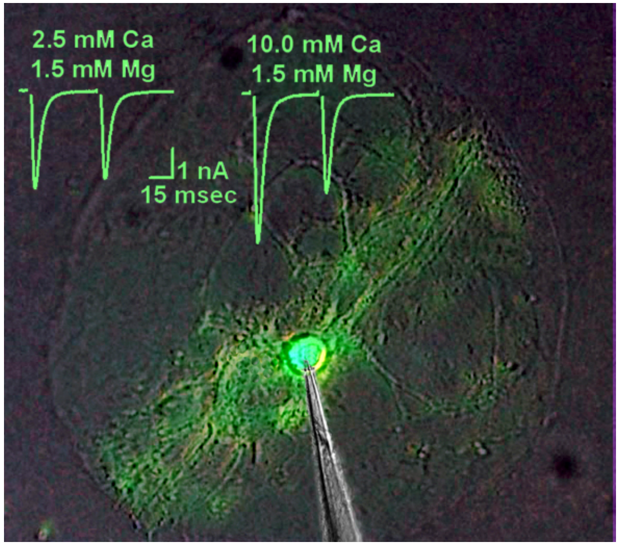
COGS 269

Spring 2018 Lecture 4

Methods of Cognitive Neuroscience

Single-Cell Recording

- Electrical activity of a neuron is recorded via electrode implanted near the cell (sometimes inside the cell – see fig).
- Only feasible in animals or special cases where human brain surgery is involved.
- Multi-cell recording is possible via array of microelectrodes. Computer programs separate signals from different neurons.
- Rate coding: the *number* of action potentials is important (e.g. 40 spikes/sec).
- Spike coding: the *timing* of each action potentials is important (e.g. spike #1 occurred at 0.52 msec).
- Excellent temporal resolution, but limited to a few neurons.



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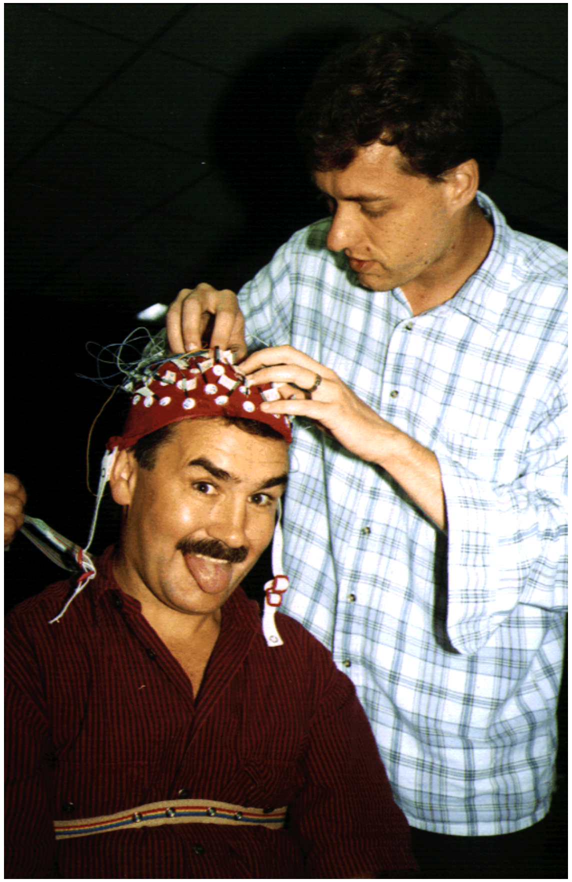
Important non-invasive techniques

- EEG: electroencephalography
- MEG: magnetoencephalography
- MRI: magnetic resonance imaging

(structural and functional *aka* fMRI).

- Positron emission tomography (PET)
- Transcranial magnetic stimulation (TMS)



Electroencephalography EEG

Quantity measured: electric potential on the scalp surface

Order of magnitude: 20uV

Temporal Resolution: ms

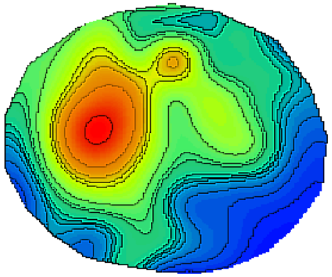
Spatial Resolution: cm

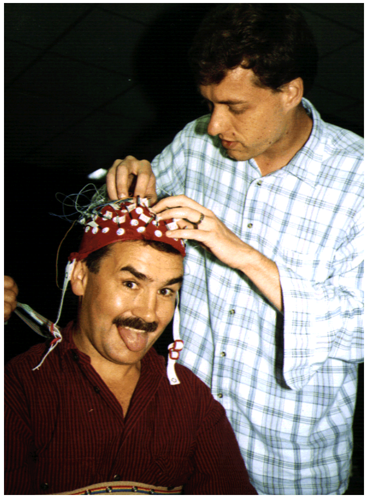
Cost: cheap

Advantage: easy to record

Disadvantage: signals get smeared before they reach the scalp

EEG Technology





EEG

The electroencephalogram (EEG) measures the activity of large numbers (populations) of neurons.

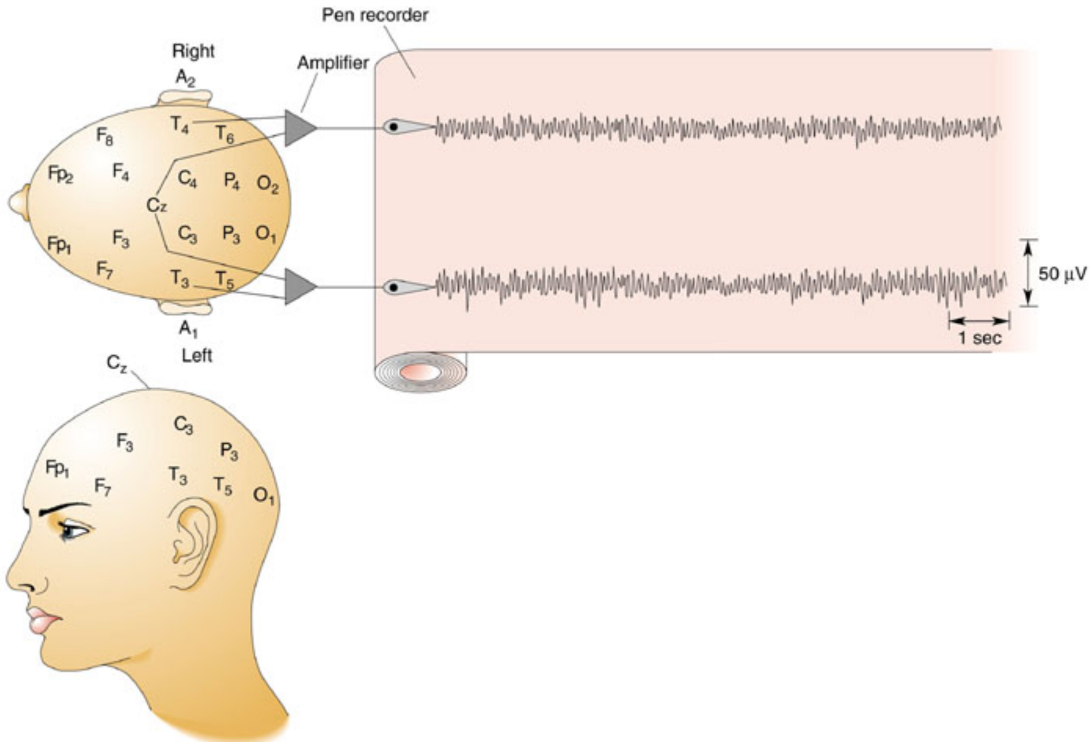
First recorded by Hans Berger in 1929.

EEG recordings are noninvasive, painless, do not interfere much with a human subject's ability to move or perceive stimuli, are relatively low-cost.

Electrodes measure voltage-differences at the scalp in the microvolt (µV) range.

Voltage-traces are recorded with millisecond resolution – great advantage over brain imaging (fMRI or PET).

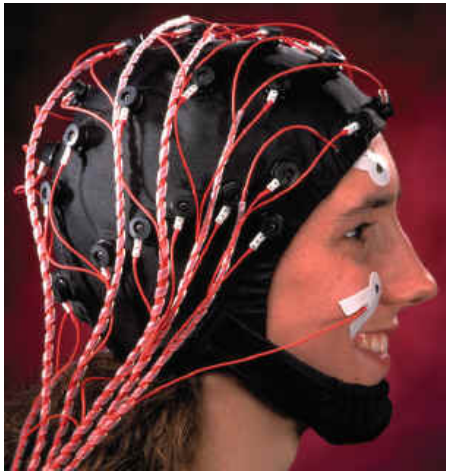
EEG



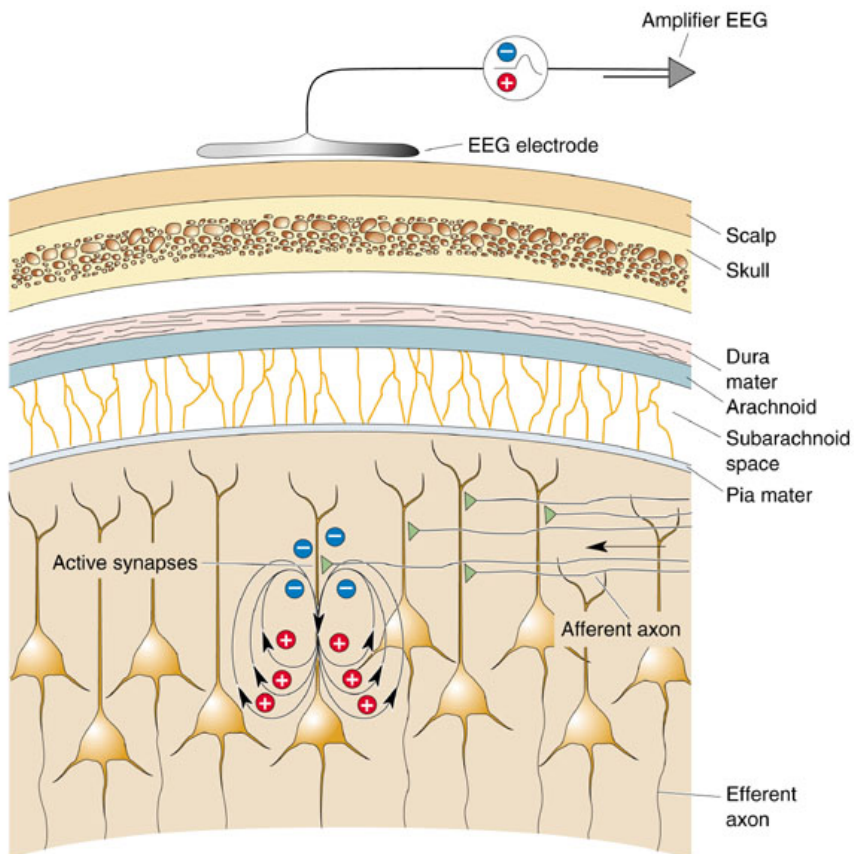
Standard placements of electrodes on the human scalp: A, auricle; C, central; F, frontal; Fp, frontal pole; O, occipital; P, parietal; T, temporal.

International system of electrode positions: 10-20 system.

EEG

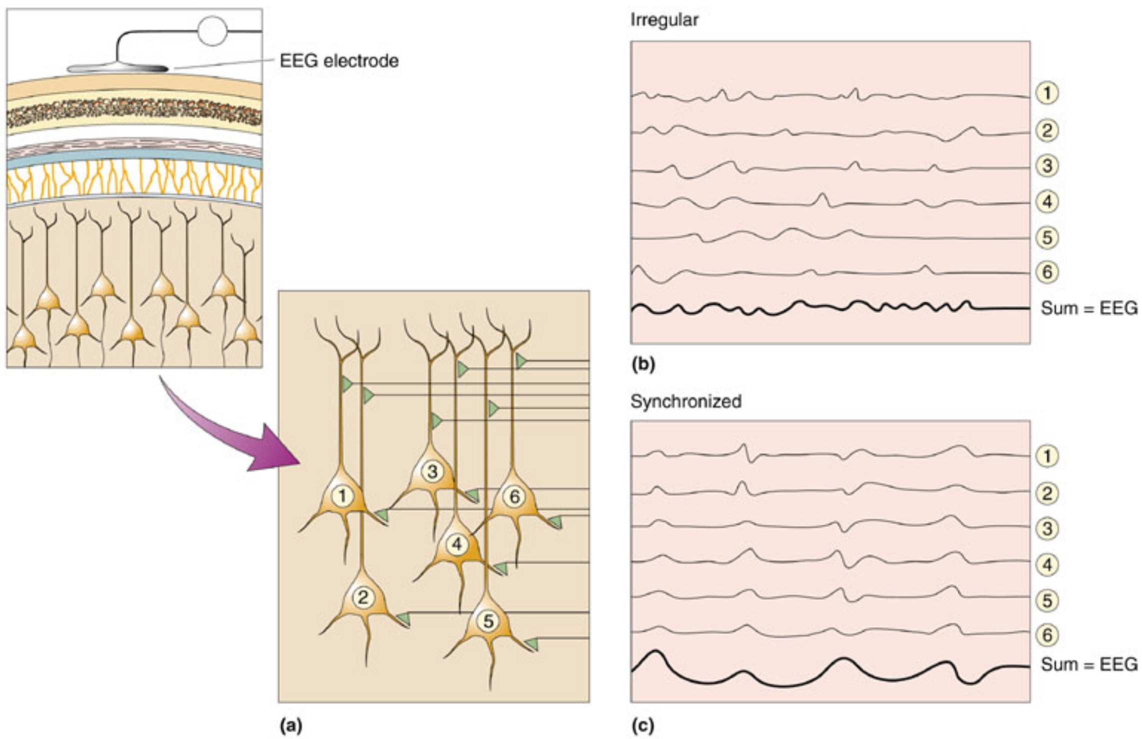


EEG



Amplifier EEG
EEG electrode
Scalp
Skull
Dura
mater
Arachnoid
Subarachnoid
space
Pia mater
Active synapses
Afferent axon
Efferent
axon

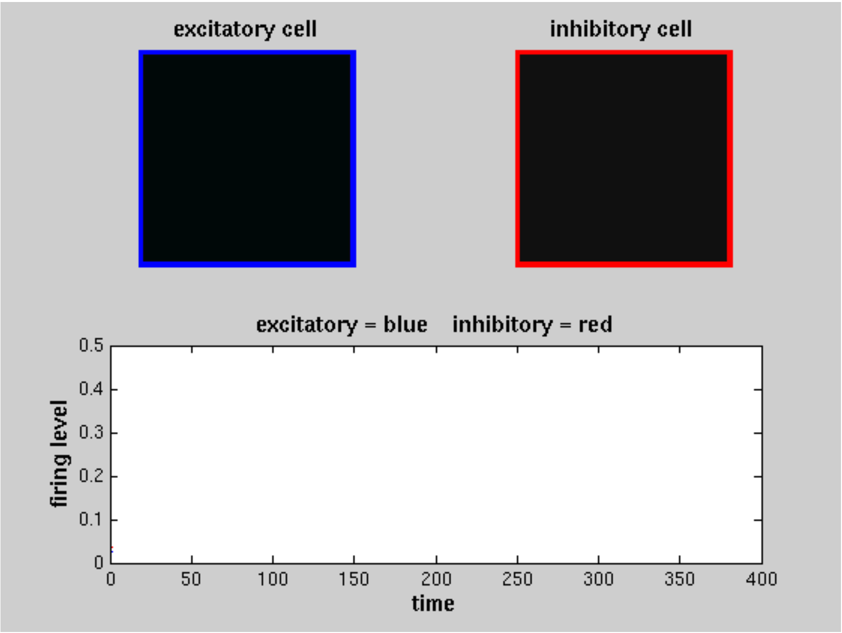
EEG

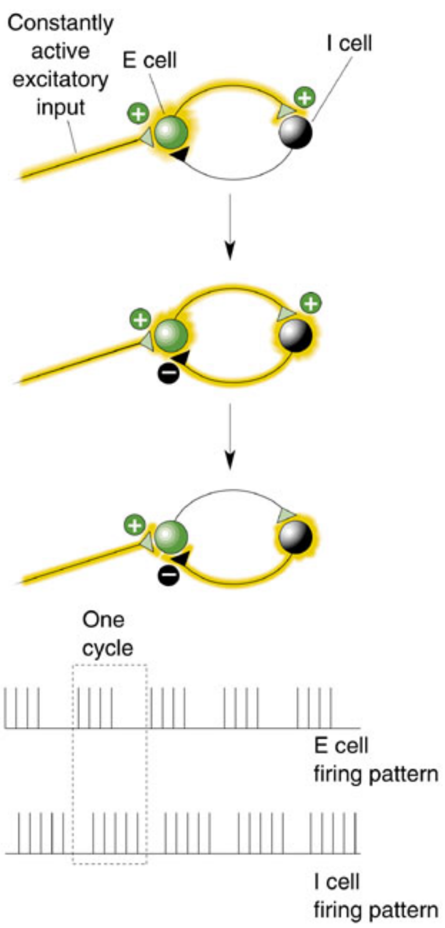


Many neurons need to sum their activity in order to be detected by EEG electrodes. The timing of their activity is crucial. Synchronized neural activity produces larger signals.

