UCLA Principles of Neuroimaging

Transcranial magnetic stimulation (TMS)

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Faraday’s law

• A time-varying current (di/dt) in a wire loop will induce a magnetic field (B)
• The magnetic field will induce an electromotive force (ε) in an adjacent conductor

\[
\vec{B} = \frac{\mu_0}{4\pi} \oint \frac{\vec{d} \times \vec{a}}{r^2} \, d\ell
\]

Biot-Savart law:
\( \vec{B} \) flux direction by right-hand rule

\[
\nabla \times \vec{E} = -\frac{\partial \vec{B}}{\partial t} \quad \vec{E} = -L \frac{di}{dt}
\]

L = inductance

Induced TMS current

Walsh and Cowey 2000

TMS has intermediate temporal/spatial resolution but unique interference qualities

Walsh and Cowey 2000

What does TMS stimulate?

Boundary effects:

– TMS stimulation is parallel to scalp surface
– Lack of radial component to stimulation
Membrane effects on axon depolarization

- Induced currents depend on tissue inhomogeneities
- Sharper bends / shorter axons = lower thresholds

Transcranial magnetic & electrical stimulation

- Epidural (spinal) recordings:
  - TMS has a 2 msec longer latency than TES

What factors influence effects of TMS on the brain?

- Coil geometry
- Pulse waveform
- Coil orientation
- Coil placement
- Frequency TMS pulses
- Intensity of stimulation
- Duration of stimulation

Physiology of magnetic stimulation

- TMS preferentially produces trans-synaptic stimulation
- Compared to electrical stimulation, TMS responses are more variable and sensitive to both internal and external factors

Coil geometries
Can TMS be used to stimulate deep brain structures?

TMS effects depend on waveform

TMS effects are waveform & orientation specific

Coil location: TMS hotspot and neuronavigation

TMS site
Forms of TMS

- **Single-pulse TMS** (1 pulse every 5-10 secs)
  - Paired-pulse TMS

- **Repetitive TMS** (rTMS)
  - Conventional rTMS
    - rTMS Low frequency rTMS (≤ 1 Hz)
    - High frequency rTMS (>1 Hz)
  - Patterned rTMS
    - Theta-burst stimulation (rTMS 50 Hz triplets at 5 Hz)

On-line vs off-line study designs

- “on-line” concurrent TMS stimulation of ongoing process
  - Reliably (relatively) produces interpretable disruptive effects
  - Single pulse highly temporally specific
  - Can explain facilitative effects by models of competitive inhibition
  - Can yield measures of excitability over primary motor/visual cortex

- “off-line” rTMS modulation method (virtual lesion)
  - Avoids interference of on-line TMS with task
  - Temporo-spatial specificity poorer
  - Effects are more heterogeneous

Common TMS study types

- **Neurophysiology studies**
  - Single-pulse TMS outcome measures (excitability)
  - Paired-pulse intra-cortical or cortico-cortical excitability

- **Perturbation studies**
  - Cortical perturbation (on-line, single-pulse or rTMS)
  - Cortical perturbation (off-line, “virtual lesion” or modulation)

- **Modulatory effects of rTMS**
  - After-effects of rTMS (neurophysiologic, behavioral, imaging)
  - Clinical trials of rTMS (single- or multisession)

Neurophysiology TMS studies

- **Motor cortex excitability:**
  - Responsiveness of the motor cortex to stimulation
  - Represents influences along the cortico-spino-motor pathway
  - Attention, motor imagery, movement, learning, practice, action observation, emotions, afferent stimulation, drugs all can affect cortical excitability
  - Outcome measures:
    - Motor threshold,
    - Motor evoked potential (MEP), Mapping motor (muscle) representation,
    - Input-output curve,
    - Cortical silent period
    - Paired-pulse studies

- **Visual cortex excitability:**
  - Responsiveness of the visual cortex to stimulation
  - Outcome measures: Phosphene thresholds

Cortical excitability
Motor cortex excitability

Motor threshold (MT)
- Minimum stimulus intensity required to elicit a small motor response in a target muscle 50% of the time
- Can be assessed at rest (RMT) or active contraction (AMT)
- Enables comparable intensity of stimulation across subjects

Motor evoked potential (MEP)
- Motor response in a target muscle evoked by TMS at a given suprathreshold intensity
- MEP size and latency can be quantified
- Most common measure of changes in cortical excitability

Intensity

TMS excitability increases during reaction time

MEP sizes demonstrate acute and chronic plasticity

Input-output curves
- MEP size plotted against TMS intensity with coil at fixed spot
- Often fitted with a sigmoid curve (MEP-S0, maxMEP, slope)

