Role of the basal ganglia in voluntary movement and mechanisms of deep brain stimulation

Robert Chen, MA, MBBChir, MSc, FRCPC

Catherine Manson Chair in Movement Disorders
Professor of Medicine (Neurology),
University of Toronto
Senior Scientist, Toronto Western Research Institute

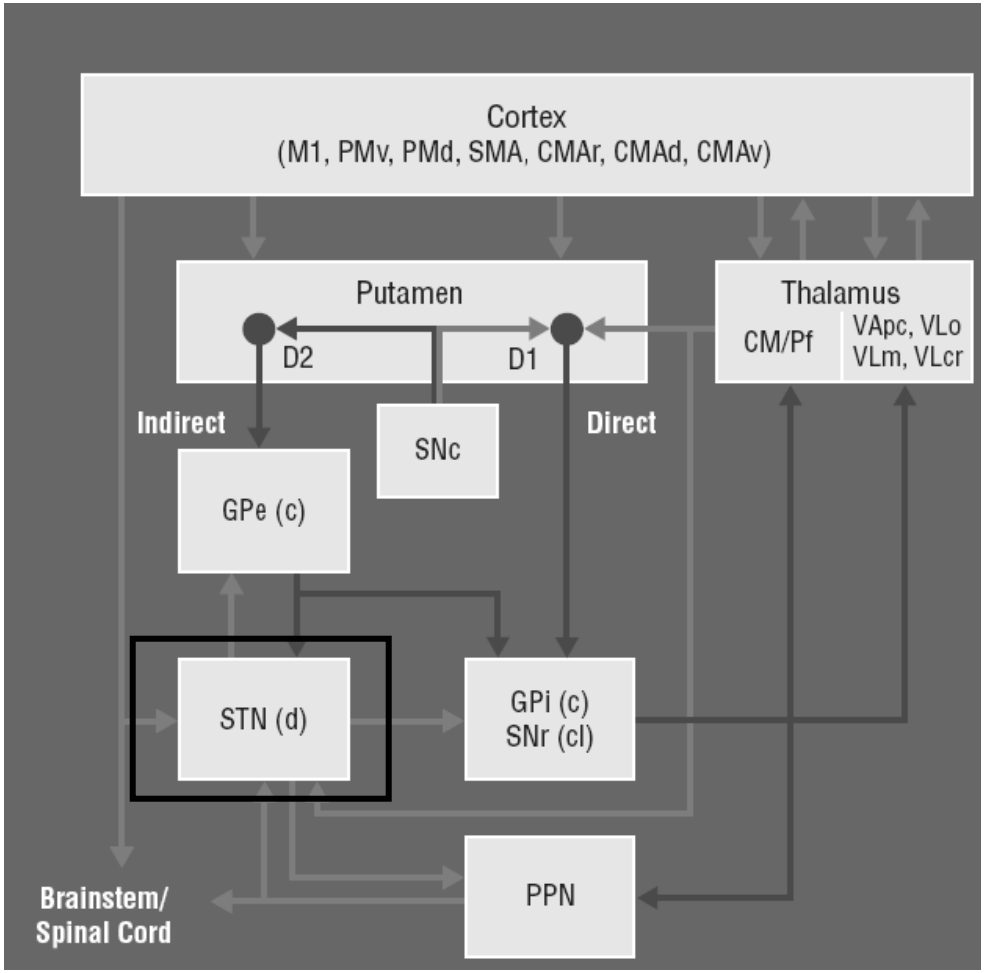
Outline

- Recordings from the basal ganglia (subthalamic nucleus, thalamus, internal globus pallidus) and pedunculopontine nucleus in humans
- Roles in movement preparation and execution
- Influence of STN stimulation on cortical activities and excitability
- Thalamic DBS □ inhibition or facilitation

Why study movement preparation?

- Movement preparation is impaired in diseases of the basal ganglia, such as PD (akinesia)
- PD patients have greater impairment of self-paced than externally triggered movement movement improves with external clues

Subthalamic nucleus (STN)

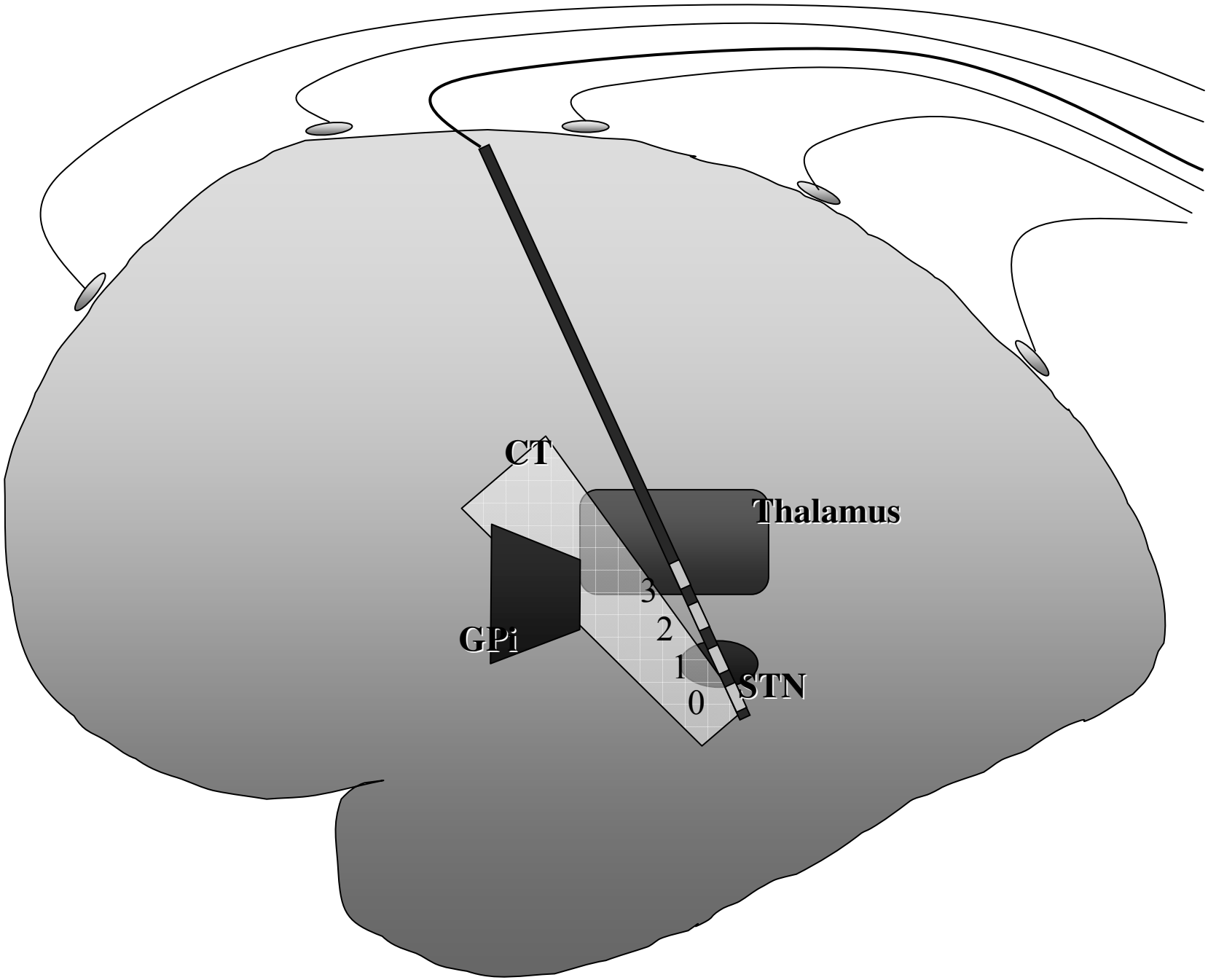


DeLong and Wichmann (2007)

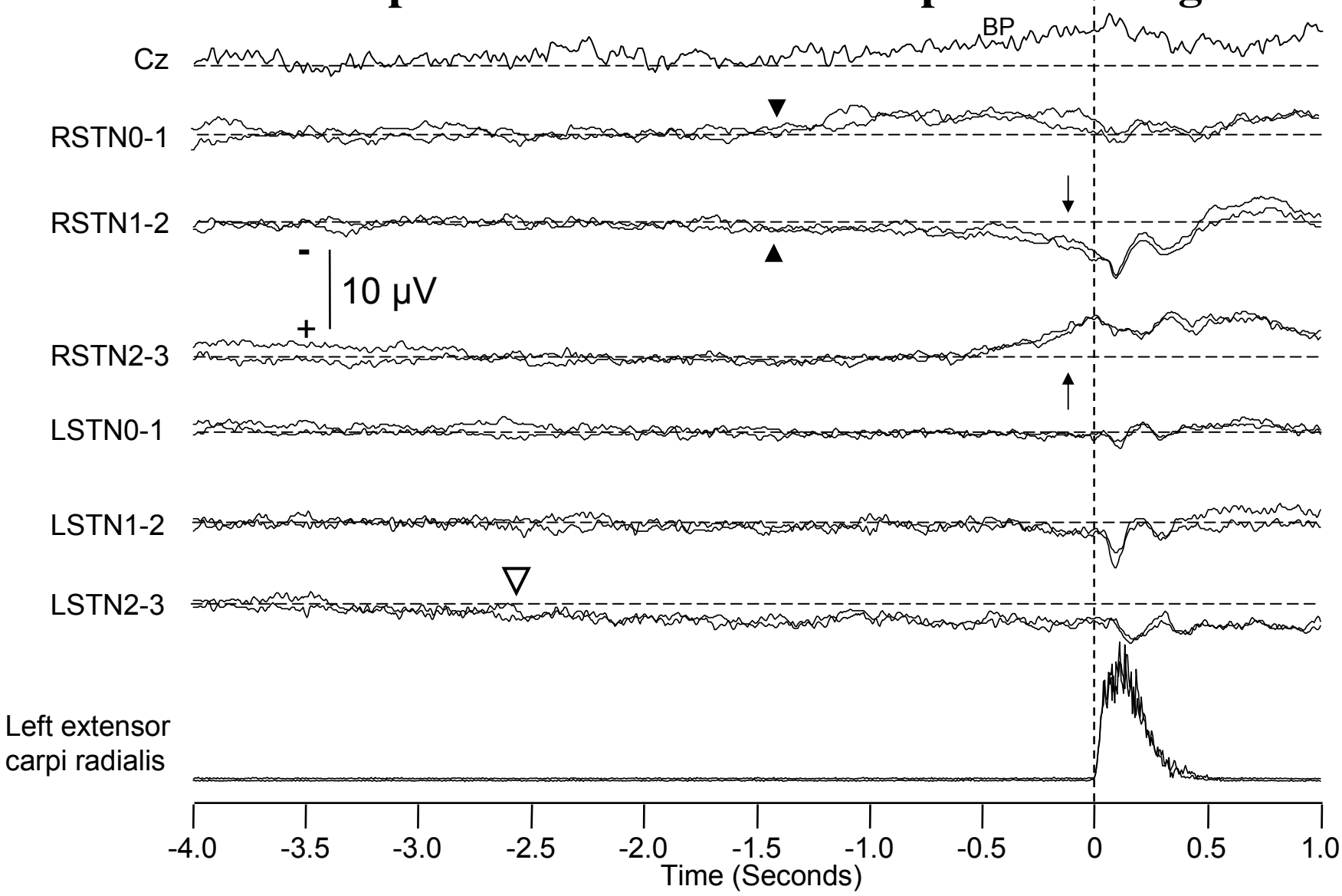
Role of STN in movement preparation

- 13 PD patients (aged 37 to 63 years)
- Patients 2-5 days after STN electrode implantation when the electrodes were externalized
- Patient performed self-paced brisk wrist extension every 5-10 seconds

Paradiso et al, Neurology 2003,61:1538-1545


CT
Thalamus
GPi
STN
3
2
1
0

Premovement potentials in the STN – bipolar montage

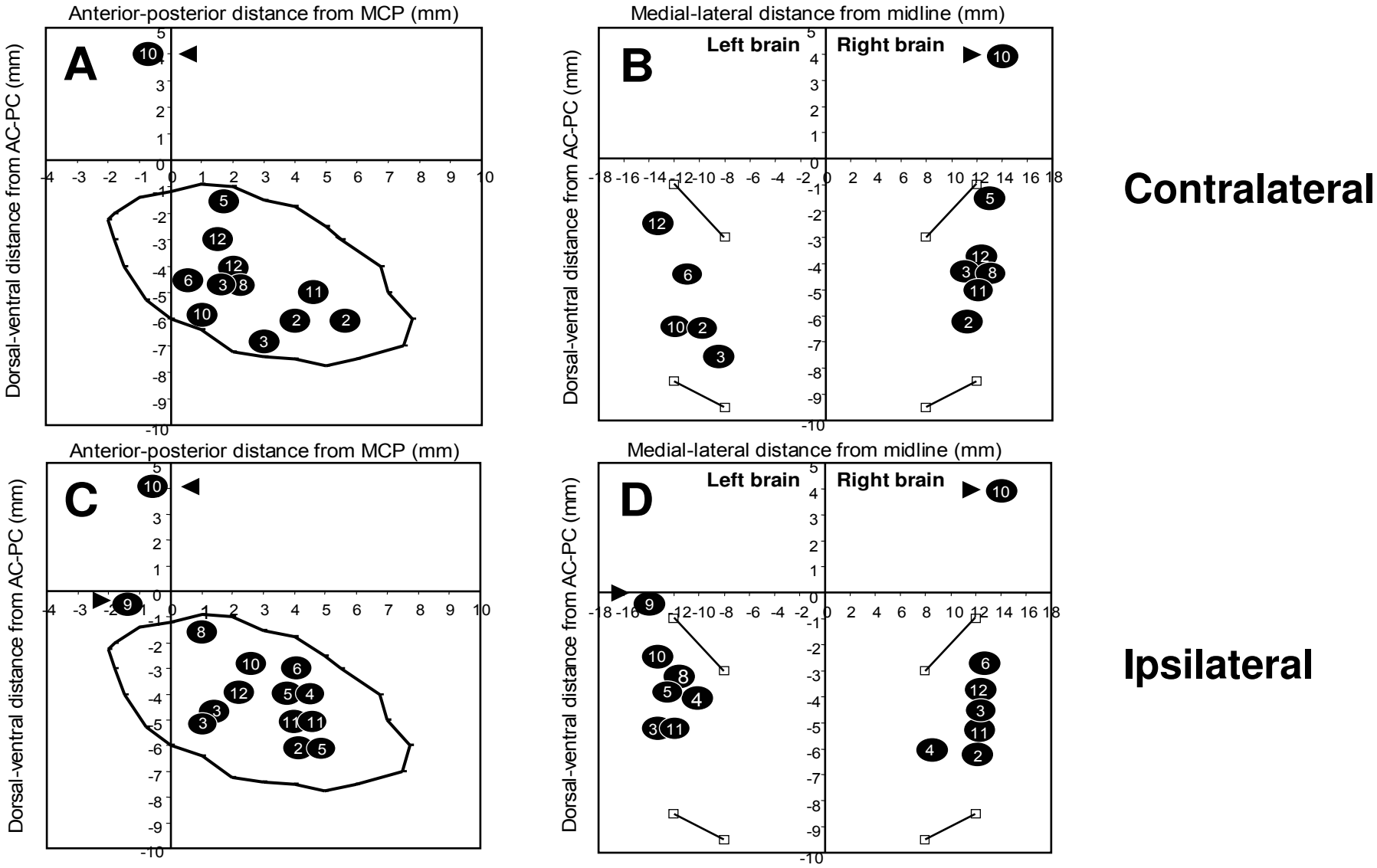


Paradiso et al, Neurology 2003,61:1538-1545

Cortical and STN Movement Related Potentials

	Cortical	Contralateral STN	Ipsilateral STN
Number	23/25	18/25	13/24
Onset (ms)	- 1690 ± 336	- 2095 ± 1005	- 2020 ± 920

Location of STN contacts with maximum premovement potential amplitude



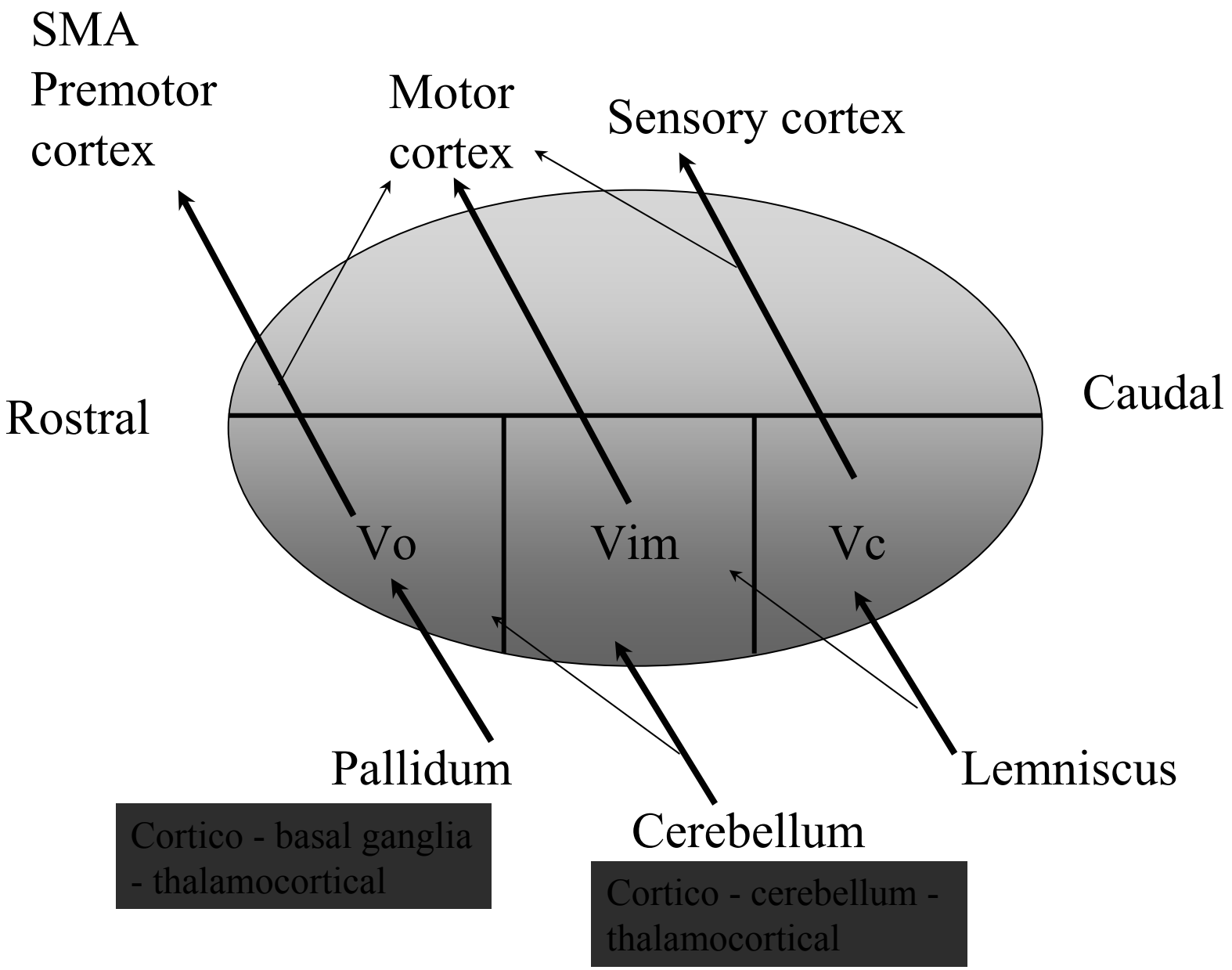
Paradiso et al, Neurology 2003,61:1538-1545

