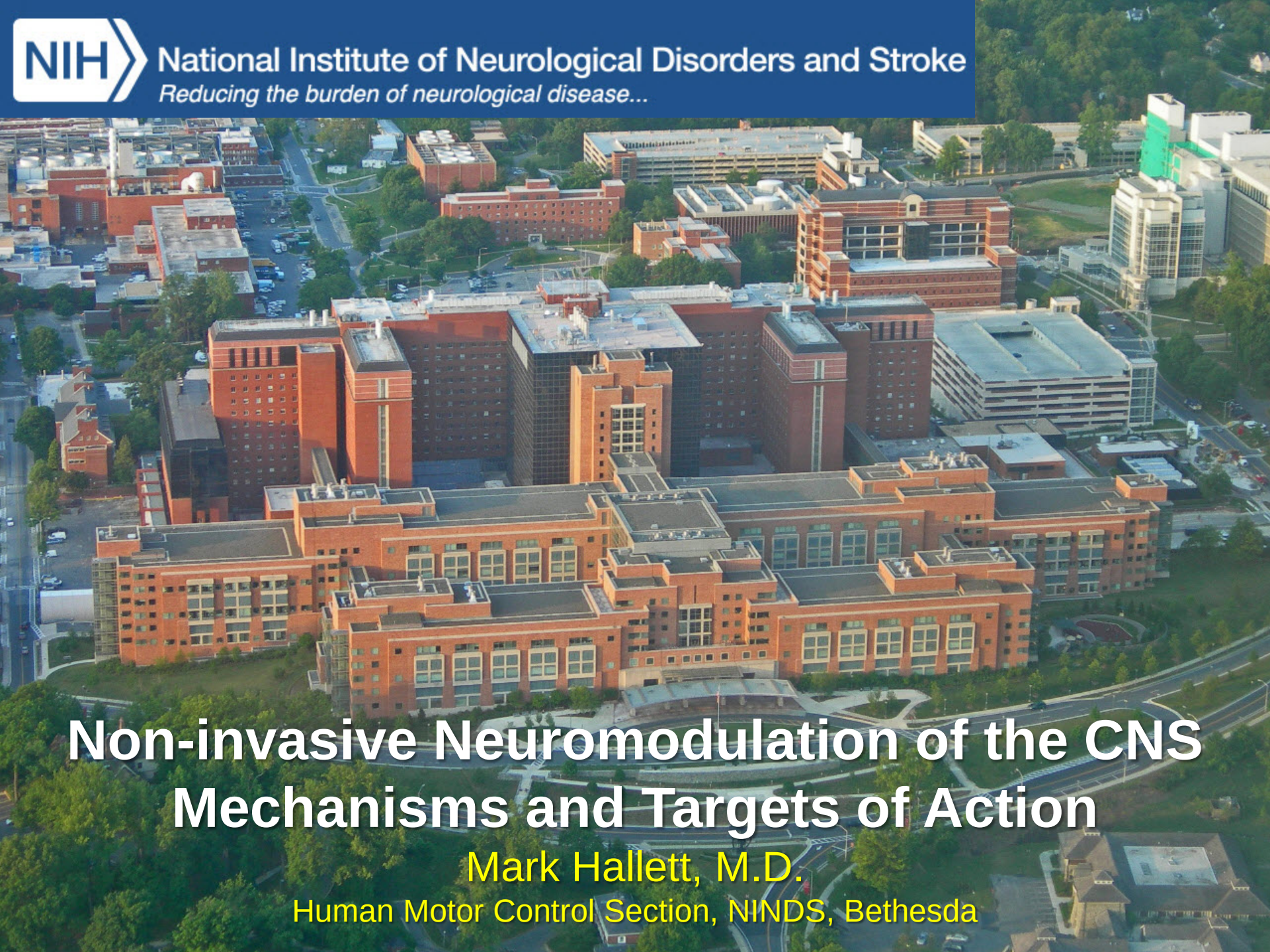

Non-invasive Neuromodulation of the CNS Mechanisms and Targets of Action

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Conflicts of Interest

- NIH holds the patent for the H-coil and I am one of the co-inventors; Brainsway has licensed the H-coil, and this is now FDA approved for the treatment of depression

History of Neuromodulation

- In ancient times, the electric fish was used to treat pain
- Aldini (Galvani's nephew)in the early 19th century used electricity to try to resusitate the dead
- Electroconvulsive shock therapy for mental illness in 1938
- TES (Merton & Morton, 1980); TMS (Barker et al. 1985); tDCS (rediscovered) – used for physiological studies and then therapies

Range of devices

- Electroconvulsive Therapy (ECT)
- Transcranial electrical stimulation (TES)
- Transcranial magnetic stimulation (TMS)
- Static magnet
- Transcranial direct current stimulation (tDCS)
- Transcranial alternating current stimulation (tACS)
- Ultrasound and focused ultrasound (FUS)
- Peripheral nerve (including cranial nerve) stimulation
- But not: deep brain stimulation, epidural cortical stimulation and invasive brain lesioning

Why neuromodulation?

