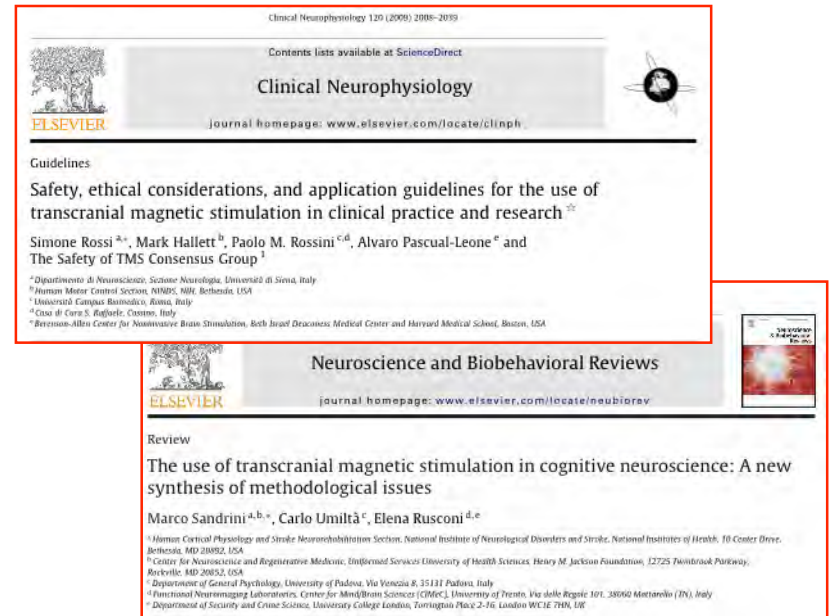


# UCLA Principles of Neuroimaging

## Transcranial magnetic stimulation (TMS)

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Dept of Neurology, UCLA  
Feb 24, 2014



## (transcranial) magnetic stimulation (TMS)

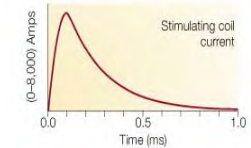
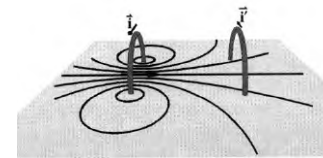


## FDA approvals of rTMS for treatment of medication-refractory major depression

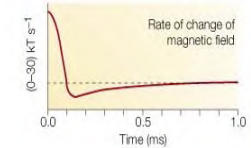


## Faraday's law of induction

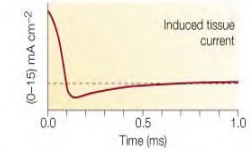
- A time-varying current ( $di/dt$ ) in a wire loop will induce a magnetic field ( $B$ )
- The magnetic field will induce an electromotive force ( $\epsilon$ ) in an adjacent conductor



$i$



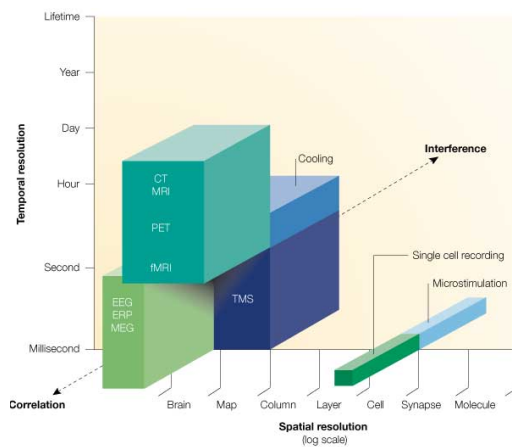
$\frac{di}{dt}$



$\epsilon$

Walsh and Cowey 2000

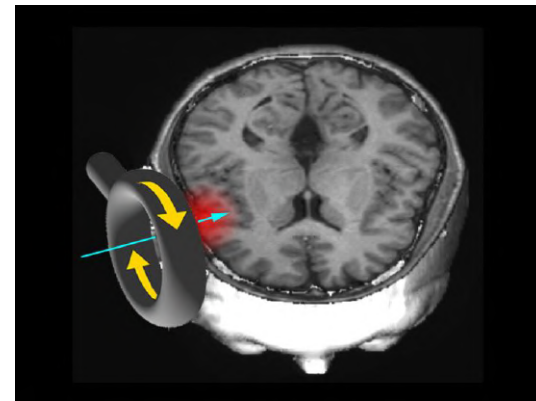
TMS has intermediate temporal/spatial resolution but unique interference qualities



