TRANSCRANIAL MAGNETIC STIMULATION (TMS)

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HEADLINES

- What is TMS
- History
- Physics
- Mechanism
- TMS terminology
- TMS type
- TMS machines
- TMS indications
- Pre TMS evaluation
- Side effects
- TMS Protocols & Coil placement

WHAT IS TMS?

- Transcranial magnetic stimulation (TMS)
- A non-invasive brain stimulation (NIBS) method widely used in neuroscience research and clinical practice
- Magnetic field are used to induce electric currents in cerebral cortex thereby depolarizing neurons

HISTORY OF TMS

HISTORY

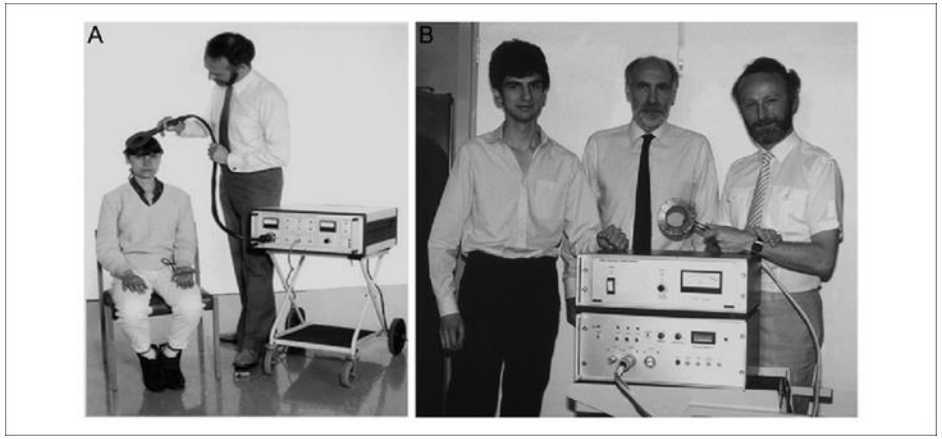
- The application of electricity and magnetic fields in medicine has a long and not always distinguished history

- Reports of the use of electrical techniques in medicine date back at least to the Roman Empire where in 46 AD Scribonius Largus, physician of the emperor Tiberius, described the use of torpedos (aquatic animals capable of electrical discharge) for medical applications

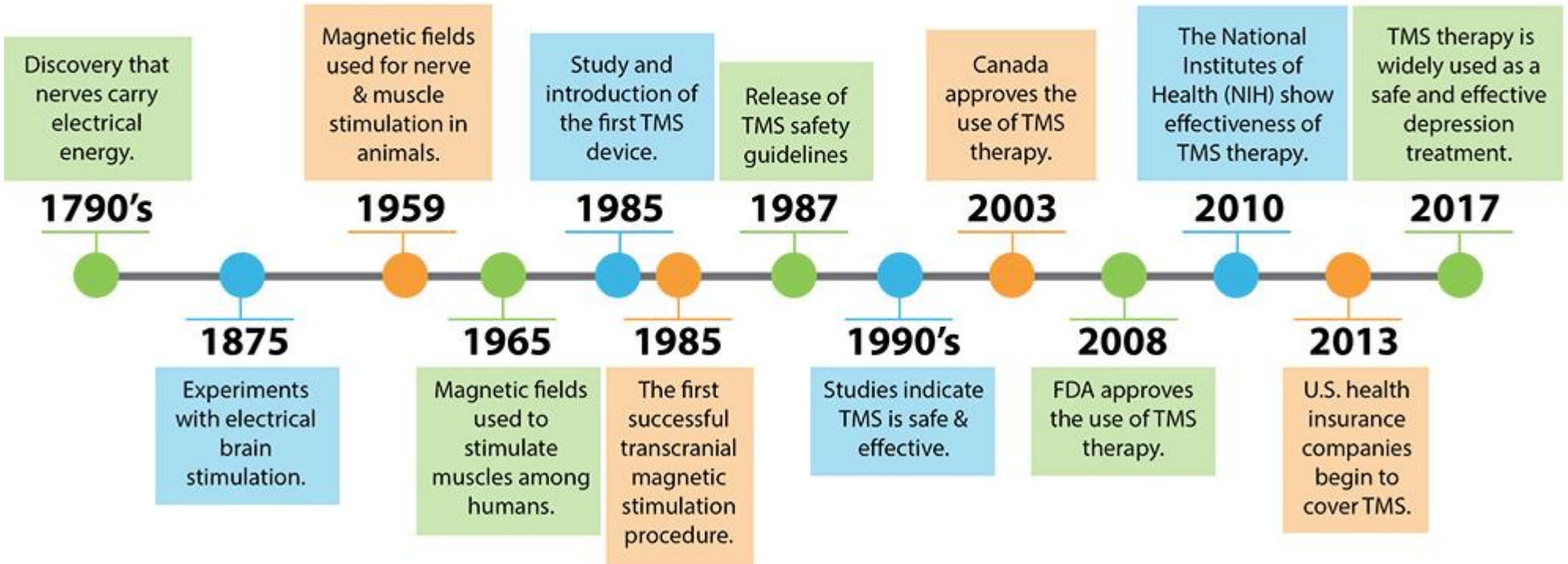
HISTORY

- The idea of using TMS goes back to the early 1900s

- In 1982 Mike Polson, **Anthony Barker** and Ian Freeston, a research team at Sheffield University in the UK, proved the viability of Transcranial Magnetic Stimulation as a method for testing brain - behavior relationships.
- The first device capable of generating cortical activity was developed by Barker and others in Shef fi eld, England, and first described in 1985



TMS Therapy: A Brief Timeline.



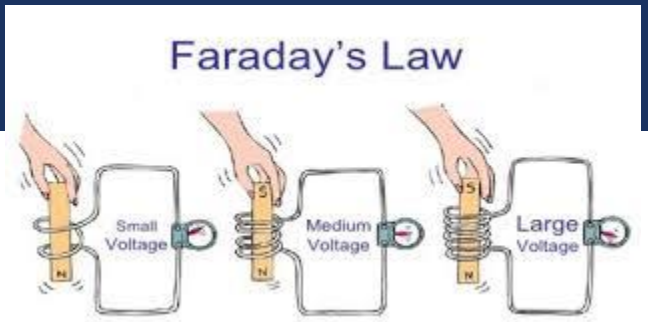
PHYSICS

- Michael Faraday who first outlined the principle of mutual induction in 1831

- This principle states that a current can be induced in a secondary circuit when its relationship to a primary circuit is altered in several specific ways, including that the primary current is turned on or off or the primary current is moved relative to the secondary current

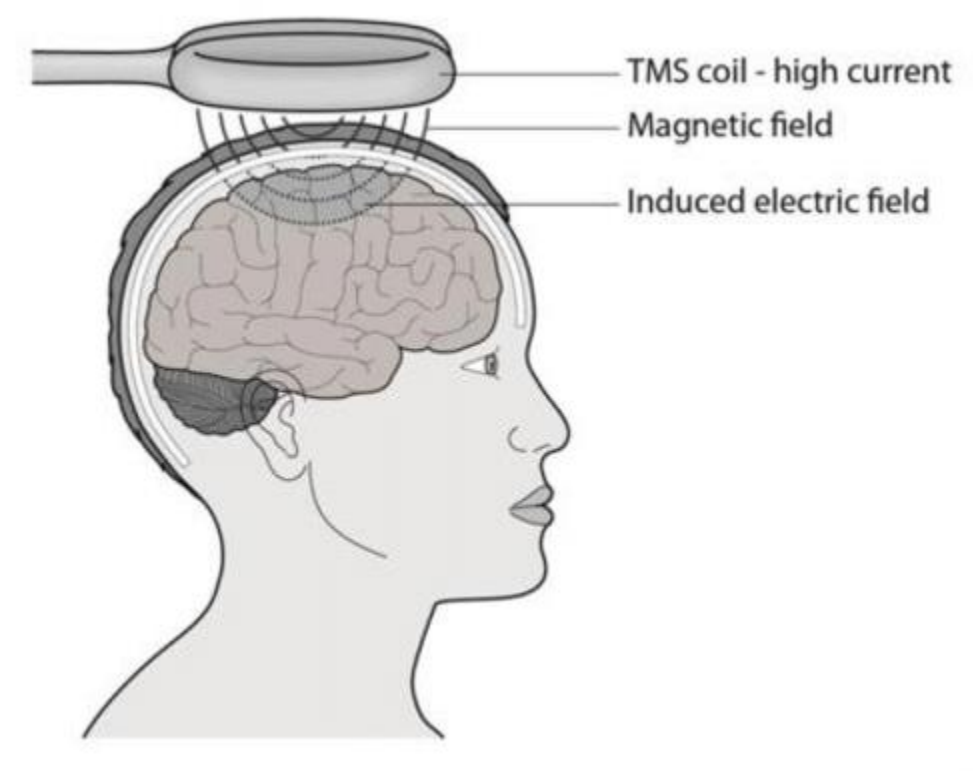
- Faraday described that this effect was mediated through the magnetic flux created by the changing circuit and that alterations in the magnetic flux would induce an electrical fi eld

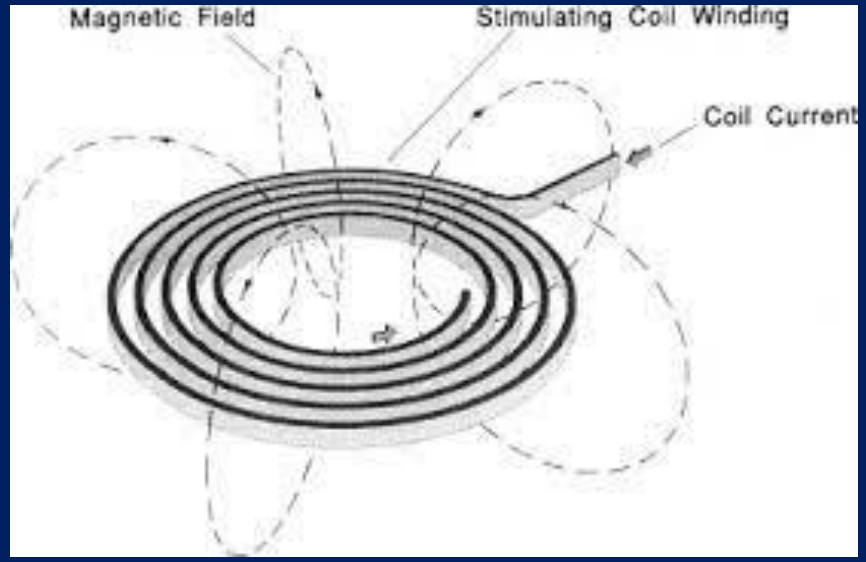
PHYSICS



- We need to remember that the current is only generated while the magnet is passing through the coil. It is the changing magnetic field that generates the electricity.

- A static magnet resting inside the coil will not generate a current


TMS coil - high current
Magnetic field
Induced electric field


Magnetic Field
Stimulating Coil Winding
Coil Current

THE MECHANISM OF TMS

- TMS produces short (~200–500 μs) but strong (>1.5 Tesla) magnetic fields that penetrate the intact skin and skull of patients

- Hence, TMS produces its major effects by inducing peak absolute electric fields (~100 mV/mm) in cortical brain regions
- Generally reach **no more than 5 cm** in to the brain

THE MECHANISM OF TMS

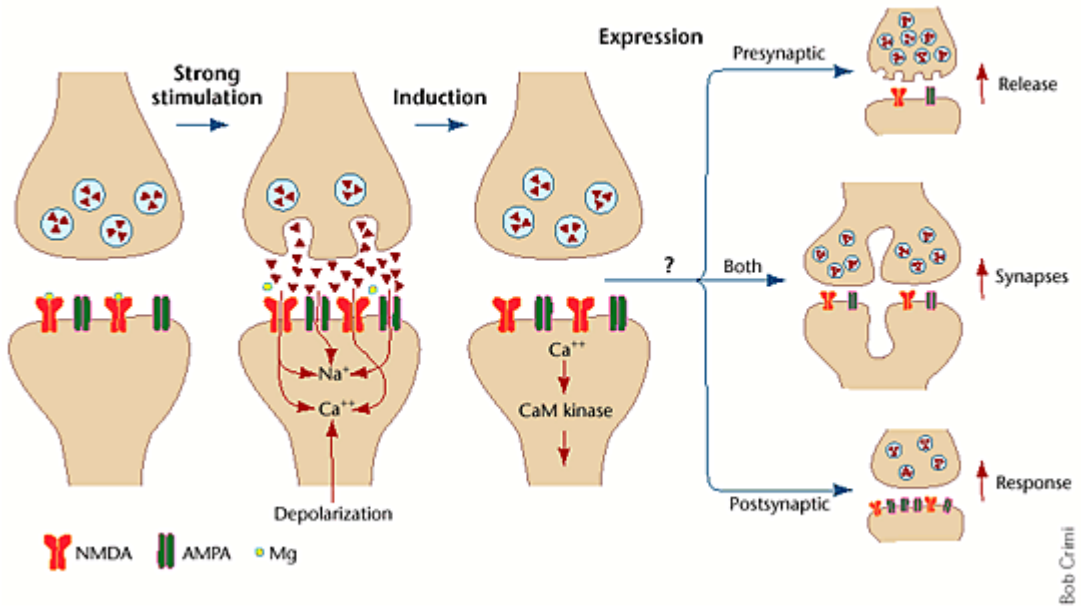
- TMS might be best conceptualized as "**electrodeless electric stimulation of the brain via electromagnetic induction**"

- The majority of TMS stimulation is restricted to superficial layers on the convexity of the brain (1.5–2 cm deep from the scalp