The Electroencephalogram

A simple circuit to generate rhythmic activity





The Electroencephalogram

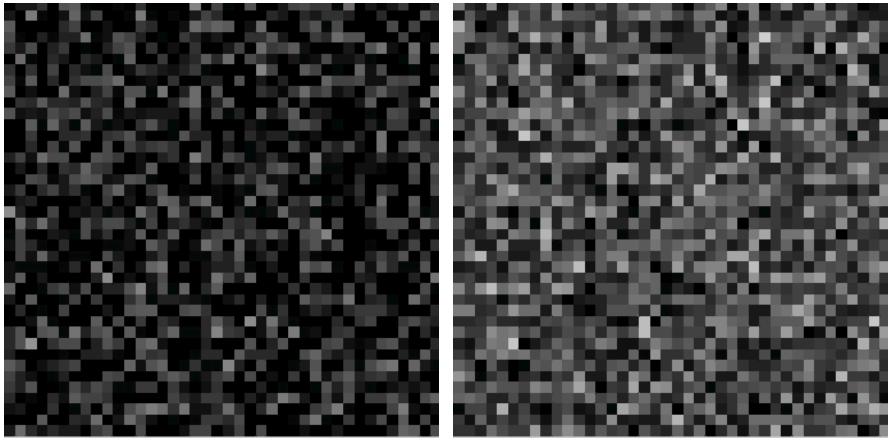
Two ways of generating synchronicity:

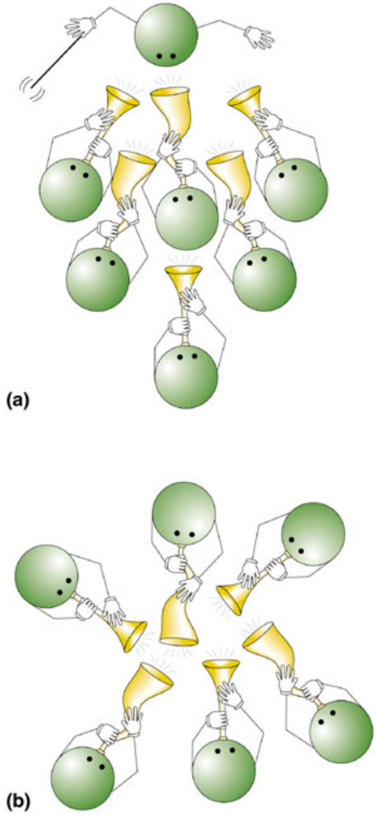
a) pacemaker; b) mutual coordination

1600 oscillators (excitatory cells)

un-coordinated

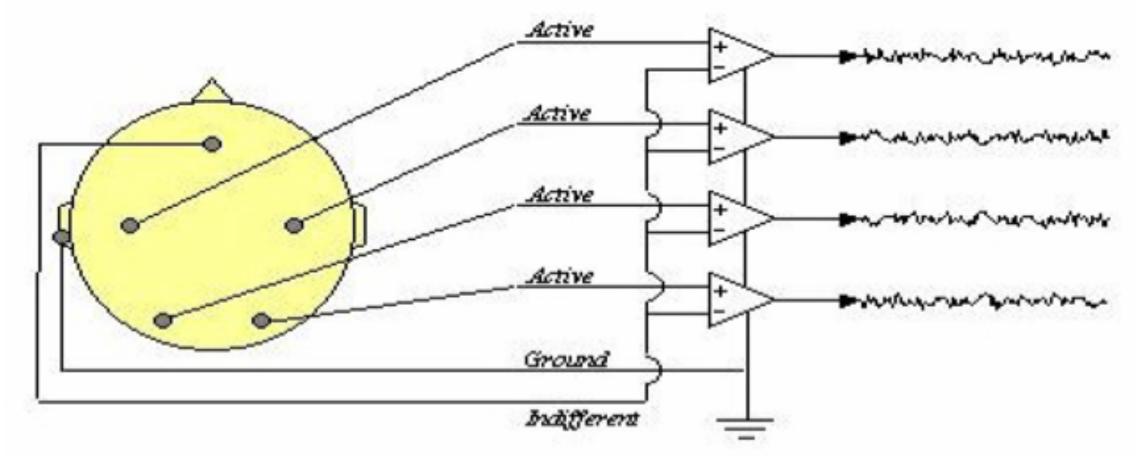
coordinated

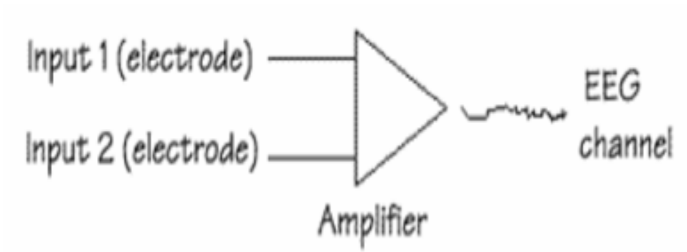




Basic Differential Amplifier

Differential amplifiers measure the voltage difference between the two signals at each of its inputs.



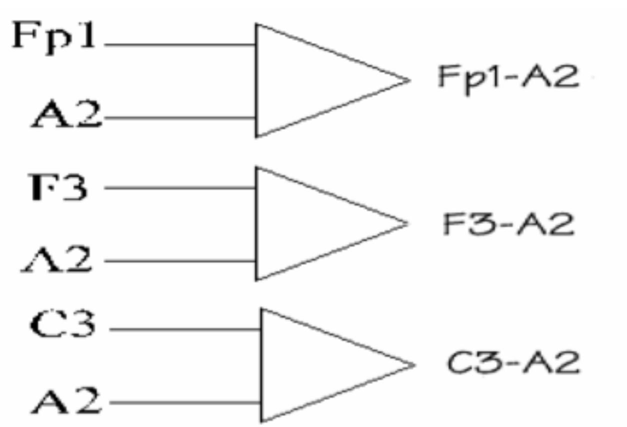


Electrodes Montages

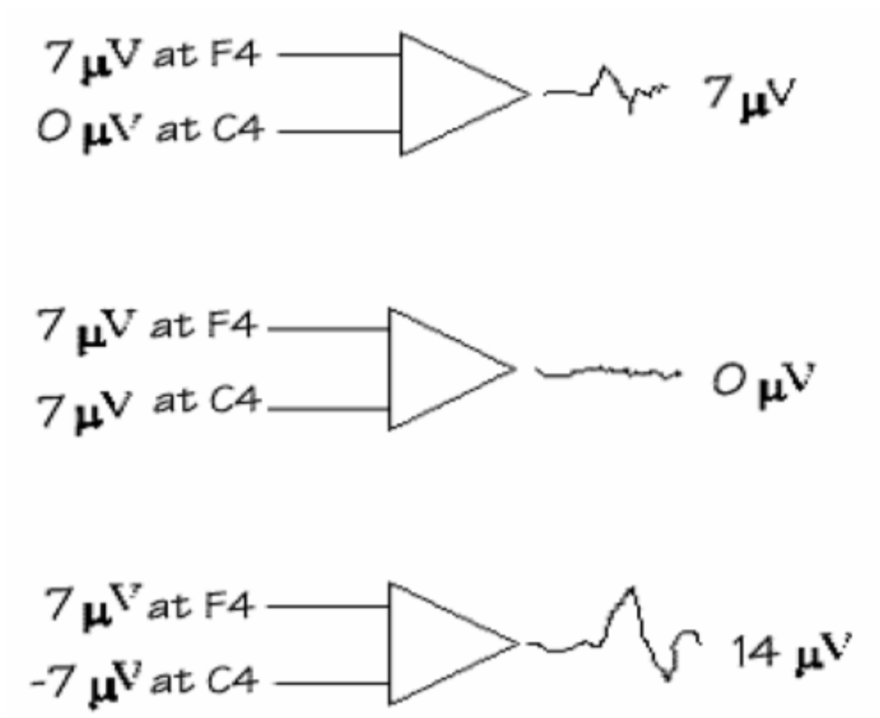
➢ The pattern of connections between the electrodes and the recording channels is known as a montage.

➢ **There are two basic types of EEG montage:**

1- Referential: The potential difference is measured between an active electrode and an inactive reference electrode.



2- Bipolar: The potential difference is measured between two active electrodes.



EEG

EEG rhythms correlate with patterns of behavior (level of attentiveness, sleeping, waking, seizures, coma).

Rhythms occur in distinct frequency ranges:

Gamma: 20-60 Hz (Somatosensory)

Beta: 14-20 Hz (activated cortex, thinking, exchange of info across areas)

Alpha: 8-13 Hz (quiet waking, eyes closed, relaxation)

Theta: 4-7 Hz (Inhibition of responses)

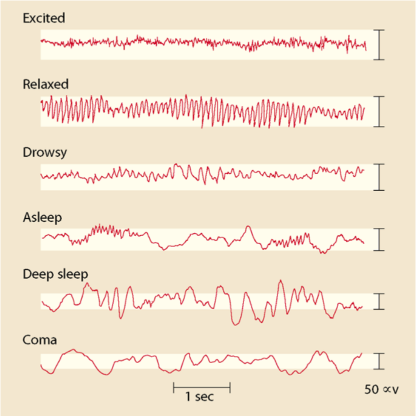
Delta: less than 4 Hz (working memory)

Mu: 8-12Hz (mostly motor neuron activity, seen during mirror activity)

Higher frequencies: active processing, relatively de-synchronized activity (alert wakefulness, dream sleep).

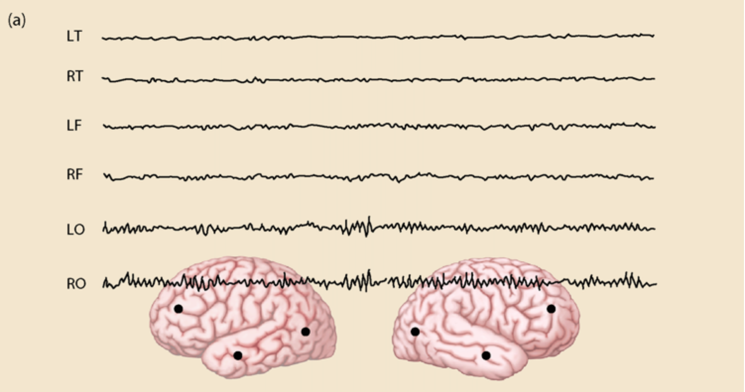
Lower frequencies: strongly synchronized activity (nondreaming sleep, coma).

EEG

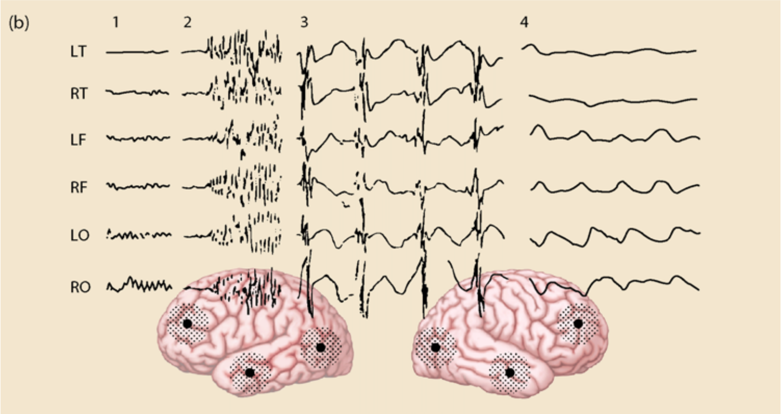


- Cinically useful as distinct brain states show characteristic EEG signal

EEG



Normal Activity

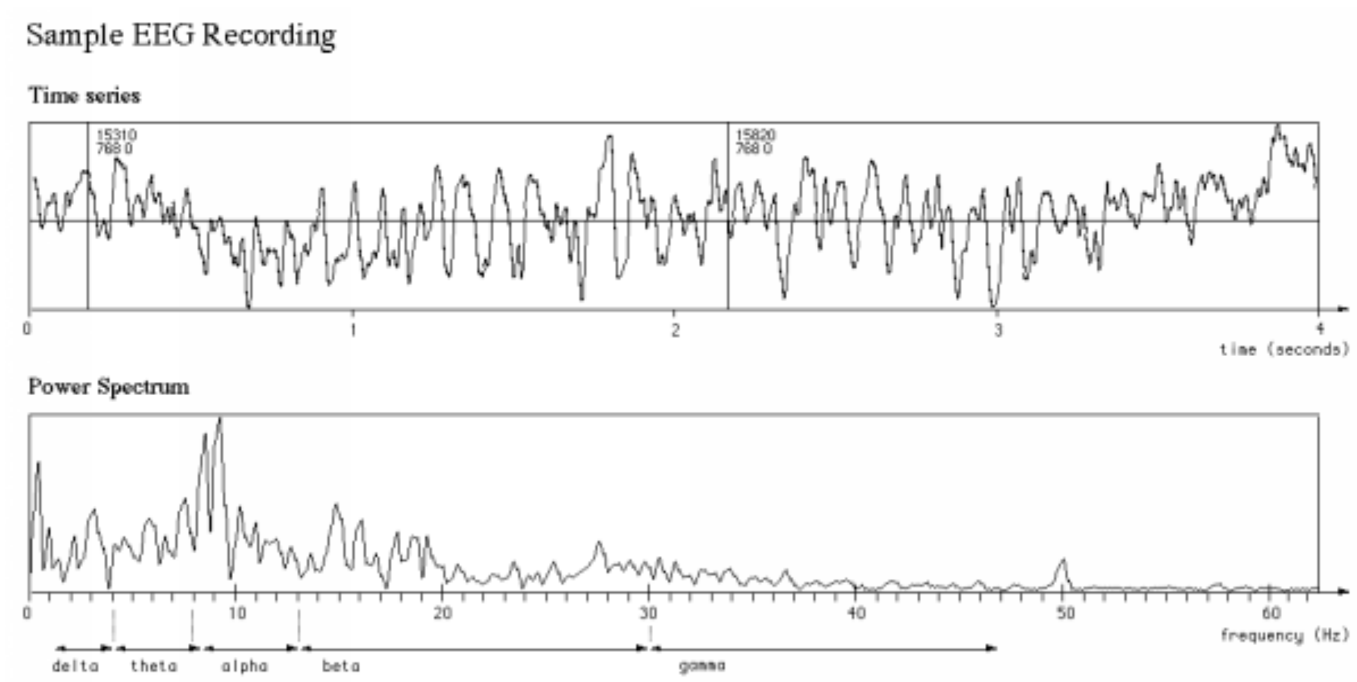


Seizure Activity

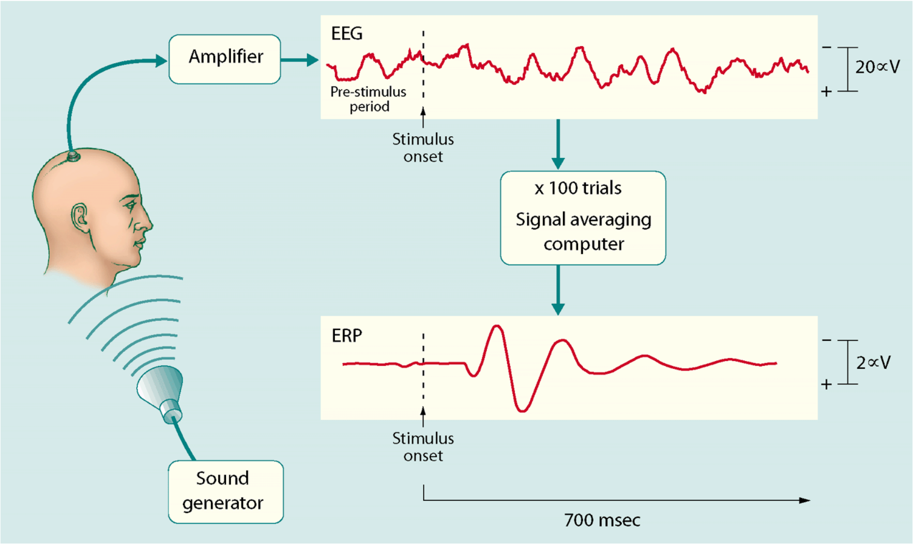
- Clinically useful in determining the focus of epileptic seizure

EEG

Power spectrum:



EEG

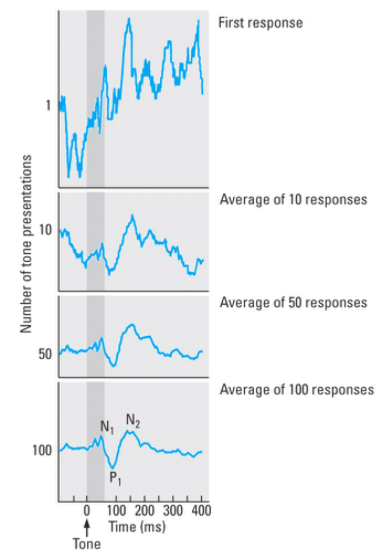


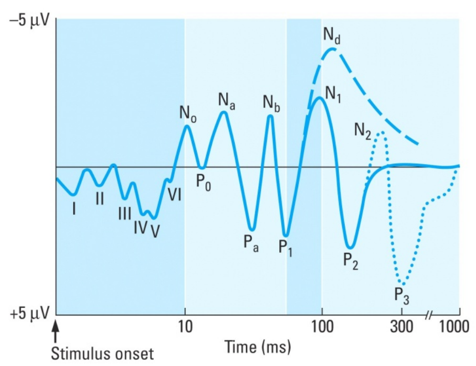
"Event-related Potentials"

- Background EEG signal can be removed by trial-averaging revealing the response of a brain region to stimuli

Event-Related Potentials (ERPs)

- Changes in the EEG signal that are correlated with a discrete sensory stimulus (e.g. a light turning on).
- ERPs difficult to detect because they are weak and embedded in noise -> averaging needed.
- Peaks and troughs in the ERP waveform associated with different stages of processing (e.g. early sensory stages vs. later cognitive stages).
- Evolution of the ERP wave through the brain over space and time shows processing pathways.