Role of the thalamus in movement preparation

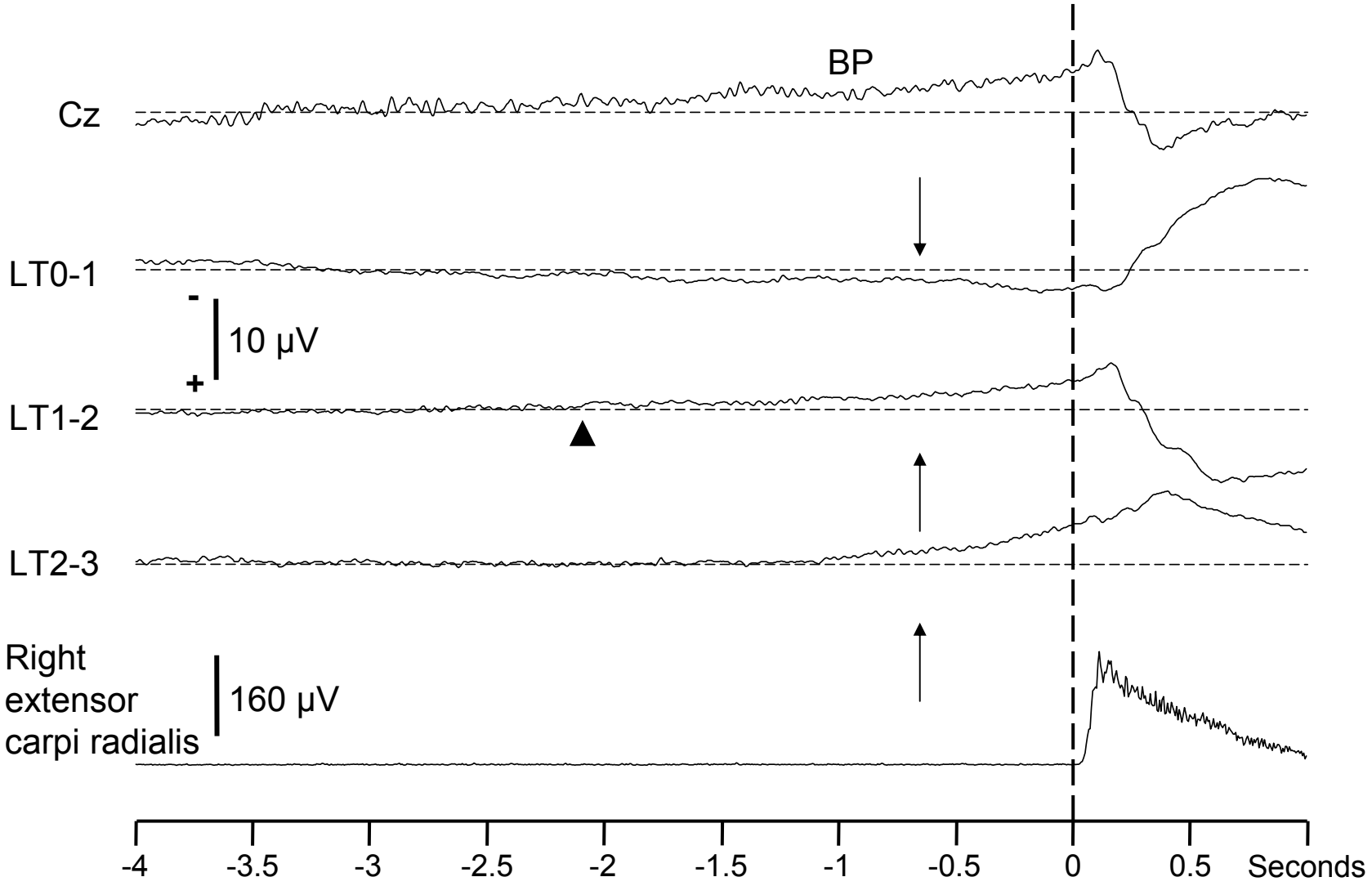
- Vim nucleus: 7 patients with tremor (5 ET, MS, trauma), 1 patient with myoclonus

Paradiso et al, Brain 2004, 127: 2717-2731

LATERAL VENTRAL THALAMUS

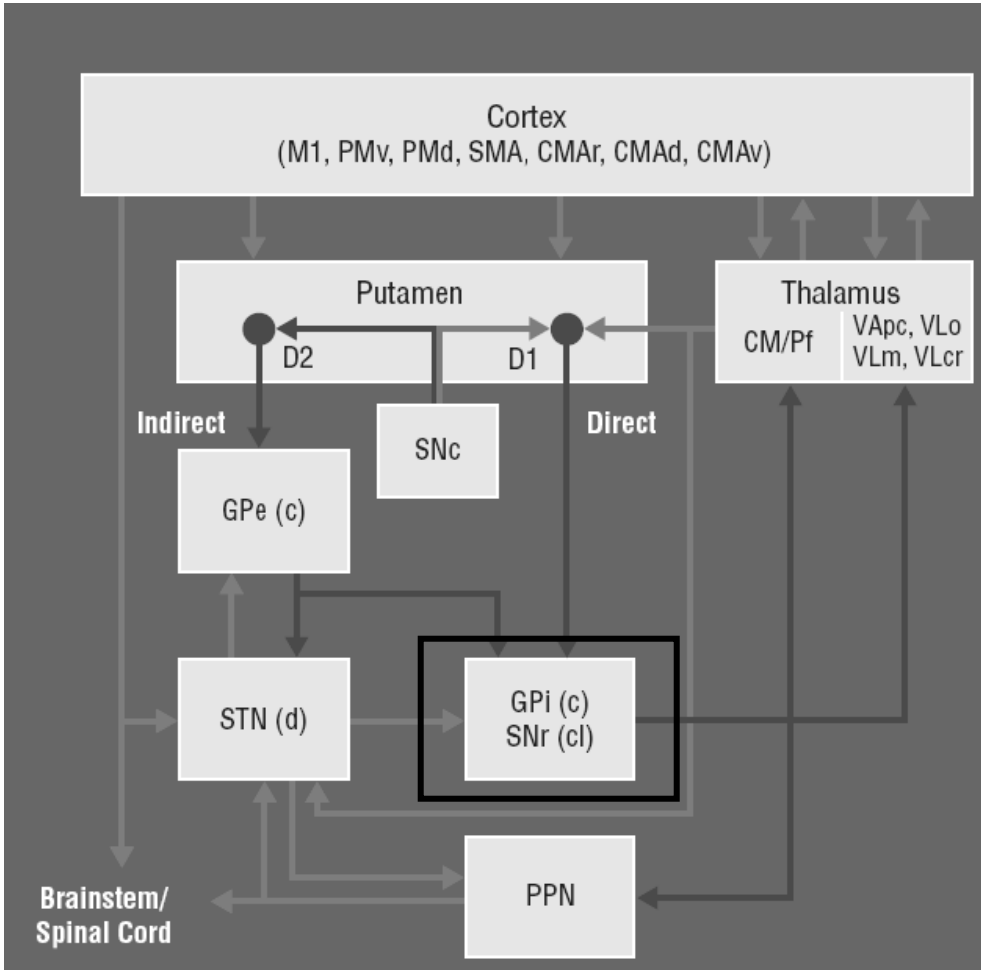


Premovement potentials in the VIM thalamus



Paradiso et al, Brain 2004, 127: 2717-2731

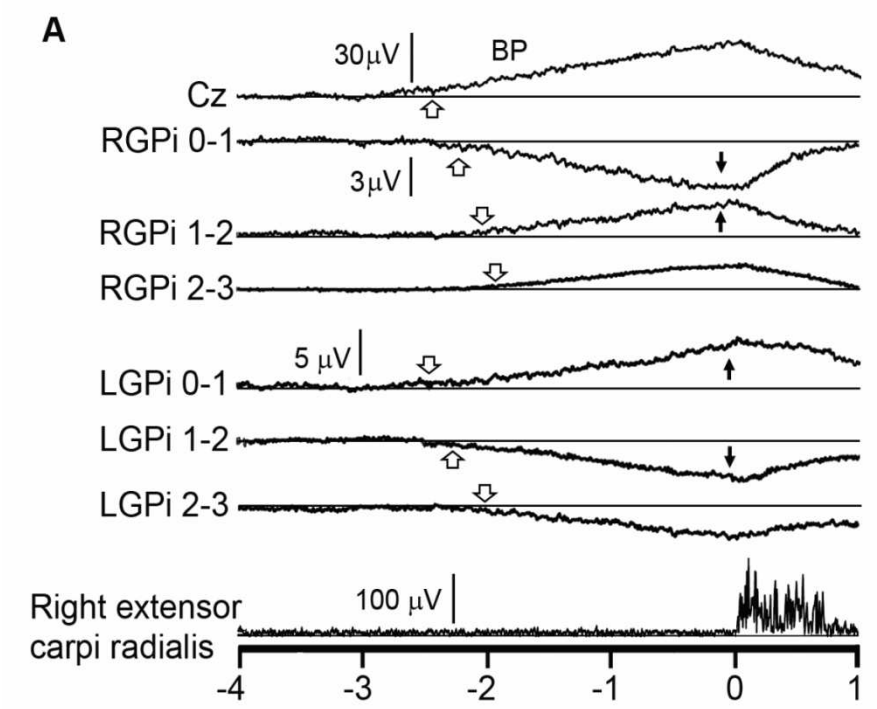
Internal globus pallidus (GPi)



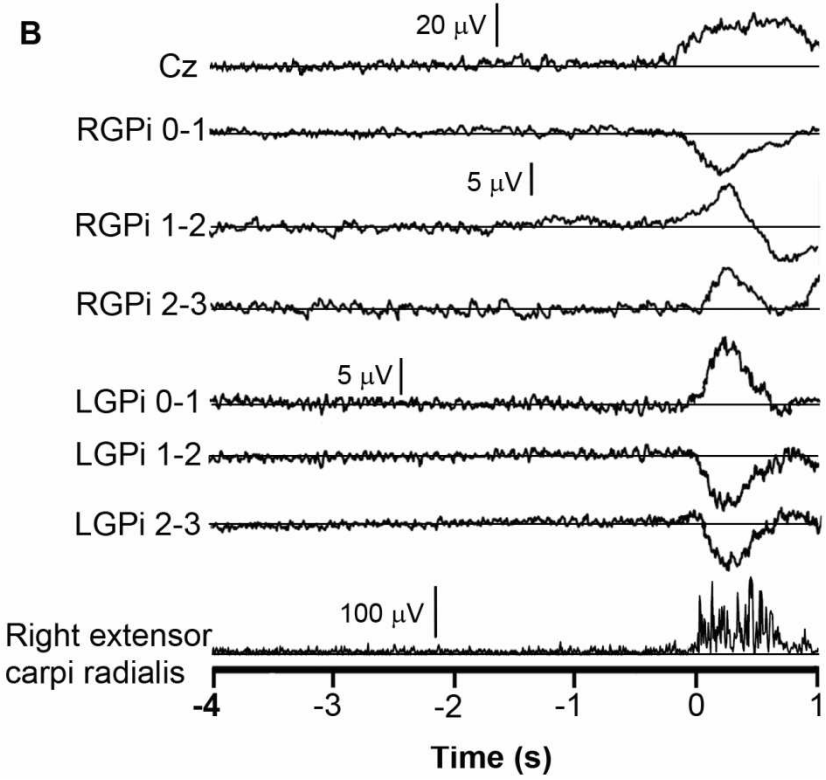
DeLong and Wichmann (2007)

Premovement potentials in the internal globus pallidus (GPi) (cervical dystonia patients)

Self-paced movements

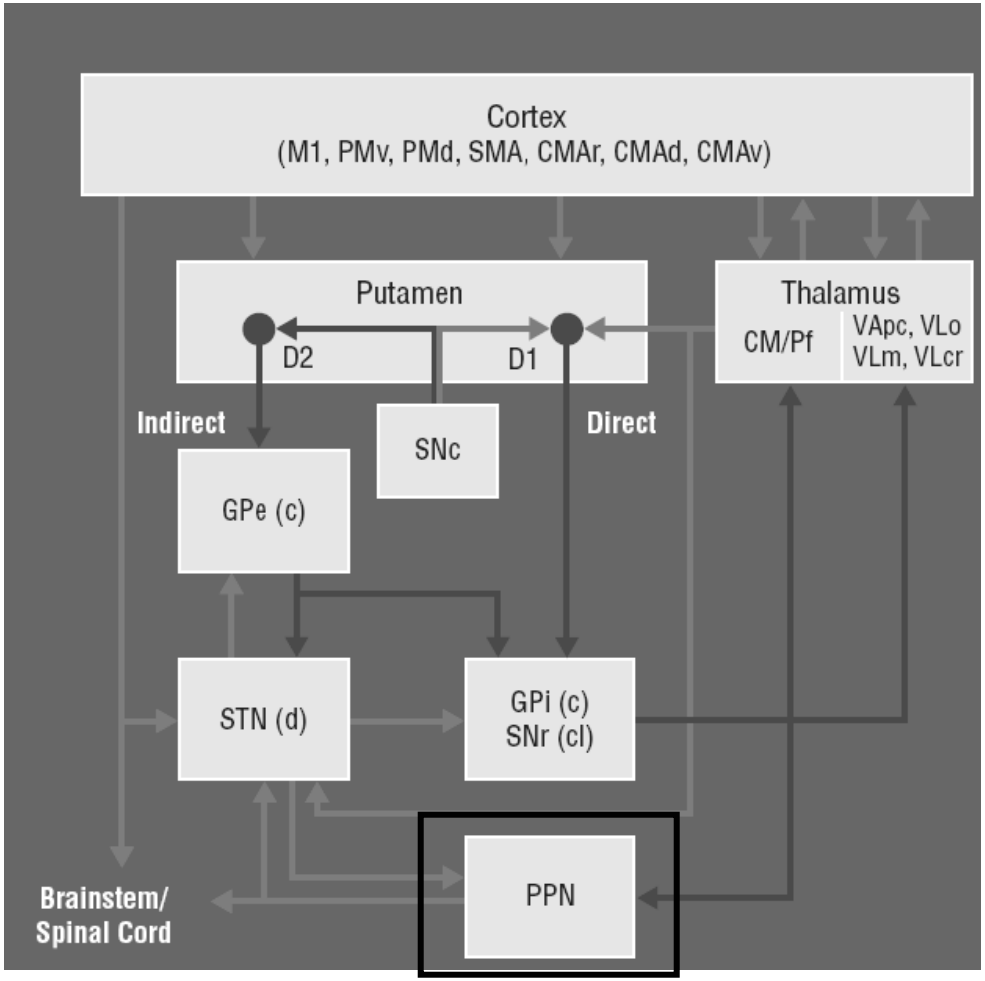


Externally-triggered movements



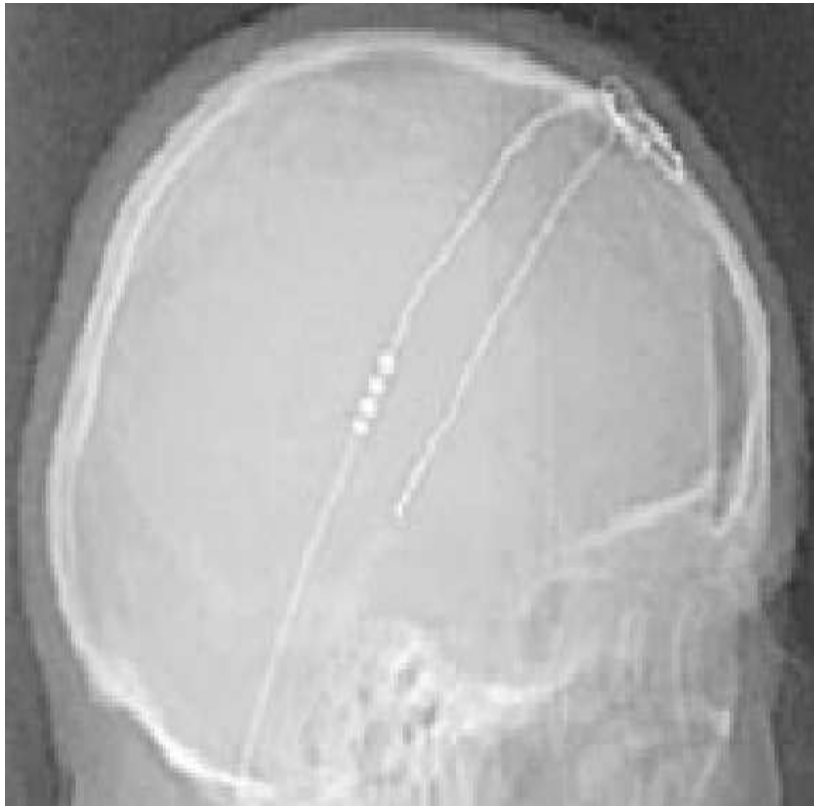
Tsang et al. J Neurol Neurosurg Psychiatry 2012

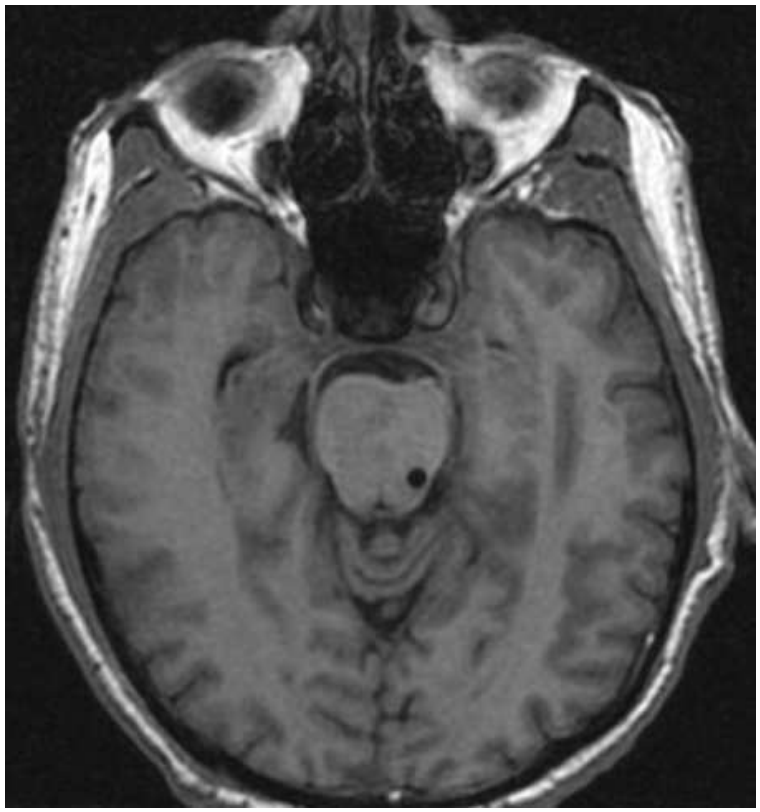
Pedunclopontine nucleus (PPN)