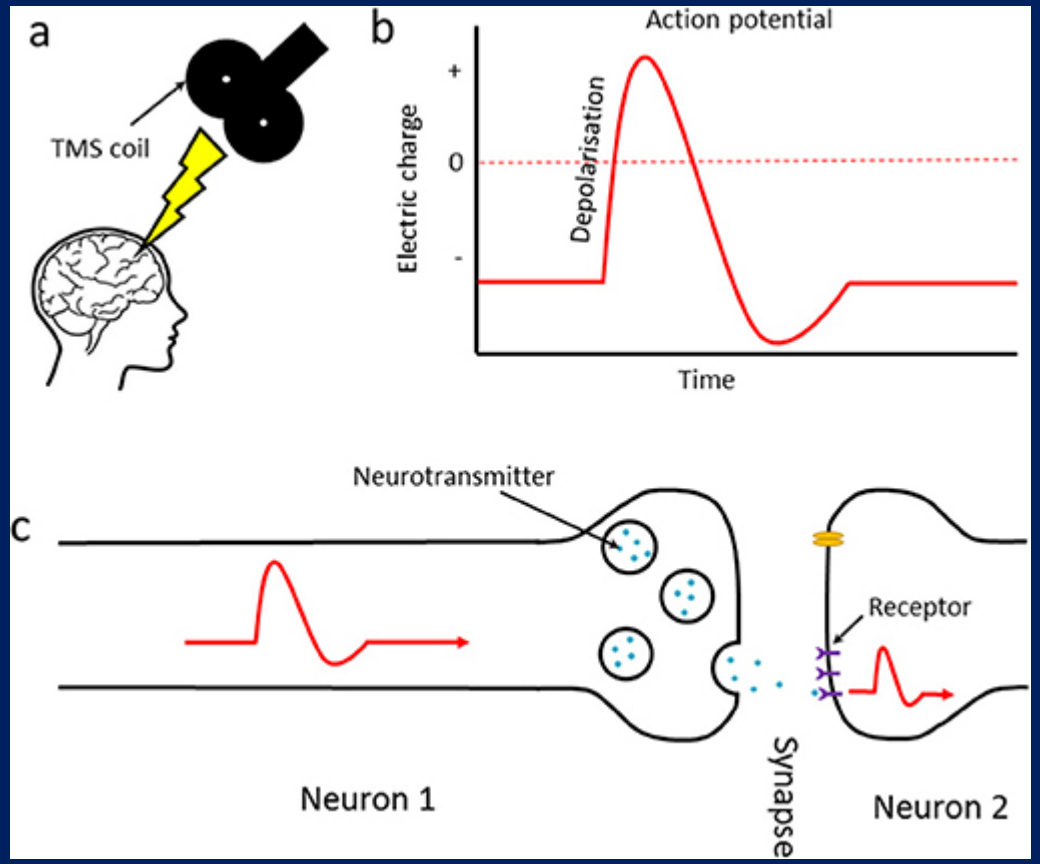
THE MECHANISM OF ACTION

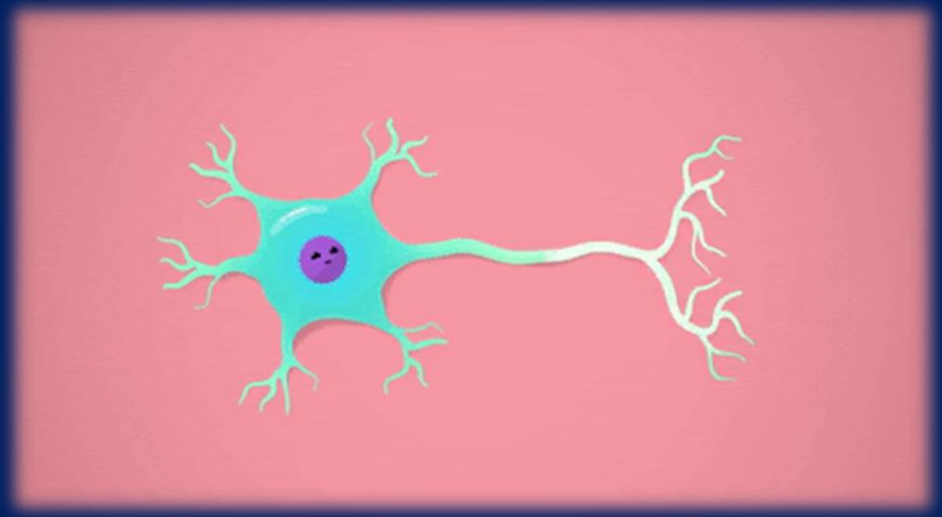
- long-term potentiation (LTP) and long-term depression (LTD)
- plasticity induction
- Brain network
- Changes in several physiological parameters in the motor cortex, including in excitability, evidenced in motor threshold (MT) and motorevoked potential (MEP) alterations; in cortical inhibition and facilitation, evidenced in silent period (SP) and paired pulse inhibition and facilitation (ppTMS) changes; and in alterations in cortical plasticity

THE MECHANISM OF TMS



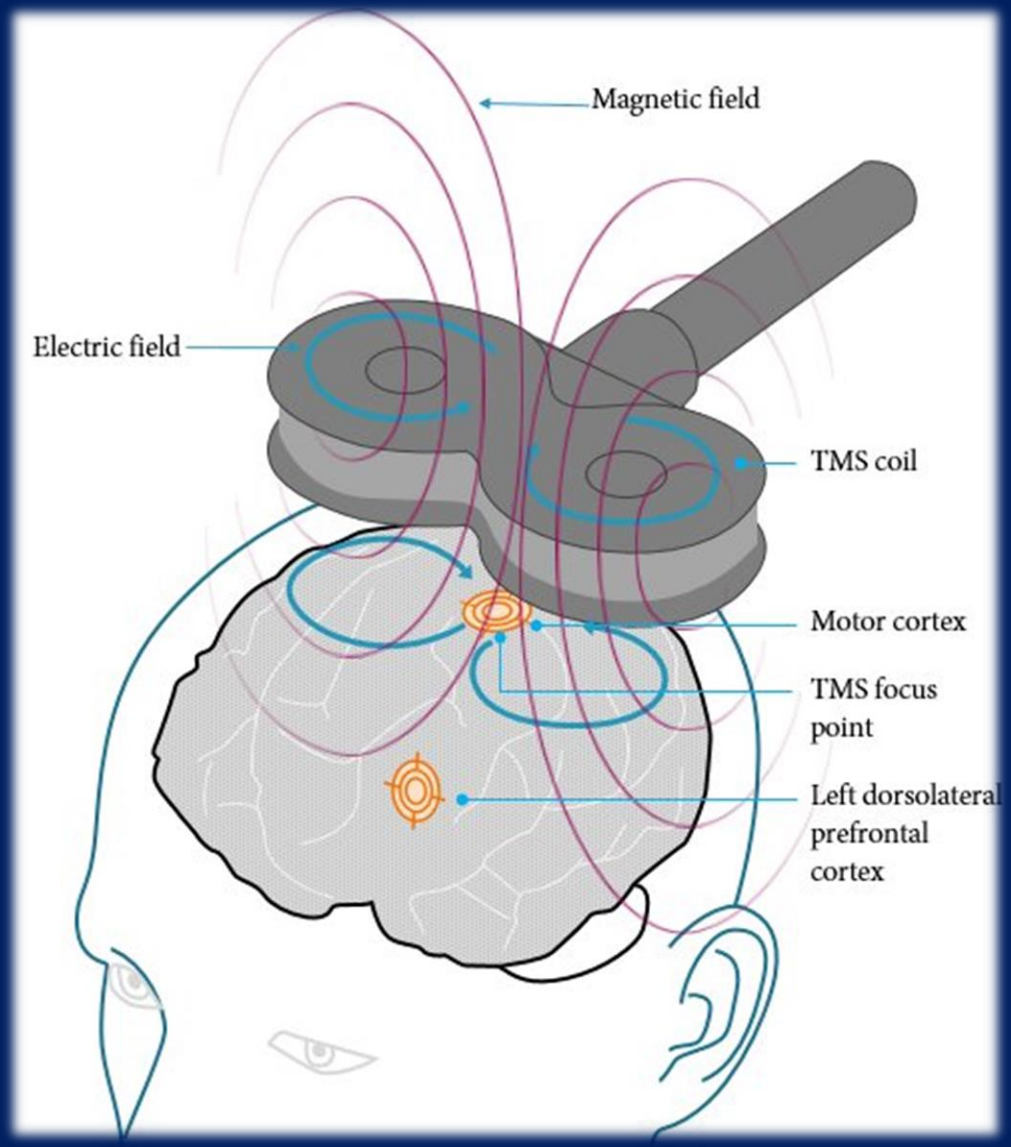
Action potential

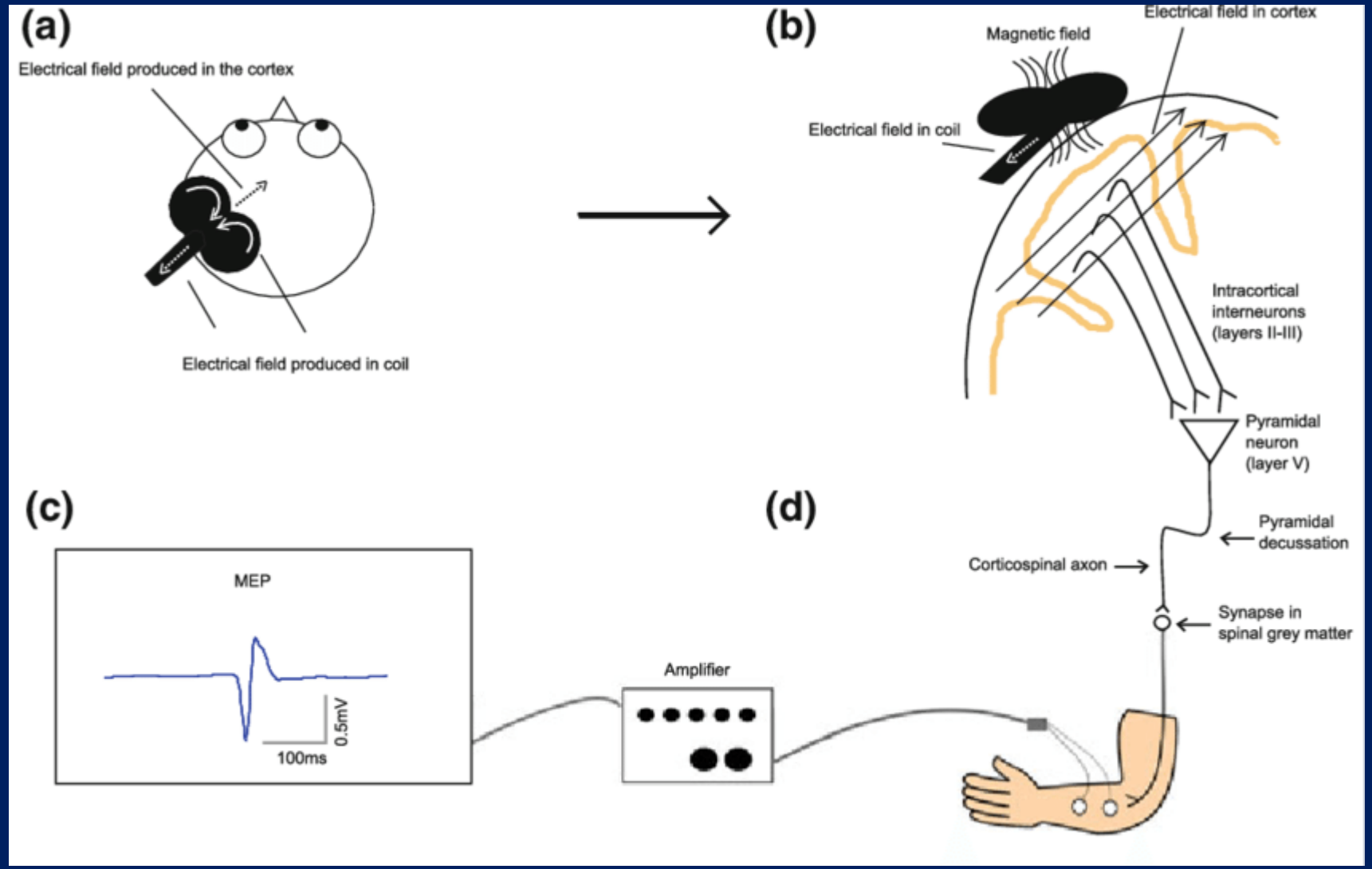




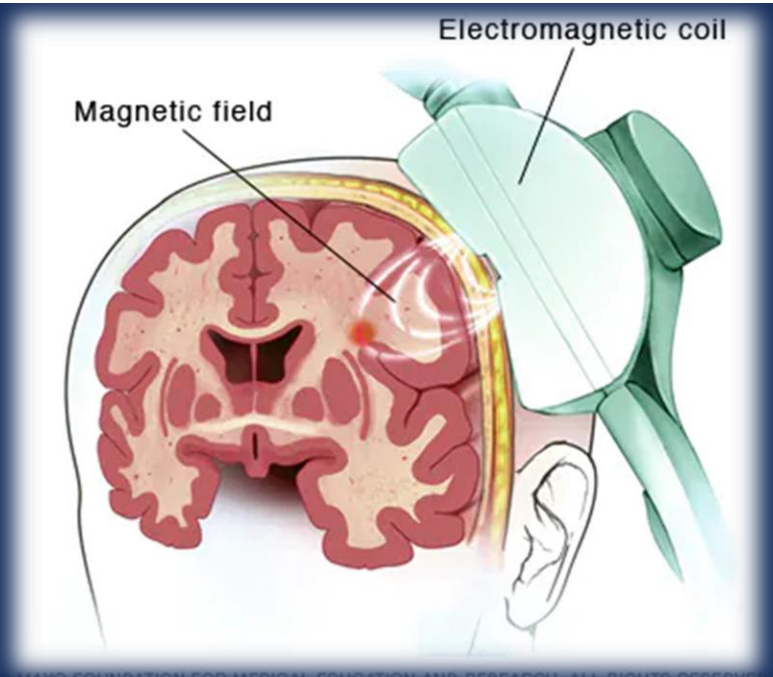
DOES TMS REALLY CHANGE BRAIN ACTIVITY?