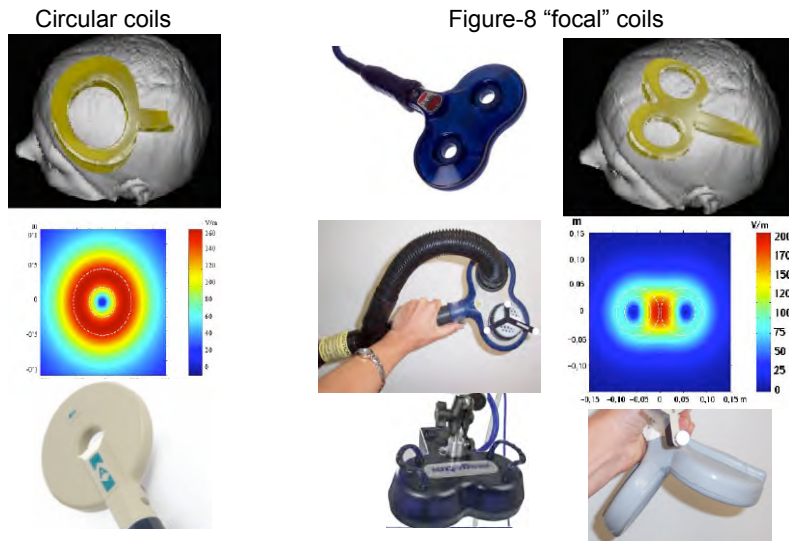
Nature Reviews | Neuroscience

Walsh and Cowey 2000

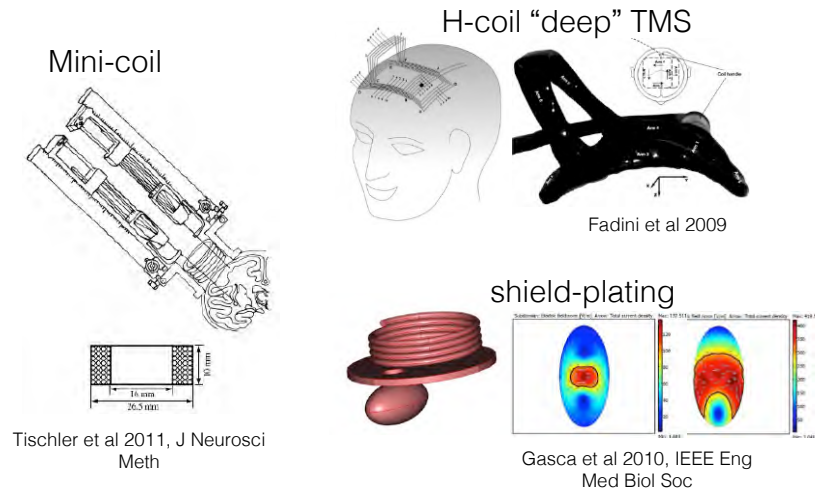
## What does TMS stimulate?



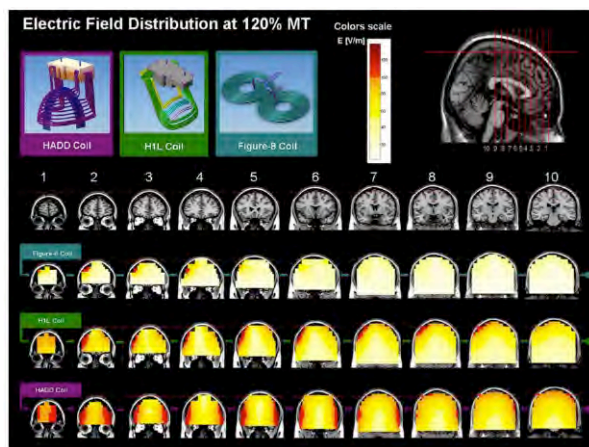
## What does TMS stimulate I? depends on coil



## Advances in TMS coil designs

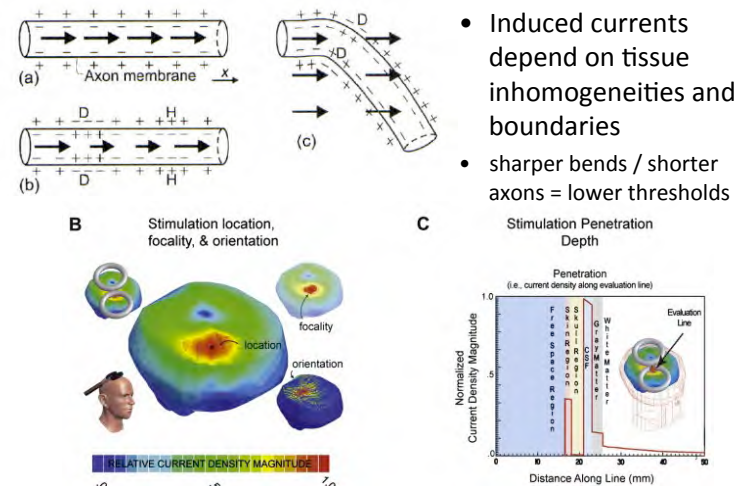


## Deeper TMS coil designs



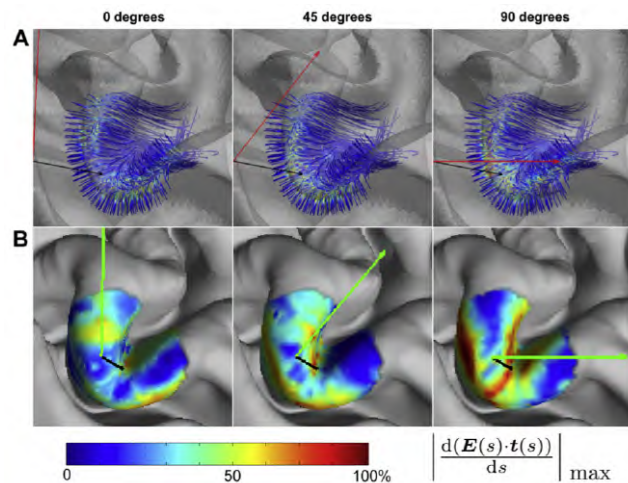
Huang et al (2009) Brain Stimul.

## What does TMS stimulate II: tissue boundaries



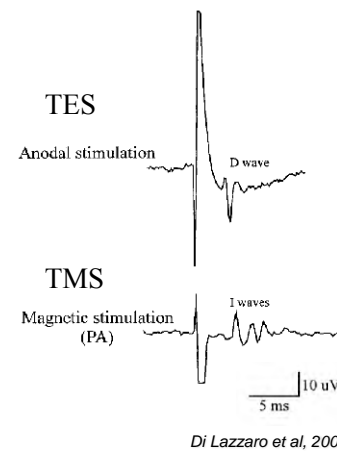
Wagner et al. (2004) IEEE Trans Biomed Eng

## What does TMS stimulate II: axon boundaries

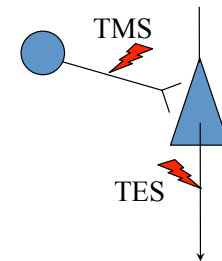


Nummenmaa et al. "Targeting of white matter tracts with transcranial magnetic stimulation." [Brain Stimulation](#)

