Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

NEURAL INTERFACES AND PROSTHESES

(Neurális interfészek és protézisek)

LECTURE 6

TRANSCRANIAL MAGNETIC STIMULATION

(Transzkraniális mágneses ingerlés)

RICHÁRD CSERCSA and GYÖRGY KARMOS

AIMS:

In this lecture, the student will become familiar with the principles and application techniques of transcranial magnetic stimulation. They will also learn about the history of magnetic stimulation, the different types of magnetic stimulation devices, and examples of possible fields of application.

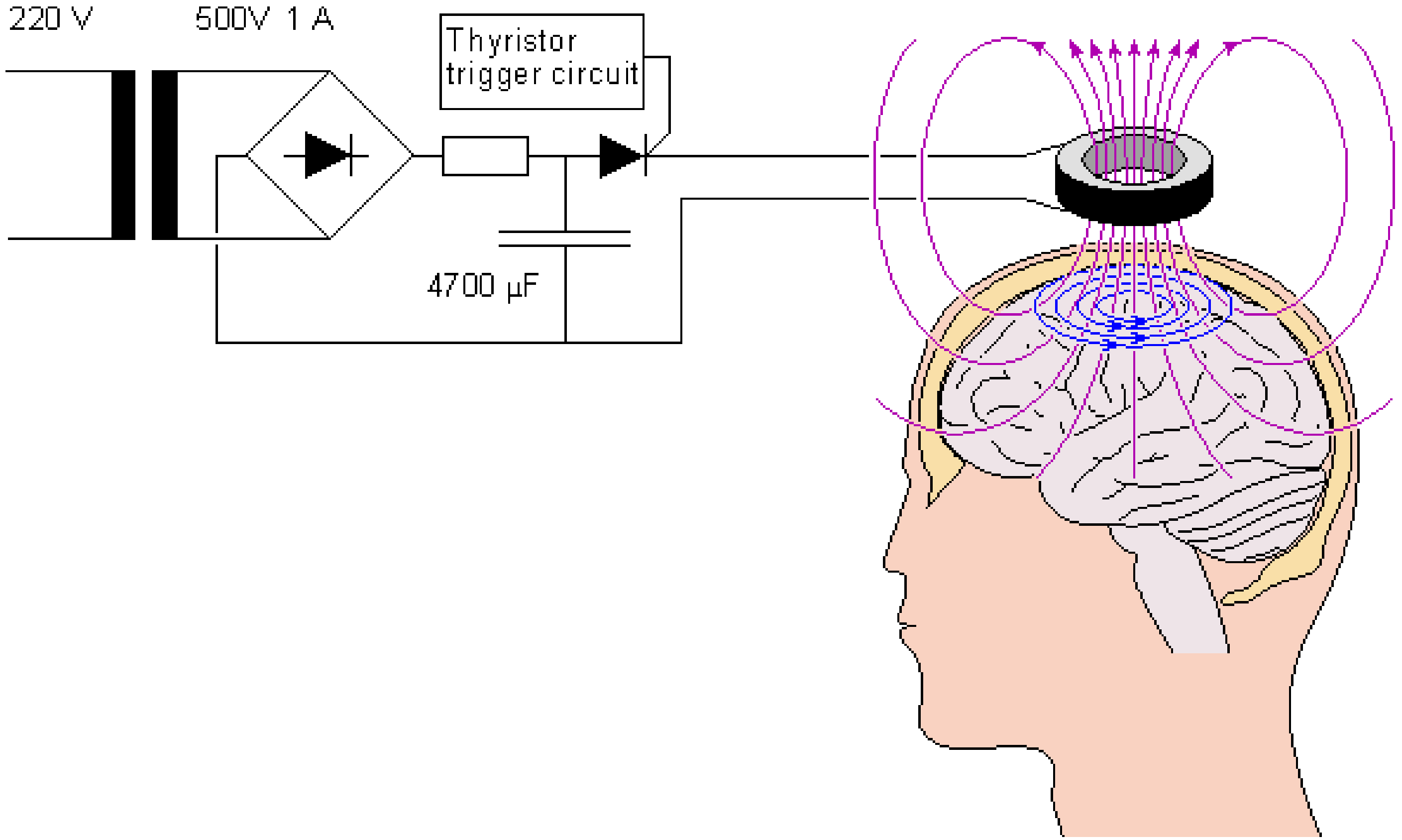
DEFINITION:

Transcranial magnetic stimulation (TMS) is a noninvasive method to cause depolarization in the neurons of the brain. TMS uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field; this can cause activity in specific or general parts of the brain with minimal discomfort, allowing the functioning and interconnections of the brain to be studied.

A variant of TMS**, repetitive transcranial magnetic stimulation (rTMS)** has been tested as a treatment tool for various neurological and psychiatric disorders including migraines, strokes, Parkinson's disease, dystonia, tinnitus, depression and auditory hallucinations.

(wikipedia)

PRINCIPLES



http://www.bem.fi/book/index.htm

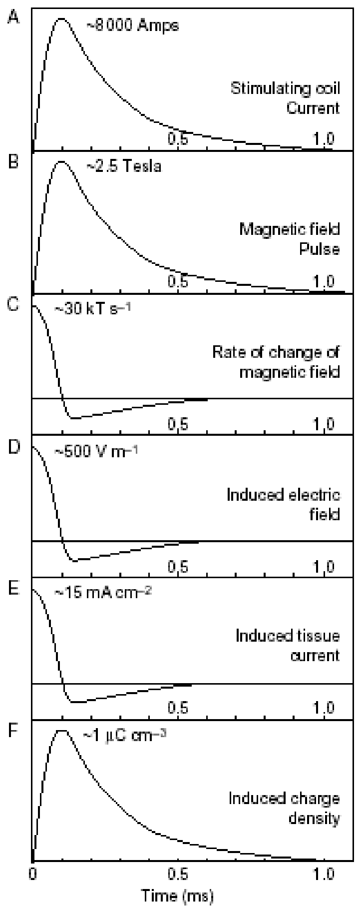
PRINCIPLES

TMS uses electromagnetic induction to generate an electric current across the scalp and skull without physical contact. The charge amount of the charged heavy-duty condenser generates voltage of max. 2000 V and current of ~1000 A in the coil through the thyristor trigger in 100-200 μs. This produces a short-lasting magnetic field oriented orthogonally to the plane of the coil (Faraday-Henry law).

The magnetic field passes unimpeded through the skin and skull, inducing an oppositely directed current in the brain that activates nearby nerve cells in much the same way as currents applied directly to the cortical surface. The magnetic field penetrates only to a maximum depth of three centimeters into the brain, in the area directly adjacent to the coil.

(wikipedia)

TIMING OF MAGNETIC STIMULATION



Stimulating coil current ~ 8000 A

Magnetic field pulse ~ 2.5 T

Rate of change of magnetic field ~ 30 kT/s

Induced electric field ~ 500 V/m

Induced tissue current ~ 15 mA/cm^2

Induced charge density ~ 1 $\mu C/cm^3$

HISTORY

1771	Luigi Galvani	animal electricity
1819	Hans Christian Oersted (1777-1851)	electromagnetism
1831	Michael Faraday (1791-1867)	electromagnetic induction
1833	Duchenne de Boulogne	stimulation of muscles with surface electrodes
1853	Hermann von Helmholtz	measurement of speed of nerve impulses with electrical stimulation and mechanical twitch recorder; pioneering discoveries in electromagnetism (reciprocity etc.)
1874	Bartholow	excitability of the human brain while stimulating the exposed cortex in a patient with a large cranial defect
1896	Arsenne d'Arsonval	"*phosphenes and vertigo, and in some persons, syncope*" when the subjects head was placed inside an induction coil

HISTORY

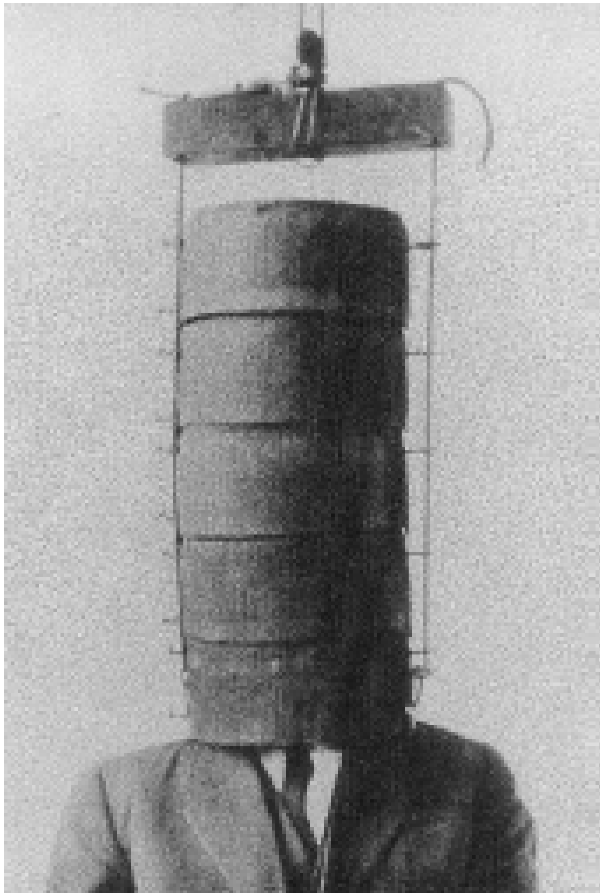
1902 **1910** **1911** **1946**	Beer Silvanus Thompson Dunlap Walsh	visual sensations, i.e., magnetophosphenes: *"a faint flickering illumination, colorless or a blush tint"*
1911	Magnusson & Stevens	"*when the direct current was initiated, a luminous horizontal bar was perceived moving downward*"
1947	Barlow & *al.*	*"as to the locus of excitation, we believe that this is retinal"*
1959	Kolin	first to stimulate magnetically nerves (a frog sciatic-nerve)
1965	Bickford & Fremming	first to stimulate the **human** nerves magnetically using harmonic magnetic fields
1970 **1970** **1973**	Maass & Asa Irwin P. A. öberg	muscle twitches in animals and human subjects
1976	Polson, Barker, & Freeston	stimulation with brief magnetic field pulses and first demonstration of peripheral nerve stimulation with simultaneous electromyographic recordings