- TMS of the motor cortex will induce corresponding muscle contractions in the appropriate arm or leg
- Seizures are a real but rare side effect of TMS
- Placing an active coil over the occipital cortex will induce visual sensations
- Repetitive TMS over Broca's area will induce temporary aphasia

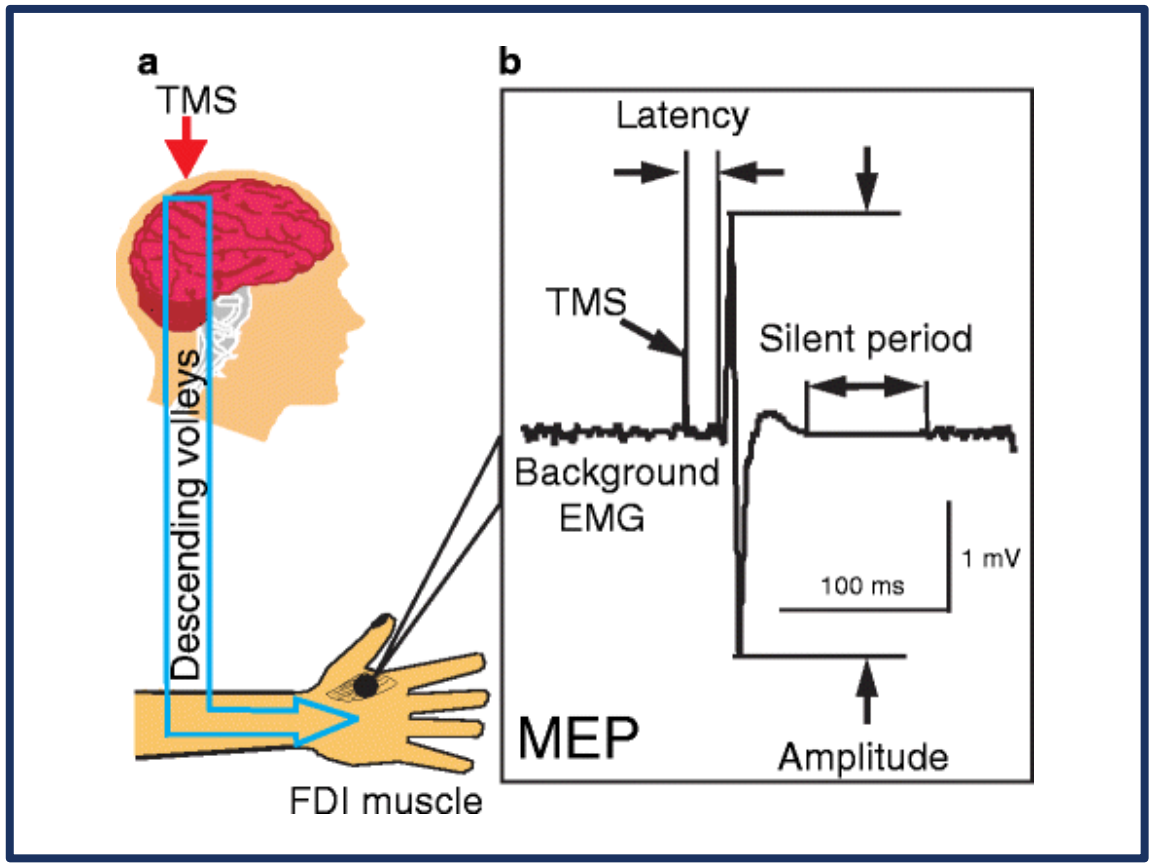

Magnetic field
Electric field
TMS coil
Motor cortex
TMS focus point
Left dorsolateral prefrontal cortex


(a)
Electrical field produced in the cortex
Electrical field produced in coil
(b)
Magnetic field
Electrical field in cortex
Electrical field in coil
Intracortical interneurons (layers II-III)
Pyramidal neuron (layer V)
Pyramidal decussation
Corticospinal axon
Synapse in spinal grey matter
(c)
MEP
0.5mV
100ms
Amplifier
(d)

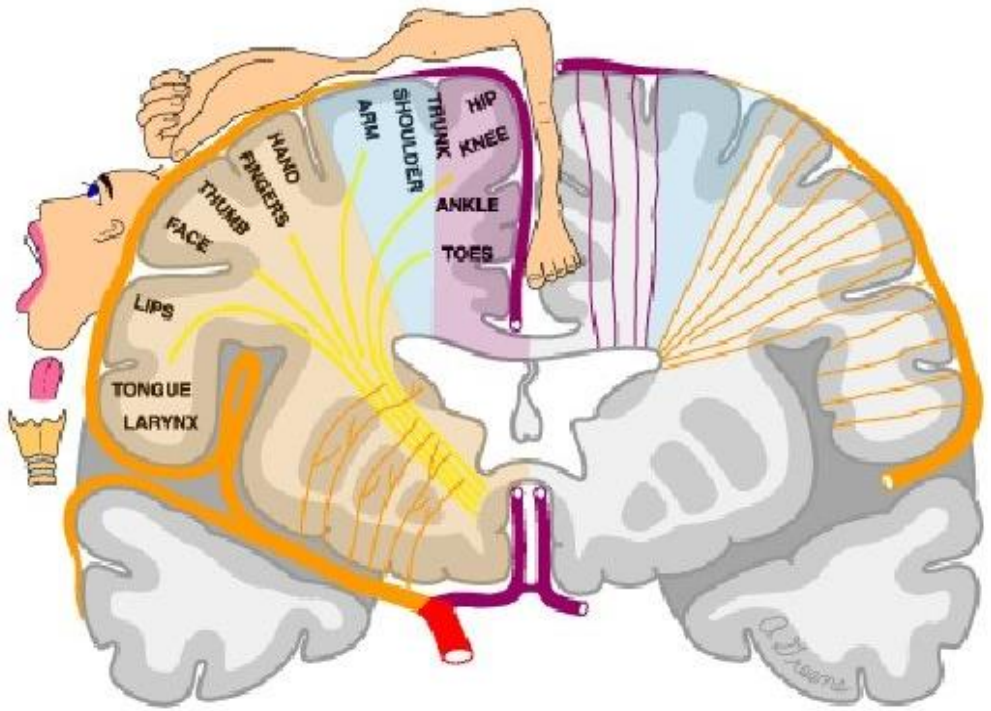
TMS TERMINOLOGY

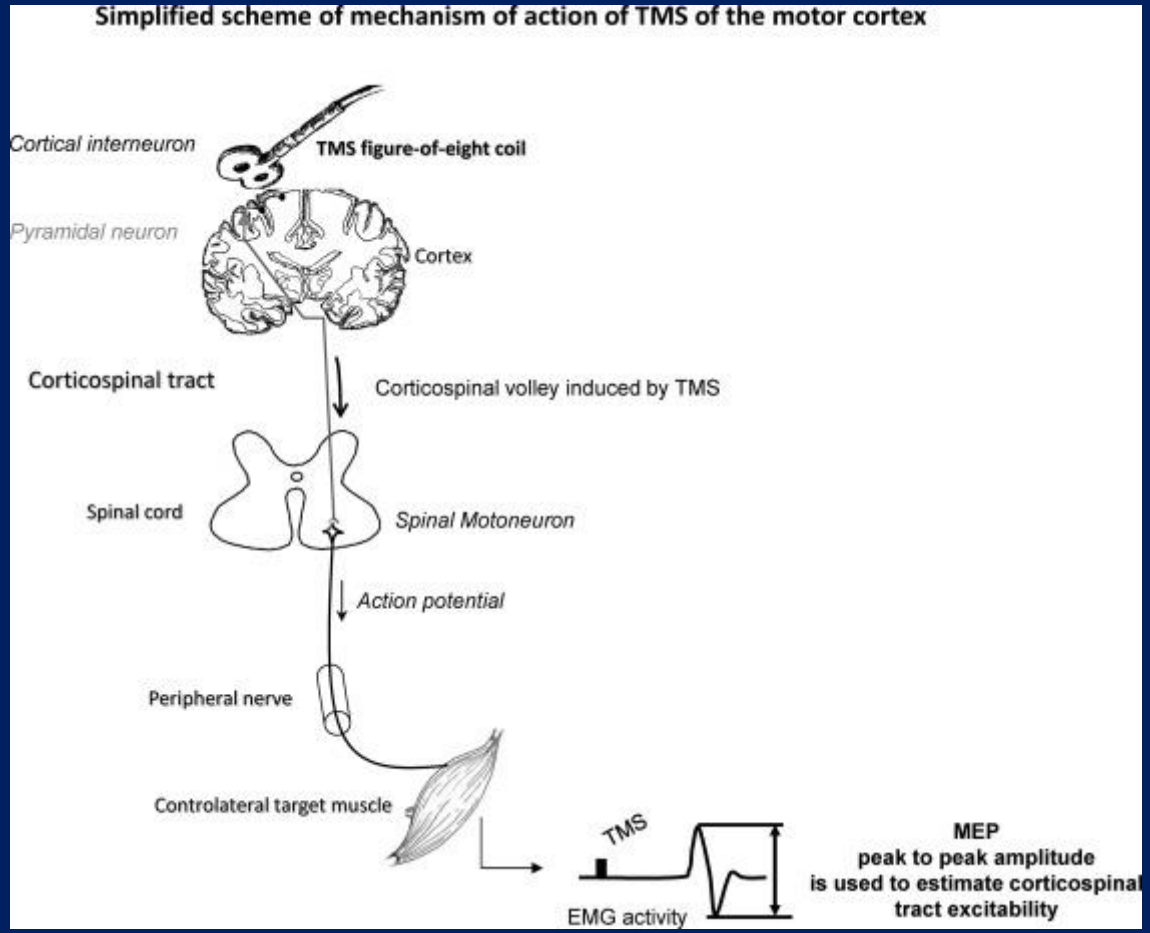


MOTOR EVOKED POTENTIAL (MEP)



- When TMS is applied to the **motor cortex** at appropriate stimulation intensity, motor evoked potentials (MEPs) can be recorded from **contralateral extremity muscles**


HIP
KNEE
TRUNK
SHOULDER
ARM
HAND
FINGERS
THUMB
FACE
ANKLE
TOES
LIPS
TONGUE
LARYNX

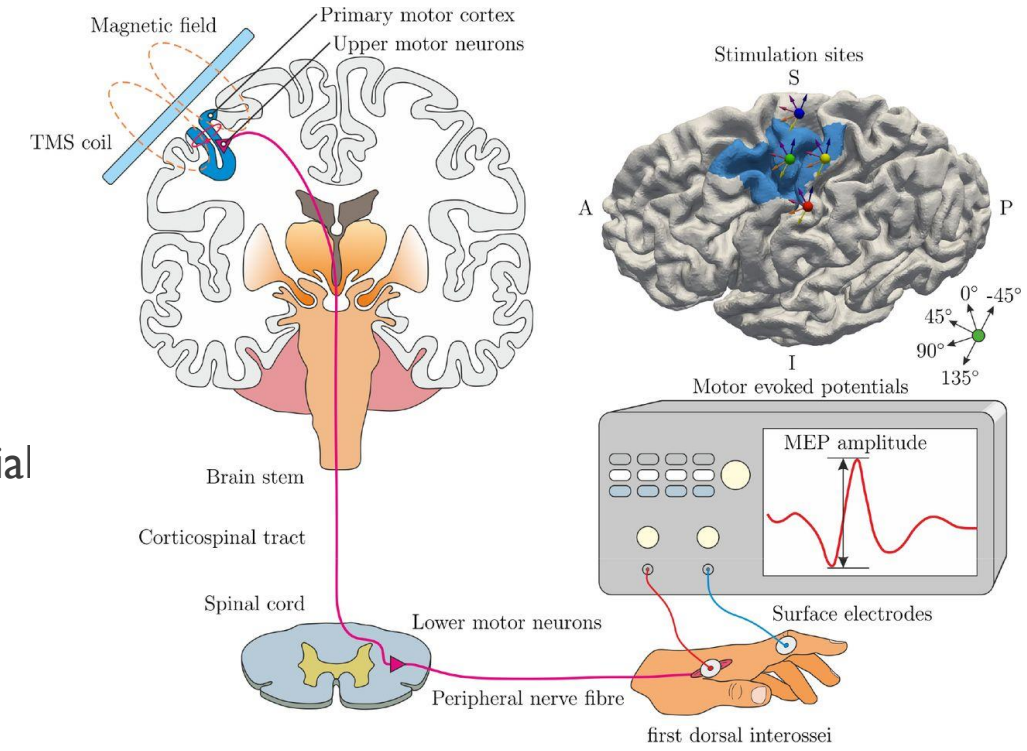

Simplified scheme of mechanism of action of TMS of the motor cortex
Cortical interneuron
TMS figure-of-eight coil
Pyramidal neuron
Cortex
Corticospinal tract
Corticospinal volley induced by TMS
Spinal cord
Spinal Motoneuron
Action potential
Peripheral nerve
Controlateral target muscle
TMS
EMG activity
MEP
peak to peak amplitude
is used to estimate corticospinal
tract excitability

MOTOR EVOKED POTENTIAL

- Motor evoked potentials (MEPs) are the **electrical signals recorded** from the descending motor pathways or from muscles following stimulation of motor pathways within the brain

MOTOR THRESHOLD (MT)

- MT is defined as the **minimum TMS intensity** sufficient to produce a predefined motor-evoked potential (MEP) in the contralateral abductor pollicis brevis in at least 50% of trial



INTENSITY

- The intensity of stimulation provided during rTMS treatment is typically de fined as a percentage (**usually between zero and 100 %**) of the total machine output provided by the rTMS device being used

- The intensity for each patient is individualized; it is typically determined relative to that individual's resting motor threshold (RMT)

SILENT PERIOD

- When an individual is instructed to maintain muscle contraction and a single supra-threshold TMS pulse is applied to the motor cortex contralateral to the target muscle, the EMG activity is arrested for a few hundred milliseconds after the MEP

