UCLA Principles of Neuroimaging

non-invasive brain stimulation with TMS and TDCS

transcranial magnetic stimulation (TMS)
(transcranial direct-current stimulation (TDCS))

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March 4, 2015

What are TMS and TDCS?

- Noninvasive neurostimulatory and neuromodulatory methods currently used in human subjects
- Modern era of use since 1985 for TMS, since 2001 for TDCS
- Brain mapping and clinical applications are growing
- Mechanisms are incompletely understood
- Animal & bioengineering models remain relatively uncommon

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journal homepage: www.elsevier.com/locate/clinph

Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research ☆

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Neuroscience and Biobehavioral Reviews
journal homepage: www.elsevier.com/locate/neubiorev

Review

The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues

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[b] Center for Neuroscience and Regenerative Medicine, Uniformed Services University of Health Sciences, Henry M. Jackson Foundation, 12725 Twinbrook Parkway, Rockville, MD 20852, USA
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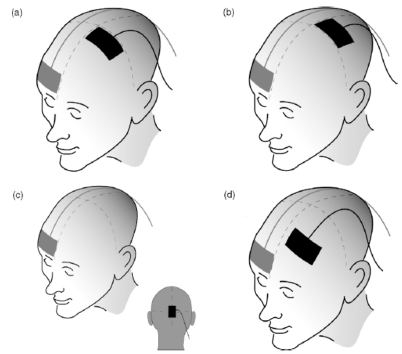
(transcranial) magnetic stimulation (TMS)

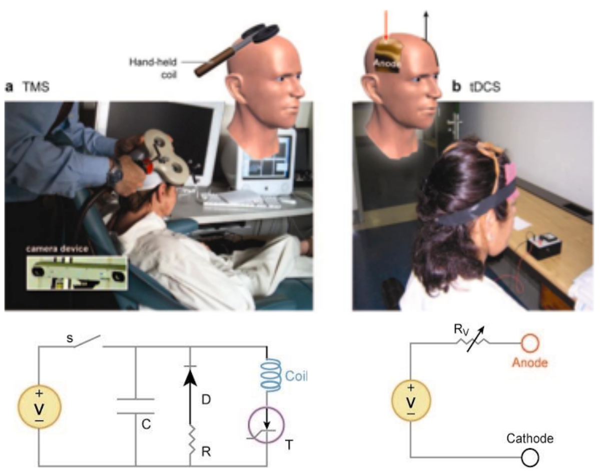
FDA approvals of rTMS for treatment of medication-refractory major depression

TDCS



Utz et al 2010 Neuropsychologia

What are TMS (magnetic stimulation) and TDCS (direct current stimulation)?



Wagner et al. (2007). Annu Rev Biomed Eng

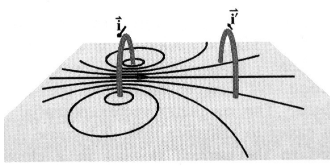
TMS and TDCS

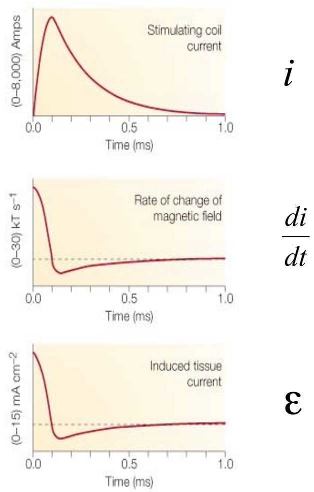
- **TMS**
- Faraday's principle of induction
- Brief stimulation period (~200 usec)
- Induces action potentials in nerve axons
- Repetitive and/or patterned stimulation can induce modulation

- **TDCS**
- Polarization across brain
- Long-duration 10-20 min DC stimulation
- Does not induce action potentials
- Modulates neural firing rates

Faraday's law of induction (TMS)

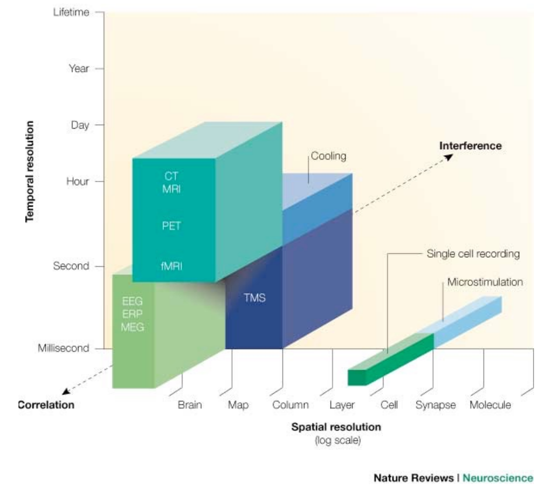
- A time-varying current (*di/dt*) in a wire loop will induce a magnetic field (*B*)
- The magnetic field will induce an electromotive force (ε) in an adjacent conductor





Walsh and Cowey 2000

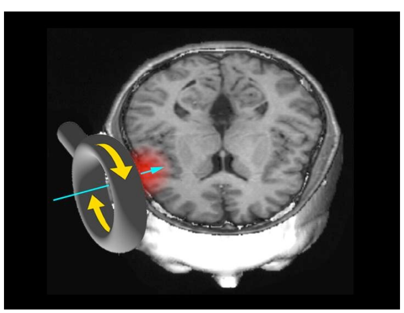
TMS has intermediate temporal/spatial resolution but unique interference qualities



Walsh and Cowey 2000

What does TMS stimulate?

