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 resuscitate 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

A

0.9 Hz stimulation (intervention)

0.1 Hz stimulation (Postintervention)

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 facilitatory 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
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
Mean walking time before (1), after (2) and 1 month after (3) TMS

Lomarev et al. 2006
Walking time (Mean±SE)

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<th>Placebo group</th>
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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!