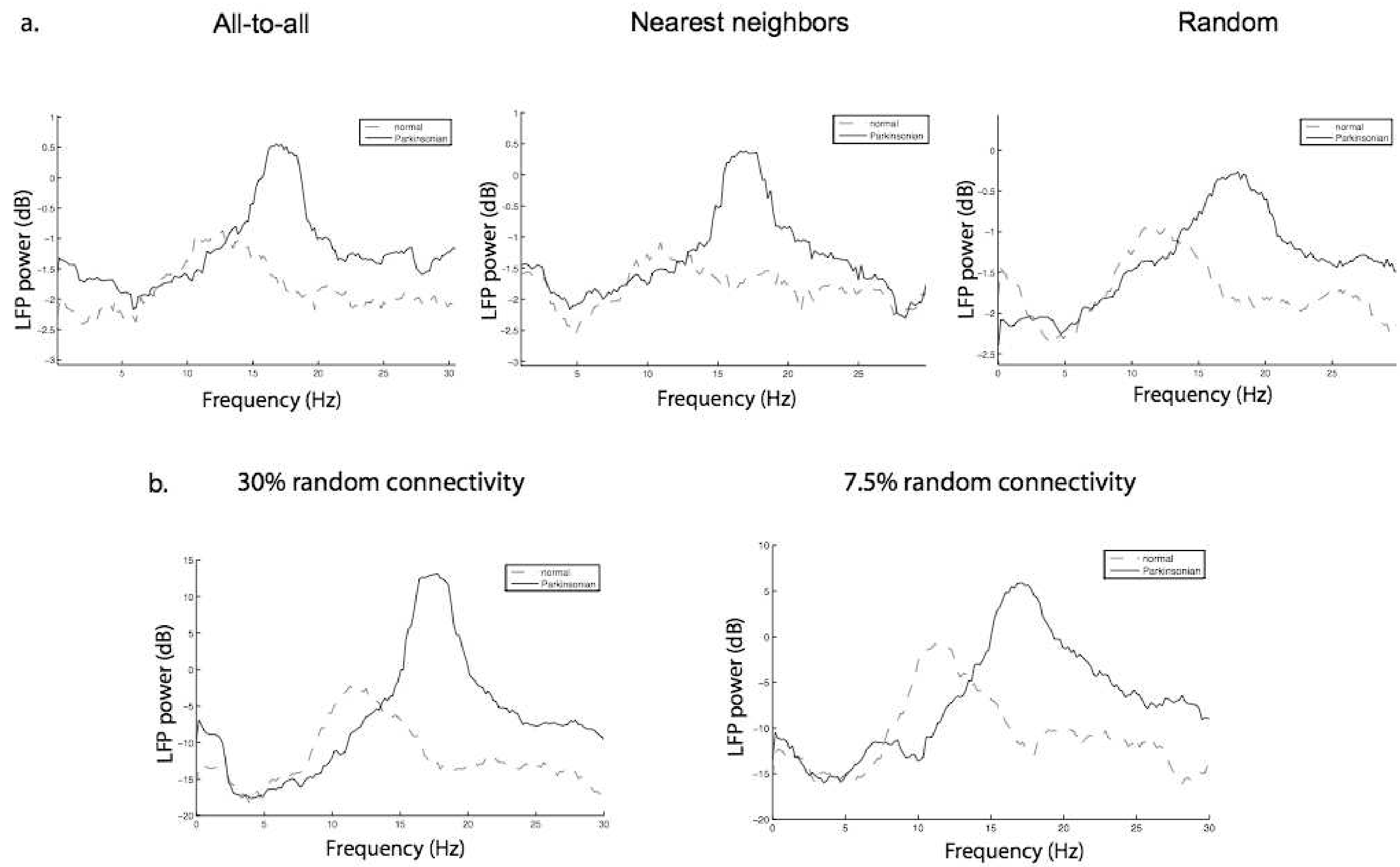
(Liang et al., 2008)

Both power and frequency of cortical beta higher in PD than in essential tremor.