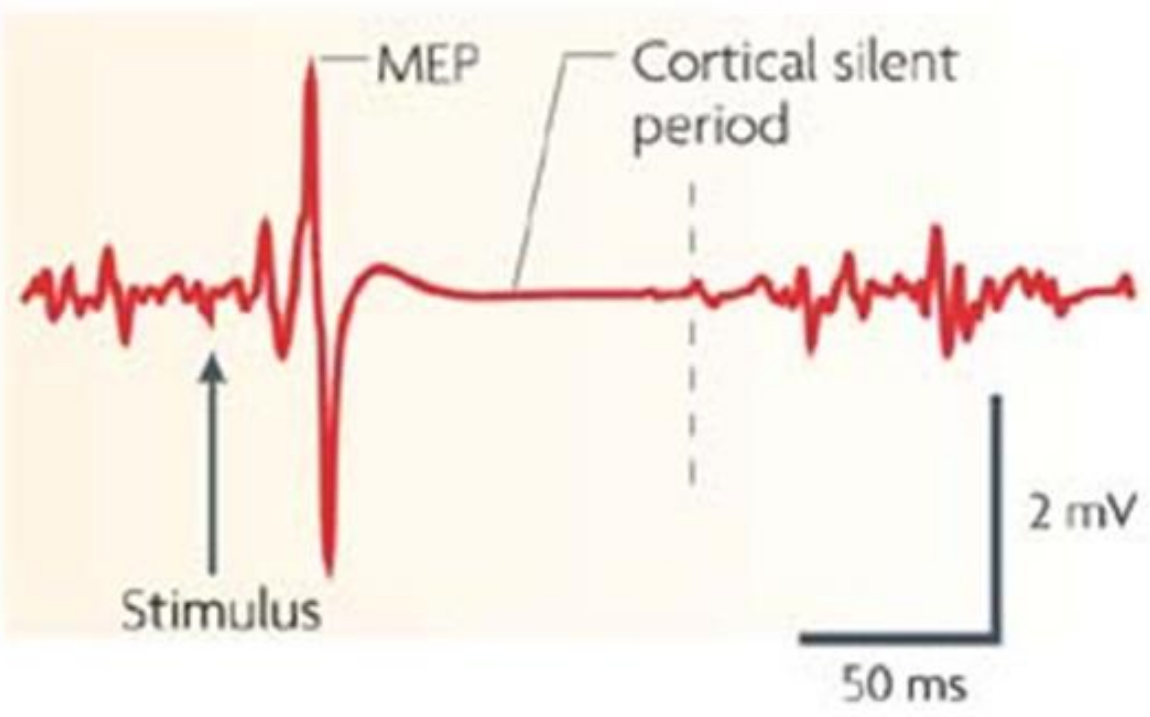
- This period of electromyographic suppression is referred to as cortical silent period (SP)

- Usually defined as the time from TMS to the return (or onset) of voluntary EMG activity

✓ Inhibitory mechanisms at the motor cortex (most likely mediated by GABA b receptors)

✓ Spinal inhibitory mechanisms

SILENT PERIOD



CAN SILENT PERIOD BE MODULATED?

- SP duration can be modulated by physiological phenomena that change cortical excitability, such as:
  - Hyperventilation
  - Sleep deprivation
  - Muscle fatigue

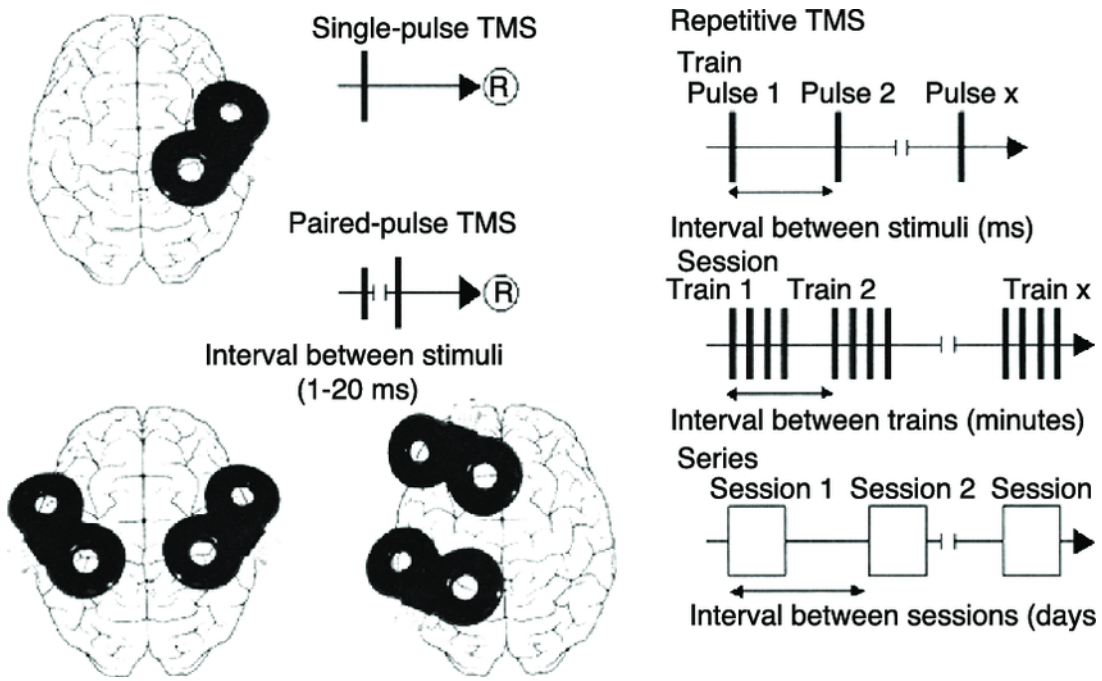
- Pharmacological studies using benzodiazepines, selective agonists of the benzodiazepine receptor subtype BZ1, baclofen,tiagabine provided evidence that the SP reflects a long-lasting cortical inhibition mediated by GABA b receptors
- Dopaminergic drugs lengthen the SP in normal subjects

- Single pulse TMS
- Paired pulse TMS
- Repetitive TMS (rTMS)
- Theta Burst Stimulation (TBS)

TMS TYPE

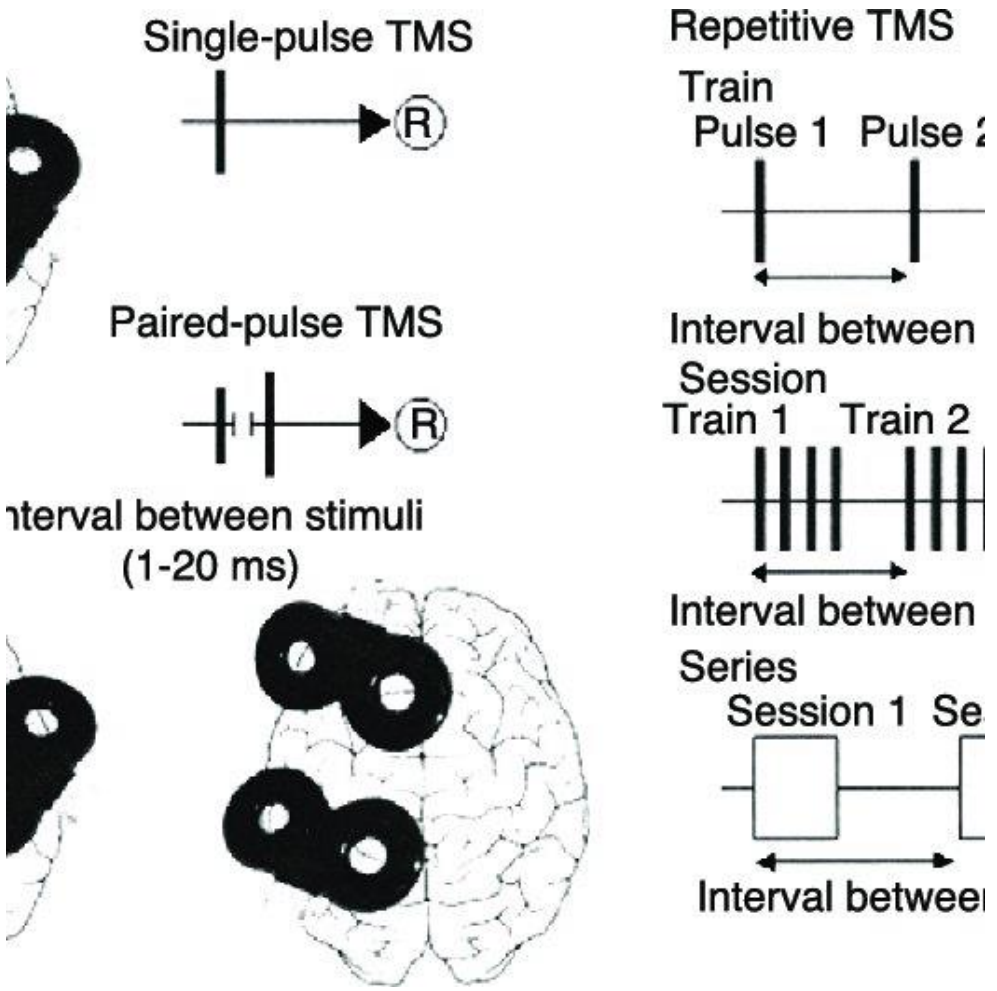
SINGLE PULSE TMS

- Single stimulus every 5-10 sec



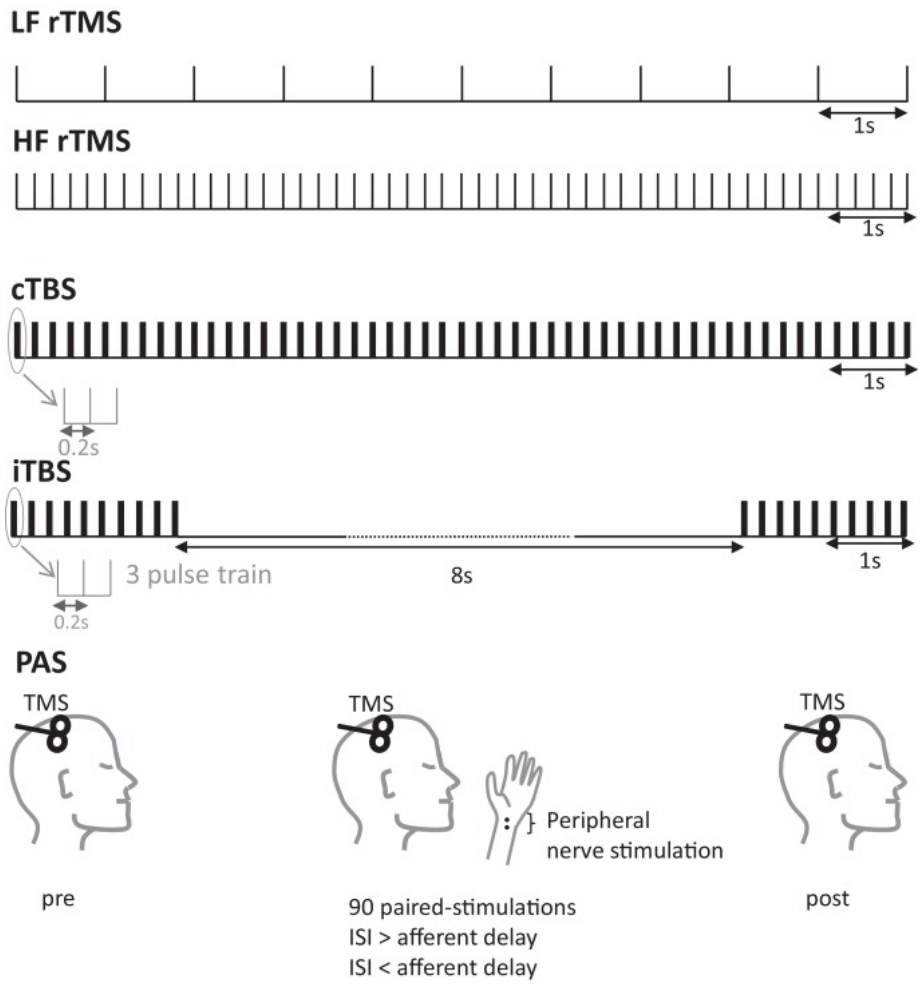
PAIRED PULSE TMS

- Pairs of stimuli separated by a variable interval
- Subthreshold stim, then suprathreshold stim (or vice versa)
- ¡Stimuli separated by 1-20 msec



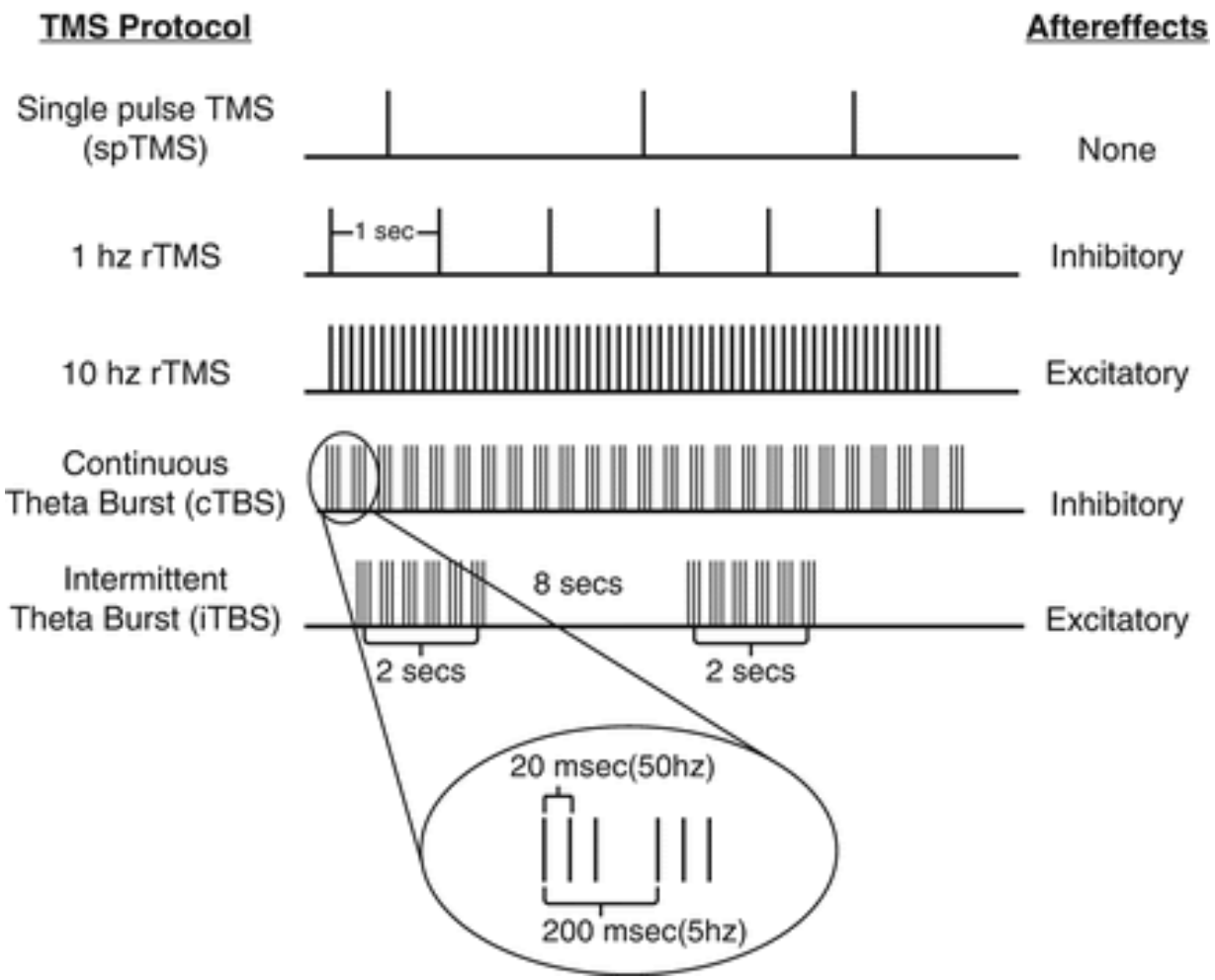
REPETITIVE TMS (RTMS)