Magnetoencephalography MEG

Quantity measured: components of the magnetic field

Order of magnitude: 100fT

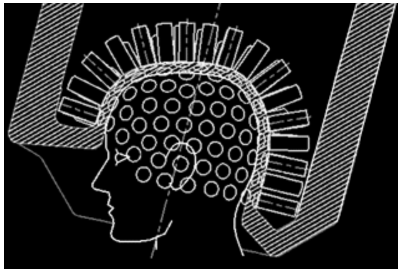
Temporal Resolution: ms

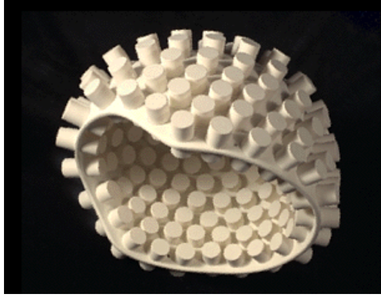
Spatial Resolution: cm

Cost: expensive

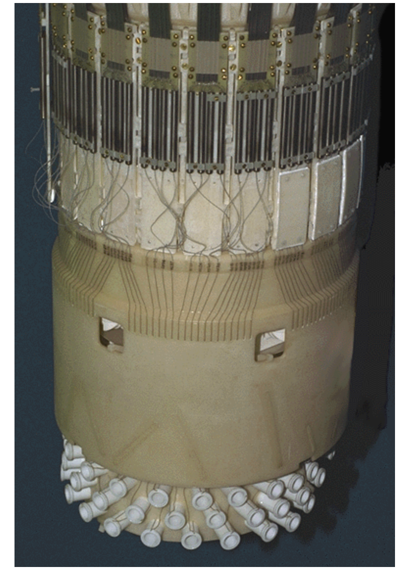
Advantage: Clean signals

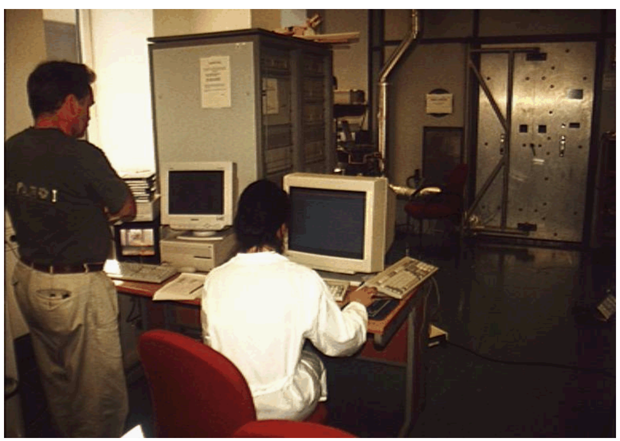
Disadvantage: Insensitive to radial currents



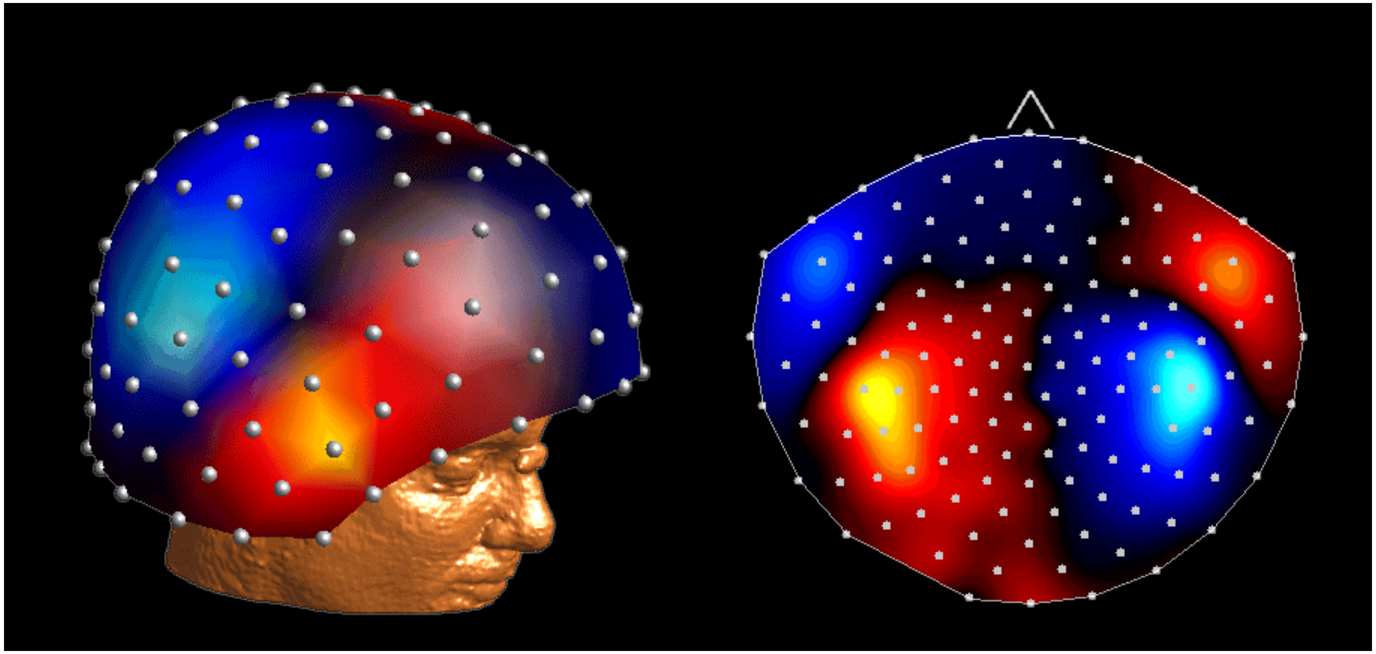


MEG Technology

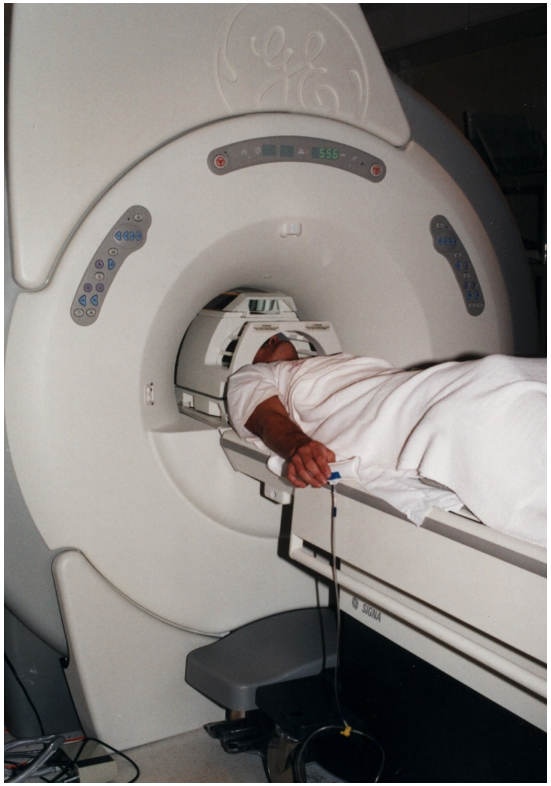




Magnetic field on subject's head and in polar projection



Magnetic Resonance Imaging: MRI



Quantity measured: 'water content' of the brain tissue

Knowledge gained: brain structure

Temporal Resolution: min

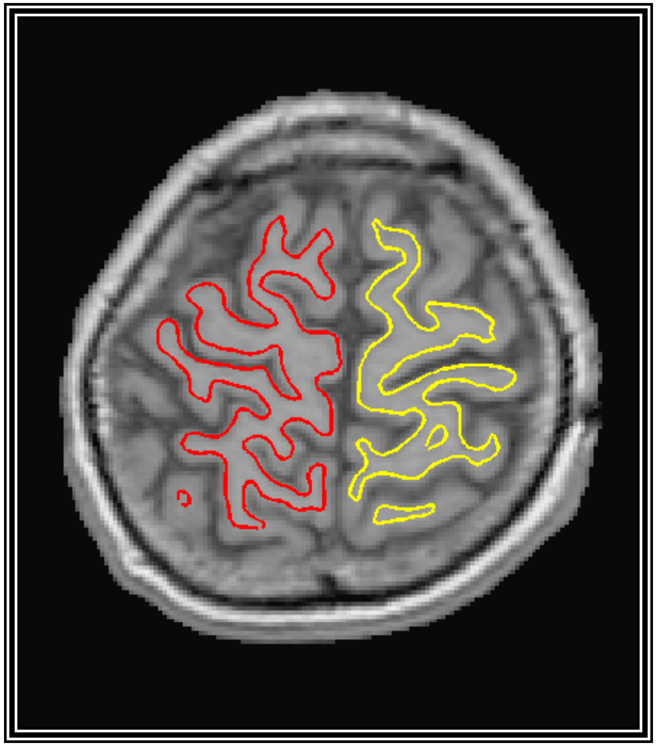
Spatial Resolution: mm

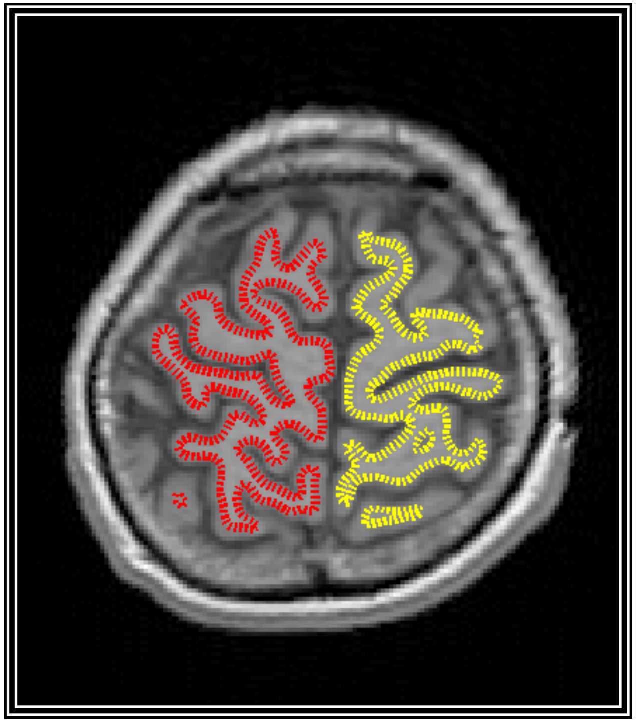
Cost: expensive

Advantage: 3D-volume resolution

Disadvantage: no functional or temporal information

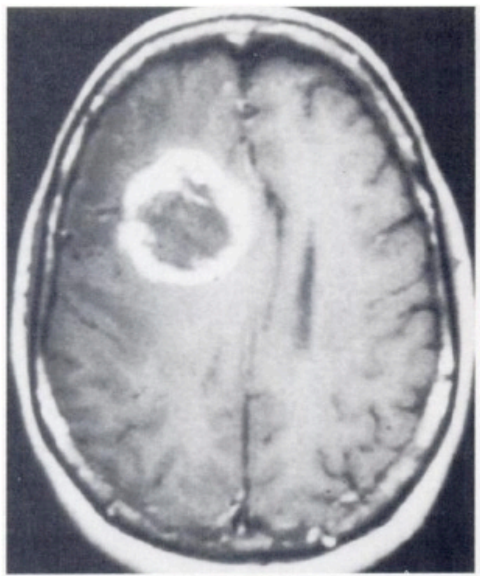
Using the gray-white matter boundary as an anatomical constraint



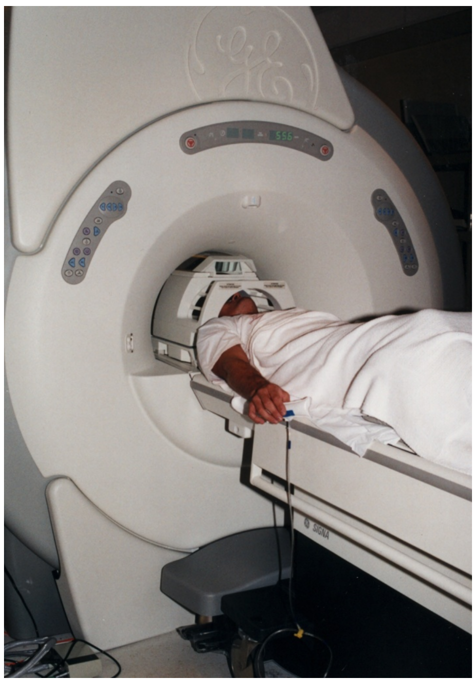


Brain Surgery

- Brain Tumors




Functional Magnetic Resonance Imaging: fMRI



Quantity measured: ratio between oxy- and deoxyhemoglobin

Knowledge gained: activated areas

Temporal Resolution: sec

Spatial Resolution: mm

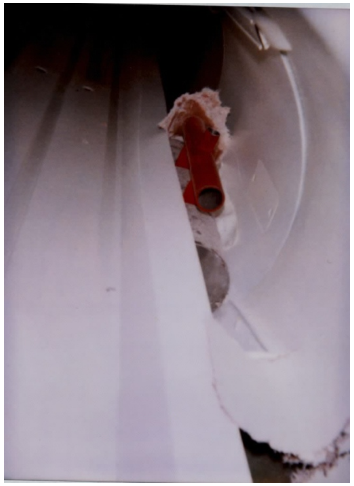
Cost: expensive

Advantage: 3D-volume resolution

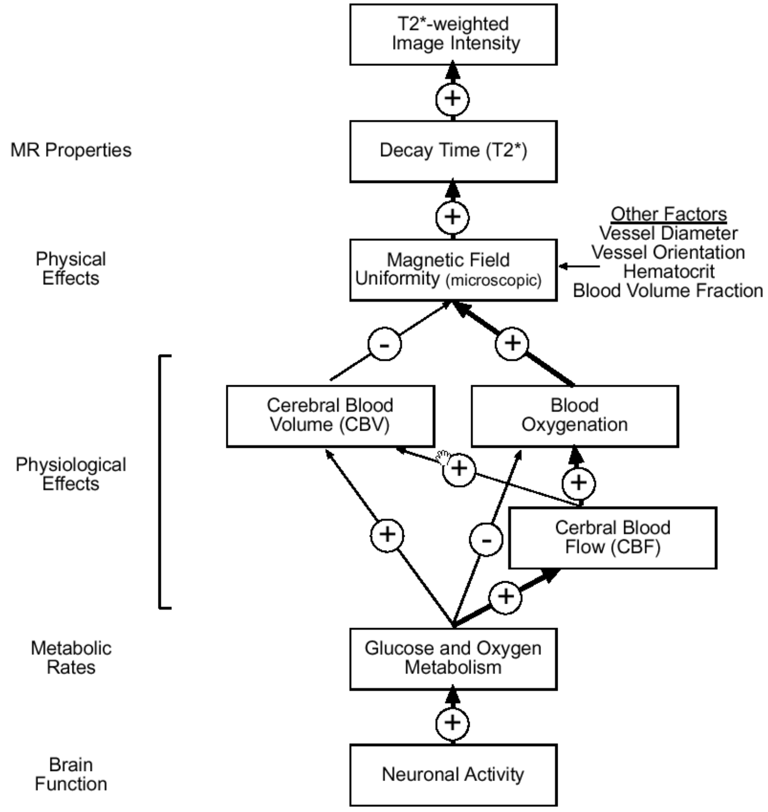
Disadvantage: low temporal resolution, no straight forward analysis

How powerful is this magnet

- About 250,000 more poweful than the earth's magnetic field.

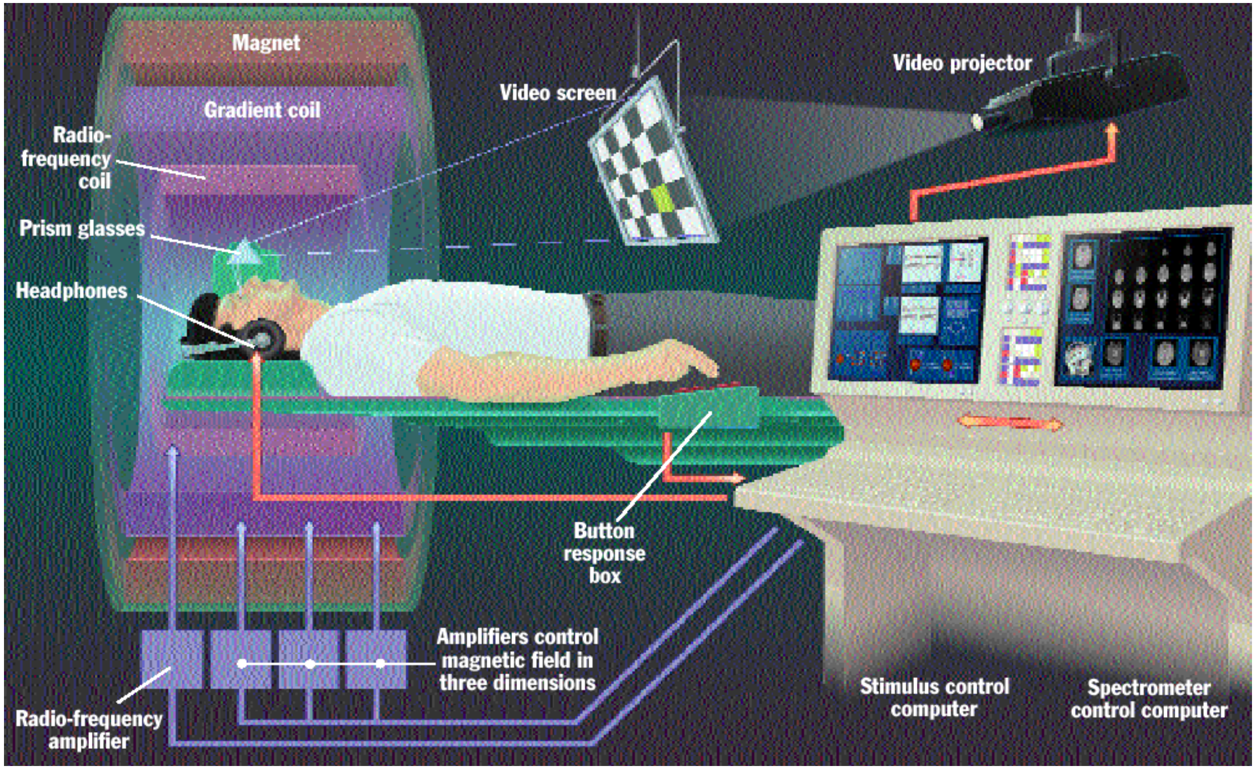


BOLD (blood oxygen level dependent) signal



Source: Doug Noll's primer

fMRI Setup


Magnet
Gradient coil
Radio-frequency coil
Prism glasses
Headphones
Video screen
Video projector
Button response box
Amplifiers control magnetic field in three dimensions
Radio-frequency amplifier
Stimulus control computer
Spectrometer control computer

fMRI Experiment Stages: Prep

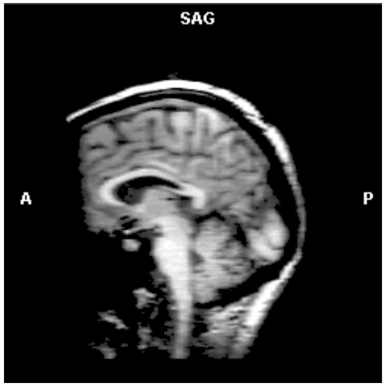
1) Prepare subject
   - Consent form
   - Safety screening
   - Instructions