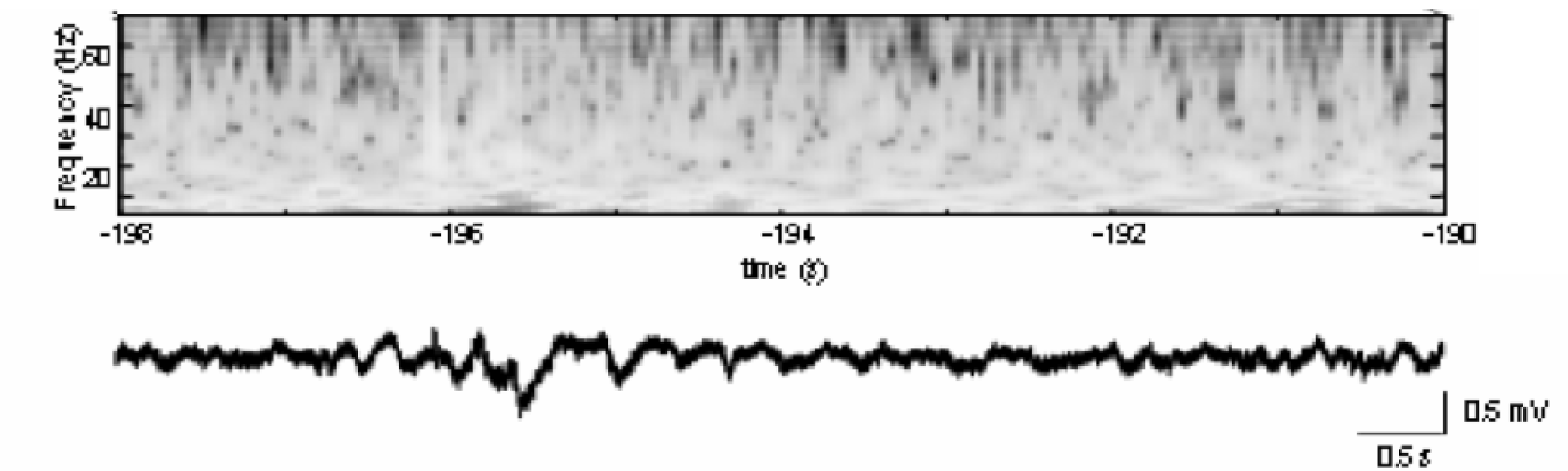
(Crowell et al., 2012)