## What does TMS stimulate III?



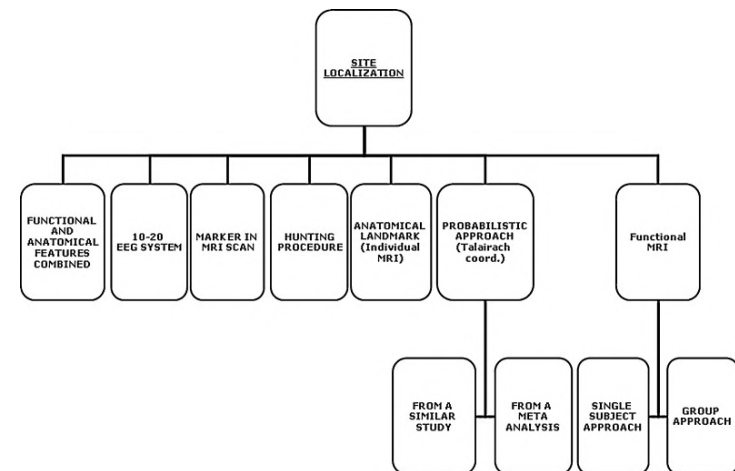
- TMS preferentially produces trans-synaptic stimulation
- Compared to electrical stimulation, TMS responses are more variable and sensitive to both internal and external factors



## What factors influence effects of TMS on the brain?

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

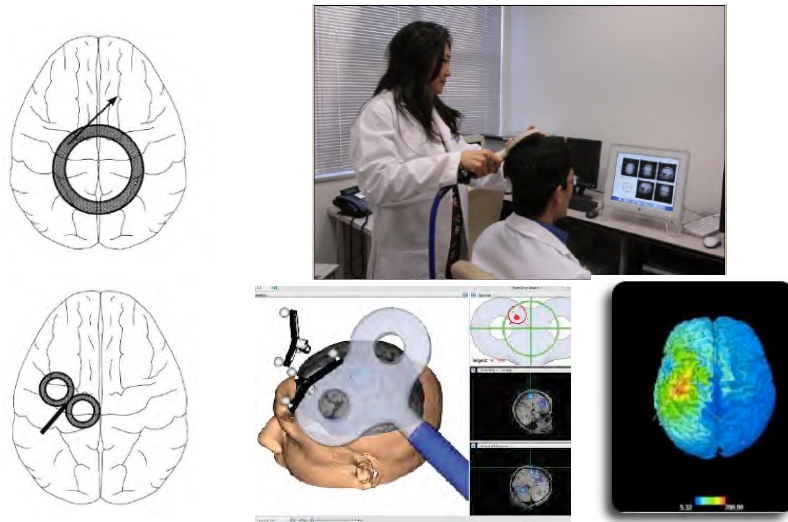
## TMS site



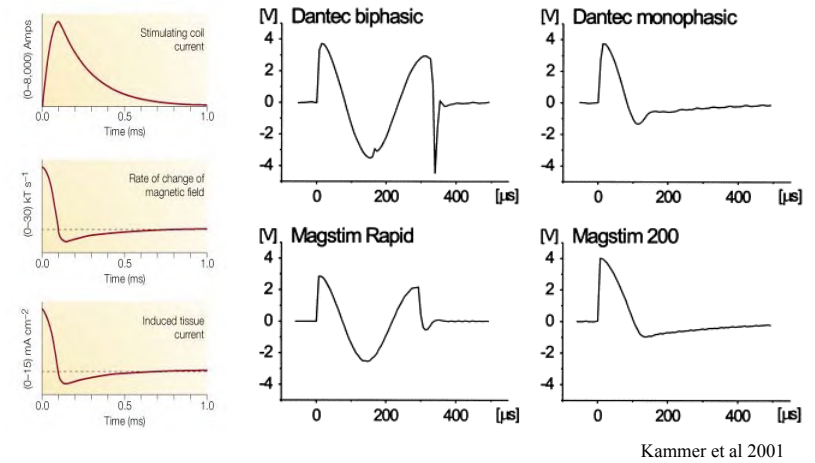
Sandrini et al 2011



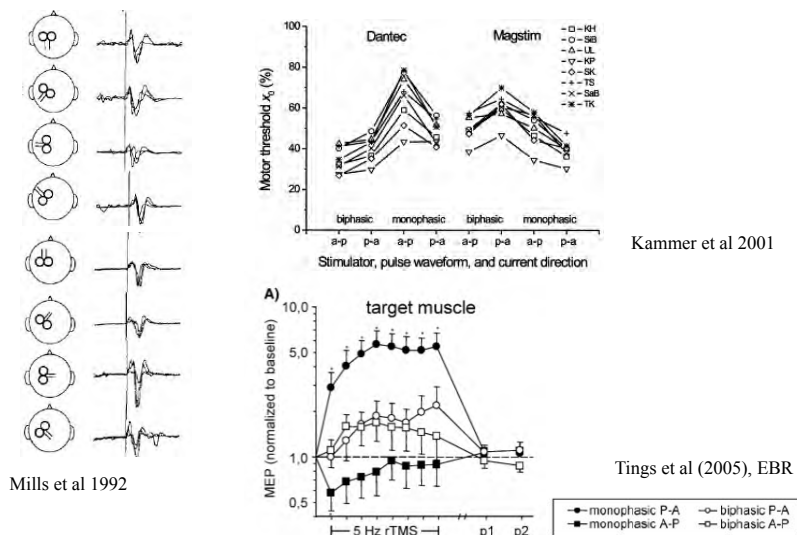
## Coil location: TMS hotspot and neuronavigation