Cortical silent period
- If a target muscle is pre-contracted, a TMS pulse will evoke a MEP which is followed by a period of EMG silence
- Duration of this silent period is a measure of inhibitory circuits
- Early period is spinal in origin; latter period (>100 msec) is considered cortical in origin
- Considered GABA-dependent

From Valls-Sole et al, Neurology 44:1994

From Kaelin-Lang, J Neuro Methods 2000

From Sandrini et al 2011

Figures adapted from Chen, Cohen, Hallett 2002

From Cantello, Neurology 1991;41:1449-56
Paired-pulse TMS can probe intracortical circuit excitability within motor cortex

Paired-pulse TMS can probe interactions among intracortical circuits

Disorders with abnormal excitability
- Parkinson's disease
- Dystonia
- Stroke
- Epilepsy
- Depression
- Schizophrenia
- Essential tremor
- Amyotrophic lateral sclerosis
- Huntington's disease
- Tourette's syndrome
- Myelopathy
- Corticobasal gang degeneration
- Cerebellar degeneration
- Polyradiculoneuropathies
- CNS demyelinating disease
- CNS tumors
- Restless leg syndrome
- Chronic fatigue syndrome
- Etc...

Paired pulses assess inter-regional connectivity

Interhemispheric connectivity

Cerebello-motor connectivity

Ugawa et al 1997

Perturbation TMS studies

Single-pulse TMS over occipital lobe can disrupt visual perception

Amassian 1989 (Handbook of TMS 2002)
Visual cortex processing is necessary for Braille reading in the early blind subjects

Perturbation TMS studies

Speech arrest with high-frequency rTMS

rTMS types

Offline conventional rTMS modulation of cortical excitability

Cohen et al 1997

Pascual-Leone et al 1991

Sandrini et al 2011

Rossi et al 2009


Theta-burst stimulation

Advantages of offline-rTMS technique

• Normal subjects can be studied
• Acute perturbation avoids CNS reorganization
• Subjects serve as own controls
• Reproducible study design allows for cleaner statistical analysis
• Avoids confound of on-line rTMS artifacts
• Neighboring brain region controls allows functional spatial specificity to results
• Led to proposed therapeutic uses of rTMS

Effects of offline rTMS

• Local effects
  — Increase (decrease) excitability to normalize abnormal excitability (or other physiologic measure)

• Distant effects
  — Modulation of distant sites in a functional network (resting or state-related)
  — Decrease excitability to release inhibition in a distant area and achieve paradoxical facilitation (for example)

• Cellular and molecular (neurotransmitter) effects
  — Stimulation release (or modulate levels) of neurotransmitters
  — Modulation of signaling pathways and gene transcription

Decreasing cortical excitability to treat dystonia

• 1 Hz rTMS over premotor cortex restores measures of inhibition (e.g. silent period) with improvement in writing (Murase et al 2005)
• Also, 1 Hz rTMS normalized paired-pulse intracortical excitability over motor cortex (Siebner et al 1999)

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Virtual lesions and competitive inhibition

- Left hemispace neglect due to chronic right hemisphere lesions can be transiently improved with rTMS perturbations over left (unaffected) hemisphere

Effects of rTMS: FDG PET

- 5 Hz subthreshold over M1
- Shows local increase in metabolism plus contralateral M1 and SMA

Offline imaging of 1 Hz rTMS over M1 on task-related connectivity (H2O PET)

- Task-specific (free finger selection vs rest)
- Reduced responsiveness of left SM1 to inputs from SMA and left PMd
- Patterns of connectivity suggest acute compensation for behavior that is otherwise unchanged

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rTMS over PFC or M1 can release subcortical dopamine in normal subjects and in PD patients

Raclopride[11C] PET imaging
Raclopride is a competitive inhibitor of extracellular dopamine

Significance of rTMS induced dopamine release remains uncertain

- Sham-rTMS induces asymmetric dopamine release in moderate stage PD patients
Cellular and molecular mechanisms of TMS

- rTMS modulates
  - c-fos and c-jun expression
  - Possible BDNF mRNA expression
  - Dopamine, serotonin, vasopressin, others
- Effects may increase with daily rTMS

Other TMS topics

- Control and sham conditions
- Therapeutic rTMS for depression
- State-dependent TMS
- Meta-plasticity
- Safety and regulatory issues

Control conditions

- FDA approved Neurostar rTMS for treatment of medication-refractory major depression in Oct 2008

Sham rTMS condition

- Impedence <25 kOhm
- Self-matched electrical stimulation to TMS at 1 Hz
- 9 of 10 naïve subjects felt electrical stimulation was TMS
- 4 of 5 non-naïve subjects correctly identified TMS
- Implementation still TBD

High-frequency rTMS for depression

- Randomized sham-controlled multicenter trial for rTMS
  - Left DLPFC rTMS 5 days per week, 4-6 weeks
  - 10 Hz rTMS (120% rMT), 4 sec on, then 26 sec rest
  - 143 active rTMS, 134 sham rTMS

Can cortical modulation be directed to target specific symptoms?