- Trains of stimuli to one brain area
- Can be of low or high frequency
- Slow = low frequency<1
- Fast = (high freq) > 1 Hz/5



THETA BURST STIMULATION (TBS)

- continuous (cTBS)
- Intermittent (iTBS)



THETA BURST STIMULATION (TBS)

- The stimulation pattern mimicking such bursts of neuronal firing, that is, the combination of the complex-spike pattern (gamma frequency at 100 Hz) with a theta frequency (~5 Hz) repetition rate, resulted in robust long-term potentiation (LTP) in the hippocampal slices

- TBS in humans involves the application of high-frequency bursts (3 pulses at 50 Hz) at low frequency interval (5 Hz) using a total of 600 pulses at 70–80% of active/resting motor threshold (a/rMT)

- TBS sessions commonly last only 3–10 min

THETA BURST STIMULATION (TBS)

- Typically, TBS in humans involves the application of high-frequency bursts (**3 pulses at 50 Hz) at low frequency interval (5 Hz)** using a total of 600 pulses at 70–80% of active/resting motor threshold (a/rMT).

TMS MSCHINES

- Apollo TMS
- BrainsWay Deep TMS
- CloudTMS
- Magstim
- MagVenture TMS Therapy
- Neurostar Advanced Therapy
- Nexstim


apollo
TM
TMS THERAPY
apollo


magstim
THE BRAINS BEHIND TMS™

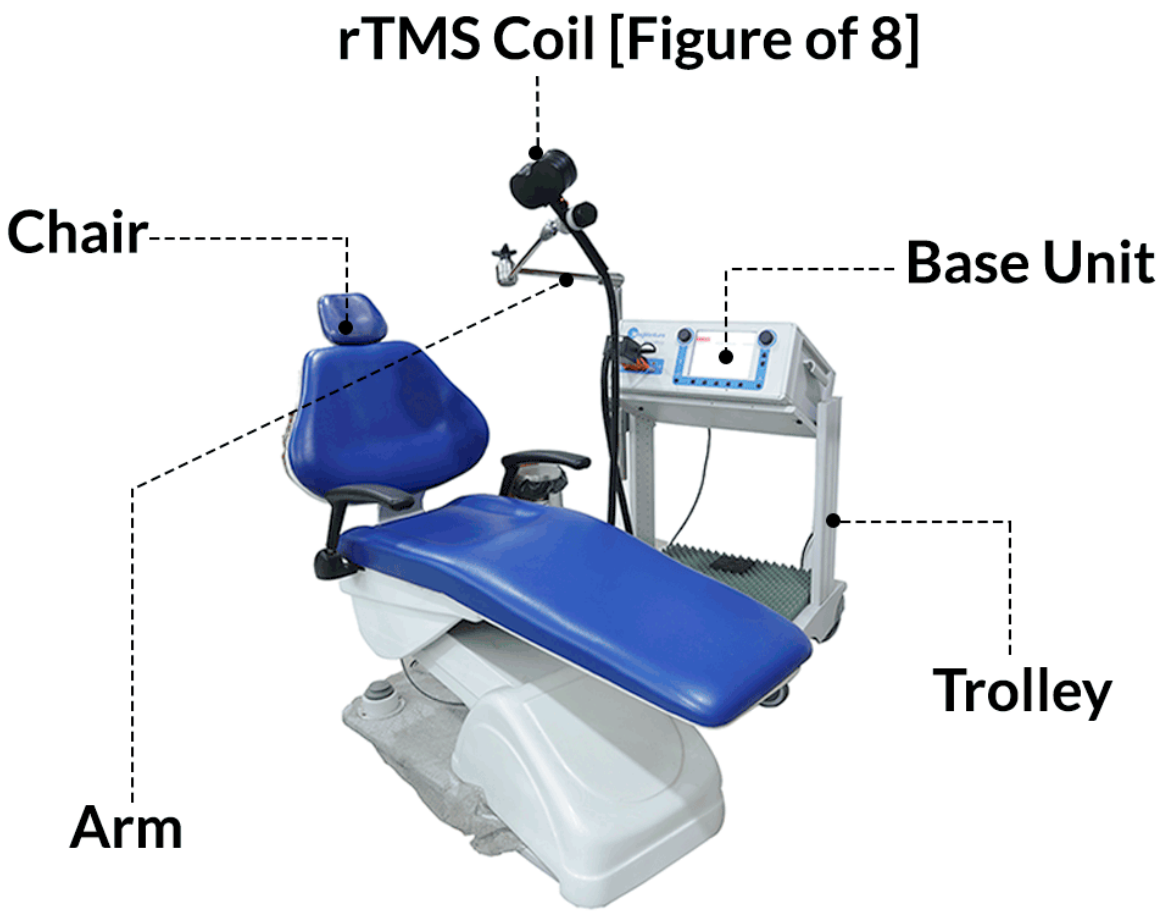

NeuroStar
Advanced Therapy

TMS MACHINE

- Each machine consists of a main unit and a stimulating coil. The main unit is composed of several components
- The stimulating coil consists of one or more well-insulated coils of copper wire (frequently housed in a molded plastic cover

TMS MACHINE

- Coil
- Monitor
- Stimulator
- Cooling system



Repetitive Transcranial Magnetic Stimulation (rTMS)

COIL SHAPE

The geometry of the coil determines:

- The focality of the magnetic field
- The induced current
- The targeted brain area

COIL SHAPE

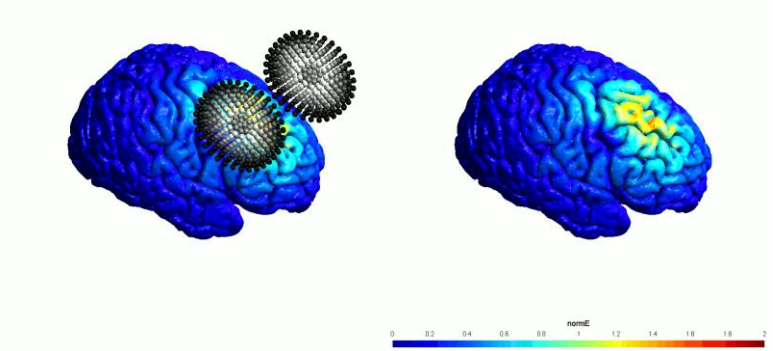
- Circular coil
- Double cone coil
- Figure & coil
- H coil

CIRCULAR COIL

- Less focused
- Used for stimulation of wide area

FIGURE-OF-8 COIL

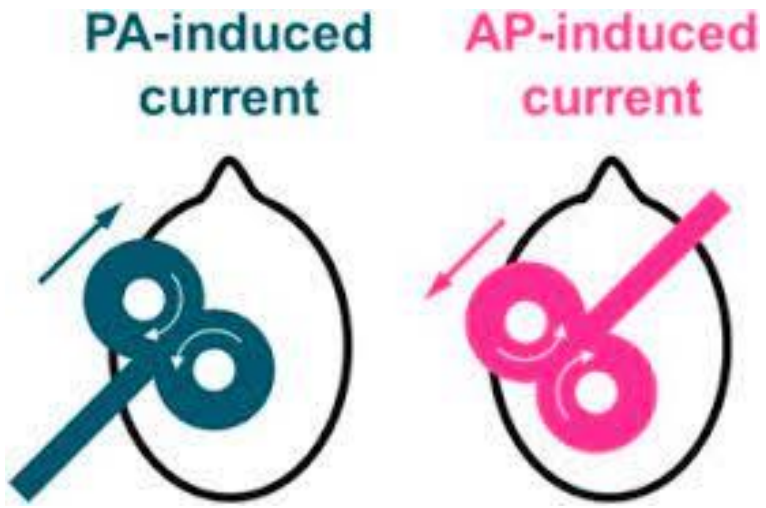
- Formed by abutting two single, circular coils against one another.
- Also referred to as Butterfl y Coil
- This type of coil is often preferred for most clinical and academic uses of TMS —including repetitive and chronometric measures

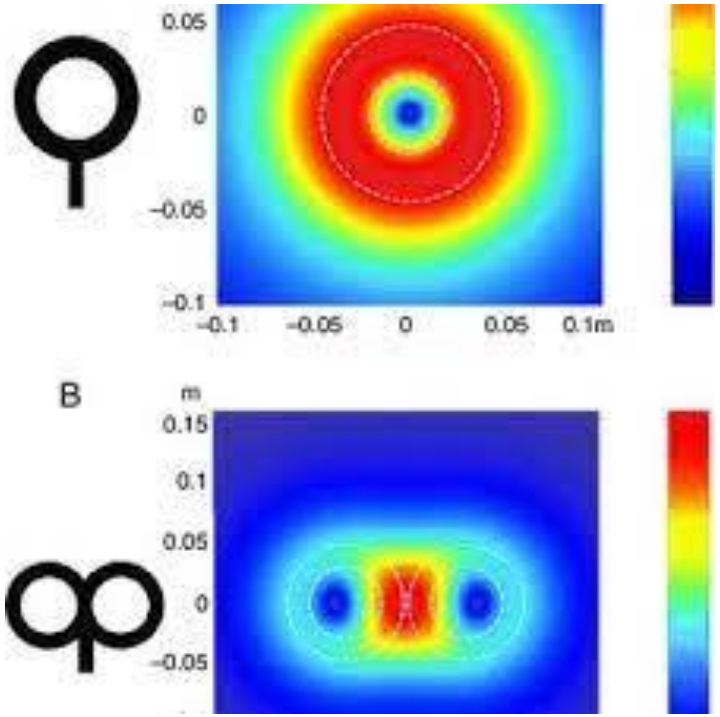


H-COIL

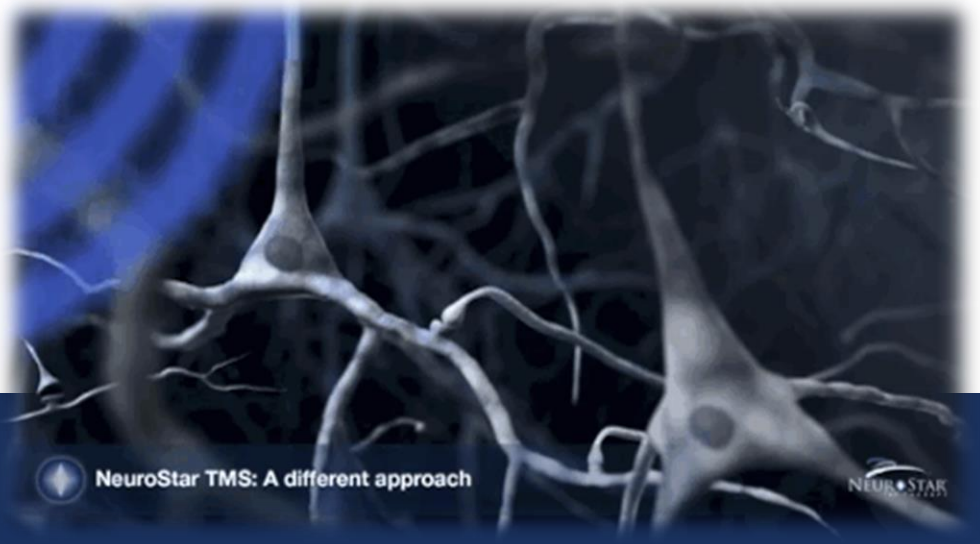
- Research suggests the H-Coil may be able to stimulate neural structures up to 6 cm below the cortical surface
- stimulate deeper, non-superficial cortical layer

COIL POSITION




0.05
0
−0.05
−0.1
−0.1
−0.05
0
0.05
0.1m
B
m
0.15
0.1
0.05
0
−0.05

HOW TO START?