HISTORY

1980	Merton & Morton	non-invasive brain stimulation with scalp electrodes
1985	***Barker & al.***	**non-invasive, painless, cortical stimulation with magnetic fields**
1984 **1988**	David Cohen, Shoogo Ueno	the idea and realization of the figure-of-eight coil
1989	RQ Cracco, VE Amassian, PJ Maccabee & JB Cracco	recording of magnetically evoked cortical responses from the scalp with electrodes placed on the other side of the head
1987/88	Cadwell Laboratory Inc.	repetitive stimulation with water-cooled coil

http://www.biomag.hus.fi/tms/index.html

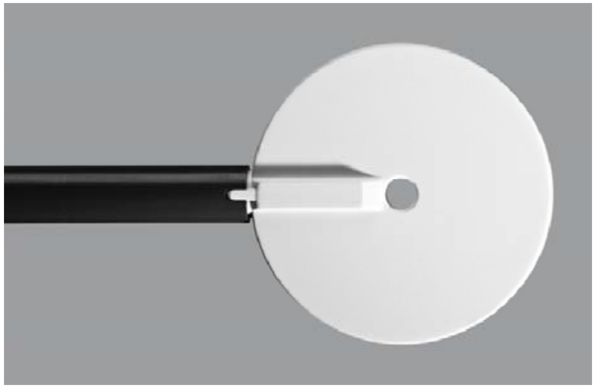
THE BEGINNINGS



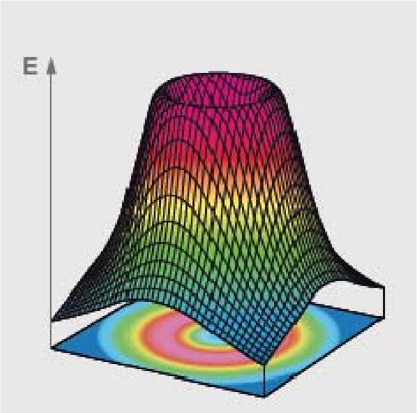
Size matters. Early attempts to induce phosphenes by brain stimulation suffered from the difficulties of producing the requisite large, rapidly-changing electromagnetic fields.

Here we see the arrangement of coils used by Magnusson and Stevens (1911). Coils were piled upon one another to create the increase in field strength.

STIMULATION PATTERNS



Round coil



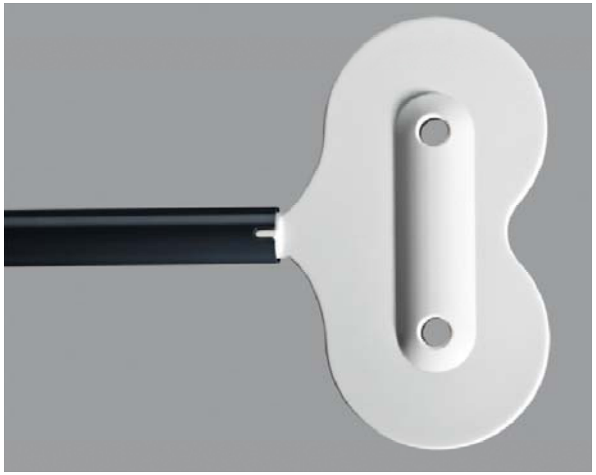
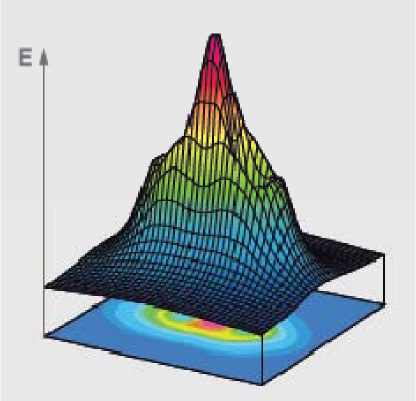
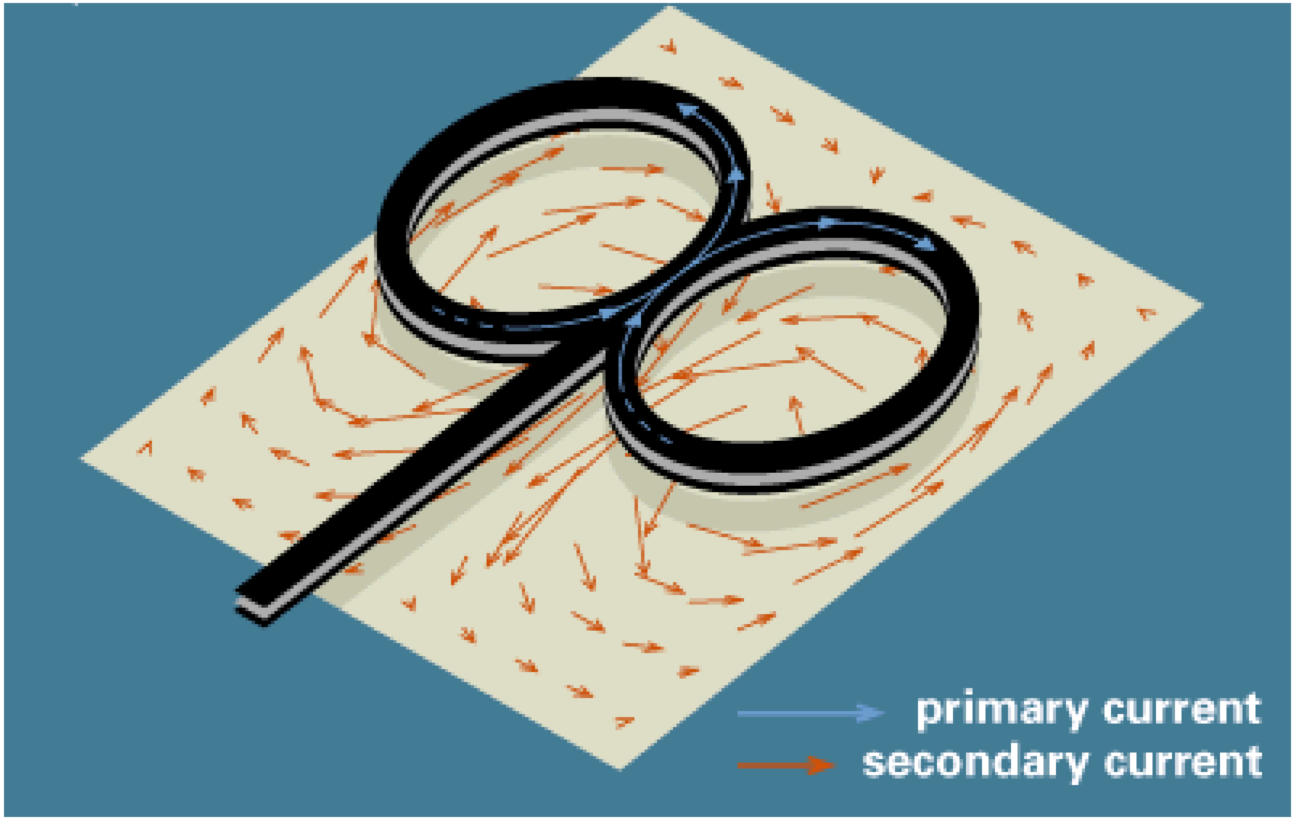


Figure-8
(butterfly) coil



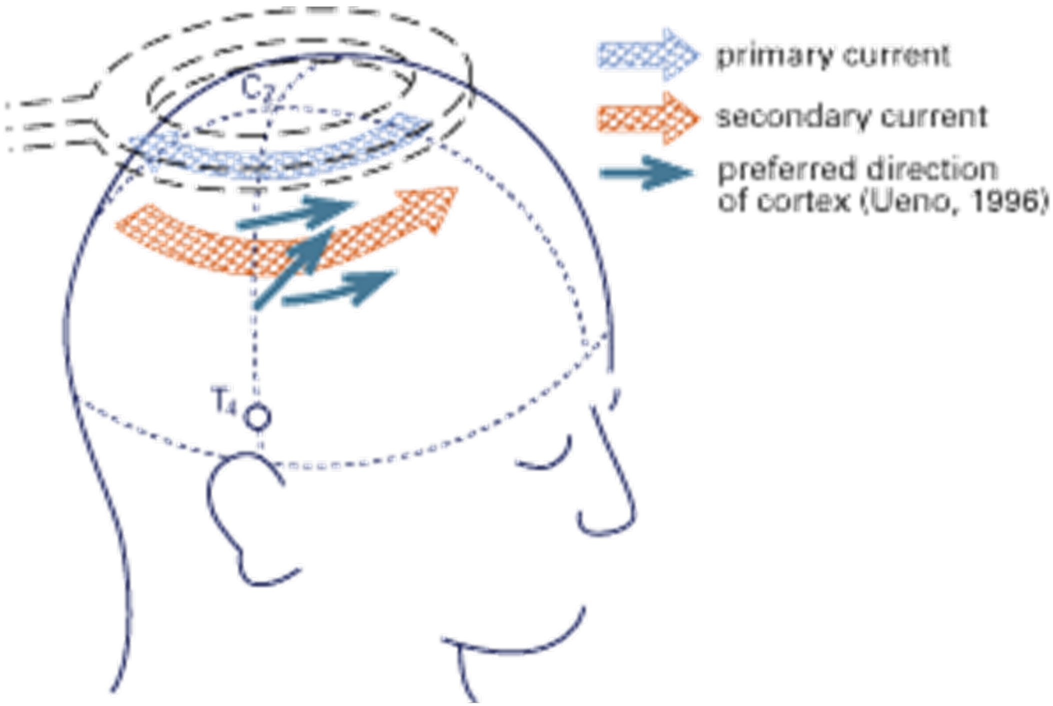
BUTTERFLY COIL-INDUCED CURRENT IN ISOTROPIC CONDUCTOR



MAGNETIC STIMULATION DURING EEG RECORDING

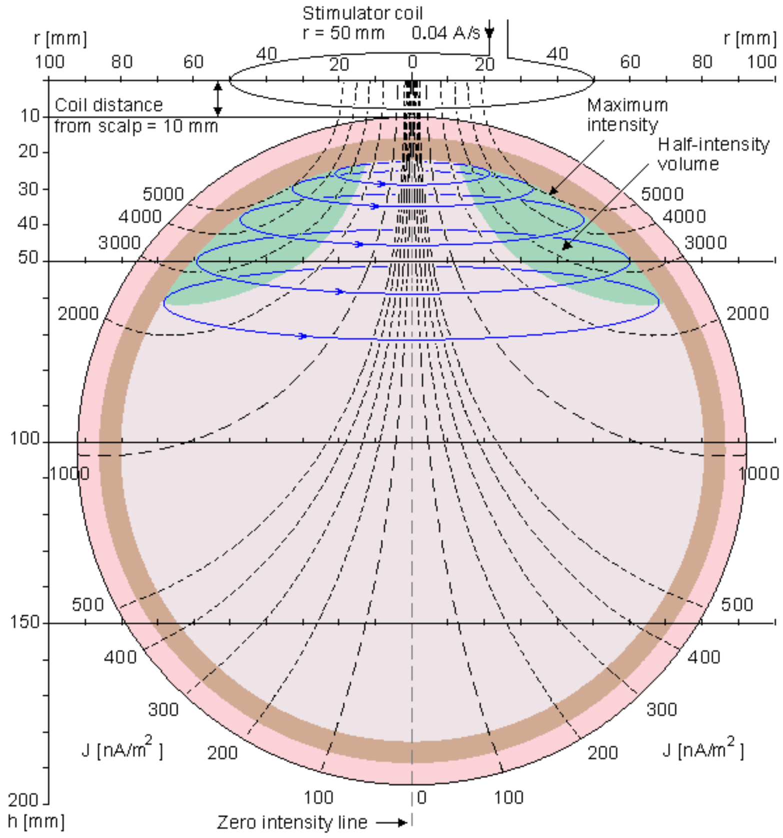
BRAIN PRODUCTS
Solutions for neurophysiological research