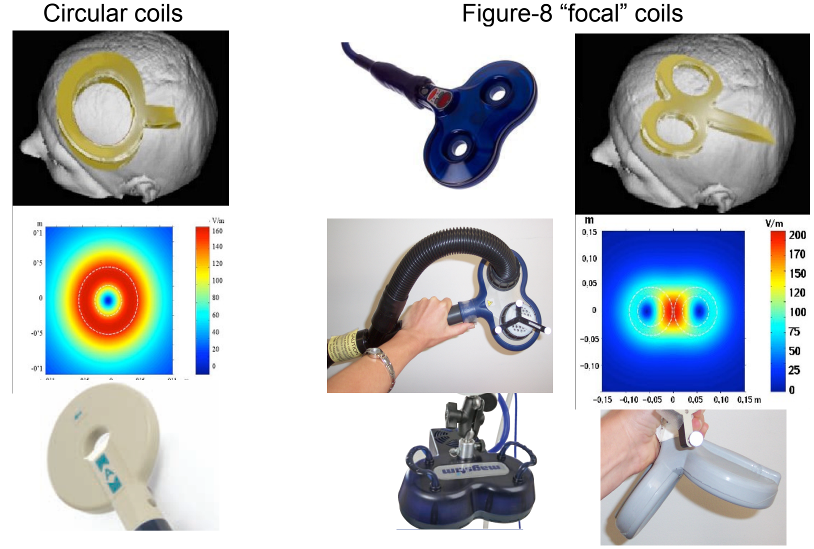
- Coil geometry
- Coil placement
- Pulse waveform
- Coil orientation
- Pattern of stimulation
- Frequency TMS pulses
- Intensity of stimulation
- Duration of stimulation



What does TMS stimulate I? depends on coil

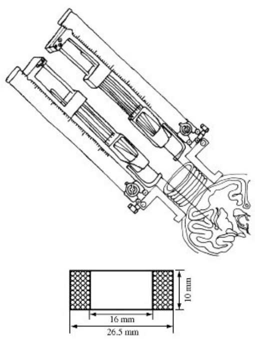
Circular coils

Figure-8 "focal" coils



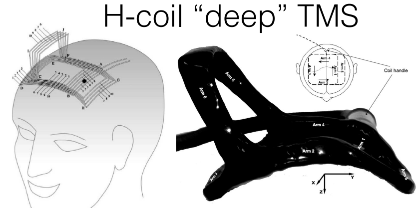
Advances in TMS coil designs

Mini-coil



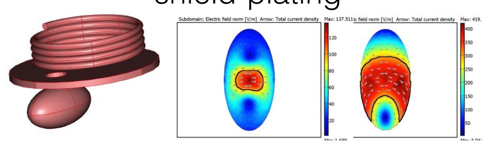
Tischler et al 2011, J Neurosci Meth

H-coil "deep" TMS



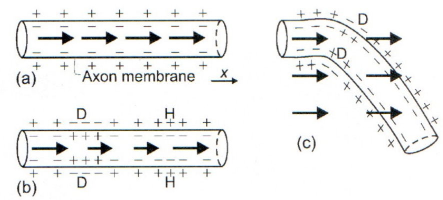
Fadini et al 2009

shield-plating

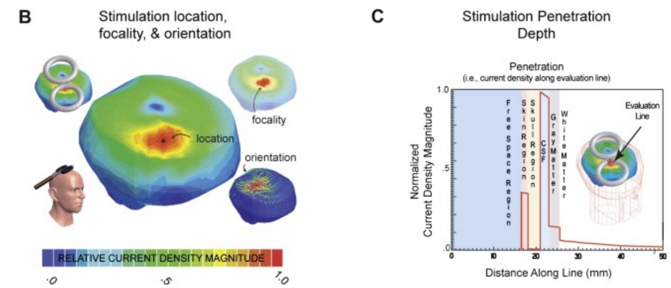


Gasca et al 2010, IEEE Eng Med Biol Soc

What does TMS stimulate II: tissue boundaries

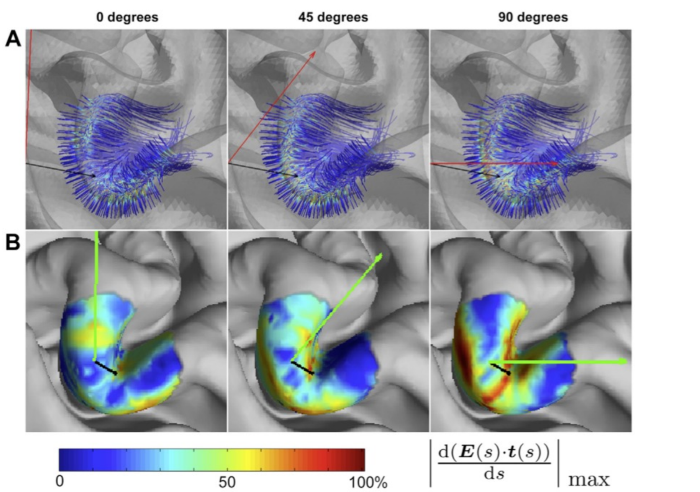


- Induced currents depend on tissue inhomogeneities and boundaries
- sharper bends / shorter axons = lower thresholds



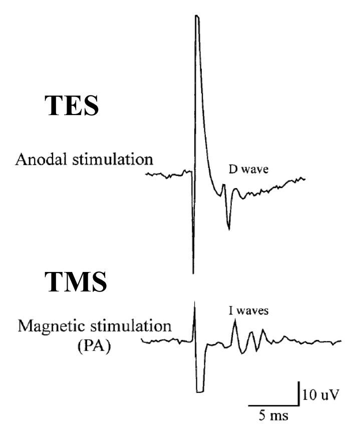
Wagner et al. (2004) IEEE Trans Biomed Eng

What does TMS stimulate II: axon boundaries



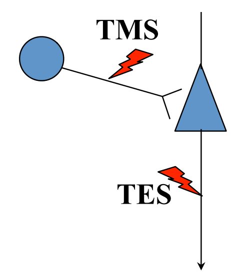
Nummenmaa et al. "Targeting of white matter tracts with transcranial magnetic stimulation." Brain Stimulation

What does TMS stimulate III?

