Basic Science of Non-invasive Neuromodulation in Psychiatry

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Sincere acknowledgements

- Dr Rashmin Cholera
- Dept. of Psychiatry, School of Medicine
- Team CCN-CRC

No conflicts of interest

Clinical Research Centre for Neuromodulation in Psychiatry: A Multi-Centre Initiative to Advance Interventional Psychiatry in India

Opportunity to get training in advanced neuromodulation techniques

Potential for pursuing PhD in the area of neuromodulation in psychiatry

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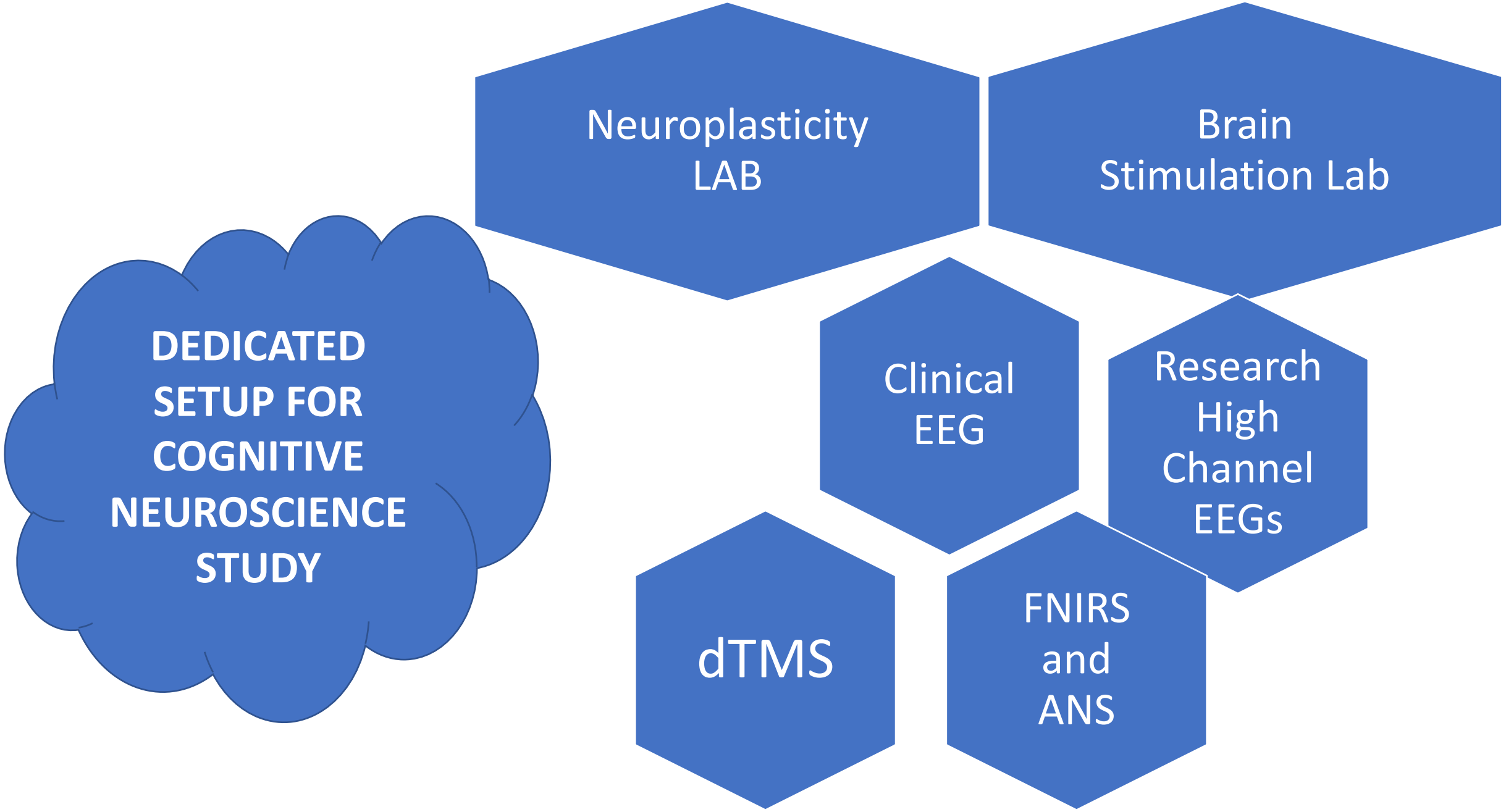
Neuroplasticity LAB
Brain Stimulation Lab
DEDICATED SETUP FOR COGNITIVE NEUROSCIENCE STUDY
Clinical EEG
Research High Channel EEGs
dTMS
FNIRS and ANS

Psychopharmacology: What now?

BJPsych | The British Journal of Psychiatry (2011)
198, 333–335. doi: 10.1192/bjp.bp.110.086207

Editorial

Has psychopharmacology got a future?

Philip J. Cowen

Summary
Fifty years ago pharmacological discoveries transformed psychiatry but progress since then has been relatively slow and there is unease about the role of industry. Despite this, the possibilities of pharmacological treatment have improved in recent years but exploiting developments for the benefit of patients requires psychotherapeutic skill as well as a high level of scientific knowledge.

Declaration of interest
P.J.C. has been a paid member of boards that have advised different drug companies on the development of antidepressant drugs. In the past 3 years these companies have included Eli Lilly, Lundbeck and Servier. P.J.C. has also received remuneration for scientific advice given to legal representatives of GlaxoSmithKline.

Psychopharmacology: Some hard truths…

- Most **prescribing of psychotropic drugs occurs outside** specialist psychiatric practice

- Between the blandishments of industry and the antipathy of critics, psychopharmacology has made **marginal incremental progress**

- **Few psychotropics in the pipeline**…recent ones not that effective as claimed in trails

- Psychopharmacology may have a golden past, but **does it have a future?**


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Perspective

The Practice of Psychiatry in the 21st Century: Challenges for Psychiatric Education

Joel Yager, M.D.

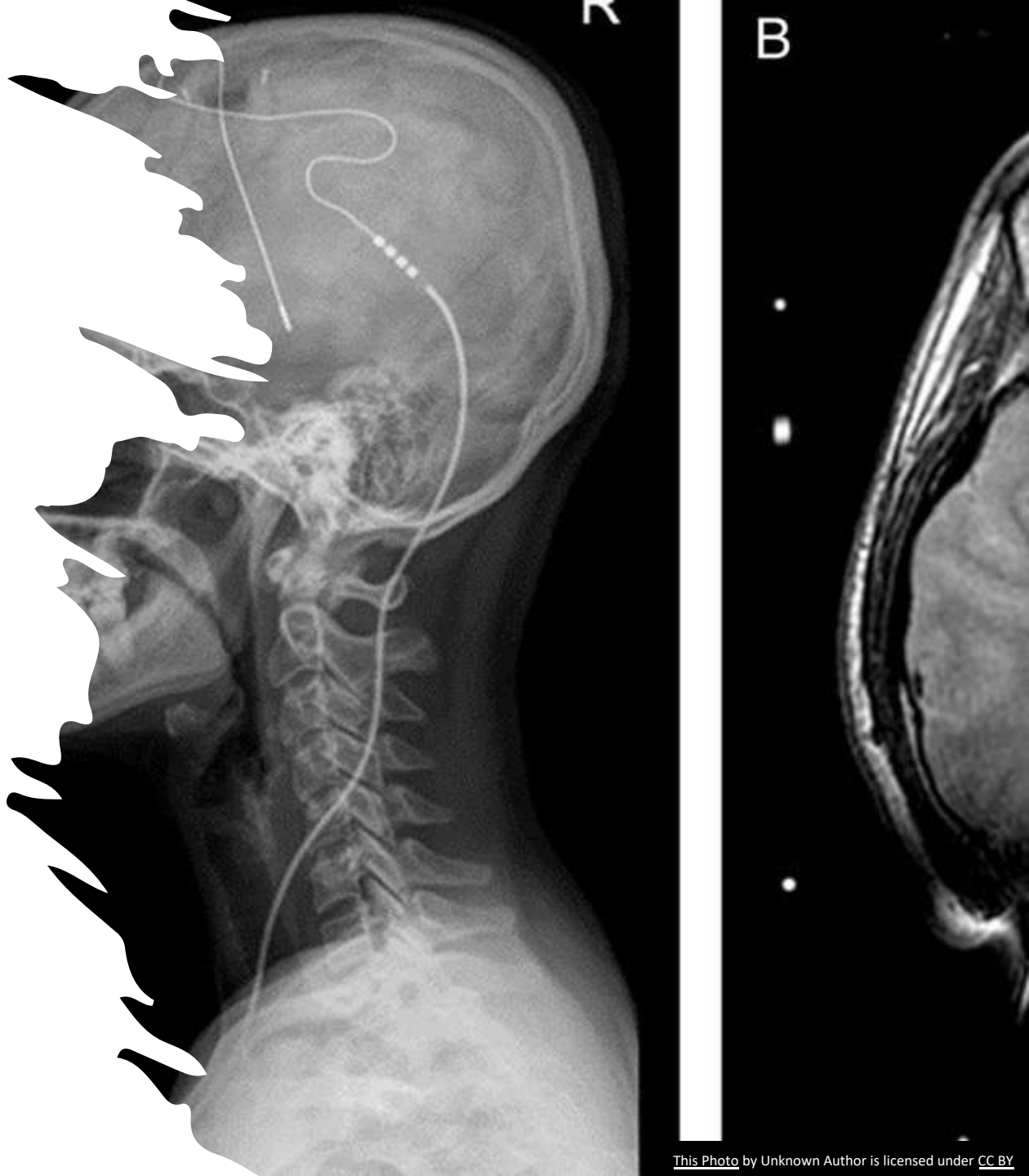
- **Technological and Scientific Advances Shaping Practice**
  - **G**enomics, **p**roteomics, **e**pigenetics, **n**euroimmunology, **n**europsychology
  - Advanced neuroimaging and studies of brain circuitry
  - Supercomputing-based advanced artificial intelligence (**AI**), Robotics and back engineering
  - Big data mining and management
  - Smart psychotherapy

- **New Areas of Psychiatric Specialization**

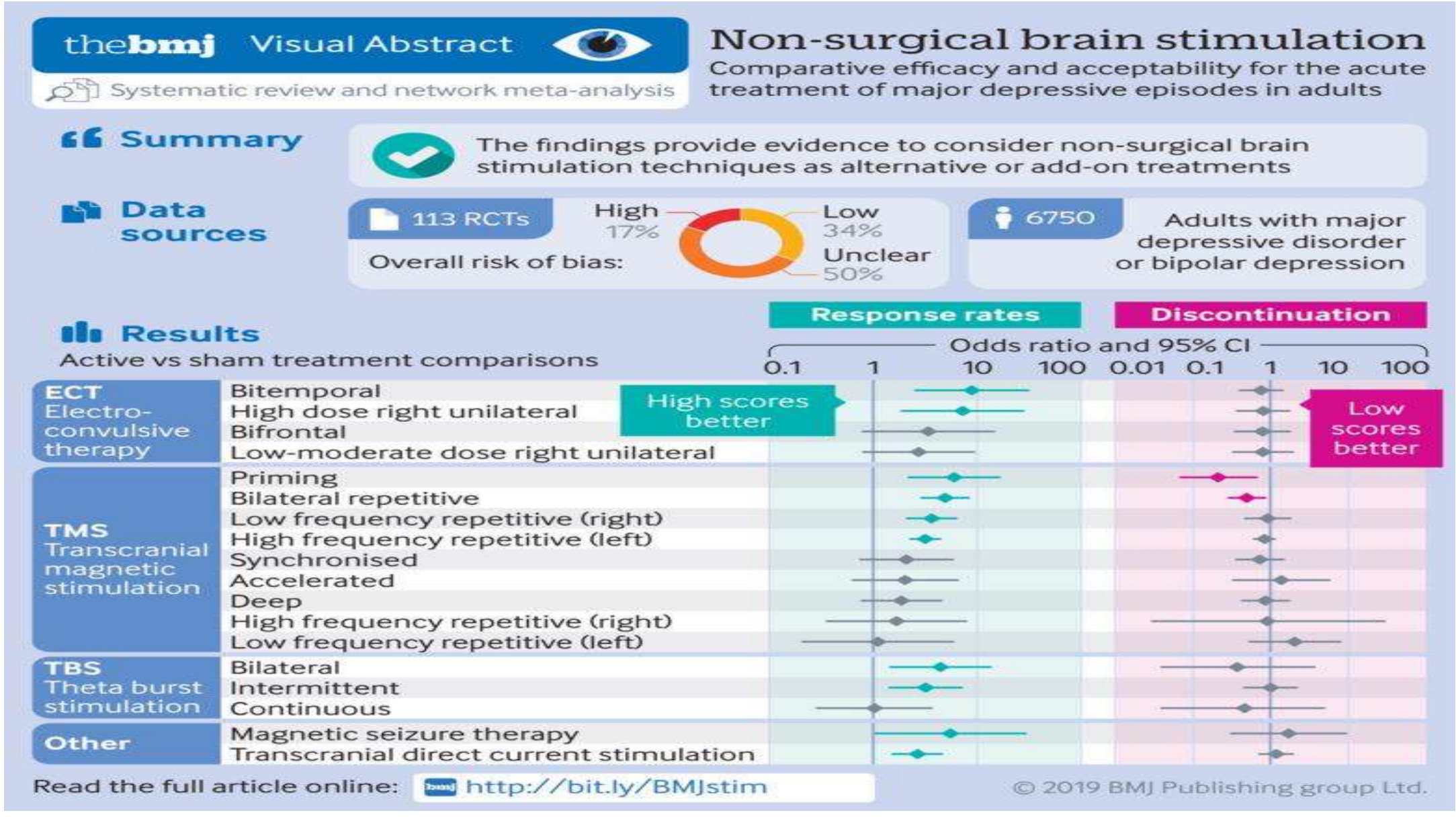
- **Precision Psychiatry/Neuromodulation: Customised Psychiatry**

What is Neuromodulation?

- Neuromodulation (or brain stimulation) is defined as a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical, for the purpose of improving quality of life and functioning of humans, by the international neuromodulation society



Success Story of NIBS/Neuromodulation



What Neuromodulation is not….

Basic Assumptions

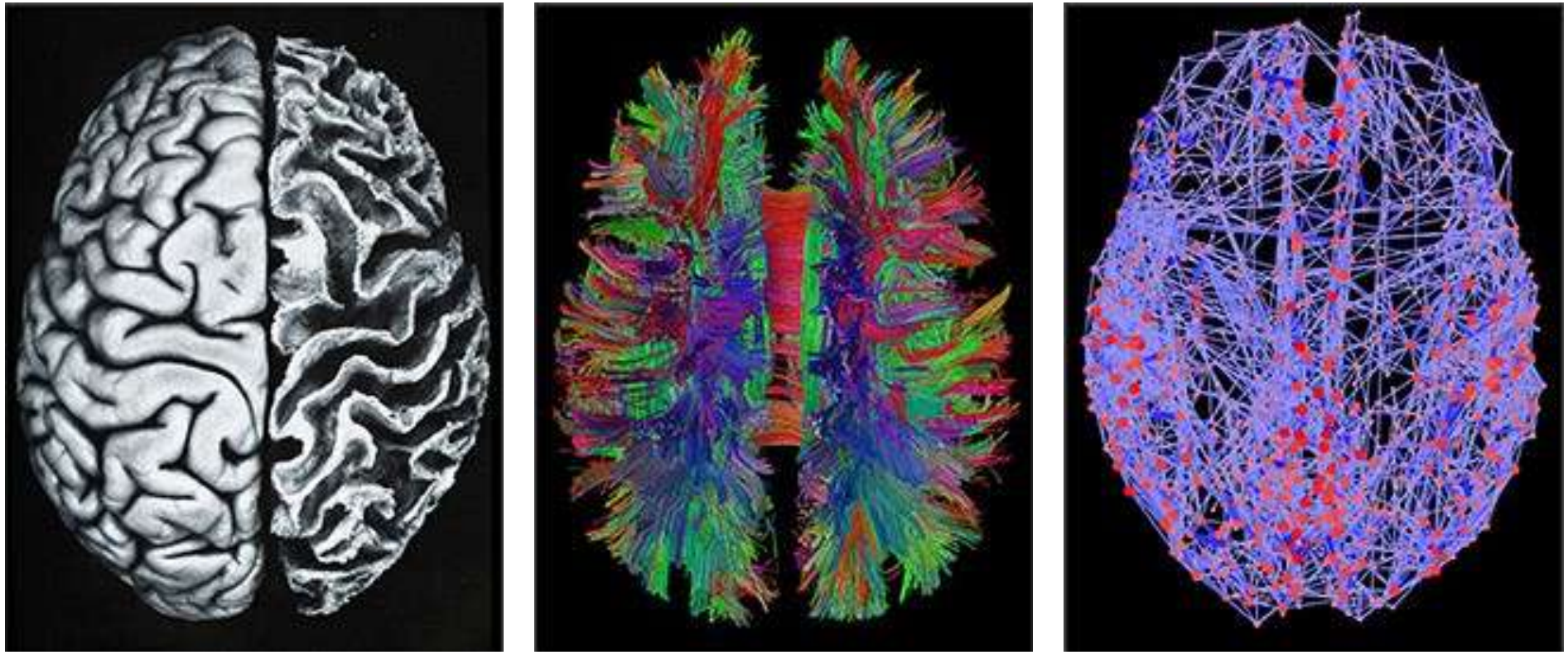
- Underlying premise of neuromodulation is that the **brain is an electrochemical organ** that can be **modulated** by pharmacotherapy or devise-based (ECT / TMS) approaches or their combination

- Explosion of new techniques for electrically stimulating the brain, primarily focally

- New tools are **changing neuroscience research and neuropsychiatric therapies**

- They validate and inform us about functional neuroanatomy

The brain is a complex, *electrochemical network*



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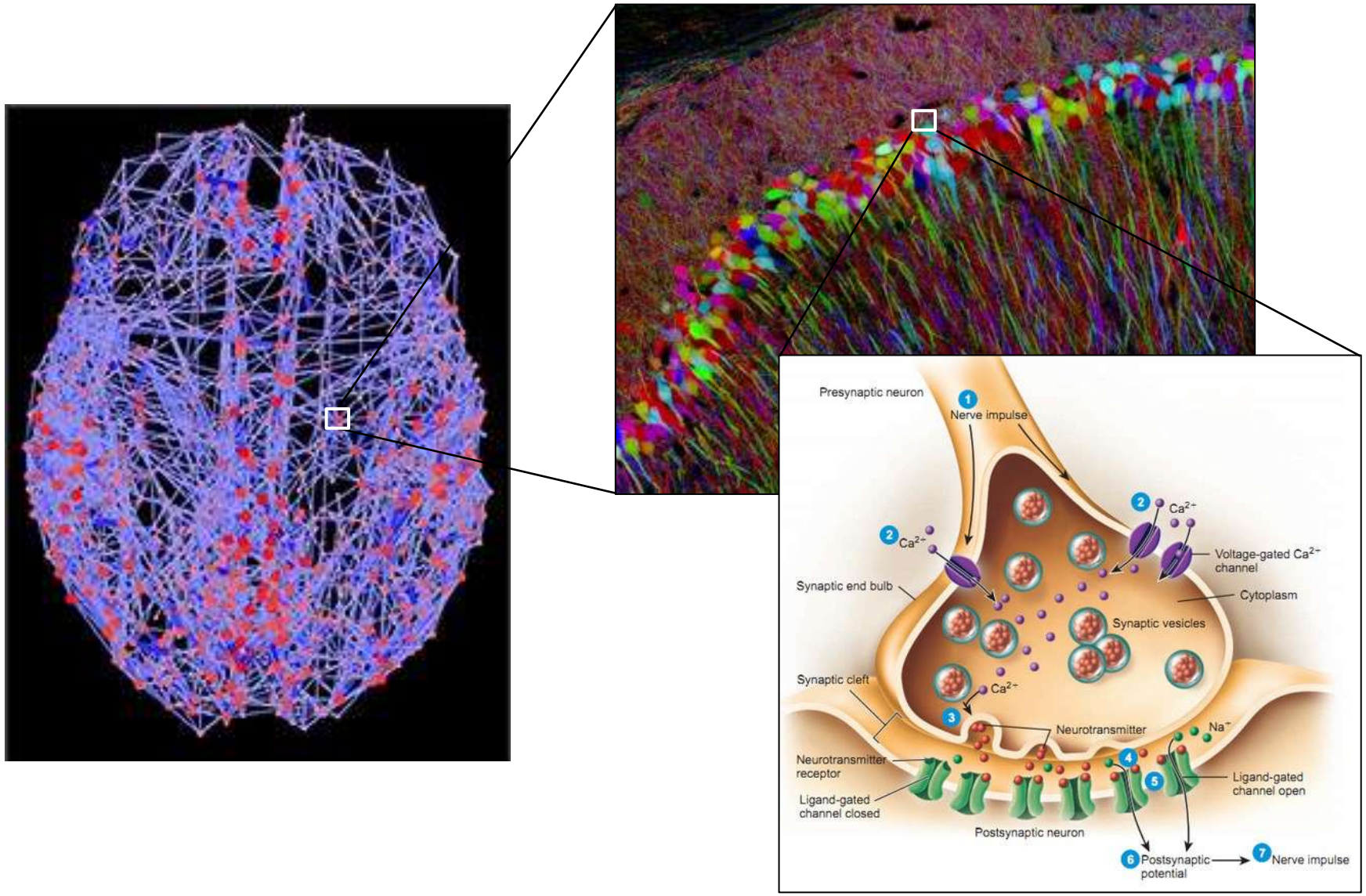

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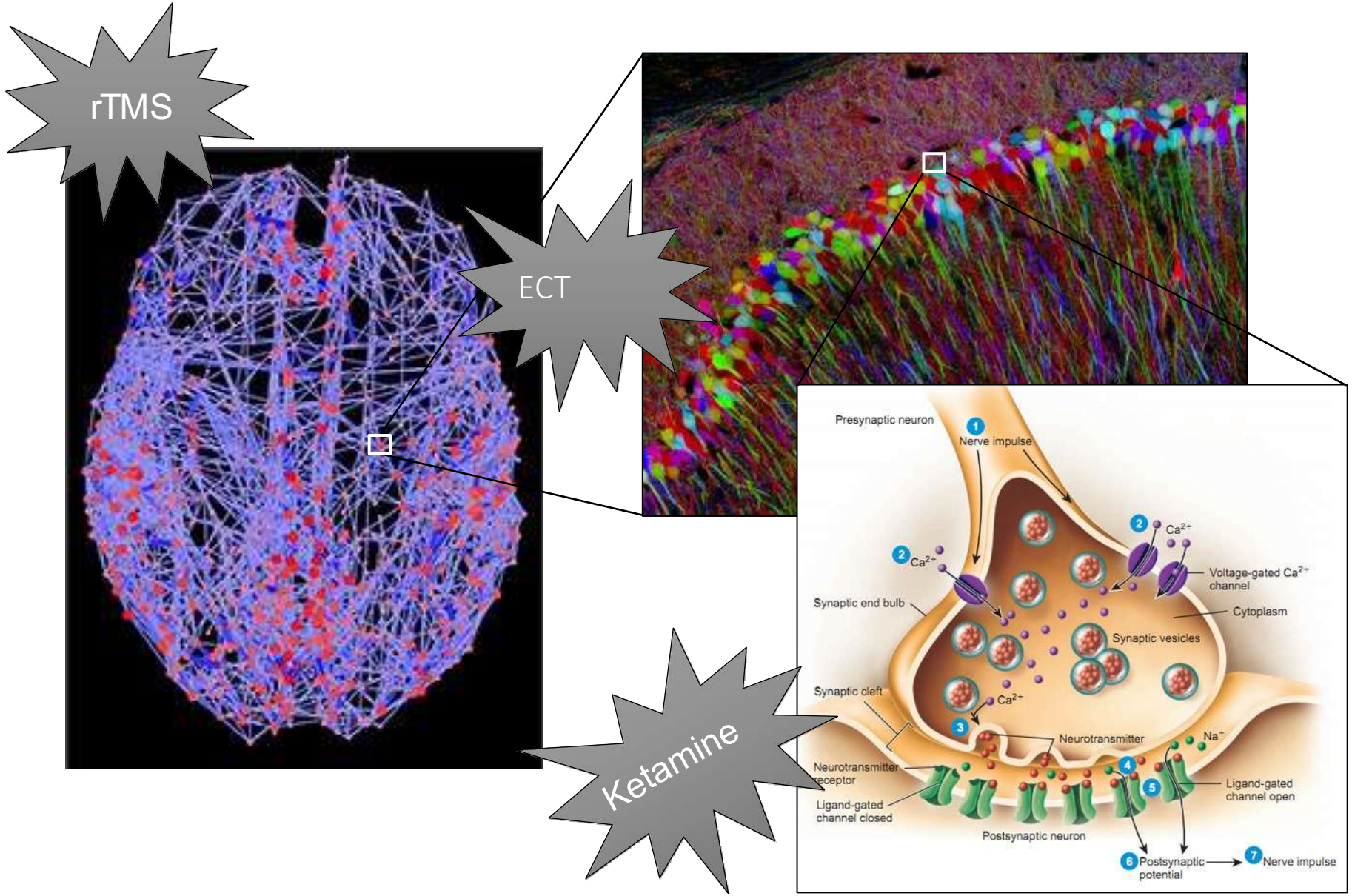
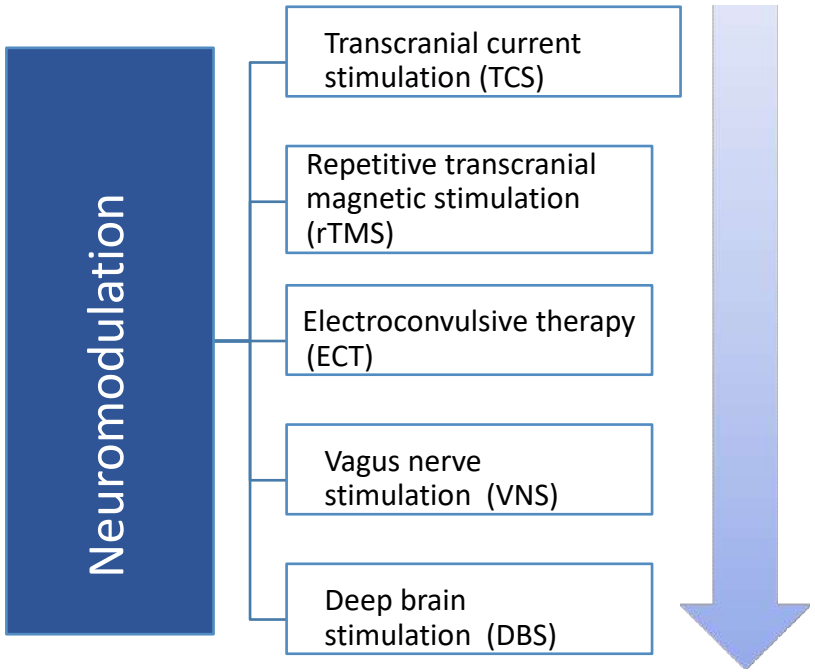


Interventional Psychiatry: Treatments



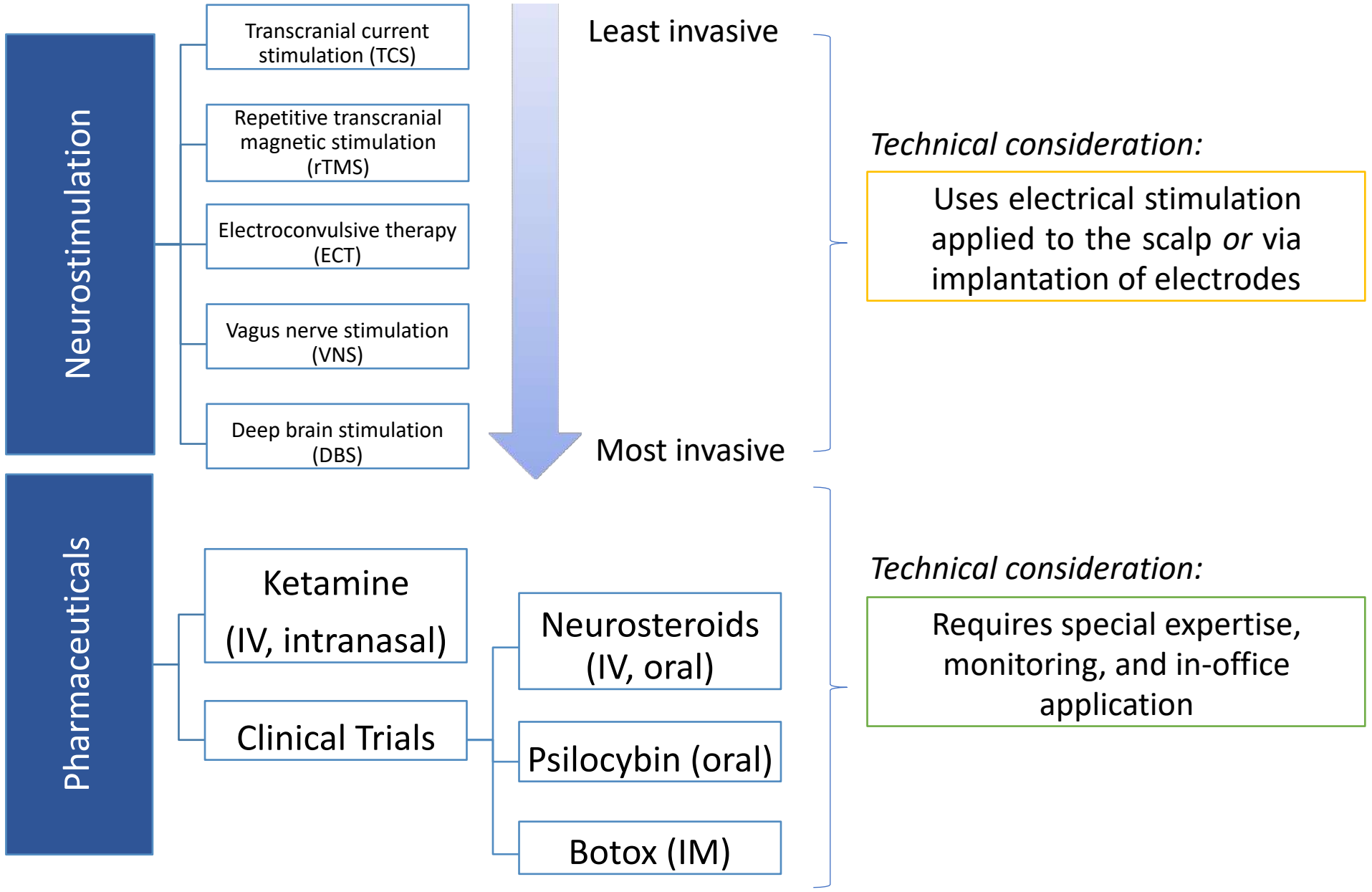
Least invasive

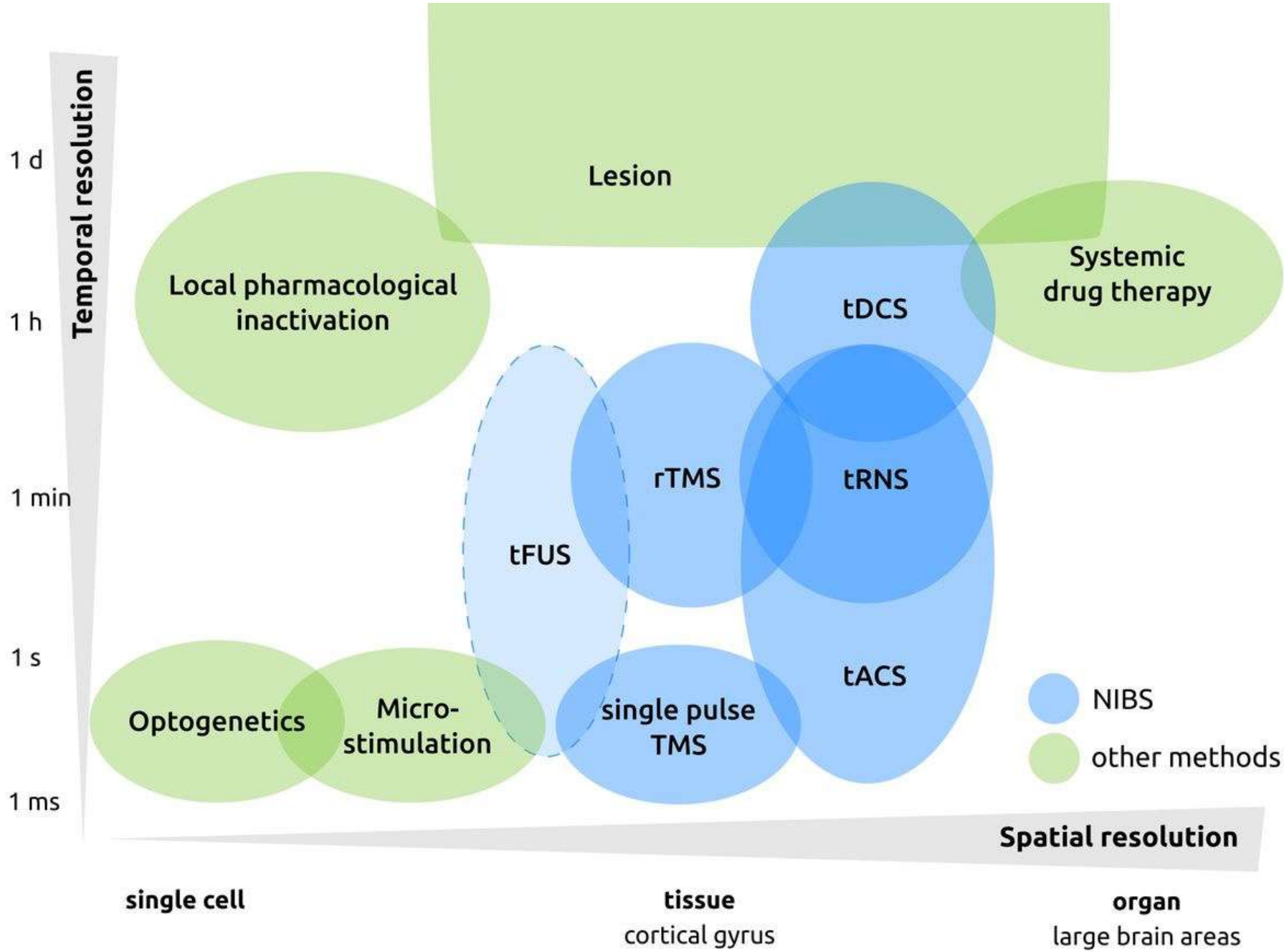
Most invasive

Technical consideration:

Uses electrical stimulation applied to the scalp or via implantation of electrodes

Interventional Psychiatry: Treatments




Temporal resolution
1 d
1 h
1 min
1 s
1 ms
Lesion
Local pharmacological inactivation
Systemic drug therapy
tDCS
rTMS
tRNS
tFUS
tACS
Optogenetics
Micro-stimulation
single pulse TMS
NIBS
other methods
Spatial resolution
single cell
tissue
cortical gyrus
organ
large brain areas

Current State of Neuromodulation

- Nearly **a dozen forms of brain stimulation** are in **development** or currently **US FDA approved** for neuropsychiatric indications

- **3 Journals** dedicated exclusively to brain stimulation

- Fortunately, leaders in psychiatric research, clinical practice, and education have recognized the **discrepancy between our field's direction and our current training schema**

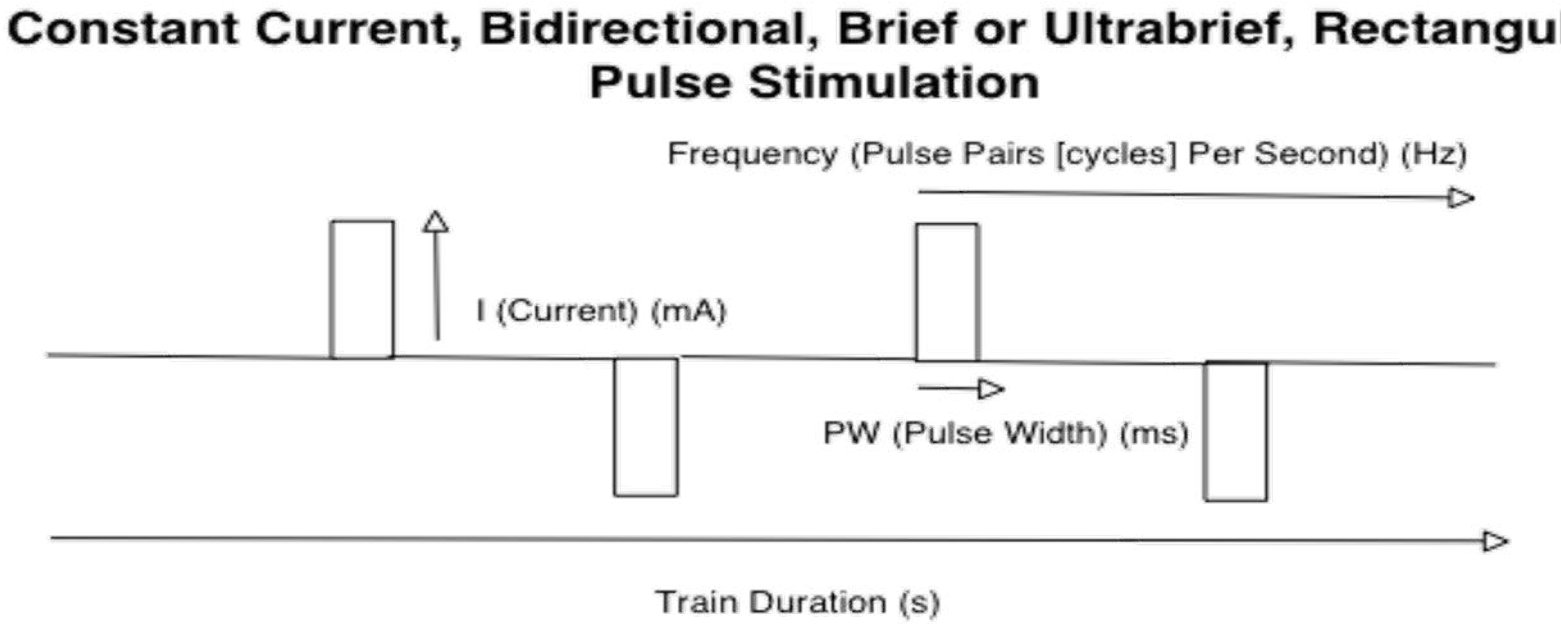
- Traditional training curricula offer **informal, inconsistent, and limited training opportunities in neurotechnologies such as neuromodulation and diagnostic modalities**

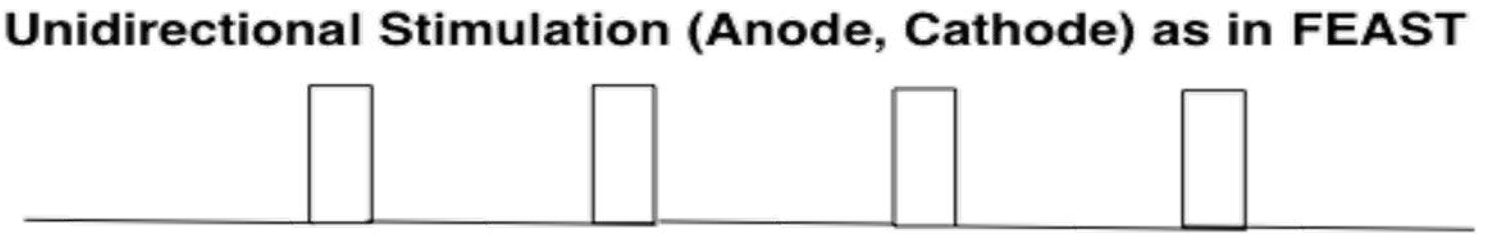
ECT

- ECT is the father of the brain stimulation
- Long way after Cerletti & Bini-more than 80 years
- Modern ECT: unilateral ultra-brief pulses-pulses are even briefer
- ECT still carries risks and has cognitive side effects

Refining the Electrical Stimulus

- Titrating and dosing in the current domain
- Unidirectional stimulation





Focal Electrically Administered Seizure Therapy

Need: L[illegible] d UL/BL

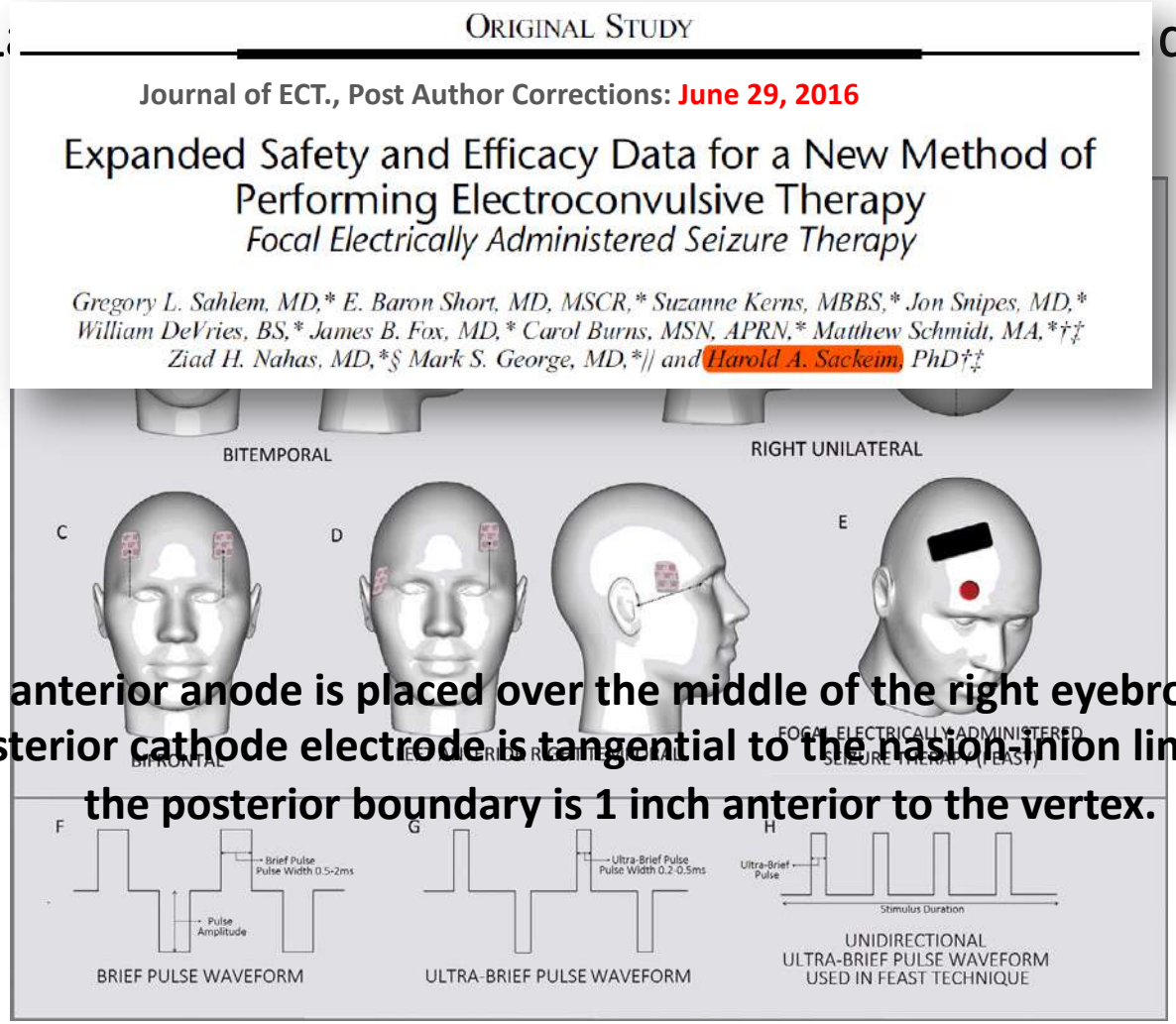
ORIGINAL STUDY

Journal of ECT., Post Author Corrections: **June 29, 2016**

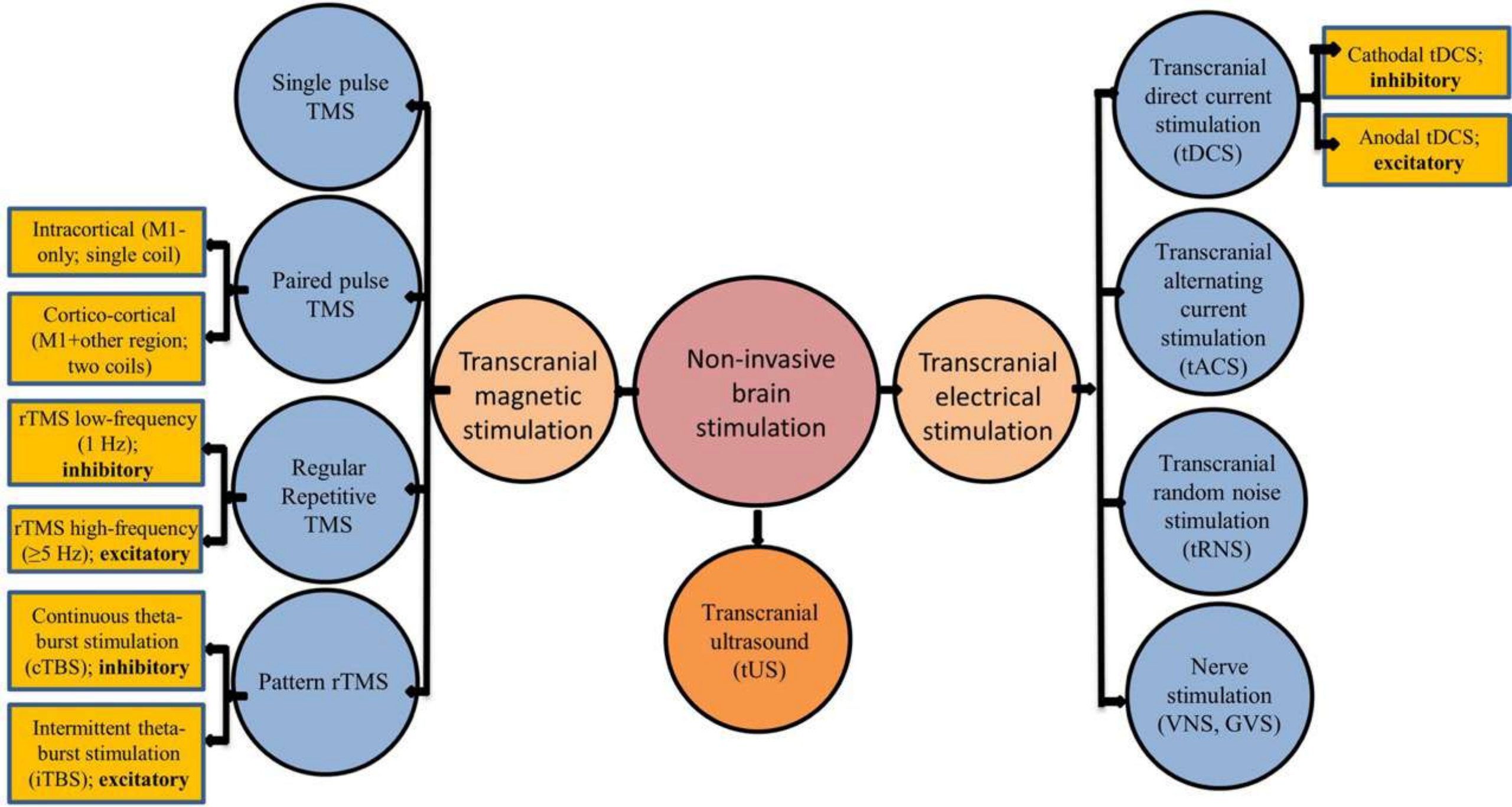
Expanded Safety and Efficacy Data for a New Method of Performing Electroconvulsive Therapy

Focal Electrically Administered Seizure Therapy

Gregory L. Sahlem, MD, E. Baron Short, MD, MSCR,* Suzanne Kerns, MBBS,* Jon Snipes, MD,* William DeVries, BS,* James B. Fox, MD,* Carol Burns, MSN, APRN,* Matthew Schmidt, MA,*†‡ Ziad H. Nahas, MD,*§ Mark S. George, MD,*|| and Harold A. Sackeim, PhD†‡*

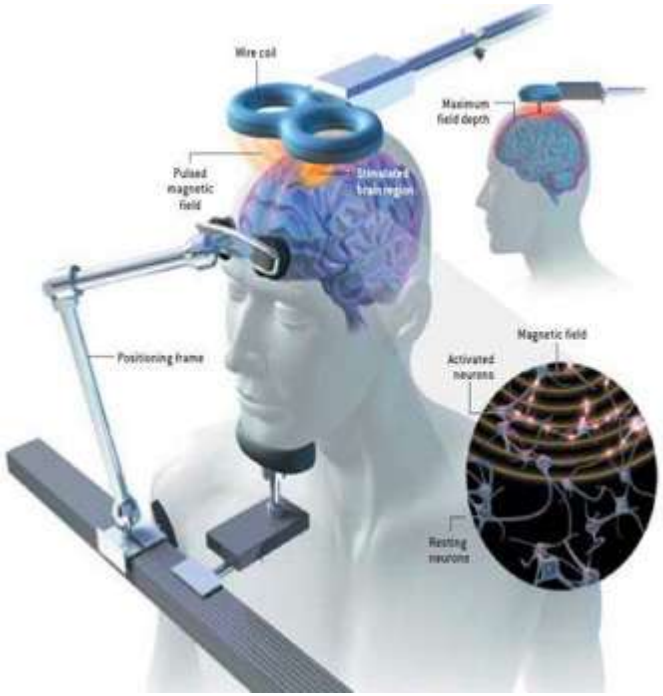


The anterior anode is placed over the middle of the right eyebrow. The posterior cathode electrode is tangential to the nasion-inion line, and the posterior boundary is 1 inch anterior to the vertex.


Non-invasive brain stimulation
Transcranial magnetic stimulation
Single pulse TMS
Paired pulse TMS
Intracortical (M1-only; single coil)
Cortico-cortical (M1+other region; two coils)
Regular Repetitive TMS
rTMS low-frequency (1 Hz); inhibitory
rTMS high-frequency (≥5 Hz); excitatory
Pattern rTMS
Continuous theta-burst stimulation (cTBS); inhibitory
Intermittent theta-burst stimulation (iTBS); excitatory
Transcranial ultrasound (tUS)
Transcranial electrical stimulation
Transcranial direct current stimulation (tDCS)
Cathodal tDCS; inhibitory
Anodal tDCS; excitatory
Transcranial alternating current stimulation (tACS)
Transcranial random noise stimulation (tRNS)
Nerve stimulation (VNS, GVS)

Functional neuroimaging studies suggest a role of cortical governance over limbic activity

Transcranial Magnetic Stimulation



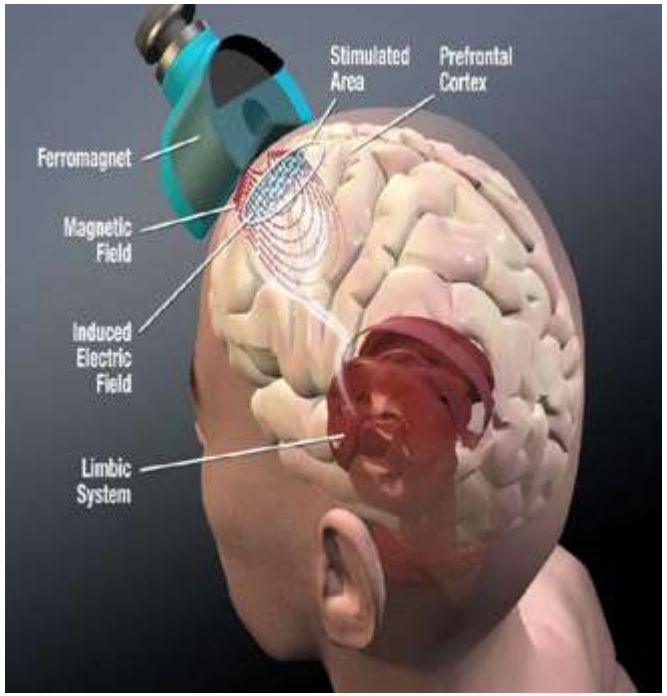
Depression

Holy Grail

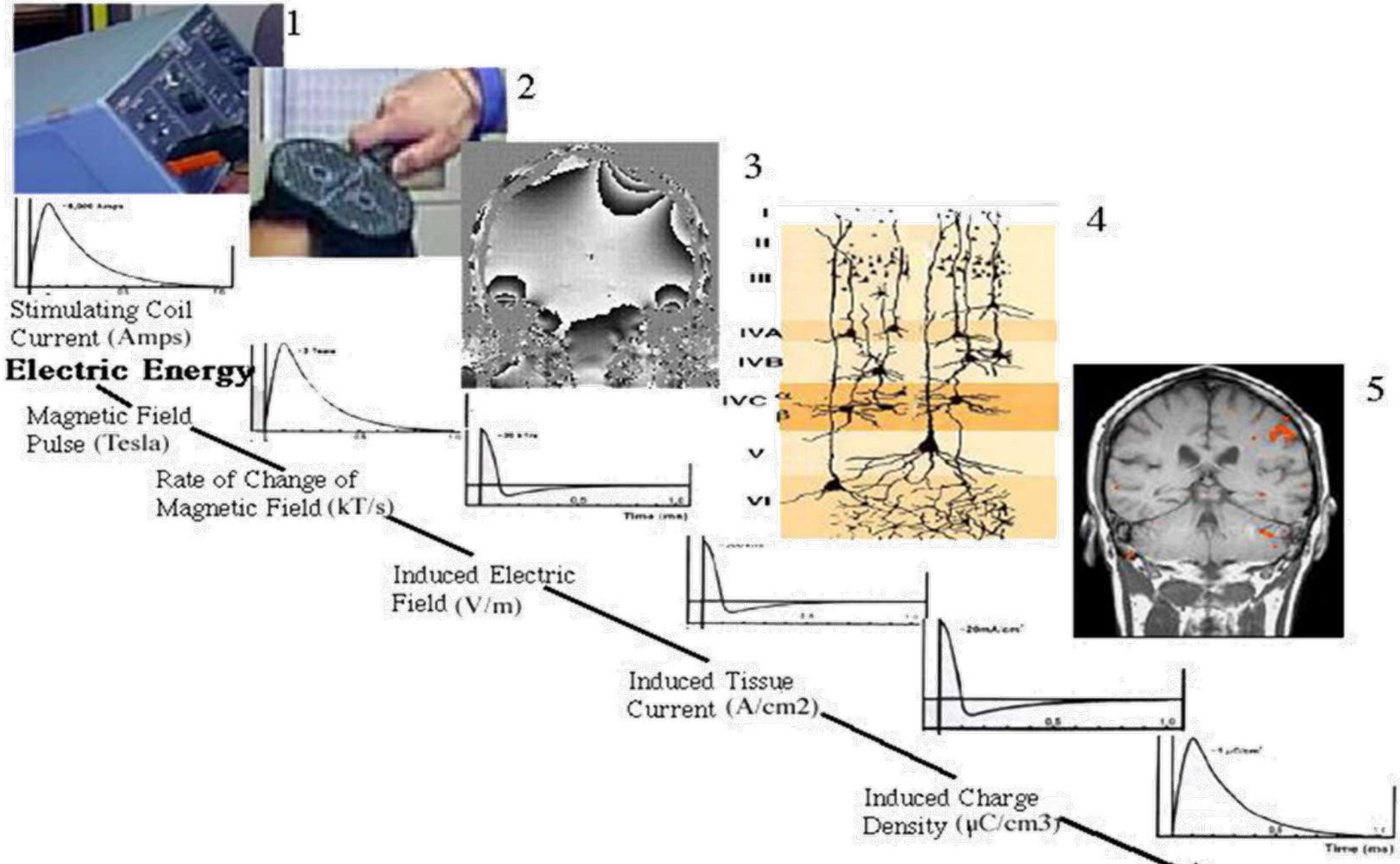
Focal

Noninvasive

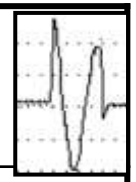
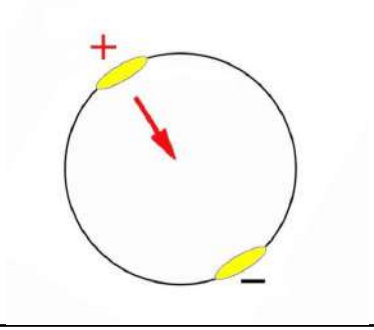
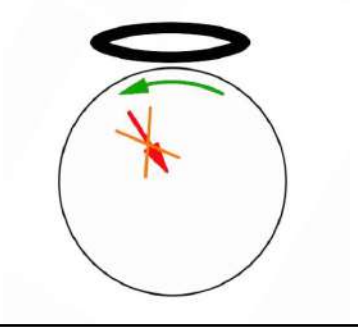
Nonconvulsive



stimulate the prefrontal cortex to

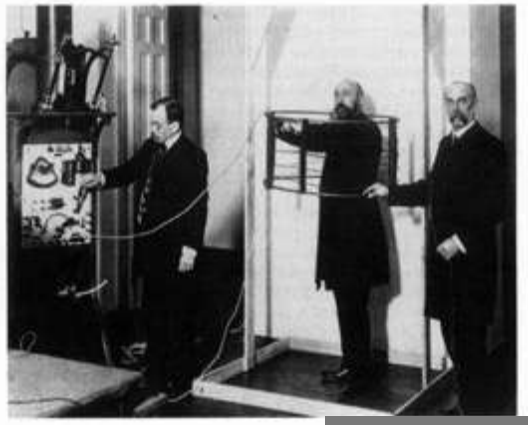

1
2
3
4
5
Stimulating Coil
Current (Amps)
Electric Energy
Magnetic Field
Pulse (Tesla)
Rate of Change of
Magnetic Field (kT/s)
Induced Electric
Field (V/m)
Induced Tissue
Current (A/cm2)
Induced Charge
Density (μC/cm3)
Behavioral Effect
I
II
III
IVA
IVB
IVC α
β
V
VI

How do ECT and TMS differ?

	ECT 	TMS 
Direction of induced current	Radial 	Tangential 
Current reaches deep structures	Yes	No
Anesthesia Required	Yes	No
Seizure induced	Yes	No

Funny Pictures

Faraday, 1831



d'Arsonval(1896/1911)

Magnusson & Stevens, 1911

Thompson, 1910

Modern Stimulator

Barker, 1984

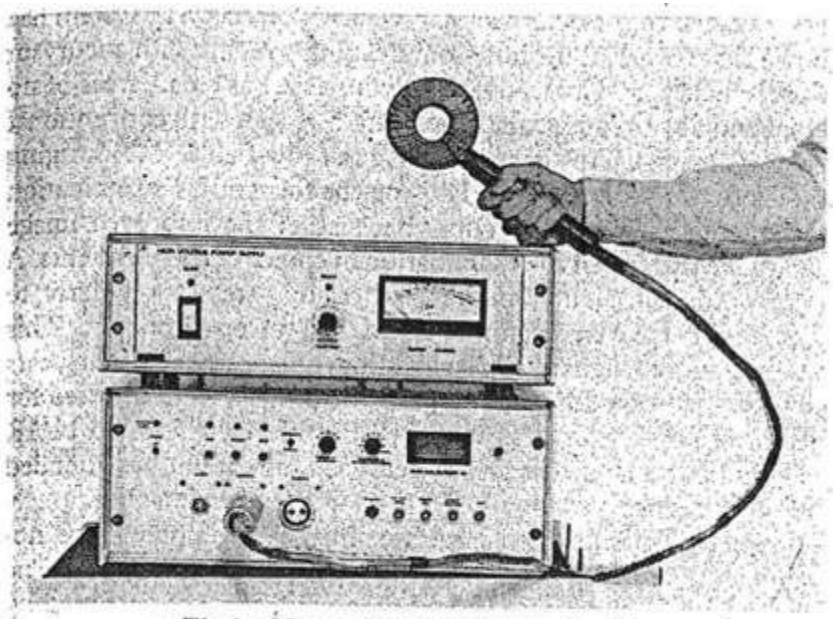


Fig 1—Magnetic stimulator and coil.

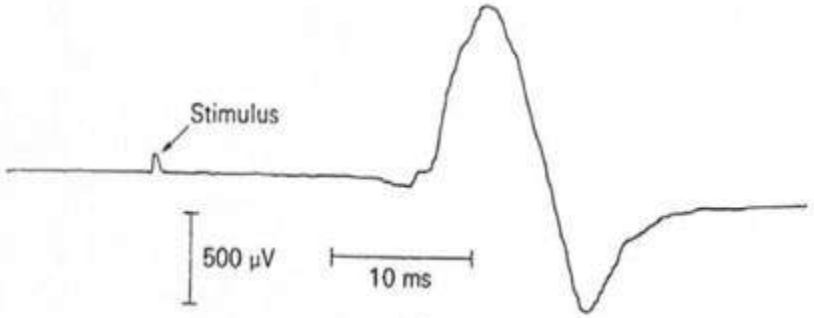


Fig. 1. Action potential (surface electrodes) in forearm flexor muscles, after a magnetic stimulus to the opposite motor area.

Physics of TMS: Electromagnetic induction

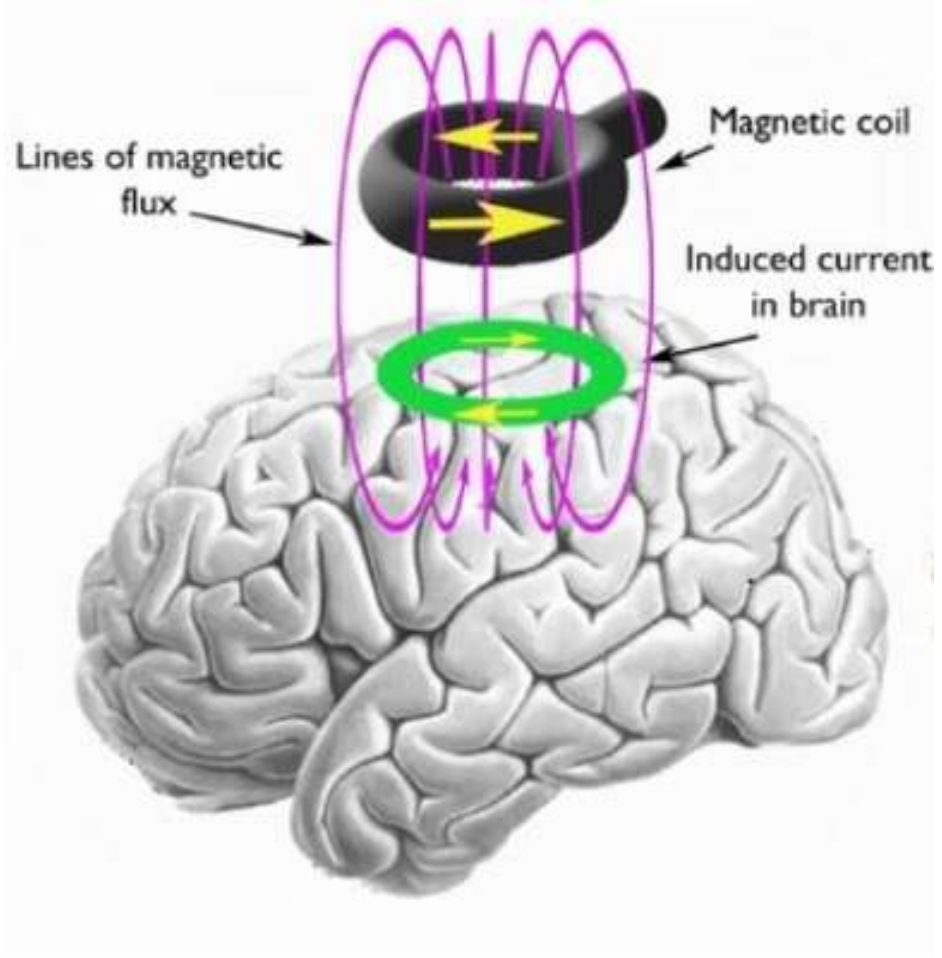
Pulsed electric current in a coil

↓

Fluctuating magnetic field

↓

Induced eddy currents in a nearby conductor



Biot Savart Law

Faraday's law

Ohm's law

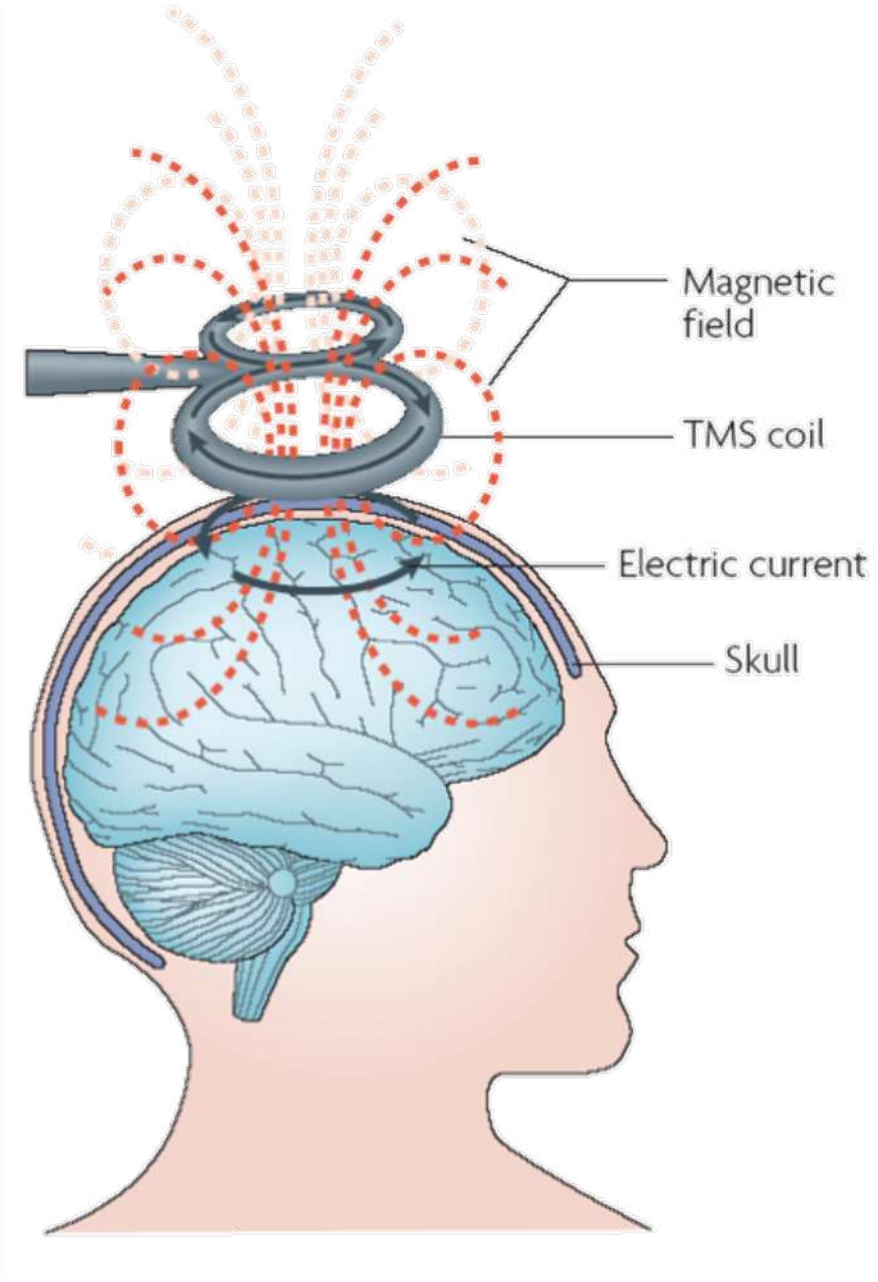
Fitzgerald, 2018: https://psychscenehub.com/