STIMULATION VECTOR DIRECTIONS IN MOTOR CORTEX MAGNETIC STIMULATION



http://www.bem.fi/book/index.htm

DISTRIBUTION OF TMS COIL-INDUCED MAGNETIC FIELD AND STIMULATING CURRENT



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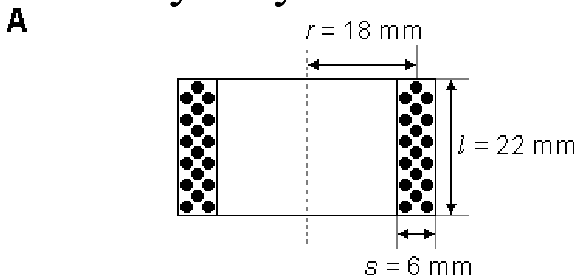
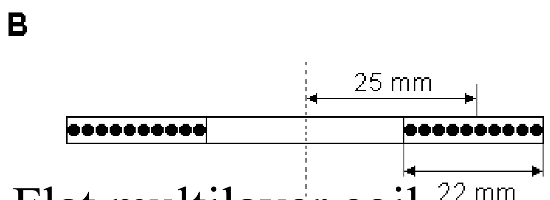
TYPES OF COILS

Multilayer cylinder coil



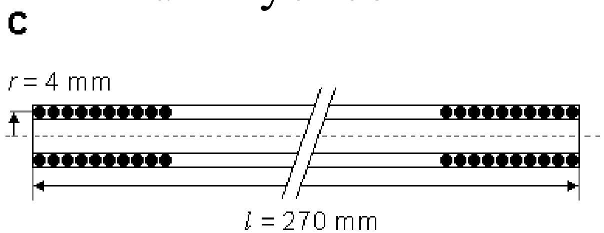
$$L \approx \mu N^2 \left(\frac{\pi r^2}{l + 0.9r} - \frac{0.3rs}{l} \right)$$

Flat single layer coil



$$L \approx \mu N^2 \frac{\pi r^2}{l}$$

Flat multilayer coil



$$L \approx \mu N^2 \frac{\pi r^2}{0.8r + 1.1s}$$

L = inductance of the coil [H]

μ = permeability of the coil core [Vs/Am]

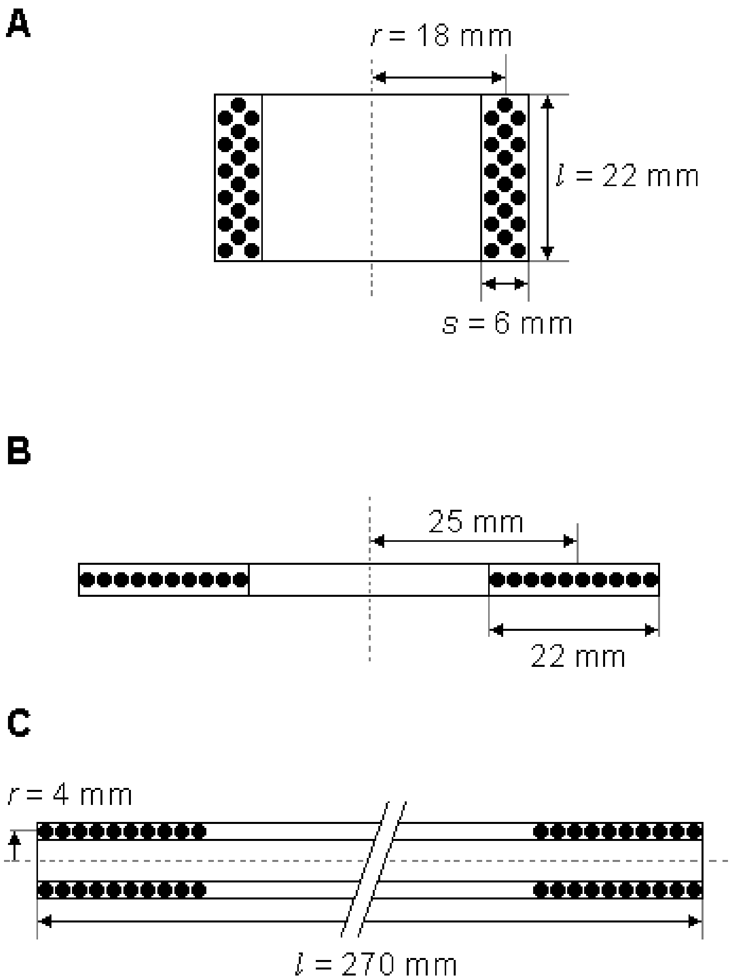
N = number of turns on the coil

r = coil radius [m]

l = coil length [m]

s = coil width [m]

http://www.bem.fi/book/index.htm

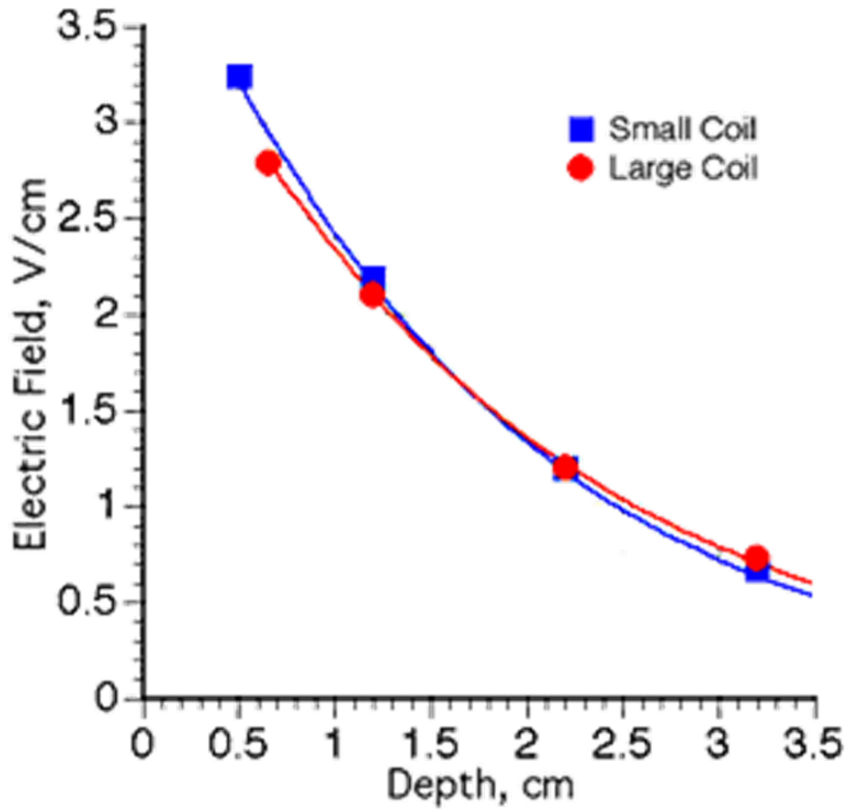


2,5 mm^2 copper wire, 19 turns
R: 14 mΩ   L: 169 μH

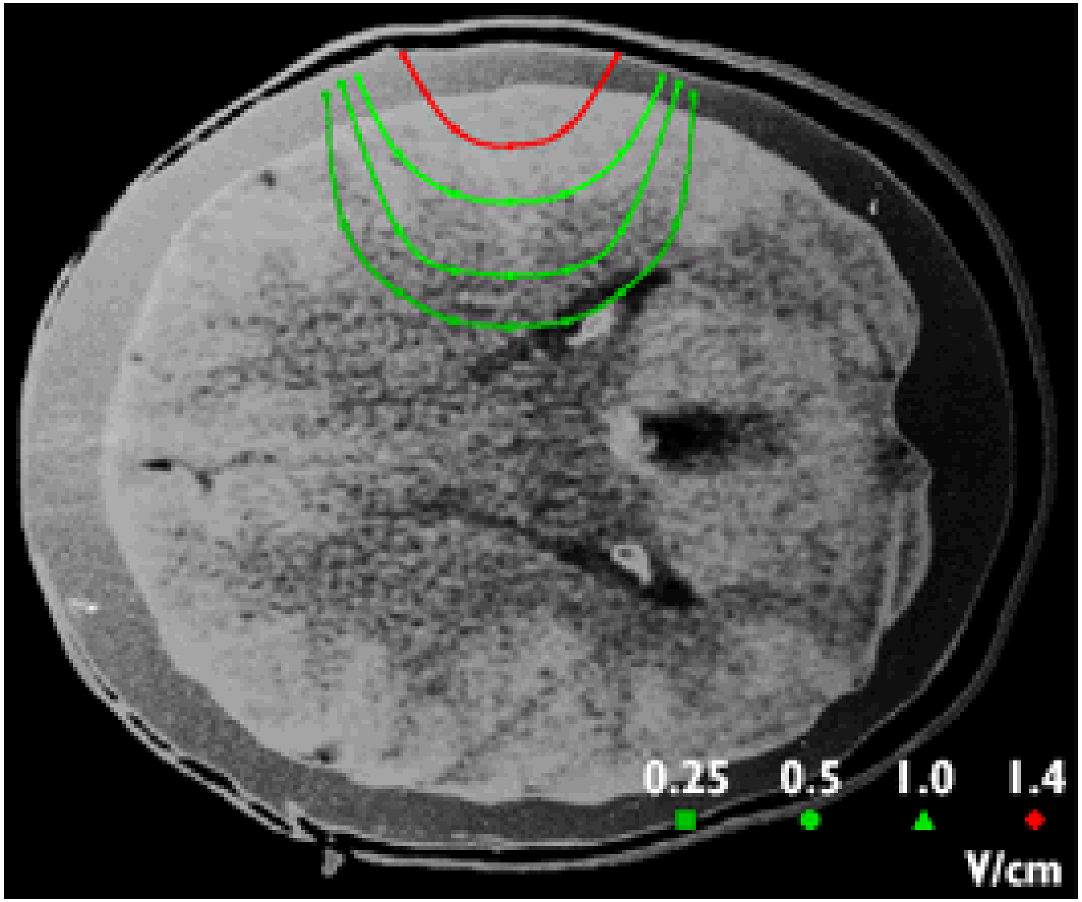
2,5 mm^2 copper wire, 10 turns
R: 10 mΩ   L: 6.67 μH