DeLong and Wichmann (2007)

Pedunclopontine region (PPNR)





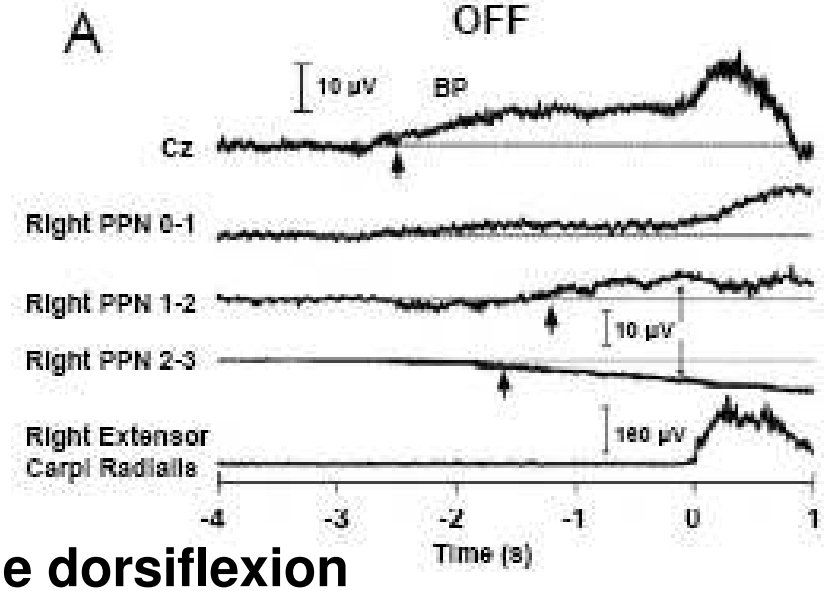
Role of the PPN in voluntary movements

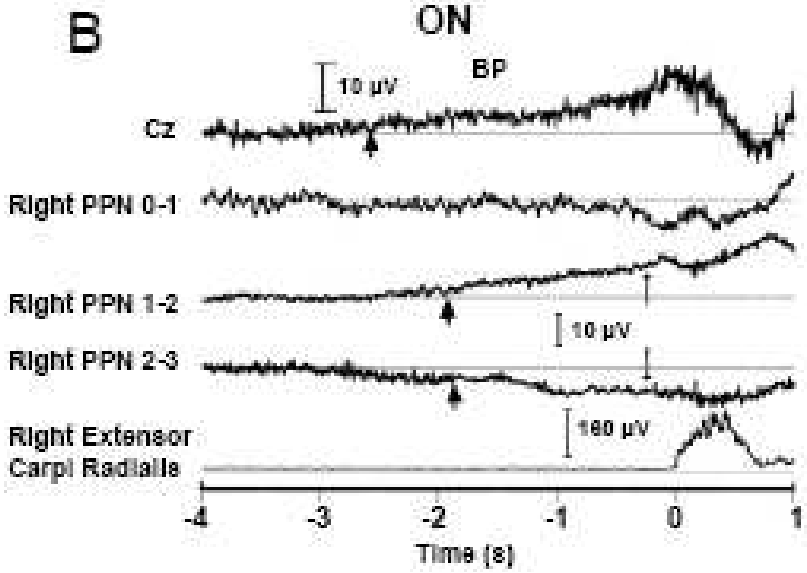
- 7 PD patients 4 studied ON and OFF medications, 1 OFF only, 3 ON only
- Unilateral PPN electrodes
- Movements studied (self paced)
  - Wrist extension (Ipsi and contralateral)
  - Ankle dorsiflexion (Ipsi and contralateral)

Tsang et al Neurology 2010

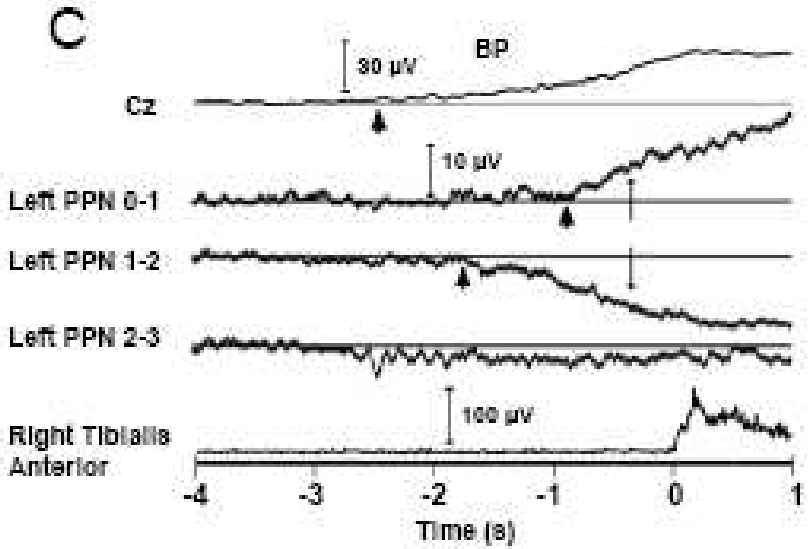
PPN – Self-paced movement

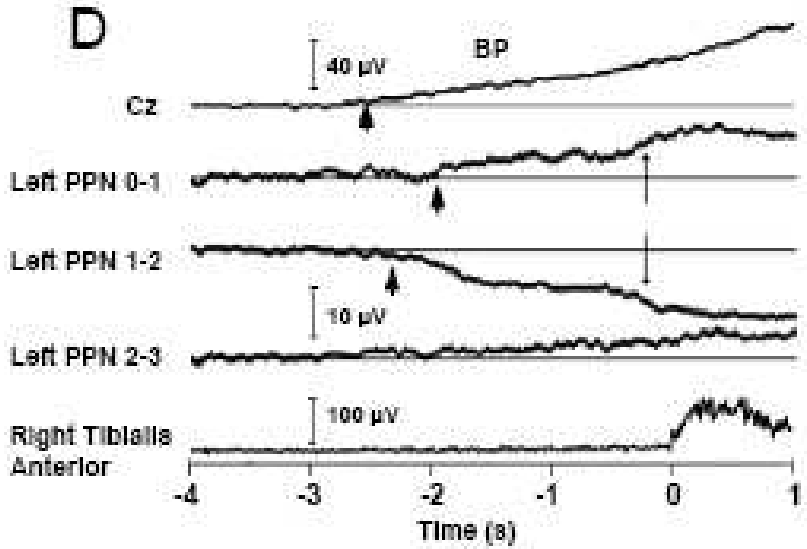
Wrist extension





Ankle dorsiflexion





Role of the basal ganglia and cerebellar thalamus in self-paced movement

- The basal ganglia (STN and GPi), cerebellum - thalamocortical circuit (VIM) and brainstem locomotor centre (PPN) are involved early in movement preparation

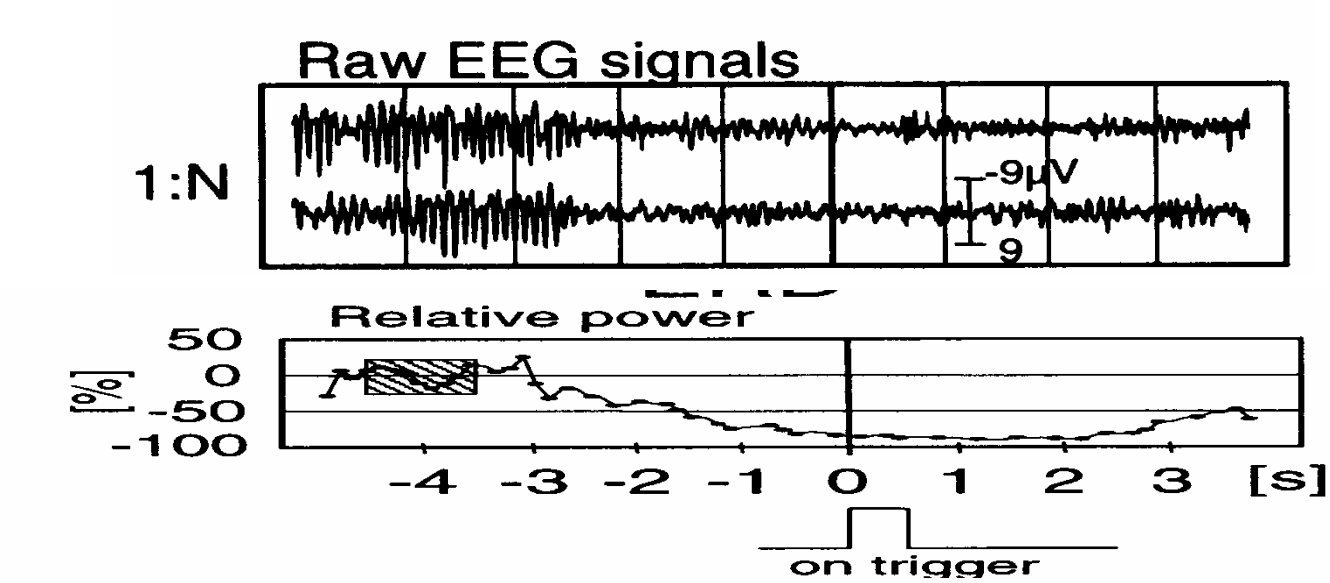
- Activity is bilateral

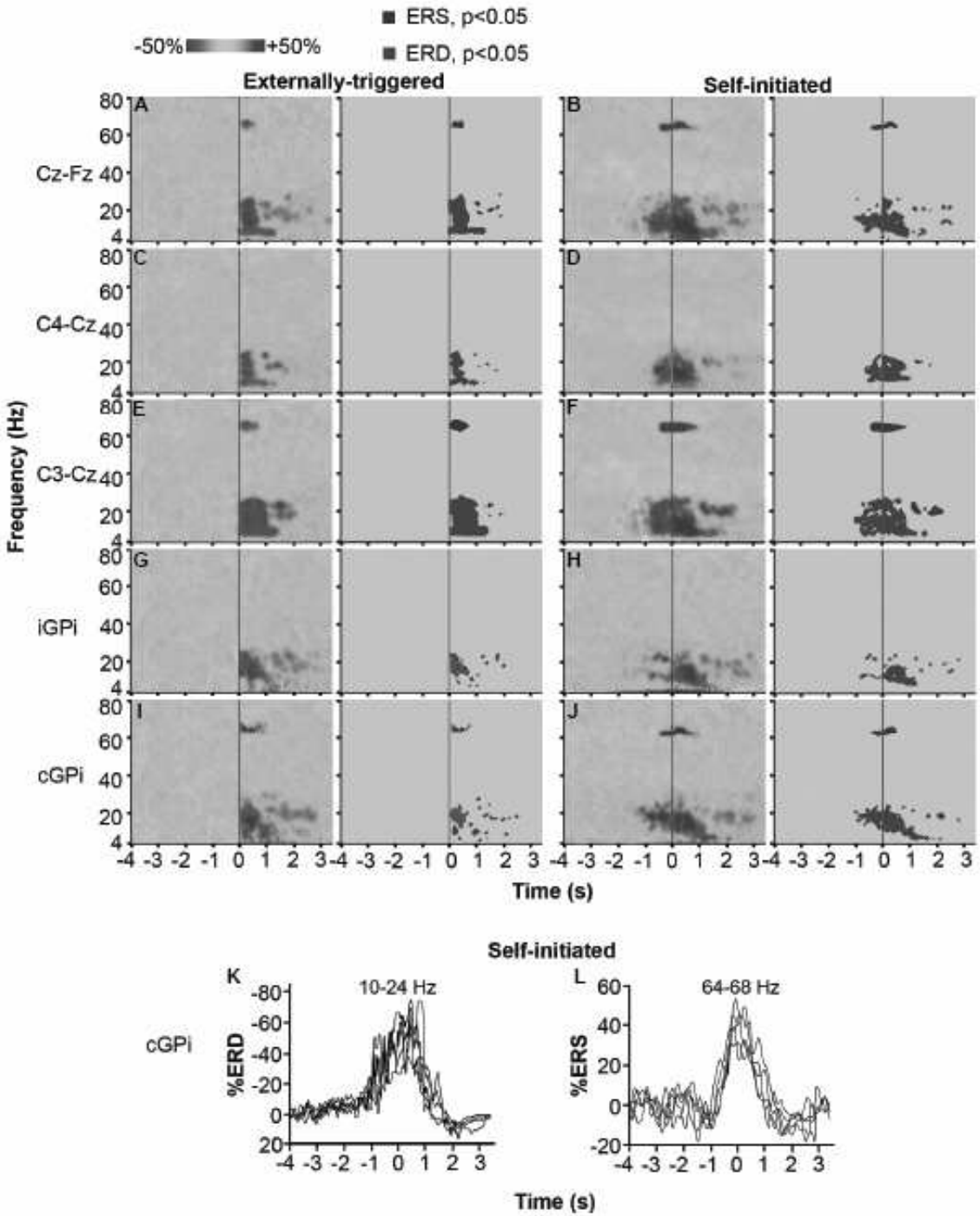
Brain rhythms and PD

- Rhythmic oscillation is a fundamental feature of the human brain
- Oscillation model of the basal ganglia (Brown): Hypothesize that excessive beta (~ 20 Hz) band oscillation is pathological and leads to akinesia, gamma (40-100 Hz) rhythm is prokinetic

Desynchronization of brain rhythms

- Blocking (desynchronization) of alpha (8-12 Hz) and beta rhythm (12 □ 30 Hz) associated with movement of the contralateral limb
- Due to decrease in synchrony of the underlying neuronal population (not necessarily related in change in overall neuronal activity)

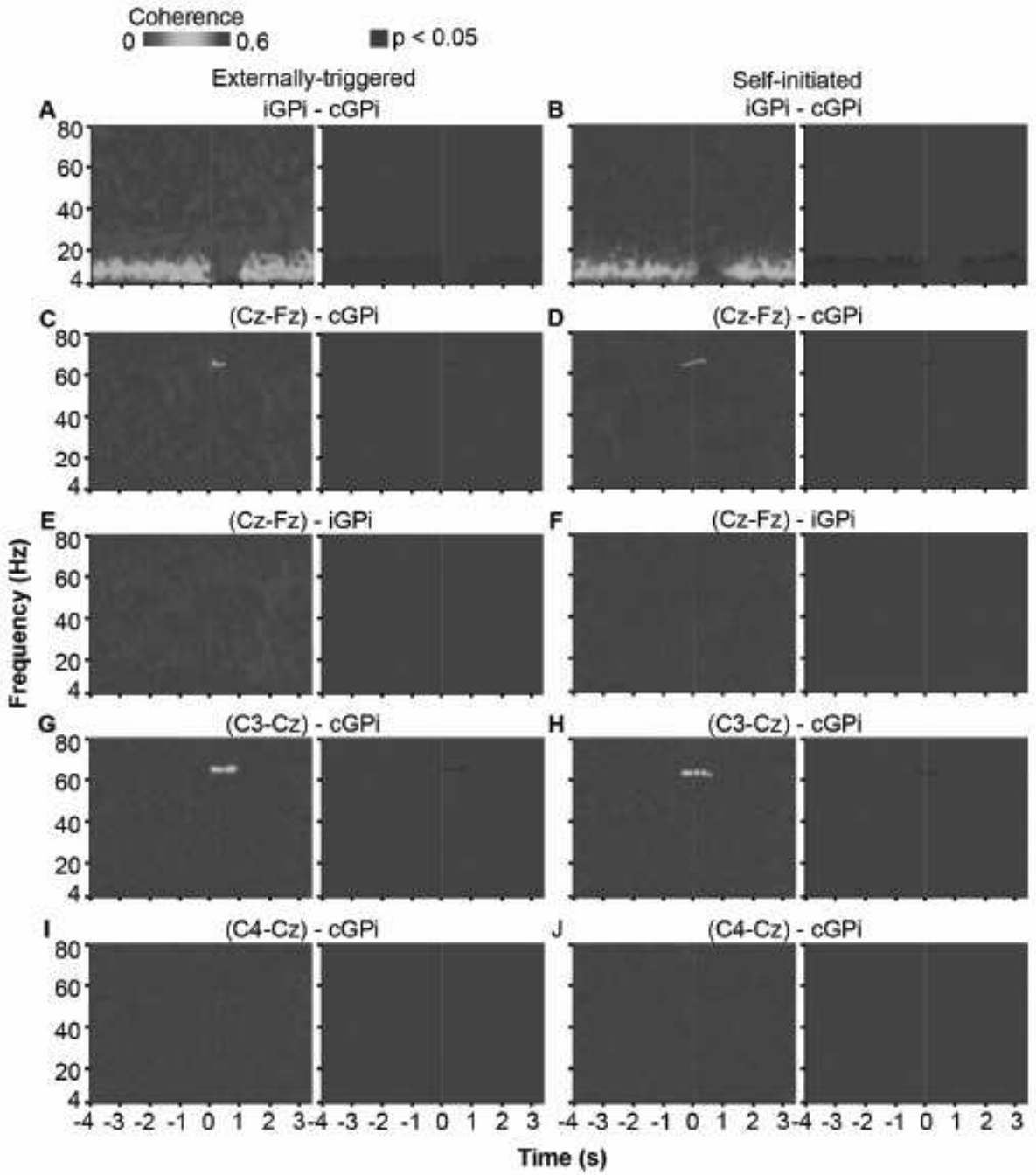




Recording from GPi in patients with cervical dystonia

- Event-related beta desynchronization and gamma synchronization before and after self-paced movements
- Beta changes are bilateral, gamma changes are strictly contralateral