## TMS effects depend on waveform



## TMS effects depend on waveform & orientation



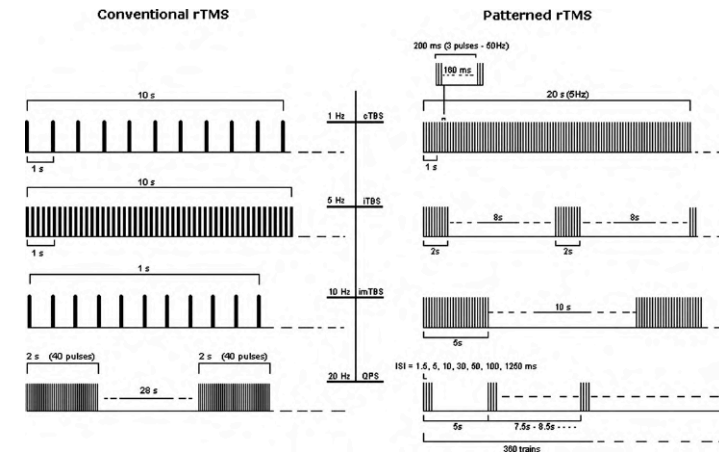
## Common TMS study types

- 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

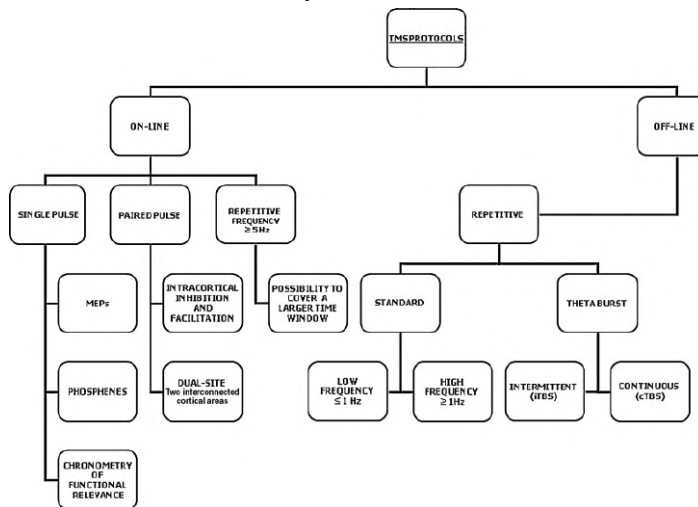
- Conventional
- Single-pulse TMS
  - (1 pulse every 5-10 secs)
  - Paired-pulse TMS
    - Same vs different sites
- Repetitive TMS (rTMS)
  - Conventional rTMS
    - rTMS Low frequency rTMS ( $\leq 1$  Hz)
    - High frequency rTMS ( $>5$  Hz)
- Non-conventional
- Single-pulse TMS
  - State-dependent 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

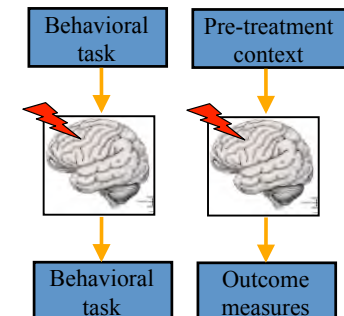
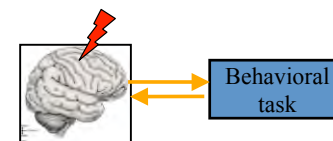
## TMS protocols



Sandrini et al 2011

## On-line vs off-line study designs

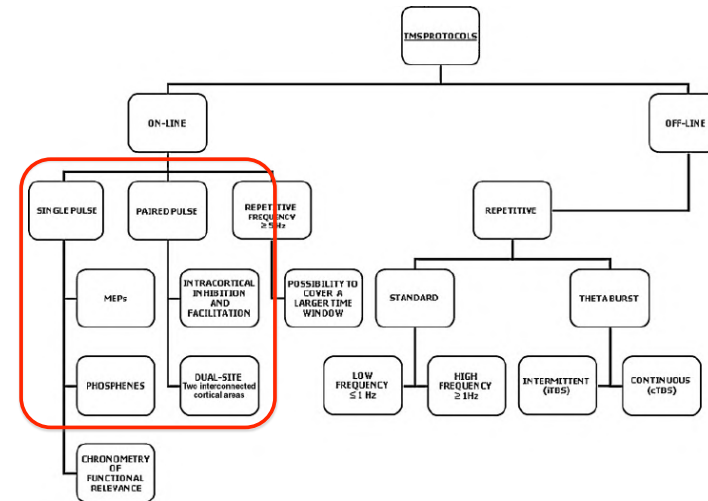
- “on-line” concurrent TMS stimulation of ongoing process
  - Reliably (relatively) produces interpretable disruptive effects
  - Single pulses highly temporally specific
  - Can explain facilitative effects by models of competitive inhibition
  - Can yield measures of excitability over primary motor/visual cortex
- “off-line” rTMS modulation method (?virtual lesion)
  - Avoids interference of on-line TMS with task
  - Temporo-spatial specificity poorer
  - Effects are more heterogeneous



# Common TMS study types

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# Neurophysiology TMS studies



Sandrini et al 2011

## 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)

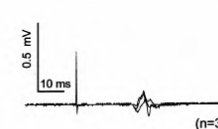
- Minimum stimulus intensity required to elicit a small motor response in a target muscle 50% of the time
- Can be assessed at rest (RMT) or active contraction (AMT)
- Enables comparable intensity of stimulation across subjects

### 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

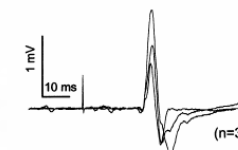
### Relaxation:

Preinnervation: peak-to-peak < 50 μV



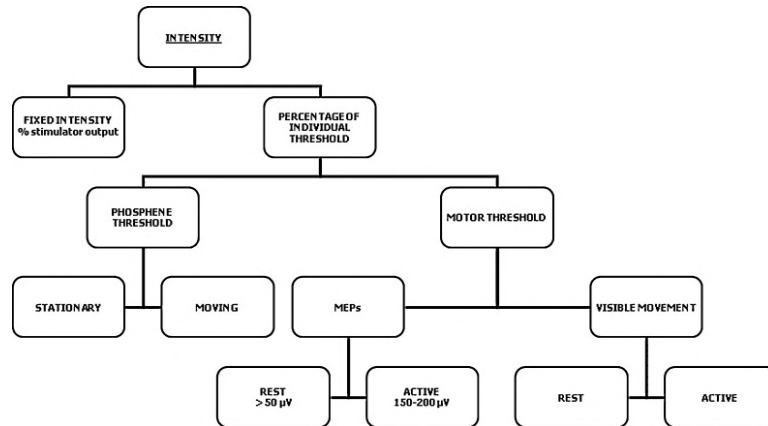
### Facilitation:

Preinnervation: 1-5% max. rms



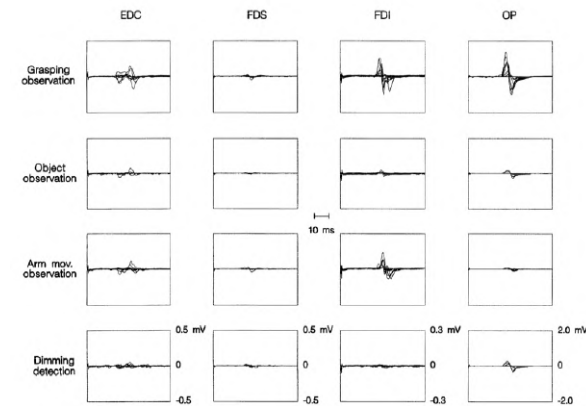
Kaelin-Lang, J Neuro Methods 2000

## Intensity



Sandrini et al 2011

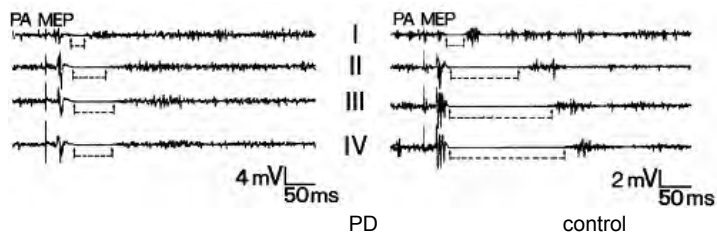
## TMS intensity and location in study of motor resonance during action observation



Fadiga et al 1995

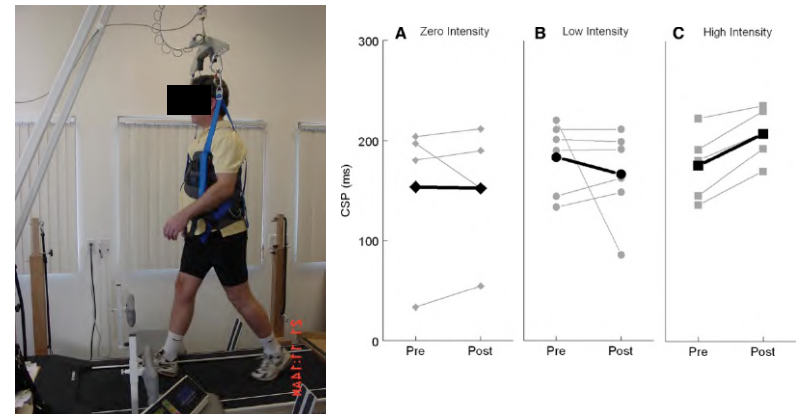
## Cortical silent period

- 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



Cantello, Neurology 1991;41:1449-56

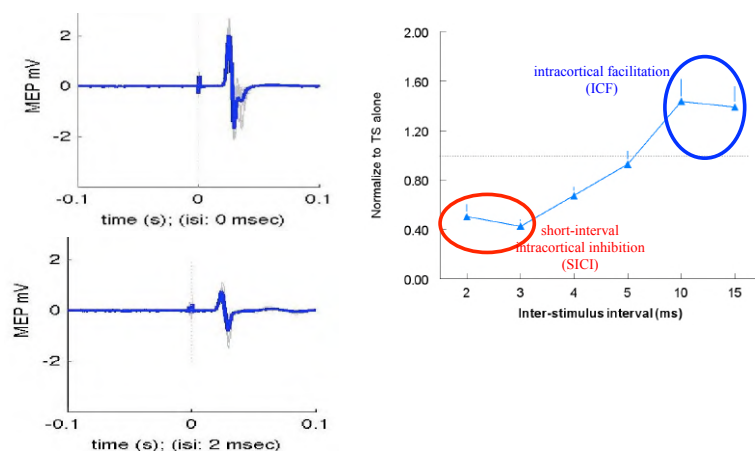
## Silent period durations respond to high-intensity treadmill training in early PD



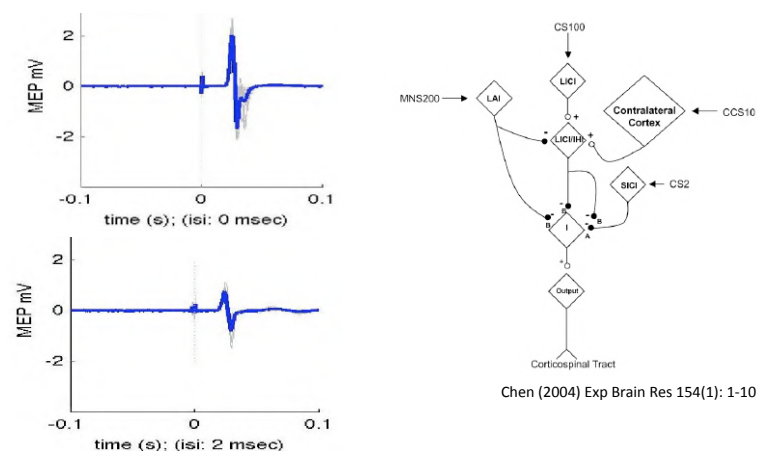
Fisher, Wu et al. (2008) Arch Phys Med Rehabil 89(7): 1221-1229