http://www.bem.fi/book/index.htm

DISTANCE VS. CHANGE OF INDUCED ELECTRIC FIELD



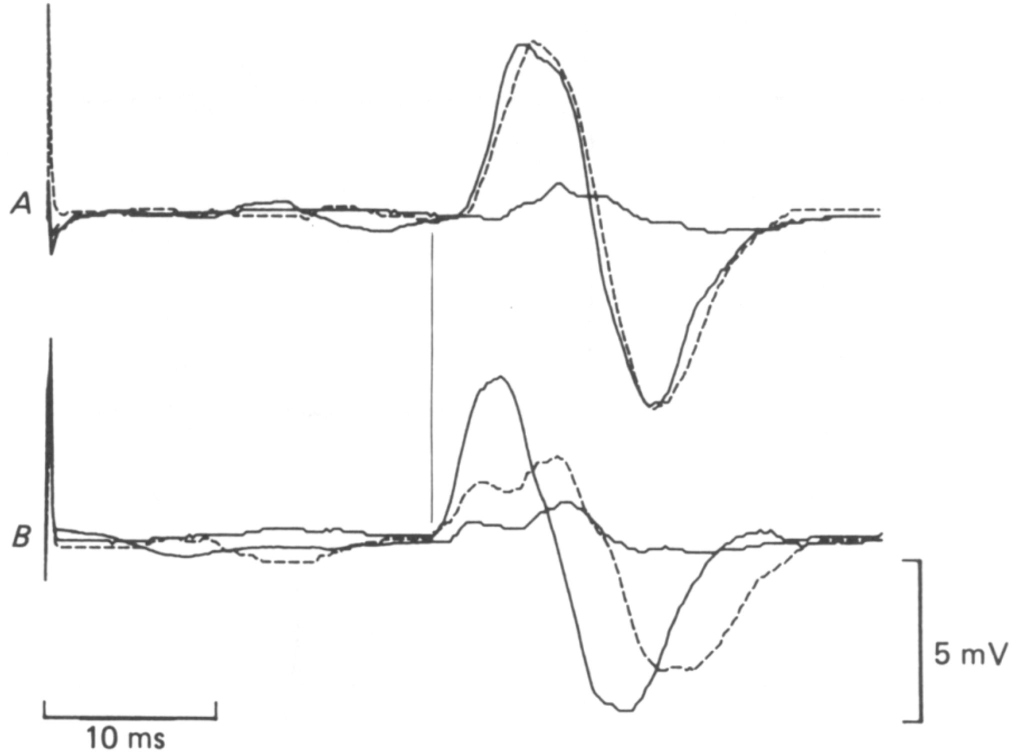
INDUCED ELECTRIC FIELD ON MR IMAGE



MOTOR POTENTIAL EVOKED BY STIMULATING MOTOR CORTEX

magnetic stimulation

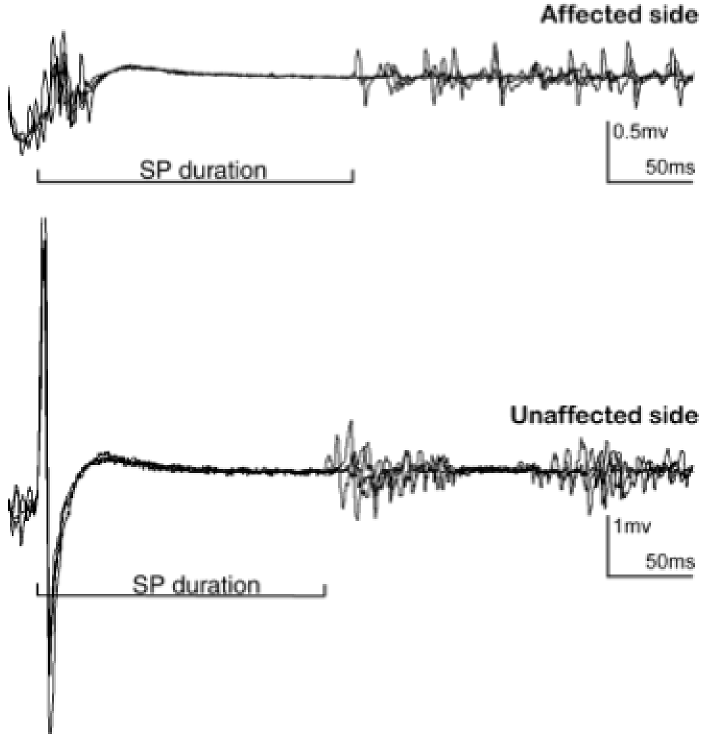
electric stimulation

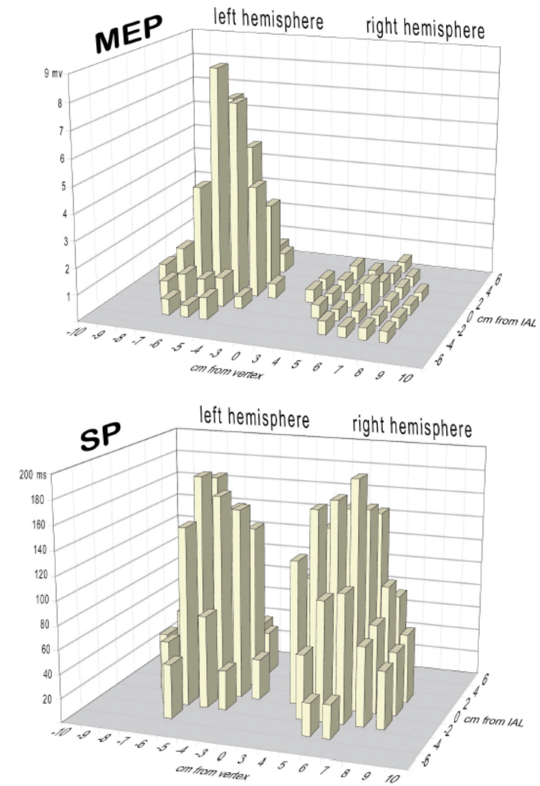


SILENT PERIOD AFTER MOTOR POTENTIAL EVOKED BY TMS IN STROKE PATIENTS

affected side

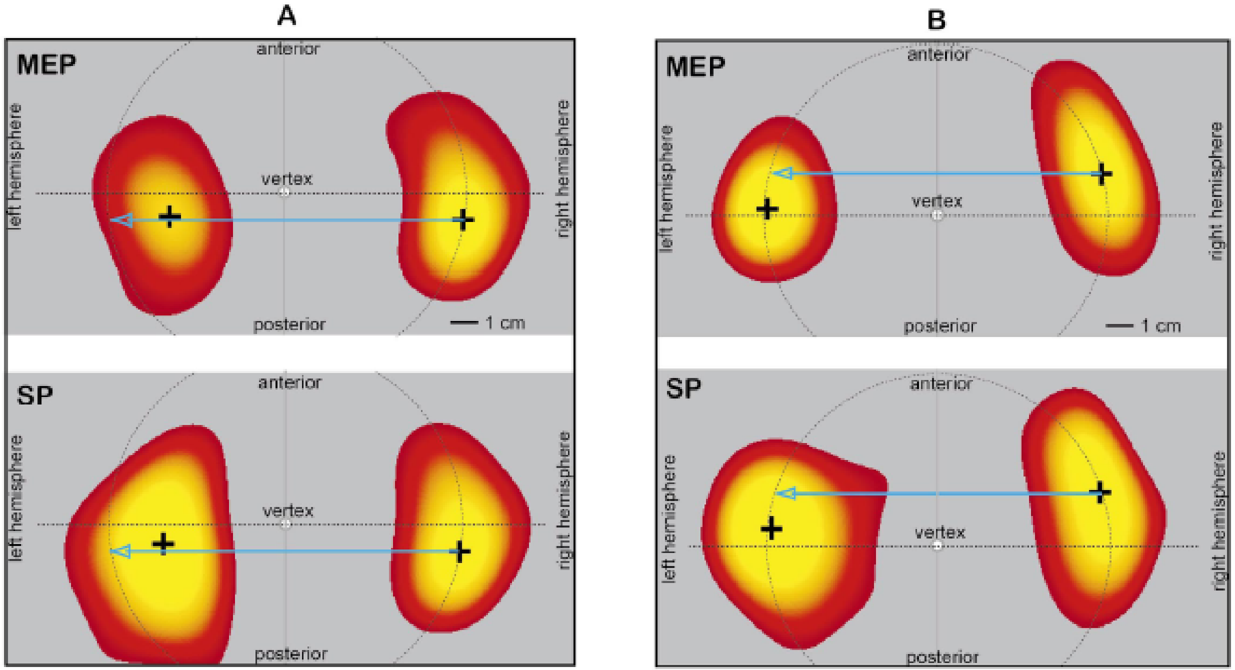
unaffected side





Byrnes et al. Brain Res. 2001

SILENT PERIOD AFTER MOTOR POTENTIAL EVOKED BY TMS IN STROKE PATIENTS



Topographic MEP and SP maps showing shifts on the affected side in two selected stroke subjects. The point of the blue arrow indicates the expected position of the map centre on the affected side.