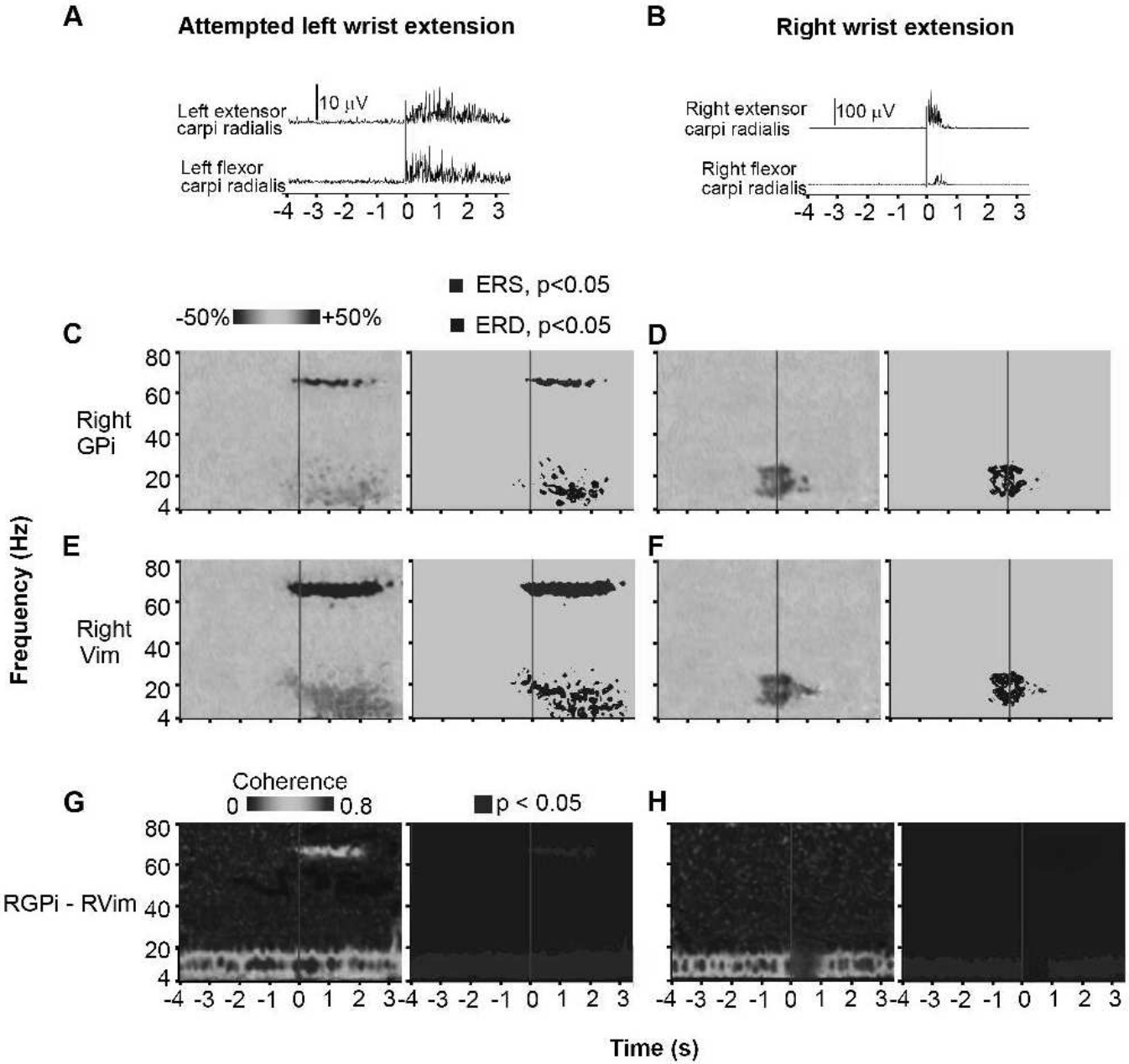
Tsang et al, J Neurol Neurosurg Psychiatry 2012



Recording from GPi in patients with cervical dystonia

- Resting coherence between bilateral GPi that attenuates with movement
- Gamma coherence between cortex and GPi, strictly contralateral

Tsang et al, J Neurol Neurosurg Psychiatry 2012



Prominent 5-18Hz oscillation in the pallidal thalamic circuit in secondary dystonia

Tsang et al. Neurology 2012

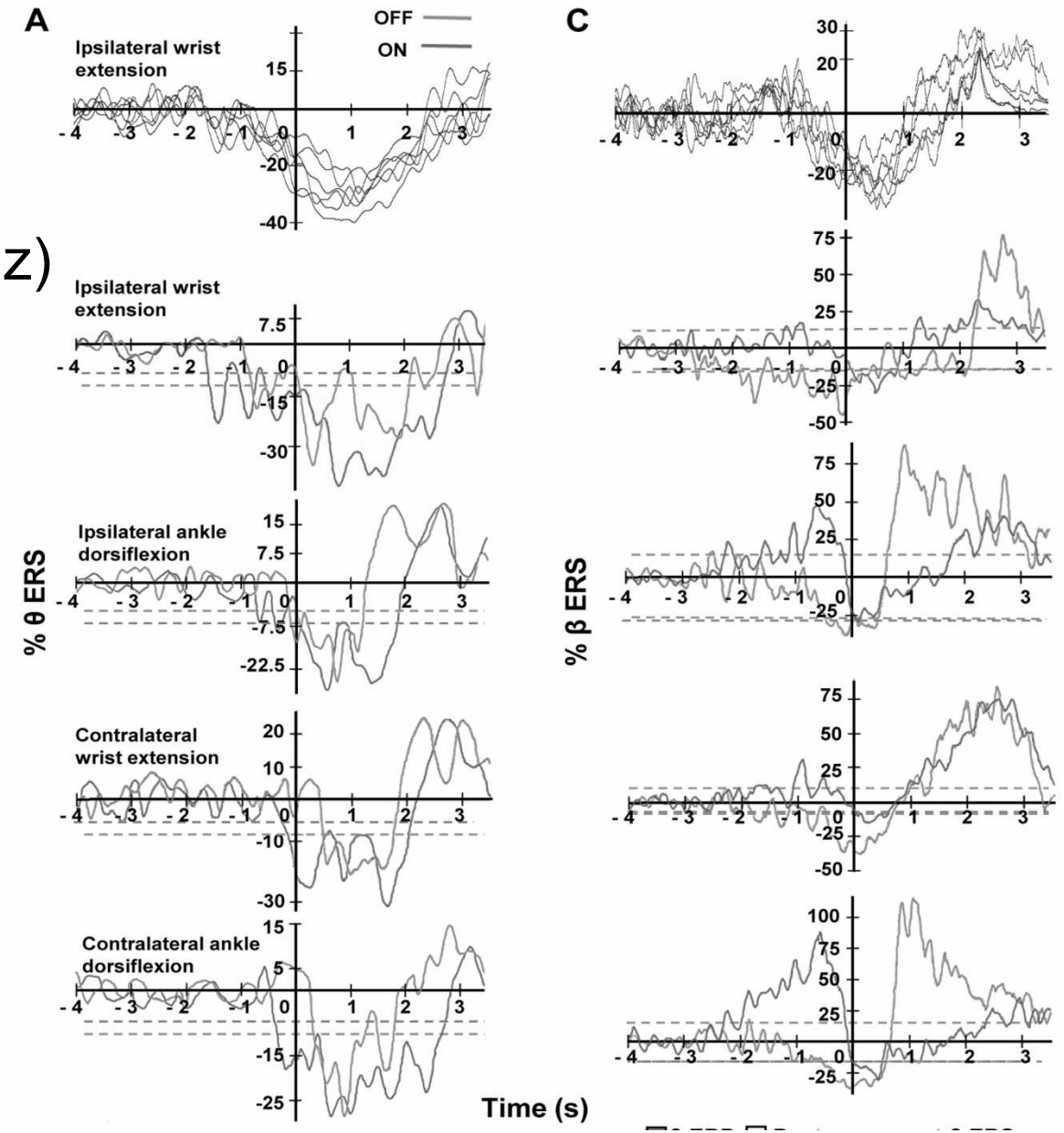
Changes in GPi oscillations in voluntary movements

- Beta frequency decrease bilaterally in the GPi with preparation and execution of voluntary movements may reflect general motor planning and execution
- A sharply tuned strictly contralateral gamma oscillation (64-68 Hz) increase with preparation and execution of voluntary movements. Coherent with motor cortical areas. May be more specific and represent communication between cortex and basal ganglia
- 5-18 Hz resting coherence between bilateral GPi may be related to dystonia

Tsang et al, J Neurol Neurosurg Psychiatry 2012,
Tsang et al, Neurology, 2012

PPN - ERD and ERS with self-paced movements

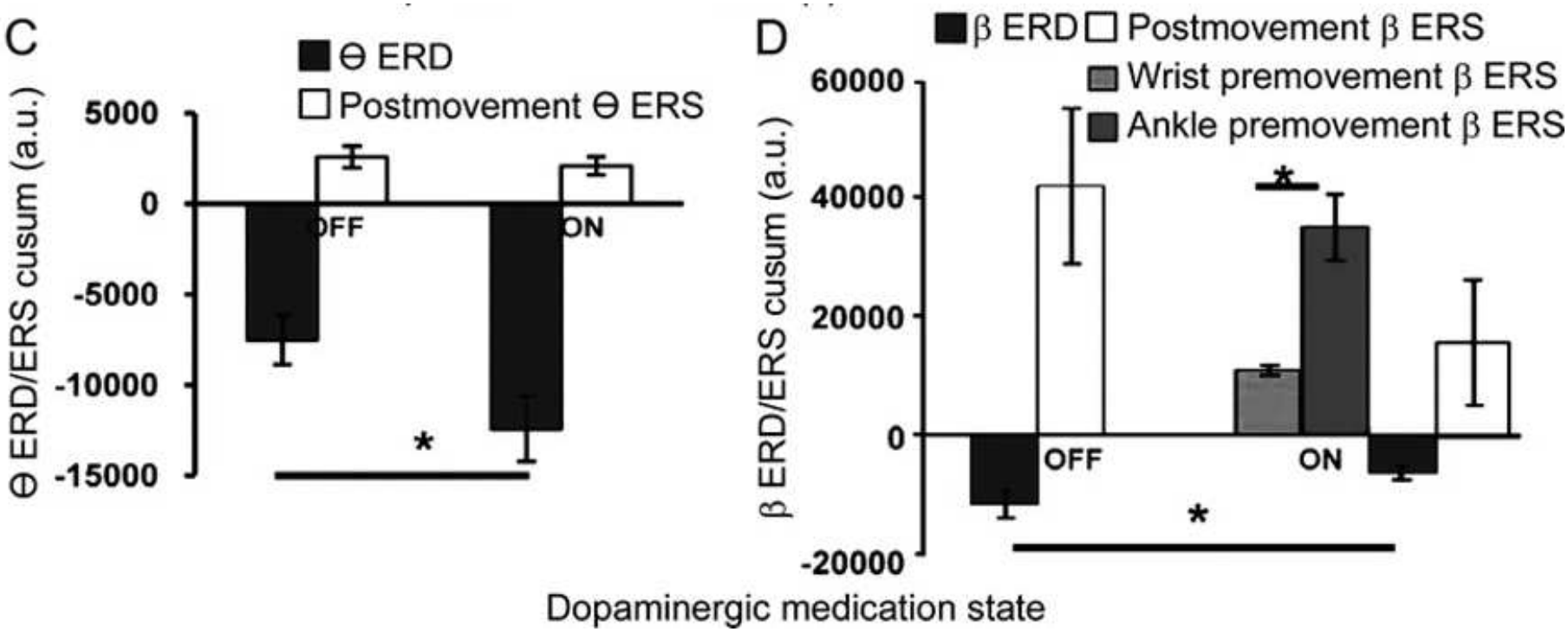
Theta
(6-10 Hz)



Beta
(14-30 Hz)

Tsang et al.
Neurology
2010

PPN - ERD and ERS with self-paced movements



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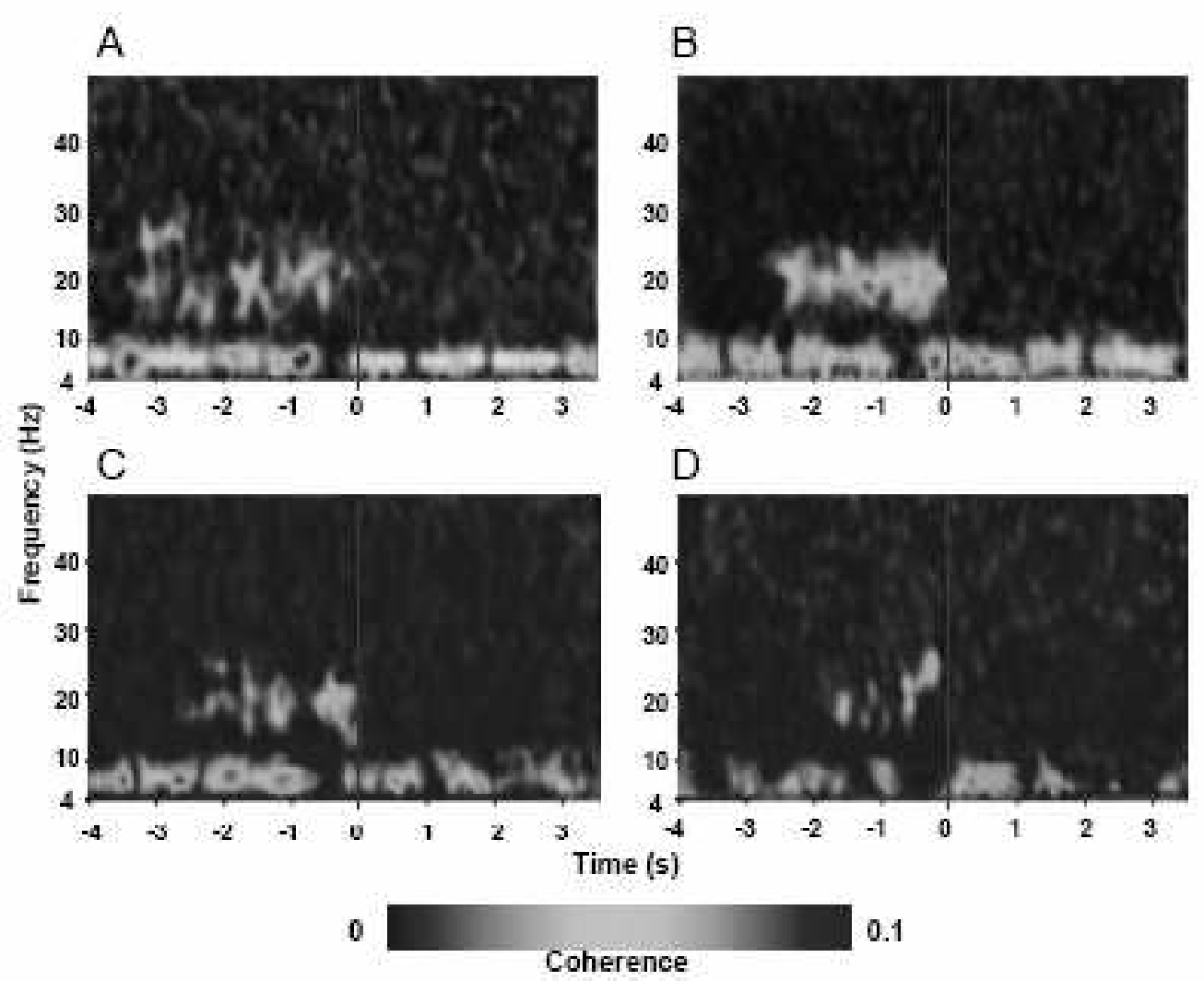
Cortex - PPN coherence: only in ON state

Wrist extension

Ankle dorsiflexion

Ipsilateral sensorimotor (C3-CP3/C4-CP4)

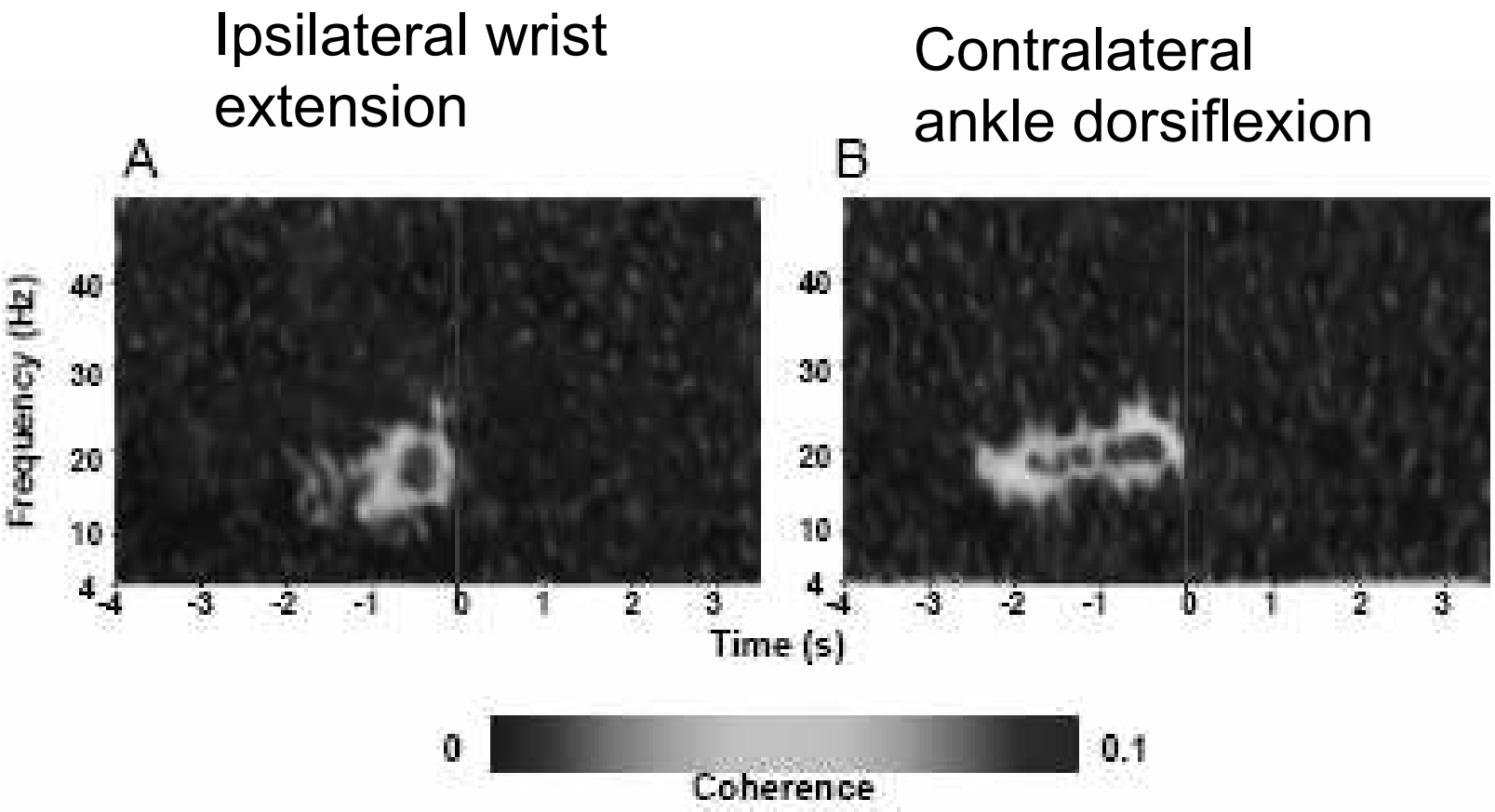
Contralateral sensorimotor



Tsang et al. Neurology 2010

Cortex - PPN coherence: only in ON state

Midline frontal Cz-Fz (SMA)



Tsang et al. Neurology 2010

Role of the PPN in voluntary movements

- PPN is involved in the preparation and execution of voluntary movements
- The involvement is bilateral
- Coherence studies showed that dopaminergic medications promote the interaction between cortex and PPN

Tsang et al Neurology 2010

Role of the PPN in voluntary movements

- The role of beta oscillations in PPN may be different from that in the basal ganglia
  - In the ON state, beta oscillations increase just prior to movement rather than decrease as seen in STN, GPi or thalamus
  - Interaction (coherence) between cortex in beta range, especially SMA and PPN just prior to movement, but not in execution phase
- Beta oscillations in PPN may not be antikinetic
- May explain why PPN stimulation is usually at lower frequencies (20 to 50 Hz)

Tsang et al Neurology 2010

STN DBS at individualized gamma frequencies for Parkinson's disease

- It has been proposed that β oscillations in the basal ganglia is antikinetic and γ oscillation is prokinetic, and deep brain stimulation (DBS) may work by imposing a desirable frequency in the basal ganglia-cortical circuits.
- The precise frequency peaks varied considerably from patient to patient.