Model results largely invariant to network connectivity

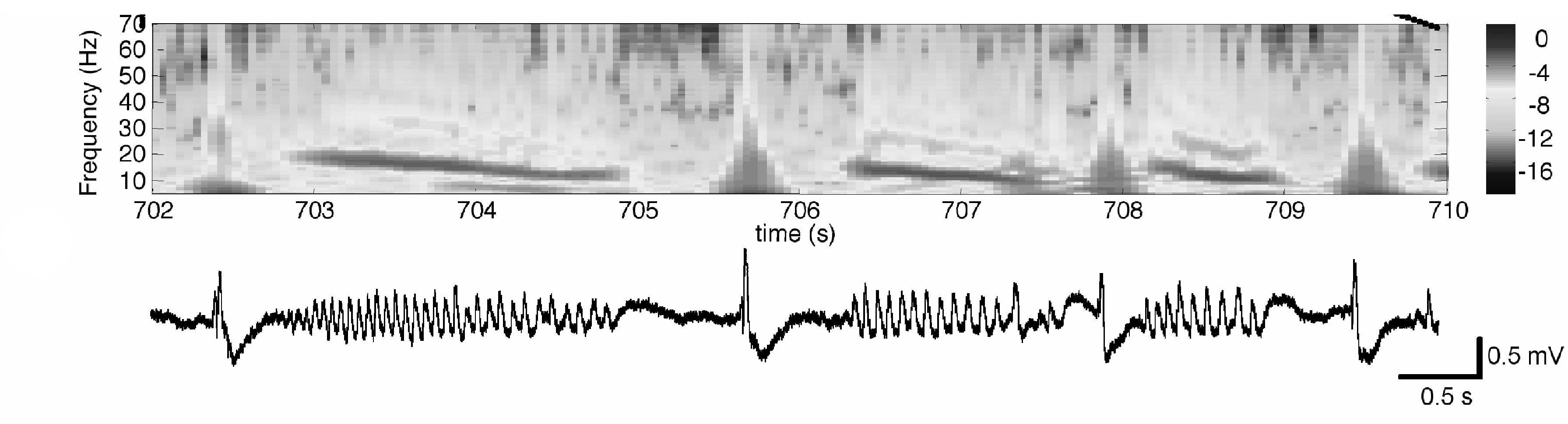


Carbachol increases beta oscillations in mouse striatum

Striatal LFP prior to carbachol infusion

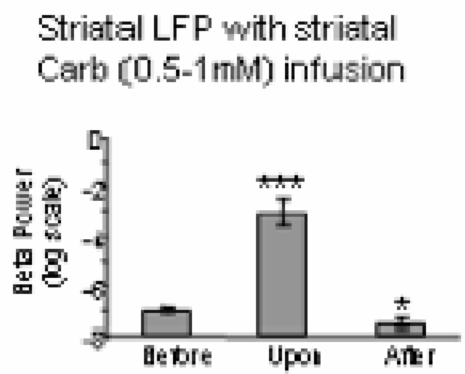


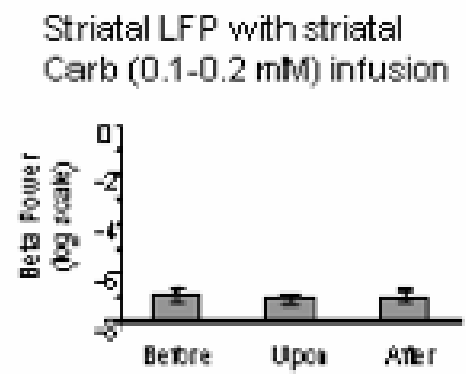
Striatal LFP after carbachol (0.5 - 1 mM) infusion



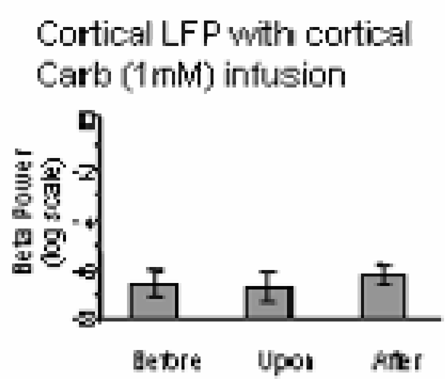
Some controls

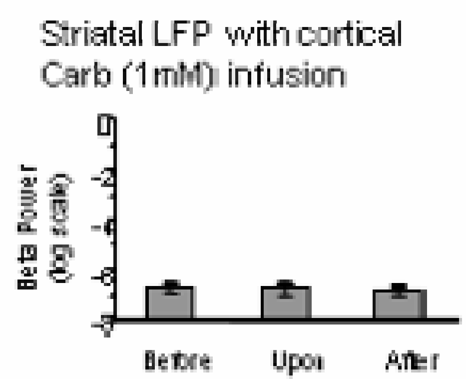
Beta oscillations are not due to pressure on striatum due to infusion