Byrnes et al. Brain Res. 2001

PROS AND CONS

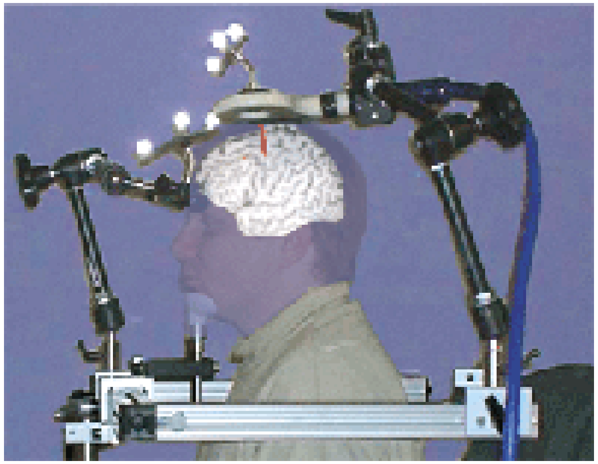
Advantages:

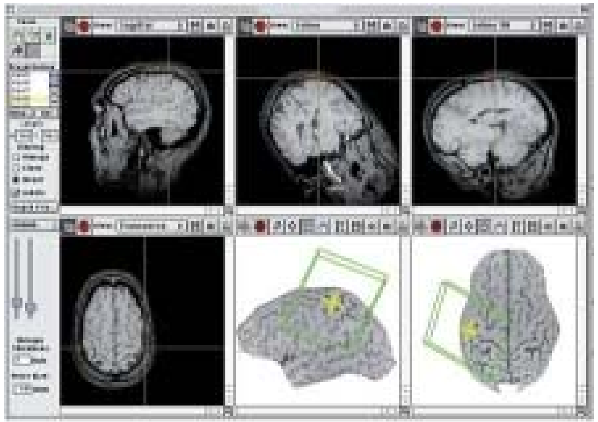
- painless
- central motor conduction time can be measured fast, without pain
- suitable for surgical monitoring

Contraindicated with:

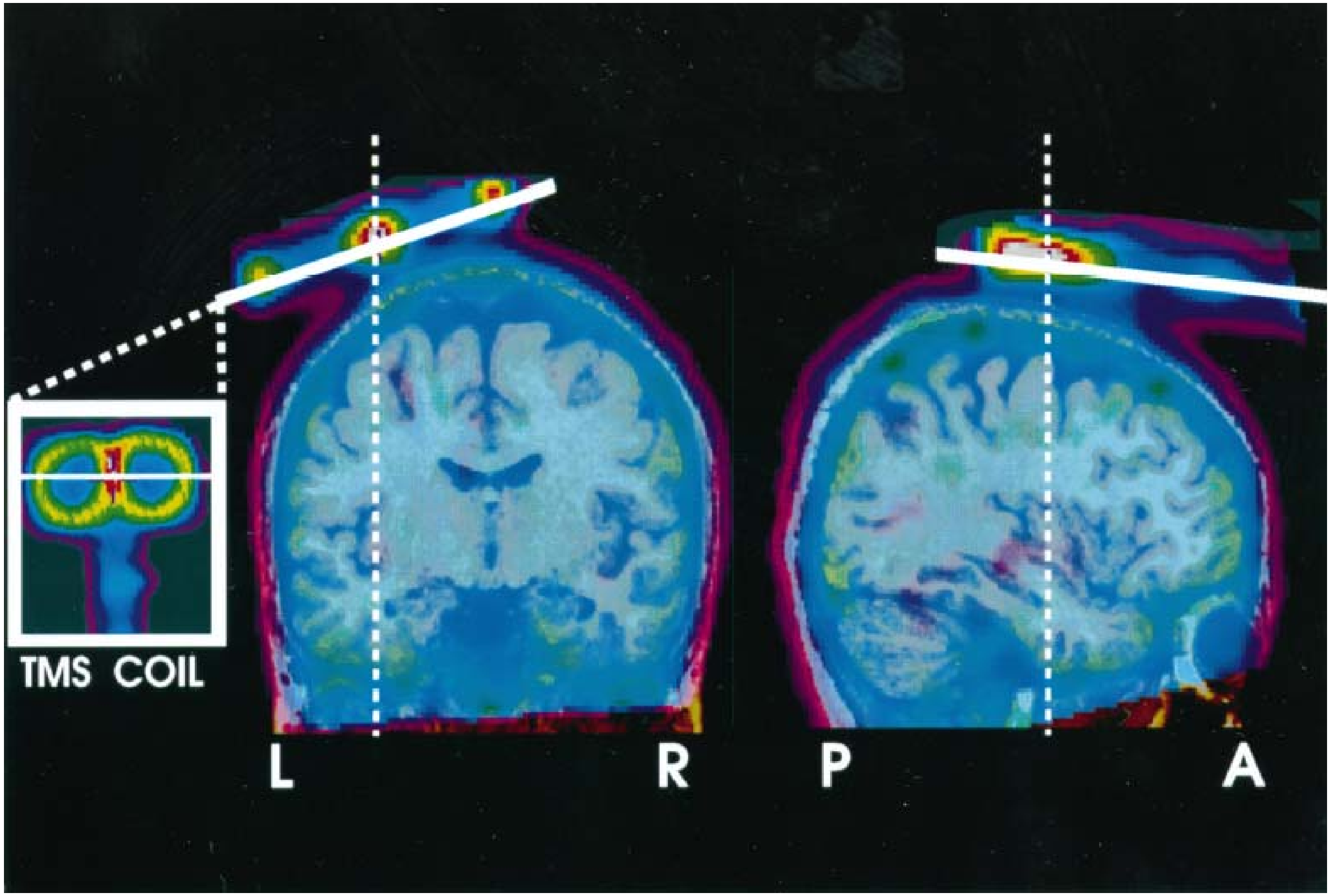
- pacemaker
- focal epilepsy
- metal in the brain

MRI LOCALIZATION AIDED TMS

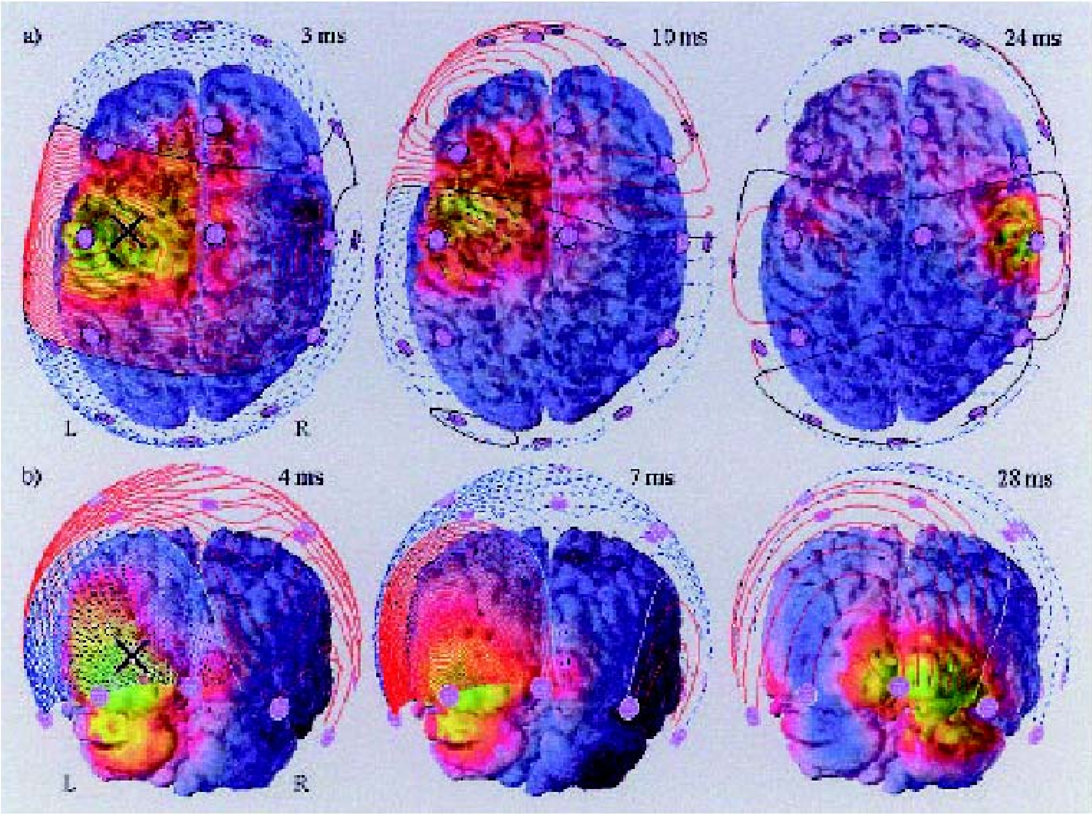




MRI LOCALIZATION AIDED TMS



TMS-EVOKED EEG RESPONSES



Ilmoniemi et al. NeuroReport, 1997

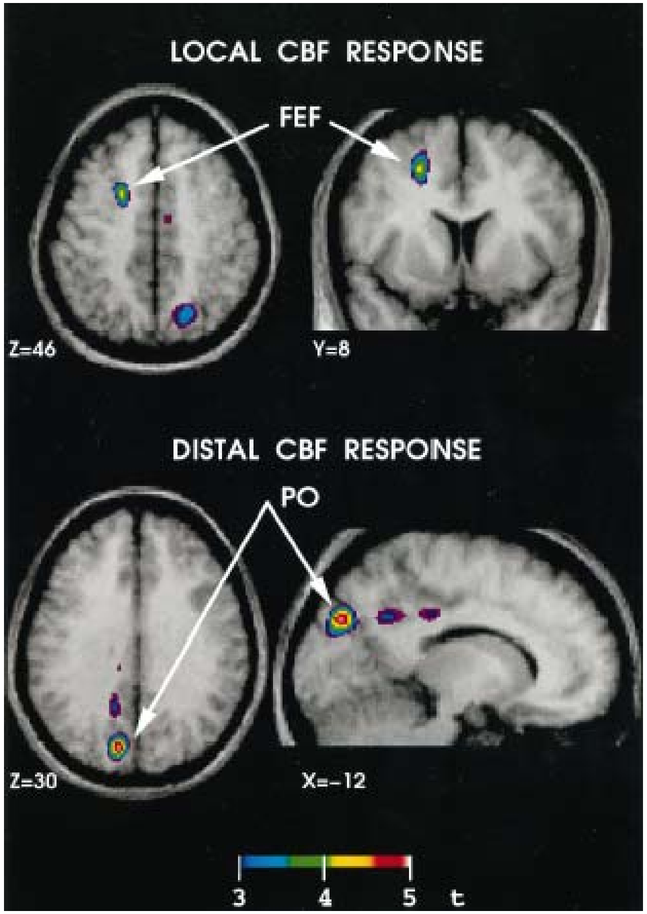
TMS-EVOKED EEG RESPONSES

TMS-evoked averaged EEG responses. Minimum-norm estimates of the cortical activity are shown as color maps drawn on three-dimensional MRI. The EEG is displayed as contour maps, with red lines indicating positive potential. The TMS coil position is indicated with a cross.