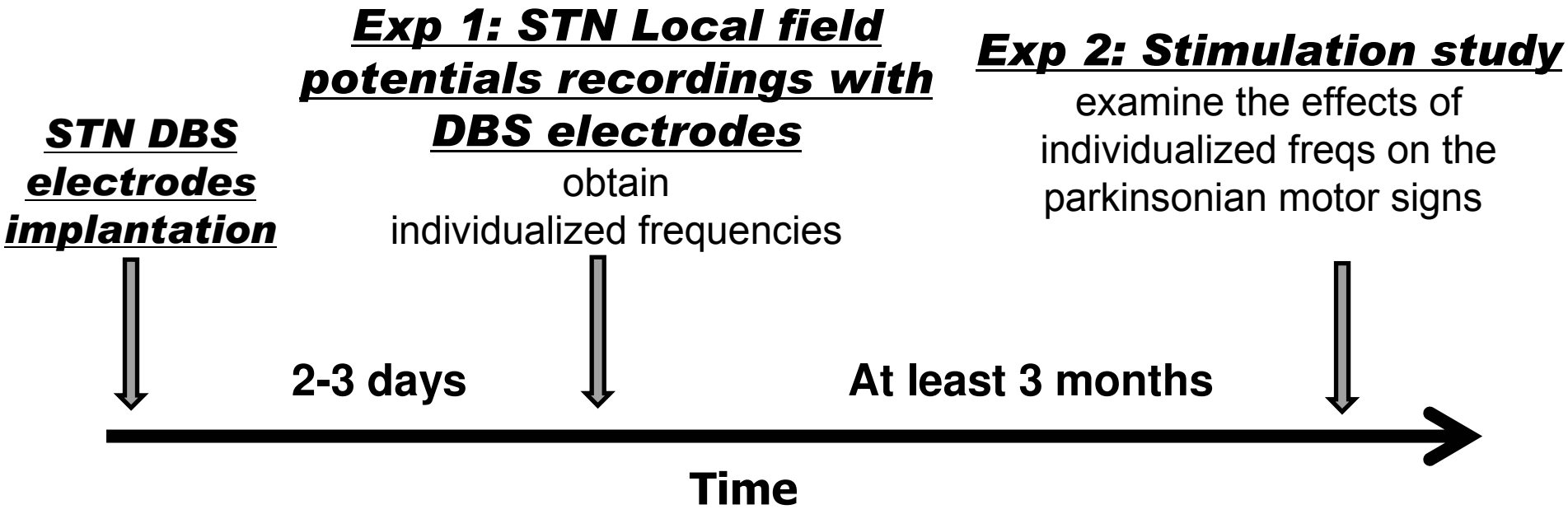
Purpose of the study

- To test the oscillation model of the basal ganglia by studying the effects of DBS at individually established peak freqs in the θ, β, and γ freq bands recorded from the STN on PD motor signs.

Tsang et al. Neurology, 2012

Methods

- 13 advanced PD patients, 10 men & 3 women
- Age: (mean ± SD) 61 ± 4.5 years
- Time since diagnoses: 14.6 ± 3 years

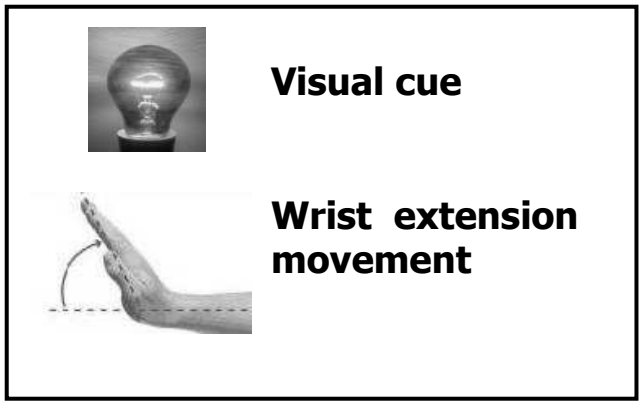


Tsang et al. Neurology, 2012

Movement Paradigm

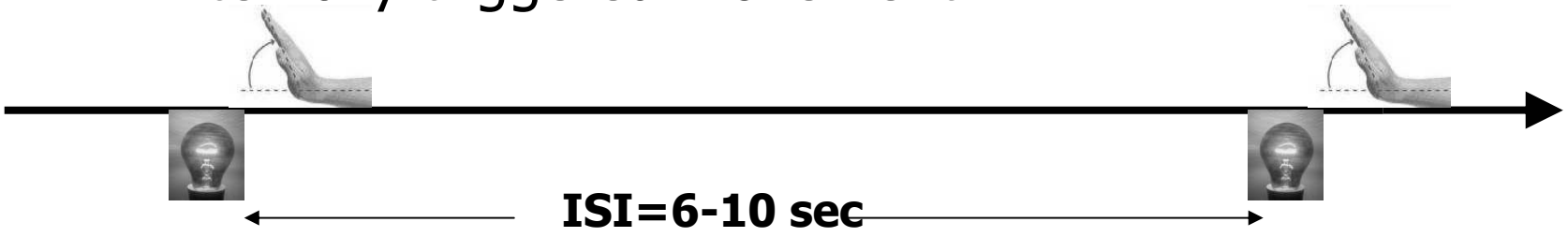
OFF and then ON (usual dose) dopaminergic medications

1. Baseline recording (Rest) ~2min



Two Tasks of Wrist Extension

2. Externally triggered movement



3. Self initiated movement

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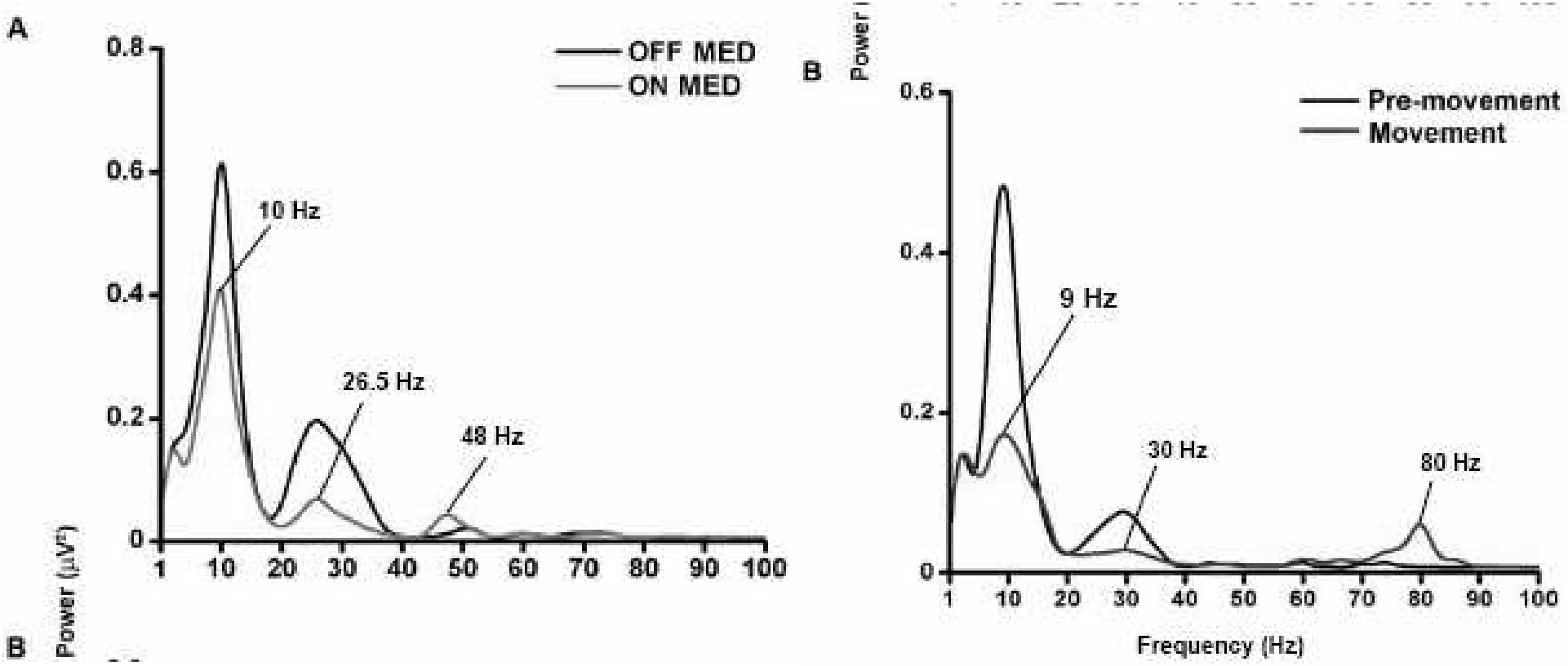
Example of individualized frequencies

Medication (MED)

Movement (MOVE)



Tsang et al. Neurology, 2012

Experiment 2: Stimulation study

- At least 3 months after DBS electrodes implantation.

8 stimulation conditions:

(1 and 2) Individualized θ freqs (4- 10Hz) showing greatest reduction with medication (MED) and movement (MOVE)

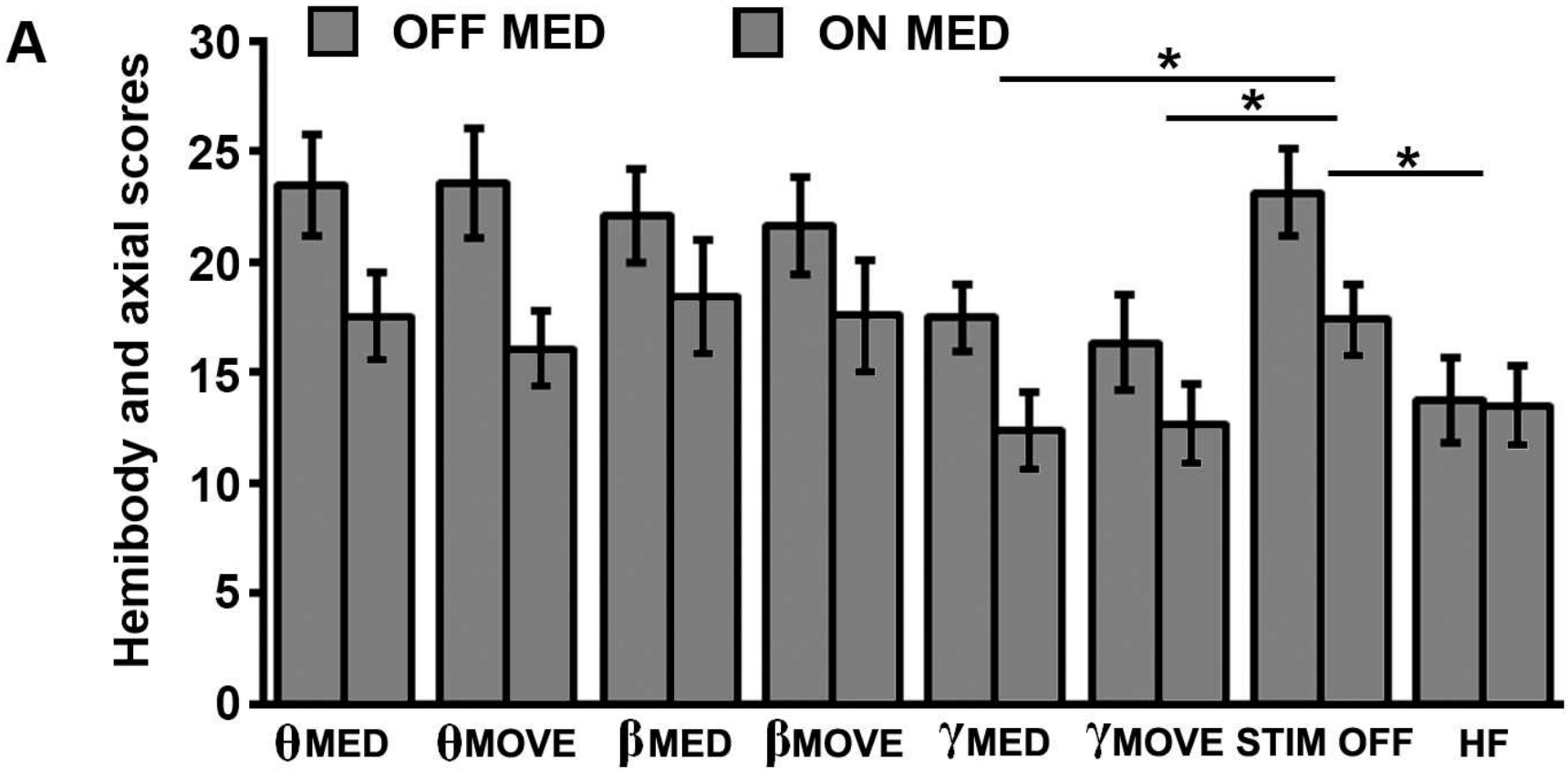
(3 and 4) Individualized β freqs (11-30Hz) showing greatest reduction with medication (MED) and movement (MOVE)

(5 and 6) Individualized γ freqs (31-100Hz) showing greatest increase with medication (MED) and movement (MOVE)

7. OFF

8. Clinical high freqs (130-185Hz)
Each condition applied for 15 min. ON and OFF med on separate days in random order

Stimulation study: Results

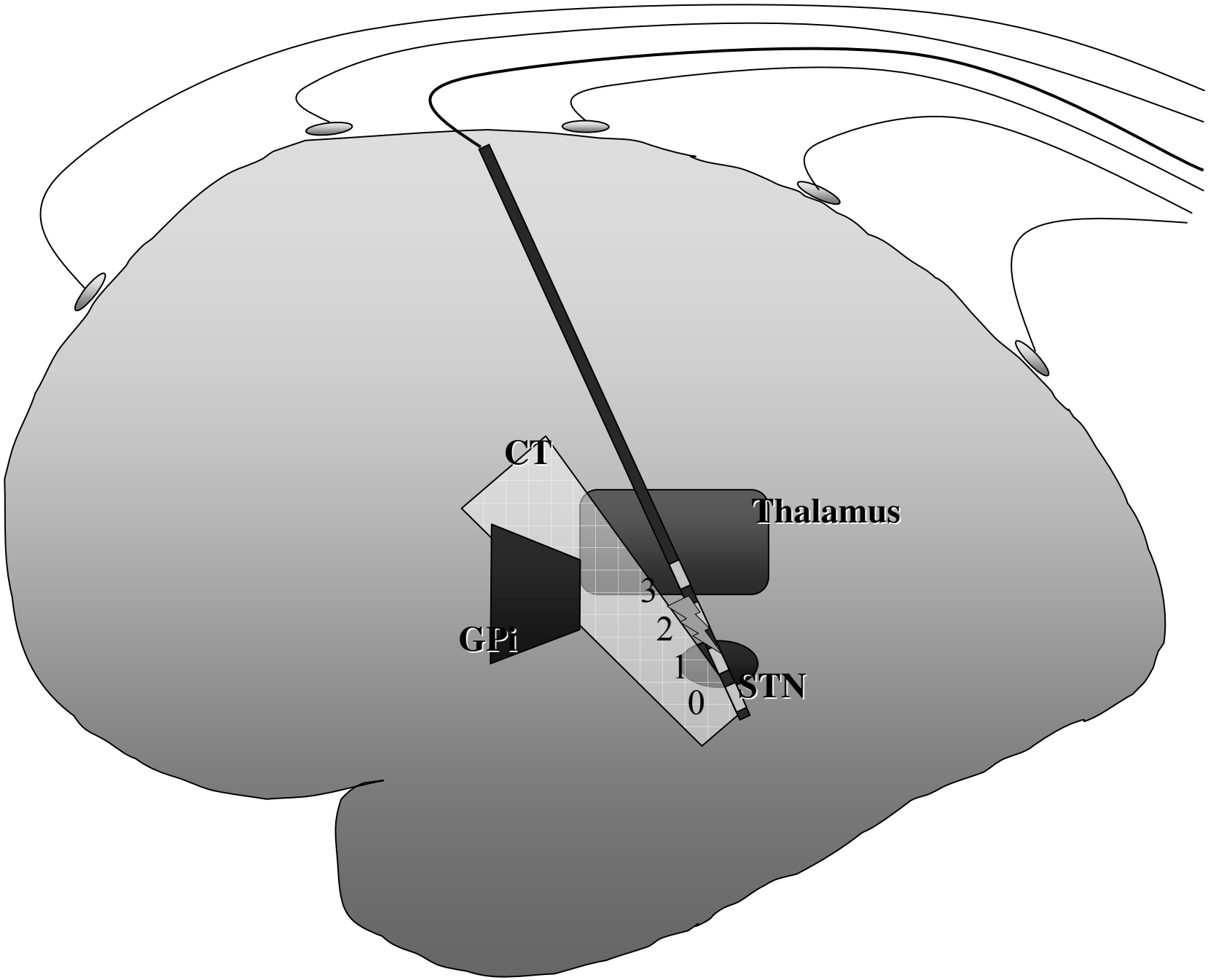


Tsang et al. Neurology, 2012

Time course of cortical activation following STN stimulation

- 8 patients with chronically implanted bilateral STN DBS
- Experiment 1: Cortical evoked potentials from STN stimulation
  - DBS changed to 10 Hz, all adjacent bipolar montages (-0+1, -1+2, -2+3, +2,-3) tested
  - ~ 1,800 epochs averaged