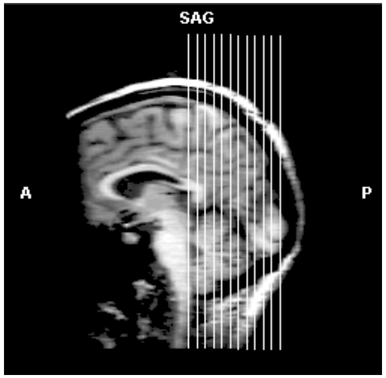
2) Shimming
   - putting body in magnetic field makes it non-uniform
   - adjust 3 orthogonal weak magnets to make magnetic field as homogenous as possible

3) Sagittals

Note: That's one g, two t's

Take images along the midline to use to plan slices

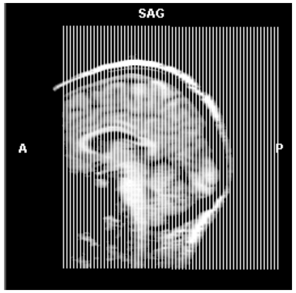


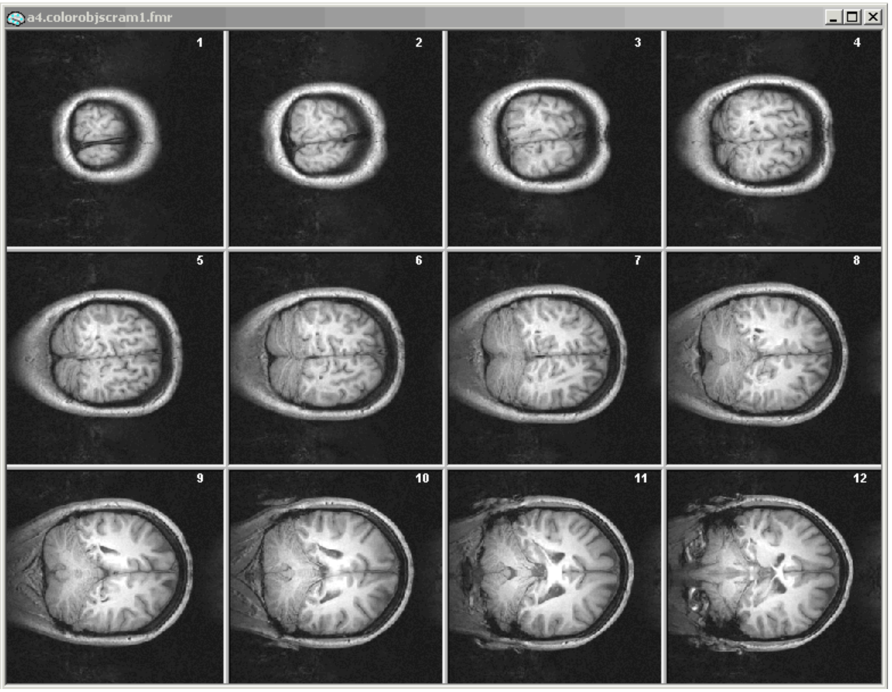


fMRI Experiment Stages: Anatomicals

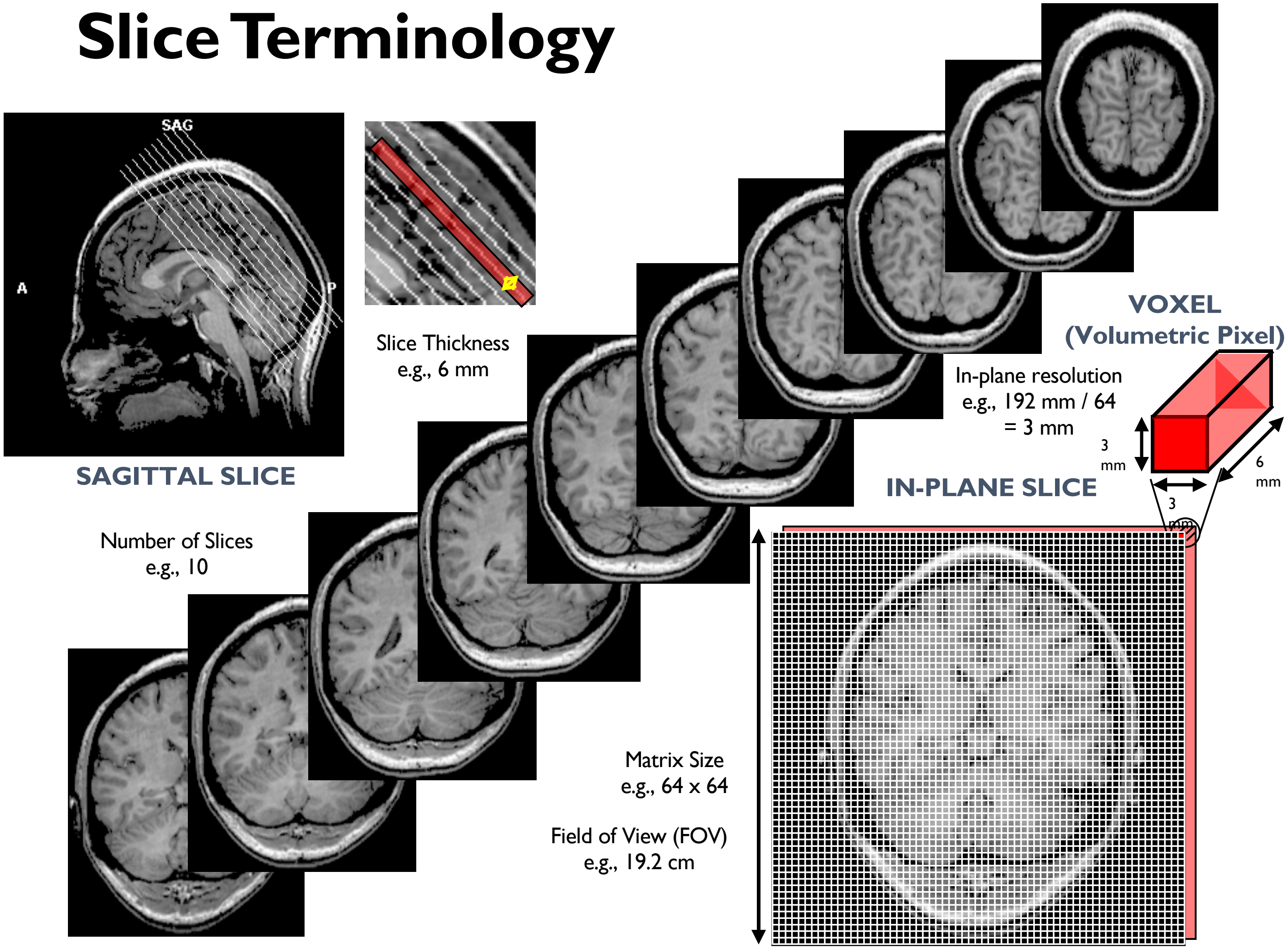
4) Take anatomical (T1) images

- high-resolution images (e.g., 1x1x2.5 mm)
- 3D data: 3 spatial dimensions, sampled at one point in time
- 64 anatomical slices takes ~5 minutes

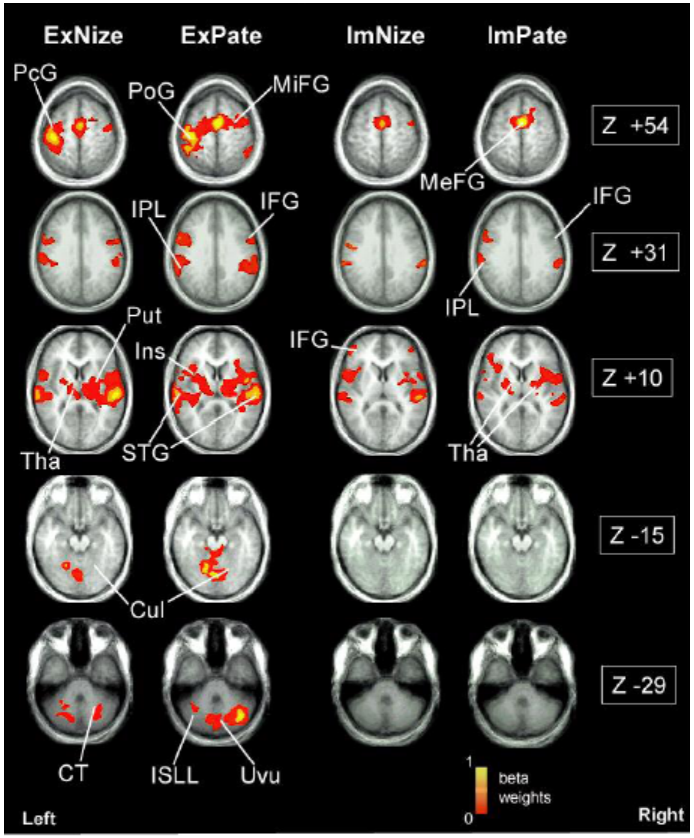




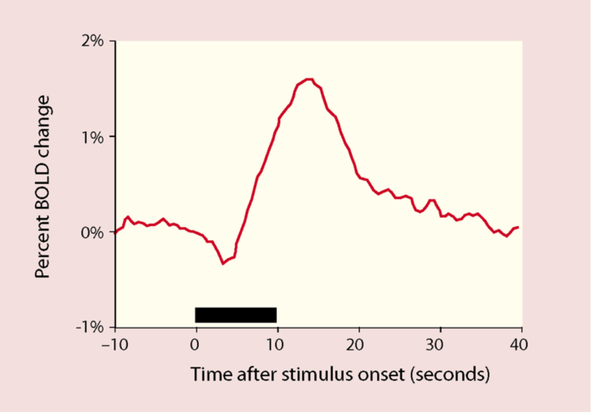
Slice Terminology



IMAGINATION vs EXECUTION OF MOVEMENTS



Functional MRI

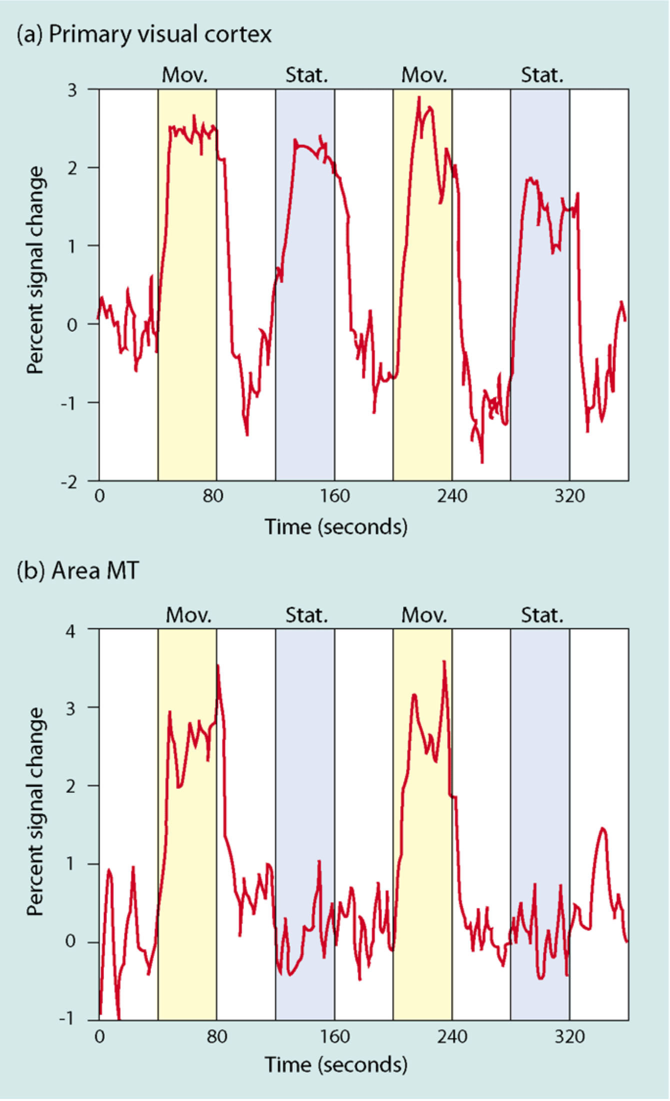


- Takes advantage of the fact that neural activity is followed by blood flow in a highly predictable manner
- Altered blood flow alters RF signal from active brain regions

Functional MRI

- Permits examination of brain regions that become active during cognitive performance

Facilitates comparison of brain activity in different populations



Functional MRI

- Analysis methods take advantage of known hemodynamic properties of the brain

Magnetic Resonance Spectroscopy (MRS)

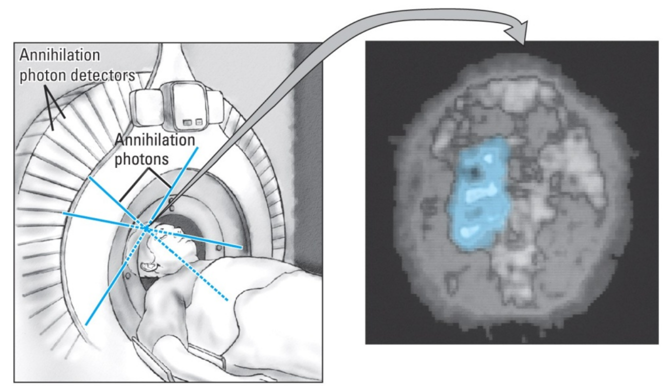
- Standard fMRI is tuned to the resonance frequency of hydrogen (component of water).
- MRI can be tuned to the resonance frequency of other chemicals (e.g. creatin -> label for neuron -> diagnosis of cell loss; choline -> precursor of ACh).

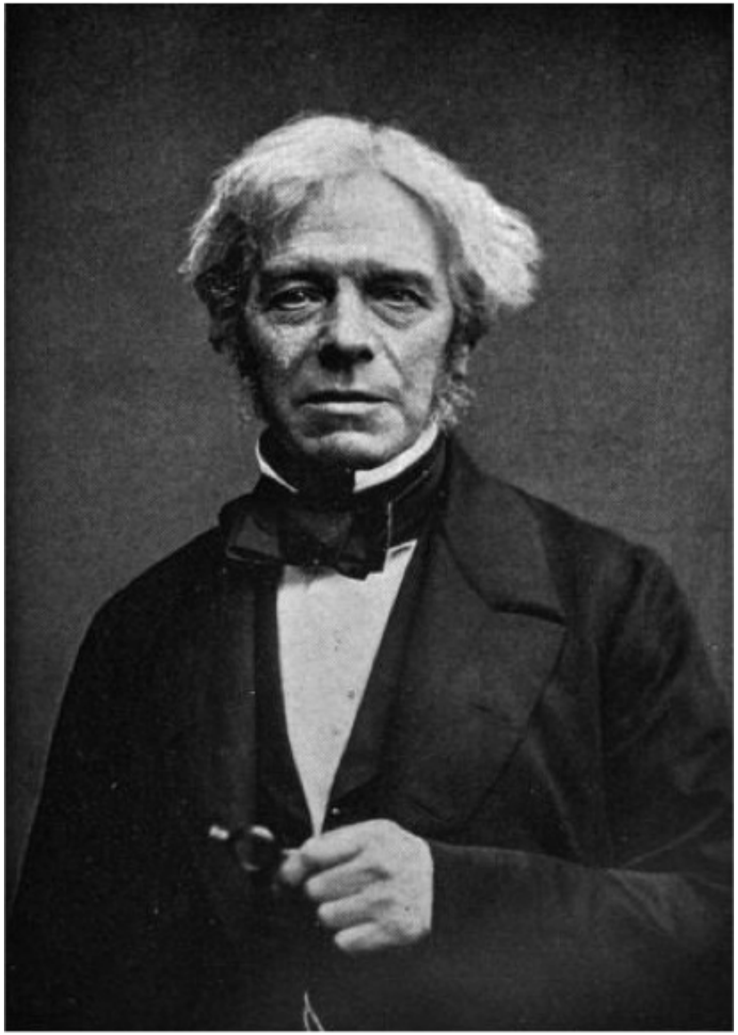
Positron Emission Tomography

- Type of tracer determines type of activity detected
  - ^{15}O radioactive oxygen, is injected into bloodstream with water
    - Measures blood flow
  - Radioactive Sugar
    - Measures metabolism

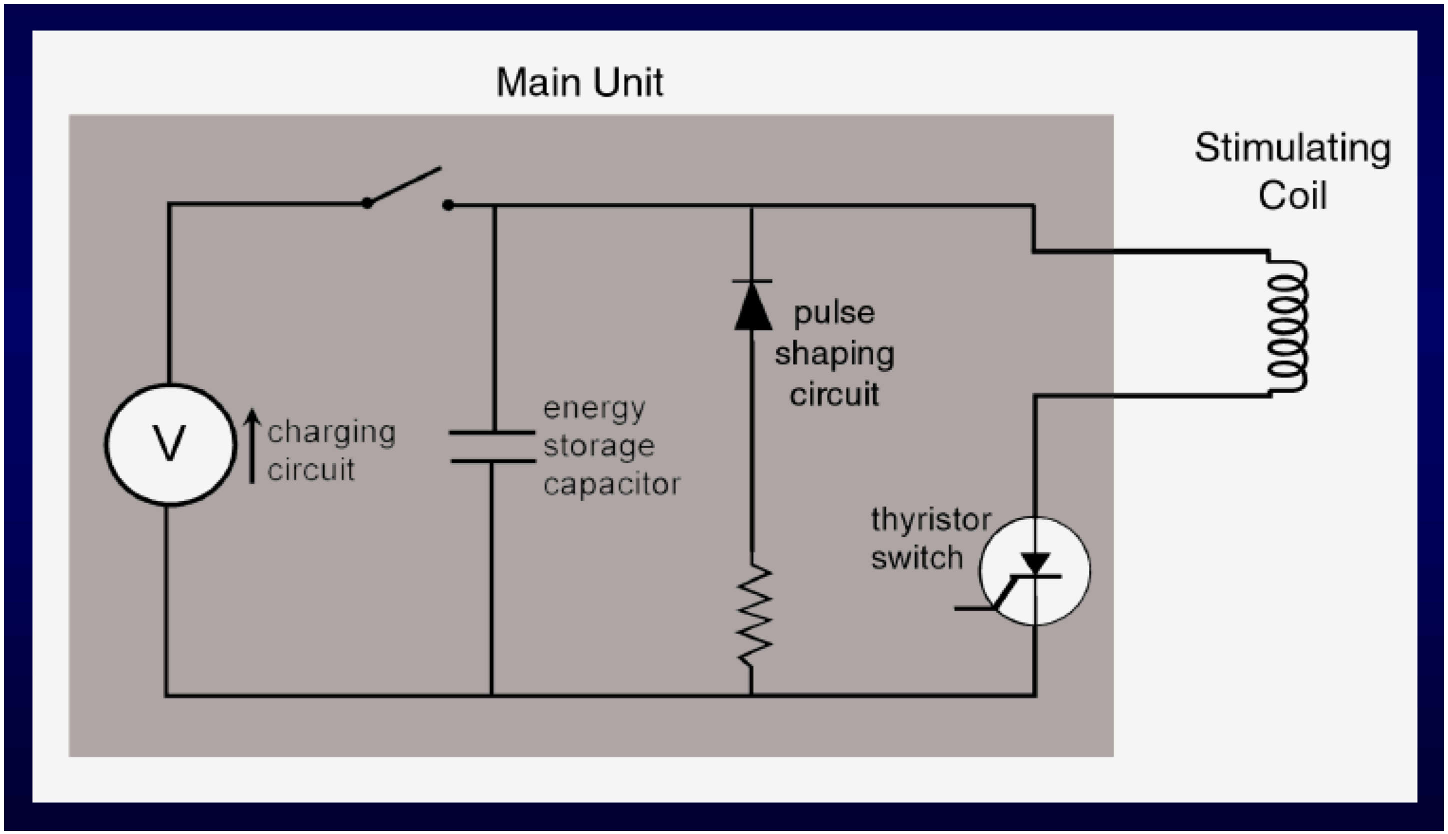
Positron-Emission Tomography (PET)

- Subject injected with radioactive substance into blood-stream.
- Radioactive substance flows to brain regions that are more active.
- Several substances can have radioactive labels (e.g. sugars, neurotransmitters).
- Doughnut-shaped camera that records radiation and reconstructs 3D model of radioactive source.
- PET images blood flow, not neural activity directly.
- Radioactive labels have short half-life and are rather safe.