(**a**) The response to left motor cortex stimulation. At latencies of 3 and 10 ms, the ipsilateral hemisphere shows prominent activation; at 24 ms, the contralateral activity dominates (between 10 and 24 ms, the two hemispheres showed simultaneous strong activation). The EEG contour spacing is 1 mV.

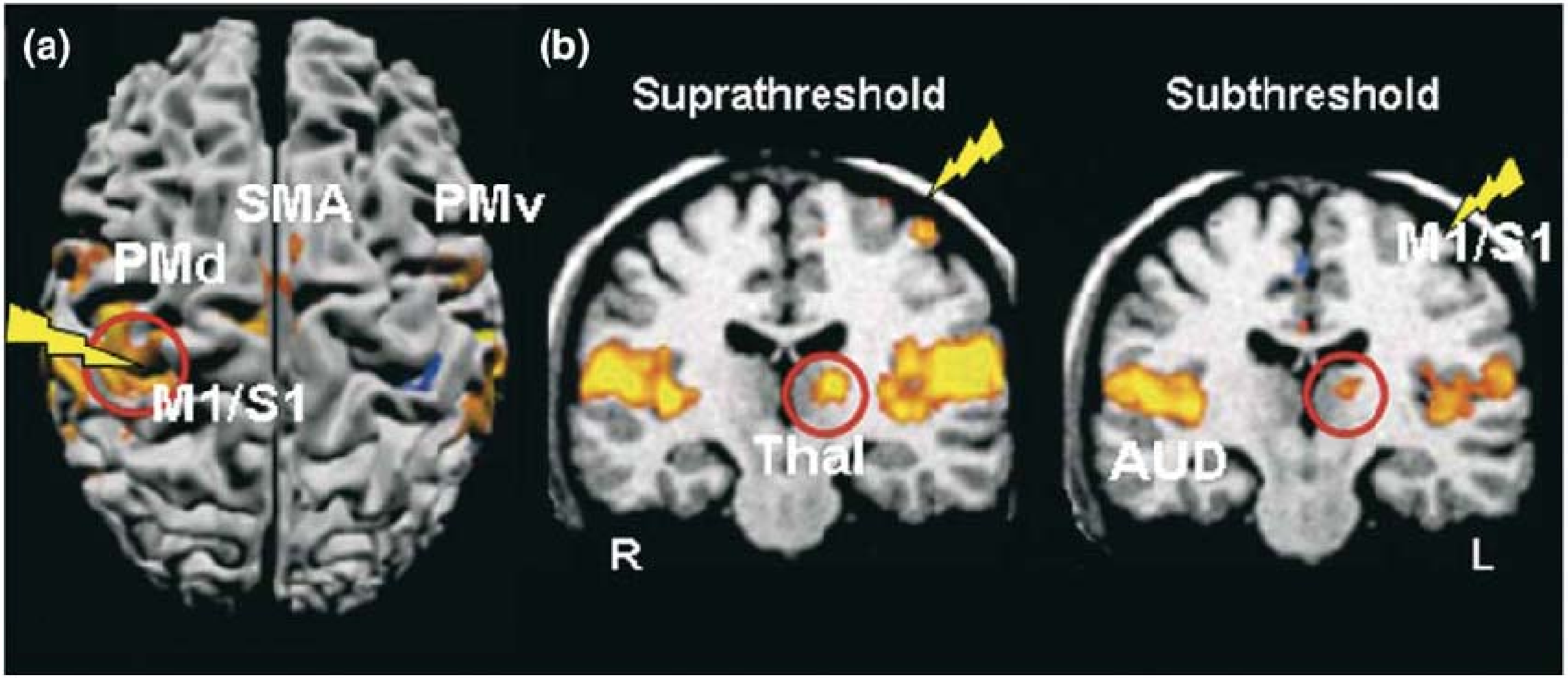
(**b**) The response to visual-cortex TMS at 4, 7 and 28 ms post-stimulus; the contour spacing is 2 mV.

TMS-EVOKED DISTAL CBF RESPONSE (PET)



Magnetic stimulation of the frontal eye field (FEF) induces local cerebral blood flow (CBF) change in the parietooccipital visual cortex (PO).

fMRI RESPONSE OF MOTOR CORTEX MAGNETIC STIMULATION



Bestman et al. Eur J Neurosci 2004

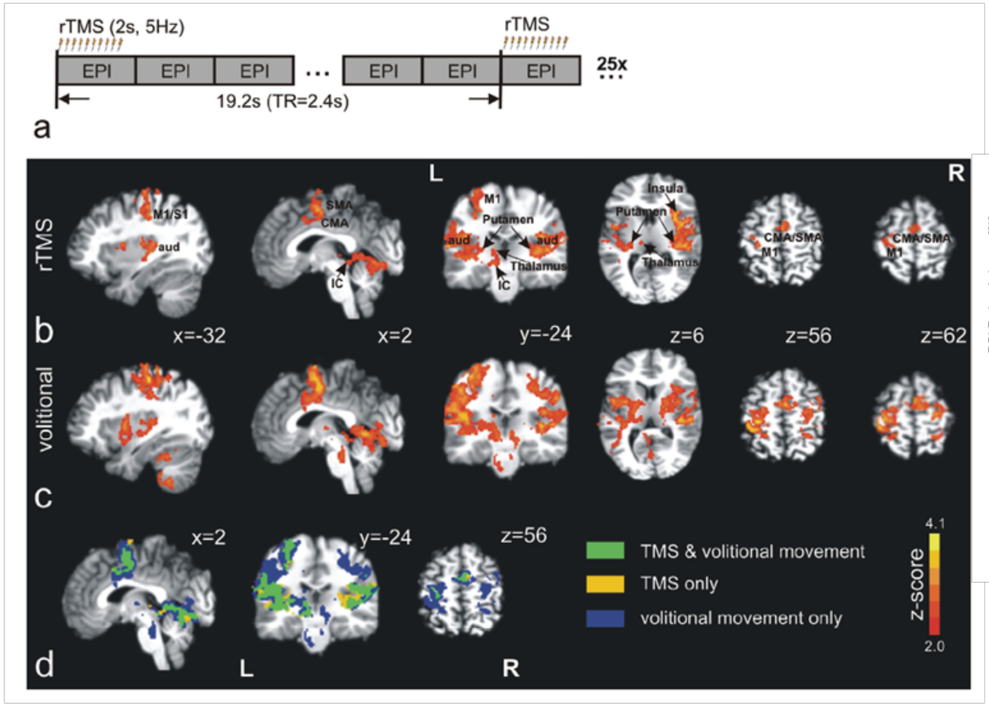
fMRI RESPONSE OF MOTOR CORTEX MAGNETIC STIMULATION

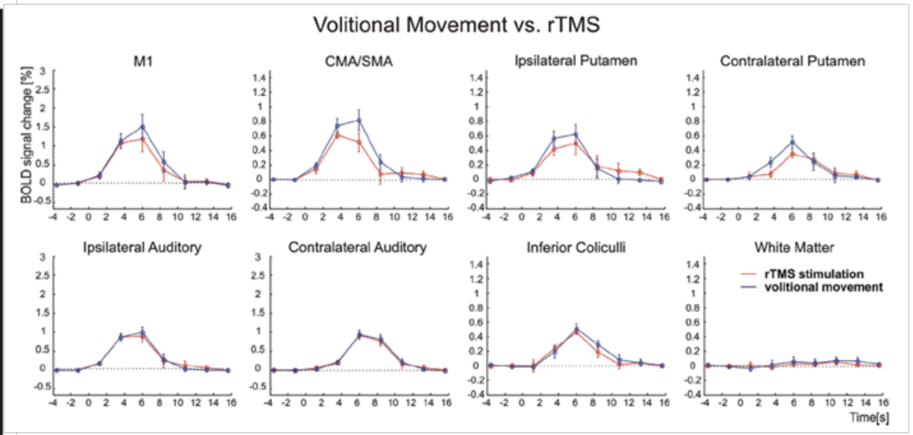
Direct and remote neural effects of focal TMS.
(a) Activity changes evoked by suprathreshold TMS (3 Hz, 10s) delivered over left sensorimotor cortex (M1/S1) during fMRI. Stimulation not only increased activity at the site of TMS but also in ipsilateral dorsal and ventral premotor cortex, contralateral ventral premotor cortex, medial motor areas, including SMA and putative cingulate motor area.
(b) Importantly, remote activity increases during TMS also occurred in the motor thalamus ipsilateral to stimulation, even at subthreshold stimulation intensities. This excludes reafferent feedback from evoked muscle responses as a contributing factor to these activity increases. Note also the additional activity increases in auditory cortex that are due to the noise generated at TMS pulse discharge. The yellow flash denotes the site of stimulation.

Abbreviations: AUD, auditory cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; SMA, supplementary motor area; Thal, motor part of the thalamus.