Kuriakose et al Cerebral Cortex 2010


CT
Thalamus
GPi
STN
3
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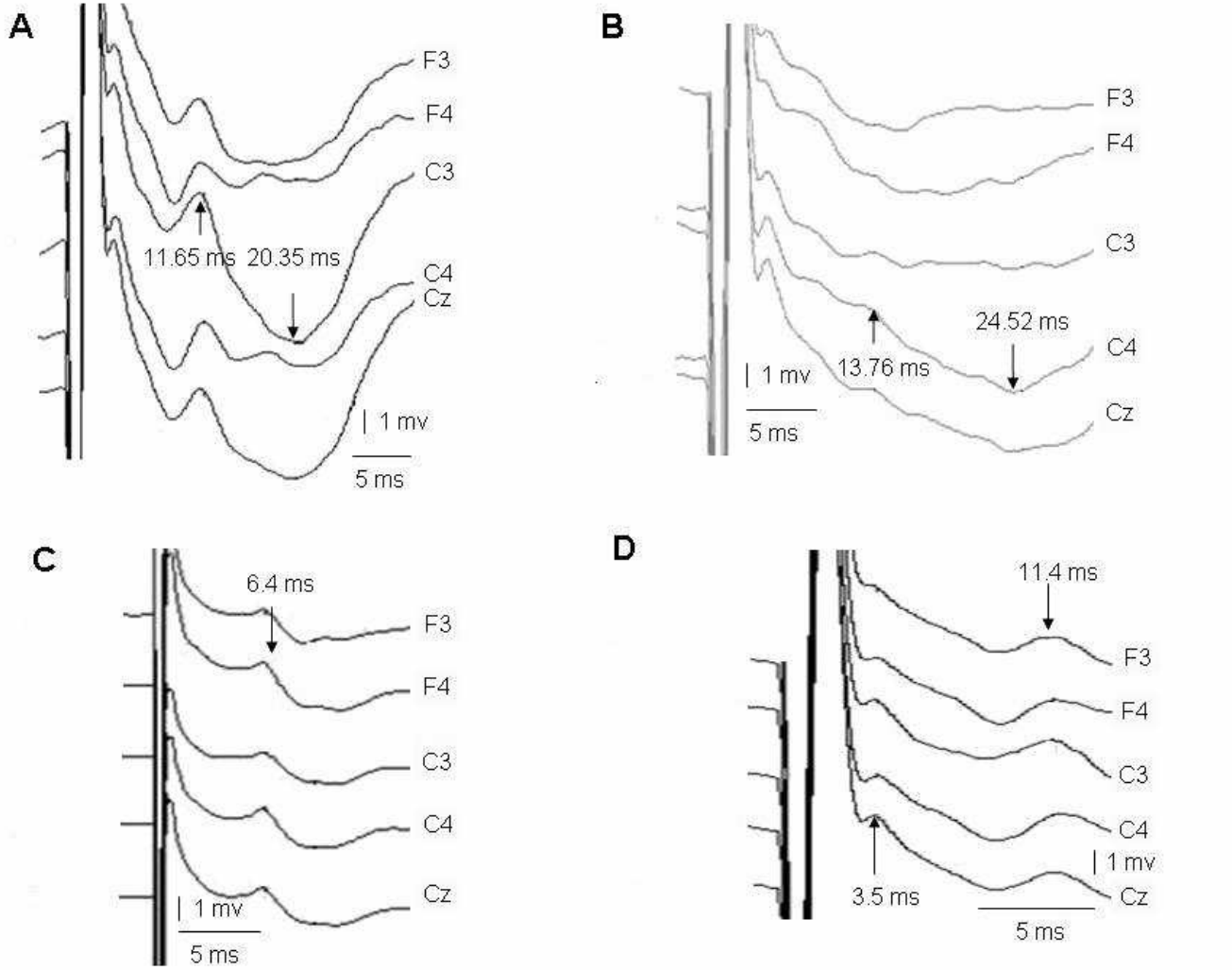
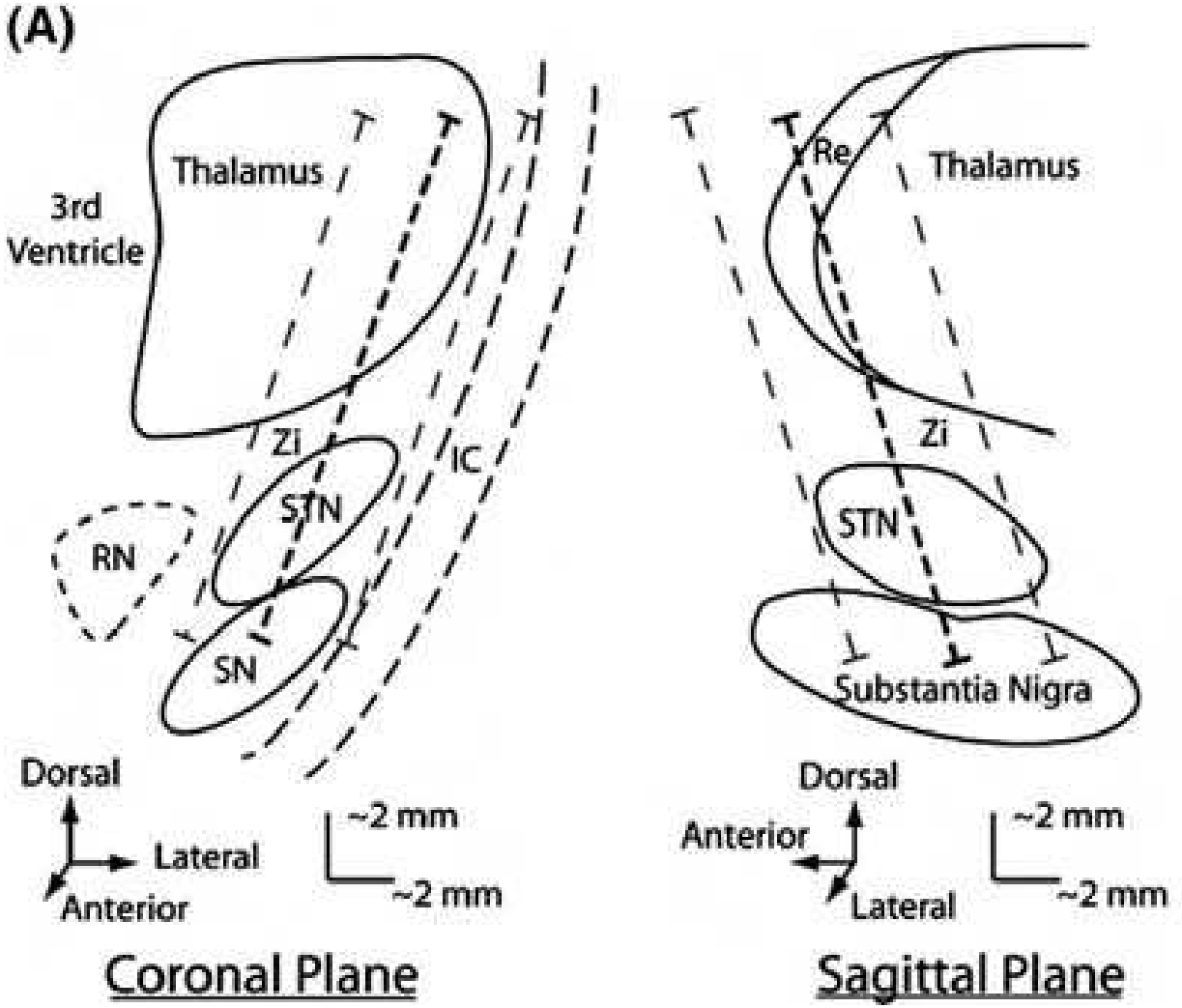
1
0

Evoked potentials from STN DBS



Kuriakose et al Cerebral Cortex 2010

Location of electrode contacts



Kuriakose et al Cerebral Cortex 2010

Evoked potentials from STN DBS

- Medium latency potential
  - Most consistent and largest amplitude, recorded in 7/8 patients
  - Mean onset latency 12.8 ms, peak 18.9 ms
  - Arise from stimulation of ZI-thal or STN-ZI area, not from stimulation of STN proper or SNr
  - Elicited from clinically used contact in 11/16 sides (1 patient (2 sides) had no contact in the STN area, 1 contact was in the thalamus)
- Short latency potentials
  - Mean onset latency 3.7 ms from 5/16 sides
  - Mean onset latency 7.4 ms from 6/16 sides
  - Elicited from contacts in ZI, STN and SN areas

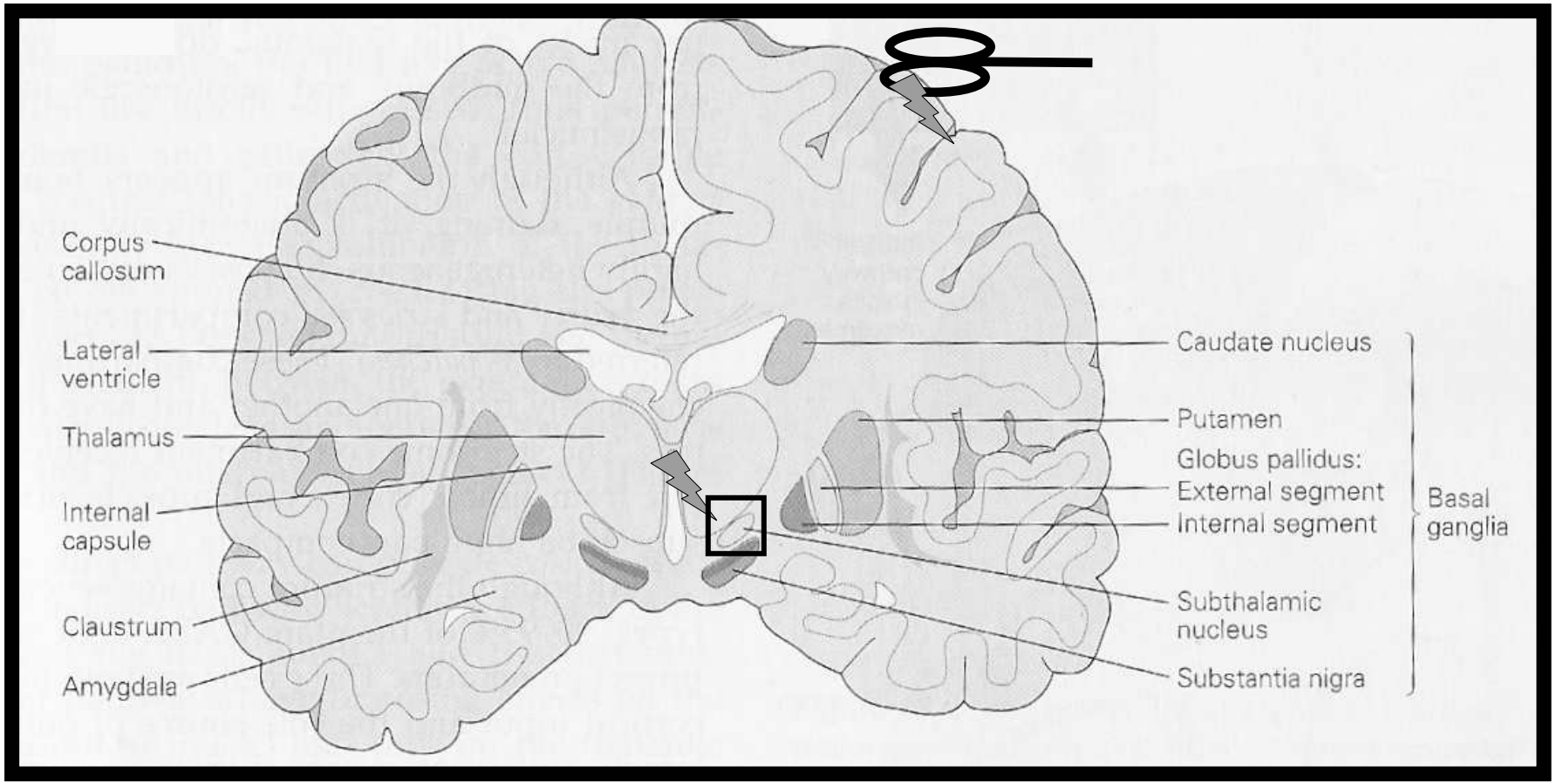
Kuriakose et al Cerebral Cortex 2010

Time course of cortical activation following STN stimulation

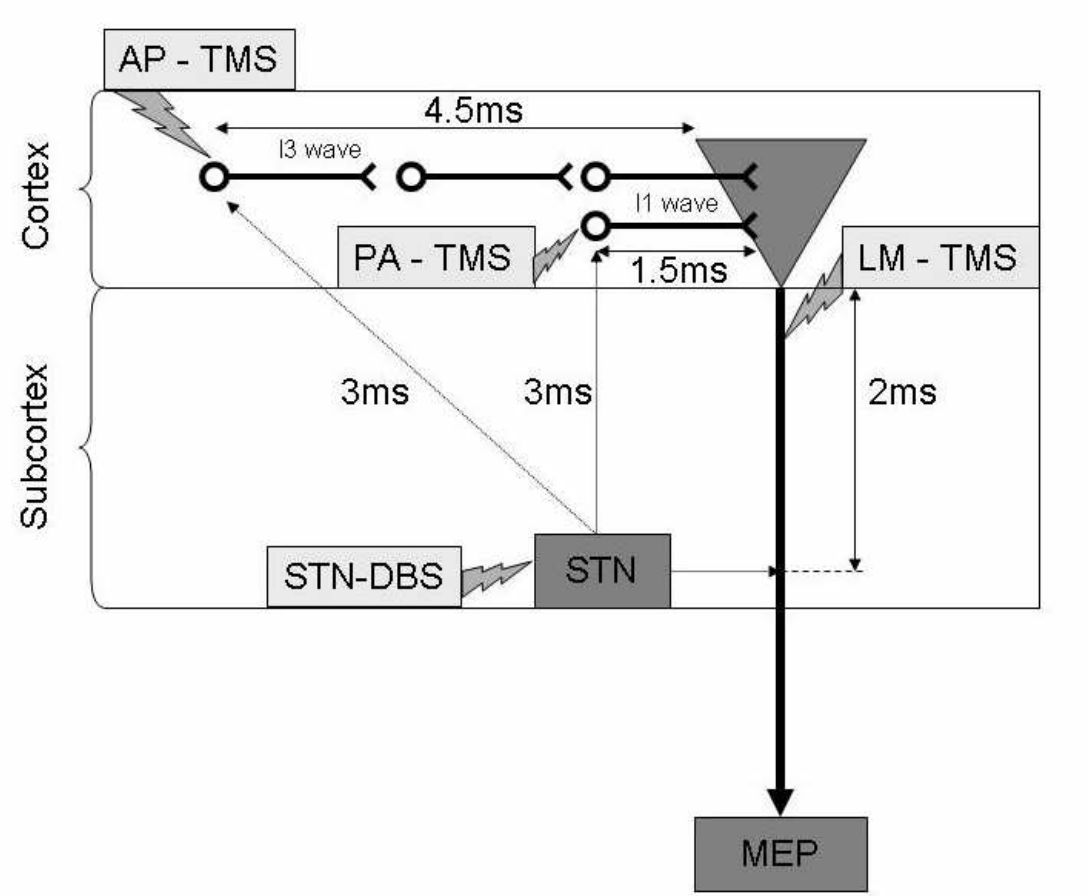
- 7 patients with chronically implanted bilateral STN DBS
- Experiment 2: Time course of cortical facilitation after STN DBS
  - Clinically used monopolar contacts used
  - DBS voltage set at 0.5 V below threshold for spread to corticospinal tract
  - TMS delivered at 2 -15 ms, EP-2, EP and EP+2 ms after STN DBS
  - TMS tested in 3 different directions: induced current anterior-posterior (AP), posterior-anterior (PA) and medial lateral (LM)