Striatal beta oscillations are not due to carbachol diffusion to nearby cortex





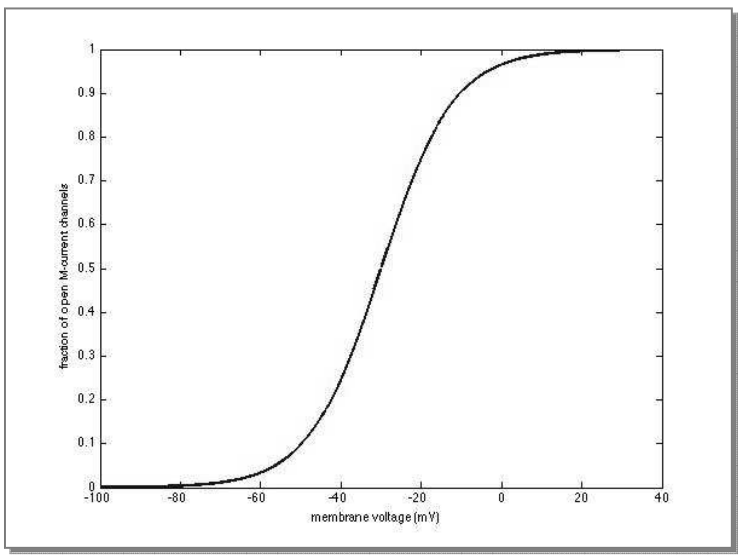
The M-current

essential properties

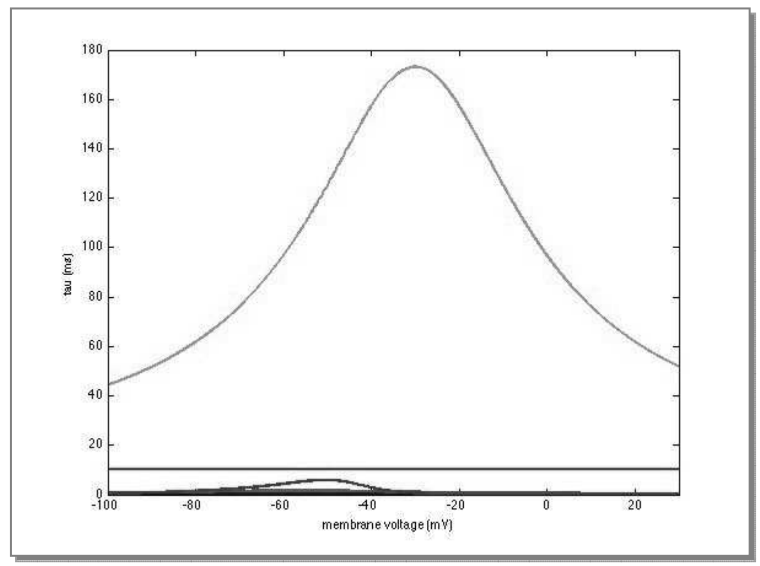
The M-current activation gate:

$$\frac{dm(v)}{dt} = \frac{m_{\infty}(v) - m(v)}{\tau_m(v)}$$

The M-current is a non-inactivating potassium current



with a slow and voltage-dependent time-constant of decay

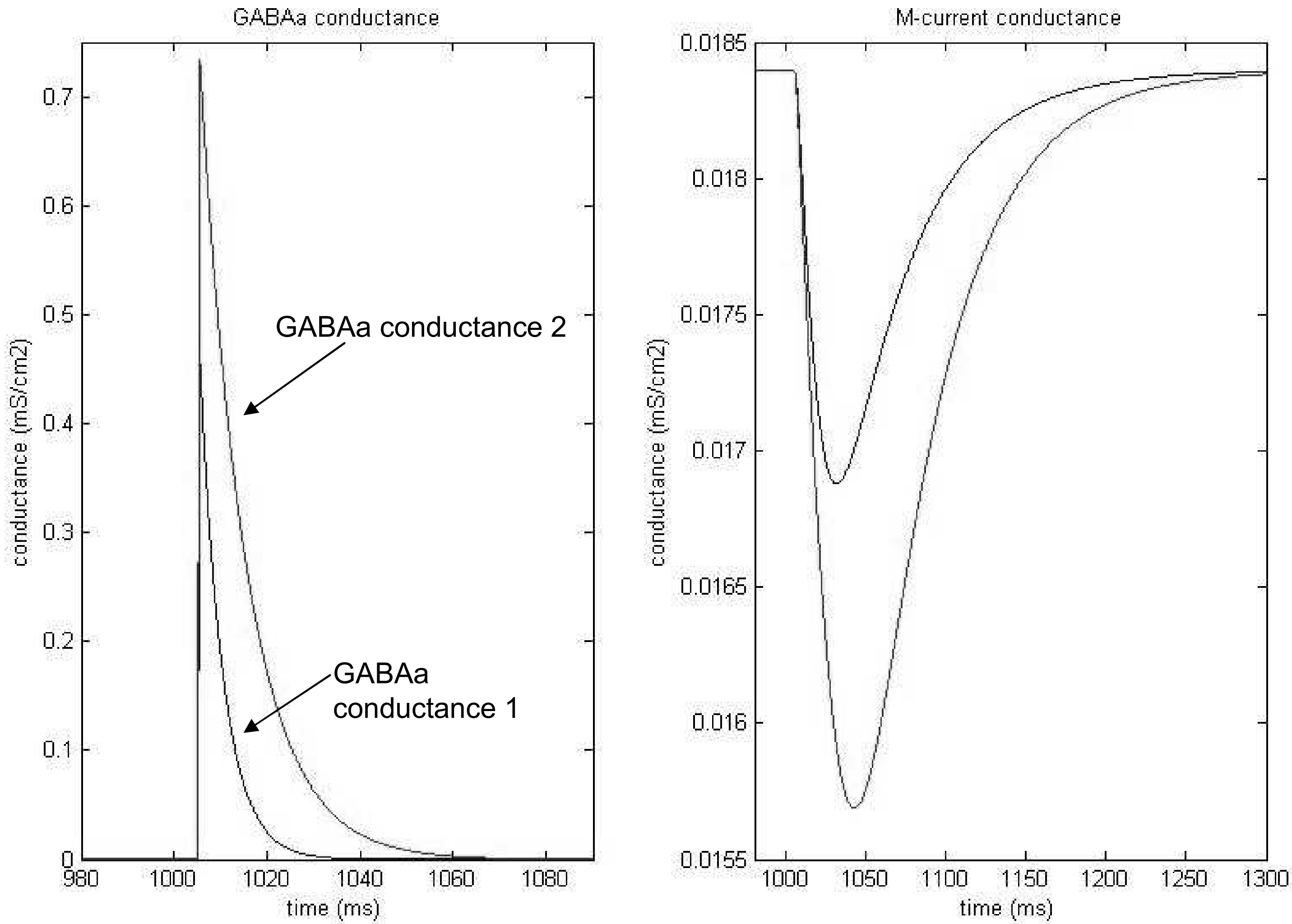


These properties allow the M-current:

- to be active at resting membrane potentials
- to influence the membrane voltage between spikes

Potassium currents hyperpolarize the membrane --> makes it harder to generate a voltage spike

M-current conductance is reduced by the GABAa current



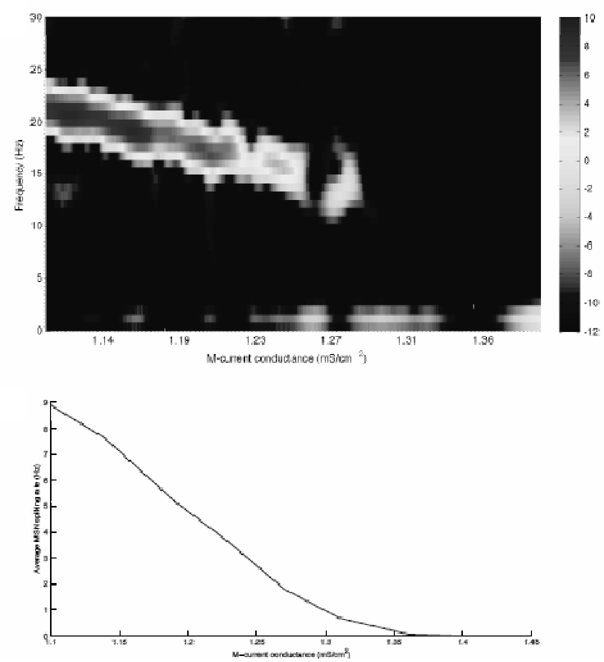
- GABAa current reduces M-current
- ↑ GABAa maximal conductance → ↑ M-current reduction
- M-current reduction continues after GABAa has decayed back to baseline and continues during the inter-spike interval → ↑ membrane excitability