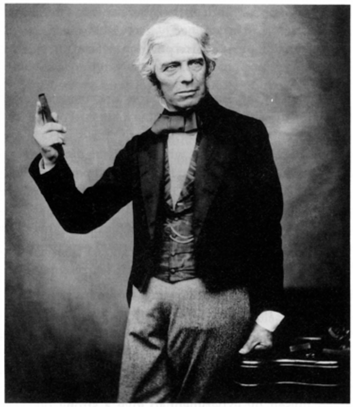


Invasion of non-invasive stimulation

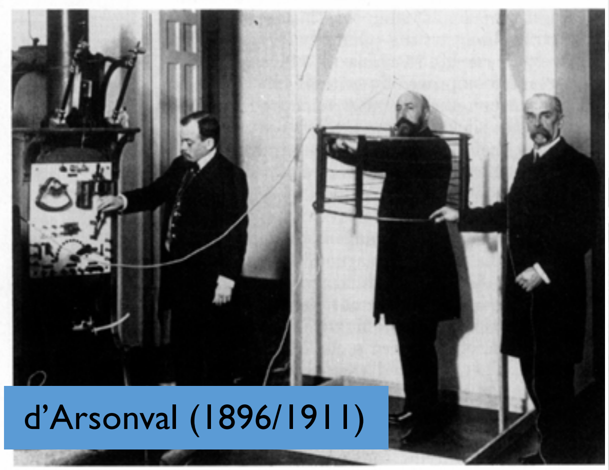


Main Unit
Stimulating Coil
V
charging circuit
energy storage capacitor
pulse shaping circuit
thyristor switch

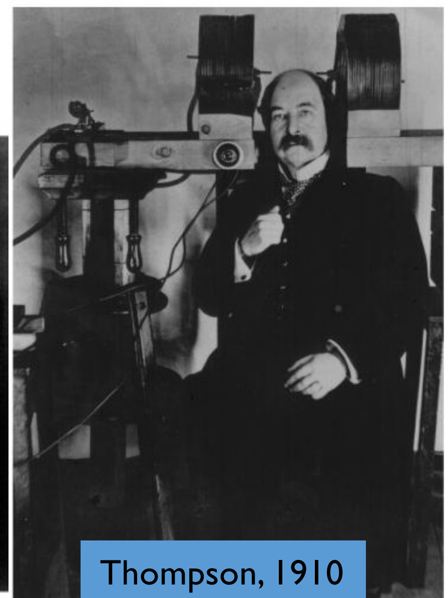
History of TMS and obligatory funny pictures



Merton &Morton (1980). Successful Transcranial <u>Electrical</u> Stimulation



d'Arsonval (1896/1911)



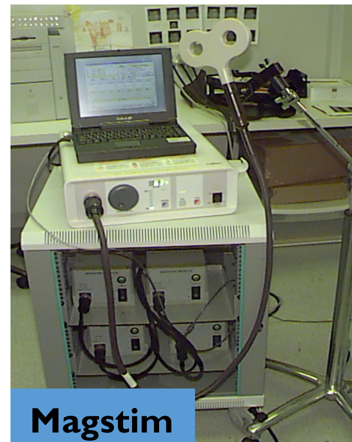
Thompson, 1910

Magnusson & Stevens, 1911

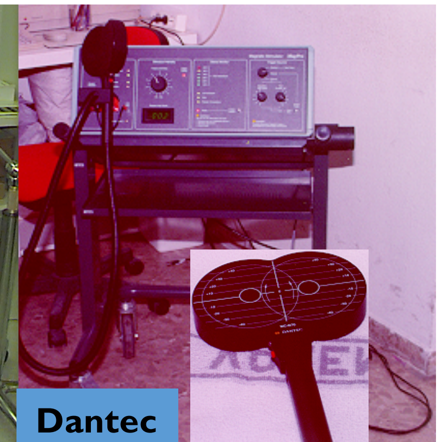
Barker, 1984

Transcranial Magnetic Stimulation allows the Safe, Non-invasive and Painless Stimulation of the cortex and the corticospinal tract

Common rTMS machines



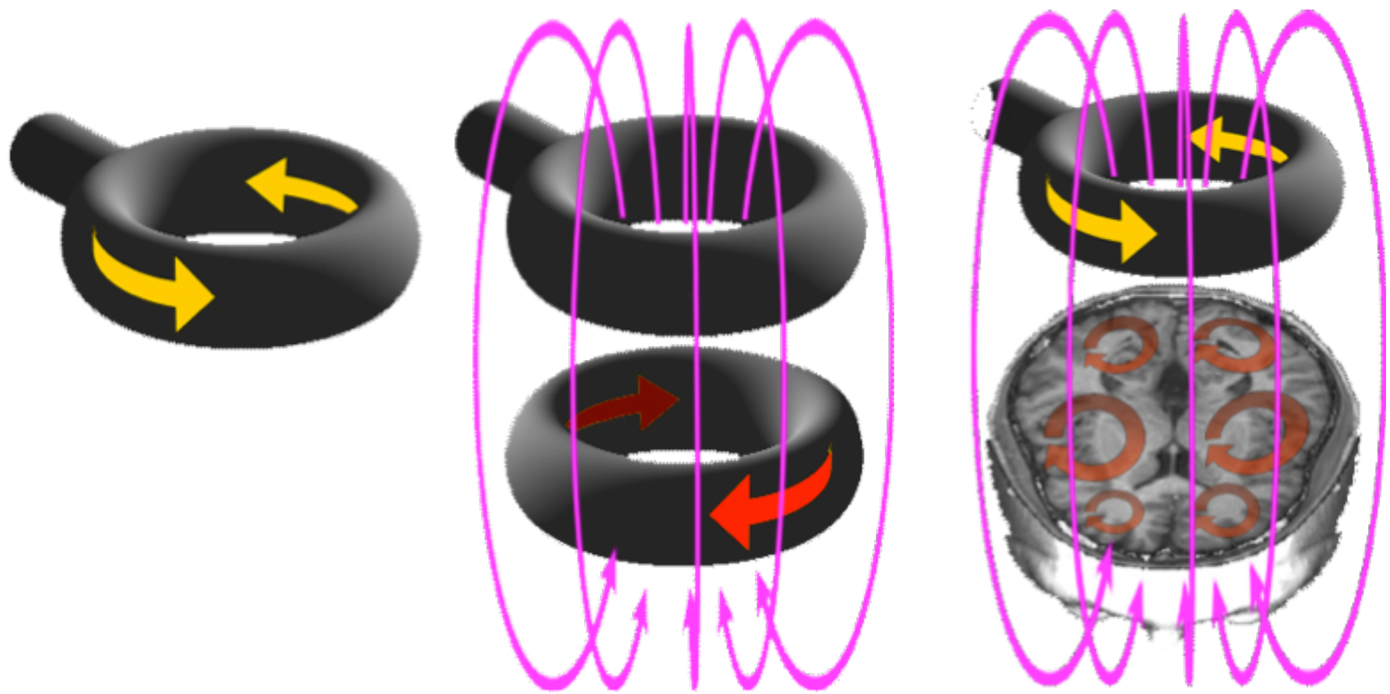
Magstim



Dantec

Cadwell

Electromagnetic Induction



Introduces disorder into a normally ordered system

TMS Terminology

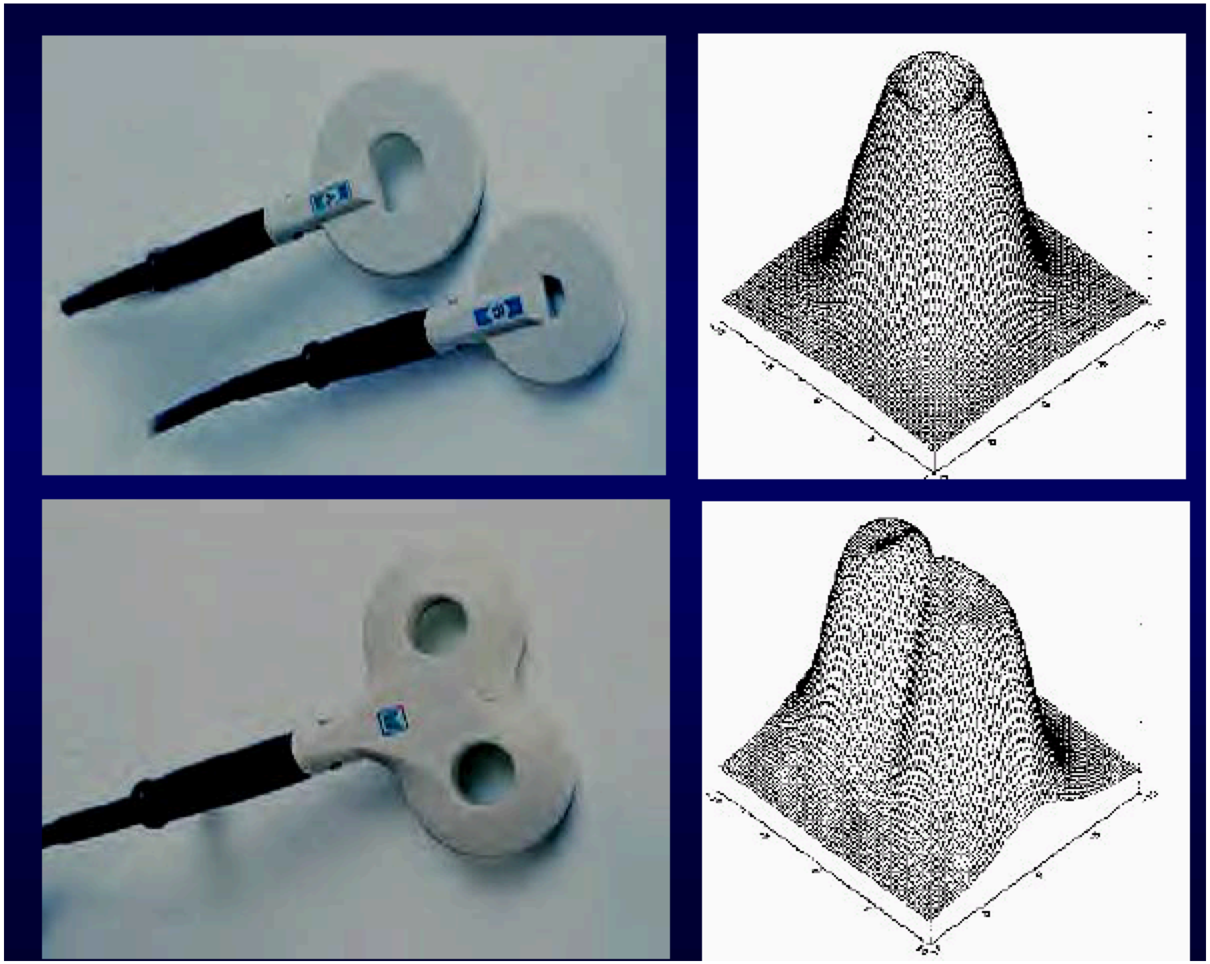
- Single pulse TMS
  - Single pulse every 5-10 sec (excitation)
- Paired pulse TMS
  - Subthreshold stimulus then supra threshold stimulation
  - Stimuli separated by 1-20msec
- Repetitive TMS (theta-burst)
  - Trains of stimuli to one brain area
  - Slow = low frequency (inhibitory)
  - Fast = high frequency (excitatory effect)

Continuous Theta-burst stimulation (cTBS)

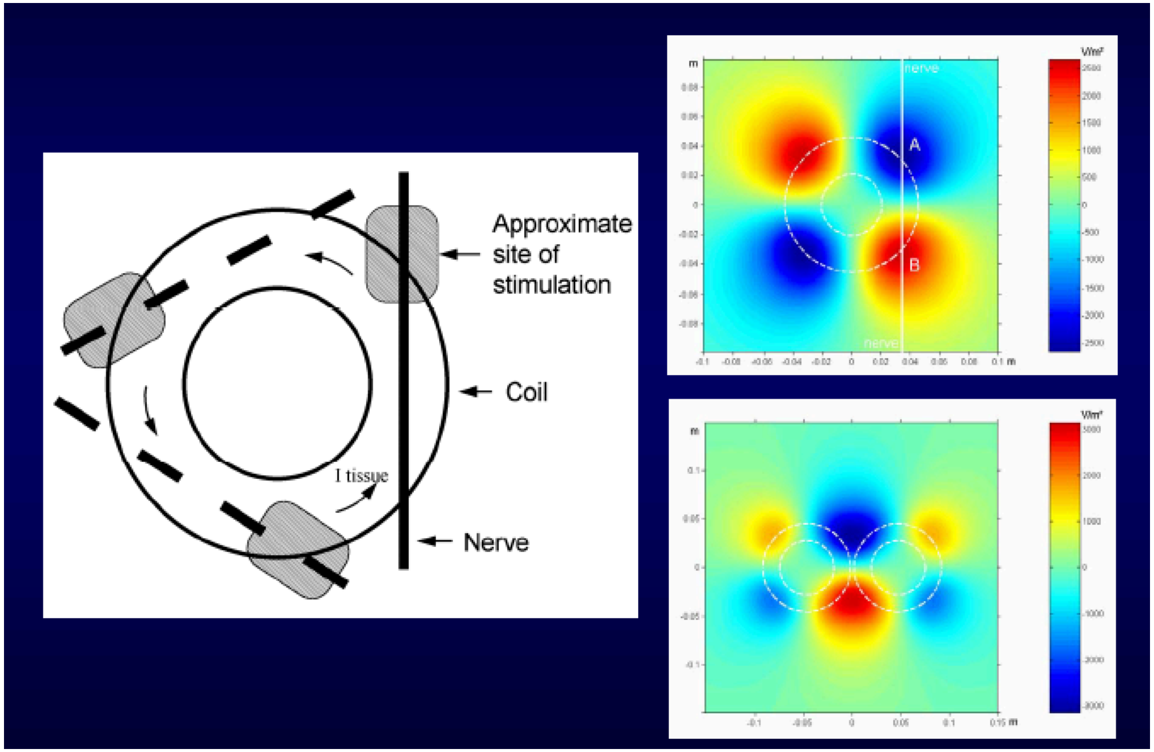
- Continuous train of pulses delivered in rapid 50Hz bursts of three with 20 ms between pulses, with a burst frequency of 5Hz and 200ms between bursts.
- Delivered at the stimulator output power corresponding to 80% of the AMT for each subject. cTBS typically lasts for a duration of 40s (600 pulses).
- The effect of the TBS stimulation outlasts the stimulation for a minimum 40 minutes.

Intermittent Theta-burst stimulation (iTBS)

- iTBS is typically delivered in bursts of 1840ms repeated every 10s for a total of 600 pulses or 191.84s.
- The effects of the intermittent stimulation are facilitatory and they typically last about 15 minutes.

