UCLA Principles of Neuroimaging

Transcranial magnetic stimulation (TMS)

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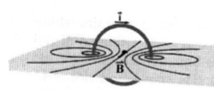
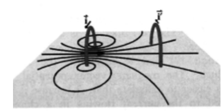
Faraday's law

- 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

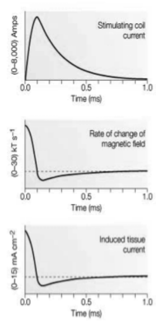
$$\vec{B} = \frac{\mu_0 I}{4\pi}\oint \frac{d\vec{l} \times \vec{u}_r}{r^2}$$

Biot-Savart law:
B flux direction by right-hand rule

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \qquad \mathcal{E} = -L\frac{di}{dt}$$

L = inductance

Induced TMS current

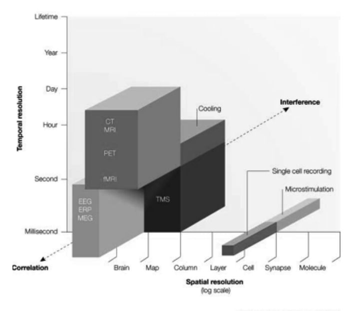
i

$\frac{di}{dt}$

ε

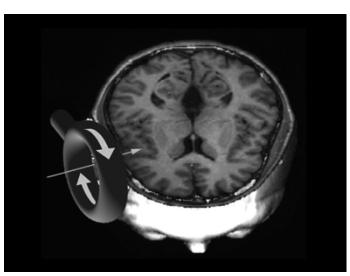
Walsh and Cowey 2000

TMS has intermediate temporal/spatial resolution but unique interference qualities



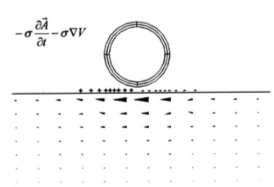
Walsh and Cowey 2000

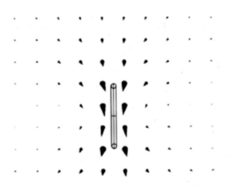
What does TMS stimulate?



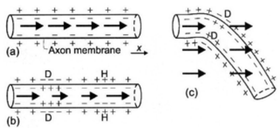
Boundary effects:

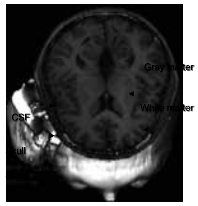
– TMS stimulation is parallel to scalp surface
– Lack of radial component to stimulation



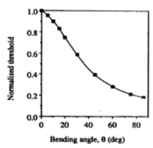


Membrane effects on axon depolarization

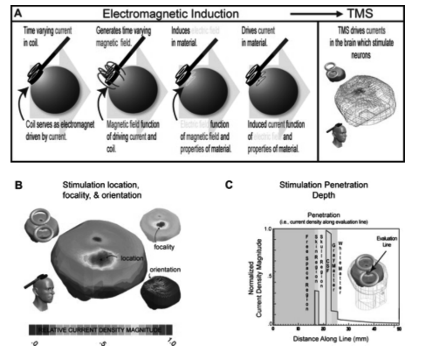




- Induced currents depend on tissue inhomogeneities
- Sharper bends / shorter axons = lower thresholds



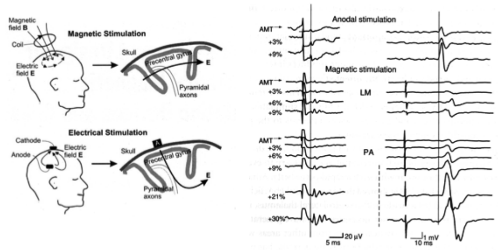
Modeling TMS effects



Wagner et al. (2004) IEEE Trans Biomed Eng

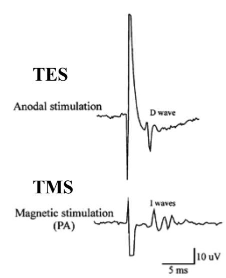
Transcranial magnetic & electrical stimulation