ADVANTAGES AND DISADVANTAGES OF TMS

- Numerous studies have demonstrated clinical efficacy in the treatment of resistant major depressive disorder
- 2008 : FDA approved (MDD)
- 2018 : FDA (OCD)

- well tolerated and safe
- Clinical trials have found no cognitive impairment

ECT VERSUS TMS

	ECT	TMS
Anesthesia, LOC	Yes	No
Induction of seizure	Yes	No
Systemic effects	Anesthetic drugs, increase HR	none
Treatment schedule	3X/ week (8 -15 tx)	Daily, M-F, six weeks (30 tx)
Rapidity of onset	2 – 3 treatments	2 – 3 weeks
Mechanism of action	SEIZURE. Massive NT release; rise in sz threshold	Reactivation of neural circuits. Precise, LOCAL release of NT's.
Side effects	Memory loss, confusion	Essentially none (mild HA 1st week)
Psychosocial impact	can't work	Drive to and from tx's, work improved
After-effects	Mild (usually transient) memory loss	None. Pro-cognitive
Insurance coverage	Almost always	Rare. Improving

TMS INDICATIONS

- MDD
- OCD
- Schizophrenia (hallucination & negative symptom)
- Stroke
- Movement dis
- Epilepsy
- Tinnitus
- Substance abuse

TMS INDICATIONS

- Major depressive disorder

- Treatment resistant depression :
- A depressive episode that has inadequately responded to initial treatment with One or more adequate medication trials

CONTRAINDICATION

- Non removable metallic objects in or near the head (exclude dental hardware)
- ✓ Conductive/ferromagnetic or other magnetic sensitive metals that are non-removable with 30 cm of treatment coil
- Implanted device that is activated or controlled by physiologic signals,even if the device is located outside 30 cm distance
- ✓ Deep Brain Stimulation
- ✓ Cochlear implant
- Patients using wearable cardiovascular defibrillators(WCD)

CONTRAINDICATION

- Implanted devices allowed :
- > 30 cm
- Not controlled with physiologic signals

✓ Implanted insulin pump

✓ staples

RELATIVE CONTRAINDICATIONS

- Pregnancy
- Childhood
- Heart disease (unstable)
- Cardiac pacemaker
- Medical pump
- TCA/Antipsychotic

SPECIAL CONSIDERATION

- VNS
- Tattoos (on scalp)

PRE TMS WORK-UP

- Medical evaluation : HX & Physical examination
- Screen for contraindications : Metal in head and Epilepsy
- Evaluating medical list for seizure lowering agent
- Screen for substance use disorder :consider drug screen
- Pregnancy test
- No labs or imaging required unless indication by HX

INFORM CONSENT

- Discussion of what expected
- Stimulation sensation
- Common side effects & risk of potential serious adverse events including seizure

SEIZURE RISK ASSESSMENT

- Seizure Hx
- Seizure family Hx
- Febrile convulsion Hx
- Medication

✓ Withdraw from medication that raise seizure threshold

- Substance use/withdrawal
- Medical disease (esp. electrolyte imbalance and BS)
- Structural brain lesion

✓ TBI ,MS ,Tumor , stroke

COMMON SIDE EFFECTS

- local scalp pain or discomfort, headache and facial muscle twitching during stimulation

- Although common, these side effects are typically mild with fewer than 2% of patients in clinical trials discontinuing treatment due to stimulation-related discomfort

In general, tolerability of rTMS improves over the course of treatment and may be eased with simple analgesia such as paracetamol

SERIOUS SIDE EFFECTS

- More serious side effects are rare and these risks diminish when safety precautions are followed

SEIZURE

- The incidence of induction of a generalized seizure has not been fully quantified but appears to be **extremely low** when patients are adequately screened for risk factors and treatment applied carefully
- All services are offering rTMS required to have protocols to manage seizure induction
- Prompt cessation of rTMS is indicated in these instances
- There is no evidence to suggest rTMS increases an individual's risk to experience a seizure in the future

A MANIC OR HYPOMANIC EPISODE

- The other **rare**, but potentially serious adverse effect is that of inducing a manic or hypomanic episode
- These episodes can occur, most commonly in patients with a pre-existing diagnosis of bipolar affective disorder
- In clinical experience they appear less common / quite rare in patients receiving mood stabilizing medication whilst undertaking rTMS

PRE TMS WORK-UP

Medical evaluation : HX & Physical examination

Screen for contraindications : Metal in head and Epilepsy

Evaluating medical list for seizure lowering agent

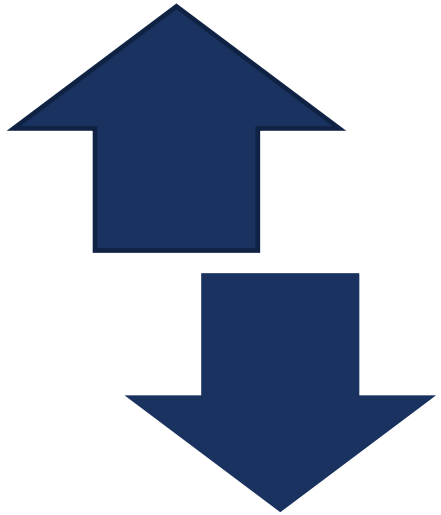
Screen for substance use disorder :consider drug screen

Pregnancy test, no labs or imaging required unless indication by HX

HEARING LOSS

- Click : 120-300 dB
- Ear plug

TMS PROTOCOLS



Excitatory

Inhibitory

TMS PROTOCOLS

- Train duration
- Pulses per train
- Intertrain interval
- Total pulses

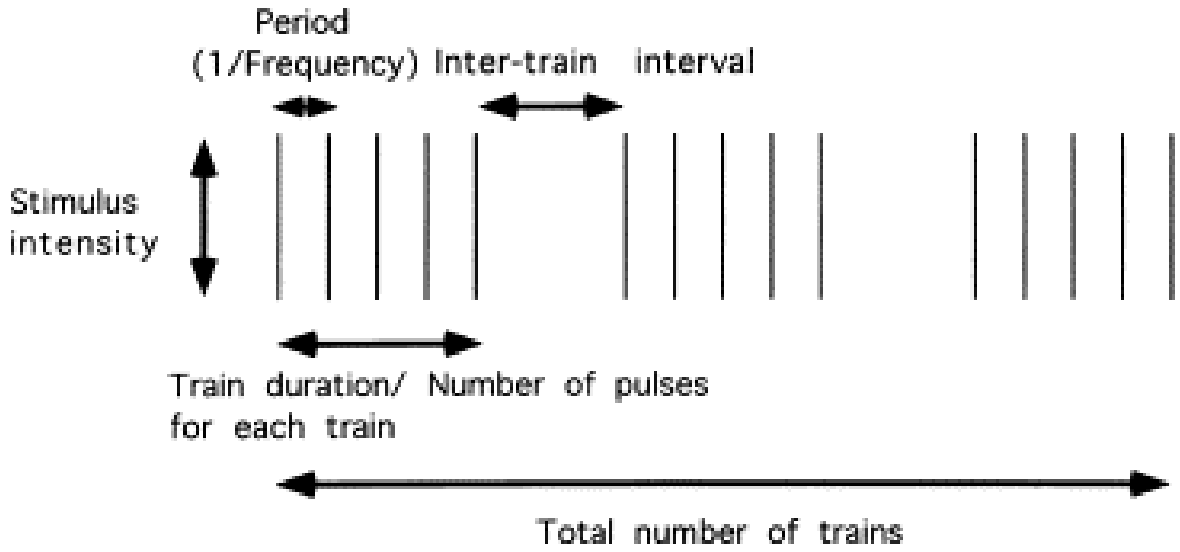
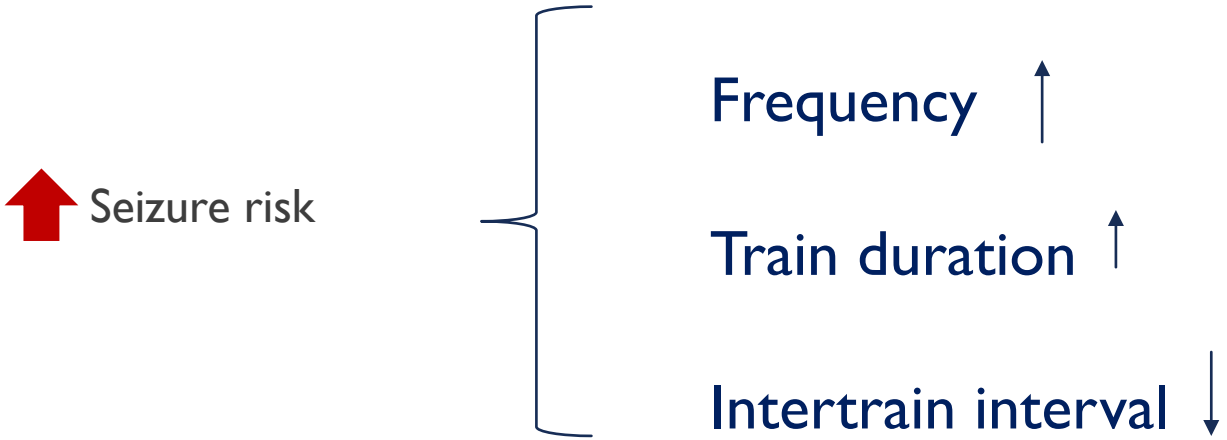


Table 1
Maximum safe duration (expressed in seconds) of single trains of rTMS

Frequency (Hz)	90 % rMT	100 % rMT	110 % rMT	120 % rMT	130 % rMT
1	>1,800	>1,800	>1,800	>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	.055
25	1.28	1.28	0.84	0.4	0.24

Safety defined as the absence of seizure, spread of excitation or after discharge of EMG activity. Numbers proceeded by > are longest duration tested. Consensus has been reached for this table (obtained with permission from [17])

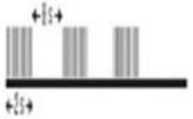
SEIZURE


Seizure risk
Frequency
Train duration
Intertrain interval

MDD PROTOCOL

- 10 HZ
- LT DLPFC
- Train duration :4 second
- Intertrain duration: 26 second
- Pulses in train : 40
- Number of train:75
- Pulses per session :3000
- 120% RMT

Table 2 Typical rTMS parameters

rTMS method	Pattern	Pulse mode	Pulses per burst	Frequency (Hz)	Total trains	Pulses per train	Inter-train intervals (seconds)	Pulses per session	Total time per session (minutes)
HF		Single pulse	NA	⩾ 10	60	50	25	3,000	30
LF		Single pulse	NA	⩽ 1	1	1,200	0	1,200	20
iTBS		Burst	3 (at 50 Hz)	5	20-30	30	8	600-900	4-7
cTBS		Burst	3 (at 50 Hz)	5	1	600-900	0	600-900	2-3

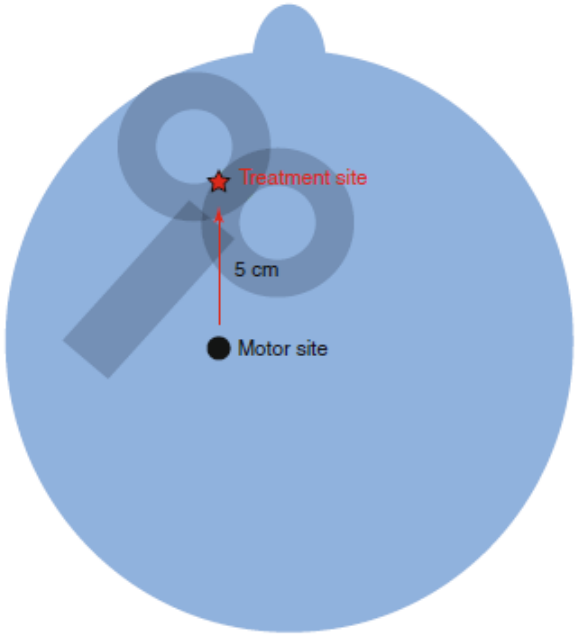
cTBS = continuous theta-burst stimulation; HF = high frequency; iTBS = intermittent theta-burst stimulation; LF = low frequency; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation.

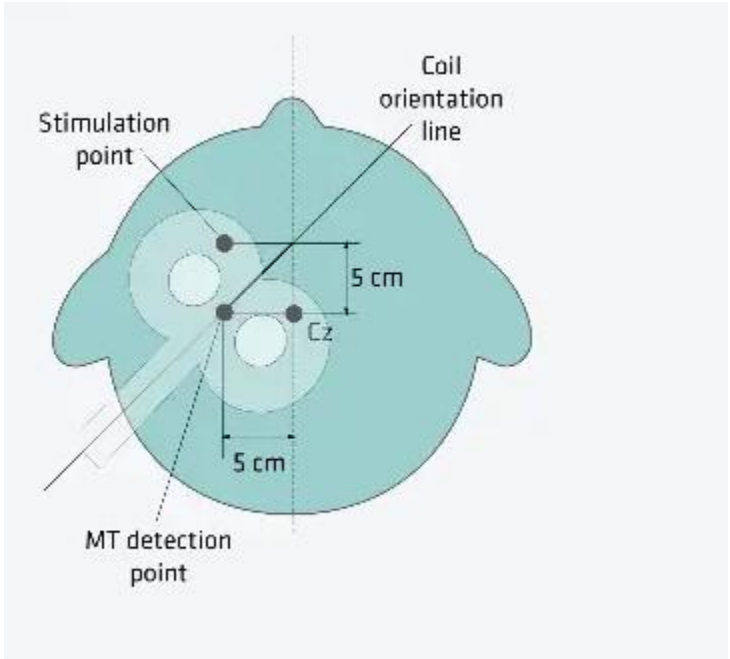
COIL PLACEMENT FOR DEPRESSION

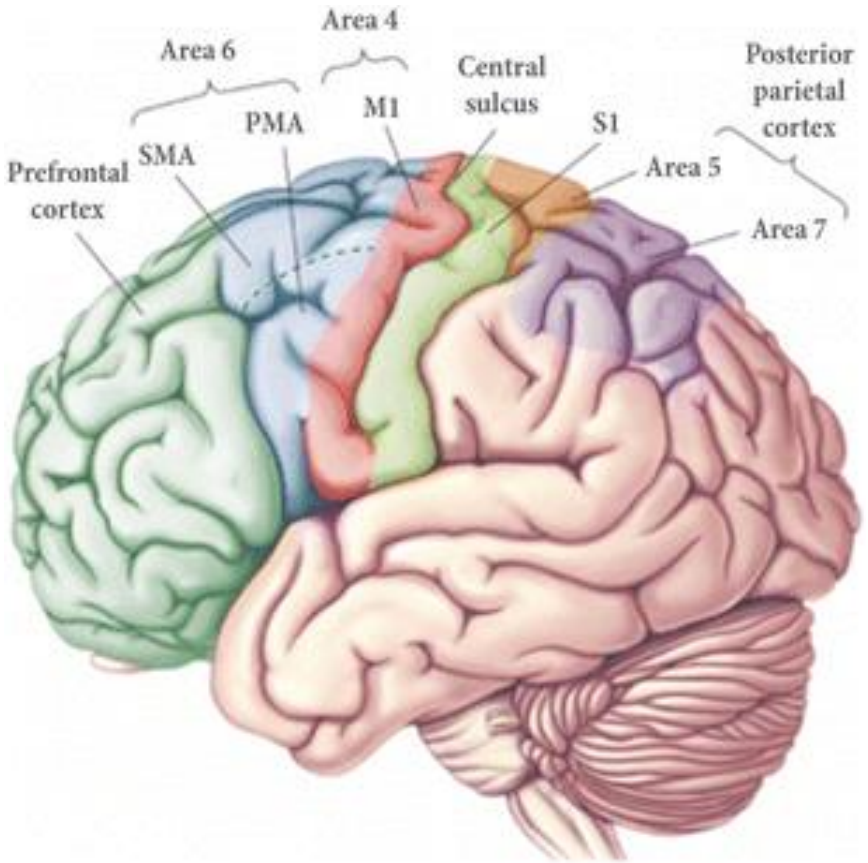
- Three approaches:

A MODIFIED 6CM RULE

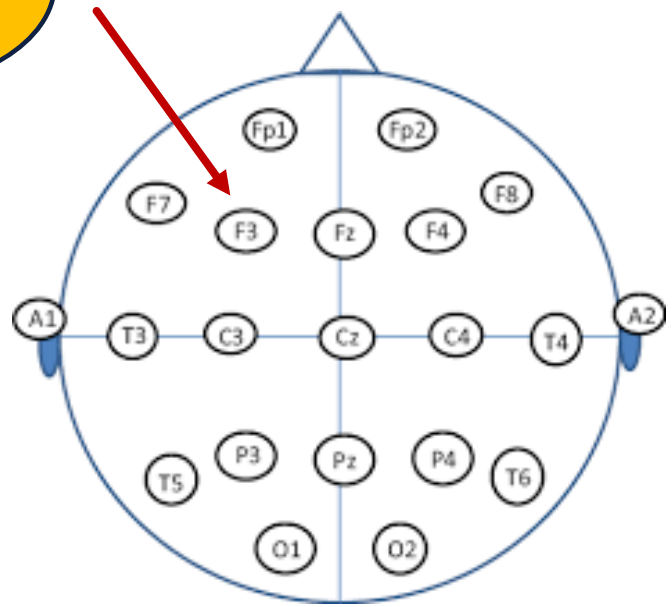
- Research has shown that the earlier 5 cm approach is inadequate in targeting the appropriate region in the prefrontal cortex and is not recommended

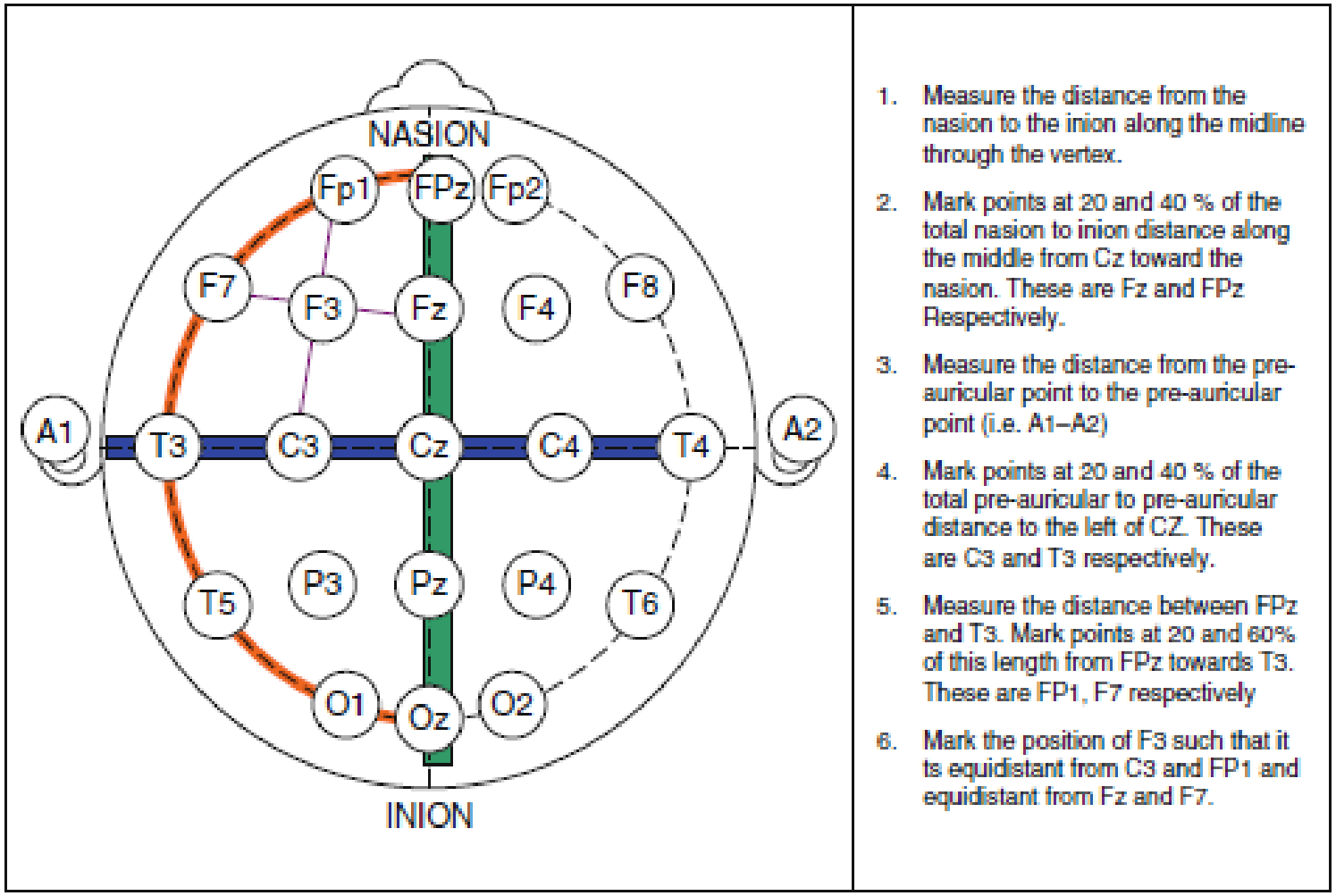





Area 6
Area 4
Central sulcus
Posterior parietal cortex
PMA
M1
S1
SMA
Area 5
Prefrontal cortex
Area 7