- Study of brain physiology
- Therapy of brain diseases
- Neuroenhancement

Targets

- Any and every part of the brain, as relevant for the desired outcome
  - Example, left dorsolateral prefrontal cortex (DLPFC) for treatment of depression
- Also spinal cord

Mechanisms

- On-line effects
- Alter brain function with a “lesion”, anatomical or functional, that would interrupt a brain circuit
- Modulate the oscillations within a brain circuit
- Persistent effects
- Modify the brain by inducing a plastic change

Mechanism: Lesioning

Fortunately, I don’t need to explain DBS

- Best example is lesioning the VIM of the thalamus for tremor
- Similarly, the bradykinesia of Parkinson disease modulates very rapidly

- Brief effect with noninvasive modulation (except for FUS); permanent effect with anatomical lesion

The possibility of therapy with devices like rTMS, where a prolonged aftereffect is sought, depends on their ability to use plasticity to change the brain

Mechanisms of Plasticity

- Synaptic strengthening/weakening
  - LTP/LTD
  - Homosynaptic & heterosynaptic
    - Spike Timing–Dependent Plasticity
- Anatomical changes
  - Dendritic spines
  - Axonal spouting, new connections
- Synaptic change and anatomical change likely occur sequentially

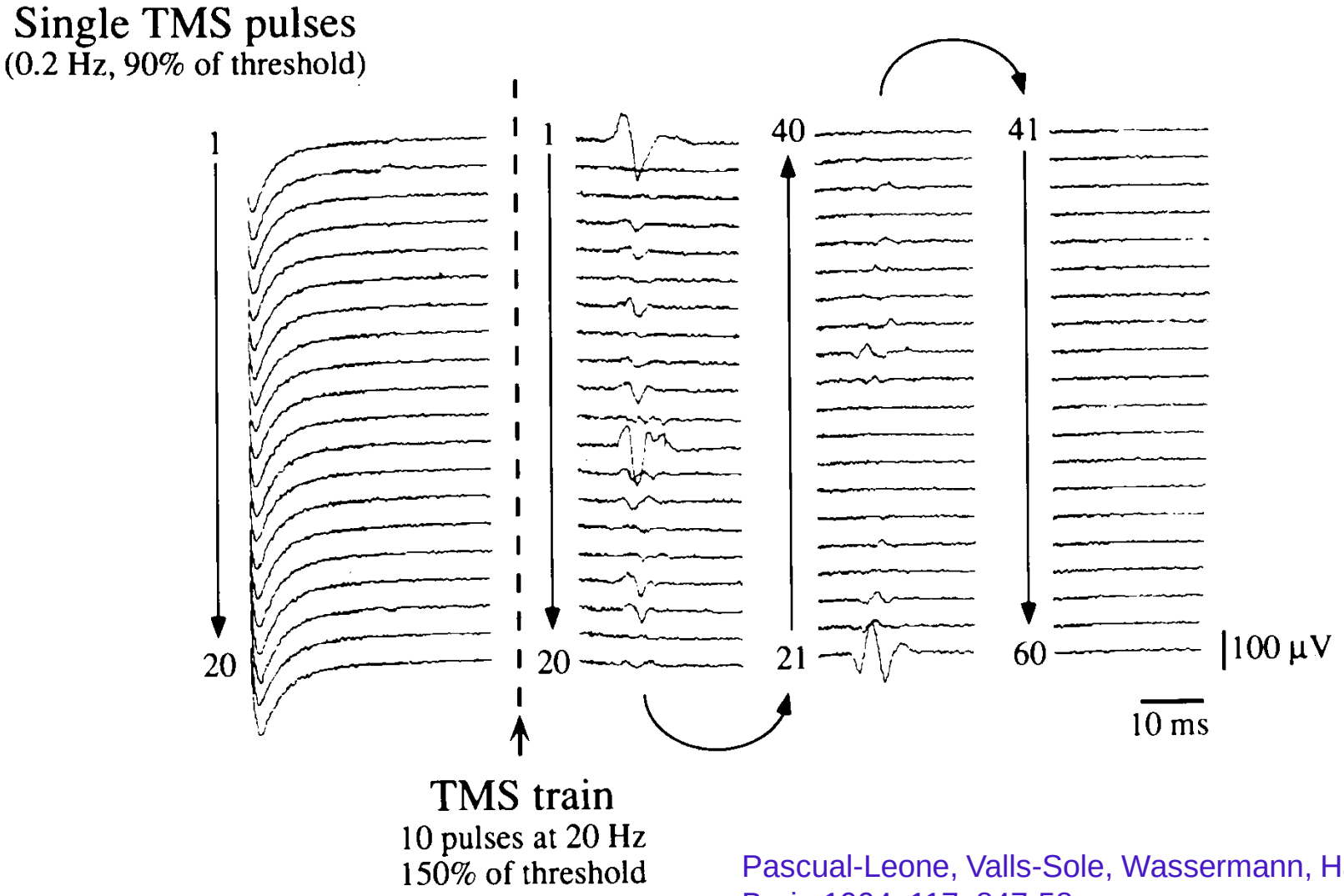
rTMS as example