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



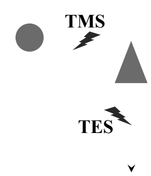
Di Lazzaro et al, 2003

Physiology of magnetic stimulation



Di Lazzaro et al, 2003

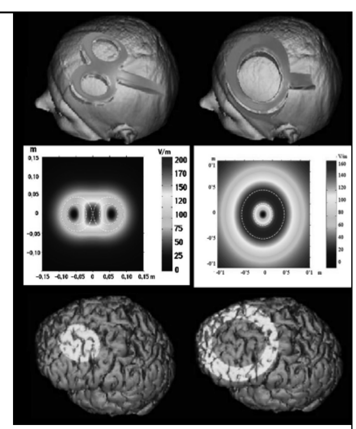
- TMS preferentially produces trans-synaptic stimulation
- Compared to electrical stimulation, TMS responses are more variable and sensitive to both internal and external factors



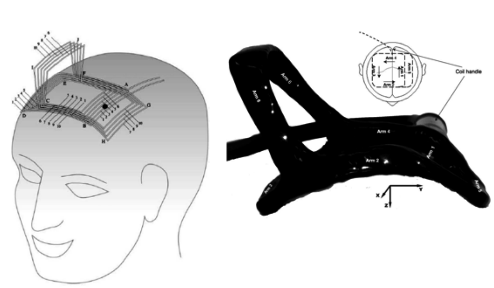
What factors influence effects of TMS on the brain?

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

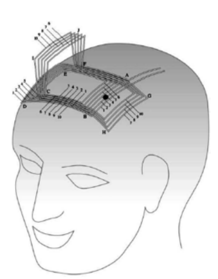
Coil geometries

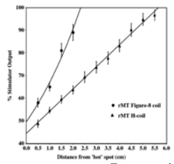


Can TMS be used to stimulate deep brain structures?

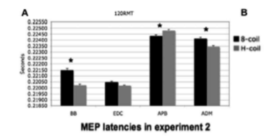


Can TMS be used to stimulate deep brain structures?