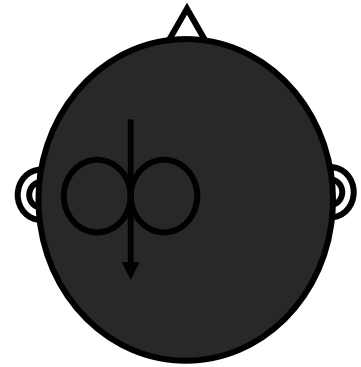
Kuriakose et al Cerebral Cortex 2010

Experimental setup

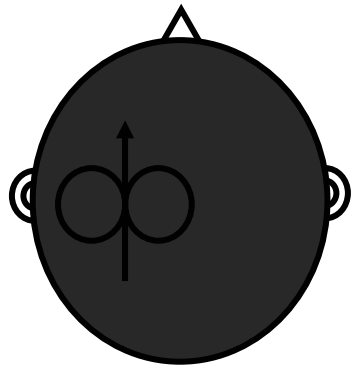


Use of different TMS current directions

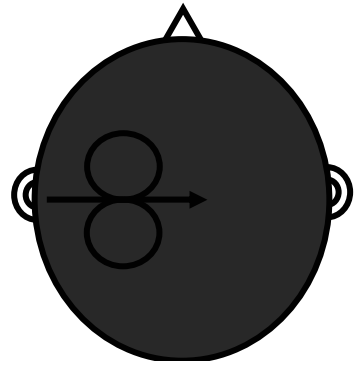




AP

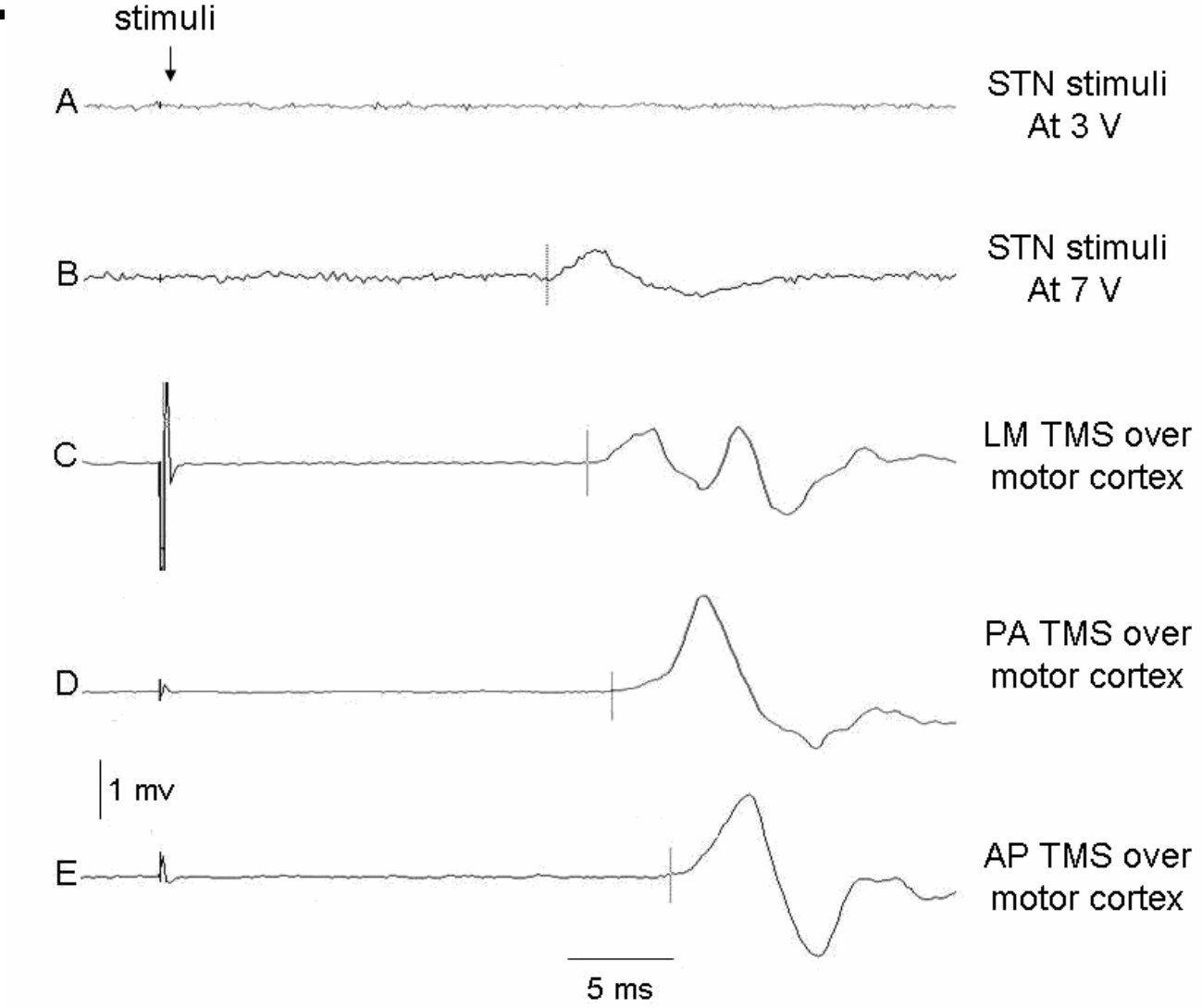


PA



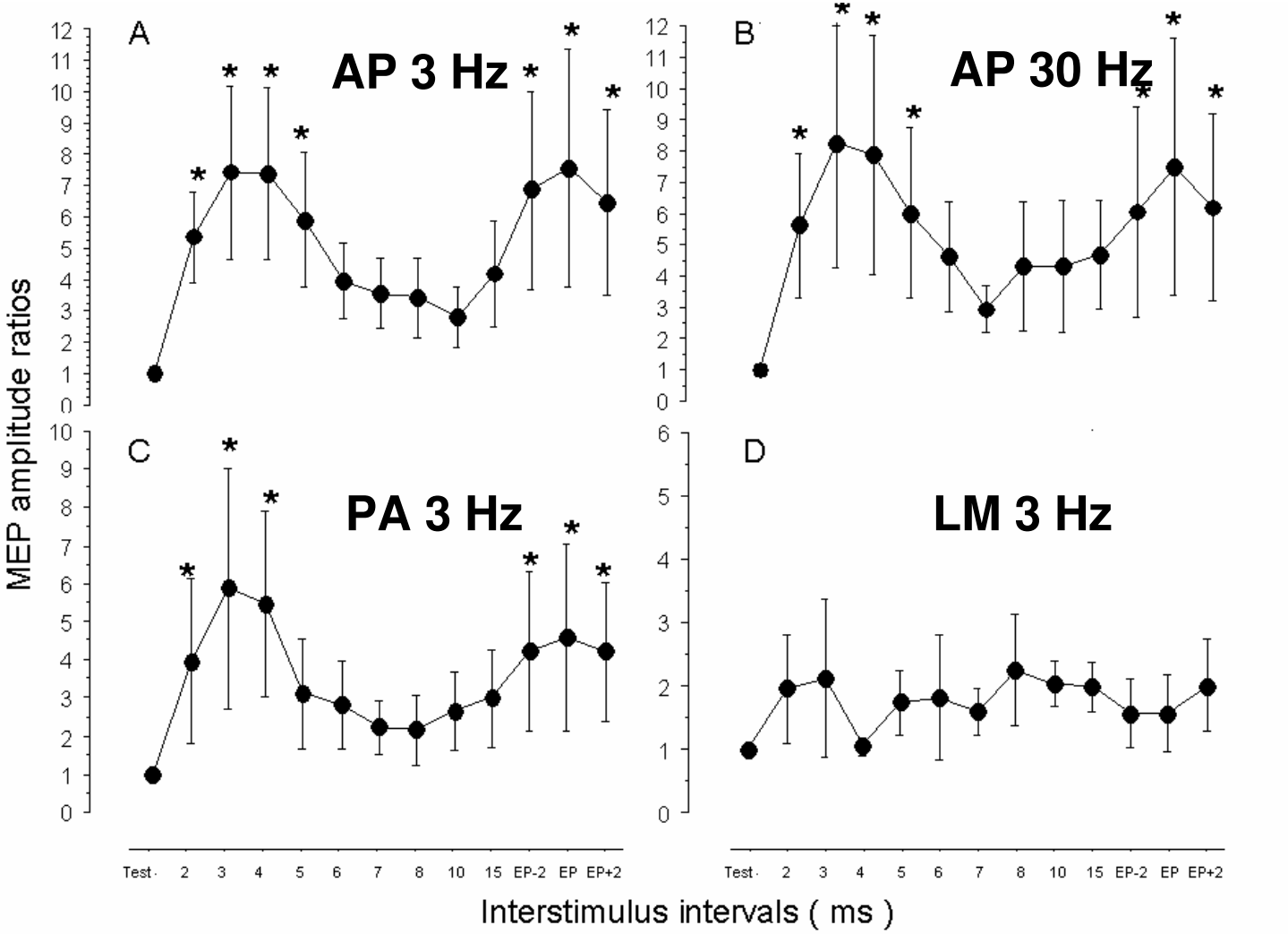
LM

Motor-evoked potentials from different stimulation sites



Kuriakose et al Cerebral Cortex 2010

Time course of motor cortex facilitation after STN DBS



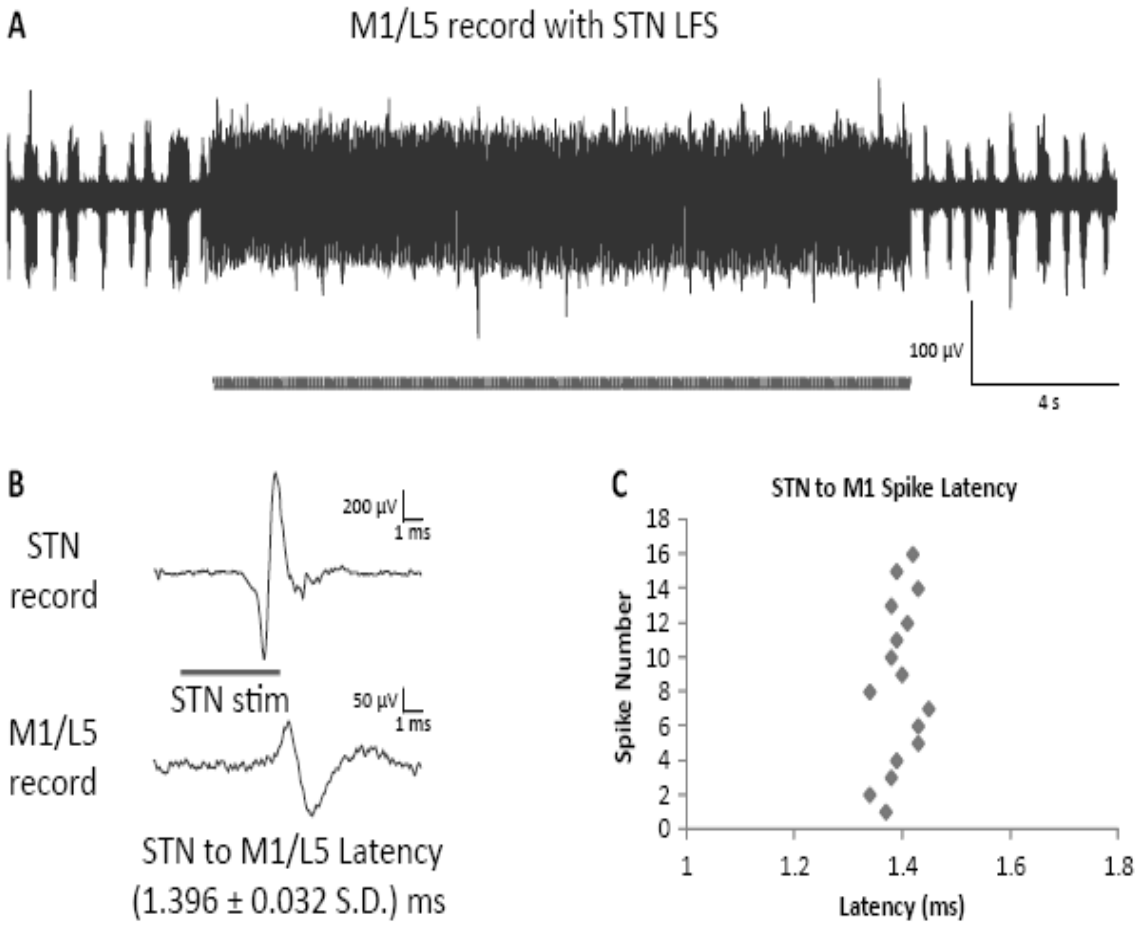
Kuriakose et al Cerebral Cortex 2010

Time course of cortical activation following STN stimulation

- Facilitation likely occurred at the cortex since MEPs from LM TMS were not facilitated
- Significant motor cortical facilitation at ~ 3 ms (2-5 ms) and at medium latency evoked potential (~ 20 ms)
- Consistent with optogenetic study that activation of STN afferent improve motor symptoms in 6-OHDA and activates layer V of M1 (Gardinaru et al, Science 2009)

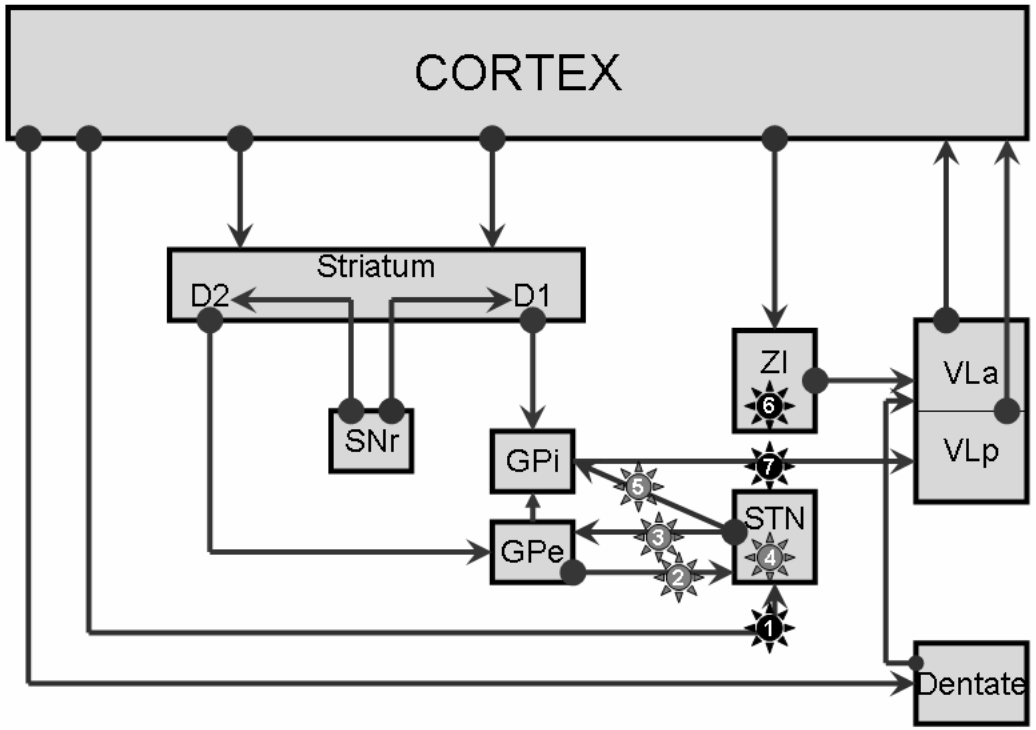
Kuriakose et al, Cerebral Cortex 2010

Stimulation of STN afferents activates M1



Gradinaru, et al., Science 2009

Possible pathways involved



Kuriakose et al, Cerebral Cortex 2010

Time course of cortical activation following STN stimulation

- Specific evoked potentials can be obtained from STN DBS and is related to the region stimulated
- The short and medium latency evoked potentials are associated with increased cortical excitability
- Increased cortical excitability may be one of the mechanism of action of STN DBS as demonstrated in animal studies

Kuriakose et al, Cerebral Cortex 2010

Induction of plasticity by pairing STN DBS and TMS

Hypothesis: Repeated, synchronous activation of M1 by STN-DBS and TMS at short (~3 ms) and medium (~23 ms) ISI will induce LTP-like effects

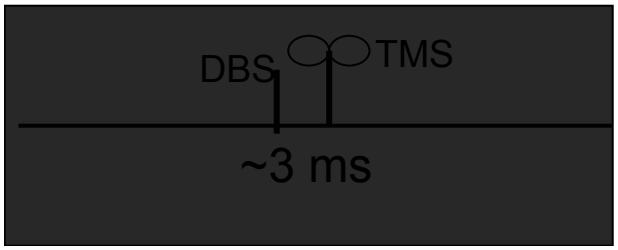
Induction of plasticity by pairing STN DBS and TMS

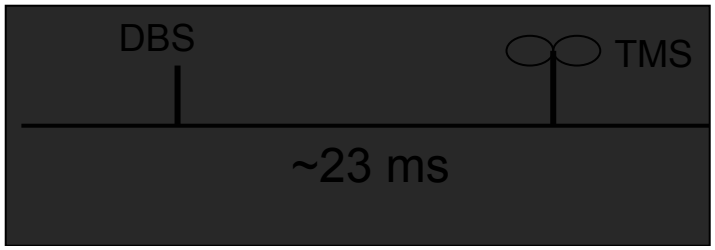
- 5 PD patients (Age: 54-64y, H&Y: 2-3) with bilateral STN-DBS for >1 y and studied in the on med state

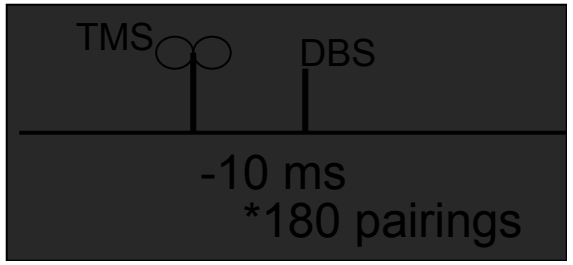
Short ISI (~3 ms)

Medium ISI (~23 ms)

Reversal short ISI M1-TMS 10 ms prior to STN-DBS

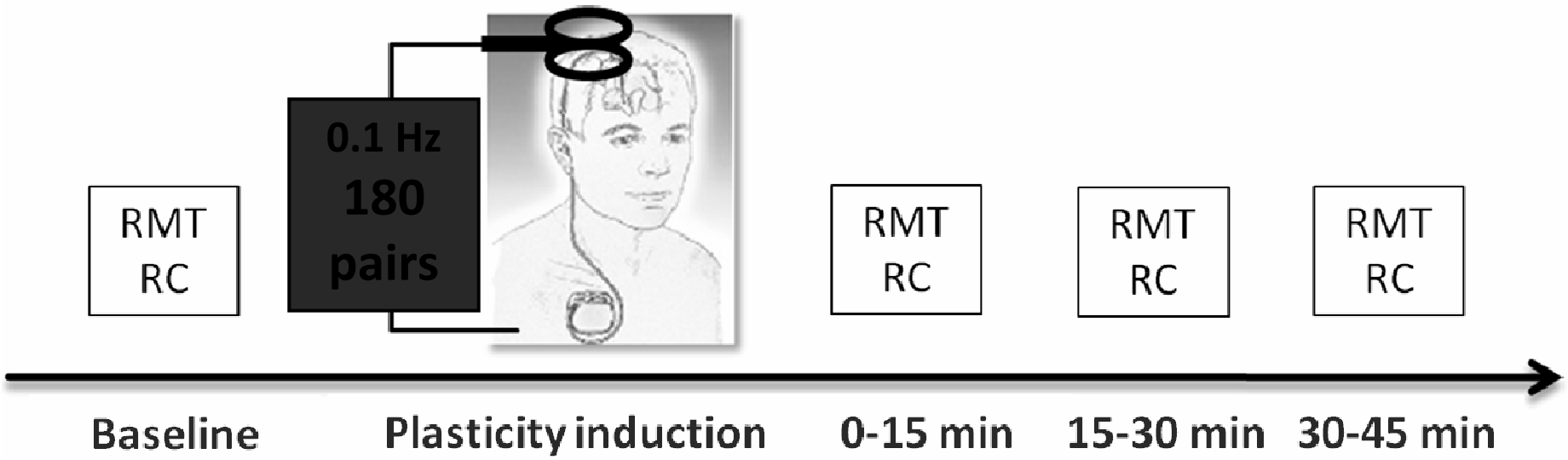




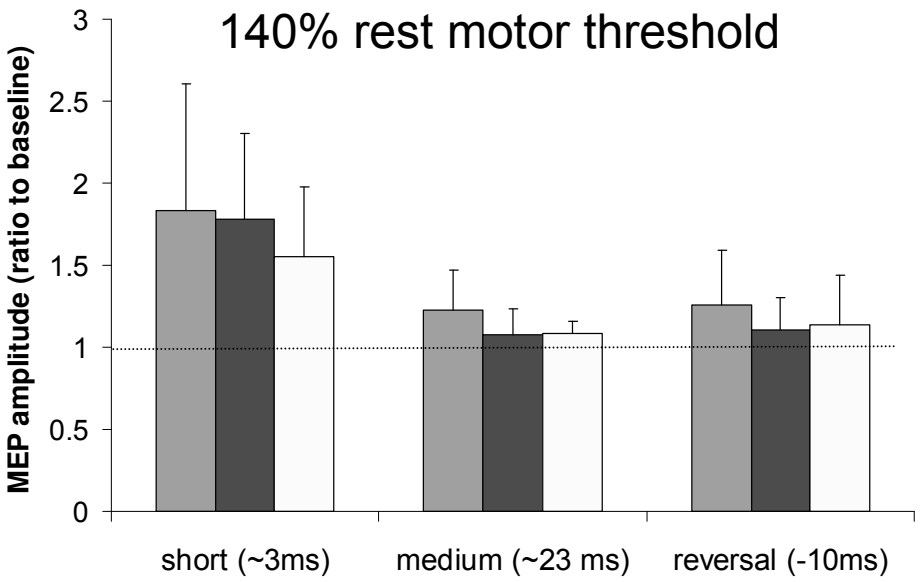


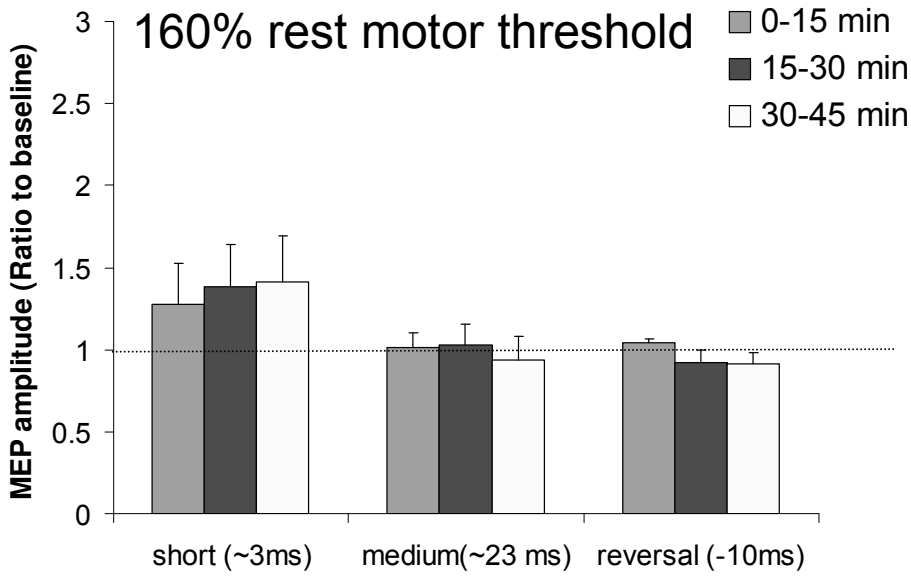
Study design

- Patients studied in three separate sessions at least one week apart
- Motor cortical excitability parameters (measured before/after plasticity protocol)
  - Rest motor threshold (RMT)
  - Recruitment curve (RC): MEP in response to increasing TMS intensities (100-160% RMT)



MEP amplitude ratios at higher intensities





Induction of cortical plasticity by STN DBS and TMS

- The time between TMS and DBS is crucial (3 ms in our study) for the induction of associative plasticity

- We induced associative plasticity in the M1 by repeated pairing of TMS and antidromic activation of the cortico-subthalamic pathway

Mechanism of action of DBS

Questions

- Inhibition or facilitation of the target area?
- What is the influence of DBS on cortical areas?