↑ GABAa / M-current interaction → ↑ the beta rhythm

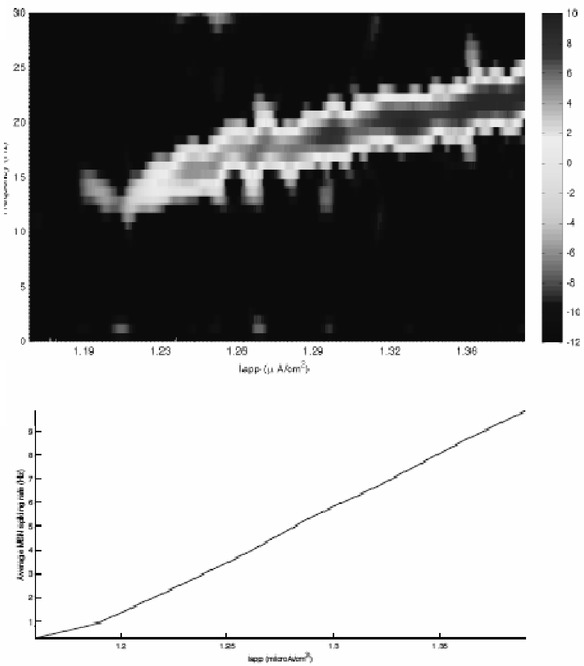
↑ MSN spiking rate

↑ GABAa conductance

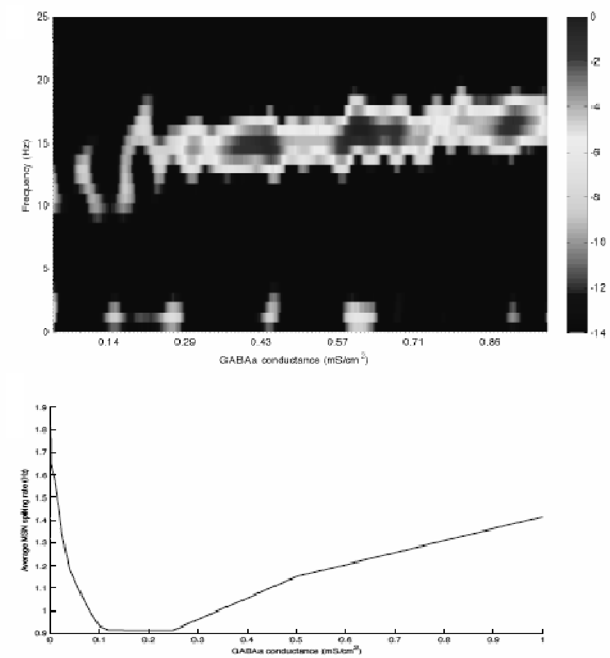
g_m



I_{app}



g_{gaba}



Modulators

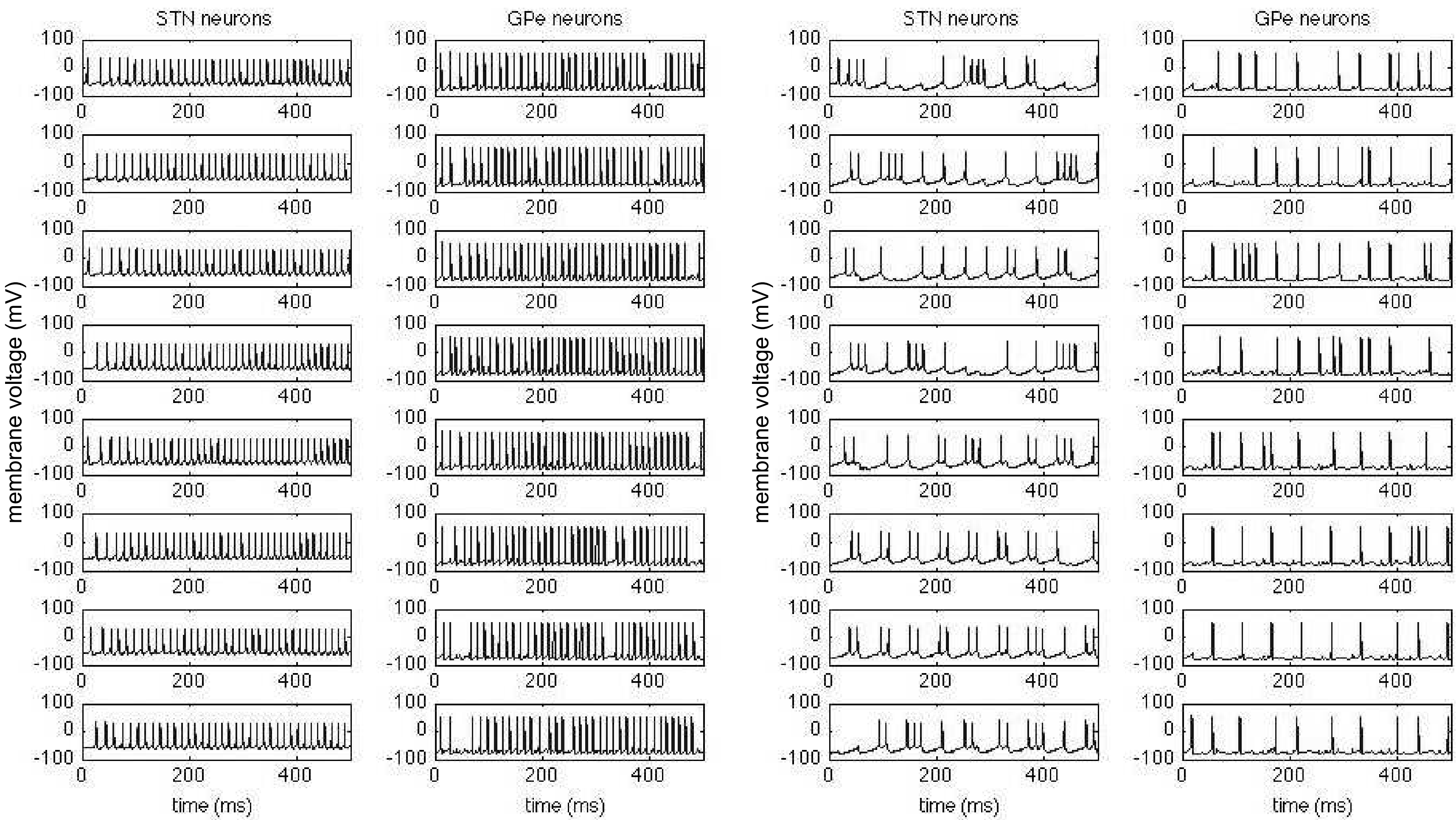
- *serotonin*
- *opioids*
- *mGluRs*
- *substance P*
- *β-adrenergic agonists*
- *somatostatin*

- *input from cortex or thalamus*

- *neurosteroids*
- *many sedatives and anesthetics*

The next step: propagation of beta rhythms to GP and STN

normal | parkinsonian



Summary and Conclusions

- Modulation of beta rhythms throughout the cortico-BG--thalamic loop is important to smooth, coordinated movement.
- Beta rhythms are exaggerated in Parkinson s disease in the cortex and basal ganglia
- The striatum appears to have the cellular and network mechanisms sufficient to produce robust beta oscillations in MSN network models
- Model MSN network shows increased beta oscillations under parkinsonian conditions.
- Experimental testing of the MSN network model by infusion of cabachol into mouse striatum produces robust beta oscillations
- Interaction between the GABAa and the M-current critical to creation of beta in model MSN networks.

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