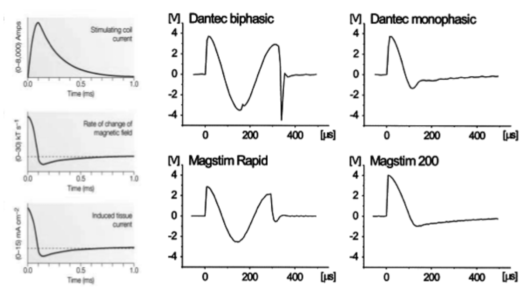


Zangen et al 2005



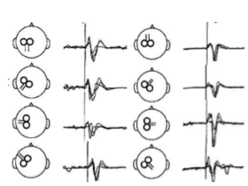
Fadini et al 2009

TMS effects depend on waveform

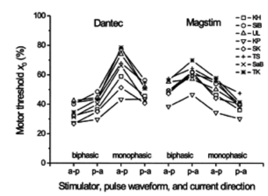


Kammer et al 2001

TMS effects are waveform & orientation specific

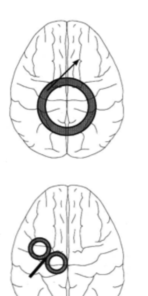


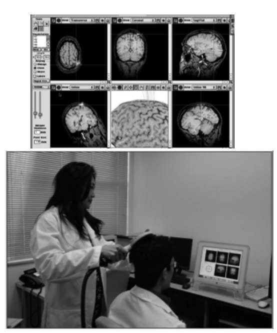
Mills et al 1992



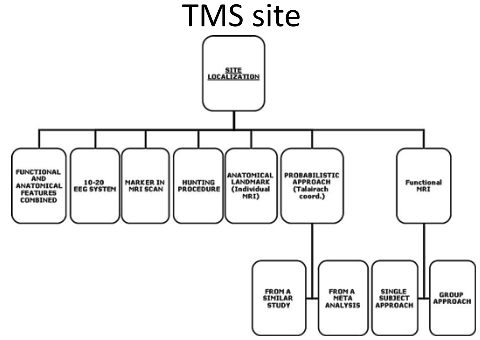
Kammer et al 2001

Coil location: TMS hotspot and neuronavigation





TMS site



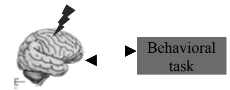
Sandrini et al 2011

Forms of TMS

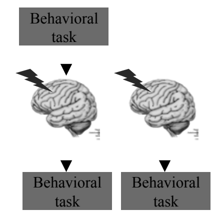
- Single-pulse TMS (1 pulse every 5-10 secs)
  - Paired-pulse TMS
- Repetitive TMS (rTMS)
  - Conventional rTMS
    - rTMS Low frequency rTMS (≤ 1 Hz)
    - High frequency rTMS (>1 Hz)
  - Patterned rTMS
    - Theta-burst stimulation (rTMS 50 Hz triplets at 5 Hz)

On-line vs off-line study designs

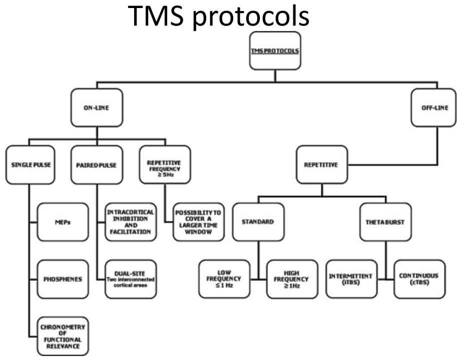
- "on-line" concurrent TMS stimulation of ongoing process
  - Reliably (relatively) produces interpretable disruptive effects
  - Single pulses highly temporally specific
  - Can explain facilitative effects by models of competitive inhibition
  - Can yield measures of excitability over primary motor/visual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



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



TMS protocols



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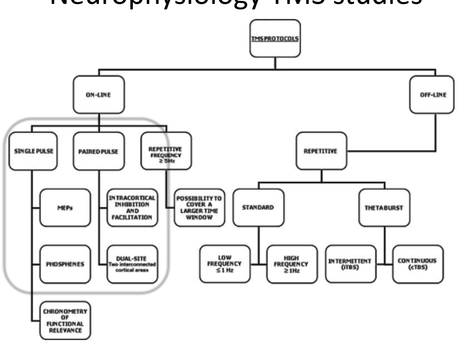
Common TMS study types

- 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



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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

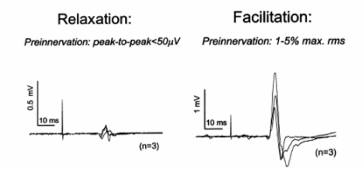
Motor cortex excitability

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

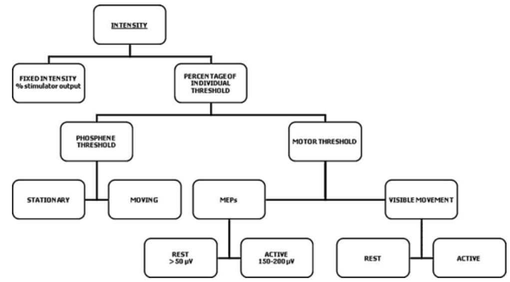
Motor evoked potential (MEP)