- There are many possible methods for rTMS and each one will likely have different effects
  - Coil shape, coil current
  - Pattern & time of stimulation
  - Site of stimulation
  - Repetition of treatment

Patterns of rTMS

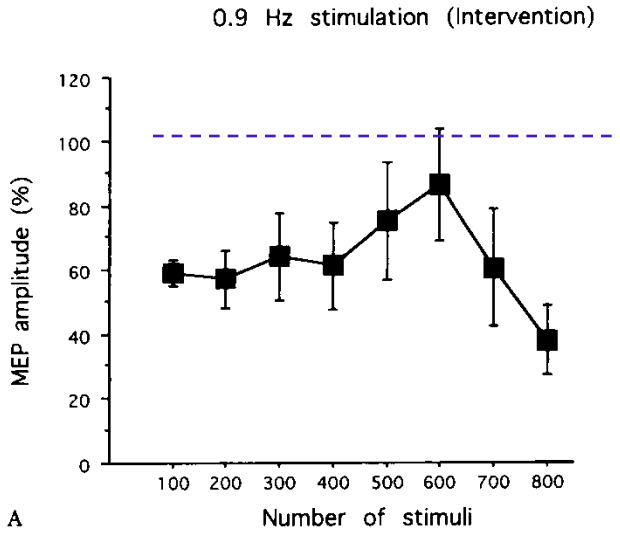
- rTMS, fast and slow
- Theta burst TMS, continuous and intermittent
- Quadripulse TMS, with different intervals between the pulses
- Paired associative stimulation (PAS); heterosynaptic plasticity with effects depending on timing

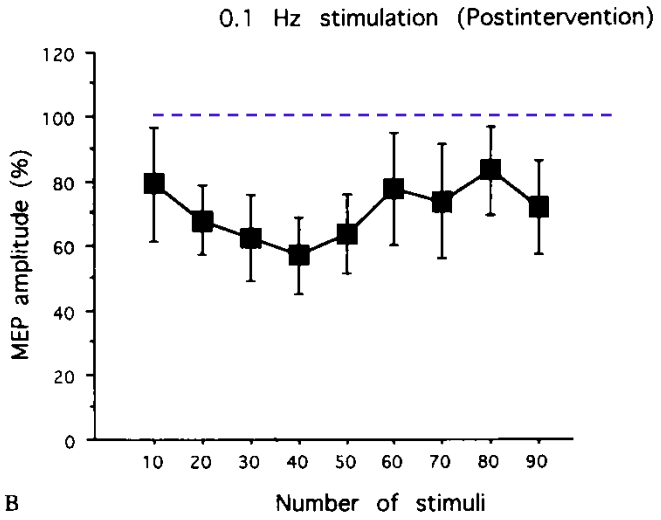
Rapid rTMS increases brain excitability



Pascual-Leone, Valls-Sole, Wassermann, Hallett
Brain 1994; 117: 847-58

Slow rTMS reduces brain excitability





Chen, Classen, Gerloff, Wassermann, Hallett, Cohen
Neurology 1997; 48: 1398-403

Therapy with rTMS

- Psychiatry
  - Depression (and possibly mania)
  - OCD
  - Suppression of auditory hallucinations
- Tinnitus
- Stroke
- Movement disorders
  - Parkinson’s disease
  - Dystonia
  - Essential tremor?
  - Ataxia?
- Epilepsy
- Pain

Logic of rTMS for Depression

- Left dorsolateral prefrontal cortex is hypometabolic
- Reversal of hypometabolism by facilatory stimulation might improve mood

One more lesson

- Treatments need to be repeated multiple times to get a substantially long lasting effect
- Perhaps similar to practicing a new skill; repetitions are needed to drive an enduring plastic change