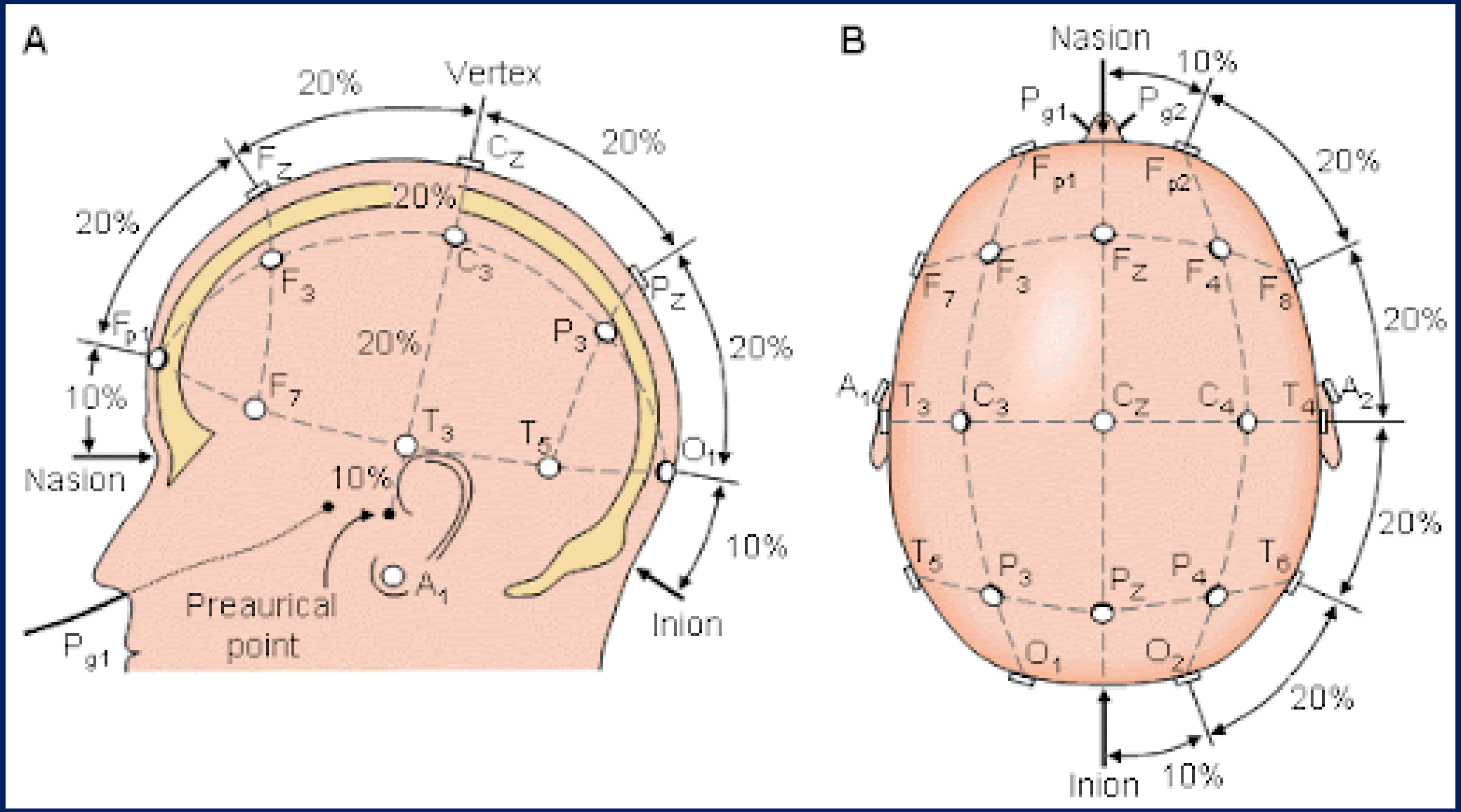
DLPFC

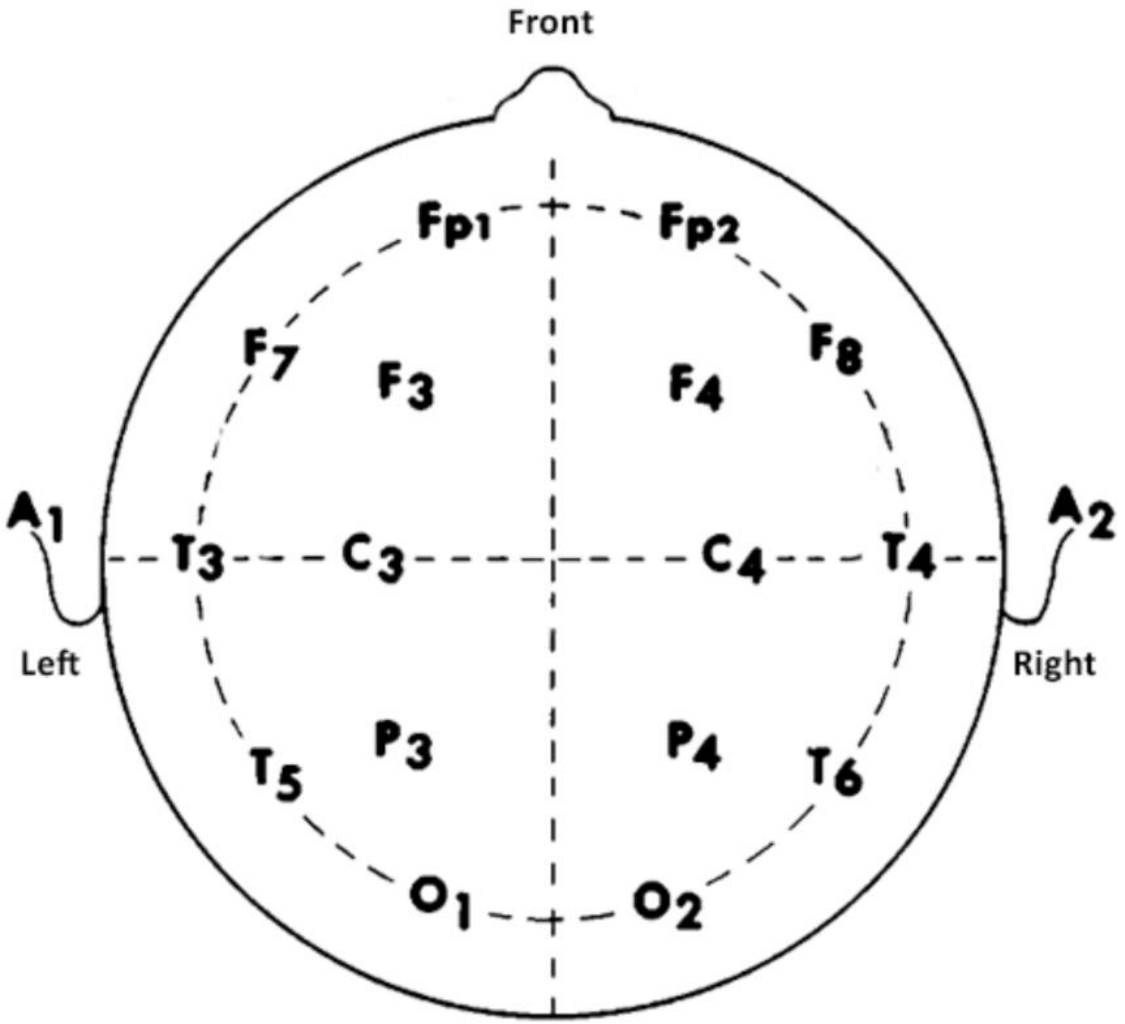




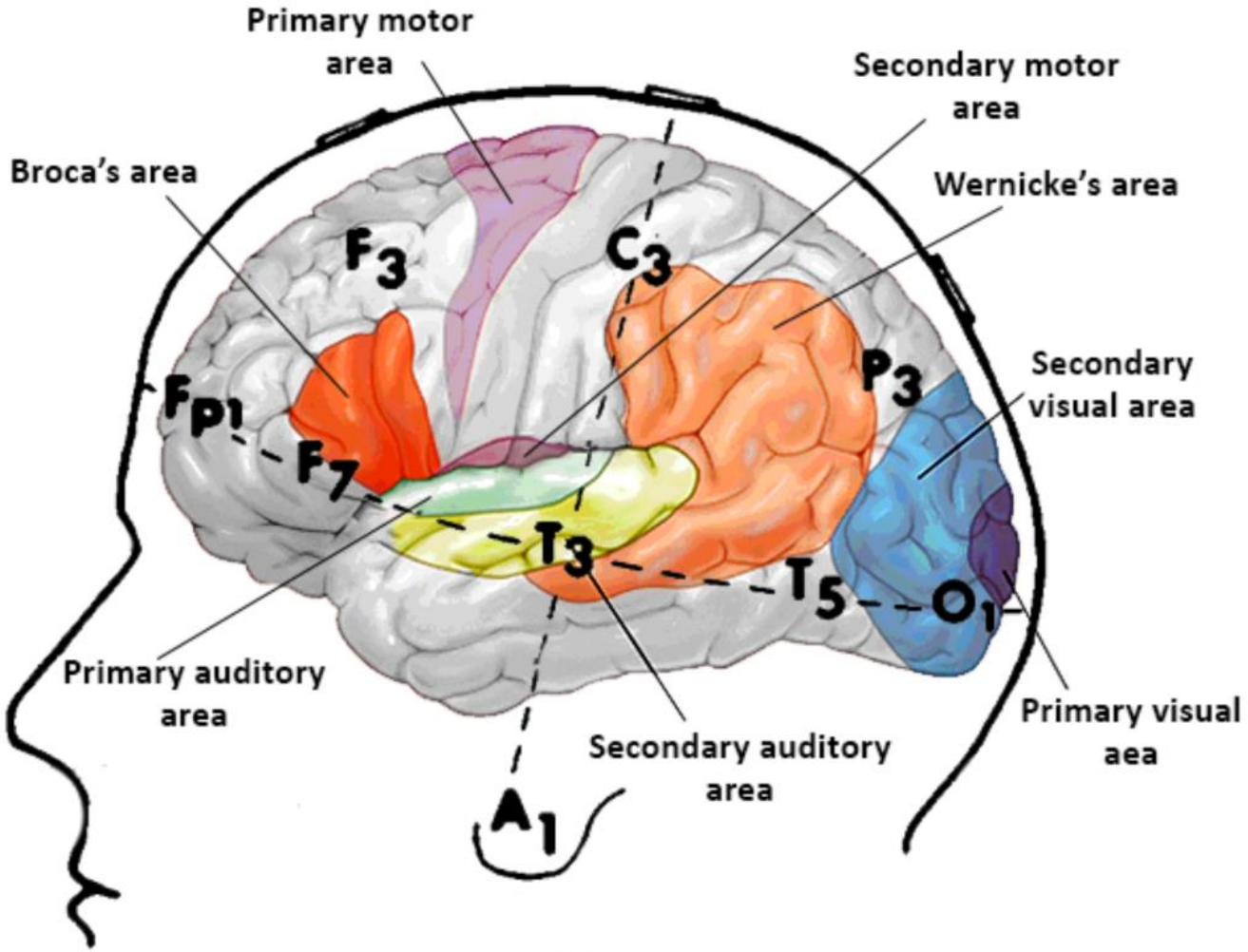
1. Measure the distance from the nasion to the inion along the midline through the vertex.
2. Mark points at 20 and 40 % of the total nasion to inion distance along the middle from Cz toward the nasion. These are Fz and FPz Respectively.
3. Measure the distance from the pre-auricular point to the pre-auricular point (i.e. A1–A2)
4. Mark points at 20 and 40 % of the total pre-auricular to pre-auricular distance to the left of CZ. These are C3 and T3 respectively.
5. Measure the distance between FPz and T3. Mark points at 20 and 60% of this length from FPz towards T3. These are FP1, F7 respectively
6. Mark the position of F3 such that it ts equidistant from C3 and FP1 and equidistant from Fz and F7.

Fig. 6.5 Method for the measurement of the site of the F3 EEG point


A
20%
Vertex
20%
20%
20%
20%
20%
20%
20%
10%
10%
10%
Nasion
Preaurical
point
Inion
B
Nasion
10%
20%
20%
20%
20%
10%
Inion


Front
Fp1
Fp2
F7
F3
F4
F8
A1
T3
C3
C4
T4
A2
Left
Right
T5
P3
P4
T6
O1
O2

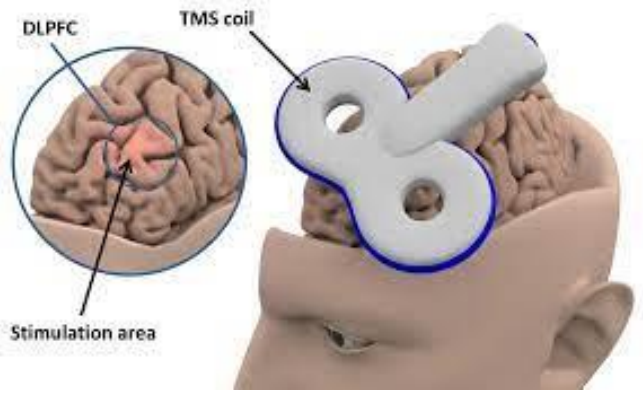
a)

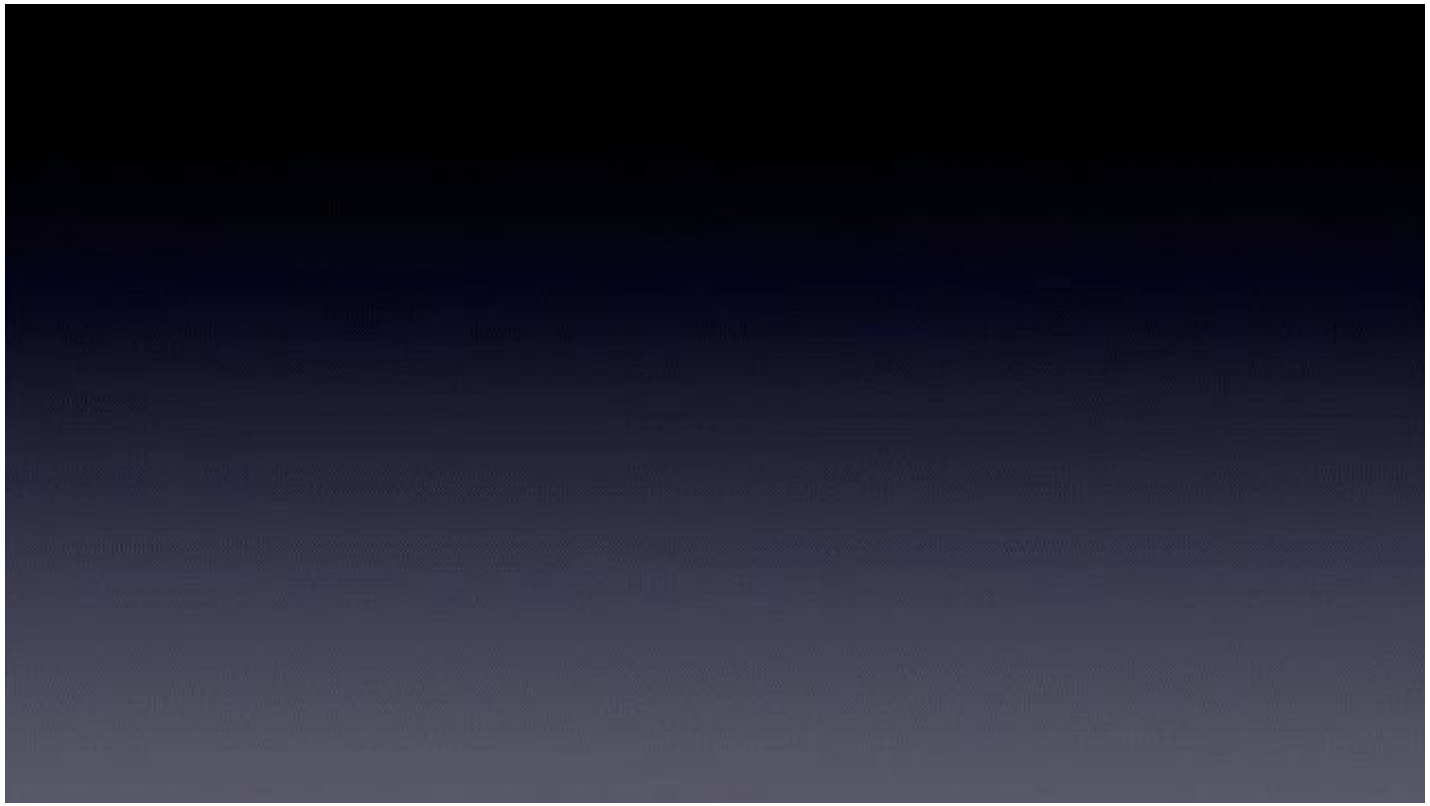

Primary motor area
Secondary motor area
Broca's area
Wernicke's area
F3
C3
P3
Secondary visual area
Fp1
F7
T3
T5
O1
Primary auditory area
Secondary auditory area
Primary visual aea
A1

b)

10-20 EEG SYSTEM

- Targeting based on the 10-20 EEG system
- DLPFC

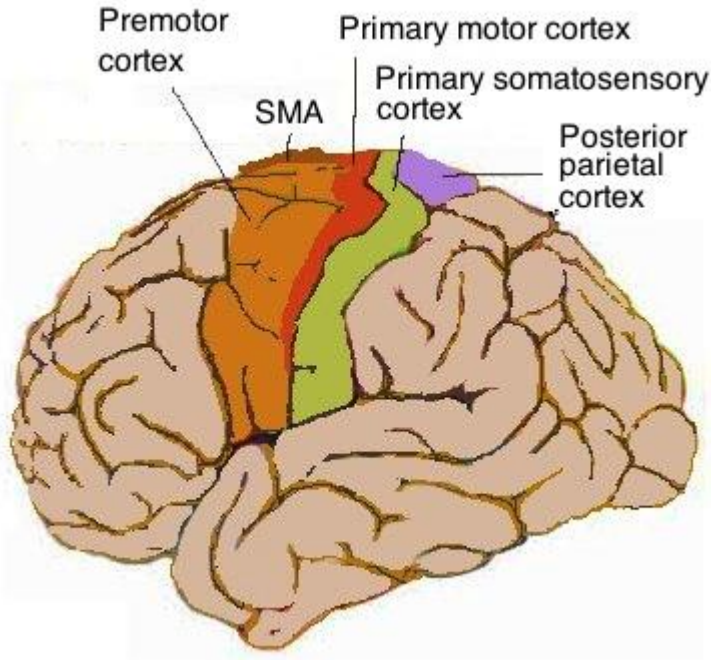




- www.Clinicalresearch.org/EEG

NEURONAVIGATION TECHNIQUE

OCD PROTOCOL

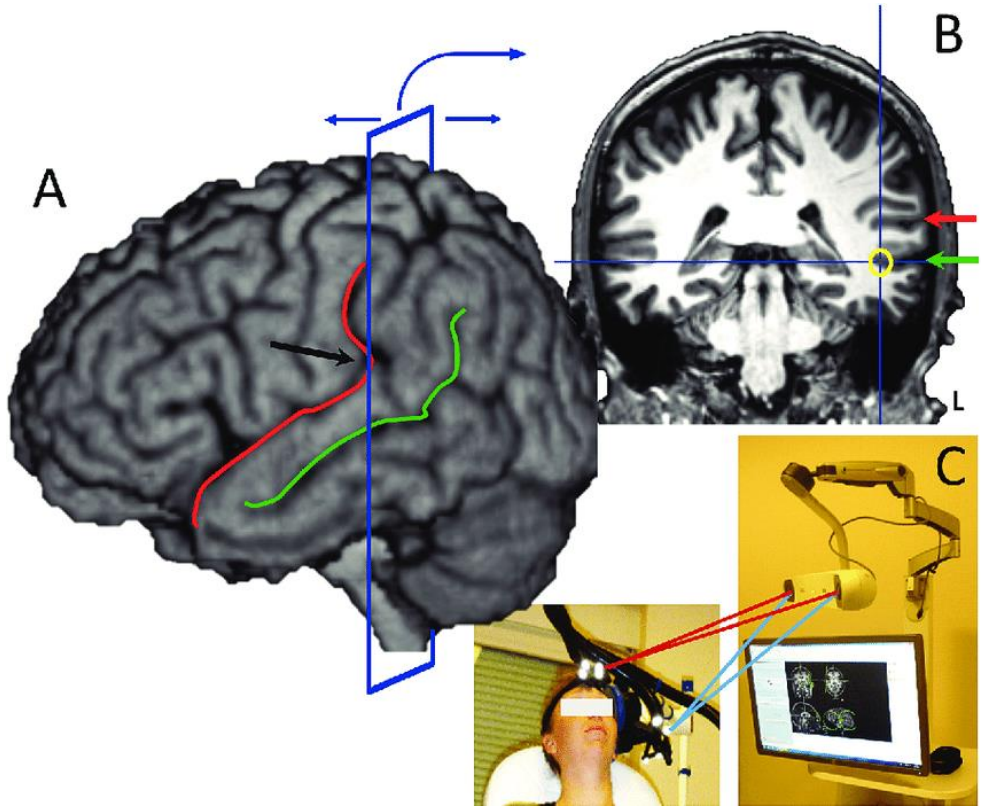


OCD

- Coil position: SMA
- Inhibitory
- 1HZ
- 100%RMT
- 1200 pulses

AUDITORY HALLUCINATION

- 1HZ
- 90-100% RMT
- Temporo- parietal T3-P3
- 1200 pulses


A
B
L
C


Thank You
For Your
Attention