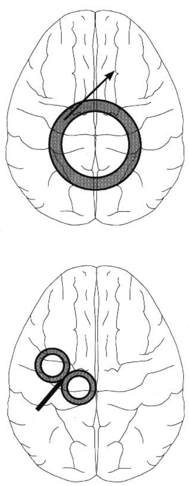


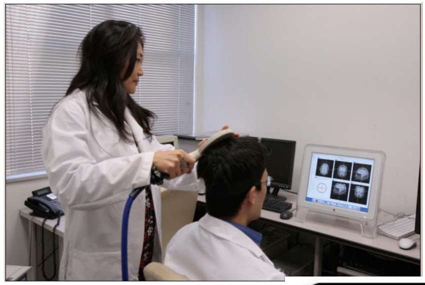
Di Lazzaro et al,

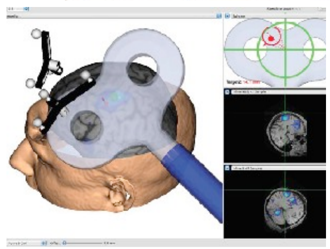
- TMS preferentially produces trans-synaptic stimulation
- Compared to electrical stimulation, TMS responses are more variable and sensitive to both internal and external factors

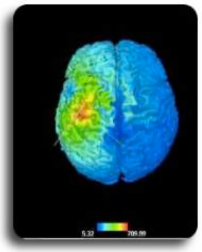


Coil location: TMS hotspot and neuronavigation

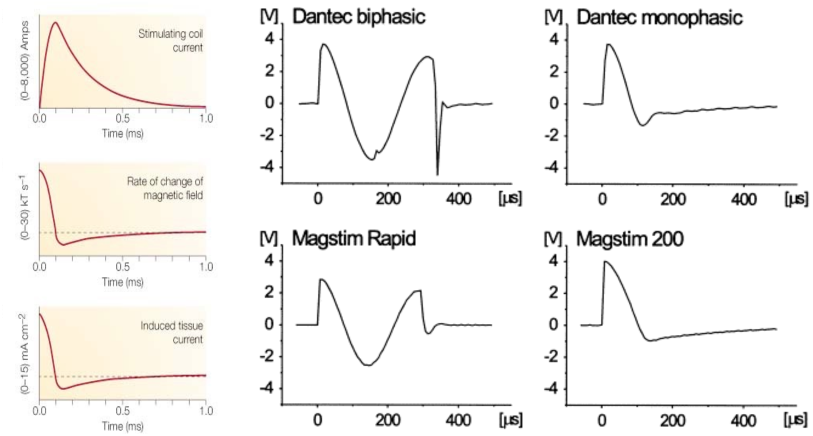






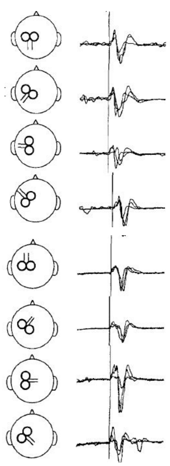


TMS produces different waveforms

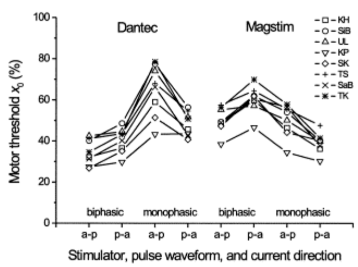


Kammer et al 2001

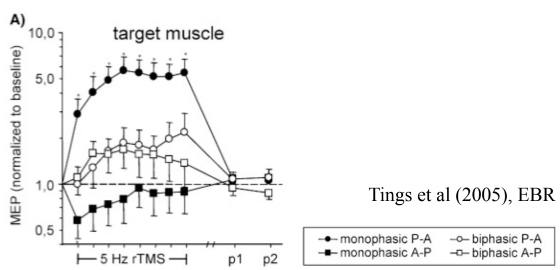
TMS effects depend on waveform & orientation



Mills et al 1992



Kammer et al 2001



Tings et al (2005), EBR

Common TMS study types

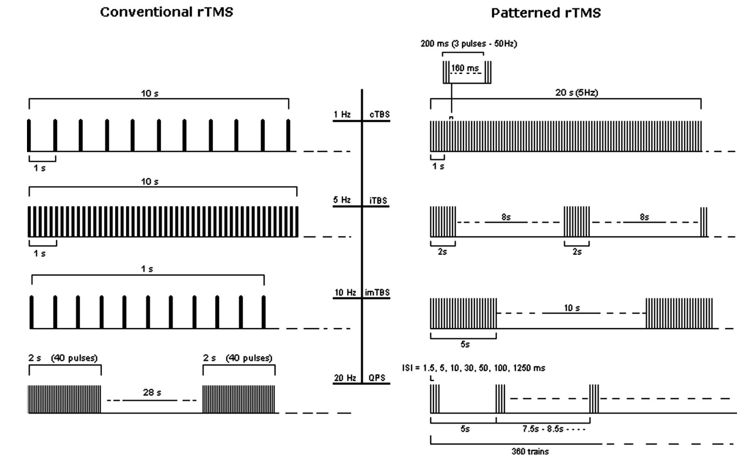
- Neurophysiology studies
  - Single-pulse TMS outcome measures (excitability)
  - Paired-pulse intra-cortical or cortico-cortical excitability
- Perturbation studies
  - Cortical perturbation (on-line, single-pulse or rTMS)
  - Cortical perturbation (off-line, "virtual lesion" or modulation)
- Modulatory effects of rTMS (e.g. plasticity effects)
  - After-effects of rTMS (neurophysiologic, behavioral, imaging)
  - Clinical trials of rTMS (single- or multisession)

Forms of TMS

- **Conventional**
- Single-pulse TMS
  (1 pulse every 5-10 secs)
  - Paired-pulse TMS
    - Same vs different sites
- Repetitive TMS (rTMS)
  - Conventional rTMS
    - rTMS Low frequency rTMS (≤ 1 Hz)
    - High frequency rTMS (>5 Hz)