- 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



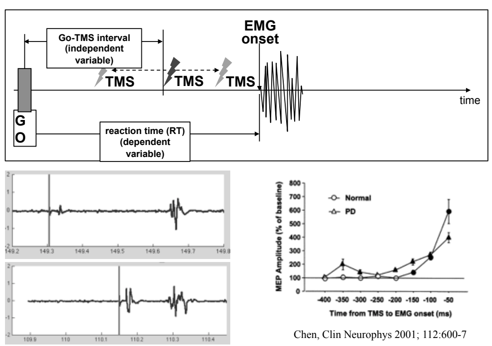
Kaelin-Lang, J Neuro Methods 2000

Intensity



Sandrini et al 2011

TMS excitability increases during reaction time

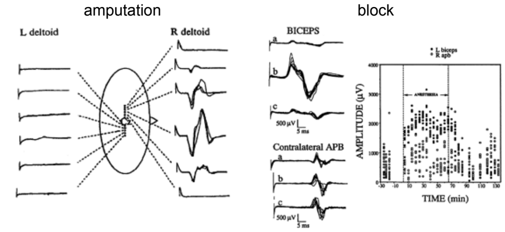


Chen, Clin Neurophys 2001; 112:600-7

MEP sizes demonstrate acute and chronic plasticity

Chronic right above-elbow amputation

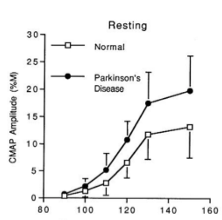
Acute forearm anesthetic block



Figures adapted from Chen, Cohen, Hallett 2002

Input-output curves

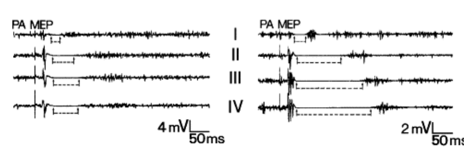
- MEP size plotted against TMS intensity with coil at fixed spot
- Often fitted with a sigmoid curve (MEP-50, maxMEP, slope)



From Valls-Sole et al, Neurology 44:1994

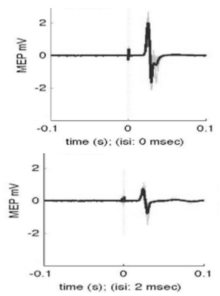
Cortical silent period

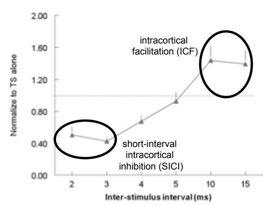
- If a target muscle is pre-contracted, a TMS pulse will evoke a MEP which is followed by a period of EMG silence
- **Duration of this silent period is a measure of inhibitory circuits**
- Early period is spinal in origin;
  latter period (>100 msec) is considered cortical in origin
- Considered GABA-dependent



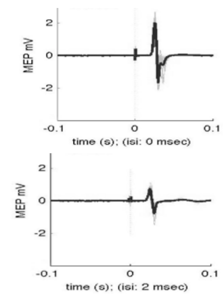
Cantello, Neurology 1991;41:1449-56

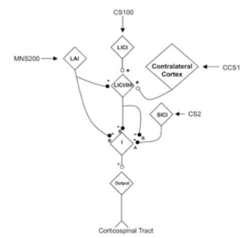
Paired-pulse TMS can probe intracortical circuit excitability within motor cortex





Paired-pulse TMS can probe interactions among intracortical circuits

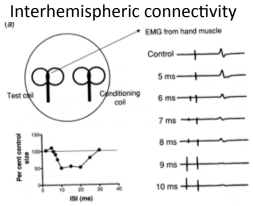




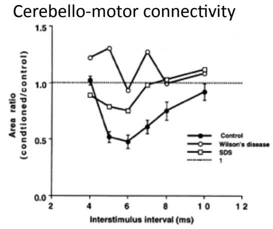
Chen (2004) Exp Brain Res 154(1): 1-10

Paired pulses assess inter-regional connectivity

Interhemispheric connectivity



Cerebello-motor connectivity

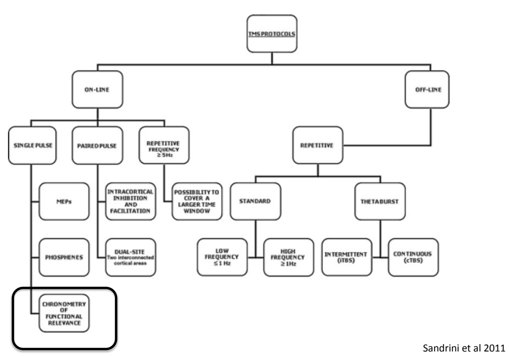


Ugawa et al 1997

Disorders with abnormal excitability

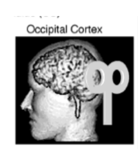
- Parkinson's disease
- Dystonia
- Stroke
- Epilepsy
- Depression
- Schizophrenia
- Essential tremor
- Amyotrophic lateral sclerosis
- Huntington's disease
- Tourette's syndrome
- Myelopathy
- Corticobasal gang degen
- Cerebellar degeneration
- Polyradiculoneuritis
- CNS demyelinating disease
- CNS tumors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