Adapted from Bestmann et al.

fMRI RESPONSE OF VOLITIONAL AND TMS-EVOKED HAND MOVEMENT IS SIMILAR





http://www.magventure.com/default.aspx?pageid=245

fMRI RESPONSE OF VOLITIONAL AND TMS-EVOKED HAND MOVEMENT IS SIMILAR

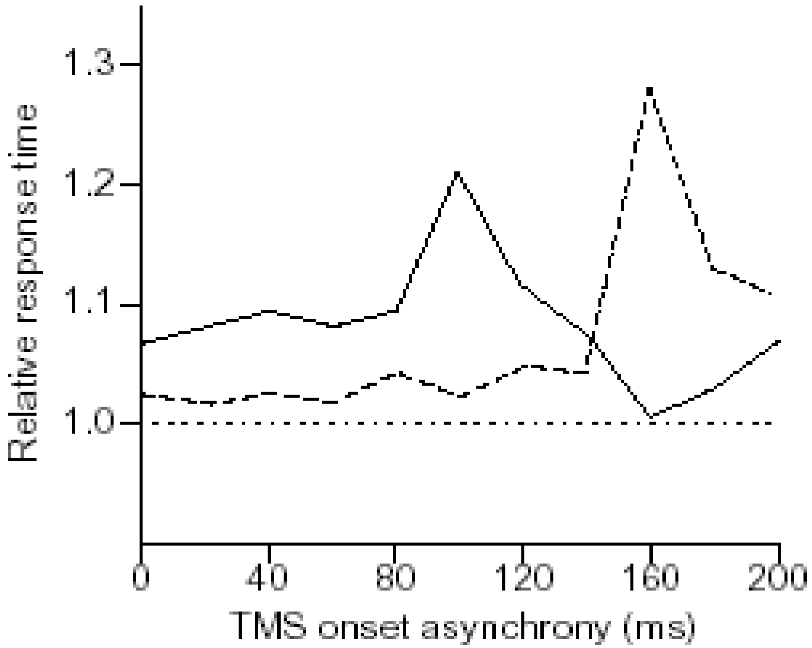
(a) rTMS-trains consisting of 10 stimuli applied every 200 ms were interleaved with the MR acquistion (b) Brain responses to rTMS stimulation. Shown is the group activation map for 5 subjects (threshold z=2.3 voxel level, p=0.05 cluster level; FSL FLAME mixed effects analysis; MNI space) (c) Brain activation caused by volitional movements acoustically triggered by rTMS trains at low intensity (same threshold level) (d) overlap between rTMS- and movement-related activations.

The rTMS-induced activations exhibit a robust spatial overlap with those obtained for volitional movement (c&d). Except for the control region in white matter, they show the expected BOLD shape. Taken together, the example demonstrates that fMRI can be used to reliably access the responses to TMS in the stimulated and in connected brain areas.

http://www.magventure.com/default.aspx?pageid=245

EFFECT OF TMS ON COGNITIVE FUNCTIONS

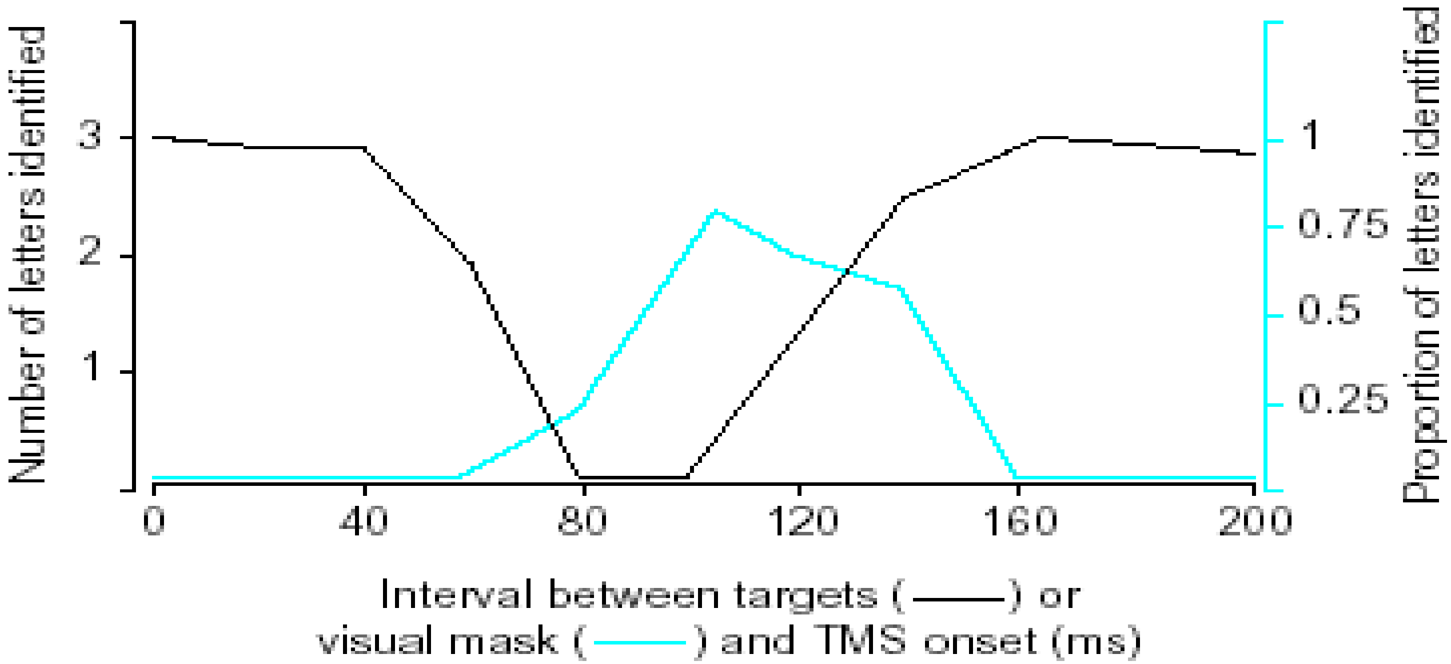
VISUAL SEARCH



TMS applied to the parietal cortex. The dotted line at 1.0 on the ordinate indicates the control reaction time in the absence of TMS. The solid line that peaks at 100 ms represents reaction time relative to control trials, when a target was present; the dashed line that peaks at 160 ms represents reaction time relative to control trials when target was absent.

Walsh and Cowey, Trends in Cognitive Sci. 1998

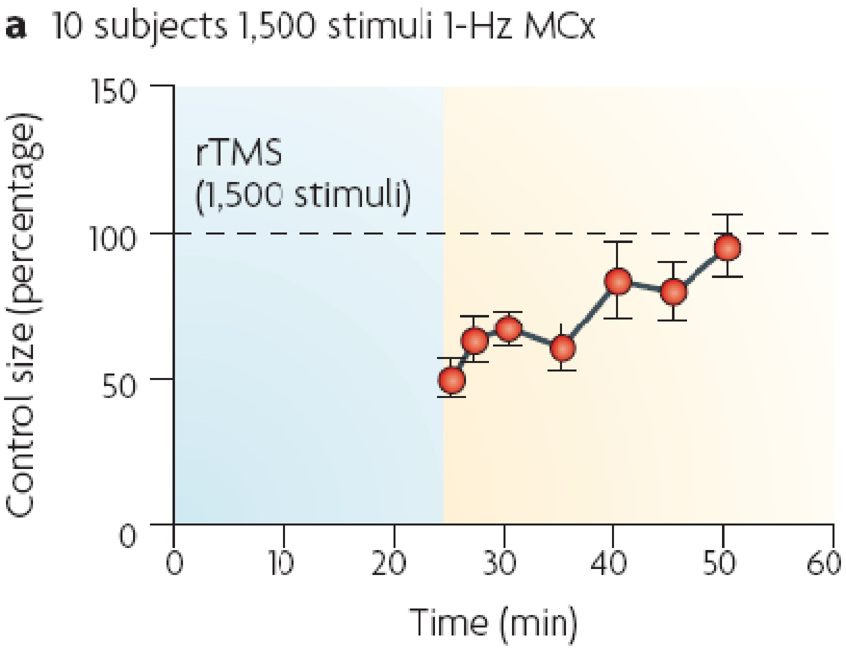
EFFECT OF rTMS ON LETTER IDENTIFICATION

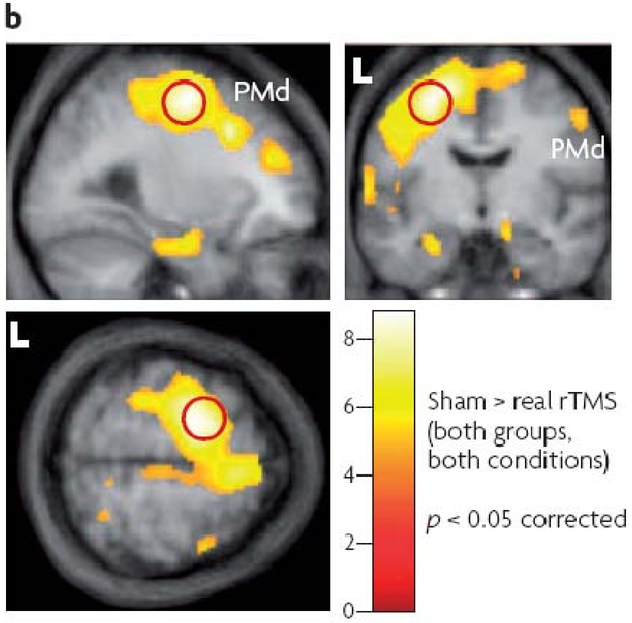


The black line (ordinate on the left representing the number of letters correctly identified in trigrams) shows the effects of TMS on recognition. The blue line (ordinate to the right showing the proportion of letters correctly identified in the presence of a visual mask).