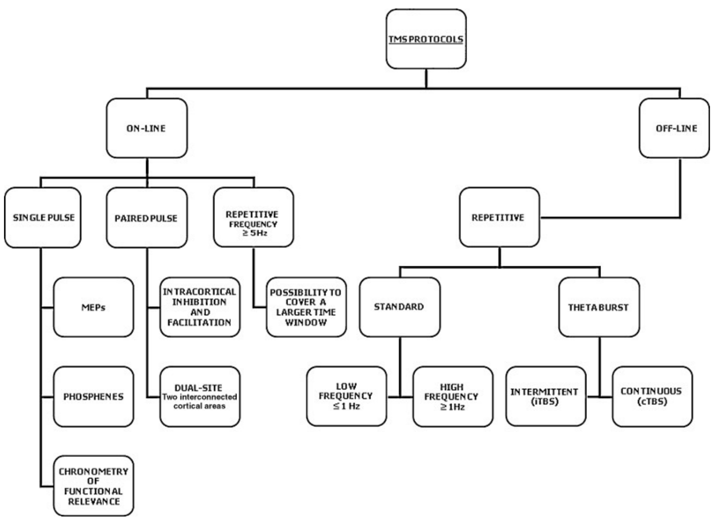
- **Non-conventional**
- Single-pulse TMS
  - State-dependent TMS
  - Paired-TMS or triggered-TMS
    - Paired-associative stimulation
- Repetitive TMS (rTMS)
  - Patterned rTMS
    - Theta-burst stimulation (rTMS 50 Hz triplets at 5 Hz)
    - Quadripulse Stimulation
    - Other

rTMS types



Rossi et al 2009

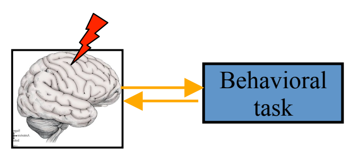
TMS protocols



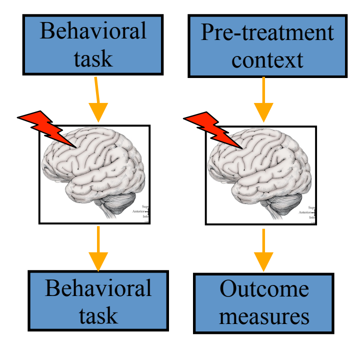
Sandrini et al 2011

On-line vs off-line study designs

- "on-line" concurrent TMS/TDCS stimulation of ongoing process
  - Reliably (relatively) produces interpretable disruptive effects
  - Single pulses 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/TDCS modulation method
  (?virtual lesion)
  - Avoids interference of on-line TMS with task
  - Temporo-spatial specificity poorer



Cortical excitability

- **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

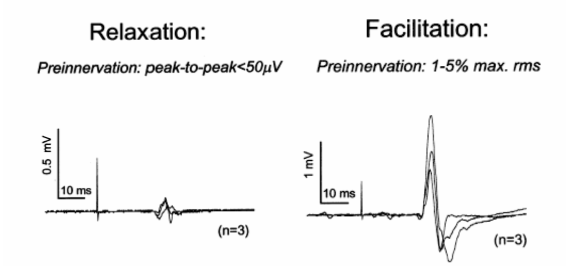
Motor cortex excitability

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

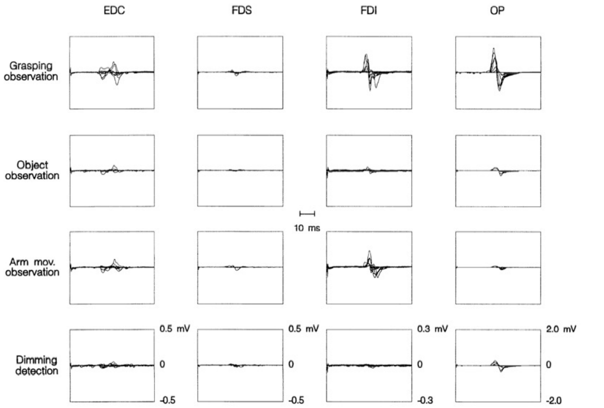
Motor evoked potential (MEP)

- Motor responses 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



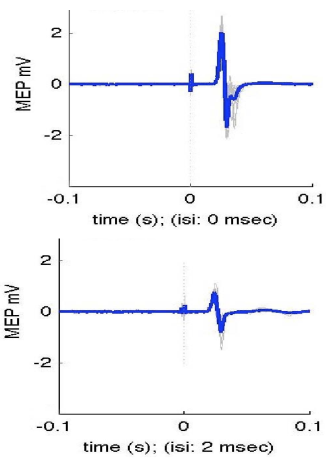
Kaelin-Lang, J Neuro Methods 2000

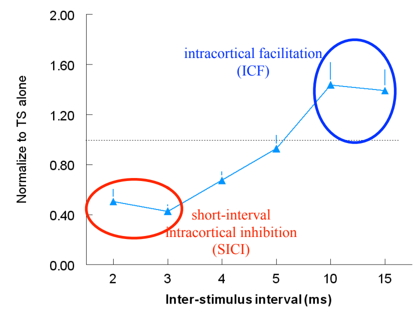
TMS intensity and location in study of motor resonance during action observation



Fadiga et al 1995

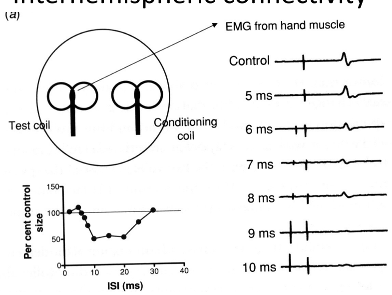
Paired-pulse TMS can probe intracortical circuit excitability within motor cortex