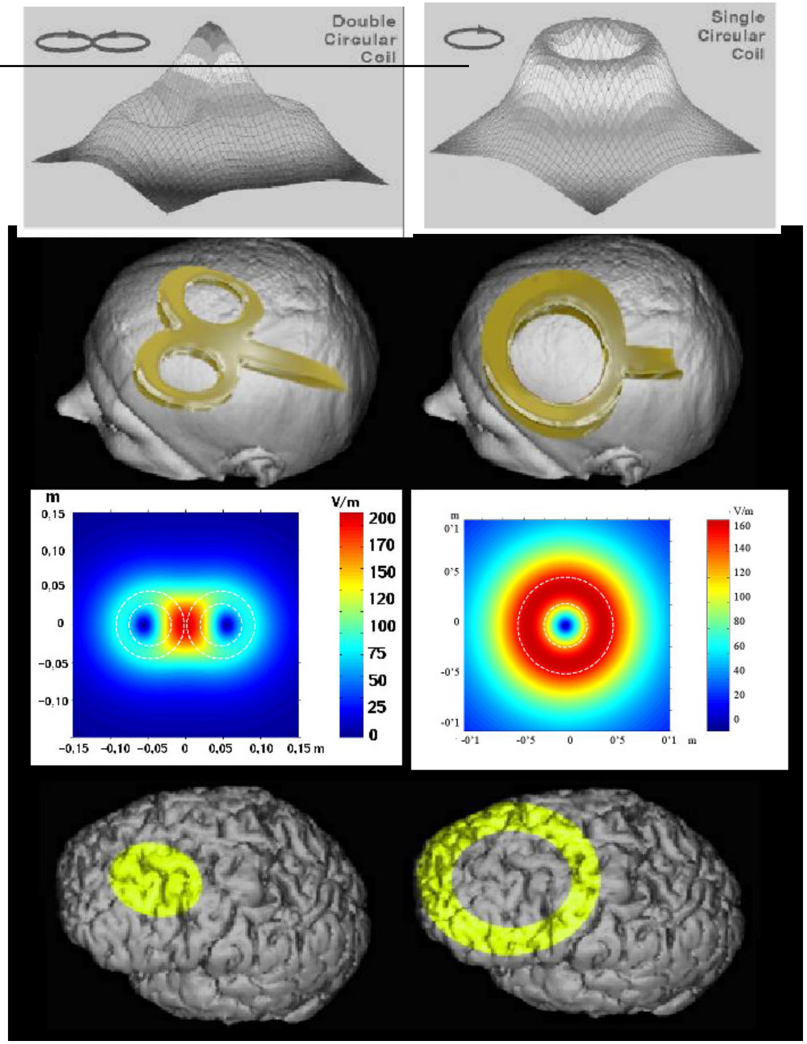


Mechanism of action



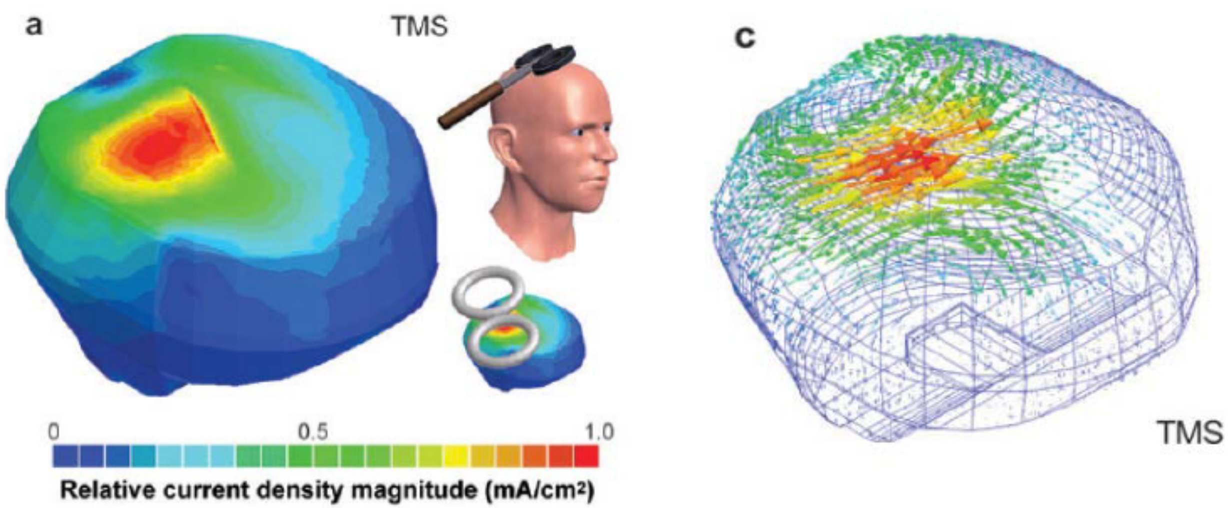
Practical considerations

Coil shape



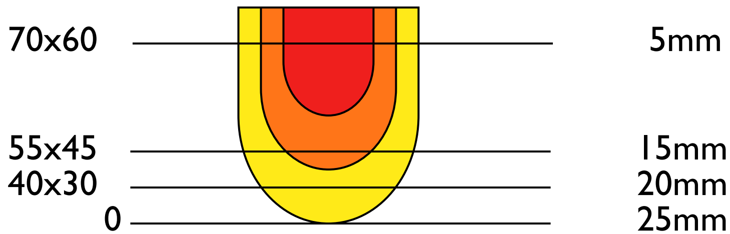
The geometry of the coil determines the focality of the magnetic field and of the induced current - hence also of the targeted brain area.

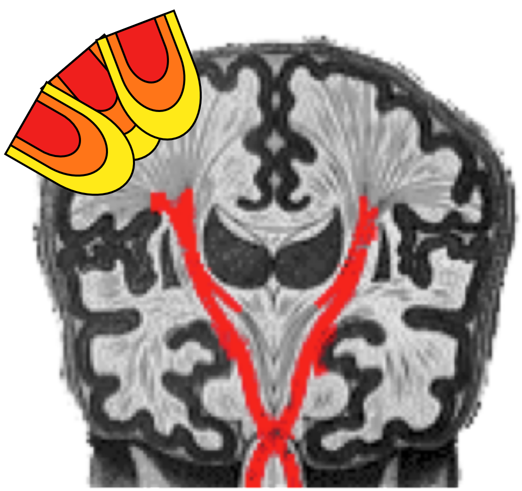
Basic mechanism: electrical vs magnetic activity

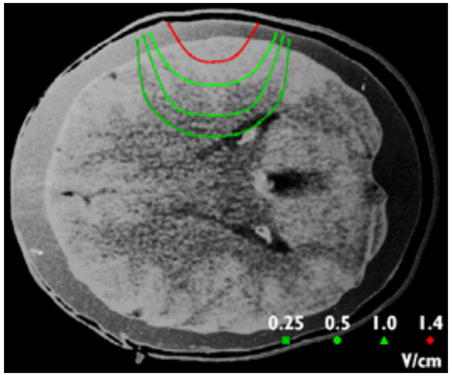


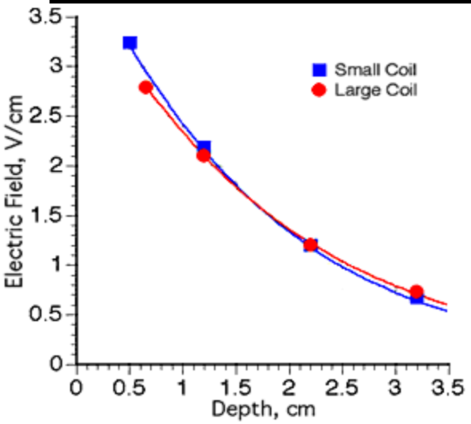
Wagner, Valero-Cabre & Pascual-Leone, 2007

Practical Considerations - stimulation depth



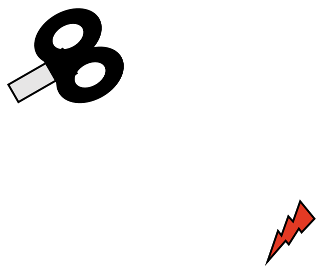




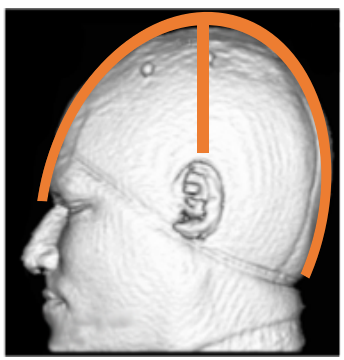


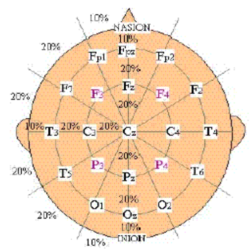
Cannot stimulate medial or sub-cortical areas

Coil localization - hitting the right spot



Find functional effect
M1 - hand twitch (MEP)
V5 - moving phosphenes



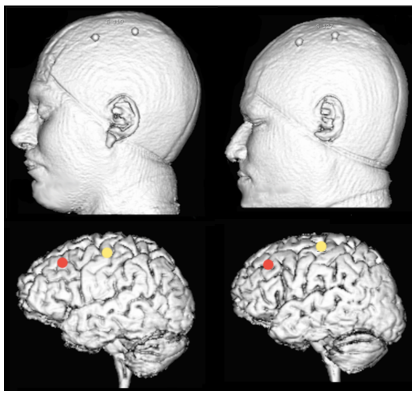


Find anatomical landmark
inion/nasion-ear/ear vertex
EEG 10/20 system

Move a set distance along and across (e.g. FEF = 2-4 cm anterior and 2-4 cm lateral to hand area)

Coil localization - hitting the right spot

But: not all brains are the same

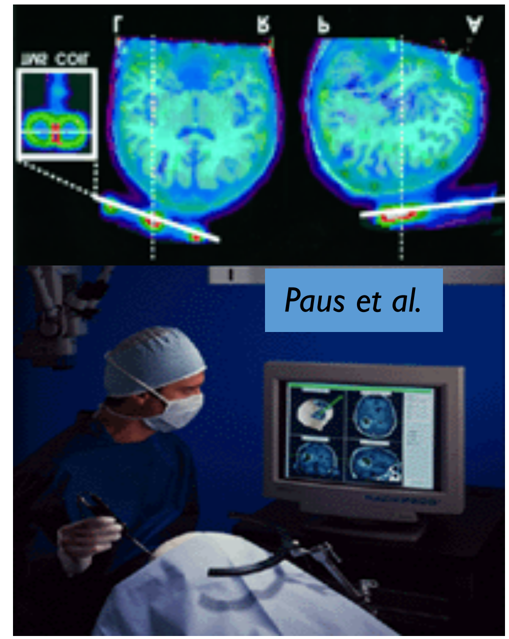


MRI co-registration

Functional and structural scan

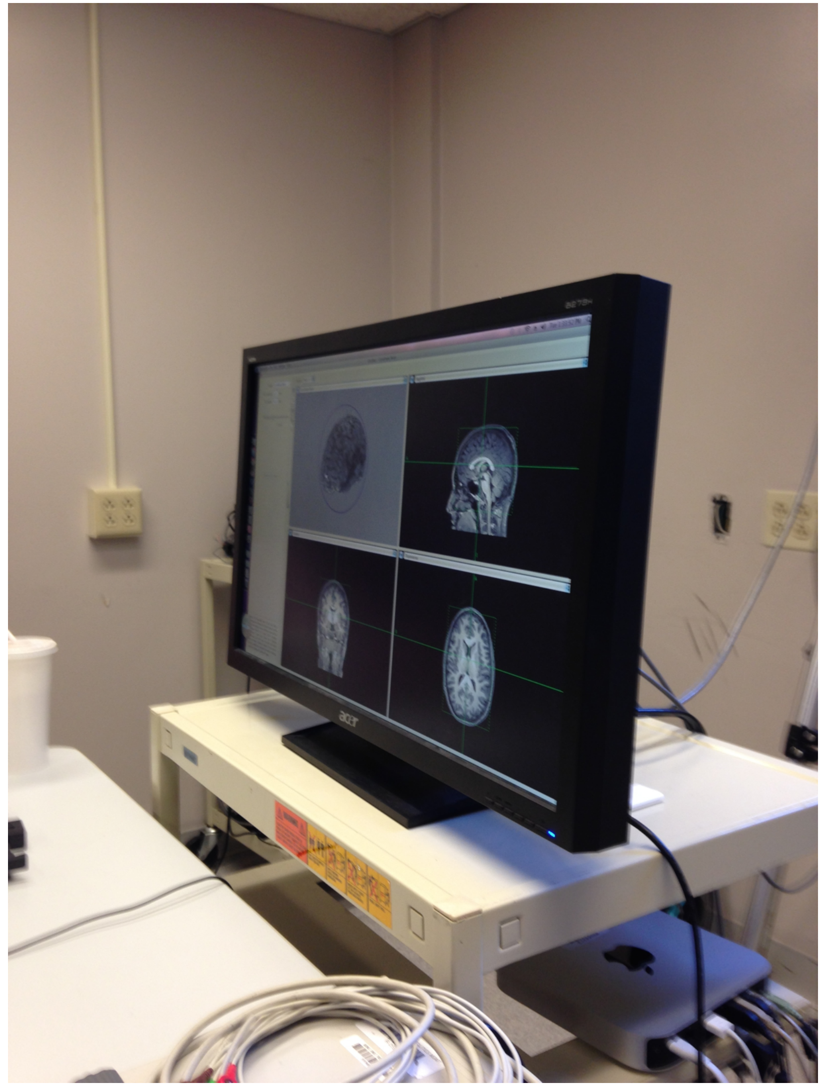
e.g. eye movement test from functional and map onto structural, then co-reg