Approach

- Stimulate the basal ganglia and determine its effect on the target area

How does DBS work?

Silencing of activity of target area

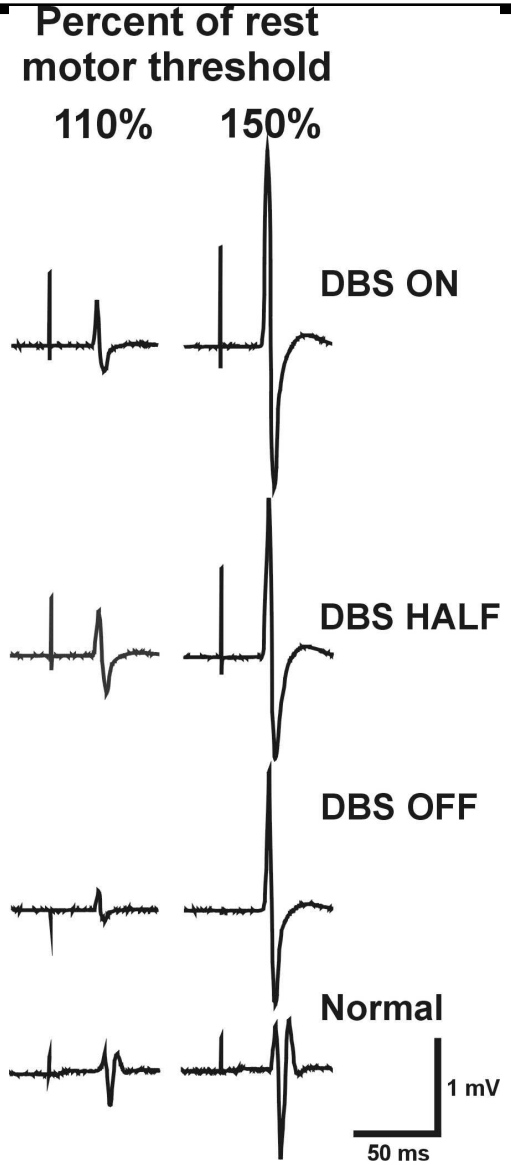
- Depolarizing block
- Neuronal energy depletion
- Synaptic failure
- Activating inhibitory neurotransmission

Generation of a new pattern of activity

- Activating target area
- Anterograde effects
- Retrograde effects

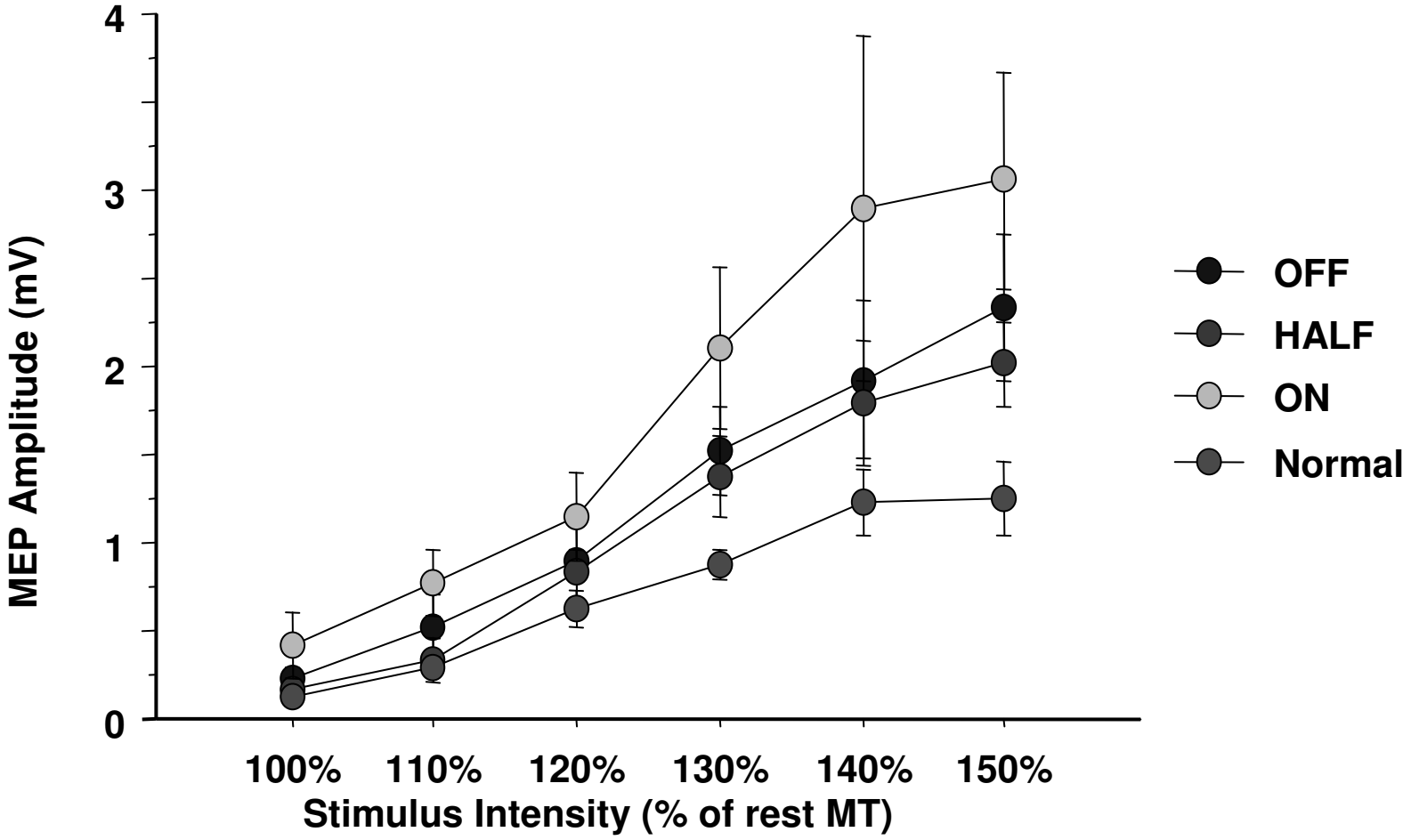
Effects of thalamic deep brain stimulation on motor cortex excitability

VIM stimulation increases motor cortex excitability



Molnar et al. Neurology, 2005

VIM stimulation increases motor cortex excitability



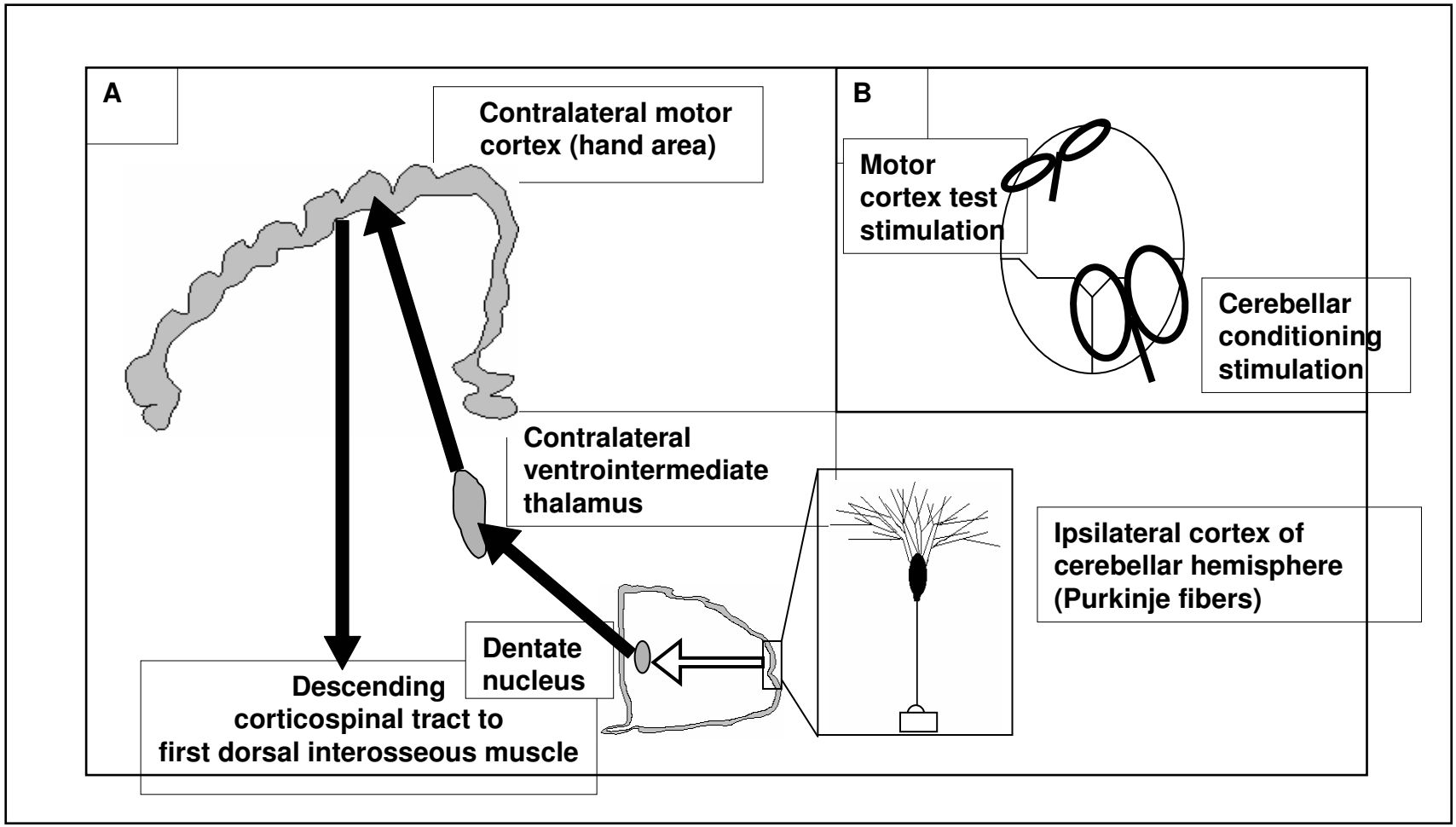
Molnar et al. Neurology, 2005

VIM stimulation increases motor cortex excitability

- Consistent with DBS activating the target area

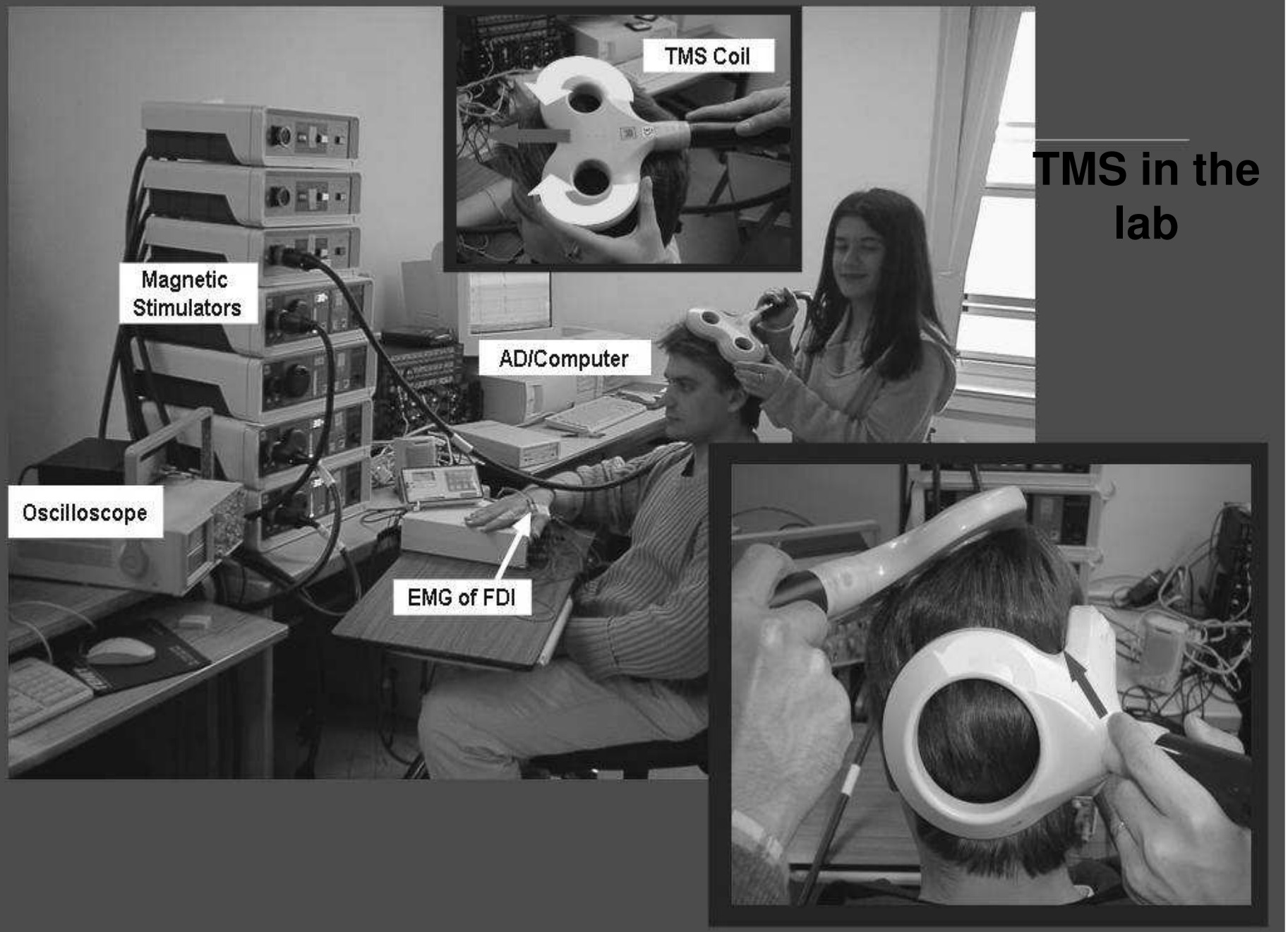
Molnar et al. Neurology, 2005

Testing the cerebellothalamocortical pathway by TMS



Pinto & Chen, Exp Brain Res, 2001

TMS in the lab

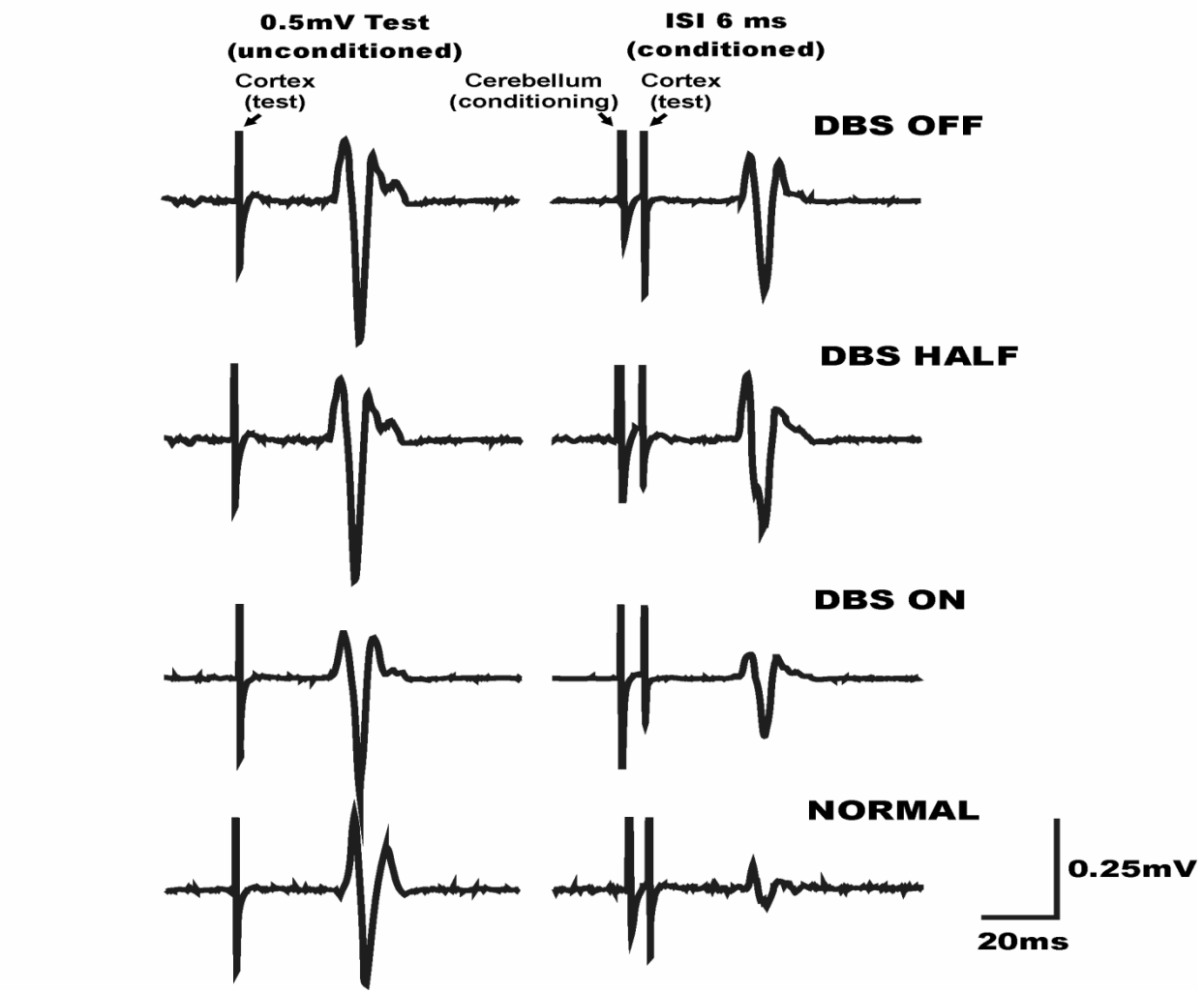


Effect of VIM stimulation on the cerebellothalamocortical pathway

- 6 patient with VIM stimulators for essential tremor
- 3 conditions studied in random order: stimulator ON, half frequency (HALF) and OFF
- CTC pathway tested with conditioning stimulation of the cerebellum followed by test stimulation of the motor cortex

Molnar et al, Neurology 2004, 63: 907-909

Effect of VIM stimulation on the cerebellothalamocortical pathway



Molnar et al, Neurology 2004, 63: 907-909

Effect of VIM stimulation on the cerebellothalamocortical pathway

- Effective thalamic DBS facilitates rather block the CTC pathway
- Thalamic DBS may not work by "blocking" the target area
- Mechanism of action of lesioning and DBS are different
- Consistent with some animal work and activation of SMA with VIM DBS from PET studies

Summary

- STN, GPi (basal ganglia), VIM (cerebellum - thalamocortical circuit) and PPN are involved early in the preparation of ipsilateral and contralateral movements

- The changes beta oscillations in the PPN with movement appear different from the basal ganglia and may not be antikinetic

Summary

- DBS may activate rather than block the target area
- STN DBS activates the motor cortex at specific time intervals that coincides with the peaks of evoked potentials, and may be one of the mechanisms of action of STN DBS

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