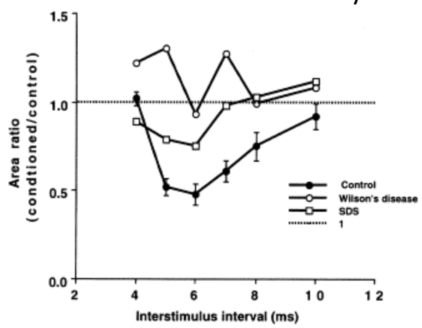


Paired pulses assess inter-regional connectivity

Interhemispheric connectivity



Cerebello-motor connectivity

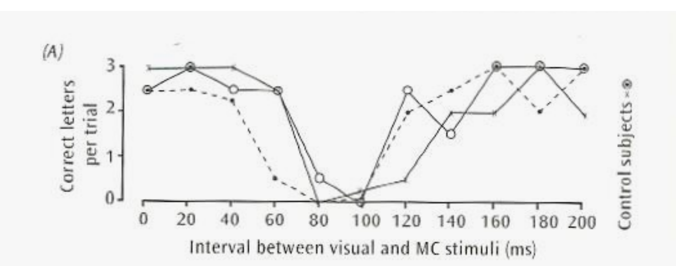


Ugawa et al 1997

Disorders with abnormal excitability

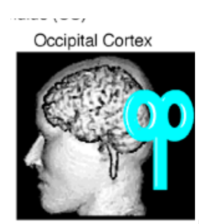
- Parkinson's disease
- Dystonia
- Stroke
- Epilepsy
- Depression
- Schizophrenia
- Essential tremor
- Amyotrophic lateral sclerosis
- Huntington's disease
- Tourette's syndrome
- Myelopathy
- Corticobasal gang degen
- Cerebellar degeneration
- Polyradiculoneuritis
- CNS demyelinating disease
- CNS tumors
- Restless leg syndrome
- Chronic fatigue syndrome
- Etc…

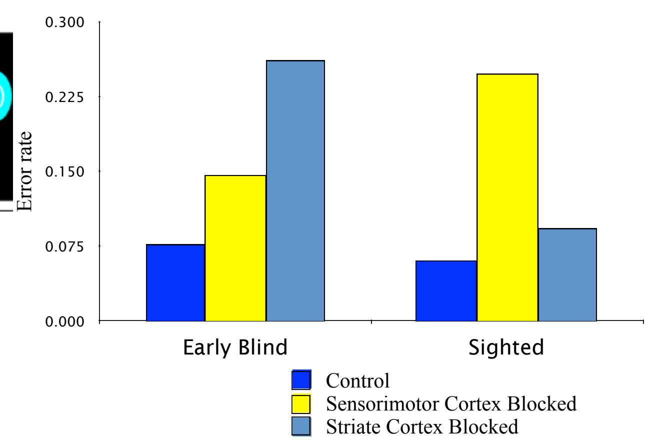
Single-pulse TMS over occipital lobe can disrupt visual perception



Amassian 1989 (Handbook of TMS 2002)

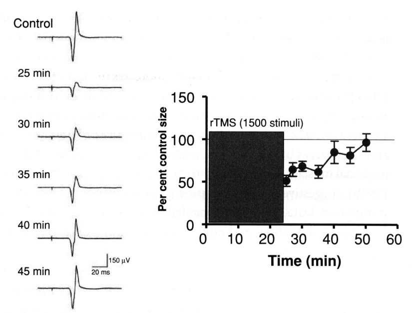
Visual cortex processing is necessary for Braille reading in the early blind subjects



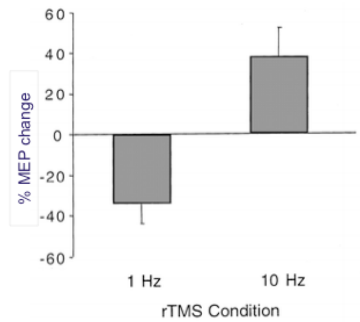


Cohen et al 1997

Offline conventional rTMS modulation of cortical excitability

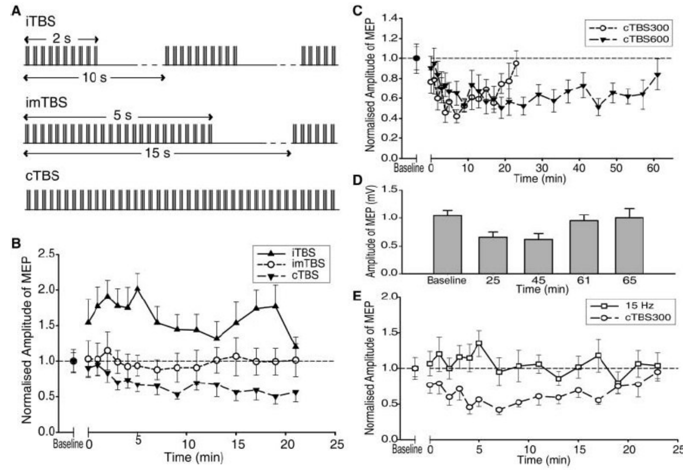


Touge et al (2001) Clin Neurophysiol



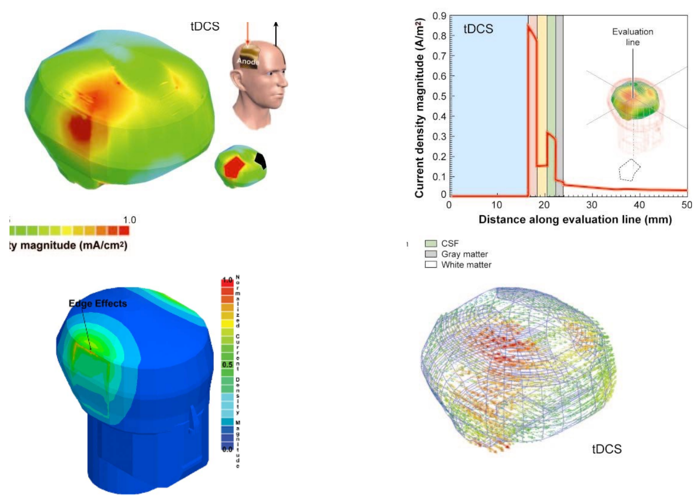
Maeda et al (2000) Exp Brain Res

Theta-burst stimulation



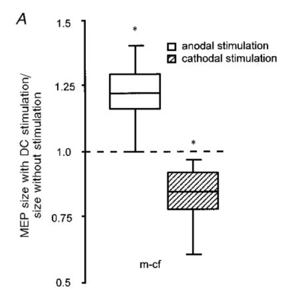
Huang et al (2005) Neuron

Modeling TDCS

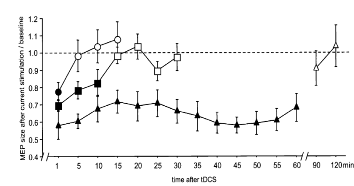


Wagner et al. (2007) Neuroimage & Wagner et al (2007). “” Annu Rev Biomed Eng

TDCS induces changes in motor excitability (MEP as outcome measure)