Mechanism of Action

- **Electrical pulses** of
  - sufficient strength,
  - short enough duration and
  - rapidly changing

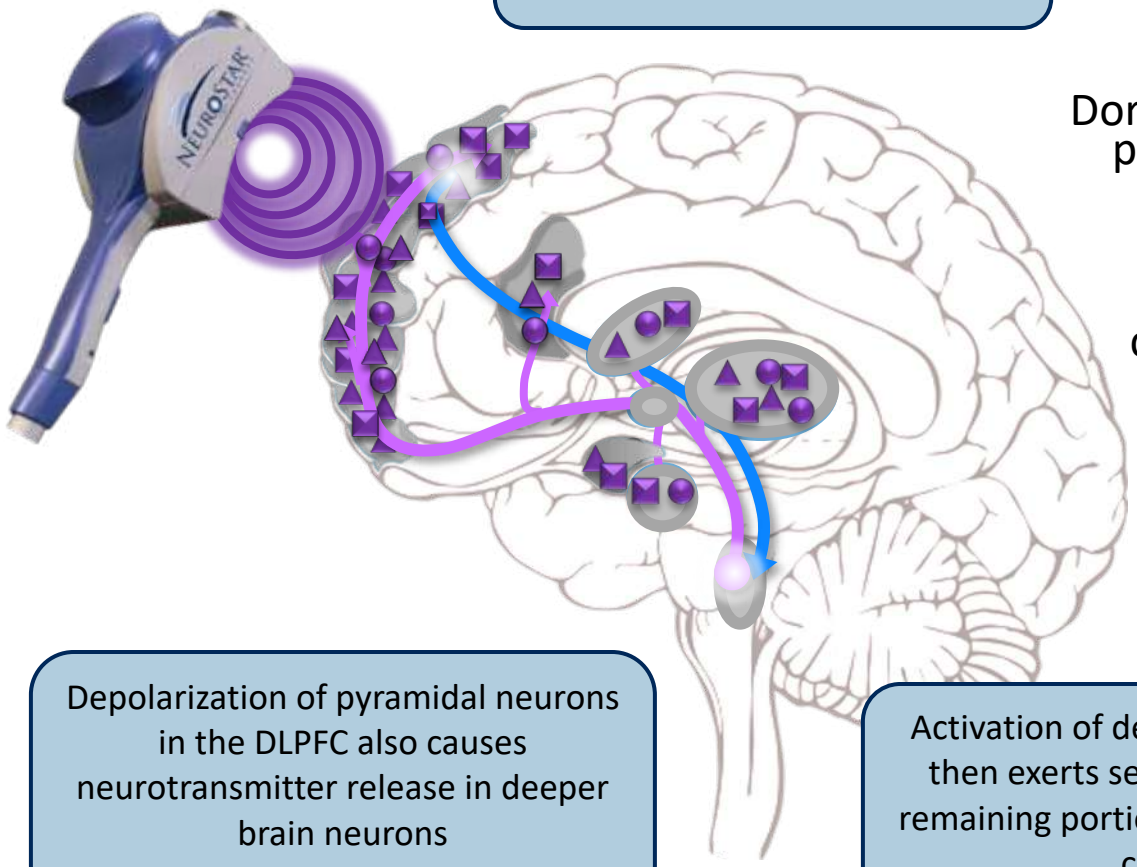
- **Rapidly changing magnetic pulses penetrate scalp and skull to reach the brain**

- These pulses induce a **secondary ionic current** in the brain leading to **neuronal depolarization**



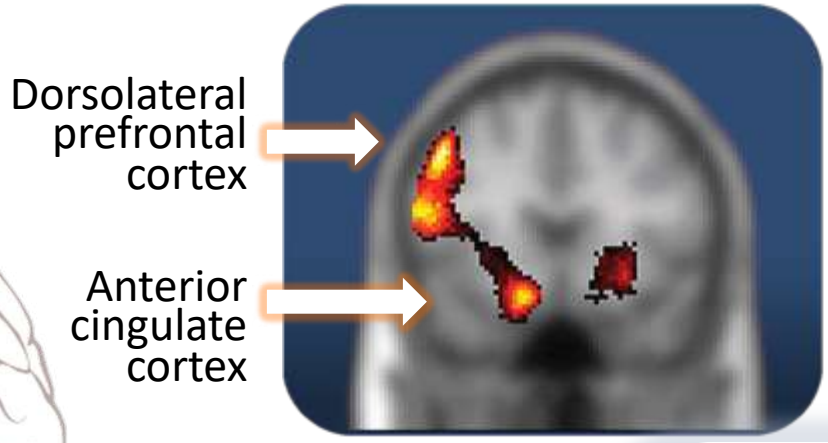
Mechanism of Action - TMS

Depolarization of neurons in the DLPFC causes local neurotransmitter release



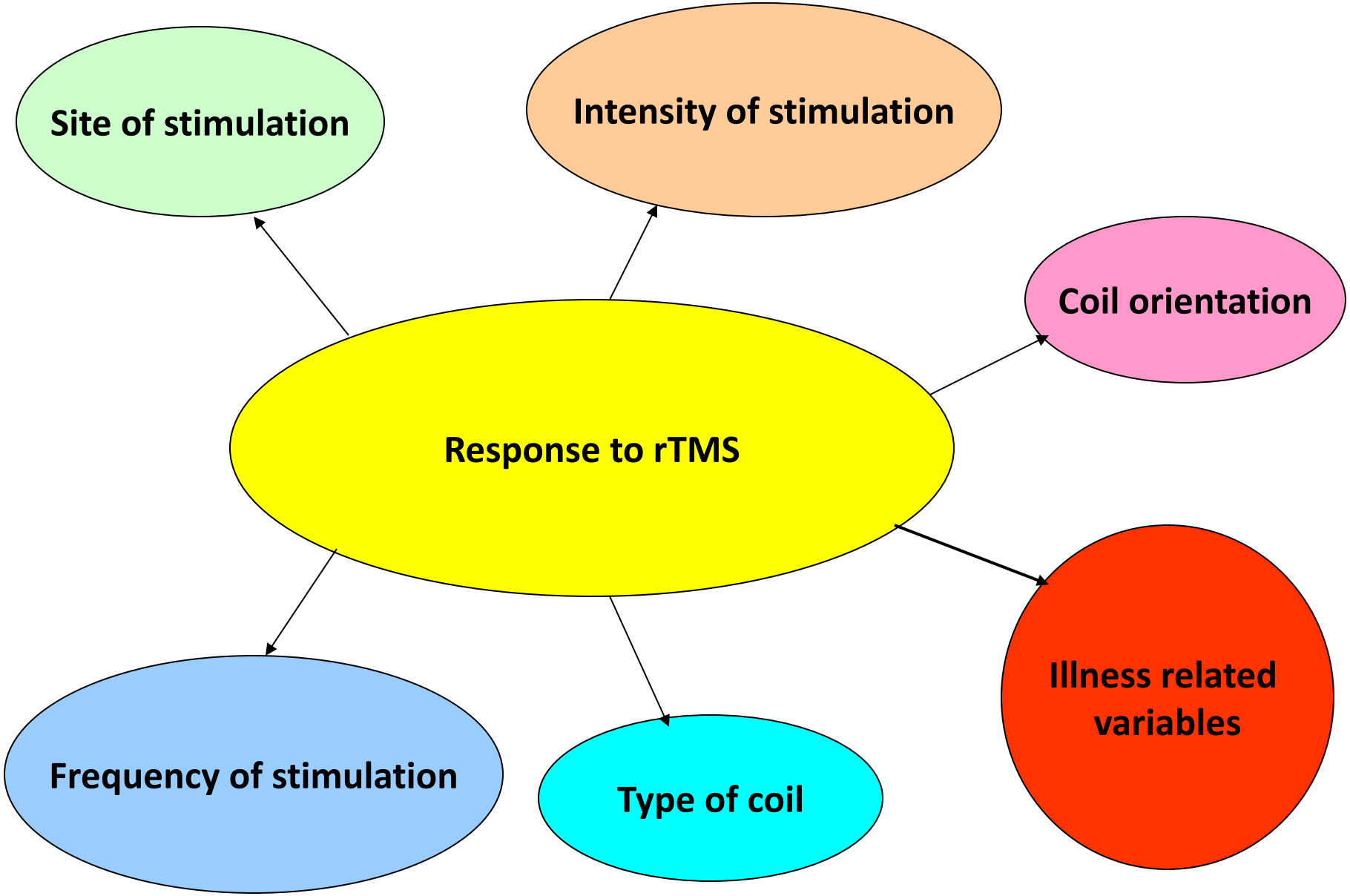
Depolarization of pyramidal neurons in the DLPFC also causes neurotransmitter release in deeper brain neurons

Activation of deeper brain neurons then exerts secondary effects on remaining portions of targeted brain circuits



Kito (2008) *J Neuropsychiatry Clin Neurr*

These effects are associated with improvements in target symptoms


Site of stimulation
Intensity of stimulation
Coil orientation
Response to rTMS
Frequency of stimulation
Type of coil
Illness related variables

Types of coils: Quest for depth

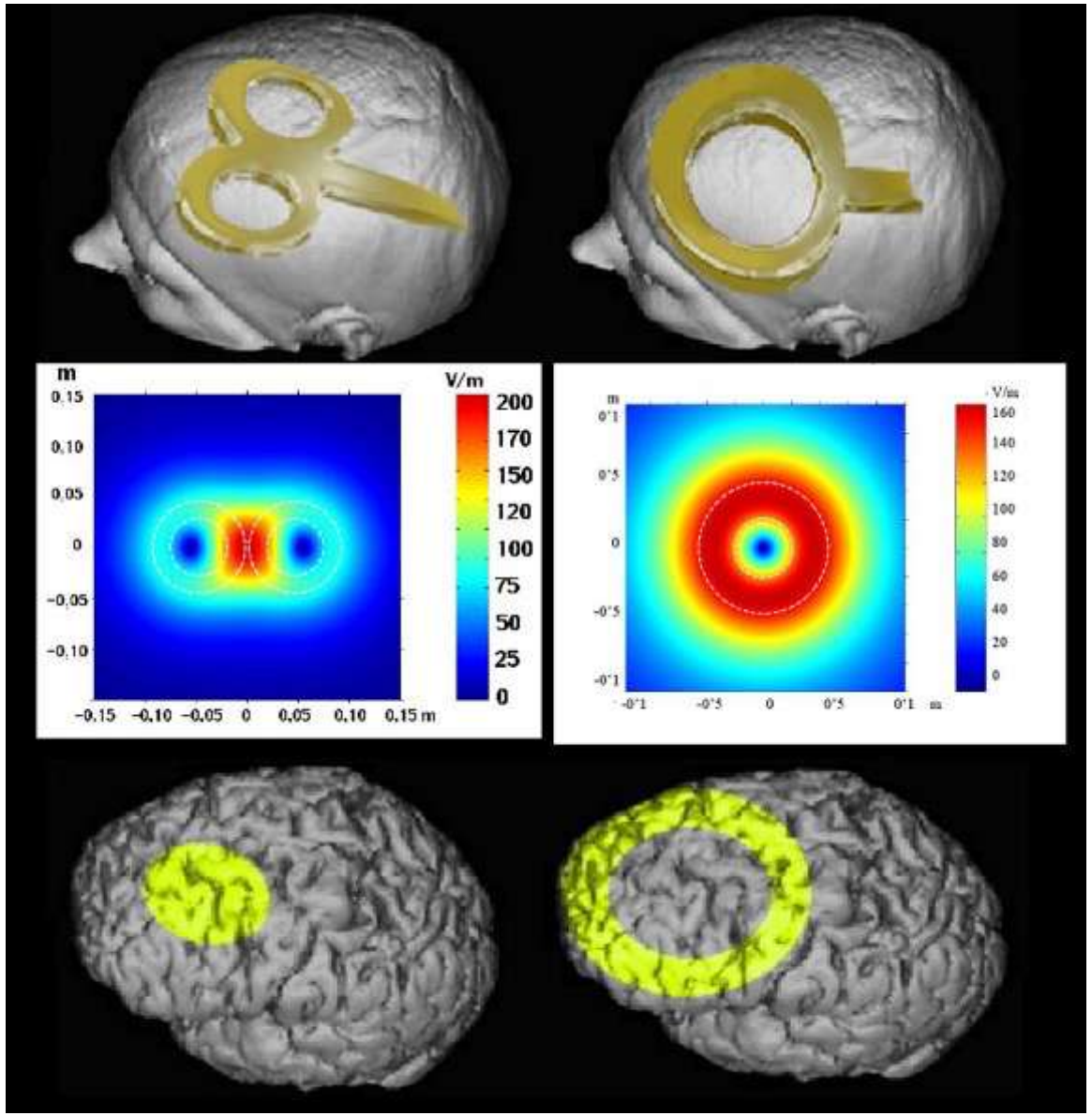
(A) Circular

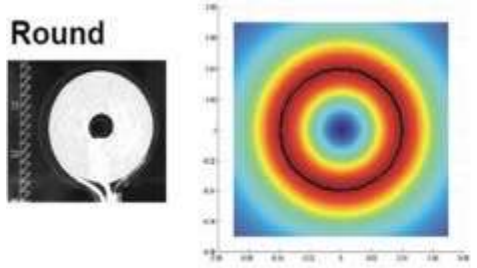
(B) Figure-of-8

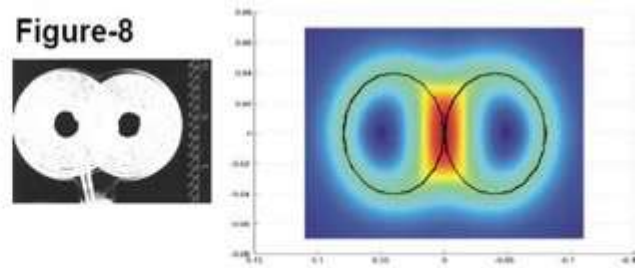
(C) Bat-wing

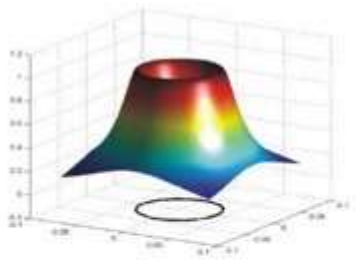
(D) Double Cone

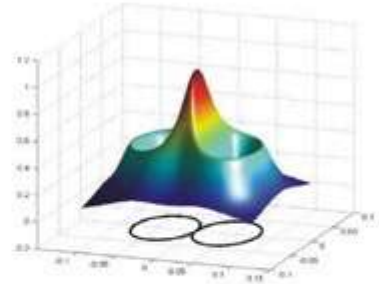
Spatial resolution: Coil Shape









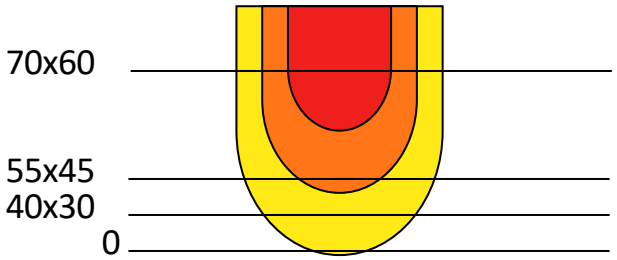


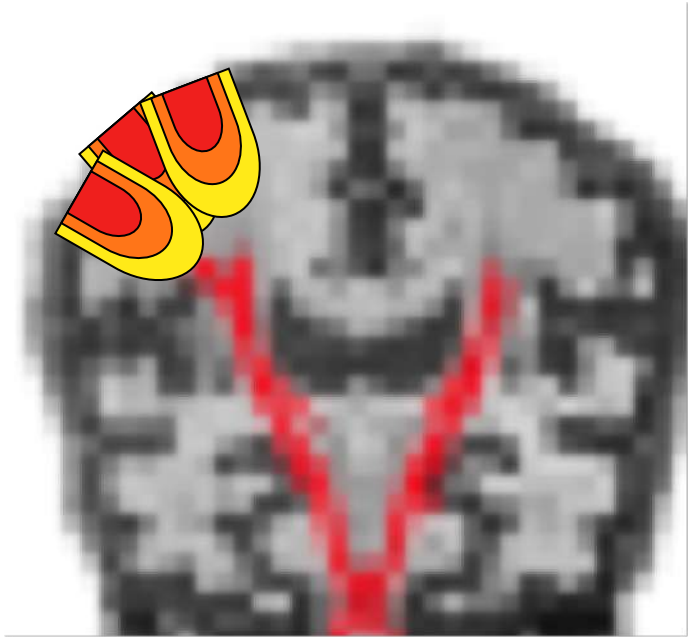
- Field has "trough shape"
- Rather unfocal

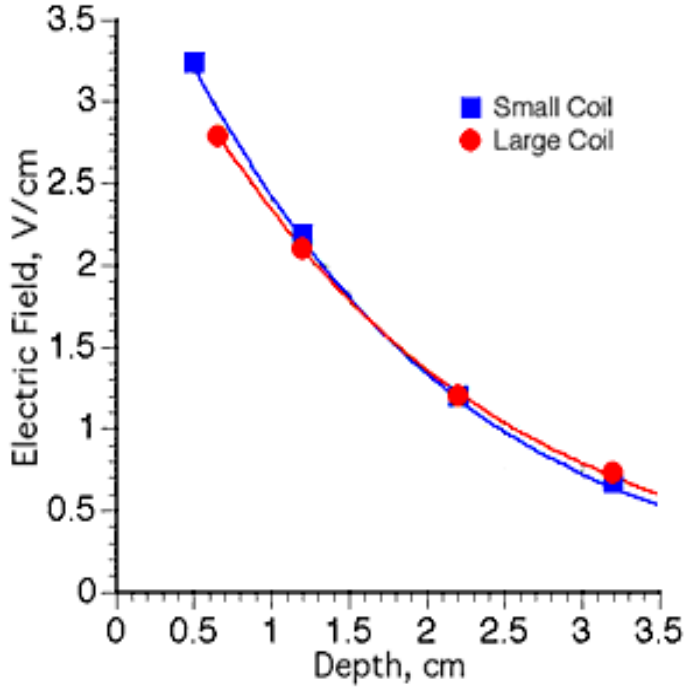
- Field peaks underneath the intersection of the two wire loops

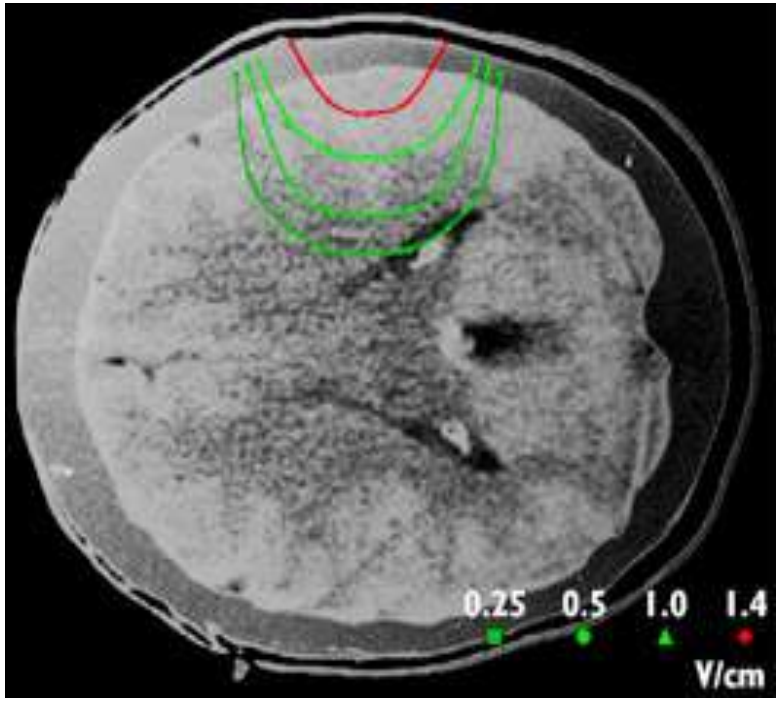
Geometry of coil determines the focality of magnetic field and of the induced current - hence also of the targeted brain area

Stimulation Depth



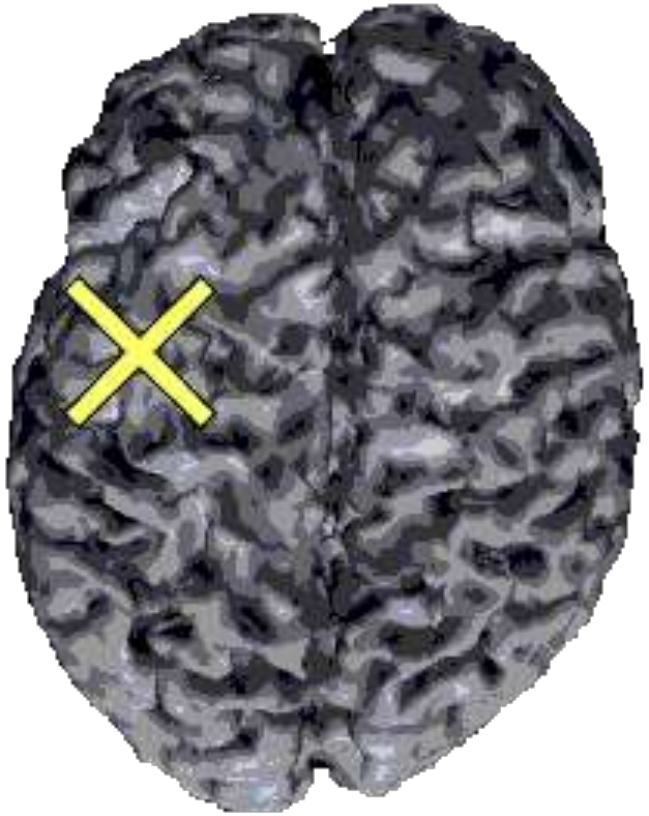


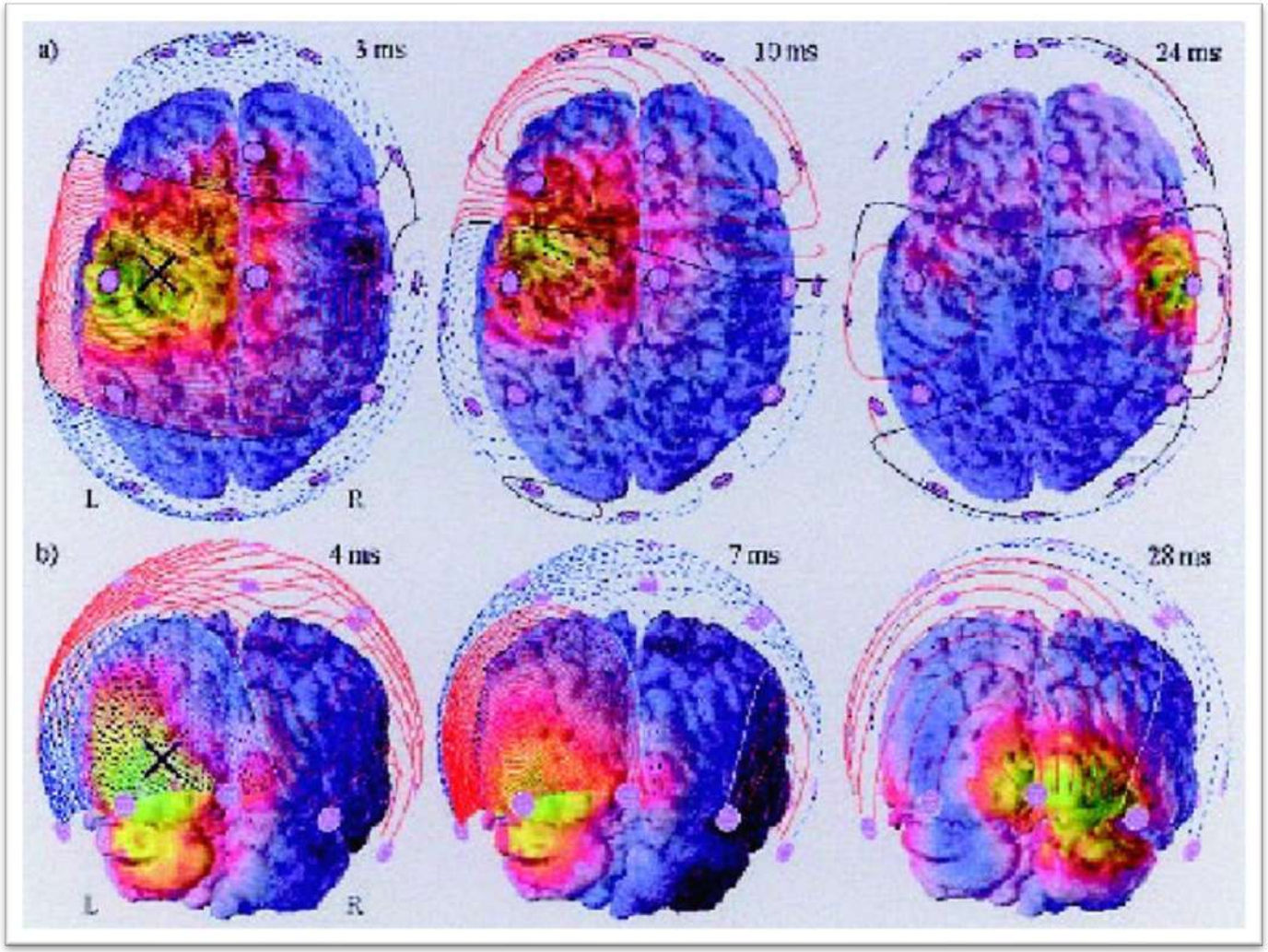




Cannot stimulate medial or sub-cortical areas

Spread of Activation

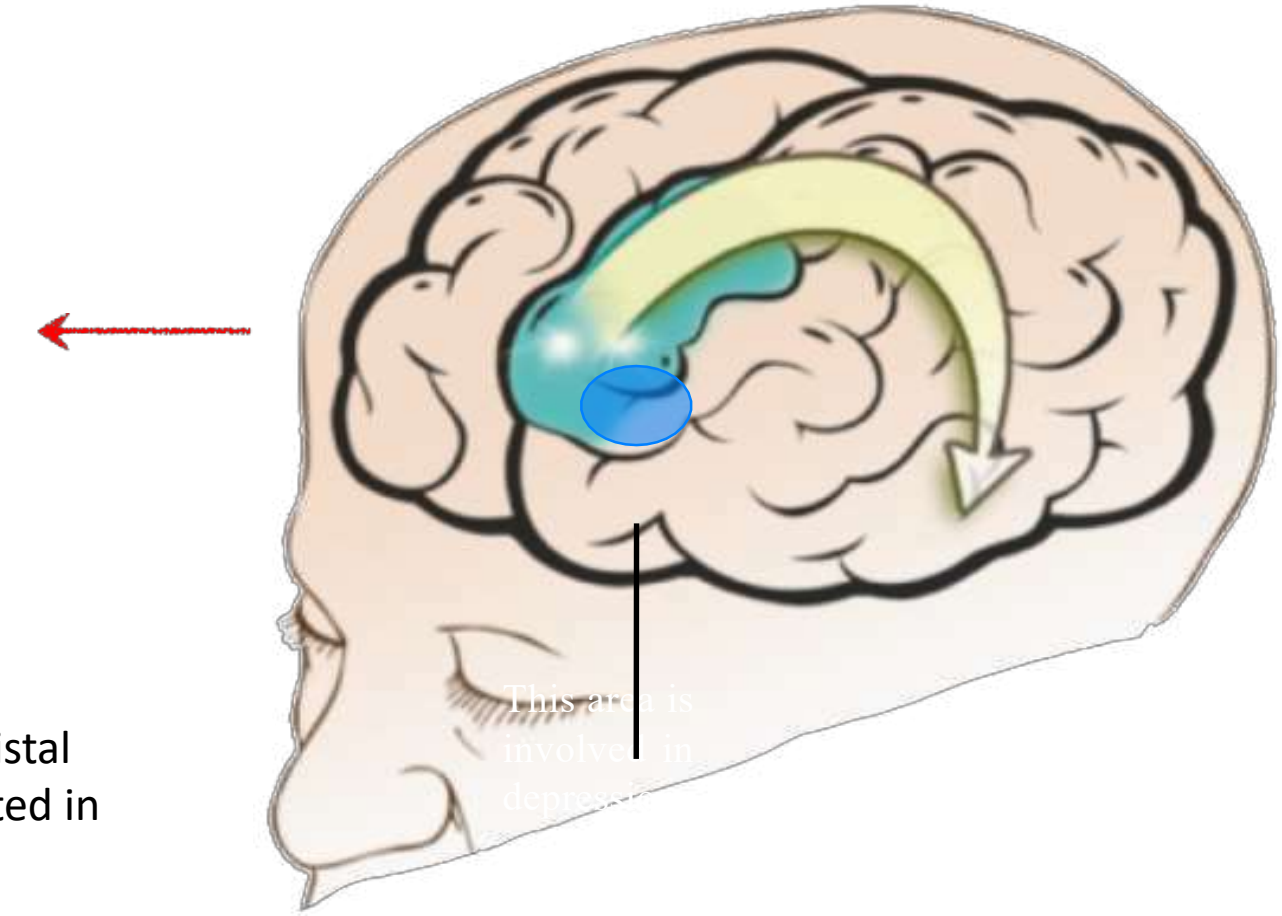




Brain Connectivity

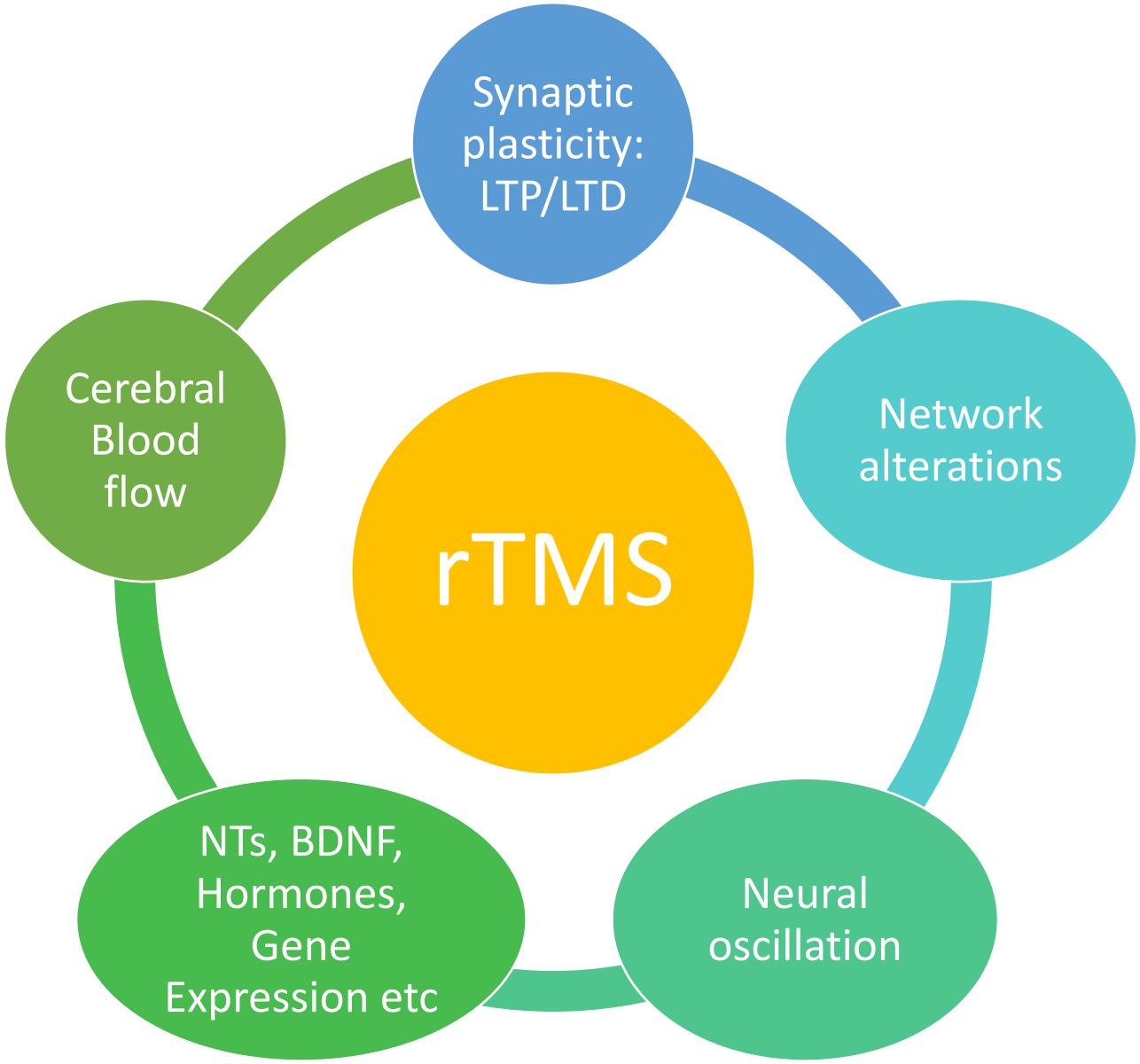
TMS

- Takes advantage of the natural brain circuitry
- Dorsolateral prefrontal cortex: DLPFC –(lateral aspect of the middle frontal gyrus)
- Interconnected with limbic structures that play a role in mood modulation & depression