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



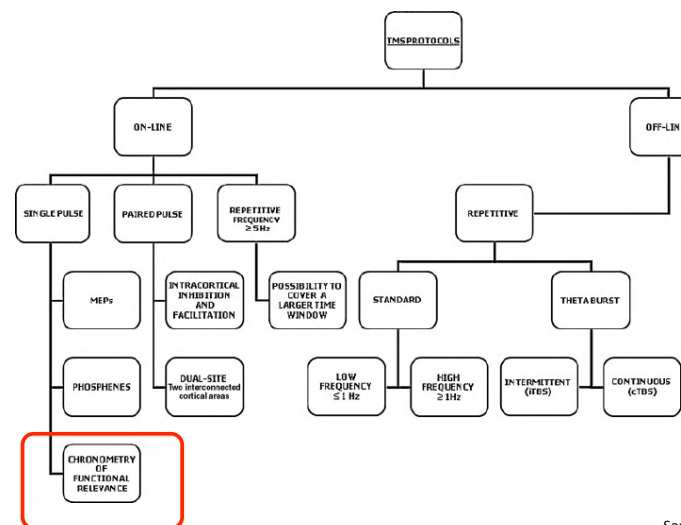
## Paired-pulse TMS can probe interactions among intracortical circuits



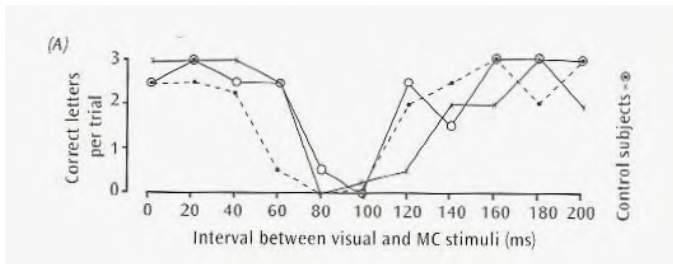
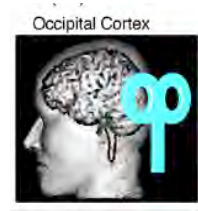
## Disorders with abnormal excitability

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

## Perturbation TMS studies

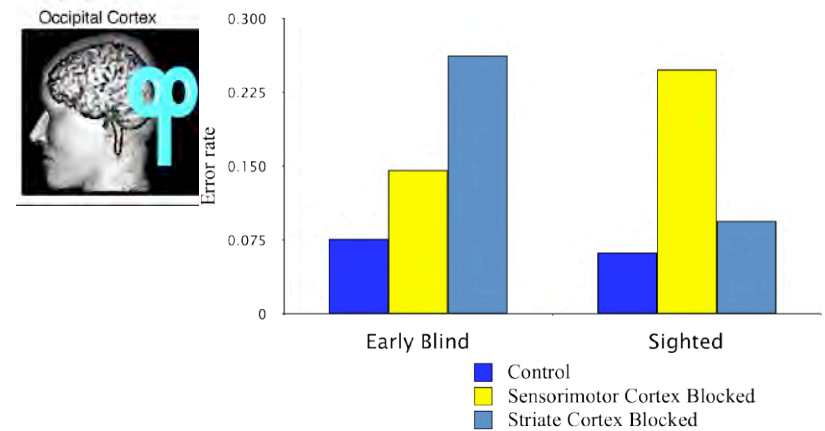


## Single-pulse TMS over occipital lobe can disrupt visual perception



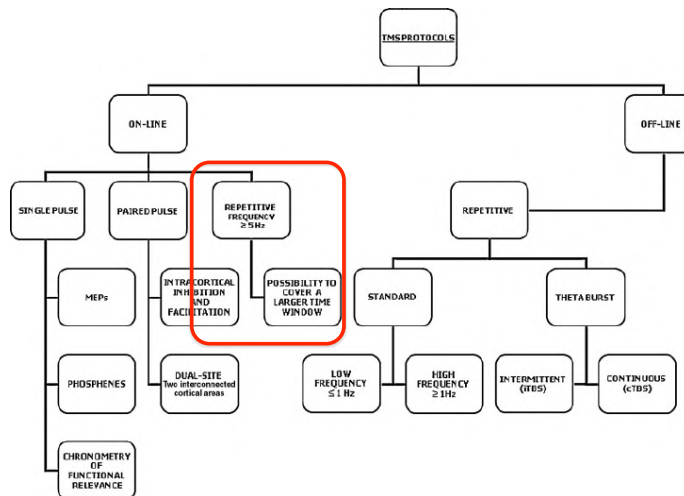
Amassian 1989 (Handbook of TMS 2002)