Nitsche & Paulus (2000) J Physiol



Nitsche, et al. (2003) Clin Neurophysiol

TDCS effects over time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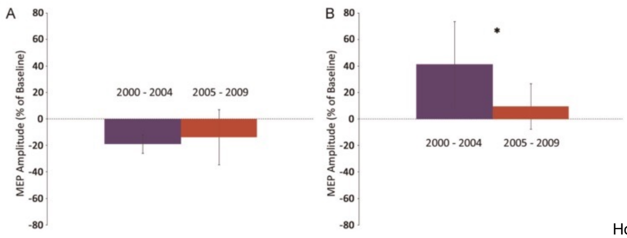
Reviews and perspectives

Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review

Jared Cooney Horvath*, Jason D. Forte, Olivia Carter

University of Melbourne, School of Psychological Sciences, Melbourne, VIC, Australia



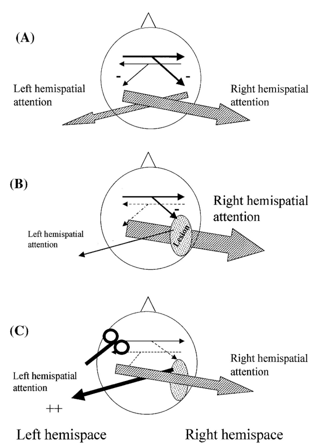
Horvath et al 2014.

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
  - Stimulate release (or modulate levels) of neurotransmitters
  - Modulation of signaling pathways and gene transcription

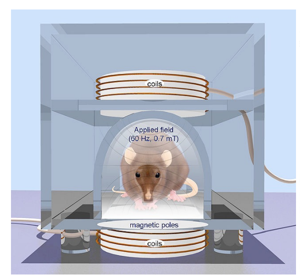
Virtual lesions and competitive inhibition

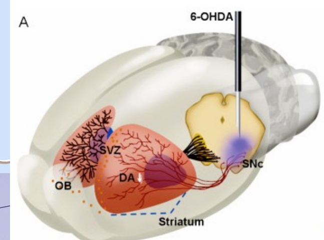
- Left hemispace neglect due to chronic right hemisphere lesions can be transiently improved with rTMS perturbations over left (unaffected) hemisphere

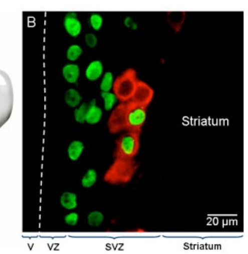


Oliveri et al 2001, Brighina et al 2003

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

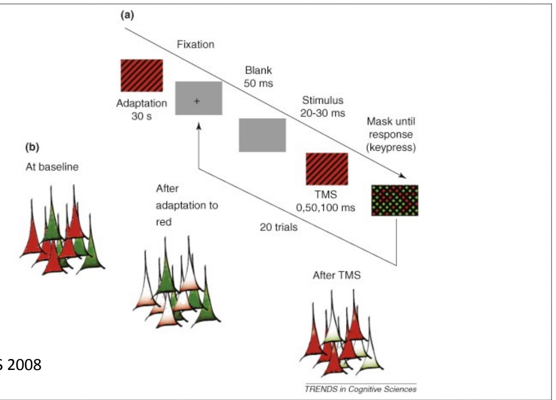
Arias-Carrion 2008

Common & other TMS study types

- Neurophysiology studies
  - Single-pulse TMS outcome measures (excitability)
  - Paired-pulse intra-cortical or cortico-cortical excitability
  - **State-dependent TMS and paired/triggered-TMS**
- Perturbation studies
  - Cortical perturbation (on-line, single-pulse or rTMS)
  - Cortical perturbation (off-line, "virtual lesion" or modulation)
- Modulatory effects of rTMS **(or other patterned TMS)**
  - After-effects of rTMS (neurophysiologic, behavioral, imaging)
  - Clinical trials of rTMS (single- or multisession)

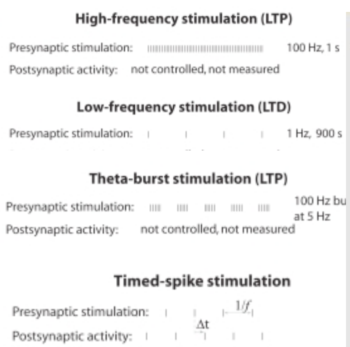
State-dependency of TMS

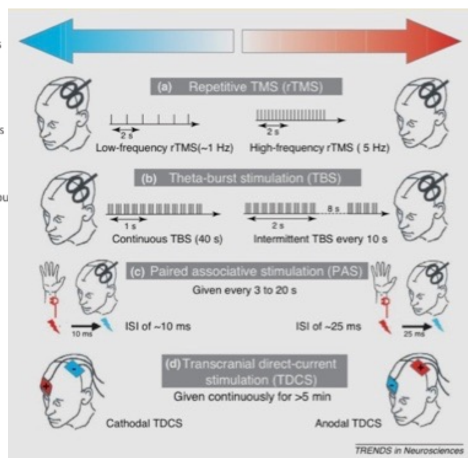
- TMS preferentially facilitates neurons that are less excitable
  - After adapting to a red stimulus, TMS induces red phosphenes