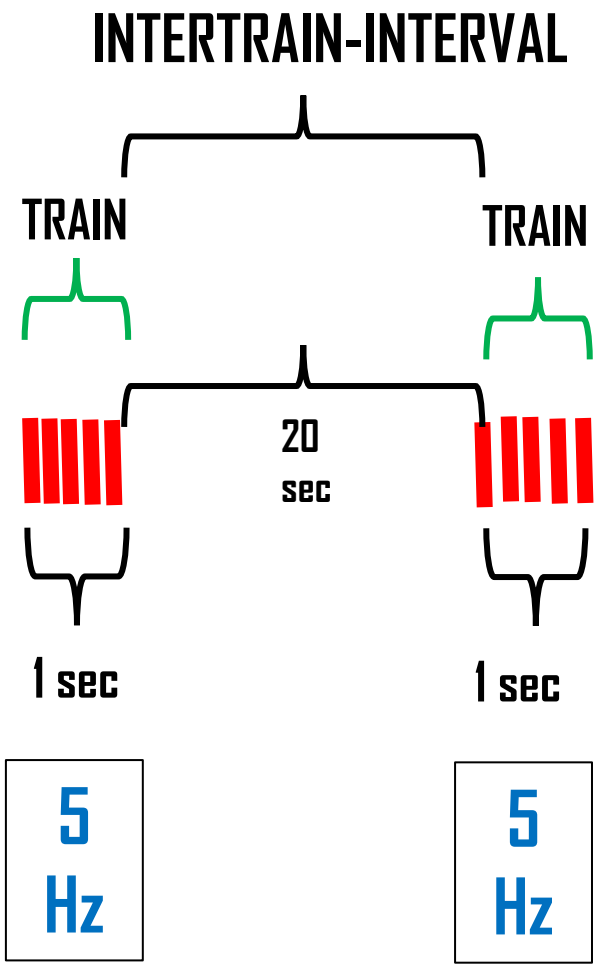
Effect neural activity at the site of stimulation as well as distal regions that are interconnected with the DLPFC – implicated in mood, motivation and arousal

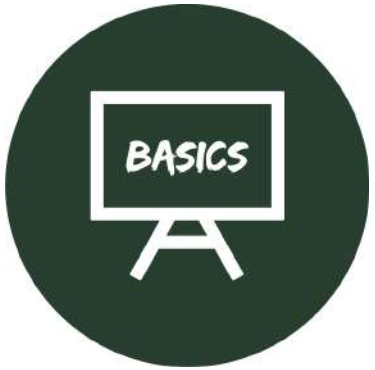
Mechanism of rTMS



Stimulation is Focal
but
Action is not local

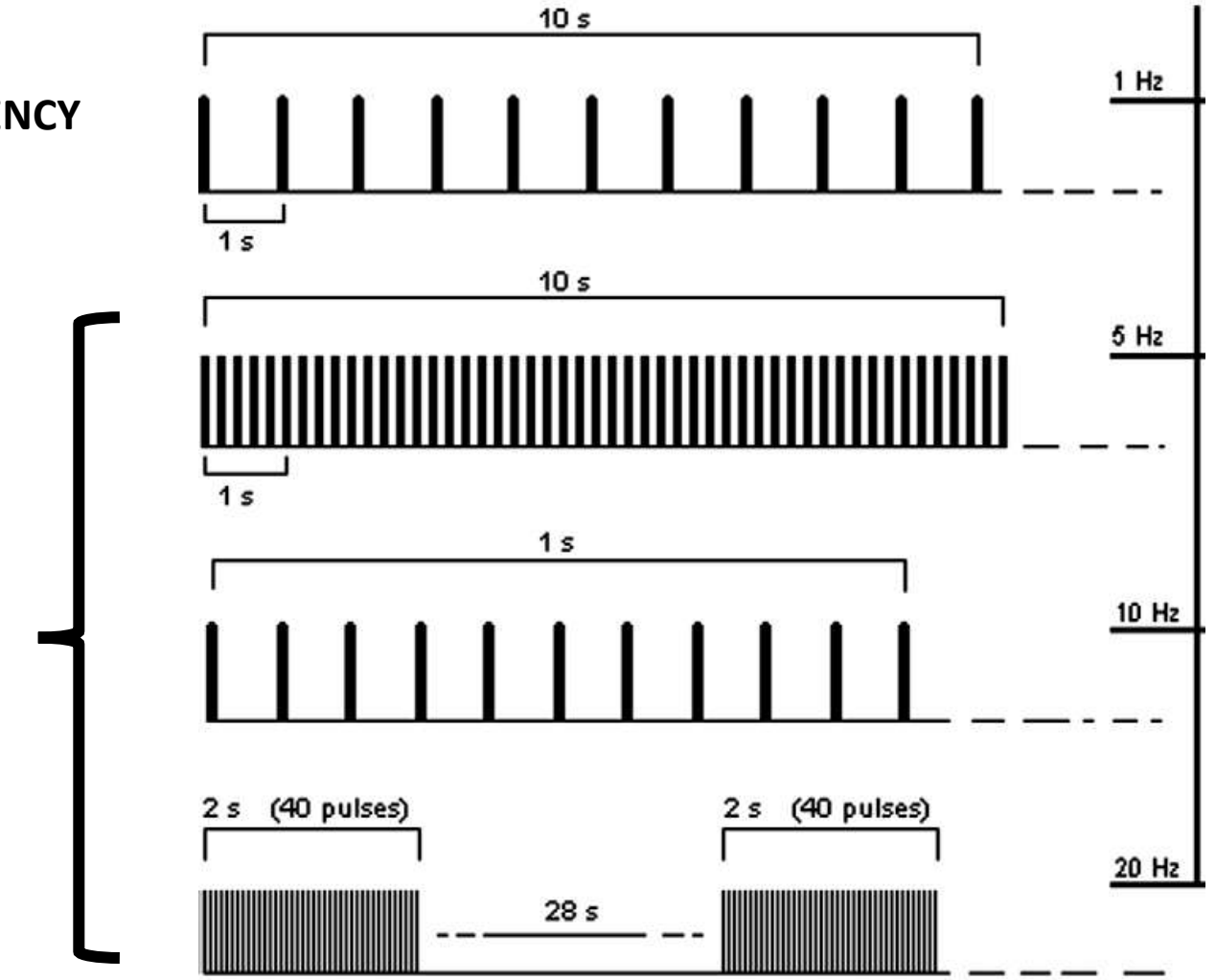
SOUND OF CLICK: **ONE PULSE**





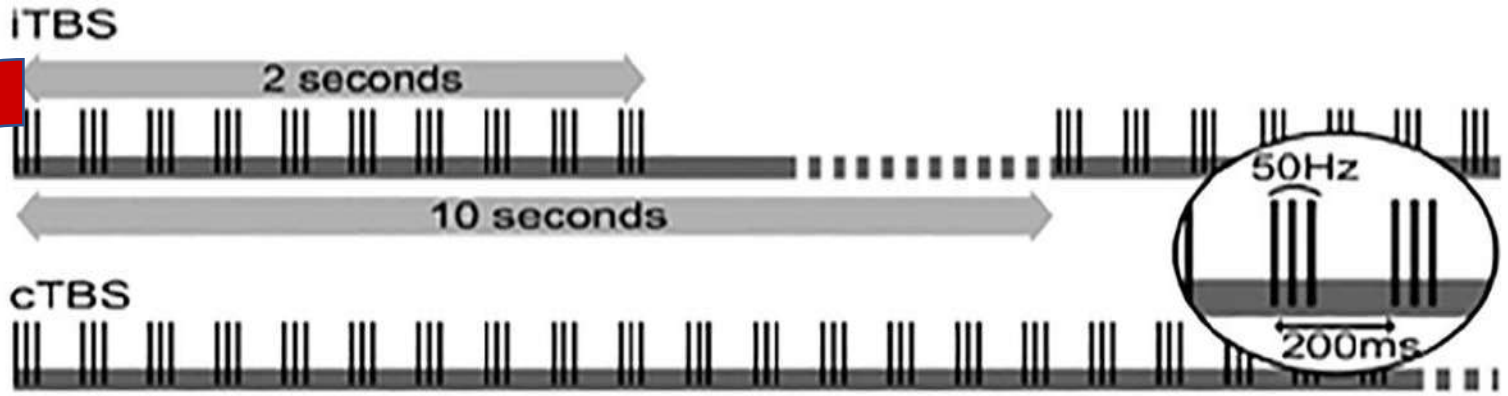
1 Hz: LOW FREQUENCY

> 5 Hz: HIGH FREQUENCY



Patterned TMS

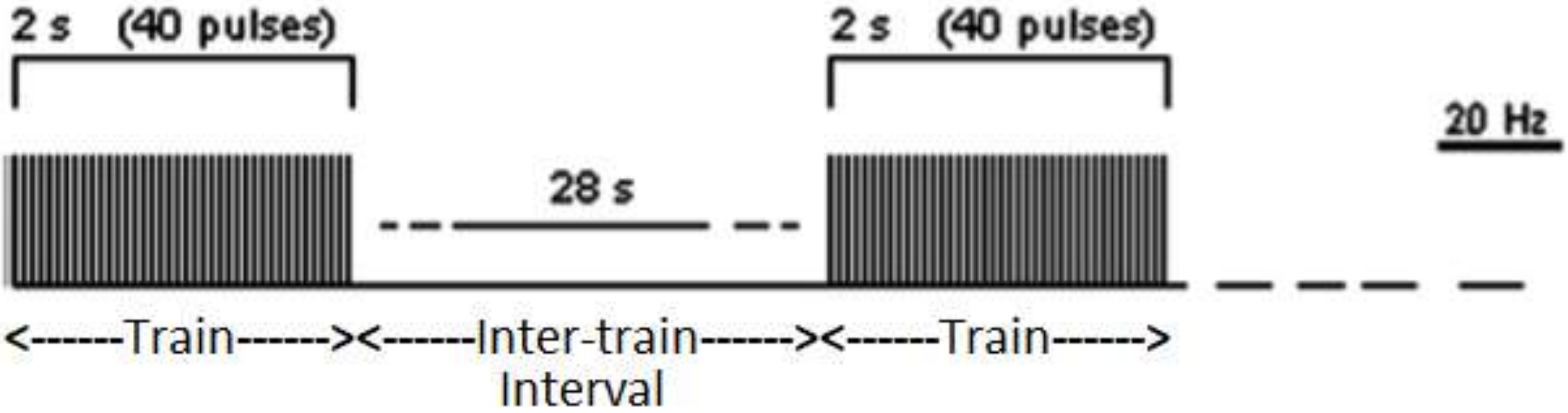
TBS (i vs c)



= HF rTMS

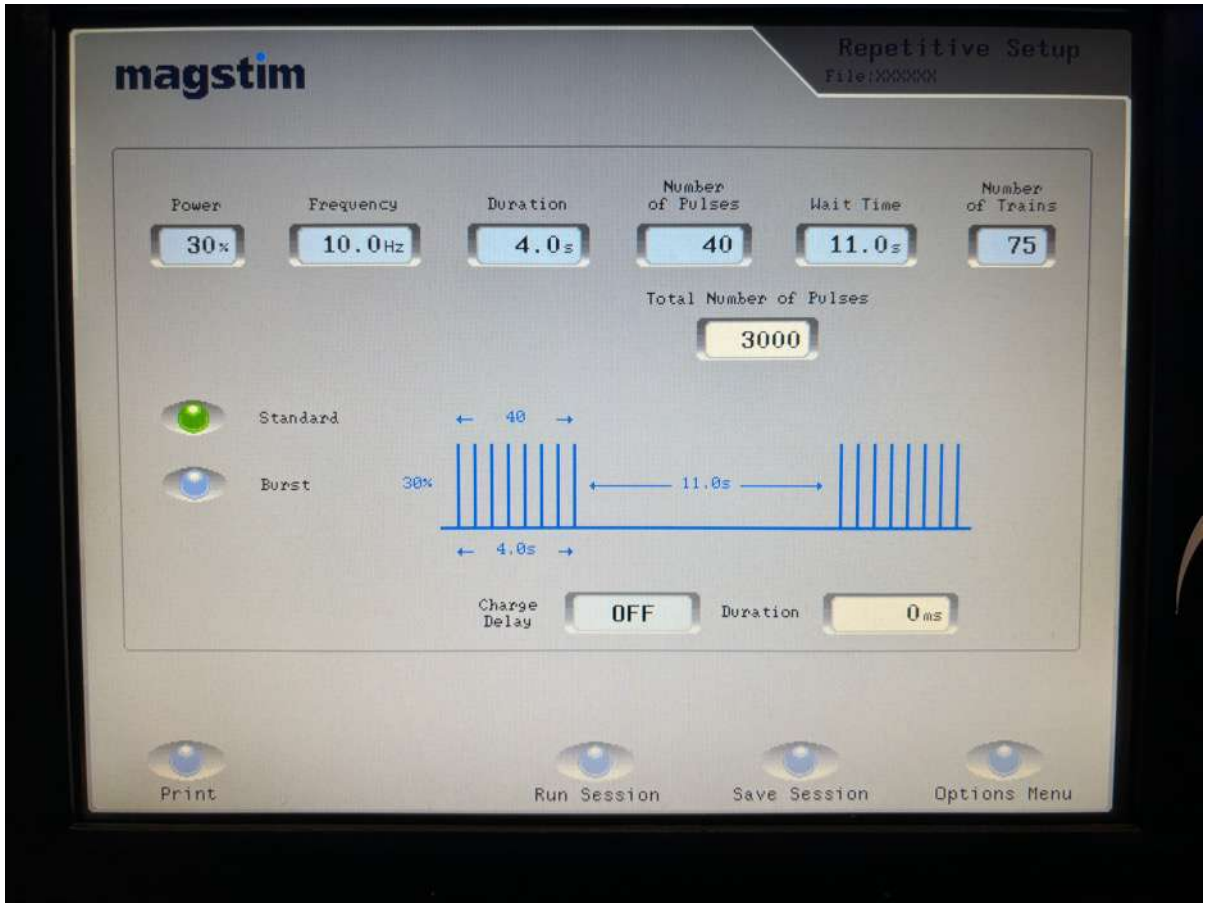
= LF rTMS

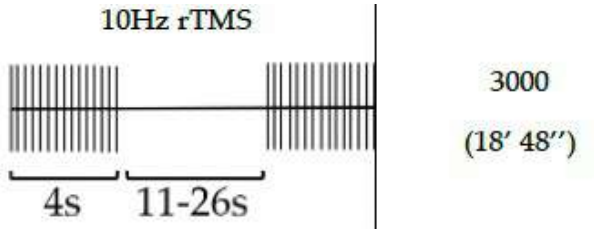
Frequency



- High frequency typically given in bursts (trains) interrupted by pauses (Inter-train interval, ITI) to prevent seizure induction.

Stimulus parameters- UI





- Frequency- 10.0Hz
- Duration- 4.0s
- Number of Pulses- 40
- Wait time- 11 secs
- Number of Trains- 3000/40 = 75 trains

- 15s (trains+ ITT)
- 75*15= 1125 secs
  = 18.75 mins (18 mins 45 secs)

Patterned rTMS

More efficient protocols, which can produce consistent aftereffects with fewer stimuli or lower stimulus intensity were needed

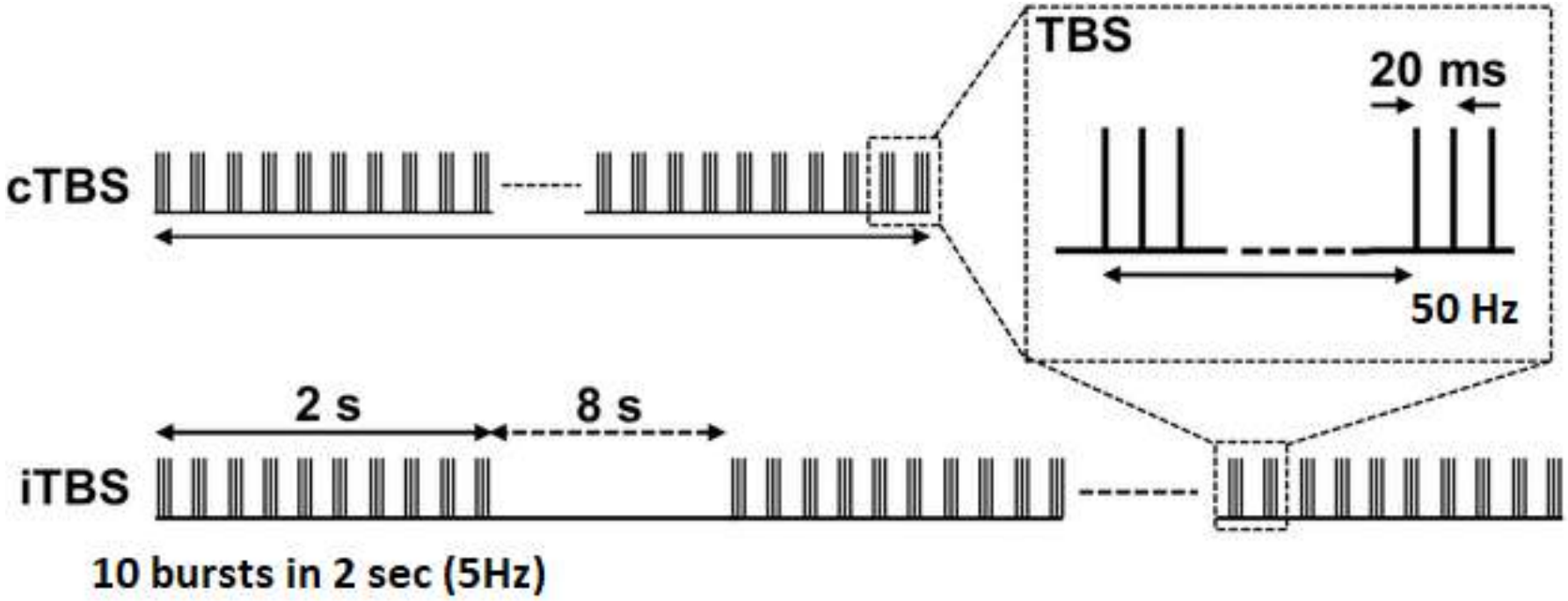
Patterned rTMS protocols introduced:

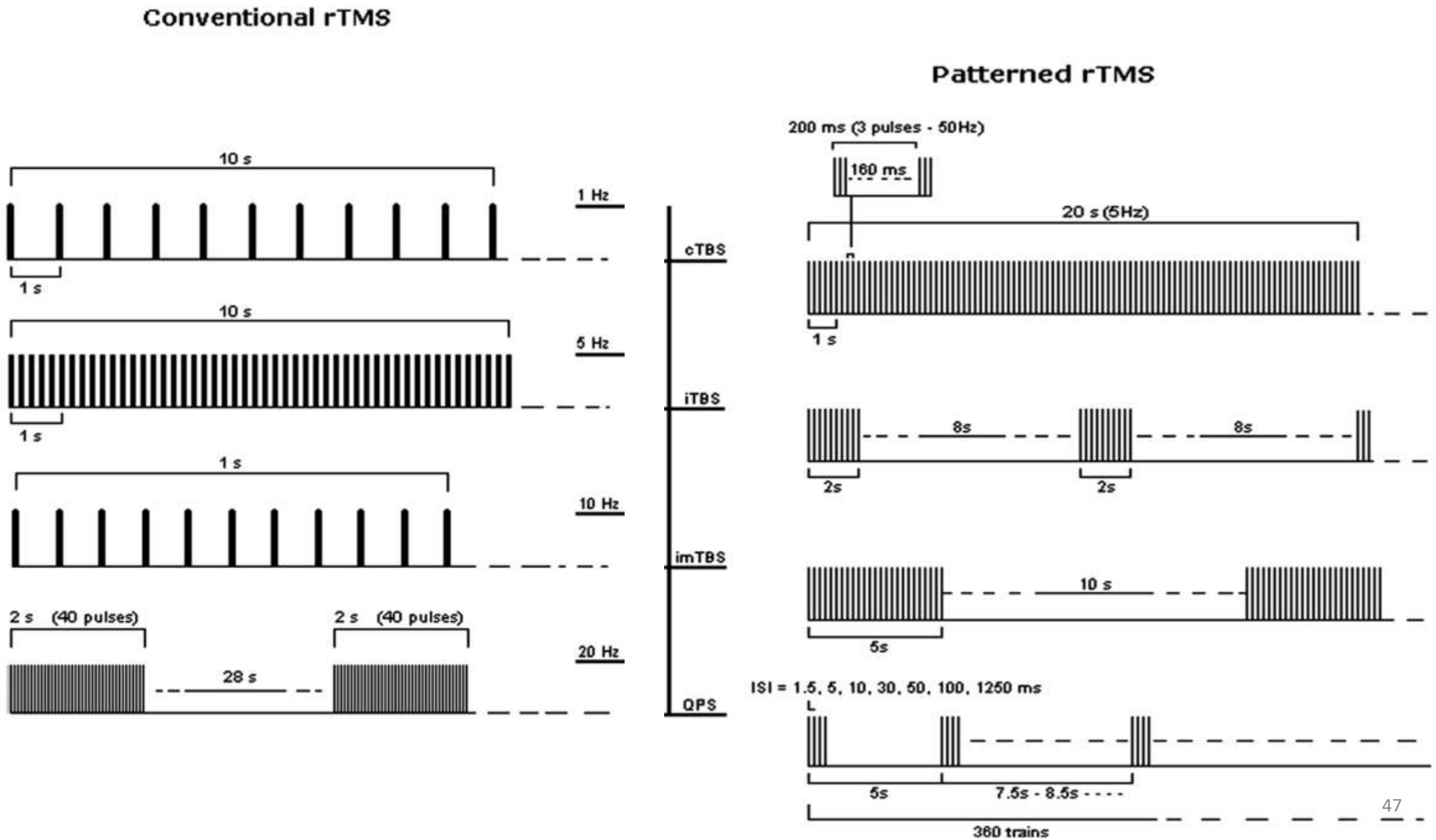
theta burst stimulation (TBS)	paired-pulse rTMS (pp rTMS)	quadri-pulse stimulation (QPS)

Patterned TMS

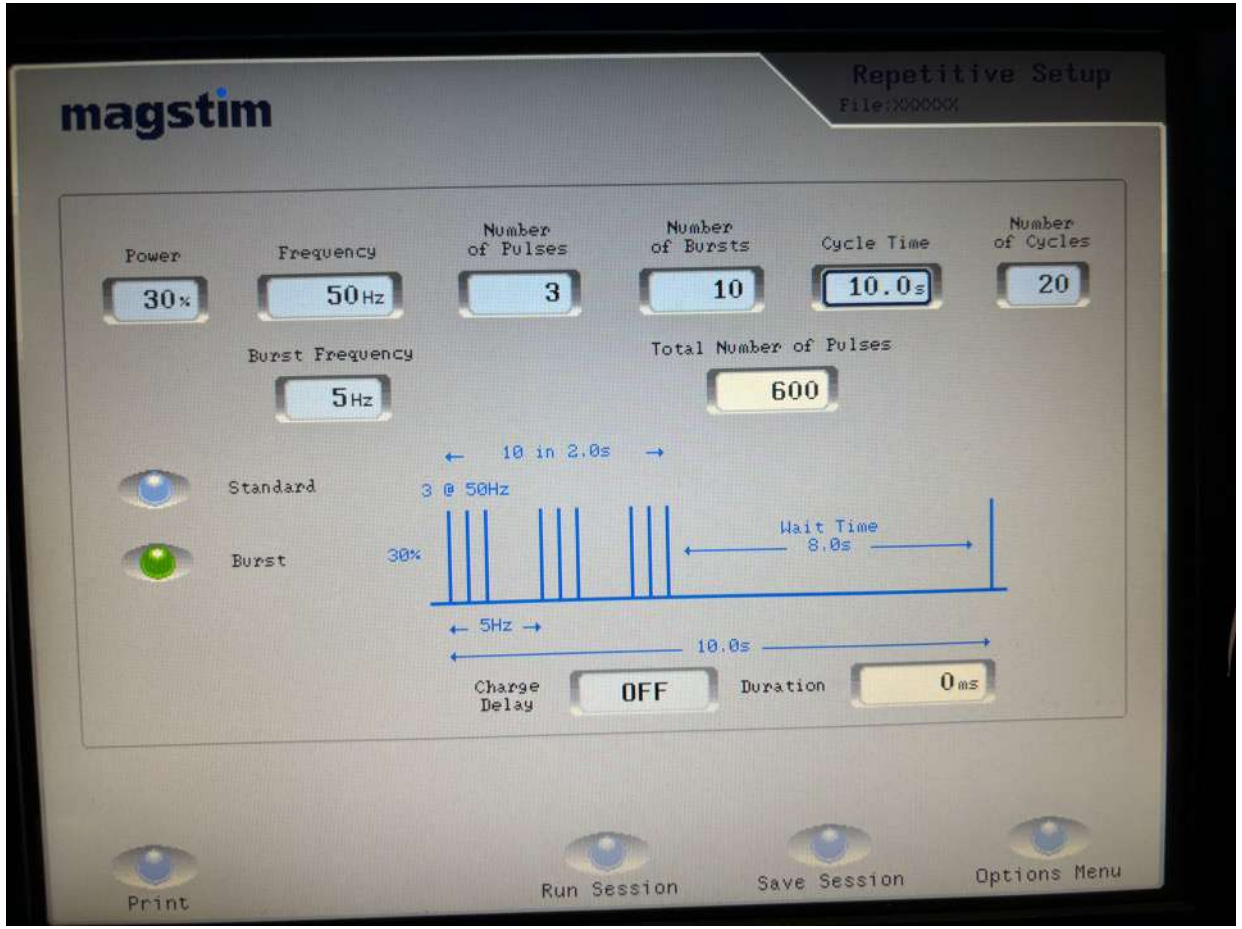
Theta burst stimulation (TBS): Shorter sessions and possibly more robust plasticity as compared to conventional rTMS

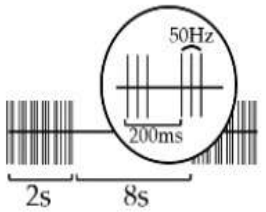
- Short bursts of 50 Hz rTMS given at 5 Hz
- **cTBS** – continuous; inhibitory to underlying cortex
- **iTBS** – intermittent; excitatory to underlying cortex




Conventional rTMS
10 s
1 Hz
1 s
10 s
5 Hz
1 s
1 s
10 Hz
2 s (40 pulses)
2 s (40 pulses)
28 s
20 Hz
cTBS
iTBS
imTBS
QPS
Patterned rTMS
200 ms (3 pulses - 50Hz)
160 ms
20 s (5Hz)
1 s
8s
8s
2s
2s
10 s
5s
ISI = 1.5, 5, 10, 30, 50, 100, 1250 ms
5s
7.5s - 8.5s - - - -
360 trains

Stimulus parameters- UI



Intermittent Theta Burst 	600 (3′ 9″)	1/d (20–30 d)
	18000 (9′ 27″)	Accelerated: 10/d (5 d)

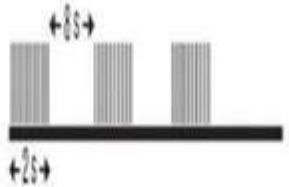
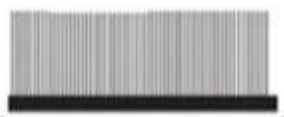
iTBS

- Frequency- 50.0Hz
- Burst Frequency- 5Hz
- Number of pulses- 3
- Number of Bursts- 10
- Cycle time- 10.0s (Wait time 8.0s)
- Number of Cycles- 20

  3*10*20= 600 pulses

- *Total time= 200 seconds*
- *3 mins 9 s*

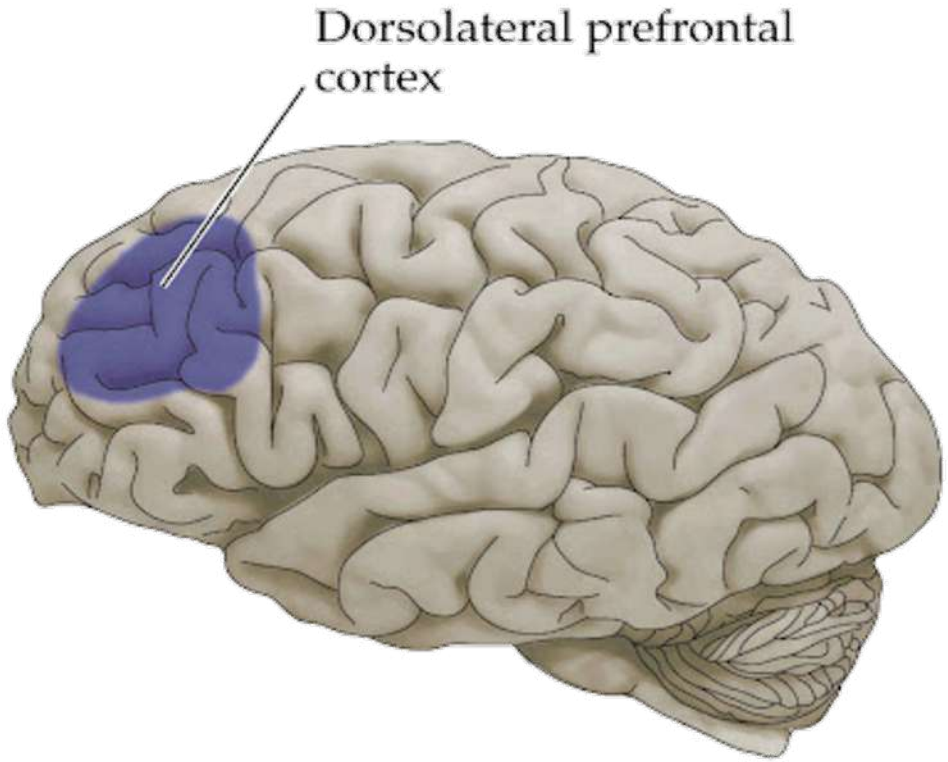
Typical rTMS parameters (Clinical setting)

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

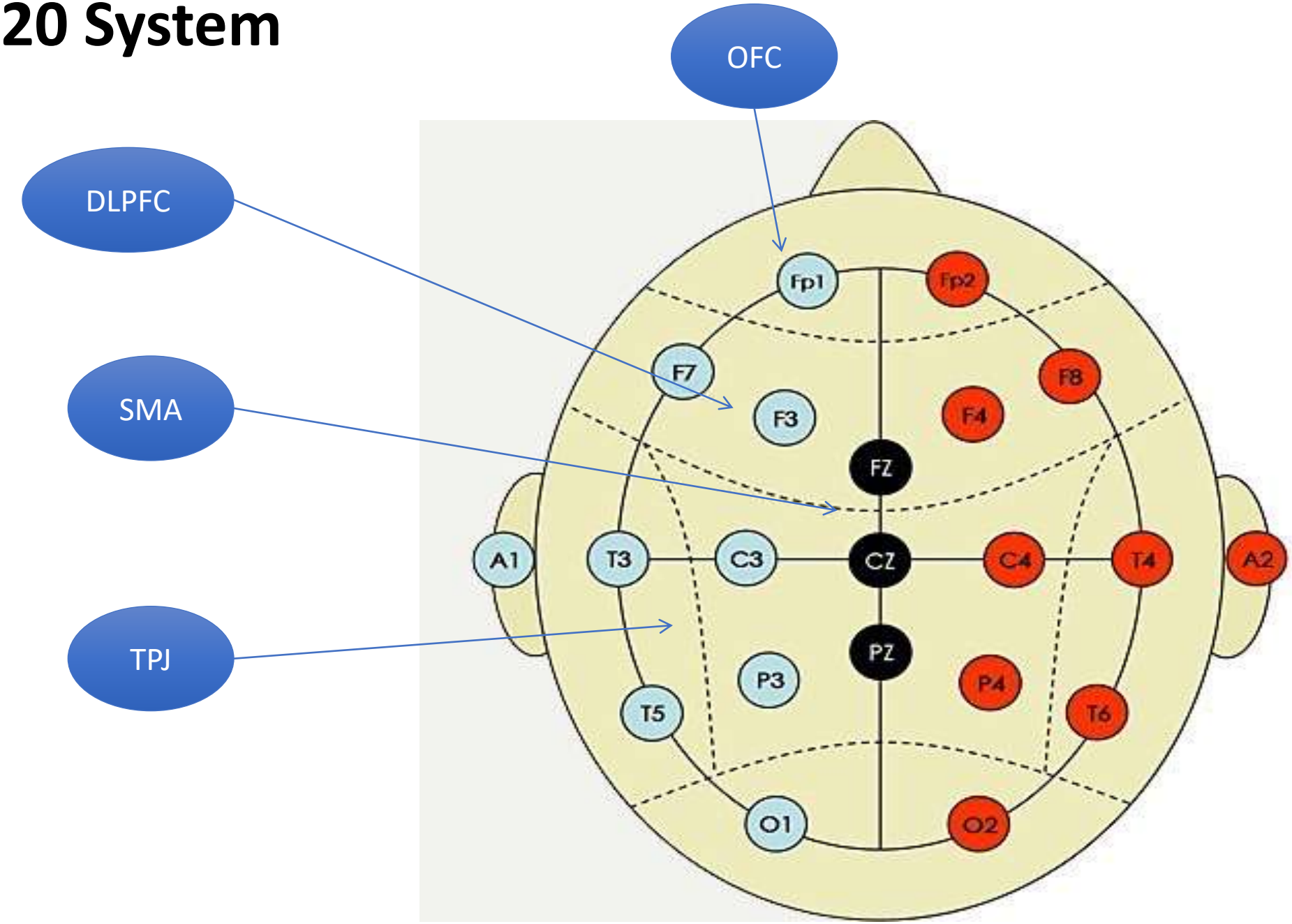
cTBS = continuous theta-burst stimulation; HF = high frequency; iTBS = intermittent theta-burst stimulation; LF = low frequency; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation.