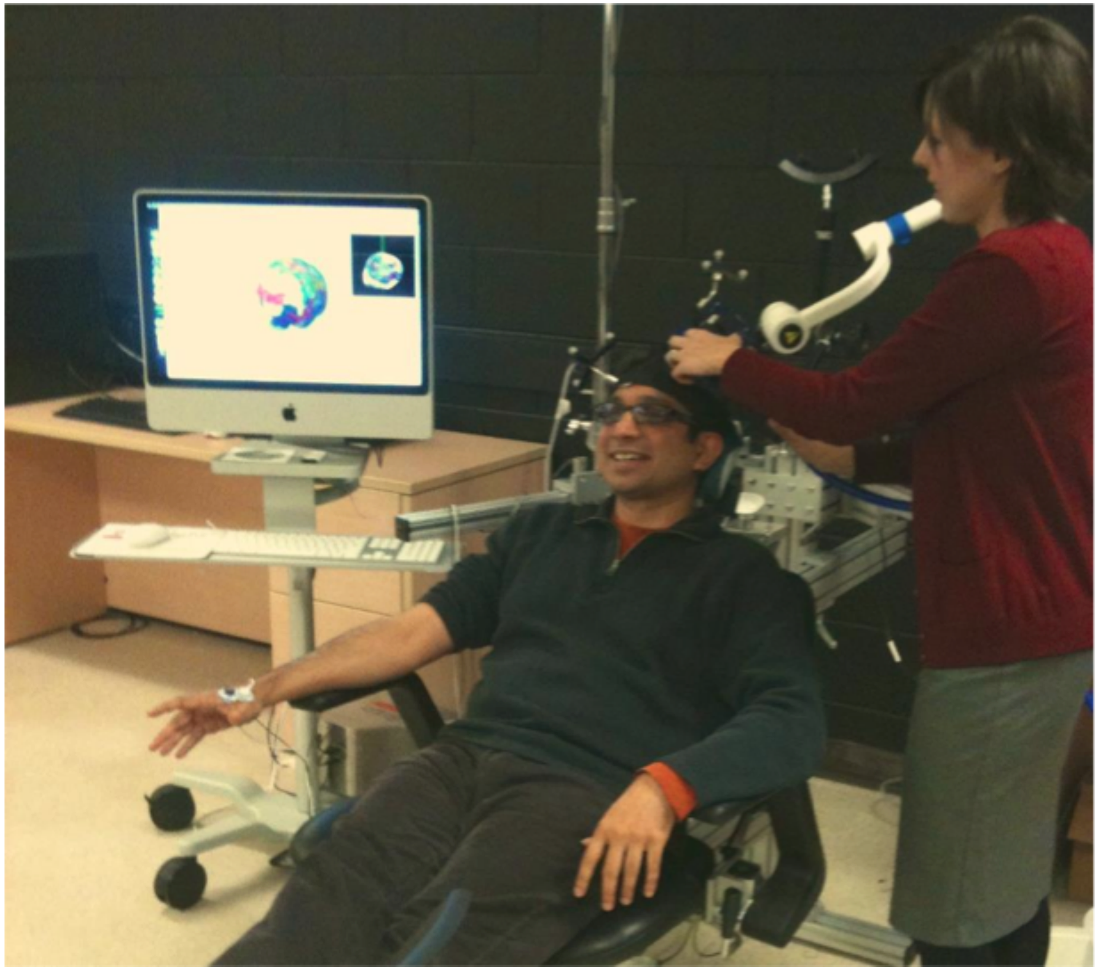
v. expensive and laborious



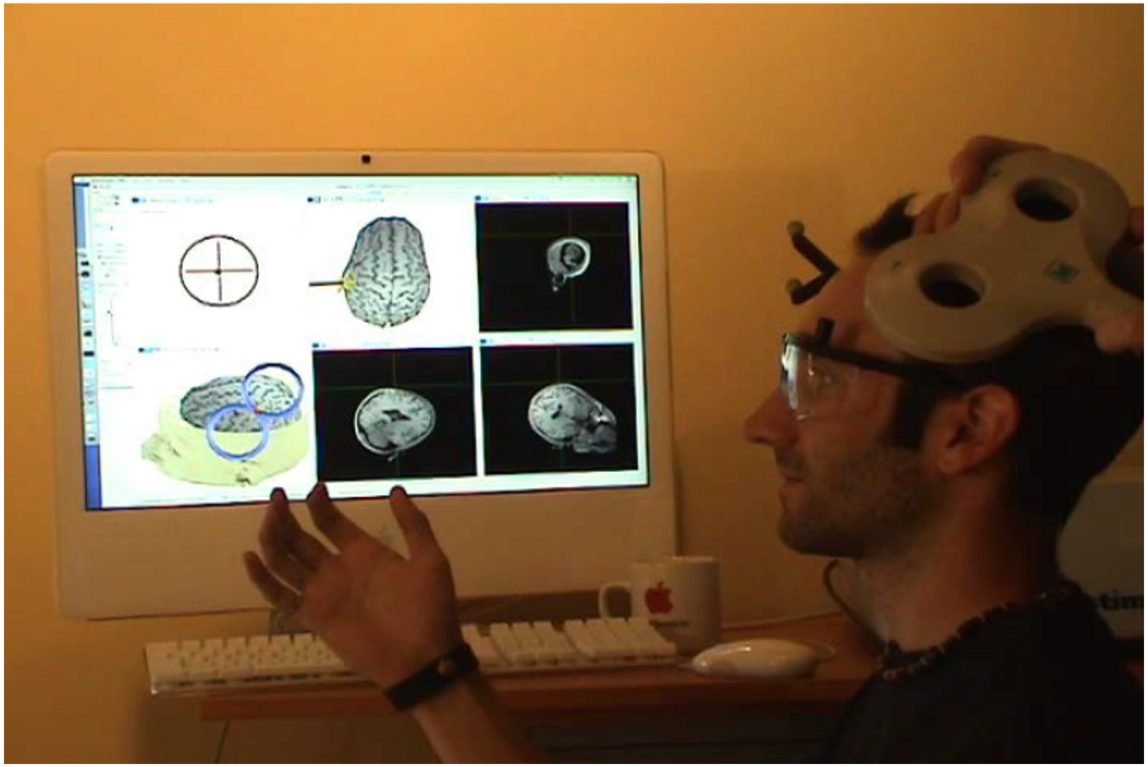
Frameless
Stereotactic System

Image guided stimulation: stereotaxic

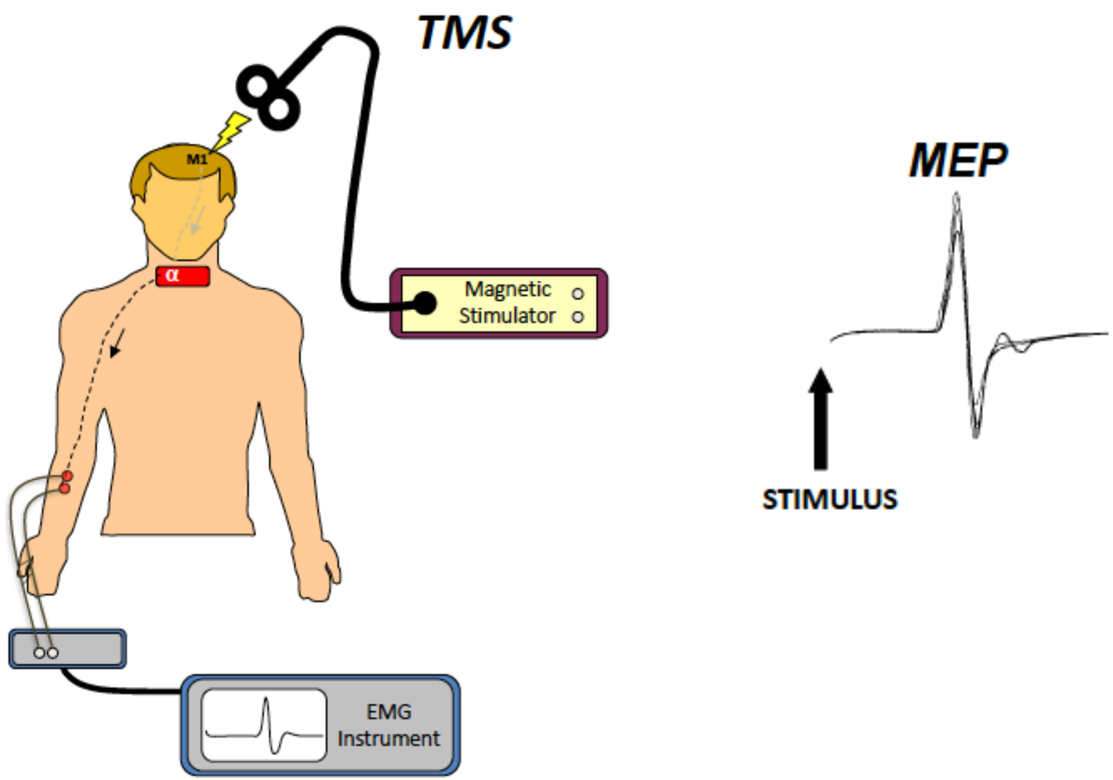




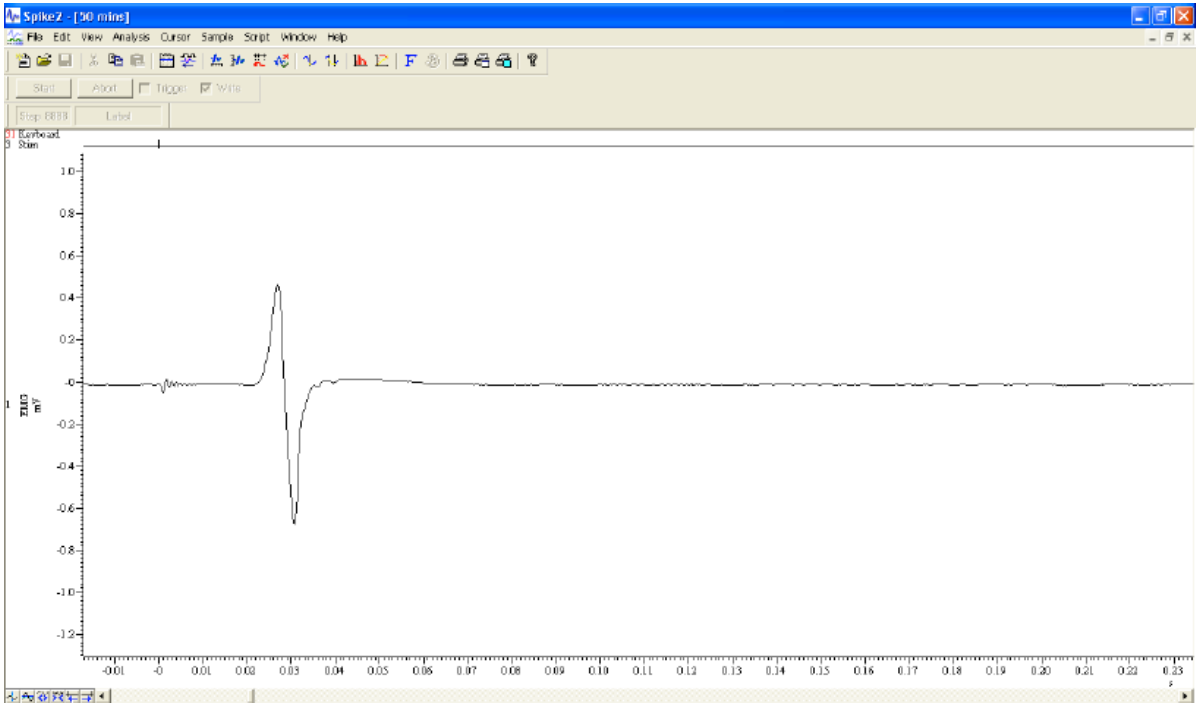
Typical TMS protocol – motor evoked potential



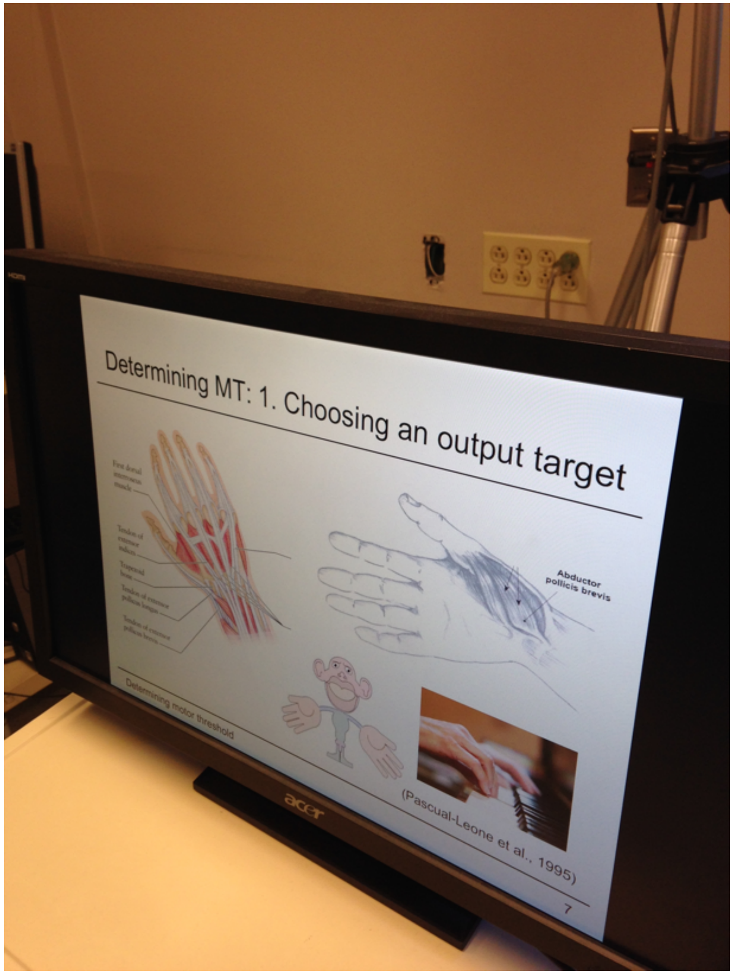
First thing to do: record MEP



Motor evoked potential



Choosing a target muscle (FDI)



Placing
the EMG
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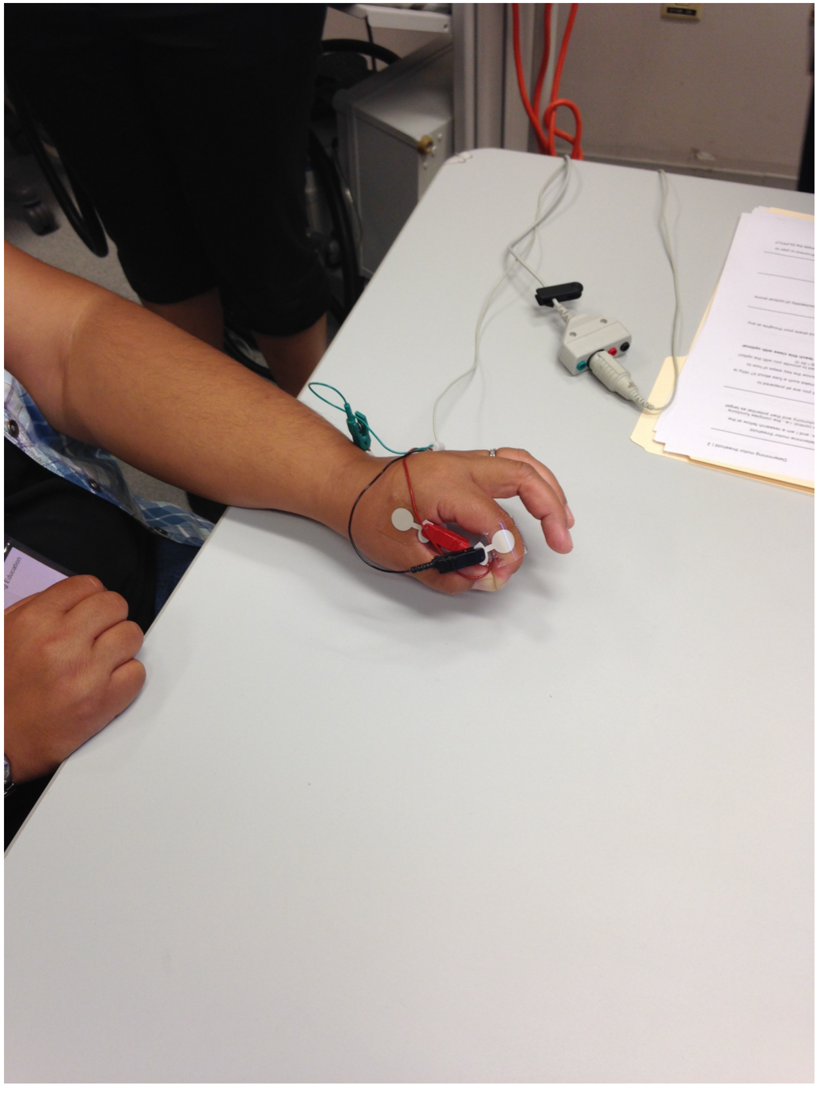
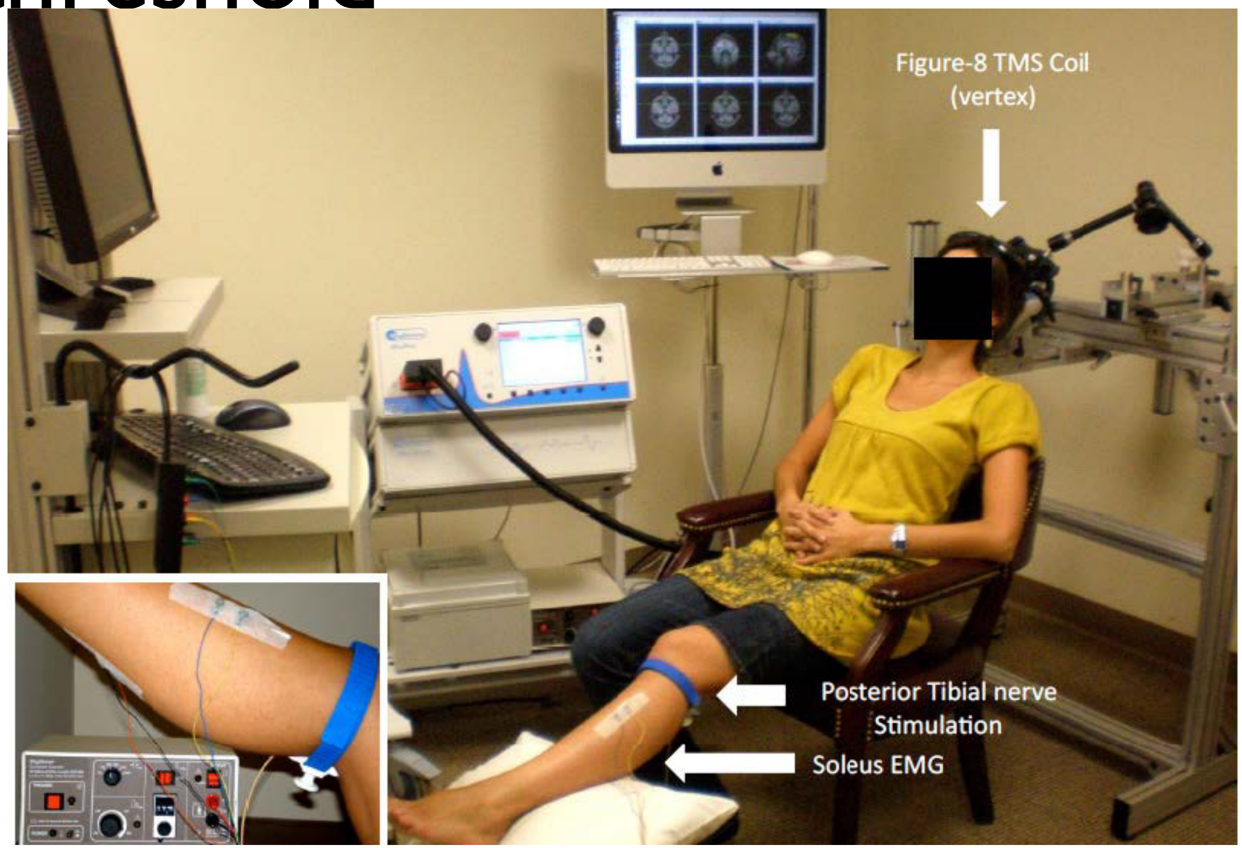


Motor hotspot

- Starting approximately 2 cm anterior and 4 cm lateral to the skull vertex, the coil is moved in 0.5–1 cm increments systematically across the anterolateral scalp surface until the site eliciting the largest average MEP in the resting FDI (stimulation intensity equal to 50–60% maximal stimulator output) is located (motor "hotspot").