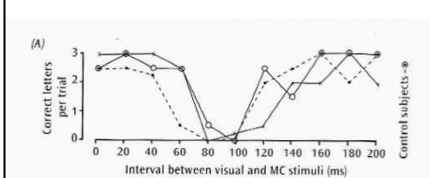
Perturbation TMS studies



Sandrini et al 2011

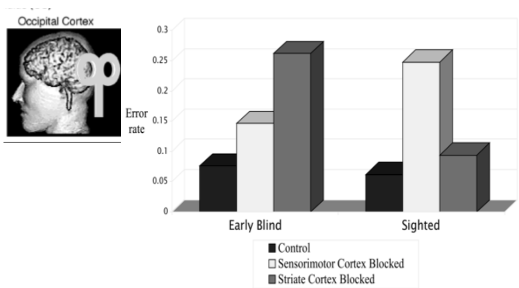
Single-pulse TMS over occipital lobe can disrupt visual perception





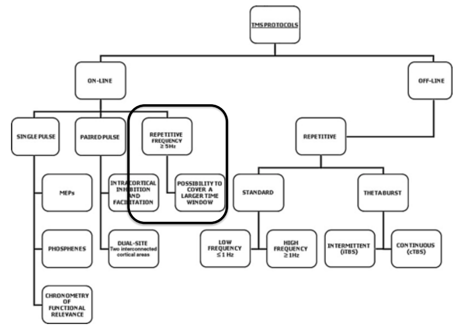
Amassian 1989 (Handbook of TMS 2002)