Walsh and Cowey, Trends in Cognitive Sci. 1998

EFFECT OF rTMS ON MOTOR CORTEX EXCITABILITY



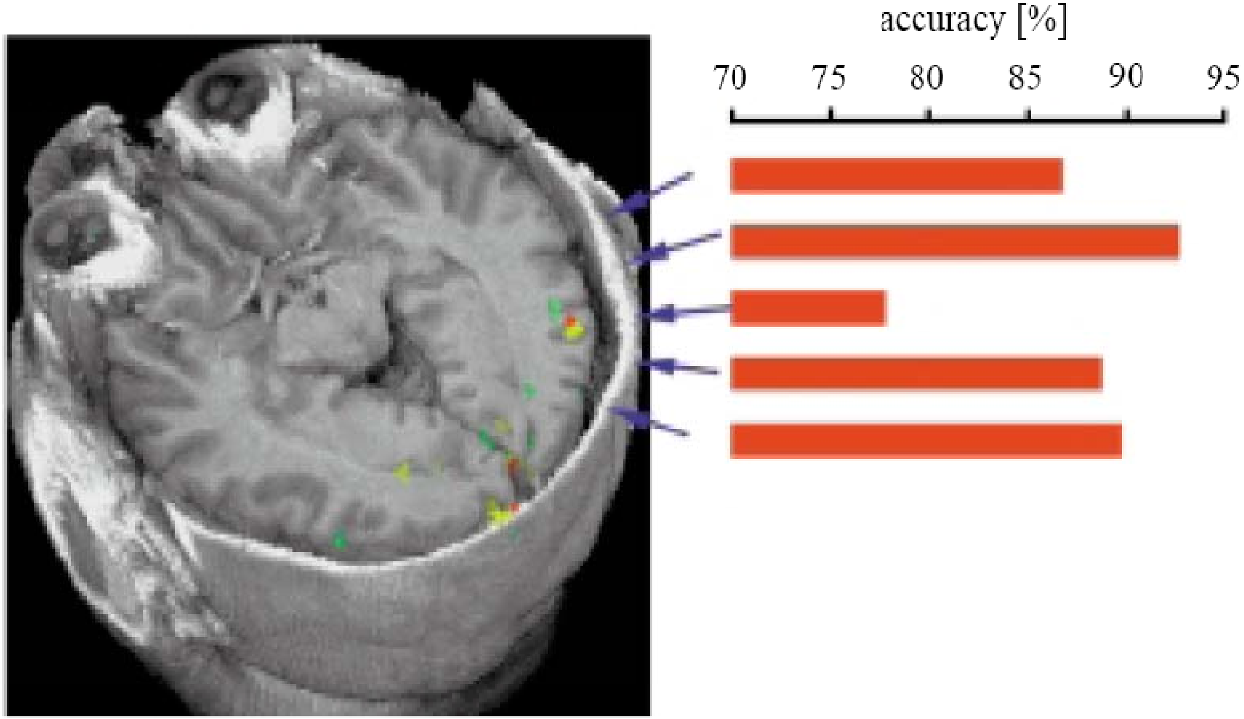


Ridding & Rothwell, Nature Revievs Neuroscience, 2007, 8: 559-567.

EFFECT OF rTMS ON MOTOR CORTEX EXCITABILITY

How repetitive TMS affects excitability in the brain. a | Time course of changes in excitability of the motor cortex after 25 min repetitive transcranial magnetic stimulation (rTMS; blue shading) at 1 Hz and an intensity of 90% resting threshold. Data reflect the amplitude of the electromyographic response to a single TMS pulse as a percentage of the amplitude before rTMS. The response is suppressed immediately after rTMS and this effect persists to a decreasing extent for the next 30 min. **b** | Brain images from a study that used positron emission tomography (PET) to measure metabolic activity. The colour coding shows the areas in which activity after a 25 min session of real 1-Hz rTMS over the dorsal premotor cortex (PMd) is less than that seen after a sham rTMS session. Numbers in the colour code bar are Z-scores, which indicate the probability that the activation differs from the rest; Z>4 is highly significant. There are significant decreases in activity after real rTMS at the site of stimulation (outlined in red) as well as at many distant sites. L, left side of the brain.

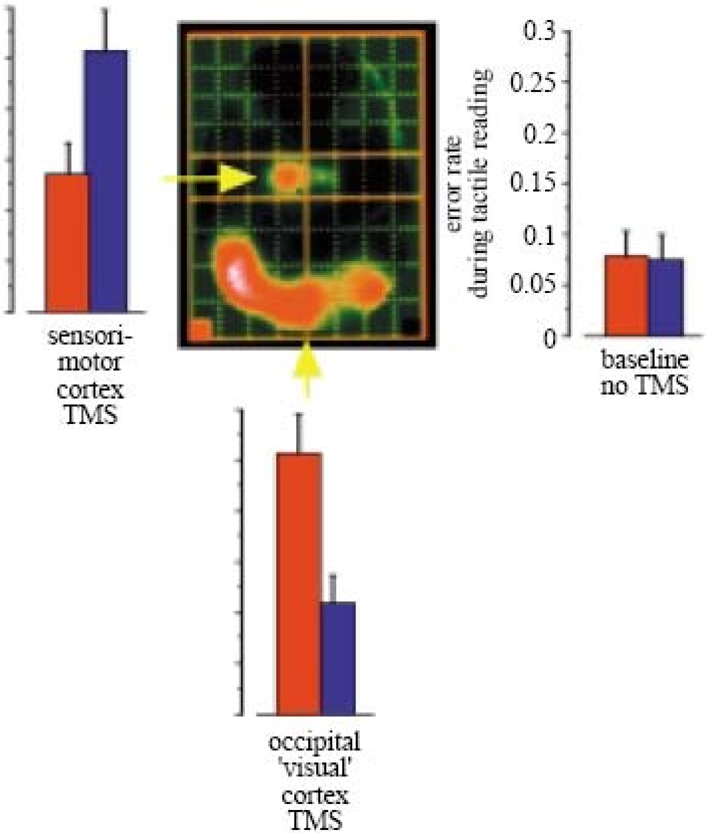
EFFECT OF TMS ON DETECTION ACCURACY



Bold fMRI shows the area of activation of visual stimulation with display of random motion (red), vertical motion (green) or both (yellow). The bars depicts the subject's accuracy in the detection of direction of random motion during TMS to five different scalp position.

Pascual-Leone et al. Phil. Trans. R. Soc. Lond. B 1999

EFFECT OF TMS ON BRAIN ACTIVATION DURING BRAILLE READING IN BLIND SUBJECTS



Activation on PET of the contralateral sensorimotor cortex and the occipital cortex in an early blind subject during Braile reading. Bars show significant increase in errors during TMS to the sensorimotor cortex in sited controls. In contrast occipitopolar TMS induced increased of errors in early and congenitally blind subjects.

Pascual-Leone et al. Phil. Trans. R. Soc. Lond. B 1999

Pascual-Leone et al. 1999

MAGNETIC SEIZURE THERAPY IN DEPRESSION

- The patient was oxygenated during anesthesia with 100 % O2.
- The motor activity of the right foot is assessed visually in order to track the duration of motor seizures, and bilateral frontal-mastoid EEG recordings is obtained by an EEG device.
- Treatments are delivered with a magnetic stimulator (MagVenture MagPro MST) using the highly efficient “Twin Coil”.
- Stimulation repetition rate 100 pps. Number of pulses: 100-600 (duration 1-6s)

MAGNETIC SEIZURE THERAPY IN DEPRESSION

- Stimulation amplitude 100%.
- During the stimulations, the center of the coil is placed at the vertex.
- The peak magnetic field induced above 2 Tesla at the coil surface.
- Seizures were elicited under general anesthesia (propofol).
- Two MST sessions per week.

http://www.magventure.com/default.aspx?pageid=253

DEEP BRAIN rTMS

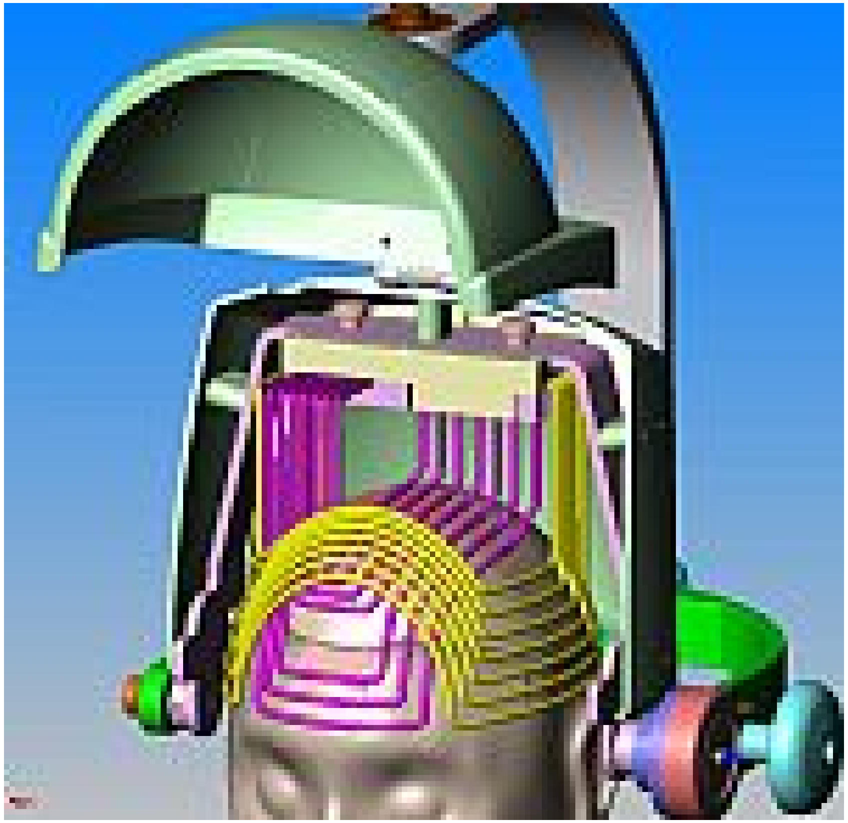
http://www.brainsway.com

DEEP BRAIN rTMS

Brainsway Inc.

Treatment Resistant Major Depression

Daily prefrontal rTMS (20 Hz, 2 sec on 20 sec off, for 20 minutes, i.e., 1680 stimuli) each day for 4 consecutive weeks (i.e. 20 treatment sessions), at 120% of the individual motor threshold.



http://www.brainsway.com

ABBREVIATIONS

MS	general term for magnetic stimulation, including TMS and stimulation of the peripheral nervous system
TMS	general term for all modes of transcranial magnetic stimulation
rTMS	repetitive transcranial magnetic stimulation
single-pulse TMS	non-repetitive TMS
low-frequency TMS slow TMS	repetition rate below 1 Hz
high-frequency TMS rapid-rate TMS	repetition rate above 1 Hz

ABBREVIATIONS

dual-pulse TMS paired-pulse TMS	stimulation with two distinct stimuli through the same coil at a range of different intervals; the intensities can be varied independently
quadruple-pulse TMS	as dual-pulse stimulation, but with 4 pulses
double TMS	stimulation with two stimulation coils applied to different cerebral loci; the timing and stimulus intensity are adjusted separately
multichannel TMS	TMS with multiple (say, 20-100) coils that are independently controlled
TMS mapping	performed by changing the coil position above the head while observing its effects

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REVIEW QUESTIONS

- What are the principles of transcranial magnetic stimulation?
- Who and when applied non-invasive, painless cortical stimulation with magnetic fields for the first time?
- What types of TMS devices do you know?
- What are the advantages and disadvantages of TMS?
- When is the application of TMS contraindicated?