Silvanto et al, TINS 2008

Types of neuromodulation to probe or shape plasticity

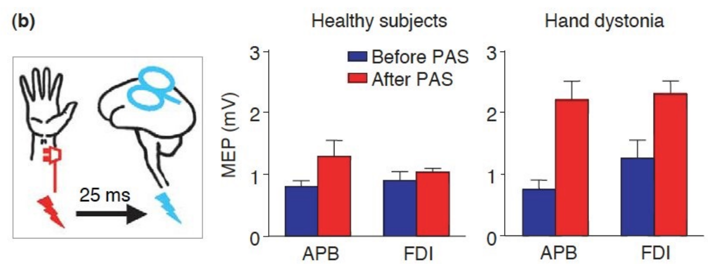




Shouval et al, Front Comput Neurosci 2010

Quartarone et al, TINS 2010

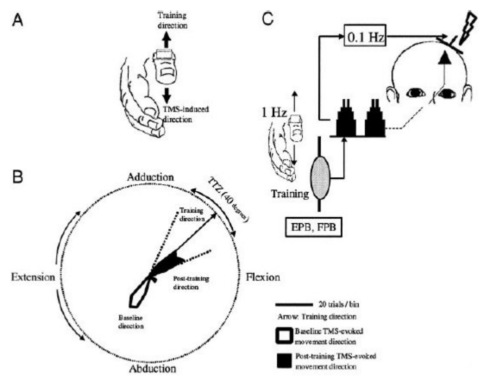
Paired associative stimulation (PAS)



- Electrical stimulation of median nerve is followed by a TMS pulse over sensorimotor cortex.
  - 90 pairs of stim-TMS are repeated every 20 sec
  - interstimulus interval 25 msec: facilitates selective MEP
  - linked to NMDA dependent LTP

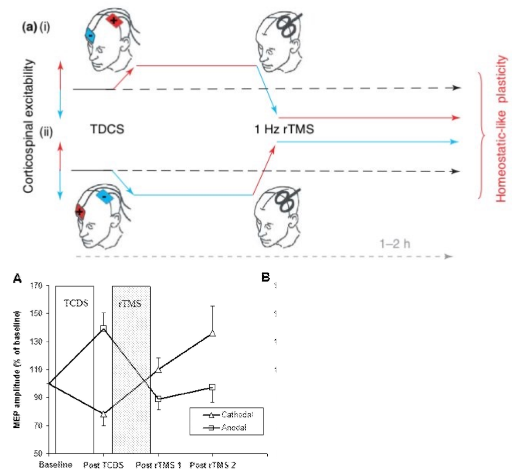
Quartarone et al, Cur Op Neuro, 2008

Pair TMS with behavior (Hebbian learning)



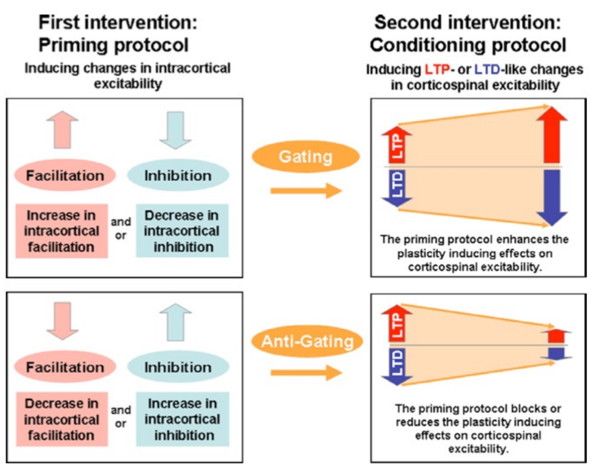
Butefisch et al 2004, J Neurophys

Homeostatic plasticity (meta-plasticity) priming "state" before rTMS



Quartarone et al. 2006 TINS

Priming protocols and meta-plasticity



Siebner 2010, Clin Neurophysiol 121(4)

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

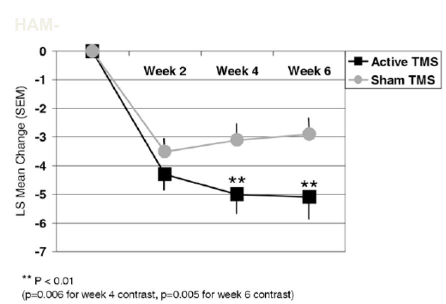


Table 3. Adverse Events Occurring in the Active Treatment Group at a Rate of 5% or More and at Least Twice the Rate for Sham (with ME-Coded Preferred Terms Shown)

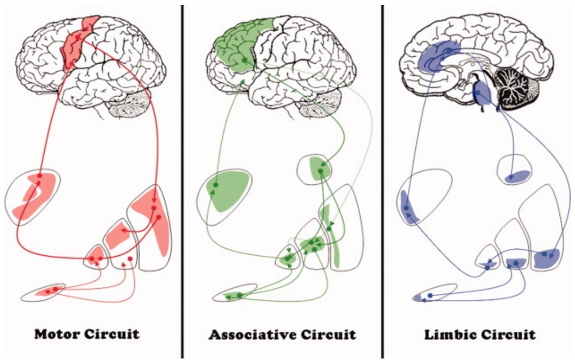
Body System / Preferred term	Active TMS (n = 165) n (%)	Sham TMS (n = 158) n (%)
Eye disorders		
Eye pain	10 (6.1)	3 (1.9)
Gastrointestinal Disorders Toothache	12 (7.3)	1 (.6)
General Disorders and Site Administration Conditions		
Application site discomfort	18 (10.9)	2 (1.3)
Application site pain	59 (35.8)	6 (3.8)
Facial pain	11 (6.7)	5 (3.2)
Musculoskeletal and connective tissue disorders		
Muscle twitching	34 (20.6)	5 (3.2)
Skin and subcutaneous tissue disorders		
Pain of skin	14 (8.5)	1 (.6)

MedDRA, *Medical Dictionary for Regulatory Activities.*

O'Reardon et al (2007) Biol Psychiatry 62(11):

Can cortical modulation be directed to target specific symptoms?

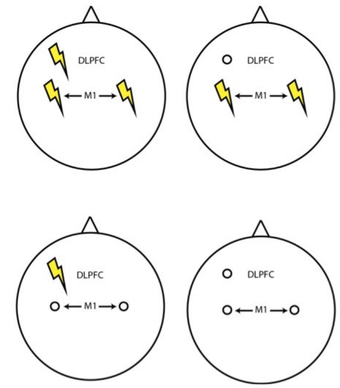
- Motor circuit = motor symptoms
- Prefrontal circuit = mood symptoms



Obeso et al (2008) Mov Disord 23 Suppl 3: S548-559.