Area of stimulation

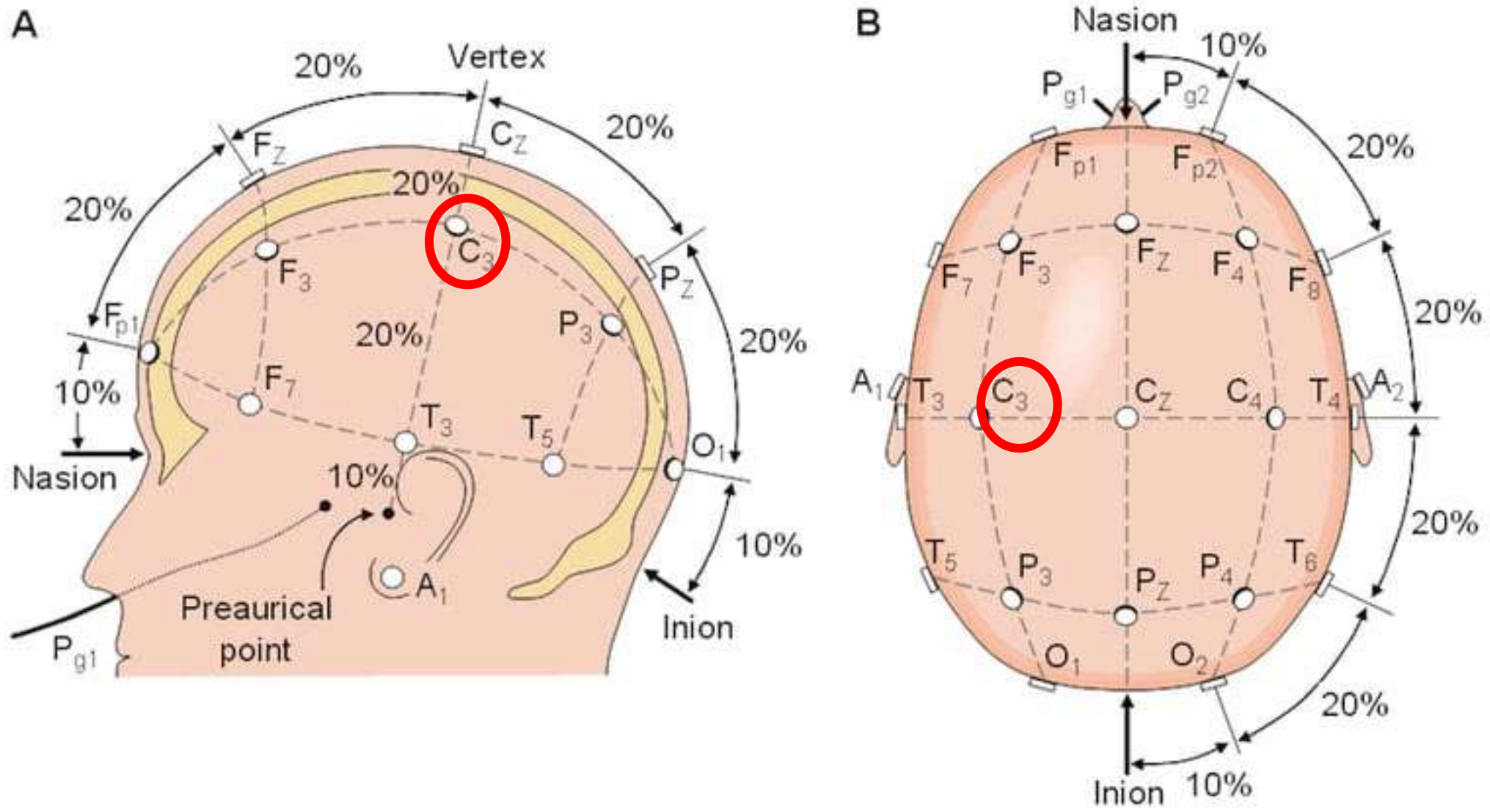
- **Dorsolateral prefrontal cortex**
- Supplementary Motor area
- Superior frontal gyrus
- Temporo-parietal junction
- Motor cortex
- Occipital cortex
- Cerebellum



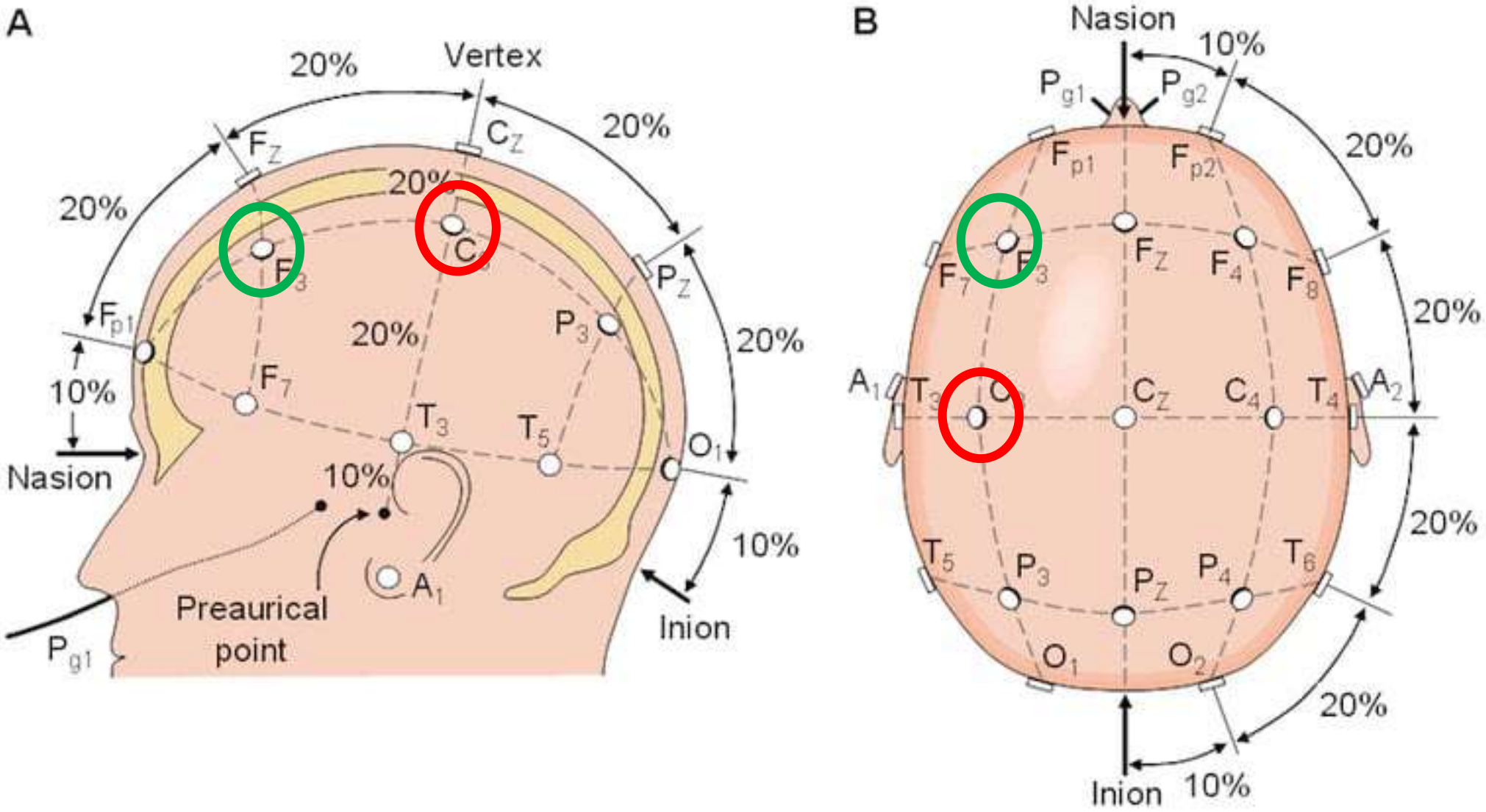
EEG 10-20 System



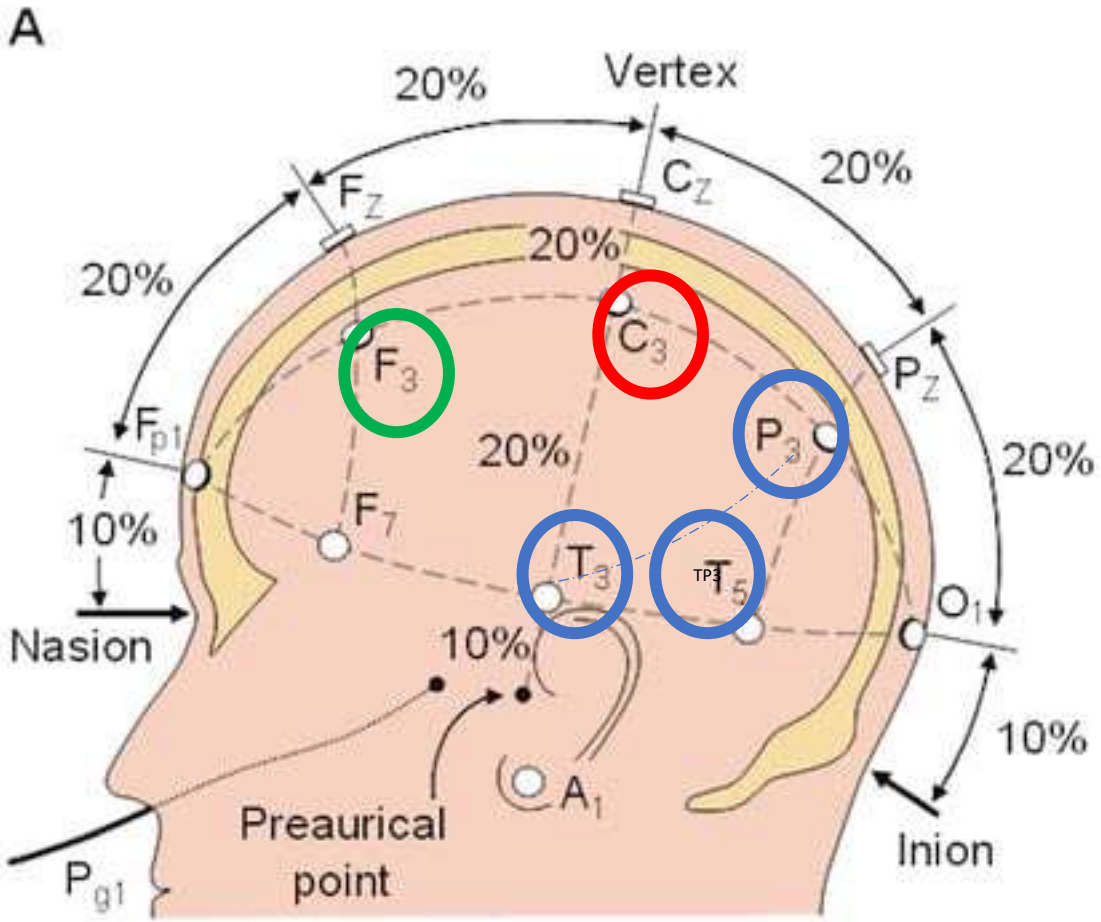
Motor cortex



DLPFC


A
20%
Vertex
20%
20%
20%
20%
20%
20%
10%
10%
10%
Nasion
Inion
Preaurical point
F_Z
C_Z
P_Z
F_3
C
F_{p1}
F_7
T_3
P_3
T_5
O_1
A_1
P_{g1}
B
Nasion
10%
P_{g1}
P_{g2}
20%
F_{p1}
F_{p2}
F_7
F_3
F_Z
F_4
F_8
20%
A_1
T_3
C
C_Z
C_4
T_4
A_2
20%
T_5
P_3
P_Z
P_4
T_6
O_1
O_2
20%
Inion
10%

TPC


A
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Vertex
20%
20%
20%
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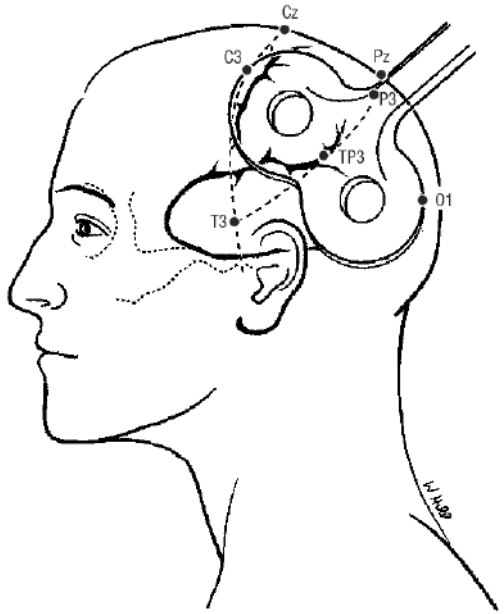
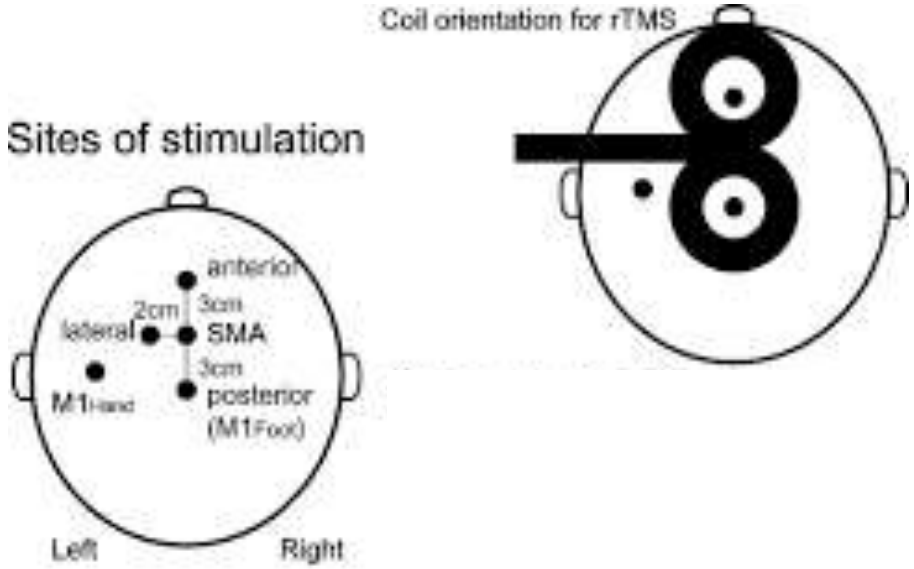
20%
20%
10%
10%
10%
Nasion
Inion
Preaurical point
F_Z
C_Z
P_Z
F_{p1}
F_3
C_3
P_3
F_7
T_3
T_5
TP3
O_1
A_1
P_{g1}


Cz
C3
Pz
P3
TP3
T3
O1

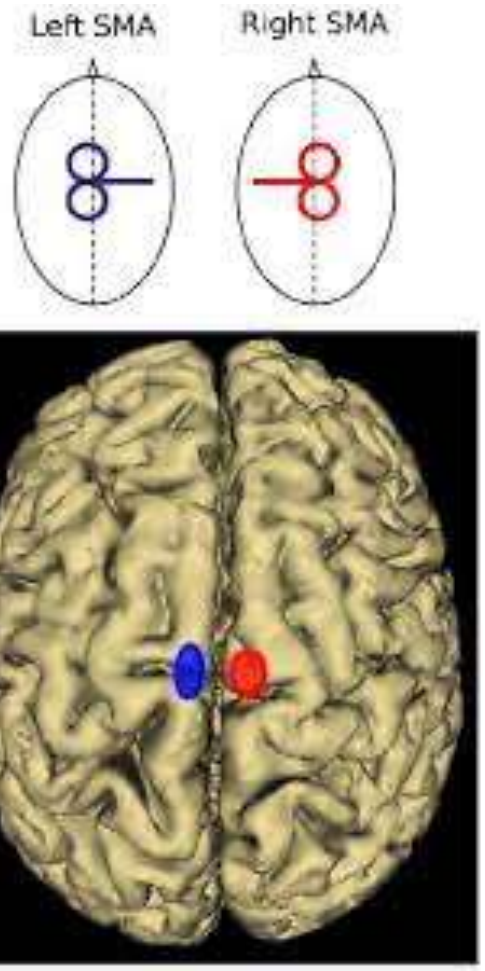
SMA- OCD



BRIEF RESEARCH COMMUNICATION

Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in treatment refractory patients with obsessive compulsive disorder

Nand Kumar, R. K. Chadda
Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India



OFC- OCD

Psychiatry Research 298 (2021) 113784

Contents lists available at ScienceDirect

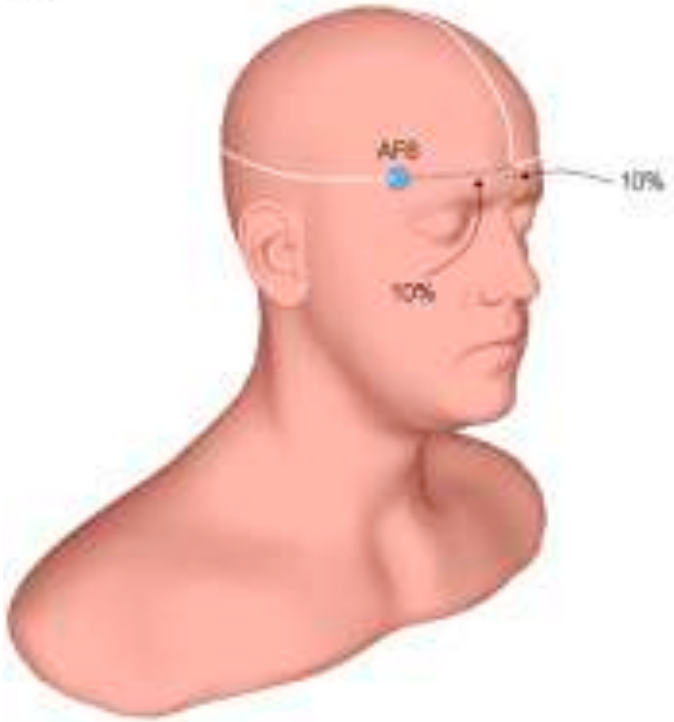
Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Efficacy of intensive orbitofrontal continuous Theta Burst Stimulation (iOFcTBS) in Obsessive Compulsive Disorder: A Randomized Placebo Controlled Study

Parth Dutta [a], Mohan Dhyani [a], Shobit Garg [a,*], Sai Krishna Tikka [b], Sumit Khattri [a], Sumit Mehta [a], Jyoti Mishra [c]

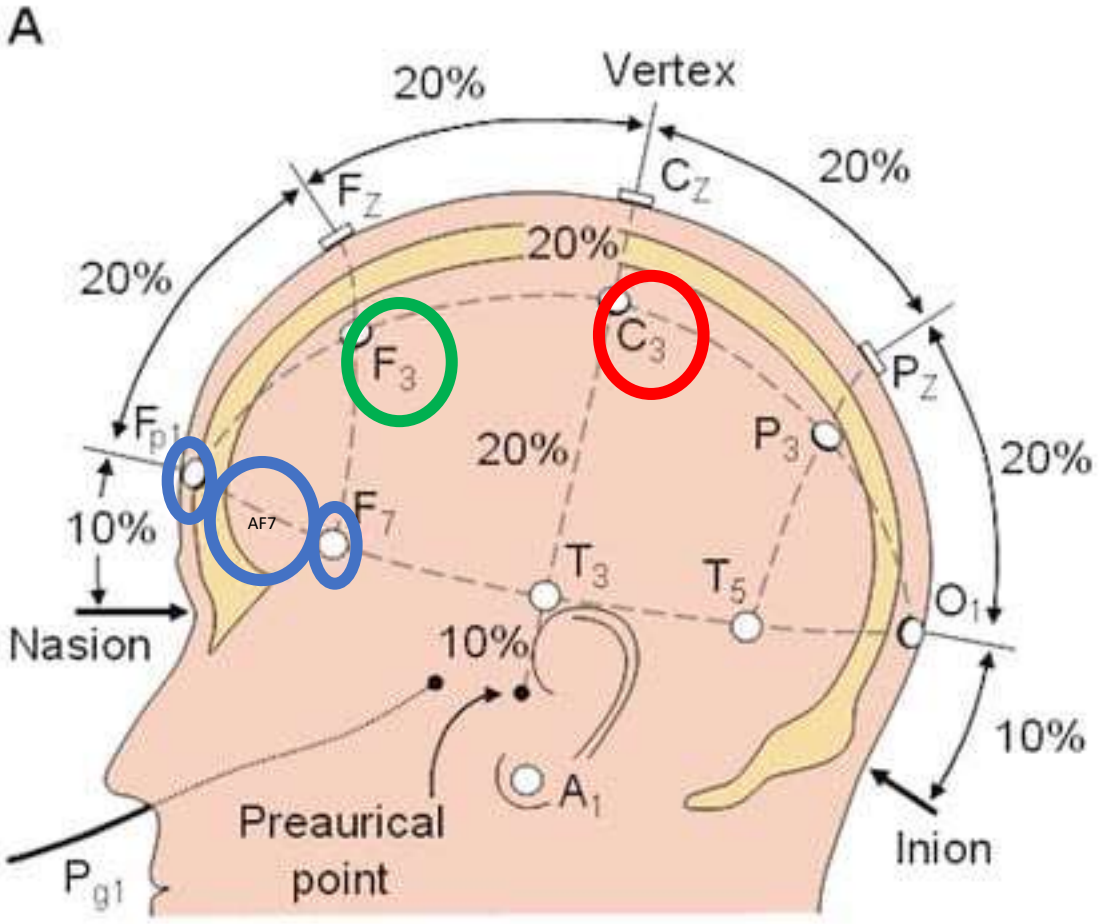
A



B

C

OFC- OCD


A
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Vertex
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20%
20%
20%
F_Z
C_Z
P_Z
F_3
C_3
P_3
F_{p1}
F_7
AF7
T_3
T_5
O_1
10%
10%
10%
Nasion
Preaurical point
A_1
P_{g1}
Inion

Cerebellum- SCZ, OCD

Psychiatry Research 243 (2016) 413–420

Contents lists available at ScienceDirect

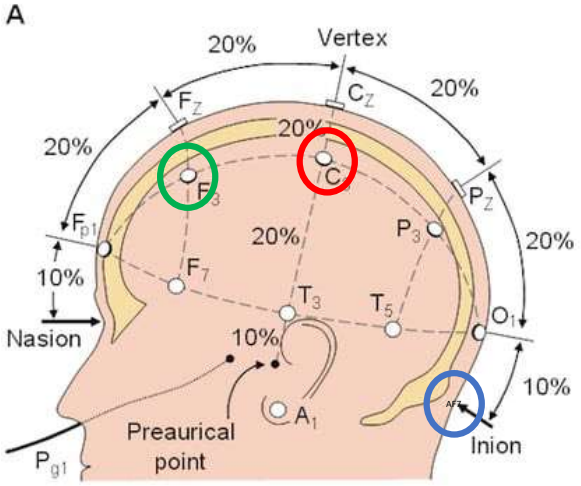
Psychiatry Research

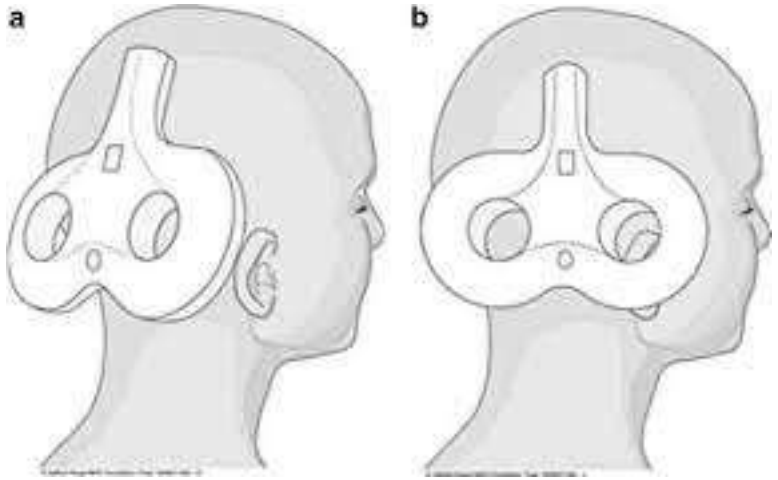
journal homepage: www.elsevier.com/locate/psychres

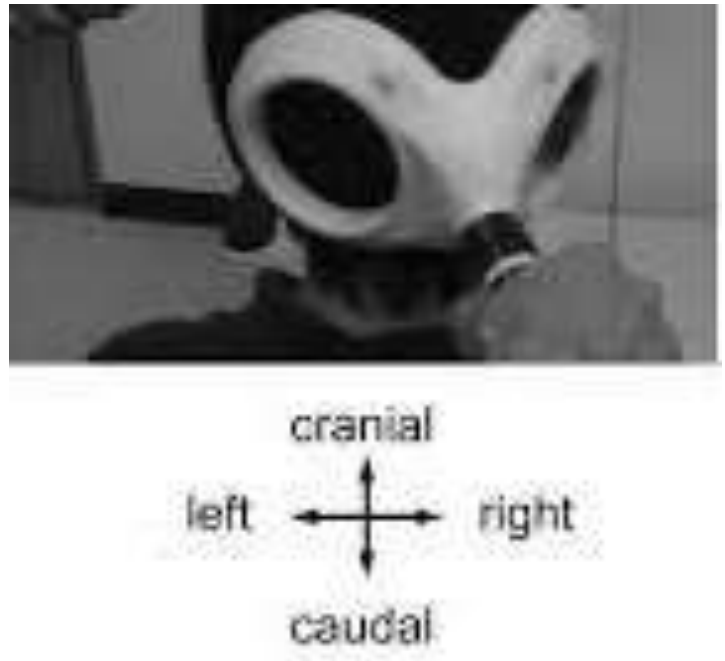
The efficacy of cerebellar vermal deep high frequency (theta range) repetitive transcranial magnetic stimulation (rTMS) in schizophrenia: A randomized rater blind-sham controlled study

Shobit Garg [a], Vinod Kumar Sinha [b], Sai Krishna Tikka [b,*], Preeti Mishra [a], Nishant Goyal [b]

[a] Department of Psychiatry, Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun, Uttarakhand, India
[b] KS Mani Center for Cognitive Neurosciences and Department of Psychiatry, Central Institute of Psychiatry, Kanke, Ranchi, Jharkhand 834006, India





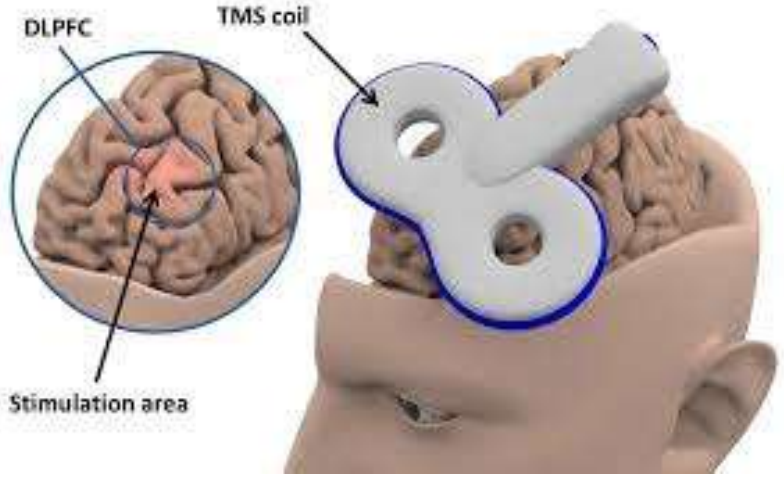


Stimulus Delivery- DLPFC

DLPFC is typically defined by areas 9 and 46 in the Brodmann classification system

How to identify?

- standard ‘5-cm method’ for coil localization (crude method)
- F3 EEG point (International 10-20 system) is known to relate to DLPFC and is likely to be more anterior than a 5-cm localized treatment
- Beam method
- MRI based neuronavigation



Accelerated TMS

- Disadvantages of conventional rTMS
  - Standard rTMS **not useful for actively suicidal patients** due to delayed time-to-response
  - **Daily administration schedule over several weeks limits the feasibility** for patients

aTMS

- Accelerated TMS (aTMS) protocols with both rTMS and TBS increasingly under study to address these limitations

- Rationale:
  1. Equal or greater effects are induced by the repeated application of stimulation within a short interval time
  2. Effects induced within a densely scheduled session have durable efficacy

- Accelerated response to treatment is another theoretical advantage of aTMS

SAINT

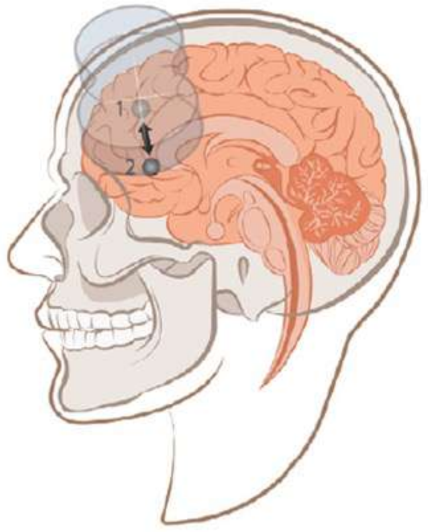
Cole et al. have developed an accelerated, high dose, resting-state functional connectivity MRI (fcMRI) guided iTBS protocol for treatment resistant depression [Stanford Accelerated Intelligent Neuromodulation Therapy]

The protocol **involves 5 consecutive days of 10 iTBS sessions per day (1800 pulses per session, 50-minute intersession intervals) delivered to specific region of left DLPFC most anticorrelated with subgenual Anterior Cingulate Cortex (sgACC), which was accurately targeted using fcMRI scans**

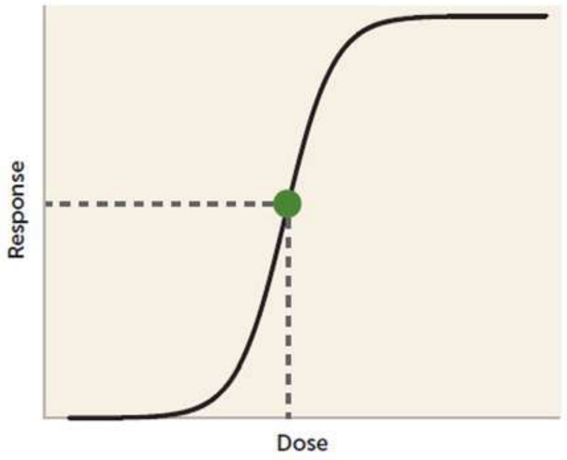
Found to be safe and well-tolerated in 21 MDD patients, 19 of whom achieved remission

SAINT Protocol
(STANFORD ACCELERATED INTELLIGENT NEUROMODULATION THERAPY FOR TREATMENT-RESISTANT DEPRESSION)

A



C



B

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

CNS Spectrums

www.cambridge.org/cns

Original Research

Cite this article: Mukherjee A, Kumre PK, Goyal N, and Khanra S (2022). Adjunctive neuronavigated accelerated continuous theta-burst stimulation in obsessive-compulsive disorder: a randomized sham-controlled study. *CNS Spectrums*
https://doi.org/10.1017/S1092852922000980

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Key words:
OCD; Obsessive Compulsive disorder; TBS; Theta burst; Neuronavigaton; Accelerated

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Adjunctive neuronavigated accelerated continuous theta-burst stimulation in obsessive-compulsive disorder: a randomized sham-controlled study

Aniruddha Mukherjee[1], Pramod Kumar Kumre[2], Nishant Goyal[1] and Sourav Khanra[3]*

[1]Centre for Cognitive Neuroscience, Central Institute of Psychiatry, Ranchi, India, [2]Department of Psychiatry, Central Institute of Psychiatry, Ranchi, India and [3]Centre for Addiction Psychiatry, Central Institute of Psychiatry, Ranchi, India

Abstract

Background. Approximately 40% of patients treated for obsessive-compulsive disorder (OCD) do not respond to standard and second-line augmentation treatments leading to the exploration of alternate biological treatments. Continuous theta burst stimulation (cTBS) is a form of repetitive transcranial magnetic stimulation inducing more rapid and longer-lasting effects on synaptic plasticity than the latter. To the best of our knowledge, only one recent study and a case report investigated the effect of cTBS at the supplementary motor area (SMA) in OCD.

Objective. This study aimed to examine the effect of accelerated robotized neuronavigated cTBS over SMA in patients with OCD.

Methods. A total of 32 patients with OCD were enrolled and randomized into active and sham cTBS groups. For active cTBS stimulation, an accelerated protocol was used. Bursts of three stimuli at 50 Hz, at 80% of MT, repeated at 5 Hz were used. Daily 2 sessions of 900 pulses each, for a total of 30 sessions over 3 wk (weekly 10 sessions), were given. Yale–Brown Obsessive-Compulsive Rating Scale (YBOCS), Clinical Global Impressions scale (CGI), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) were administered at baseline and at end of weeks 3 and 8.