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



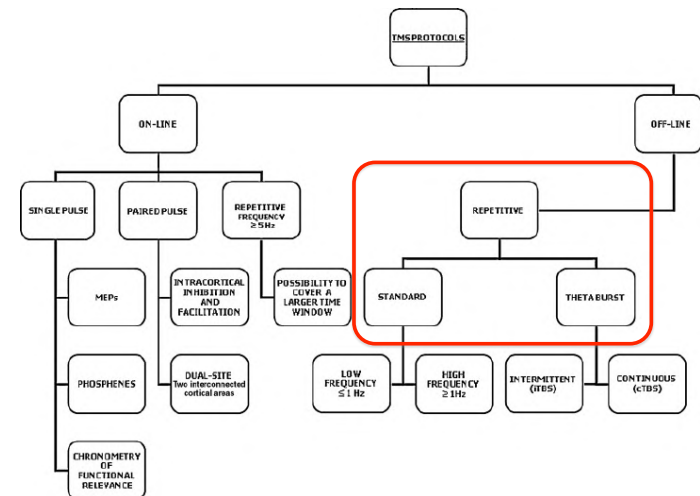
Cohen et al 1997

## Perturbation TMS studies



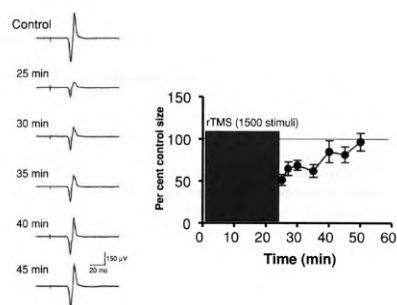
Sandrini et al 2011

## Repetitive TMS

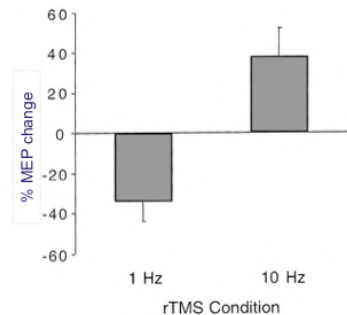


Sandrini et al 2011

## Offline conventional rTMS modulation of cortical excitability

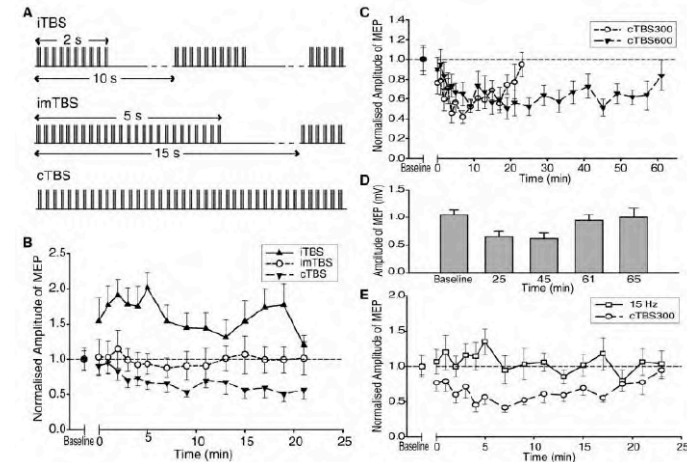


Touge et al (2001) Clin Neurophysiol



Maeda et al (2000) Exp Brain Res

## Theta-burst stimulation



Huang et al (2005) Neuron

## Advantages of offline-rTMS technique

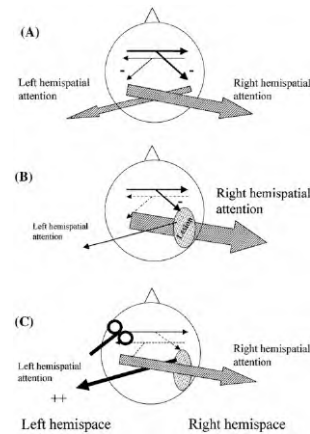
- Normal subjects can be studied
- Acute perturbation avoids CNS reorganization
- Subjects serve as own controls
- Reproducible study design allows for cleaner statistical analysis
- Avoids confound of on-line rTMS artifacts
- Neighboring brain region controls allows functional spatial specificity to 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
  - Stimulate release (or modulate levels) of neurotransmitters
  - Modulation of signaling pathways and gene transcription

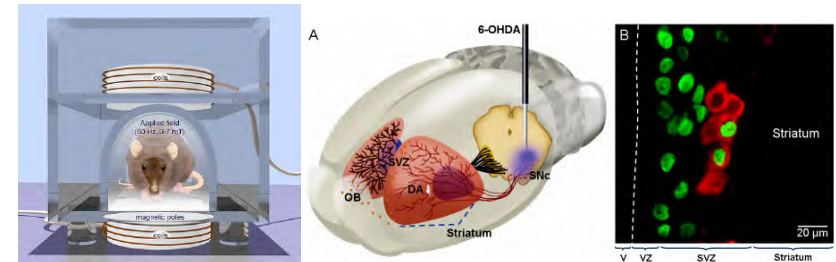
## Virtual lesions and competitive inhibition

- 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



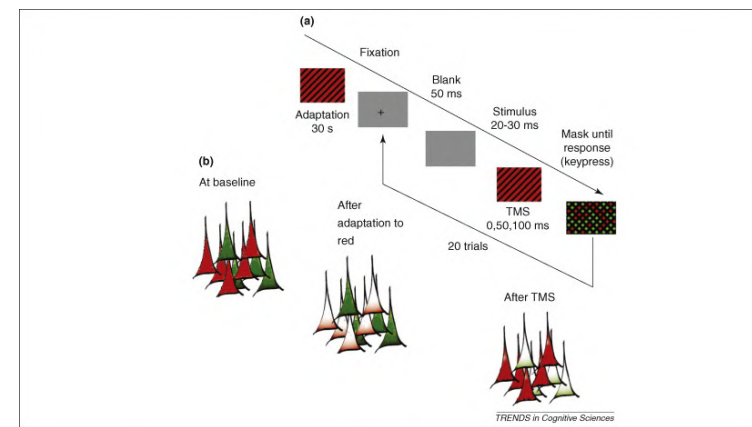
- rTMS modulates
  - c-fos and c-jun expression
  - Possible BDNF mRNA expression
  - Dopamine, serotonin, vasopressin, others
- Effects may increase with daily rTMS

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)