Magnetic **S**timulation for the **Tr**eatment of Motor and Mood Symptoms of **P**arkinson's **D**isease (MASTER-PD trial)

- First prospective, double-blind, sham-controlled, parallel-group multicenter rTMS clinical trial in PD in North America
- Avoids medication side-effects and surgical risks
- Potential selectivity of effects (motor vs mood)
- Only multisession rTMS trial testing somatotopic effects of rTMS
- Realistic sham-rTMS conditions
- Rigorous safety and tolerability monitoring



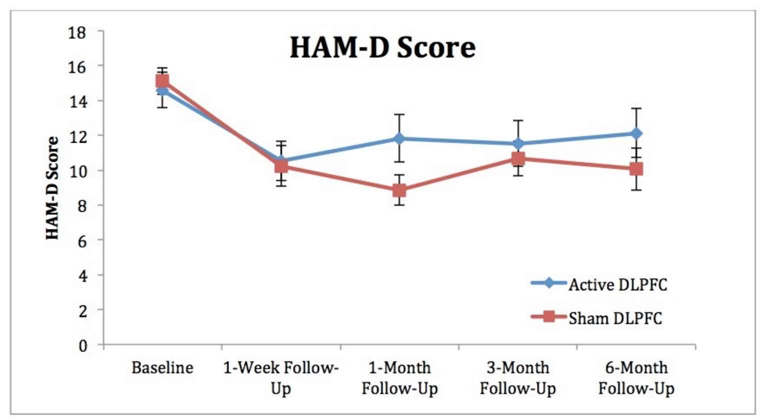
Clinicaltrials.gov: NCT01080794

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

Baseline OFF med evaluation	2 weeks of daily rTMS (ON meds)	0 mo post-rTMS OFF eval	1 mo post-rTMS OFF eval	3 mo post-rTMS OFF eval	6 mo post-rTMS OFF eval

- Patients with PD for >3 years, both motor (movement) symptoms and depression (with current or past treatment with an antidepressant)
- Outcome measures: UPDRS Part III (motor), HAM-D (mood/depression)
- Locations: Beth Israel Deaconess Medical Center (Harvard), UCLA, Toronto, Florida, Cleveland Clinic, Oregon, NYU
- Interim analysis: 450 patients screened, 71 patients enrolled, 58 with complete datasets

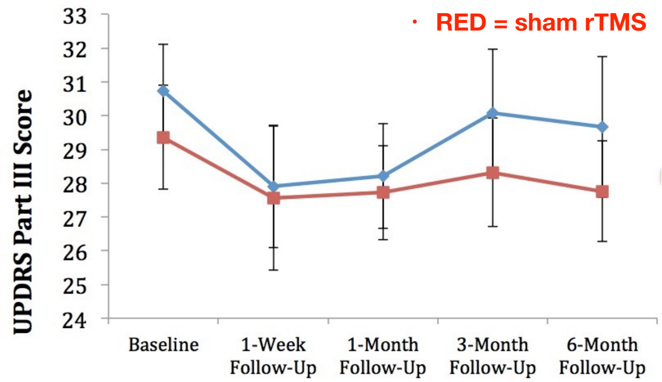
MASTER-PD - HAM-D depression score



Movement Disorders Congress 2015

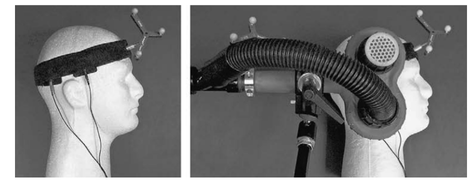
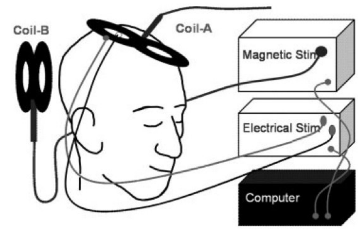
MASTER-PD - UPDRS motor score

- **BLUE = real M1 rTMS**
- **RED = sham rTMS**

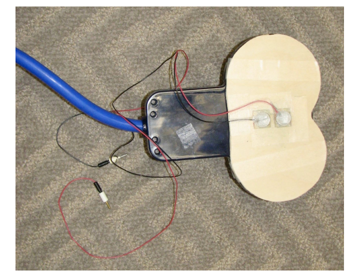


Movement Disorders Congress 2015

Sham rTMS conditions

Hamada et al, Movement Dis 2008

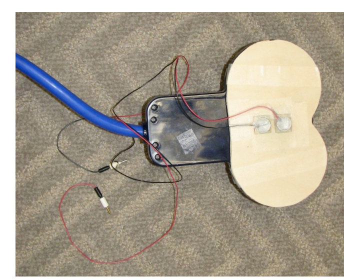


Magnetic Stimulation for the Treatment of Motor and Mood Symptoms of Parkinson's Disease (MASTER-PD)

- No significant differential effect on mood or motor function of real versus sham TMS.
- Multifocal M1 and/or DLPFC HF rTMS was no better than sham stimulation for motor or mood symptoms of PD.
- Sustained improvement of depression, regardless of stimulation status, points to universal benefit from study participation or from a perceived intervention.
- Transient improvement of UPDRS III indicates strong placebo response (perhaps related to salient electrical sham stimulation) preclude specific conclusions regarding multi-target rTMS efficacy.
- Better understanding of sham rTMS response in this particular population may help designing future efficacy studies.

Realistic sham rTMS conditions

- 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



Mennemeier et al 2009

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.
- ..., so 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."

Future directions and applications of modeling TMS and TDCS effects

- TMS and TDCS are unique noninvasive methods of stimulating the human brain
- Most studies
  - TMS/TDCS as modulation/perturbation to interpret behavioral, neurophysiologic, clinical outcomes; some effects lasting.
- Gaps in knowledge
  - Mechanisms of effect (more realistic brain models, effects on networks/ connectivity, animal and tissue models)
  - Developing novel coils for focusing surface field (improved resolution) or deeper structures (greater effects)
  - Use as biomarker or surrogate marker for neuropsychiatric disorders of plasticity (not just function)
  - Predictive ability to predict response to potential invasive neurointerventions
  - Making TMS/TDCS as part of multimodal adjunctive treatment for neuropsychiatric disease