Results. A total of 26 patients completed the study. Active cTBS group showed significant group × time effect in YBOCS obsession ($P < .001$, $\eta^2 = 0.288$), compulsion ($P = .004$, $\eta^2 = 0.207$), YBOCS total ($P < .001$, $\eta^2 = 0.288$), CGI-S ($P = .010$, $\eta^2 = 0.248$), CGI-C ($P = .010$, $\eta^2 = 0.248$), HAM-D ($P = .014$, $\eta^2 = 0.224$) than sham cTBS group.

Conclusions. Findings from our study suggest that adjunctive accelerated cTBS significantly improves psychopathology, severity of illness, and depression among patients with OCD. Future studies with larger sample sizes will add to our knowledge.

rTMS

Integrated 100 Hz rTMS System at CIP

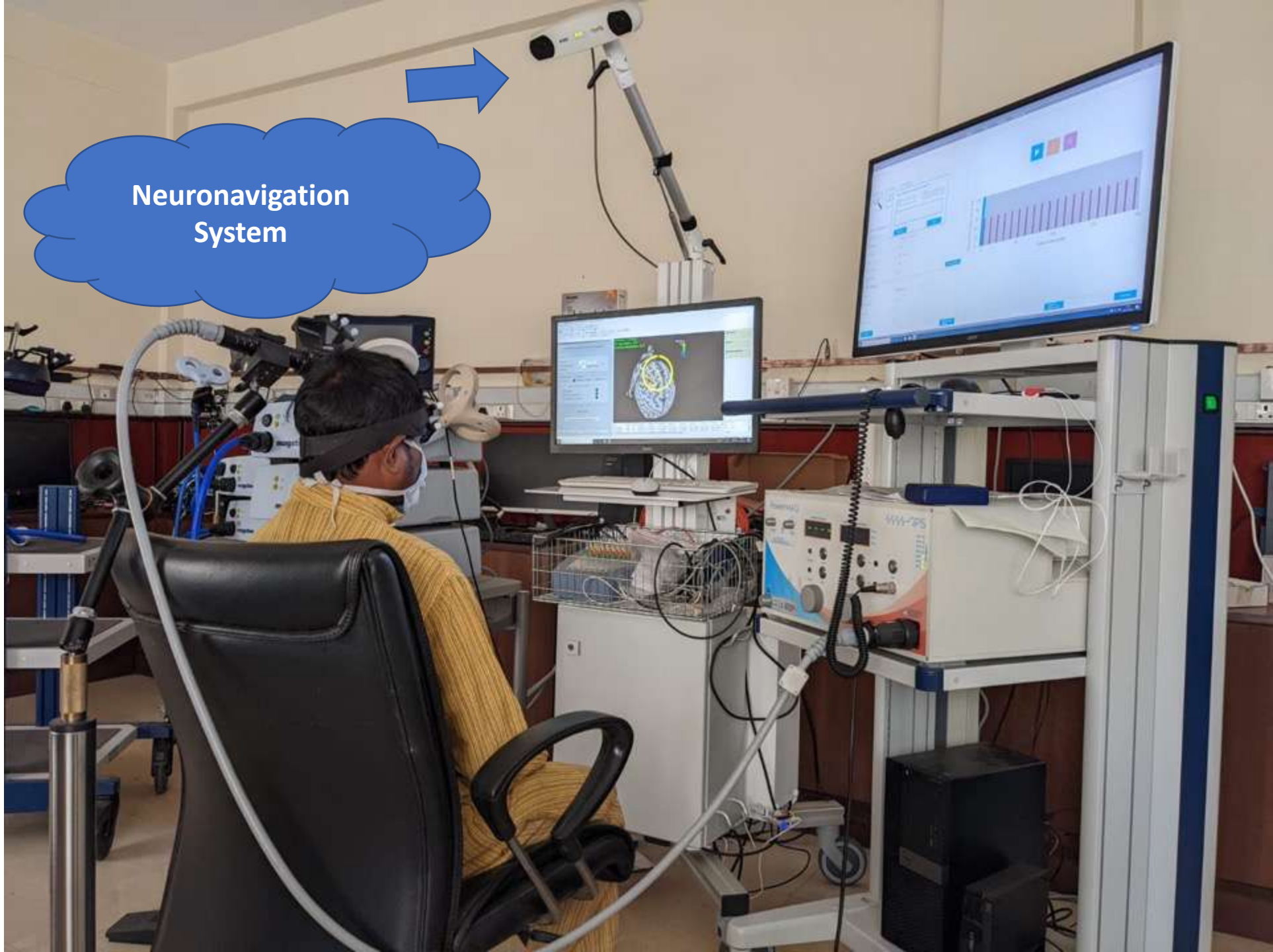
Robotized TMS


magstim
magstim
magstim
PowerMAG
rTMS
rTMS ,
QPS

DOUBLE CONE COIL,
AIR COOLED COILS,
FIGURE OF 8 COILS

rTMS
DELIVERY

Neuronavigated rTMS



Deep TMS

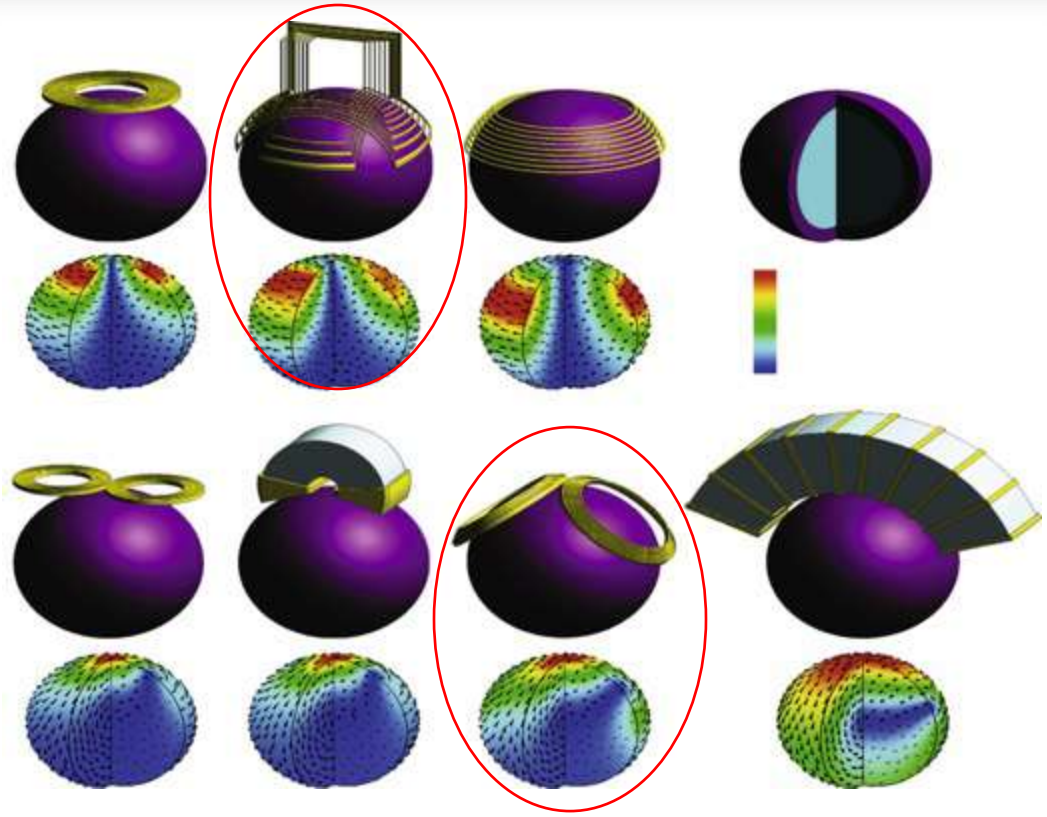
Contents lists available at ScienceDirect

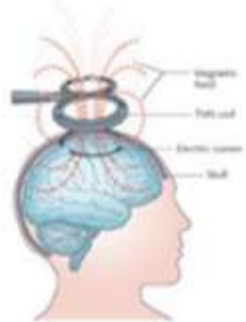
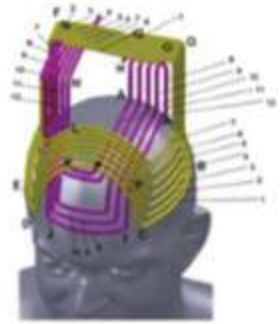
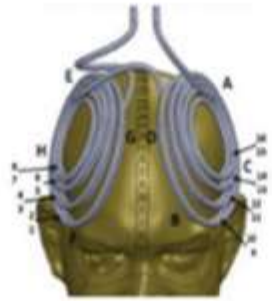
Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Coil design considerations for deep transcranial magnetic stimulation

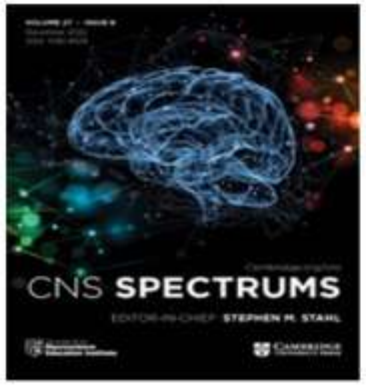
Zhi-De Deng [a], Sarah H. Lisanby [a,b], Angel V. Peterchev [a,c,d,*]



	TRADITIONAL rTMS	DEEP rTMS or DEEP TMS		
COIL DESIGN	**Figure-8 coil**	**H1-coil Bilateral** PFC & DLPFC	**H7-coil Medial** PFC & ACC	**H4-coil Bilateral** Insula and PFC
				
DEPTH	0.7cm subdural	1.8cm subdural **2.5x deeper**	3cm subdural **4x deeper**	1.5cm subdural **2.1x deeper**
BREADTH	3cm^3 volume	18cm^3 volume millions of more neurons	40.3cm^3 volume millions of more neurons	15.2cm^3 volume millions of more neurons
INDICATION	**MDD**	**MDD**	**OCD**	**Smoking Cessation**


H COIL FOR
DEEP TMS

Studies from CIP



CNS Spectrums

Brain activation alterations with adjunctive deep transcranial magnetic stimulation in obsessive-compulsive disorder: an fMRI study

Published online by Cambridge University Press: **10 May 2022**

Sachin Reddy, Umesh Shreekantiah, Nishant Goyal and Chandramouli Roy Hide author details

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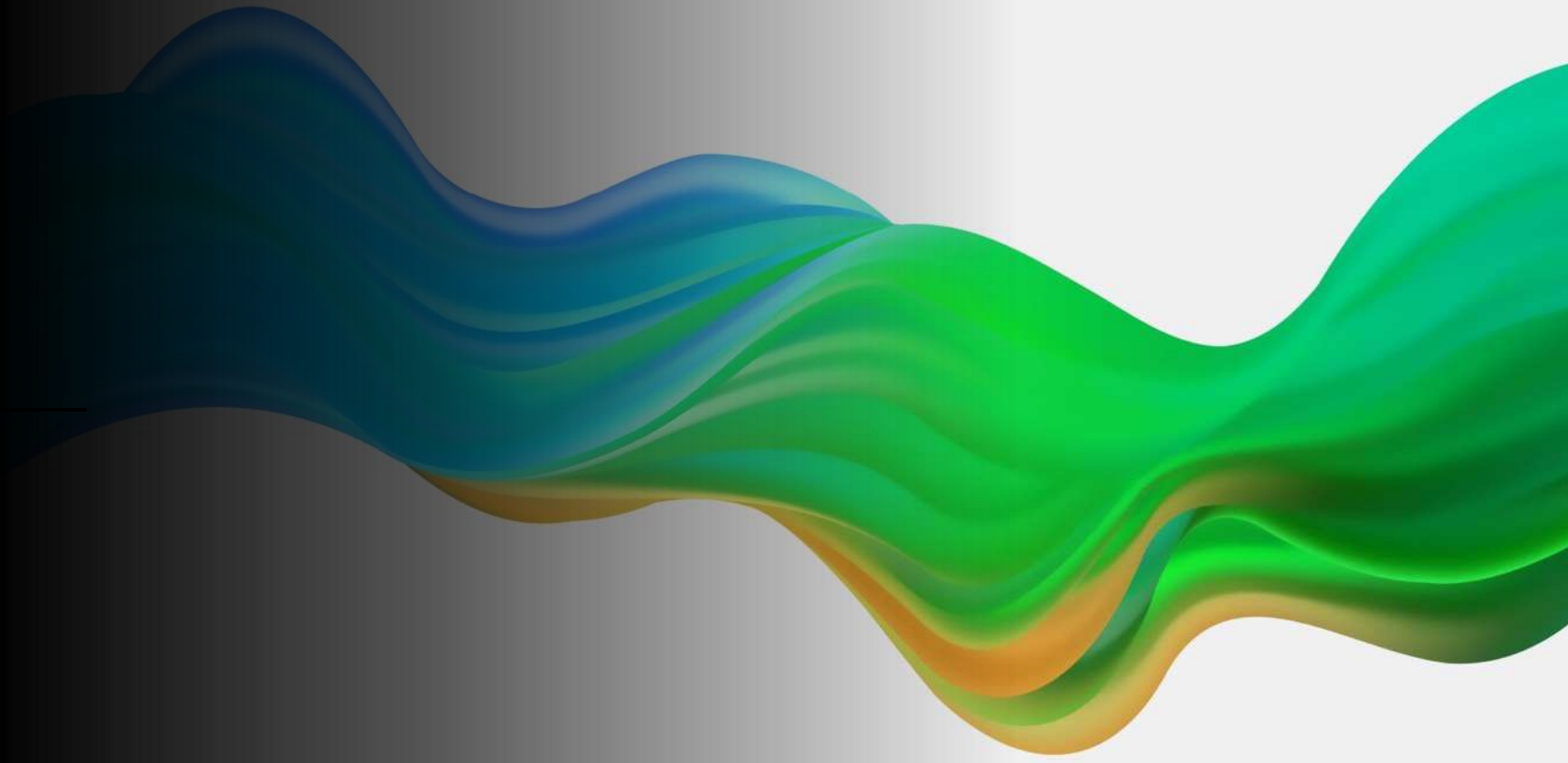
New Innovations

Recent studies have been published examining **newer forms of patterned TMS**

In a study aiming to measure changes in cortico-spinal excitability, Jung et al. introduced a new protocol **combining QPS and TBS** (Jung et al., 2016)

HDtDCS priming of iTBS is studied in **depression**

Evidences for TMS



Practice recommendations

Available positive evidence/Indications

Depression (unipolar, bipolar treatment resistant depression)

Peripartum depression

Post-stroke depression, depression associated with Parkinson's disease

Generalized Anxiety Disorder

Obsessive Compulsive Disorder

Post Traumatic Stress Disorder

Schizophrenia (negative symptoms and resistant auditory hallucinations)

Nicotine use disorder (smoking cessation)

Alzheimer's Dementia

Insomnia

Migraine

Fibromyalgia, Tinnitus

Insufficient or negative sham-controlled evidence

Suicidality

Maintenance treatment of depression

Mania/ Bipolar mania

Panic disorder

Tourette disorder

Positive symptoms (except resistant auditory hallucinations) of schizophrenia

Treatment resistant schizophrenia

Substance use disorders except smoked nicotine

ADHD

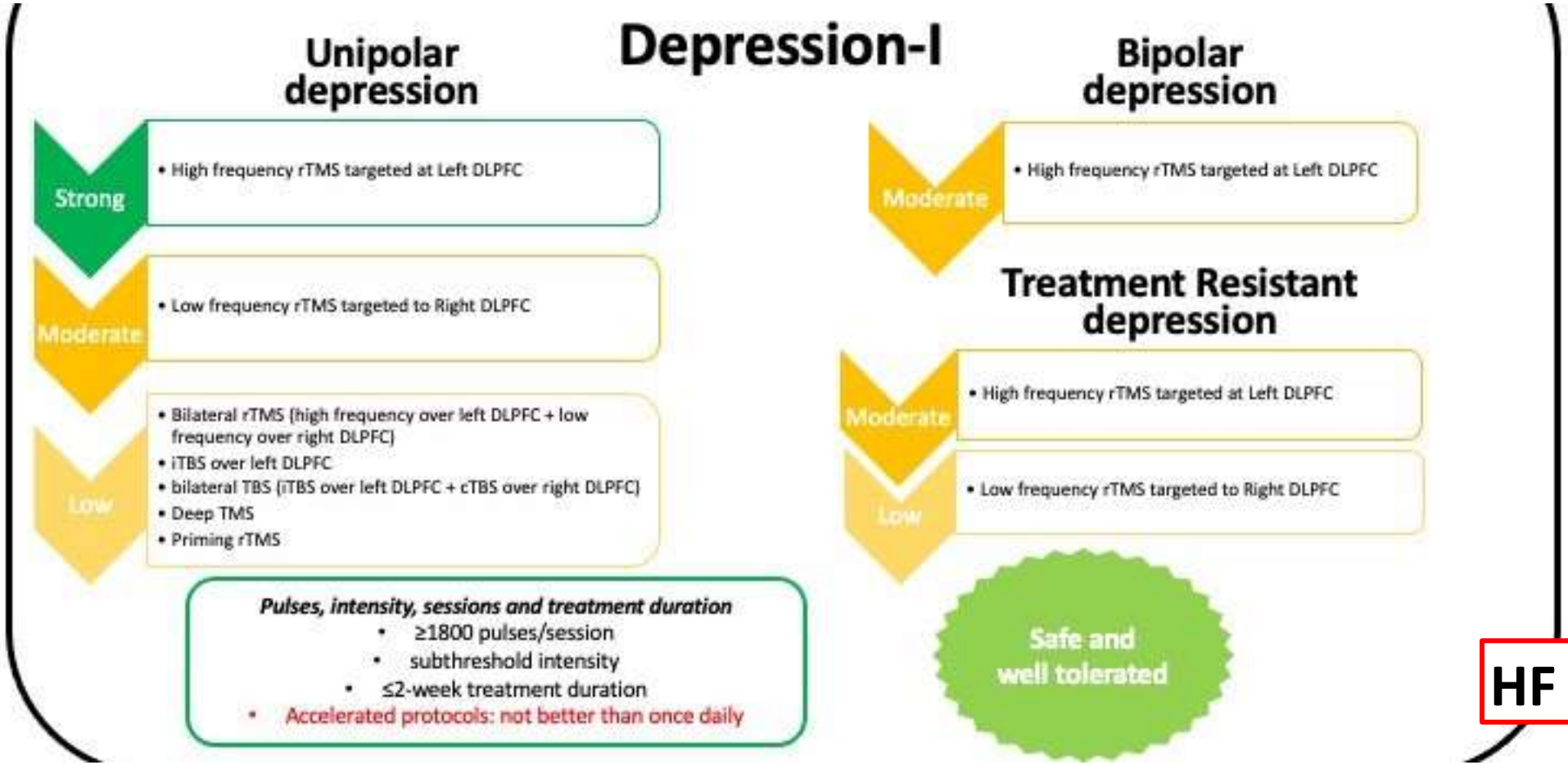
Autism Spectrum Disorder (Lack of evidence for uniformity in rTMS form and target location)

Specific learning disorder; Intellectual disability

Tension type Headache

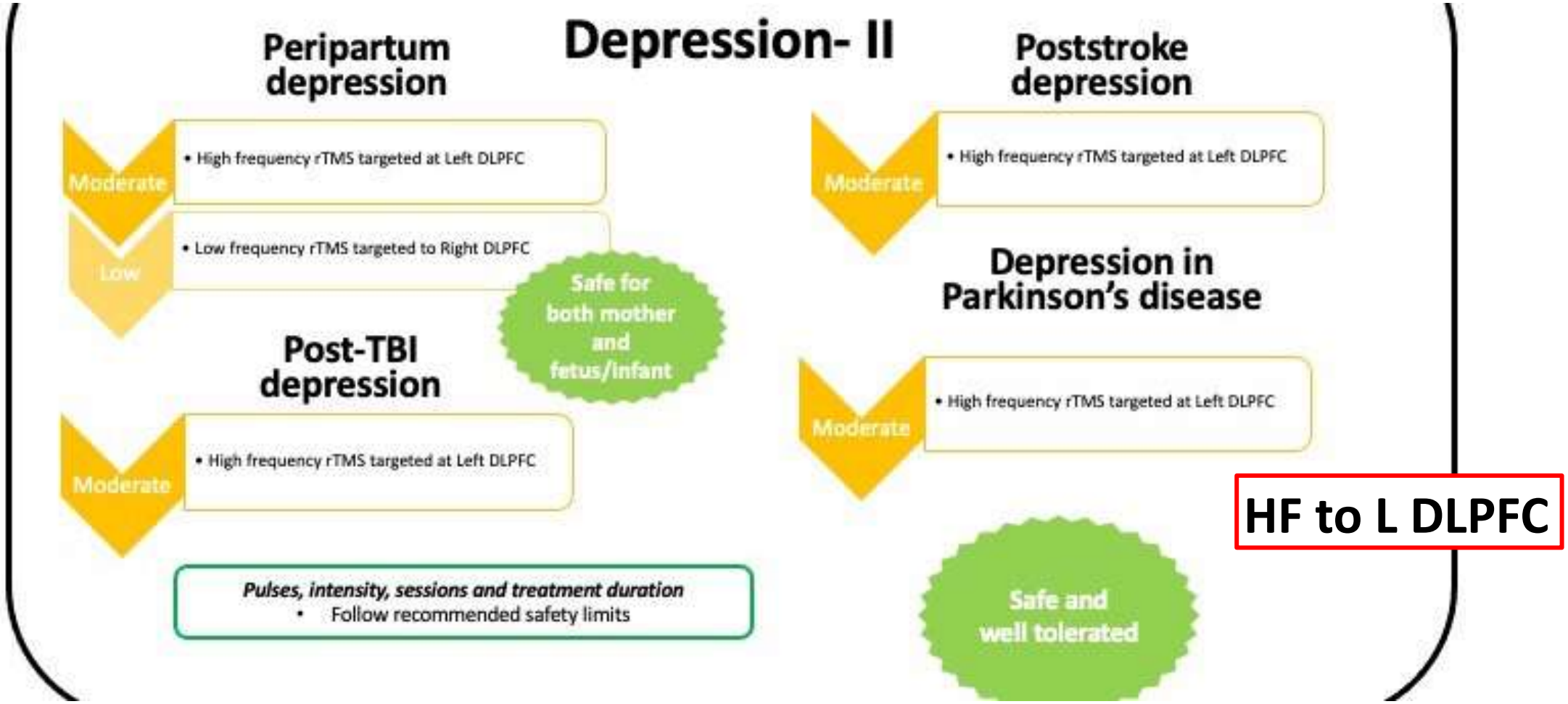
PNES (Dissociative disorders)