Determine resting motor threshold



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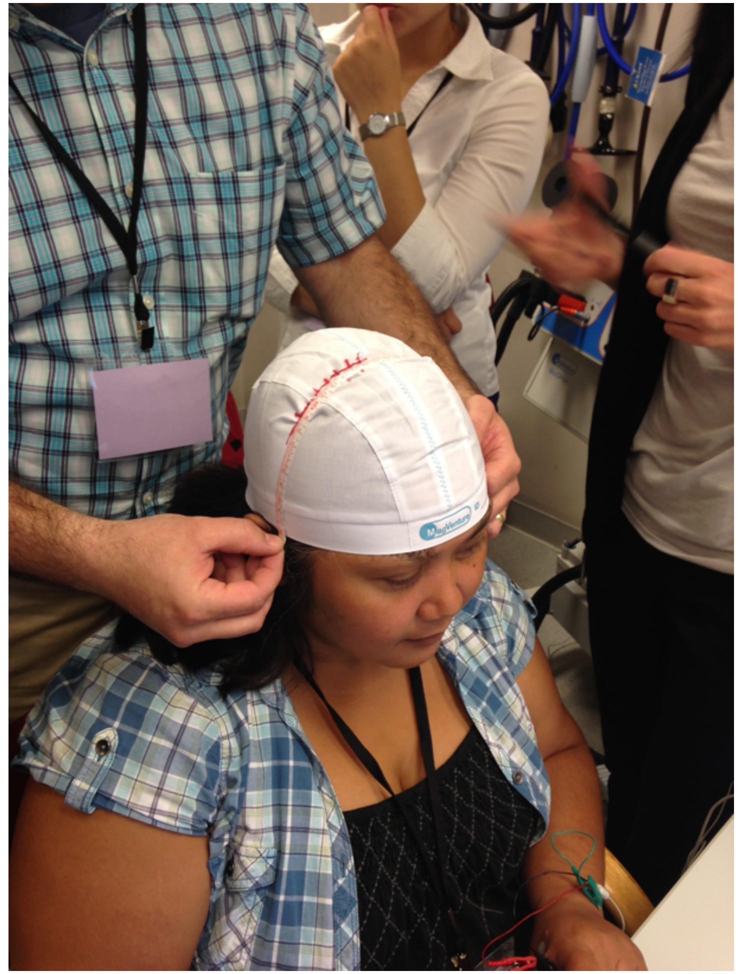


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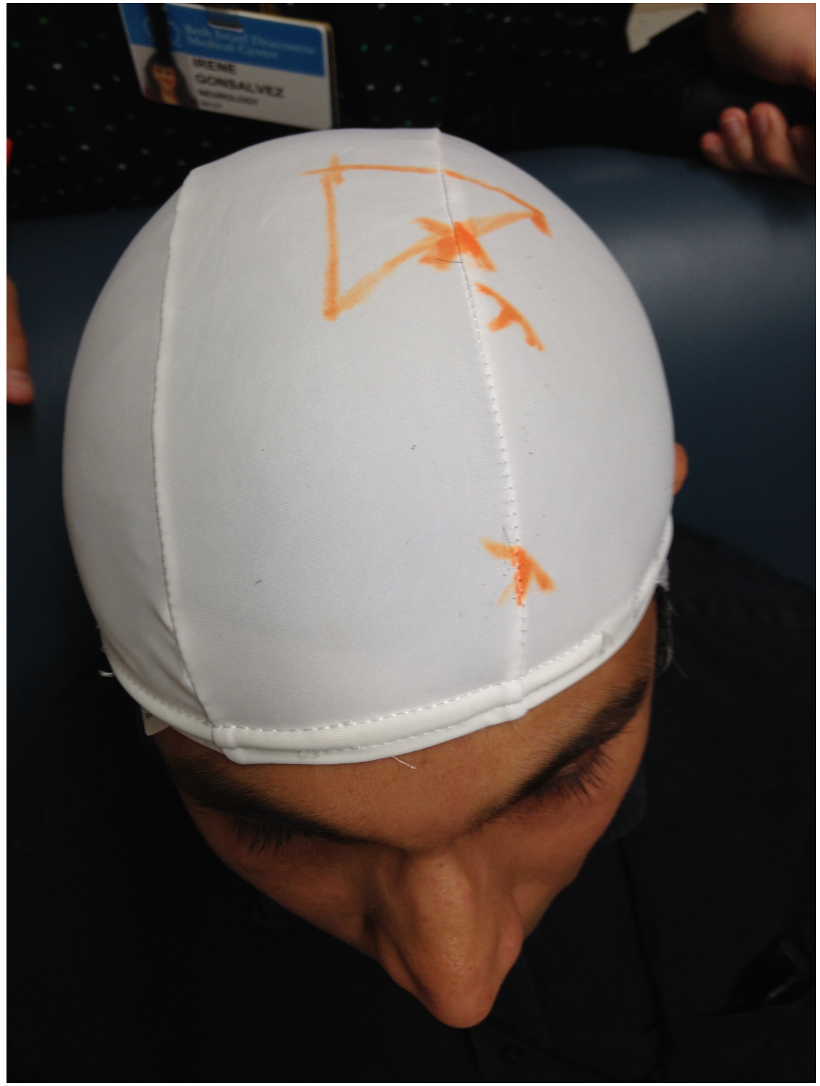

IRENE
GONSALVEZ


D-B80
School - Continuing Education

Eliciting phosphenes:

not reliable, but notice coil orietation

Safety

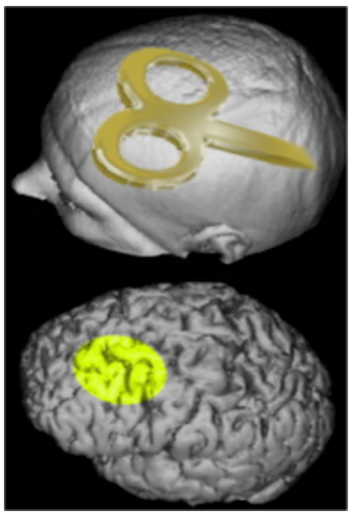
Seizure induction - Caused by spread of excitation. Single-pulse TMS has produced seizures in patients, but not in normal subjects. rTMS has caused seizures in patients and in normal volunteers. Visual and/or EMG monitoring for afterdischarges as well as spreading excitation may reduce risk.

Hearing loss - TMS produces loud click (90-130 dB) in the most sensitive frequency range (2–7 kHz). rTMS = more sustained noise. Reduced considerably with earplugs.

Heating of the brain - Theoretical power dissipation from TMS is few milliwatts at 1 Hz, while the brain's metabolic power is 13 W

Engineering safety - TMS equipment operates at lethal voltages of up to 4 kV. The maximum energy in the capacitor is about 500 J, equal to dropping 100 kg from 50 cm on your feet. So don't put your tea on it.

Advantages of TMS in the Study of Brain-Behavior Relations



- Study of normal subjects eliminates the potential confounds of additional brain lesions and pathological brain substrates
- Acute studies minimize the possibility of plastic reorganization of brain function
- Repeated studies in the same subject
- Study multiple subjects with the same experimental paradigm
- Study the time course of network interactions
- When combined with PET or fMRI, can build a picture of not only which areas of brain are active in a task, but also the time at which each one contributes to the task performance.

- Study internal double dissociations and network interactions by targeting different brain structures during single a task and disrupting the same cortical area during different related tasks

Summary: What can TMS add to Cognitive Neuroscience ?

- "Virtual Patients": causal link between brain activity and behavior
- "Chronometry": timing the contribution of focal brain activity to behavior
- "Functional connectivity": relate behavior to the interaction between elements of a neural network
- Map and modulate neural plasticity

Safety

Scalp burns from EEG electrodes - Mild scalp burns in subjects with scalp electrodes can be easily avoided using, e.g., small low-conductivity Ag/AgCl-pellet electrodes.

Local neck pain and headaches - Related to stimulation of local muscles and nerves, site and intensity dependent. Particularly uncomfortable over fronto-temporal regions.

Effect on Mood in normal subjects - Subtle changes in mood are site and frequency dependent. High frequency rTMS of left frontal cortex worsens mood. High frequency rTMS of right frontal cortex may improve mood.

Safety

Follow published safety guidelines for rTMS

Maximum safe duration of single rTMS train at 110% MT

Frequency (Hz)	Max. duration (s)
1	1800+
5	10
10	5
20	1.6
25	.84

+ minimum inter-train interval
e.g. at 20Hz @1.0-1.1 T leave
>5s inter train

Caution: Guidelines not perfect

Safety TMS Adult Safety Screen

Have you ever: had an adverse reaction to TMS?
Had a seizure?
Had an EEG?
Had a stroke?
Had a head injury(include neurosurgery)?
Do you have any metal in your head (outside of the mouth,) such as shrapnel, surgical clips, or fragments from welding or metalwork? (Metal can be moved or heated by TMS)
Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines? (TMS may interfere with electronics and those with heart conditions are at greater risk in event of seizure)
Do you suffer from frequent or severe headaches?
Have you ever had any other brain-related condition?
Have you ever had any illness that caused brain injury?
Are you taking any medications? (e.g. Tricyclic anti-depressants, neuroleptic agents, and other drugs that lower the seizure threshold)

If you are a woman of childbearing age, are you sexually active, and if so, are you not using a reliable method of birth control?

Does anyone in your family have epilepsy?
Do you need further explanation of TMS and its associated risks?

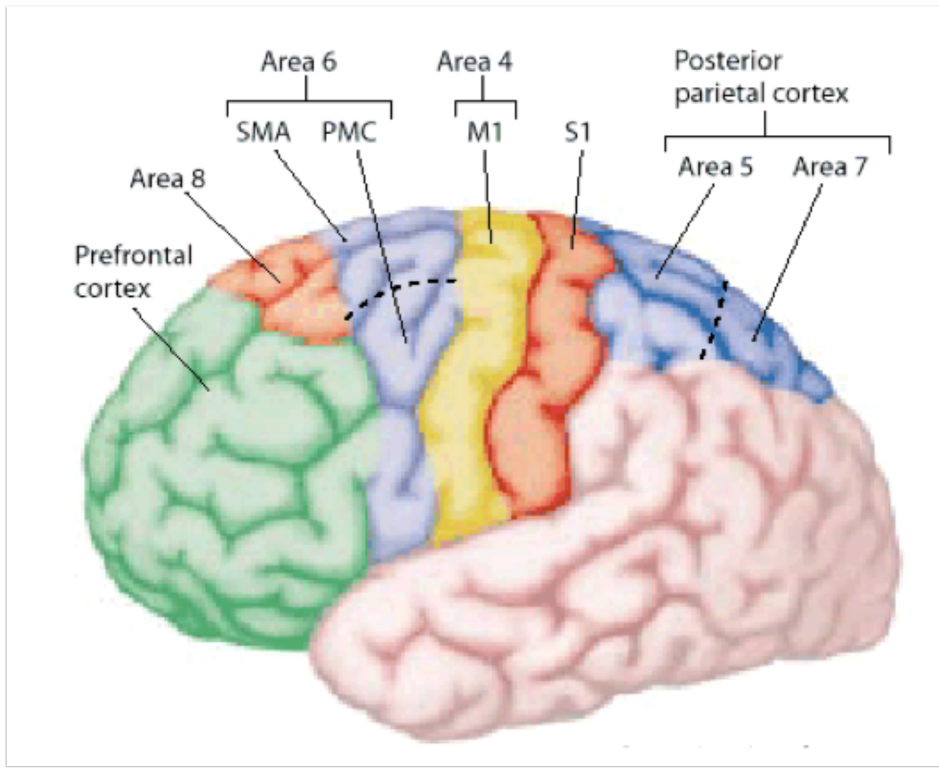
Major advantages summary

Reversible lesions without plasticity changes
Repeatable
High spatial and temporal resolution
Can establish causal link between brain activation and behaviour
Can measure cortical plasticity
Can modulate cortical plasticity
Therapeutic benefits

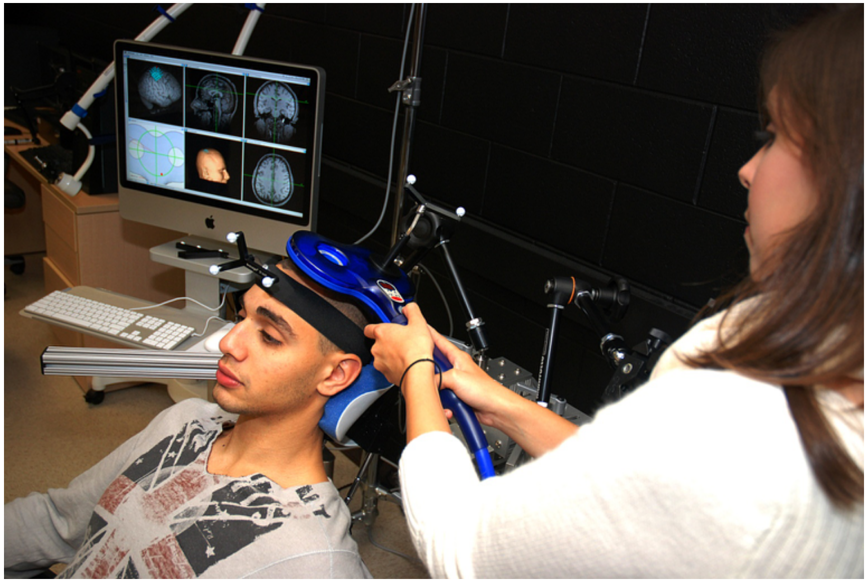
Major limitations summary

Only regions on cortical surface can be stimulated
Can be unpleasant for subjects
Risks to subjects and esp. patients
Stringent ethics required (can't be used by some institutions)
Localisation uncertainty
Stimulation level uncertainty

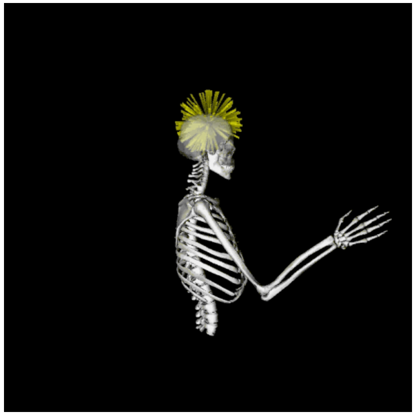
Application areas



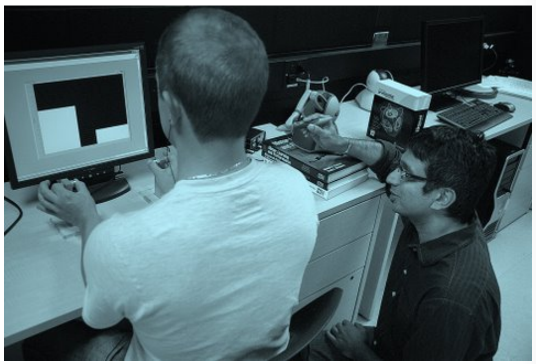
Using rTMS/TBS

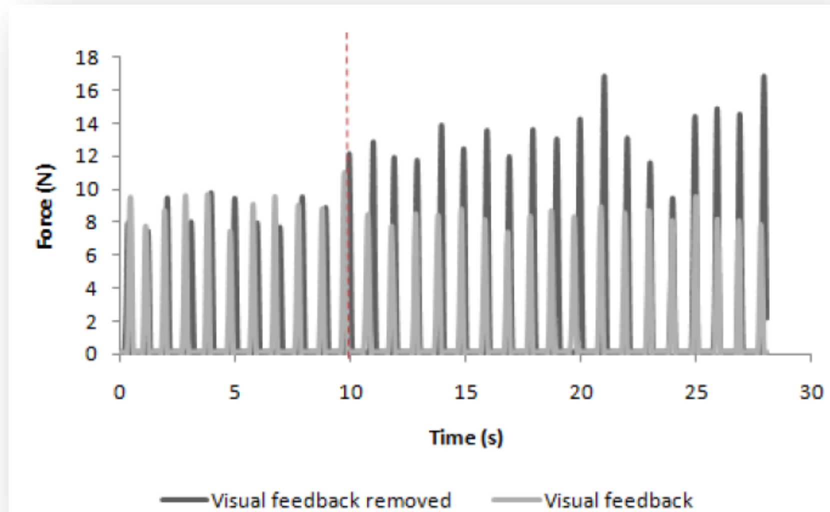


Michael Hove

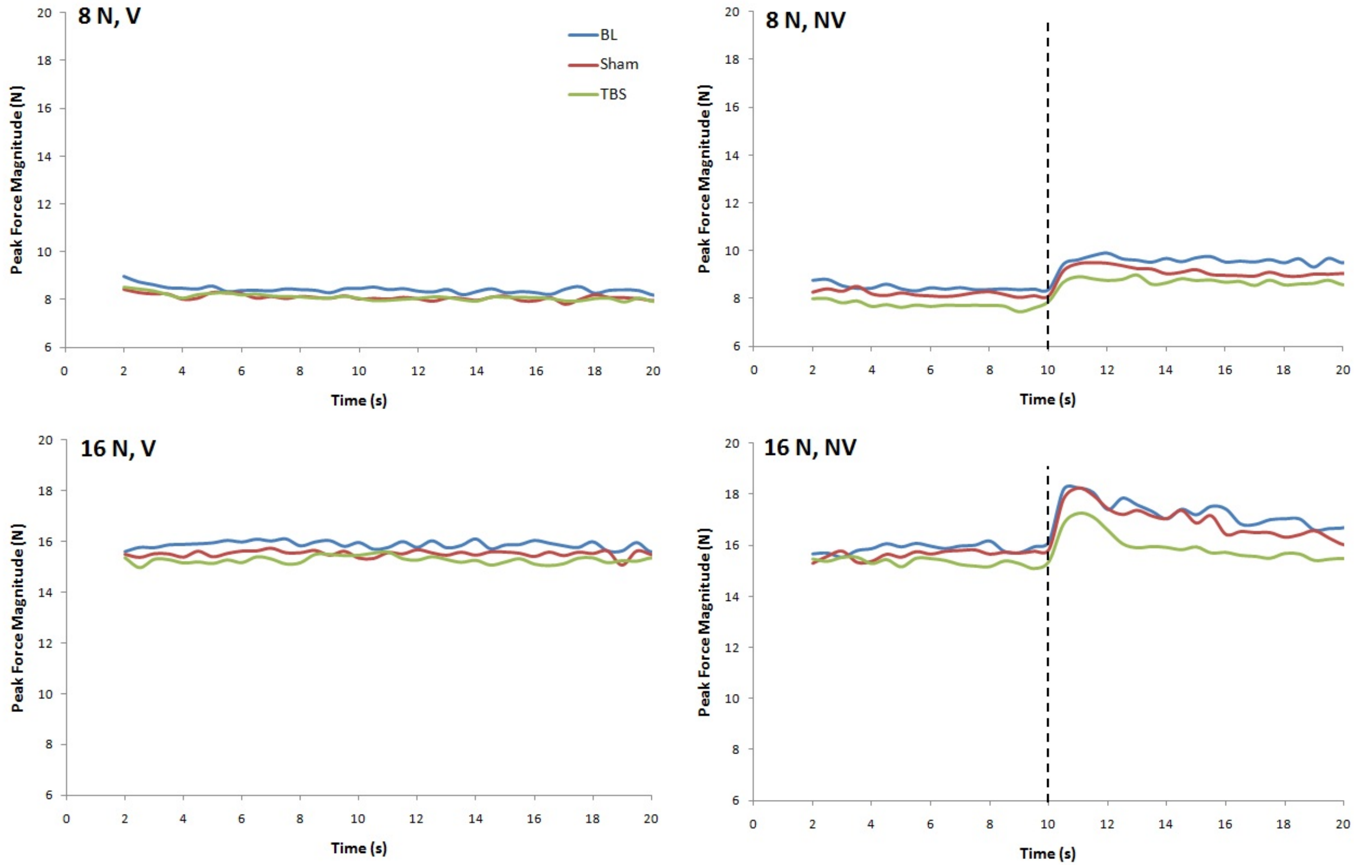


Role of visual feedback: calibration





Therrien & Balasubramaniam, 2010
Experimental Brain Research



8 N, V
BL
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TBS
Peak Force Magnitude (N)
Time (s)
8 N, NV
Peak Force Magnitude (N)
Time (s)
16 N, V
Peak Force Magnitude (N)
Time (s)
16 N, NV
Peak Force Magnitude (N)
Time (s)

Projects

- TBS and beat perception (in collaboration with John Iversen @ UCSD)
- Lombard effect in speech
- Combined EEG-TMS

Summary & what to expect in the next few weeks

- Practical introduction to EEG
- Independent component analysis
- Basic stimulation basics with TMS
- Recording MEPs
- Stereotaxic image-guided stimulation
- Then simultaneous TMS/EEG
- Ideas for experiments