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



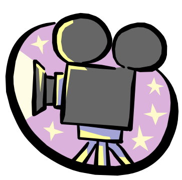
Cohen et al 1997

Perturbation TMS studies



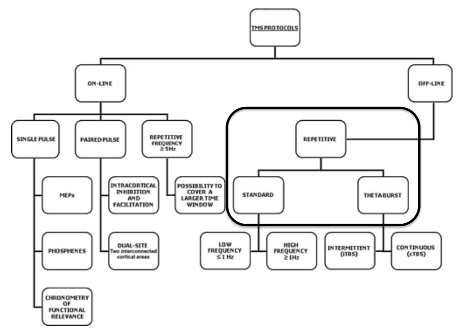
Sandrini et al 2011

Speech arrest with high-frequency rTMS



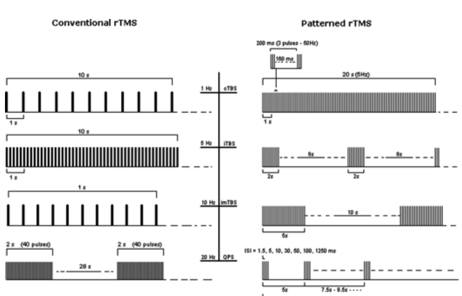
Pascual-Leone et al 1991

Repetitive TMS



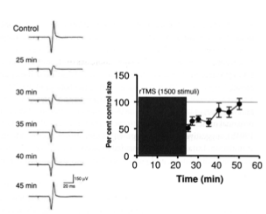
Sandrini et al 2011

rTMS types

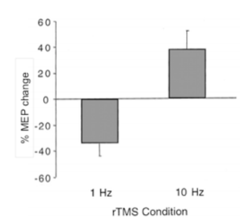


Rossi et al 2009

Offline conventional rTMS modulation of cortical excitability

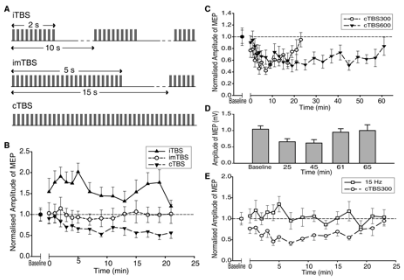


Touge et al (2001) Clin Neurophysiol



Maeda et al (2000) Exp Brain Res

Theta-burst stimulation



Huang et al 2005

Advantages of offline-rTMS technique

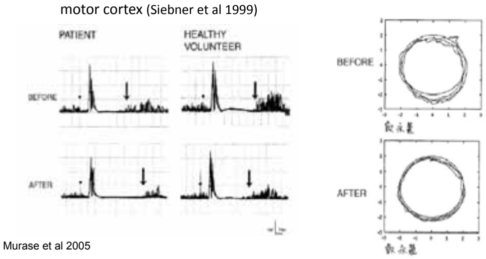
- Normal subjects can be studied
- Acute perturbation avoids CNS reorganization
- Subjects serve as own controls
- Reproducible study design allows for cleaner statistical analysis
- Avoids confound of on-line rTMS artifacts
- Neighboring brain region controls allows functional spatial specificity to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

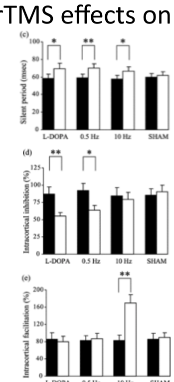
Decreasing cortical excitability to treat dystonia

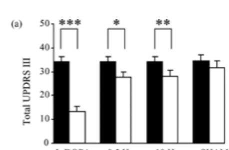
- 1 Hz rTMS over premotor cortex restores measures of inhibition (e.g. silent period) with improvement in writing (Murase et al 2005)
- Also, 1 Hz rTMS normalized paired-pulse intracortical excitability over motor cortex (Siebner et al 1999)



Murase et al 2005

rTMS effects on cortical excitability in PD





Lefaucheur et al 2004

Effects of offline rTMS

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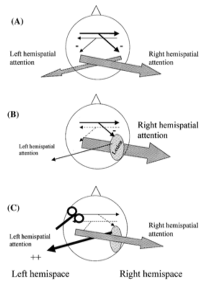
- **Distant effects**
  - Modulation of distant sites in a functional network (resting or state-related)
  - Decrease excitability to release inhibition in a distant area and achieve paradoxical facilitation (for example)
- Cellular and molecular (neurotransmitter) effects
  - Stimulate release (or modulate levels) of neurotransmitters
  - Modulation of signaling pathways and gene transcription

Virtual lesions and competitive inhibition

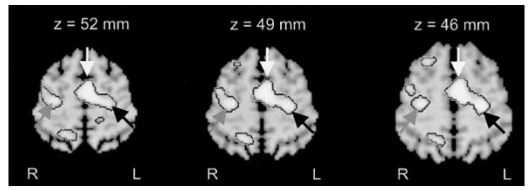
- Left hemispace neglect due to chronic right hemisphere lesions can be transiently improved with rTMS perturbations over left (unaffected) hemisphere



Oliveri et al 2001, Brighina et al 2003

Effects of rTMS: FDG PET

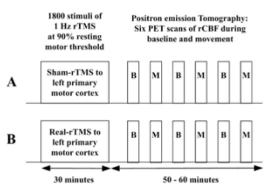
- 5 Hz subthreshold over M1
- Shows local increase in metabolism plus contralateral M1 and SMA

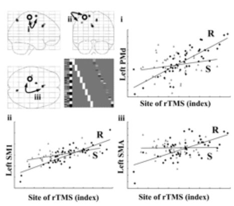


Siebner et al 2000

Offline imaging of 1 Hz rTMS over M1 on task-related connectivity (H_2O 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



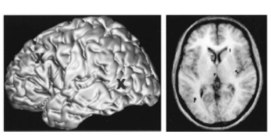


Lee et al, 2003

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

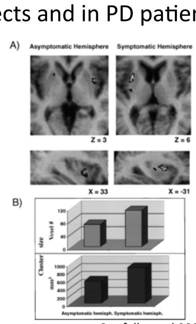
rTMS over PFC or M1 can release subcortical dopamine in normal subjects and in PD patients