Practice recommendations

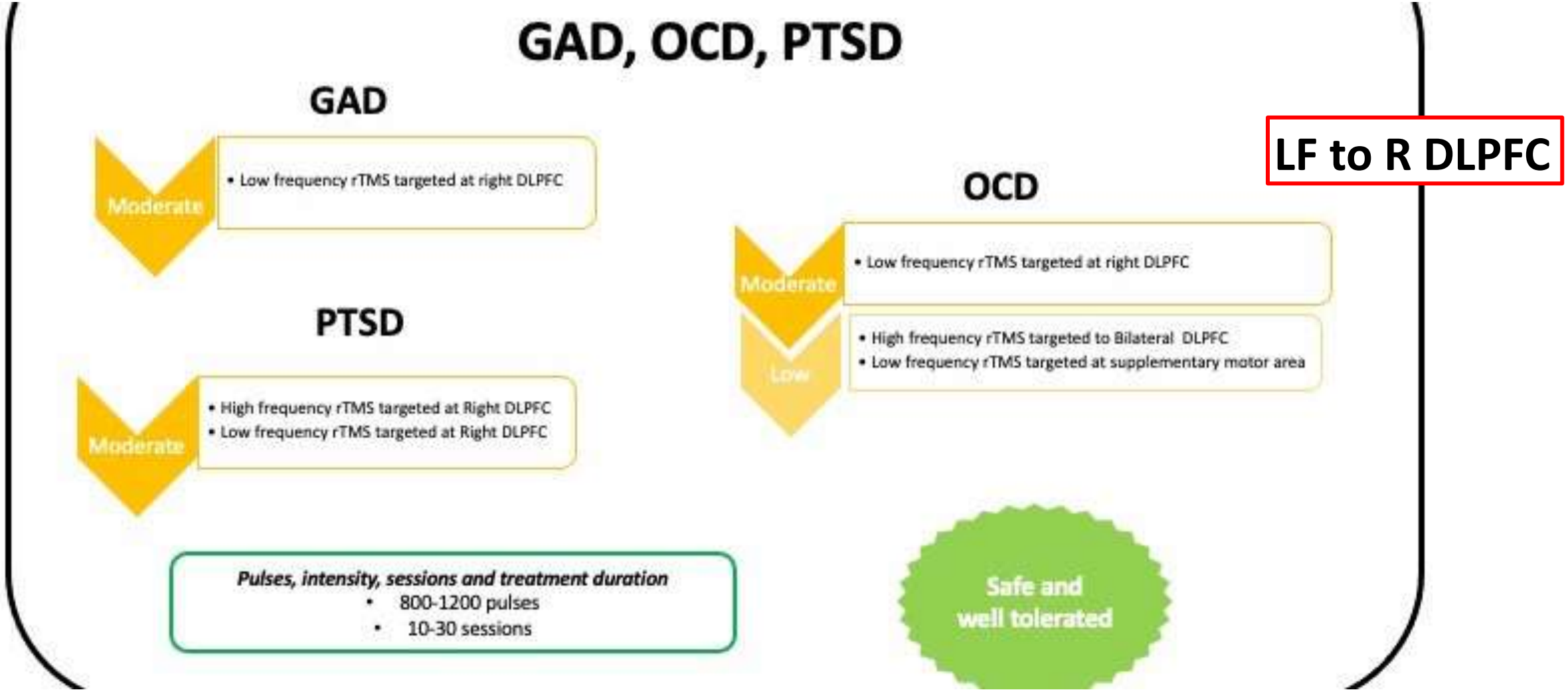


HF to L DLPFC

Practice recommendations

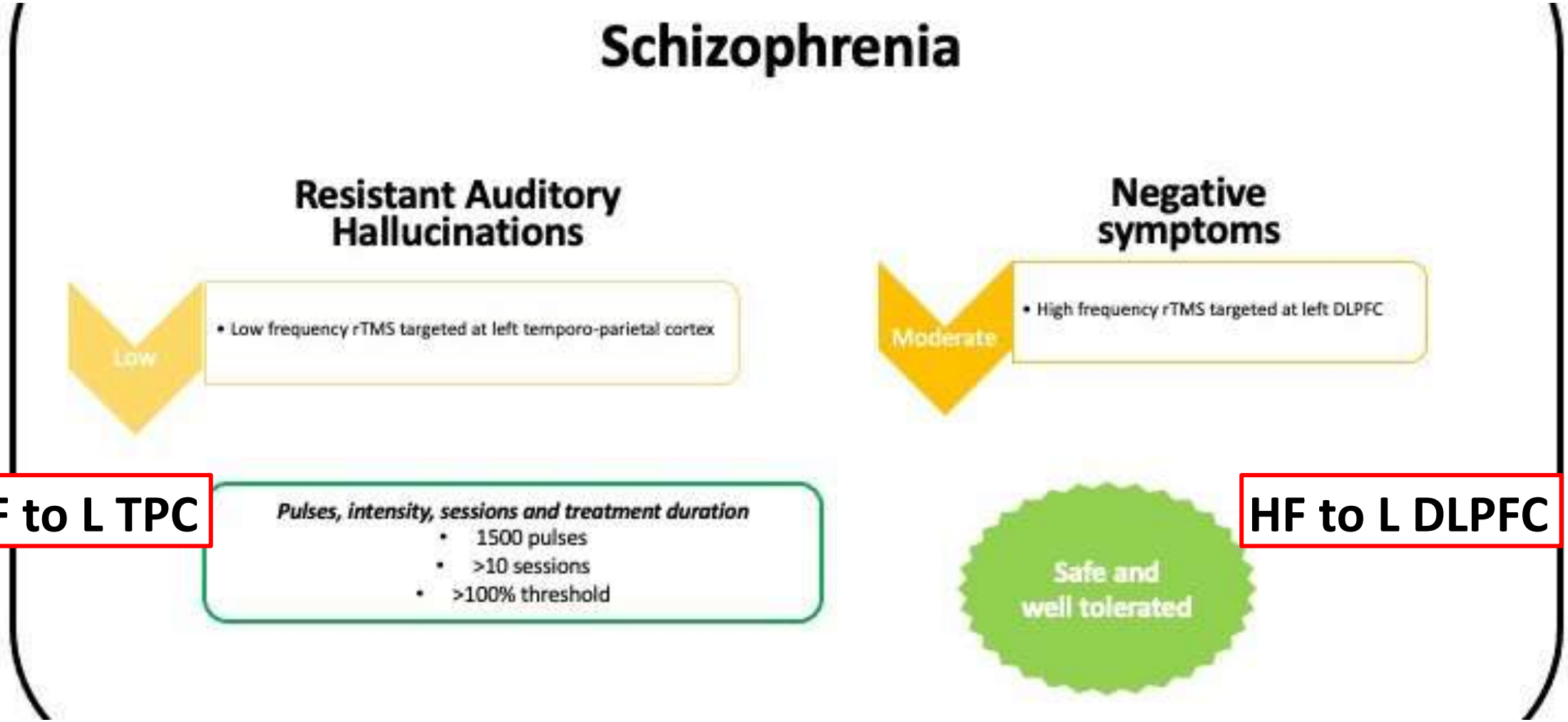


Practice recommendations

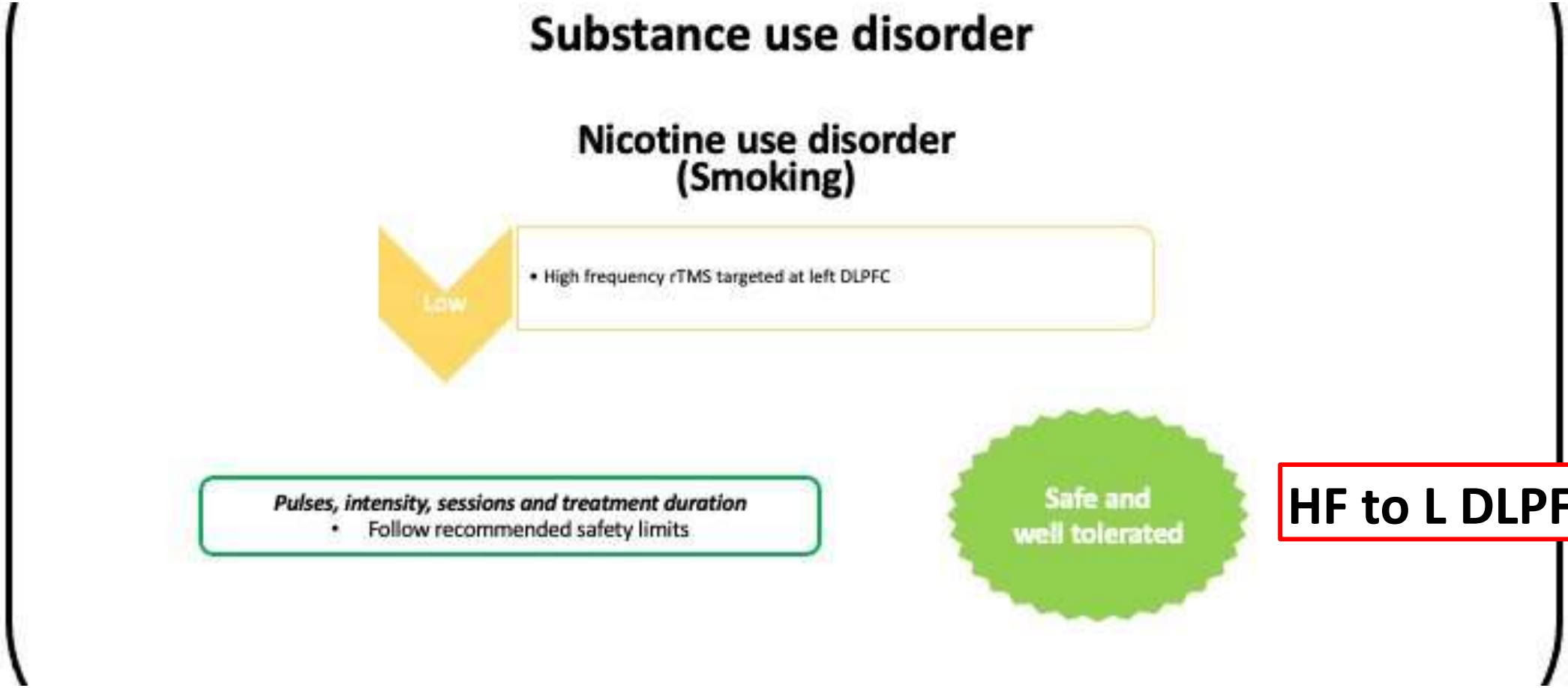


LF to R DLPFC

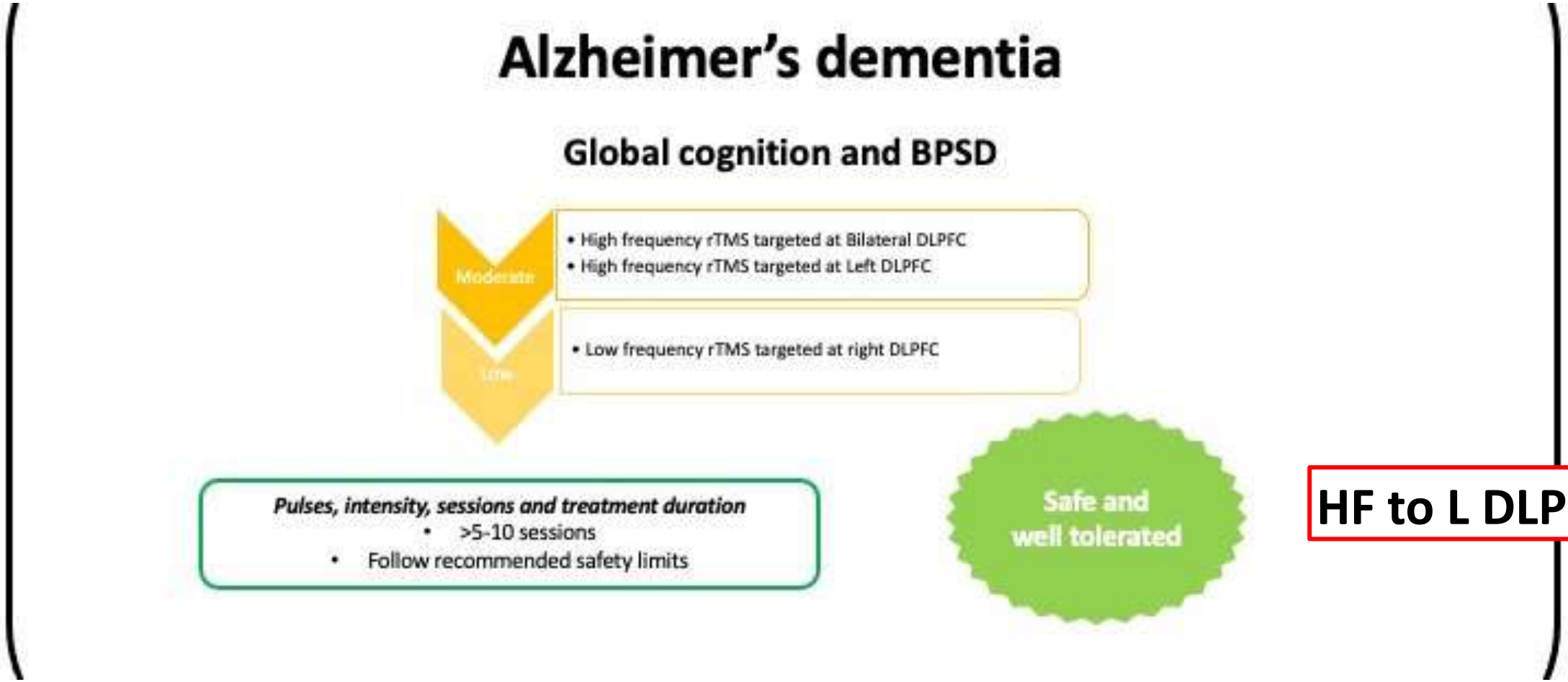
Practice recommendations



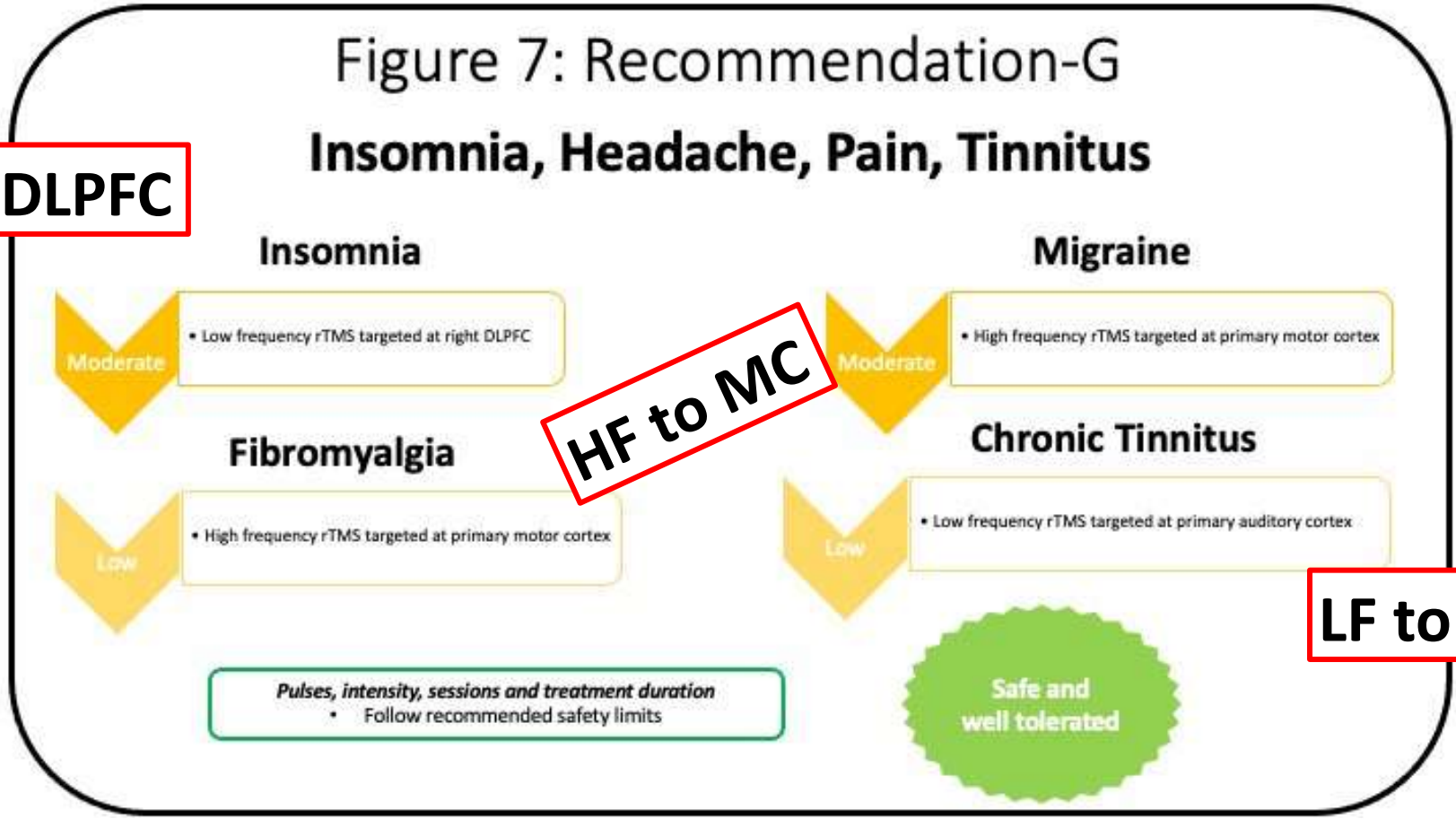
Practice recommendations



Practice recommendations



Practice recommendations



LF to R DLPFC

HF to MC

LF to AC

Table 18: Indications and evidence for rTMS in treatment of various psychiatric disorders				
Disorder/Condition	**Mode**	**Target**	**Recommendation**	**FDA**
Depression Acute/Unipolar	HF	Left DLPFC	**Strong**	**Yes**
	LF	Right DLPFC	**Moderate**	
	Bilateral (HF to Left and LF to Right DLPFC)		**Low**	
	iTBS	Left DLPFC		
	Bilateral (iTBS to Left and cTBS to Right DLPFC)			
	Deep 'H1' HF	Left DLPFC		
	Priming (HF followed by LF)	Right DLPFC		
Bipolar depression	HF	Left DLPFC	**Moderate**	**Yes**
Treatment resistant depression	HF	Left DLPFC	**Moderate**	**Yes**
	LF	Right DLPFC	**Low**	**Yes**
Peripartum depression	HF	Left DLPFC	**Moderate**	No
	LF	Right DLPFC	**Low**	
Post-stroke depression	HF	Left DLPFC	**Moderate**	No
Depression in Parkinson's Disease	HF	Left DLPFC	**Moderate**	No
Generalized Anxiety Disorder	LF	Right DLPFC	**Moderate**	No
Obsessive Compulsive Disorder	LF	Right DLPFC	**Moderate**	**Yes**
	HF	Bilateral DLPFC	**Low**	
	LF	SMA	**Low**	No
Post-Traumatic Stress Disorder	HF	Right DLPFC	**Moderate**	No
	LF	Right DLPFC		No
Schizophrenia-Auditory Hallucinations	LF	Left TPC (TPJ+STG)	**Low**	No
Schizophrenia-Negative symptoms	HF	Left DLPFC	**Moderate**	No
Nicotine Use Disorder (Smoking Cessation)	HF	Left DLPFC	**Low**	No
Alzheimer's Dementia	HF	Bilateral DLPFC	**Moderate**	No
	HF	Left DLPFC		No
	LF	Right DLPFC	**Low**	No
Insomnia	LF	Right DLPFC	**Moderate**	
Migraine	HF	Primary Motor Cortex	**Moderate**	
Fibromyalgia	HF	Primary Motor Cortex	**Low**	
Chronic Tinnitus	LF	Primary Auditory Cortex	**Low**	

rTMS= repetitive transcranial magnetic stimulation; iTBS=intermittent theta burst stimulation; cTBS=continuous theta burst stimulation; HF=high frequency; LF=low frequency; DLPFC=dorsolateral prefrontal cortex; TPC=temporoparietal cortex; TPJ=temporoparietal junction; STG=superior temporal gyrus; FDA=Food and Drug Administration

Practice recommendations

Left DLPFC	Right DLPFC	LMC	LAC
Depression	GAD/OCD/PTSD	Migraine	Chronic Tinnitus
Negative symptoms of schizophrenia	Insomnia	Fibromyalgia	
Nicotine smoking			
Alzheimer's dementia			

Excitatory (HF/iTBS)	Inhibitory (LF/cTBS)
Depression	GAD/OCD/PTSD
Negative symptoms of schizophrenia	Auditory Hallucinations
Nicotine smoking	Insomnia
Alzheimer's dementia	Chronic Tinnitus
Migraine	
Fibromyalgia	

FDA Approved dTMS Treatments

H1 COIL

FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD) / ANXIOUS DEPRESSION

Stimulates the prefrontal cortex, particularly the left dorsolateral prefrontal cortex

- In addition to numerous published, double-blind, randomized controlled trials validating the efficacy of Deep TMS for depression, **clinical data of over 1,000 patients in real practice settings has shown compelling results**.
- Among patients who completed 30 sessions, **approximately 1 in 2 achieved remission and 3 in 4 achieved response**.

Standard 20-minute sessions or Intermittent Theta Burst (iTBS) 3-min sessions with 20 sessions across 4 weeks, followed by 10-16 sessions across additional 5-8 weeks

H7 COIL

FOR THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER (OCD)

Stimulates the anterior cingulate cortex and prefrontal cortex

- Complementing a large scale, double-blind, multicenter randomized controlled trial which demonstrated strong response rates, **greater than 1 in 2 patients who completed 29 sessions in real clinical practice achieved sustained response**.

Standard 18-minute sessions with 29 sessions across 6 weeks

FDA Approved dTMS Treatments (Cont.)

H4 COIL

FOR THE TREATMENT OF SMOKING ADDICTION

Stimulates the bilateral
insula and prefrontal cortex

- **Nearly 1 in 3 patients that completed 18 sessions achieved 4 or more weeks of abstinence from smoking** in a large scale, double-blind, multicenter randomized controlled trial. 2 of 3 patients who quit smoking by the end of treatment, remained abstinent for at least an additional 3 months.
- Many additional patients experienced **significant reduction in average number of cigarettes smoked per week**.

Standard 18-minute sessions with 18 sessions across 6 weeks

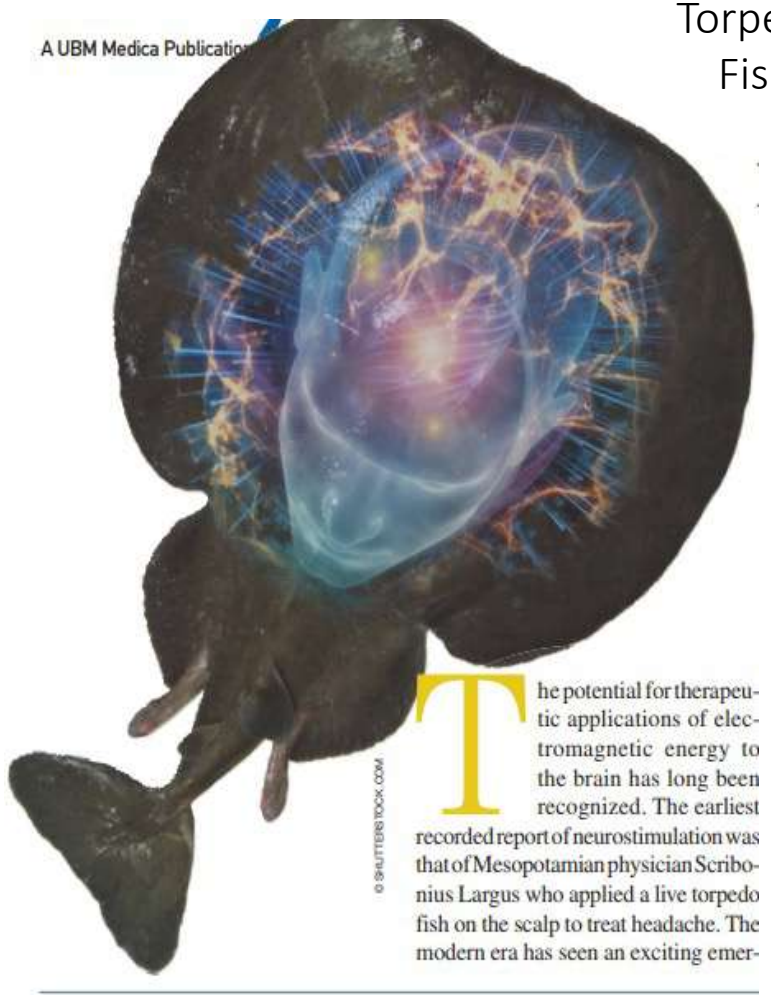
Direct Current Stimulation

rTMS vs tDCS

- Compared to repetitive transcranial magnetic stimulation (rTMS), tDCS is
  - Relatively **cheaper**
  - **Easier** to use
  - More **portable**
  - **Less adverse effects**

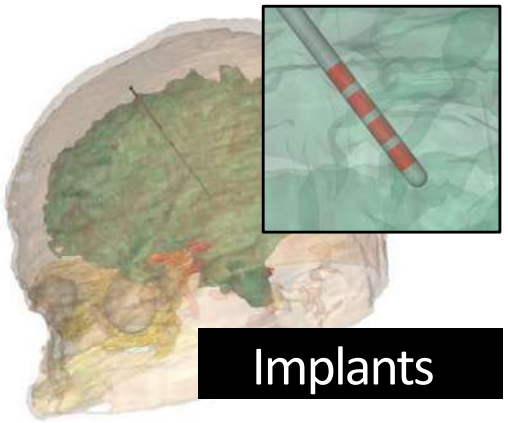
History: “Torpedo" effect

- Natural electrical phenomena fascinated humans since antiquity
- Electrical discharges produced by the fish were highly appreciated among ancient physicians
  - Hippocrates, Scribonius Largus and Galen prescribed for headache, gout and prolapsed anus



Torpedo Fish

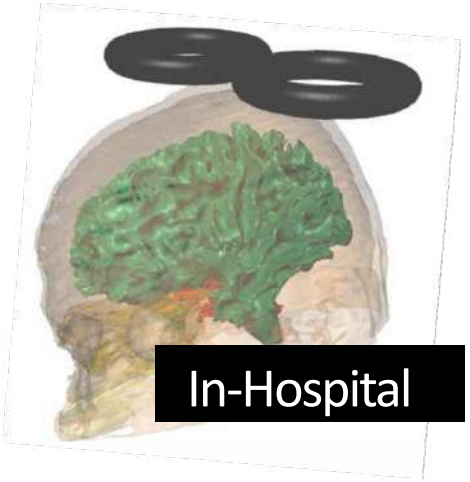
Neuromodulation platforms vary in how energy is delivered to what target



Implants

Deep Brain Stimulation (DBS)

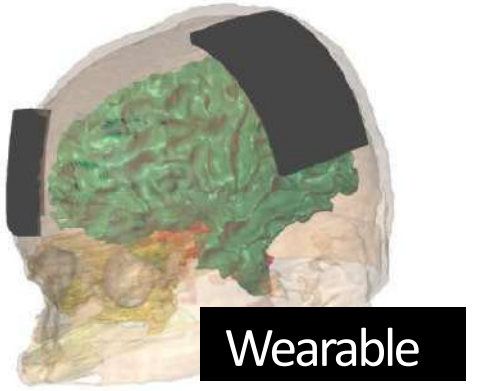
Spinal Cord Stimulation (SCS)



In-Hospital

Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy

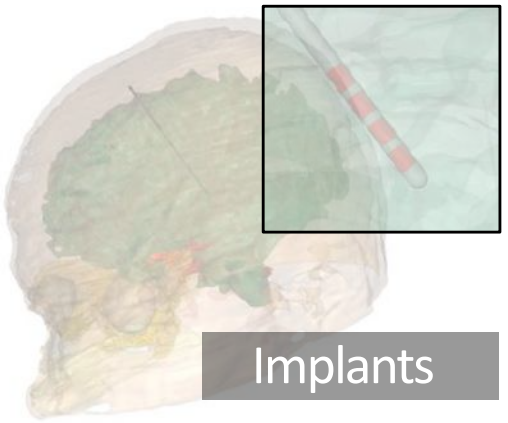


Wearable

Transcranial Electrical Stimulation (tES)

Transcranial Direct Current Stimulation (tDCS)

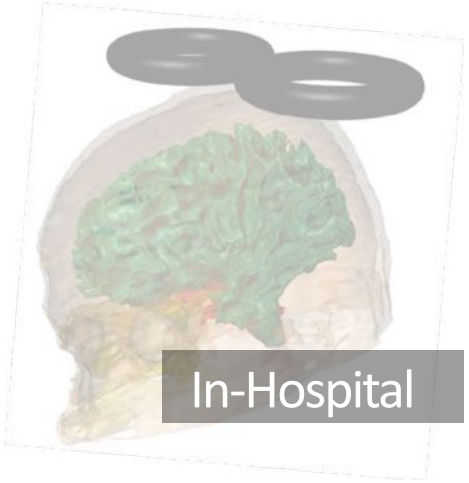
Neuromodulation platforms vary in how energy is delivered to what target



Implants

Deep Brain Stimulation (DBS)

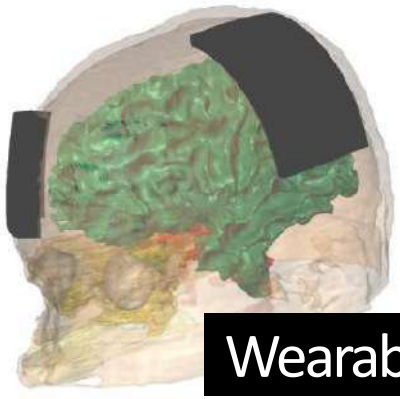
Spinal Cord Stimulation (SCS)



In-Hospital

Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy



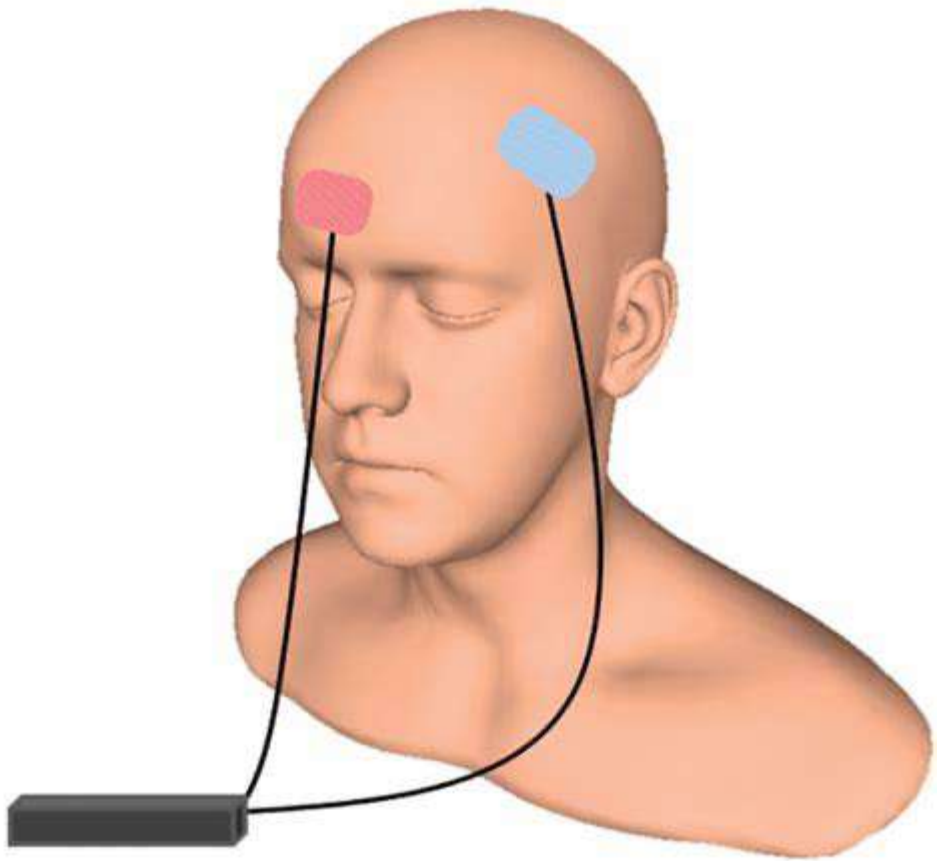
Wearable

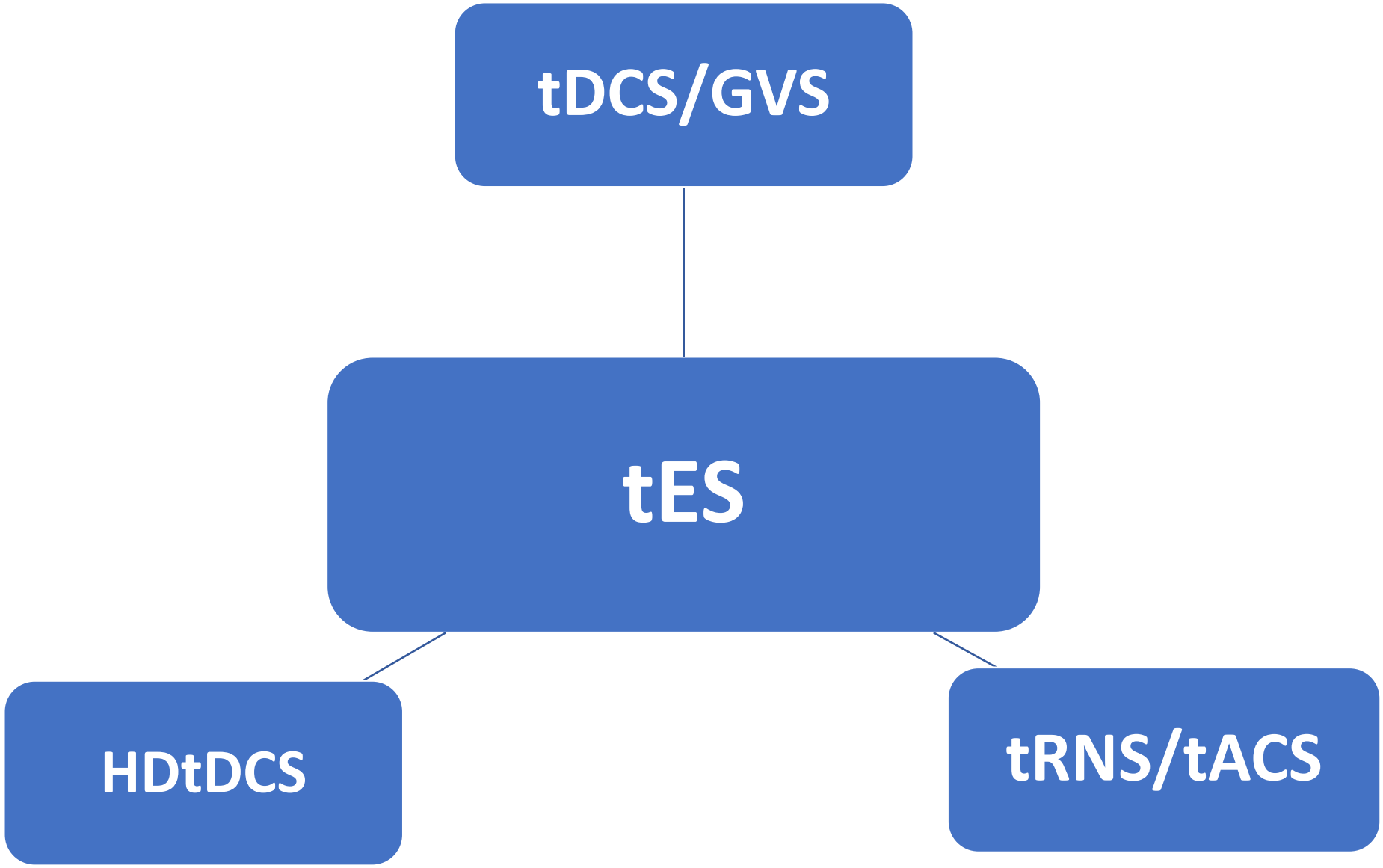
Transcranial Electrical Stimulation (tES)

Transcranial Direct Current Stimulation (tDCS)

What is tES?

All forms of application of electrical currents to the brain non-invasively using (at least one) electrodes on the head

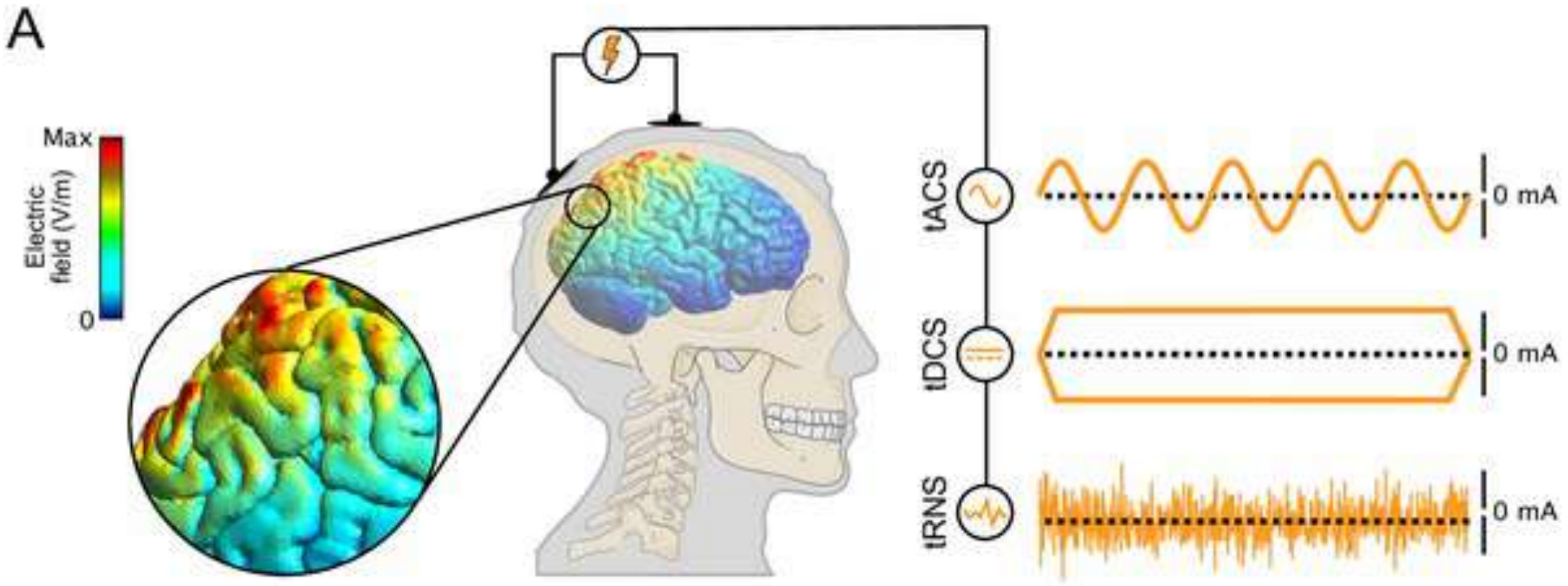



tDCS/GVS
tES
HDtDCS
tRNS/tACS

Transcranial stimulators since 1990

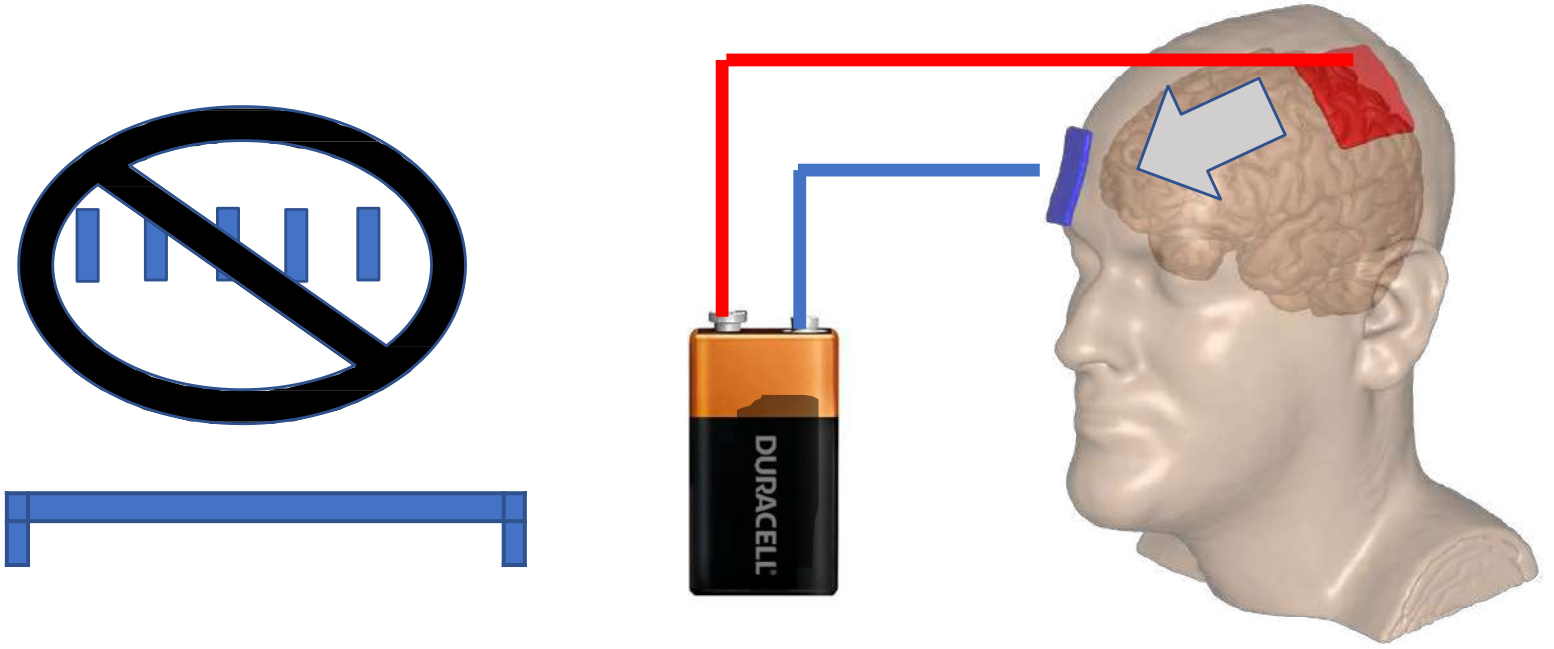
Guleyupoglu B, Schestatsky P, Edwards D, Fregni F, Bikson M. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods. 2013 Oct 15;219(2):297-311.

Commonly used Modern tES



Krause MR, Vieira PG, Pack CC (2023) Transcranial electrical stimulation: How can a simple conductor orchestrate complex brain activity?. PLOS Biology 21(1): e3001973.