- Motor circuit = motor symptoms
- Prefrontal circuit = mood symptoms

### Magnetic Stimulation for the Treatment of Motor and Mood Symptoms of Parkinson’s Disease (MASTER-PD trial)

- Investigates rTMS as a noninvasive therapy for PD symptoms
  - Investigates potential selectivity of effects (motor vs mood)
- Four-site study of 10 Hz rTMS sessions (10 Hz) over 2 weeks
- First prospective, double-blind, sham-controlled, parallel-group multicenter rTMS clinical trial in PD in North America
- Outcome measures: motor (UPDRS part III), mood (HAM-D)

<table>
<thead>
<tr>
<th>Group</th>
<th>M1 (bilateral)</th>
<th>DL-PFC (left)</th>
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<tbody>
<tr>
<td>M1 group</td>
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<tr>
<td>Sham group</td>
<td>sham rTMS</td>
<td>sham rTMS</td>
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### State-dependency of TMS

- TMS:
  - FDA approvals exist for
    - Magnetic stimulation of peripheral nerves
    - rTMS for medication-refractory depression
  - All other uses of TMS are “off-label” use
    - Single-pulse TMS does not generally require an Investigational Device Exemption (IDE)
    - Repetitive TMS may require an IDE

### Homeostatic plasticity (meta-plasticity)

- **Known Risks**
  - Seizure induction
  - Local pain and headache
  - Hearing threshold shift
  - Effects on cognition & mood
  - Burns from scalp electrodes
  - Metal in the head
  - Other reported adverse events:
    - nausea, dental pain, fainting, pseudoseizures, tinnitus

- **Potential risks of rTMS**

- **Theoretical Risks**
  - Neurotoxicity
  - Kindling
  - Endocrine effects
  - Social and psychological consequences of a seizure
Accidental Seizures & TMS

- Very rare in single pulse TMS (only in patients)
- 8 seizures reported by 1998 all with high-frequency rTMS
- Currently 16 seizures reported worldwide with TMS

- Seizure risk probably related to “dose” of rTMS
- Risks of seizure increase with:
  - Higher frequencies (> 3 Hz)
  - Higher intensities (> 100% MT)
  - Longer durations
  - Shorter inter-train intervals

Seizures induced by TMS

<table>
<thead>
<tr>
<th>Source</th>
<th>Seizure type</th>
<th>Frequency (Hz)</th>
<th>Intensity (% of MT)</th>
<th>Statement</th>
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<table>
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<th>Intensity (% of MT)</th>
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Consensus statement on rTMS (Belmaker et al. 2003)

- Those who administer rTMS should be trained as “first responders”
- rTMS should be performed in a medical setting with appropriate emergency facilities.
- Patients and research subjects should be continuously monitored
- Participants should be informed of the risk of seizure and its possible medical and social consequences.
- Dosage of rTMS should generally be limited by published safety guidelines (Wassermann et al 1998)

Current consensus risk assessment for TMS

- Absolute contraindication:
  - Metallic hardware/implanted devices
- Increased / uncertain risks by TMS protocol
  - Non-conventional rTMS including priming paradigms, long-lasting plasticity paradigms, multi-site TMS
  - Conventional high-frequency rTMS beyond safety parameters
- Increased / uncertain risk by subject
  - History of seizures, lesions of the brain, drugs that lower seizure threshold, sleep deprivation, alcoholism

- Uncertain risk due to other events
  - Pregnancy, severe or recent heart disease, implanted brain electrodes

- No risk category
  - None of above uncertain/increased risks
  - Single- or paired-pulse TMS
  - Conventional low- or high-frequency rTMS within safety parameters (intensity, frequency, train length, inter-train duration)

Comments about rTMS and neuromodulation (Huang et al, Neuron, 2005)

- “The effectiveness of these paradigms raises ethical issues about the use of these methods in normal human subjects, who have nothing to gain from modulation of synaptic plasticity, in contrast to patients with particular neurological disorders.
- “...in addition to putting our proposed experimental methods before the ethics committee of our institution and gaining consent from subjects, we pursued the experiments in an incremental fashion starting with smaller intensities and lower frequencies of stimulation than those reported here.
- “We found in all experiments that cortical excitability eventually returned to baseline, and no subject reported any side effects from experimentation
- “However, as methods for inducing plastic changes in human cortex become more powerful, such issues will require constant scrutiny and vigilance on the part of experimenters.”