Movement Disorders
Vol. 21, No. 3, 2006, pp. 325–331

Placebo-Controlled Study of rTMS for the Treatment of Parkinson's Disease

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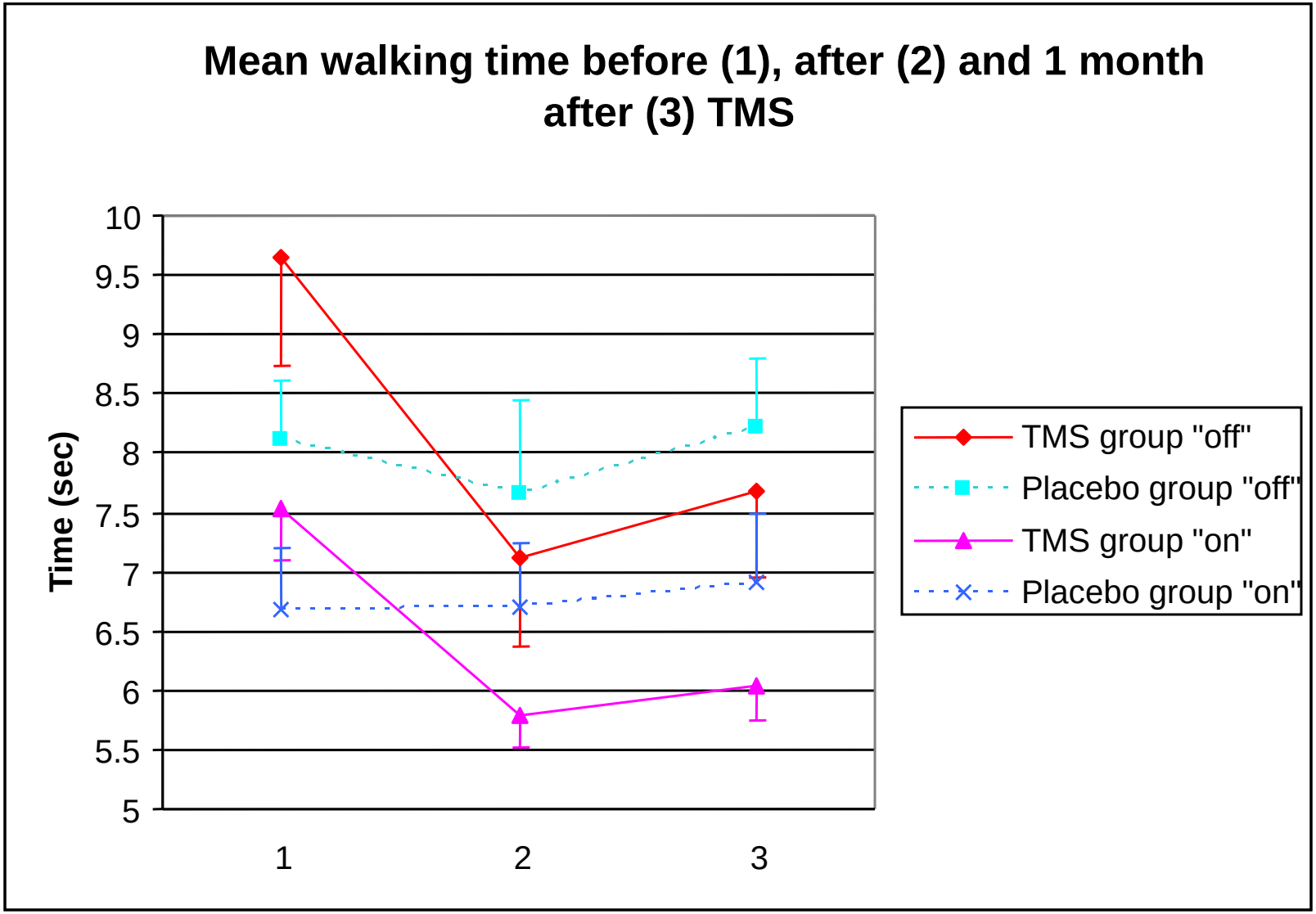
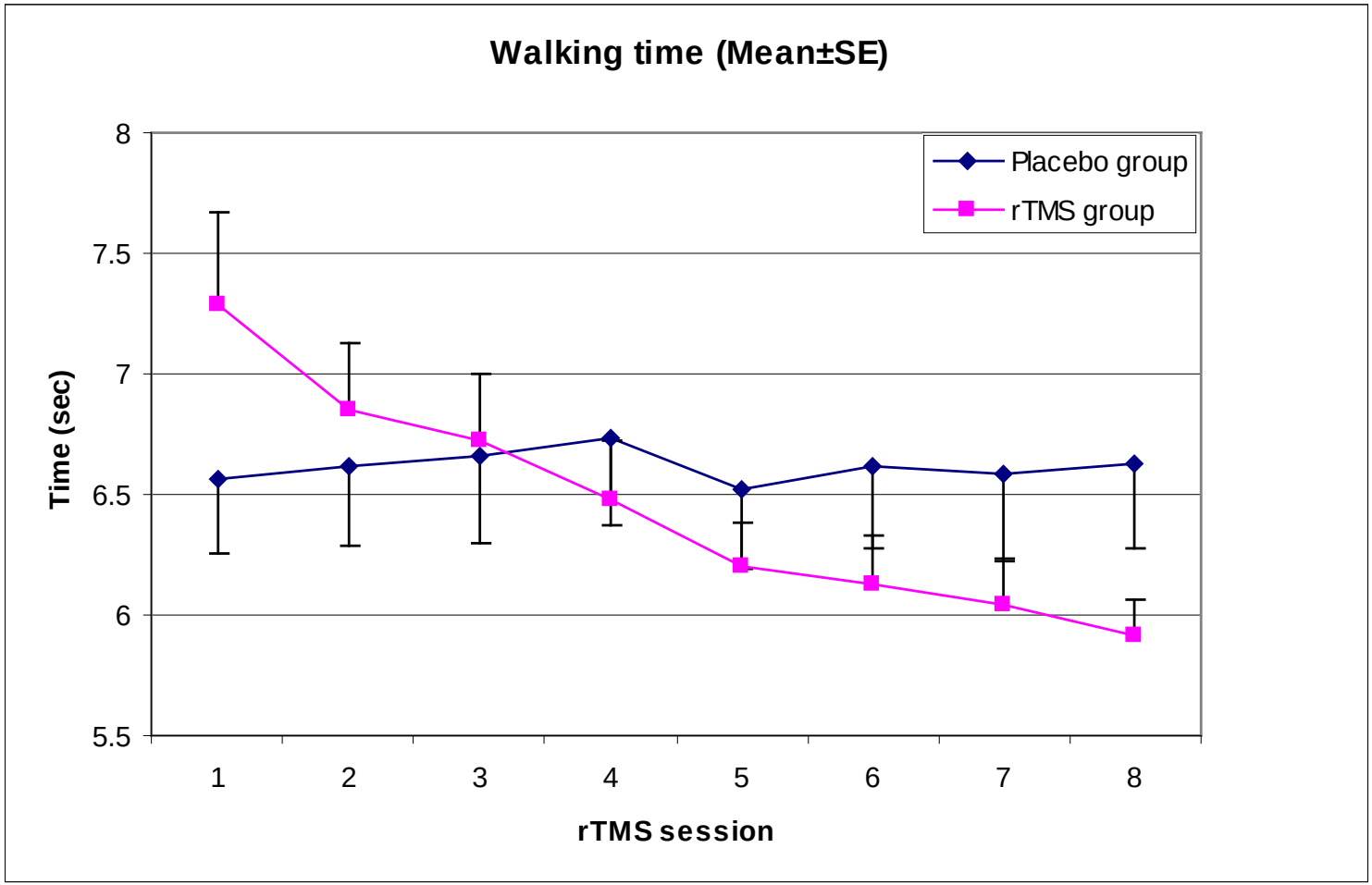
8 sessions over 4 weeks of 25 Hz rTMS at 100% MT delivered to left and right primary motor cortex and dorsolateral prefrontal cortex with 300 pulses each



Lomarev et al. 2006



Lomarev et al. 2006

One more lesson

- Combination with drugs or behavior might improve any effect
- Example: Combination of rTMS and treadmill training for walking in PD
  - Yang et al. Neurorehab Neural Repair 2013; 27:79-86
  - 12 sessions over 4 weeks, 6 min of 5Hz rTMS (real or sham), then 30 min of treadmill training

Safety concerns and side effects

Rossi, Hallett, Rossini, Pascual-Leone
Safety…considerations…in clinical practice and research
Clin Neurophysiol 2009; 120: 2008-2039

- Heating
- Forces and magnetization
- Seizures
- Hearing
- Syncope
- Local discomfort
- Cognitive or psychiatric changes

Conclusions

- Non-invasive brain stimulation can modify brain function and may be therapeutic in some circumstances
  - BUT – treatment must be repetitive
  - AND – combination with behavior or drugs might be useful/necessary
  - Other than for depression, other indications are currently experimental

Thank you!