Strafella et al 2001

Raclopride[11C] PET imaging

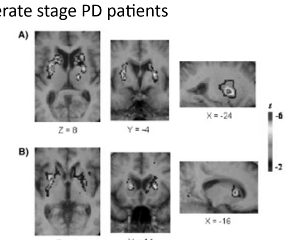
Raclopride is a competitive inhibitor of extracellular dopamine



Strafella et al 2006

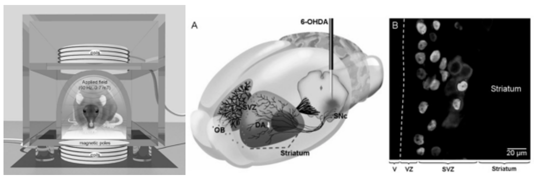
Significance of rTMS induced dopamine release remains uncertain

- Sham-rTMS induces asymmetric dopamine release in moderate stage PD patients



Strafella et al 2006

Cellular and molecular mechanisms of TMS



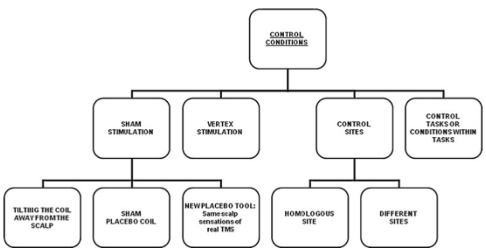
- rTMS modulates
  - c-fos and c-jun expression
  - Possible BDNF mRNA expression
  - Dopamine, serotonin, vasopressin, others
- Effects may increase with daily rTMS

Arias-Carrion 2008

Other TMS topics

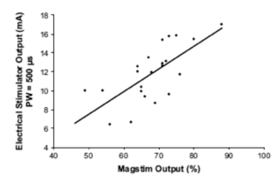
- Control and sham conditions
- Therapeutic rTMS for depression
- State-dependent TMS
- Meta-plasticity
- Safety and regulatory issues

Control conditions



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



Mennemeier et al 2009

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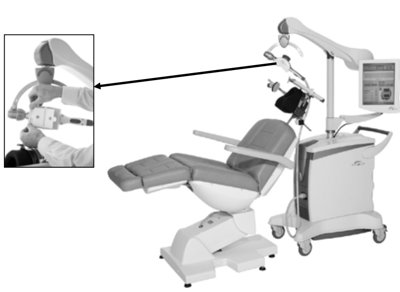
FDA approved Neurostar rTMS for treatment of medication-refractory major depression in Oct 2008



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

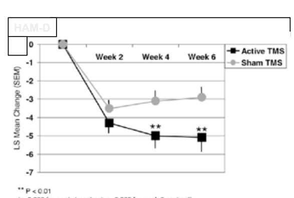


Table 3. Adverse Events Occurring in the Active Treatment Group at a Rate of 5% or More and at Least Twice the Rate for Sham (with ME-Coded Preferred Terms Shown)

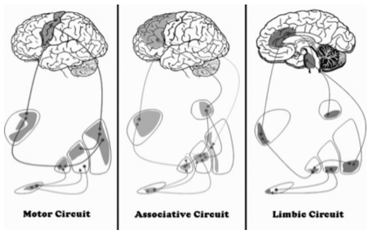
Body System / Preferred term	Active TMS (n = 165) n (%)	Sham TMS (n = 158) n (%)
Eye disorders		
Eye pain	10 (6.1)	3 (1.9)
Gastrointestinal Disorders Toothache	12 (7.3)	1 (.6)
General Disorders and Site Administration Conditions		
Application site discomfort	18 (10.9)	2 (1.3)
Application site pain	59 (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): 1208-1216

Can cortical modulation be directed to target specific symptoms?