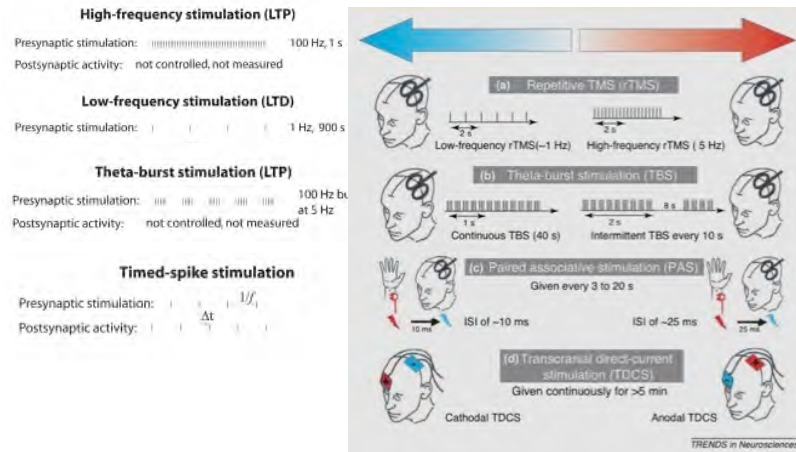
## State-dependency of TMS



Silvanto et al, TINS 2008



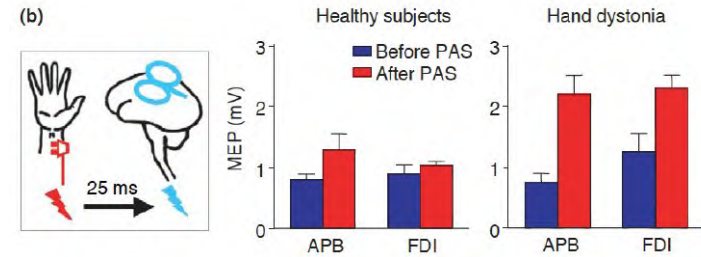
## Types of neuromodulation to probe or shape plasticity



Shouval et al, Front Comput Neurosci 2010

Quartarone et al, TINS 2010

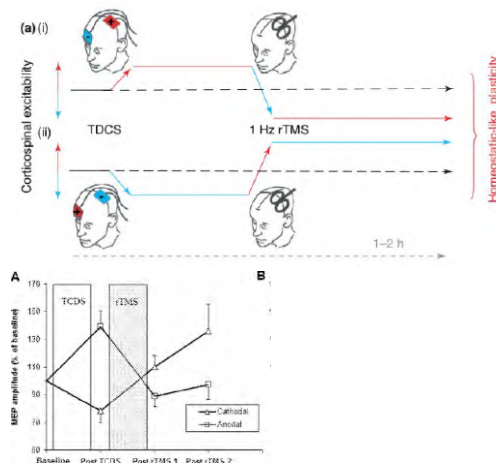
## Paired associative stimulation (PAS)



- 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

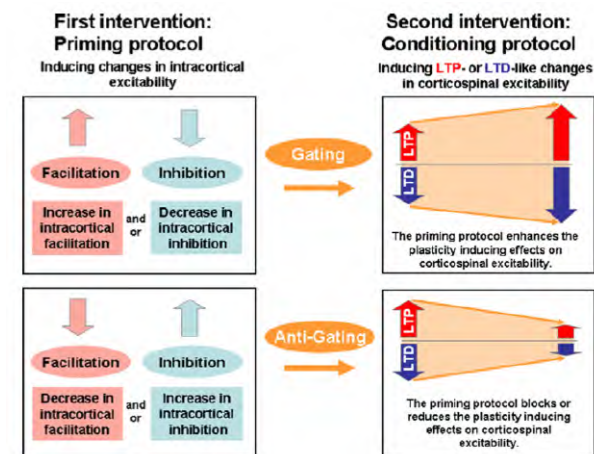
Quartarone et al, Cur Op Neuro, 2008

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



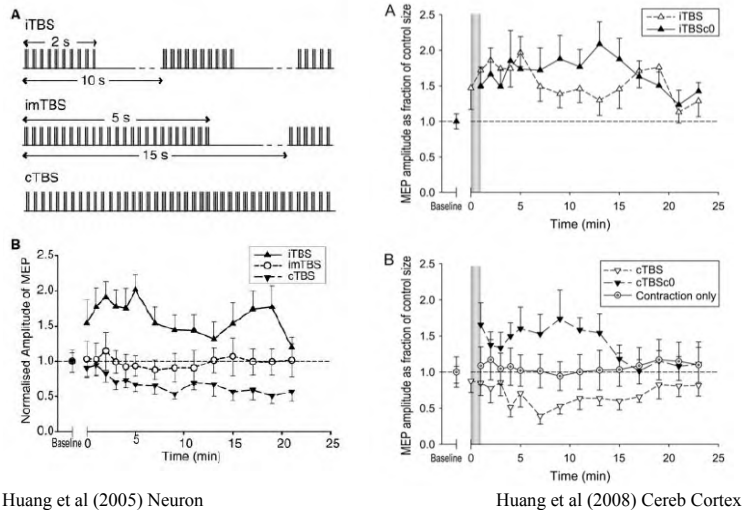
Quartarone et al. 2006 TINS

## Priming protocols and meta-plasticity

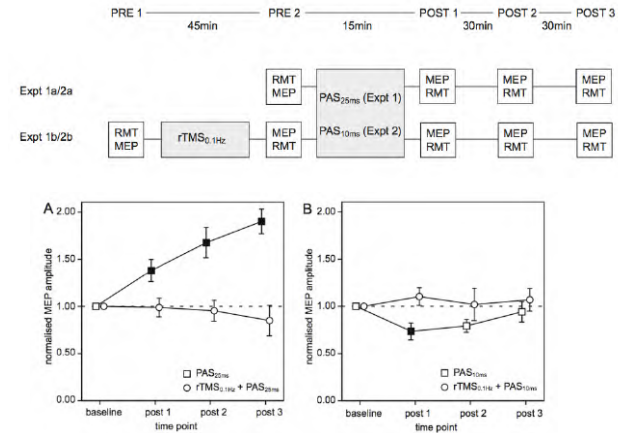


Siebnier 2010, Clin Neurophysiol 121(4)

## Theta-burst effects modulated by activity



## Single-pulse TMS may induce priming effects



Delvendahl et al (2010) Clin Neurophysiol

## Potential risks of rTMS

### 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

### Theoretical Risks

- ◆ Neurotoxicity
- ◆ Kindling
- ◆ Endocrine effects
- ◆ Social and psychological consequences of a seizure

## 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."