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



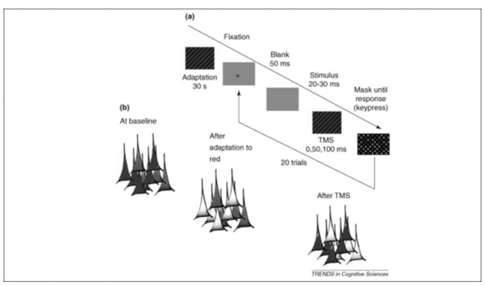
Obeso et al (2008) Mov Disord 23 Suppl 3: S548-559.

***Ma**gnetic **S**timulation for the **Tr**eatment of Motor and Mood Symptoms of **P**arkinson's **D**isease (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)

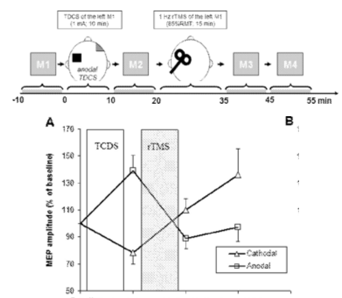
	M1 (bilateral)	DLPFC (left)
M1 group	real-rTMS	sham-rTMS
PFC group	sham-rTMS	real-rTMS
M1-PFC group	real-rTMS	real-rTMS
Sham group	sham-rTMS	sham-rTMS

State-dependency of TMS



Silvanto et al, TINS 2008

Homeostatic plasticity (meta-plasticity)



Quartarone et al. Brain 2005

TMS: FDA issues

- ♦ 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

Potential risks of rTMS

<u>Known Risks</u>

- ♦ 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

<u>Theoretical Risks</u>

- ♦ 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
  - Led to safety parameters (Wassermann 1998, Rossi et al 2009)
- 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

Table 4
Maximum safe duration (expressed in seconds) of single trains of rTMS. Safety defined as absence of seizure, spread of excitation or afterdischarge of EMG activity. Numbers preceded by > are longest duration tested. Consensus has been reached for this table.

Frequency (Hz)	Intensity (% of MT)				
	90%	100%	110%	120%	130%
1	>1800[a]	>1800	>1800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

[a] In Japan, up to 5000 pulses have been applied without safety problems (communication of Y. Ugawa).

Seizures induced by TMS

source	seizure type	rTMS intensity	frequency	duration	intertrain interval	comment
Pascual-Leone 1993	2nd generalized	250% MT	25 Hz	10 sec	Long	1st deg relative with seizures
Wassermann 1996	2nd generalized	105% MT	15 Hz	0.75 sec	0.25 sec	short intertrain interval
"	2nd generalized	110% MT	25 Hz	0.8 sec	1 sec	short intertrain interval
NINDS unpublished	2nd generalized	120% MT	15 Hz	2.5 sec	Long (2min)	
Mercuri unpublished	partial motor seizure	130% MT	3 Hz	7 sec	n/a	
Pascual-Leone unpublished	2nd generalized	90% MT	10 Hz	10 sec	60 sec	depressed on neuroleptics and tricyclic antidepressants
Flitman 1998	seizure	120% MT	15 Hz	0.75 sec	0.25 sec	short intertrain interval (increase this)
Conca 2000	partial complex seizure	110% MT	20 Hz	5 sec	60 sec	depressed, history of maprotiline-induced sz; (may be syncope)
Bernabeu 2004	2nd generalized	110% MT	20 Hz	2 sec	1 train	fluoxetine (SSRI)
Rosa 2004	generalized	100% MT	10 Hz	10 sec		beyond parameters but at 100% MT
Prikryl 2005	generalized	110% MT	15 Hz	10 sec		sleep deprivation, long duration
Figiel 1998	left motor seizures	110% MT	10 Hz	5 sec		antidepressants, 6hrs after rTMS session, may be pseudoseizure
Nowak 2006	generalized	90% MT	**1 Hz**	580 pulses		for tinnitus, after rTMS previously, may be convulsive syncope
Haupts 2004	generalized	66% MSO	**single-pulse**			multiple sclerosis with brain lesions, on olanzapine (antipsychotic)
Tharayil 2005	generalized	**during thresholding**	**single-pulse**			bipolar depression, on chlorpromazine, lithium, family history of epielpsy

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."