Transcranial Direct Current Stimulation (tDCS) is a wearable brain stimulator applying Direct Current (no pulses)



(Probably) most investigated interventional neurotechnology

tDCS (transcranial Direct Current Stimulation)

Cathode (-) Electrode

Anode (+) Electrode

2 mA

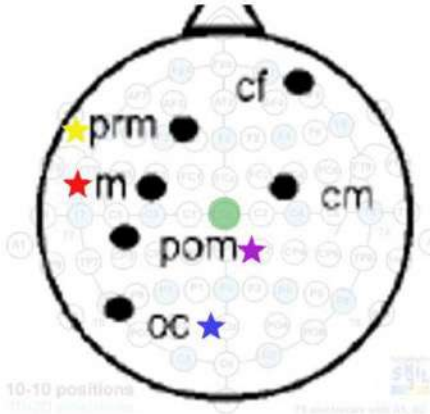
"Anodal" / "Cathodal" refer to proximity of target

20-minute session

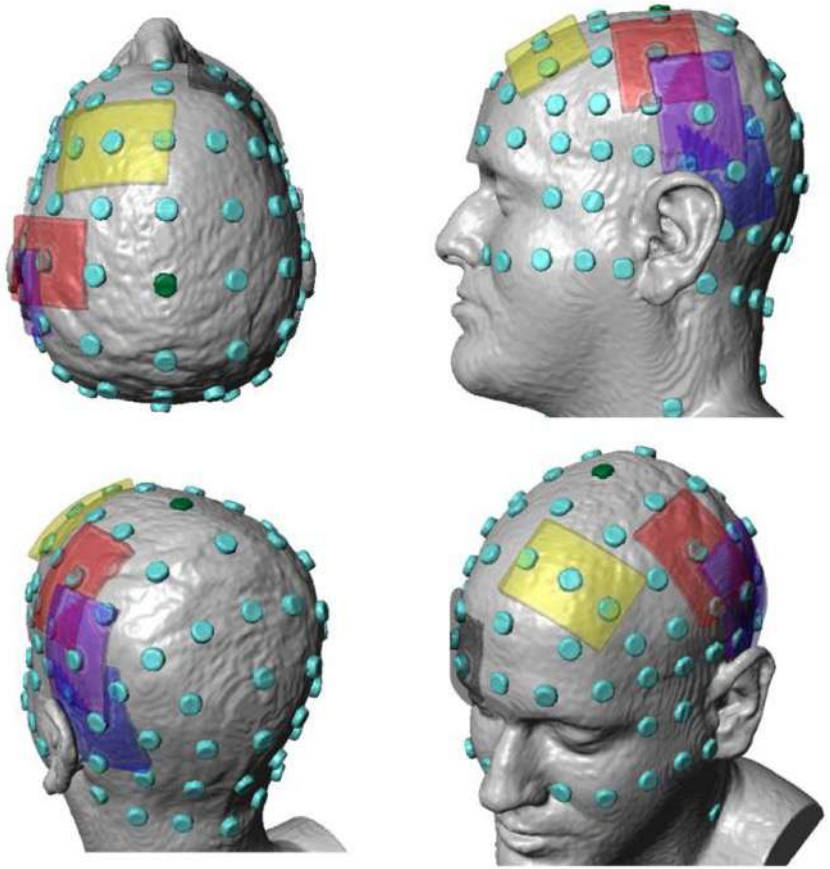
How do we do it ?

- Size, position, and current applied to electrodes

- Example: 5x5 cm^2 electrodes, C3 Anode, SO Cathode, 2 mA for 20 minutes



Contralateral Forehead:	AF8
PreMotor:	F1
Motor:	C3
PostMotor:	CP5
Occipital:	P7

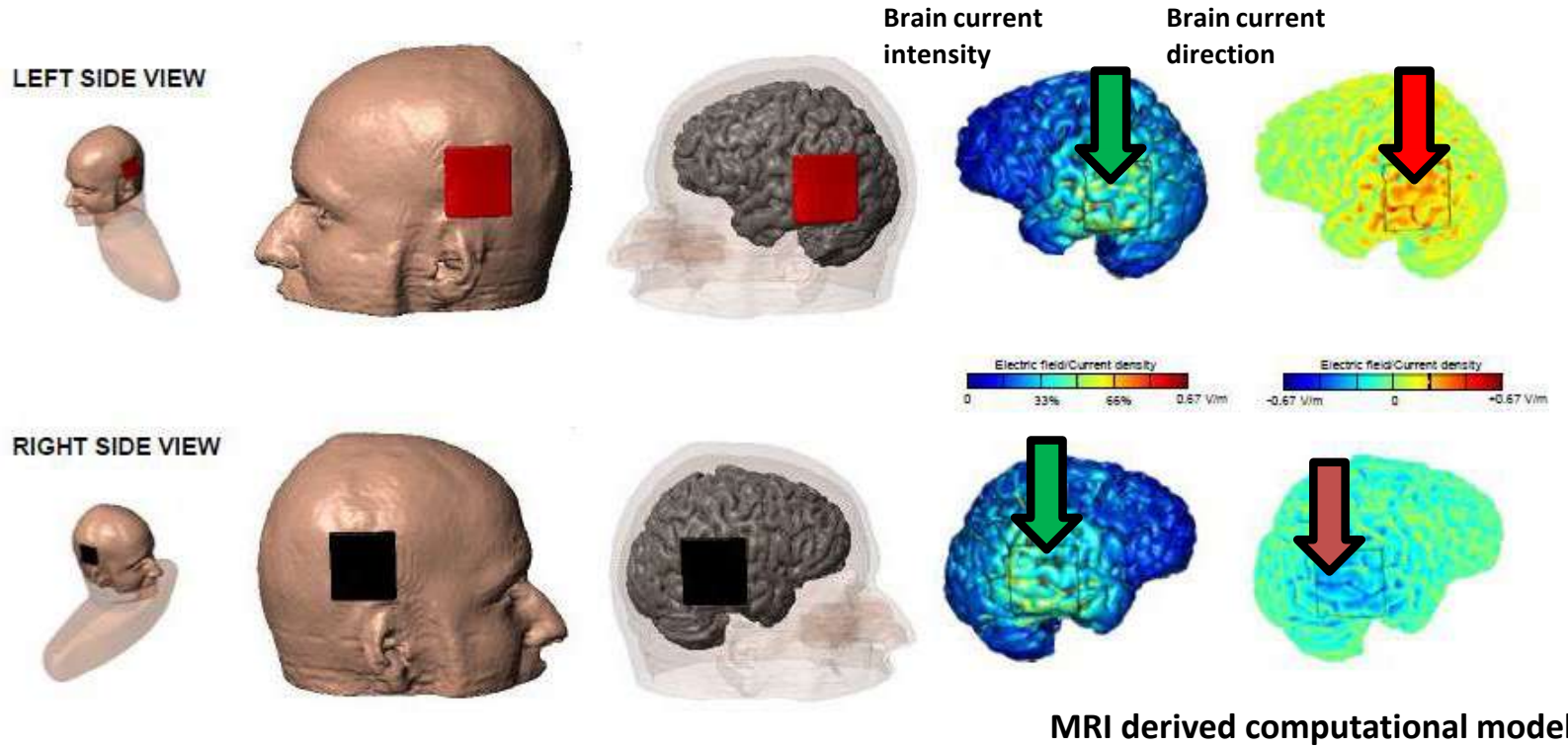


Peterchev, Bikson et. al.

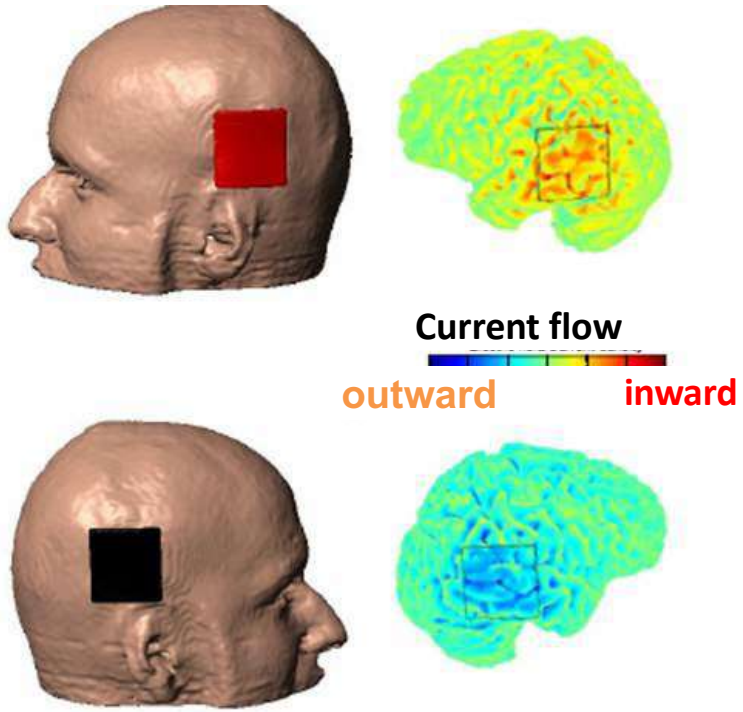
Brain Stim 2012

Mechanism: tDCS

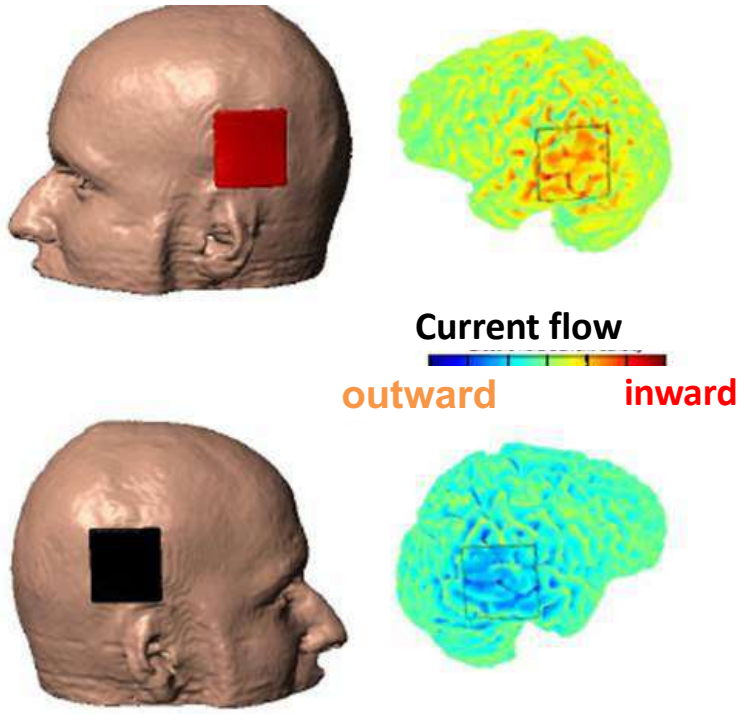
- Current passed between ANODE(+) and CATHODE(-)
- DC CURRENT FLOW across cortex.
- Current is INWARD under ANODE and OUTWARD under CATHODE



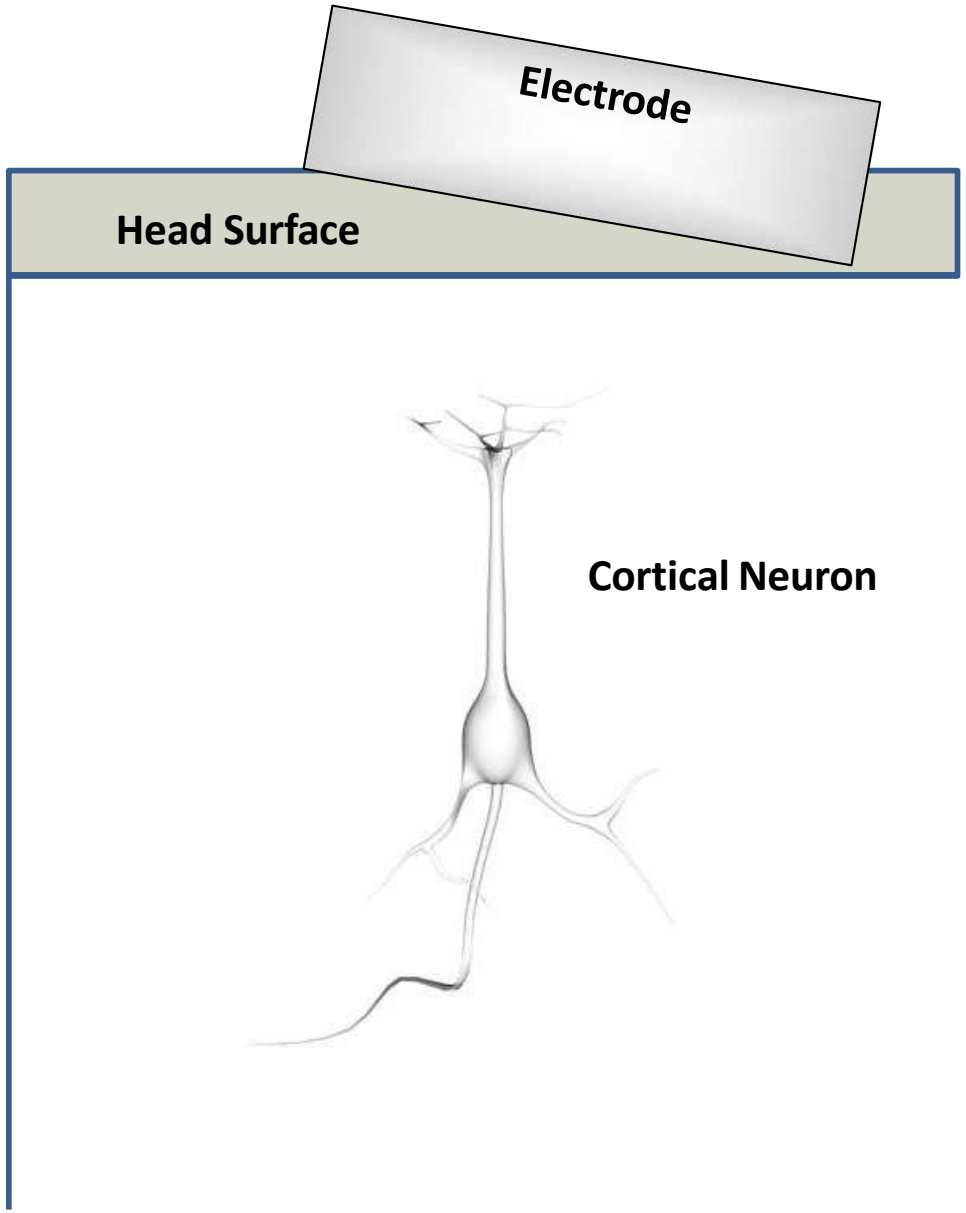
MRI derived computational model

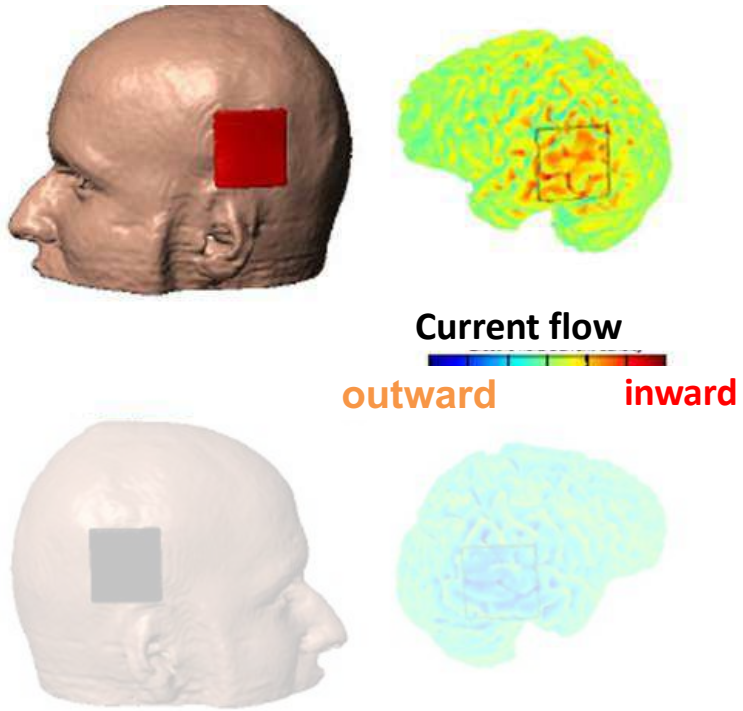


Radman et al.
Brain Stim. 2009

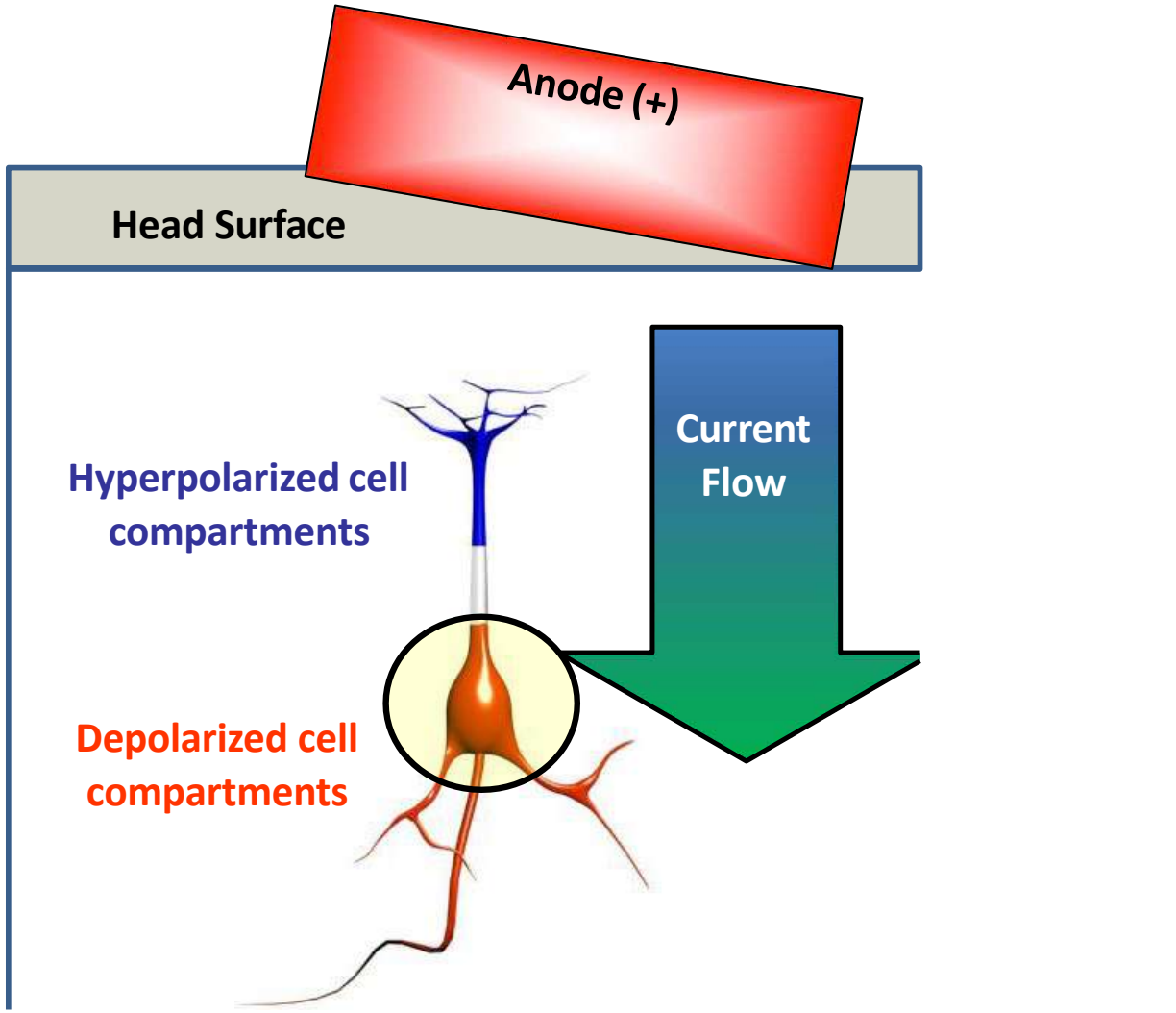


Radman et al.
Brain Stim. 2009

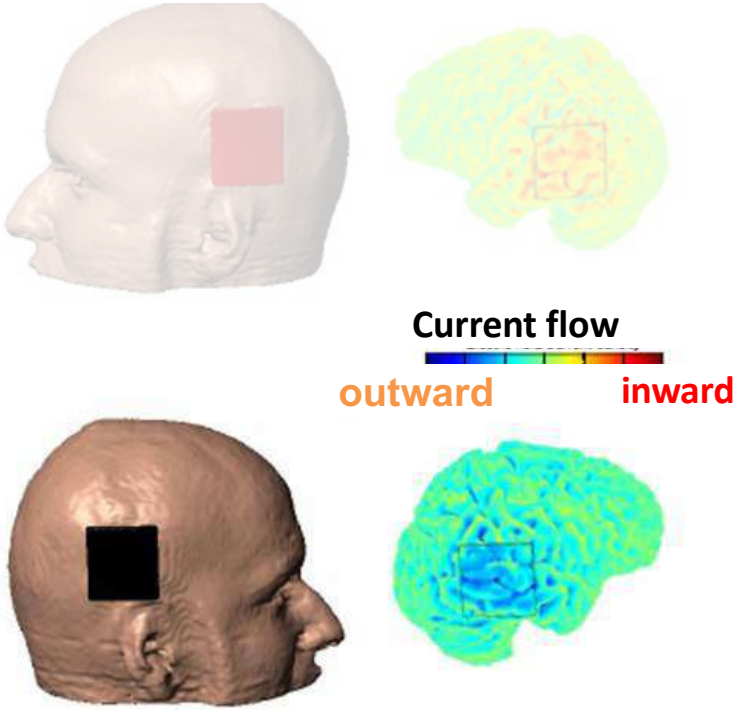




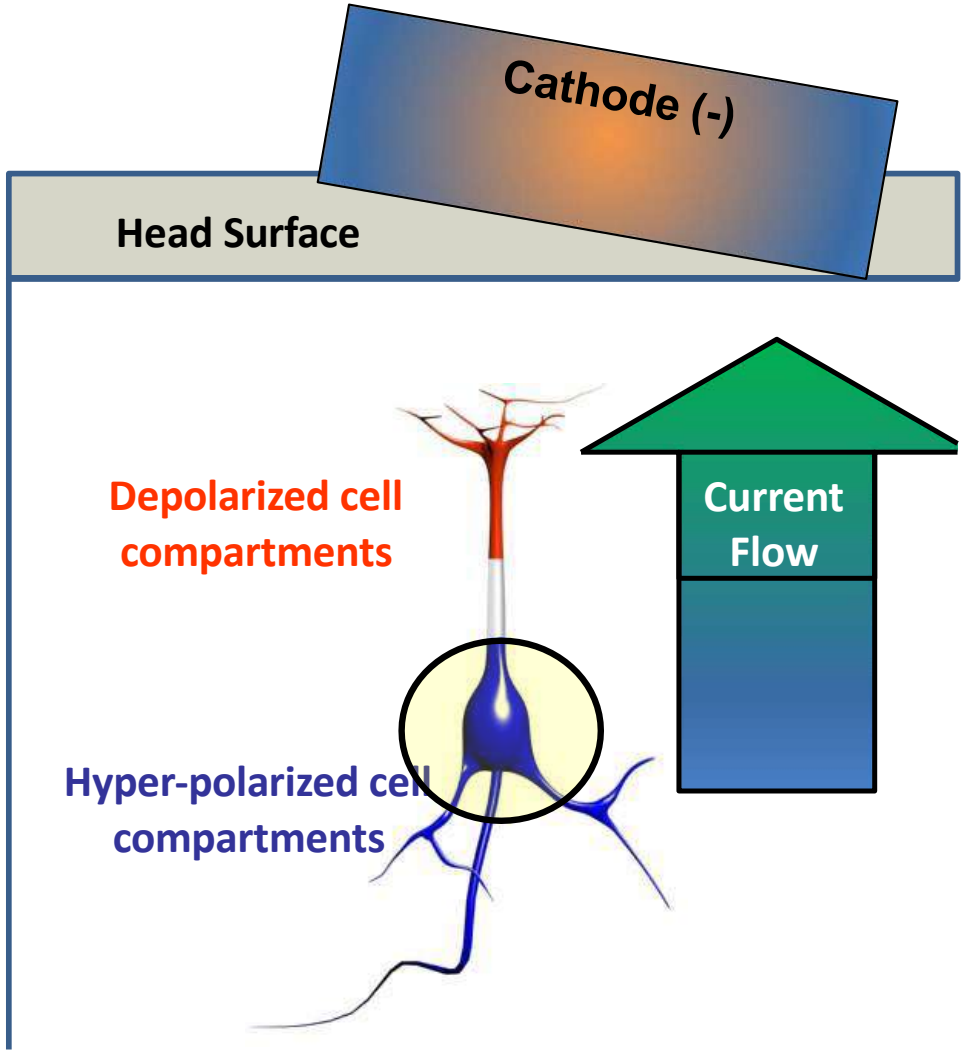
Radman et al.
Brain Stim. 2009



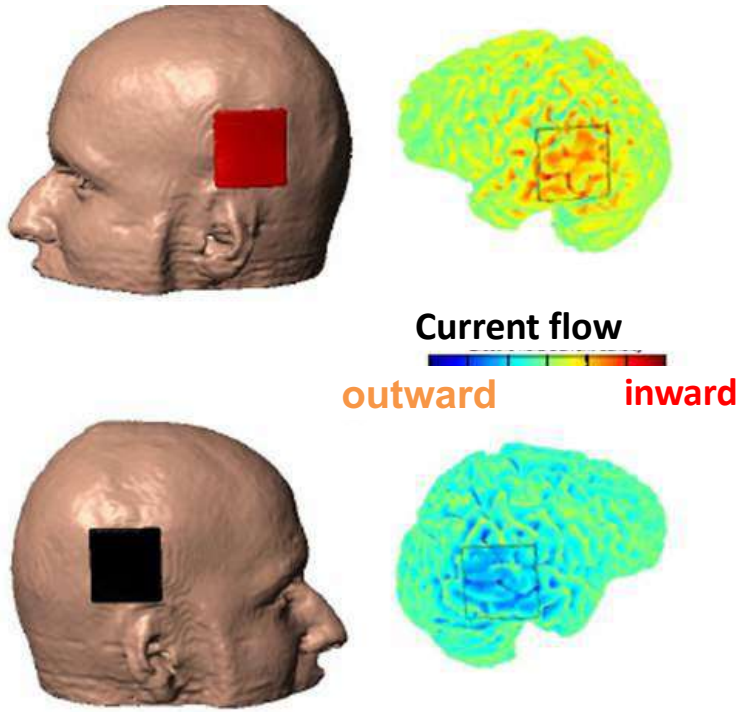
Increased Excitability / Plasticity



Radman et al.
Brain Stim. 2009



Decreased Excitability / Plasticity



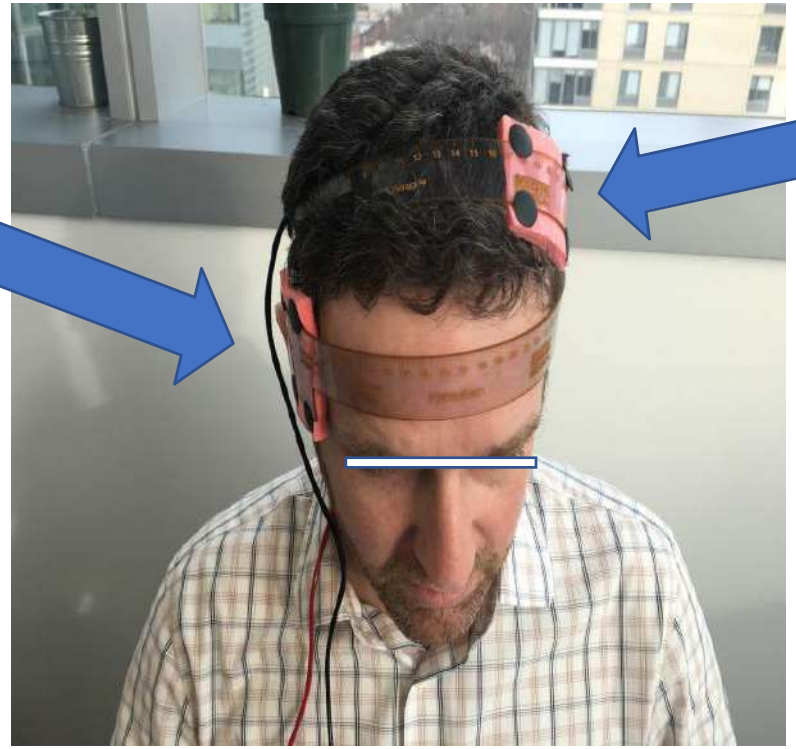
Central assumption: **Inward/Outward current flow produces Excitation/Inhibition**

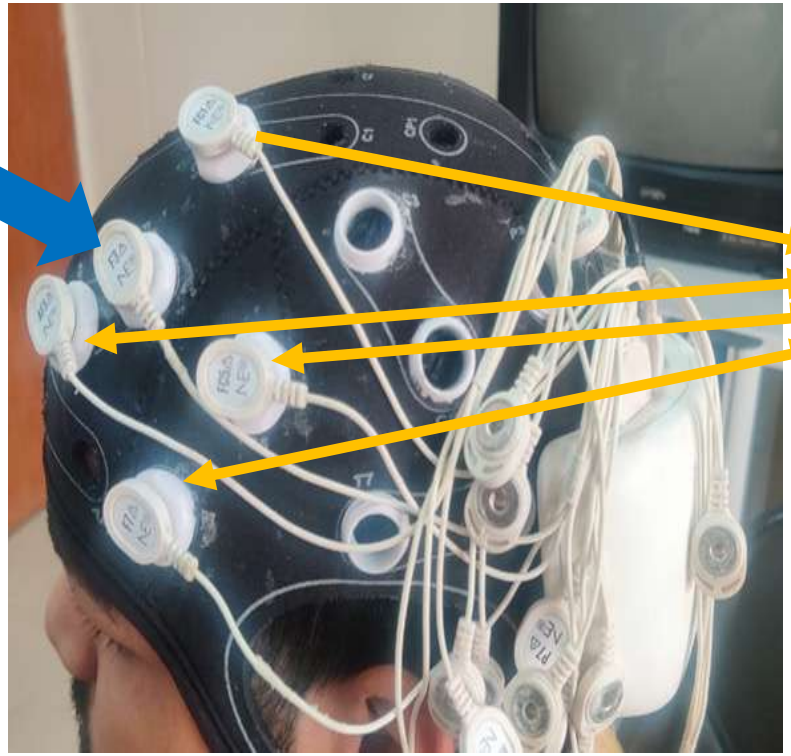
Then, classic tDCS design:

- **“Active” electrode placed over the target and polarity selected to Excite (Anode) or Inhibit (Cathode)**
- **“Return” (“reference”) electrode placed somewhere else, and ignored**

HD tDCS

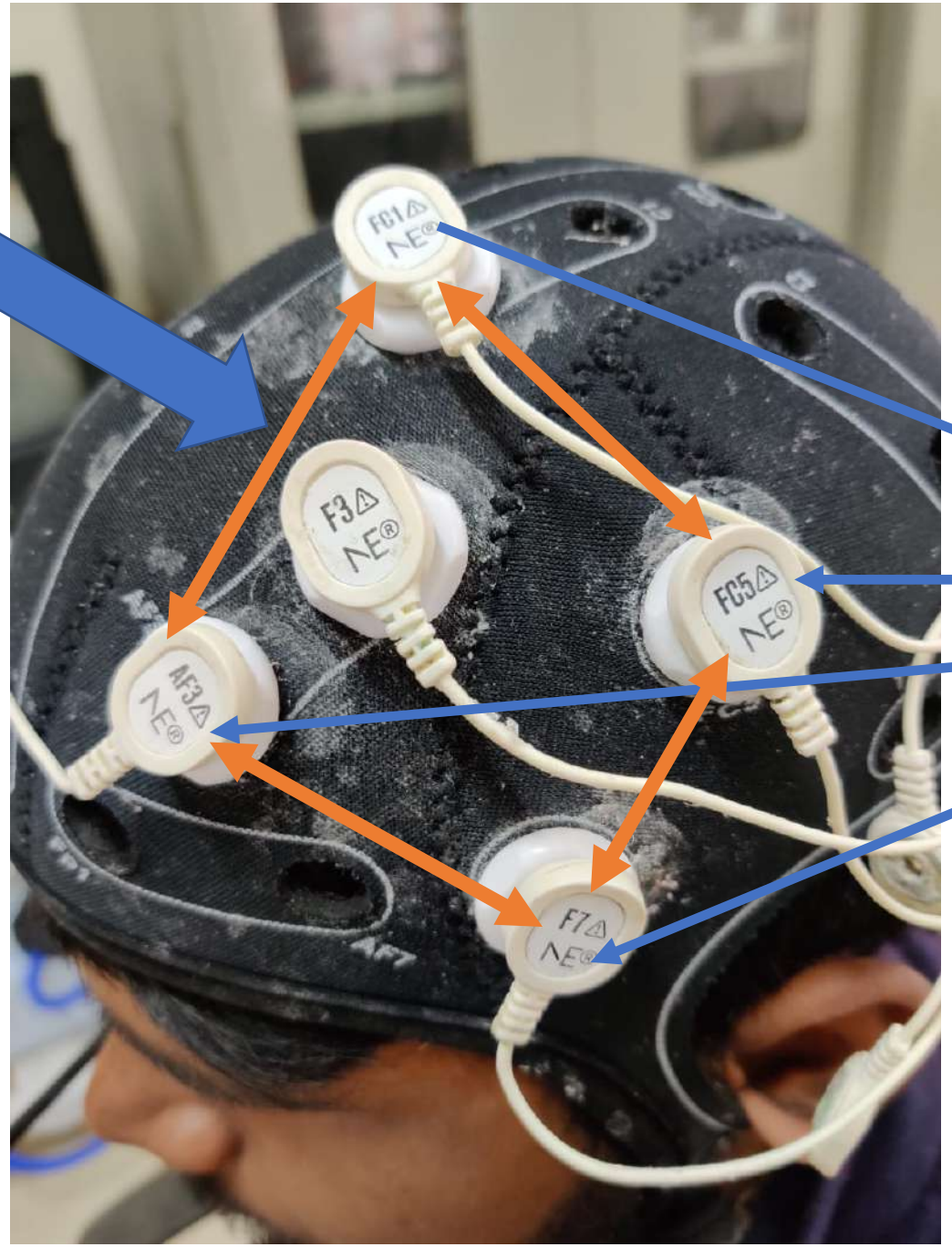
Conventional tDCS vs HD-tDCS





Polarity of the central HD electrode determines the dominant polarity of stimulation

LEFT DLPFC
ANODAL



CATHODAL

4*1 RING ARRANGEMENT

tDCS Recommendations

Table 1: tDCS indications and precautions

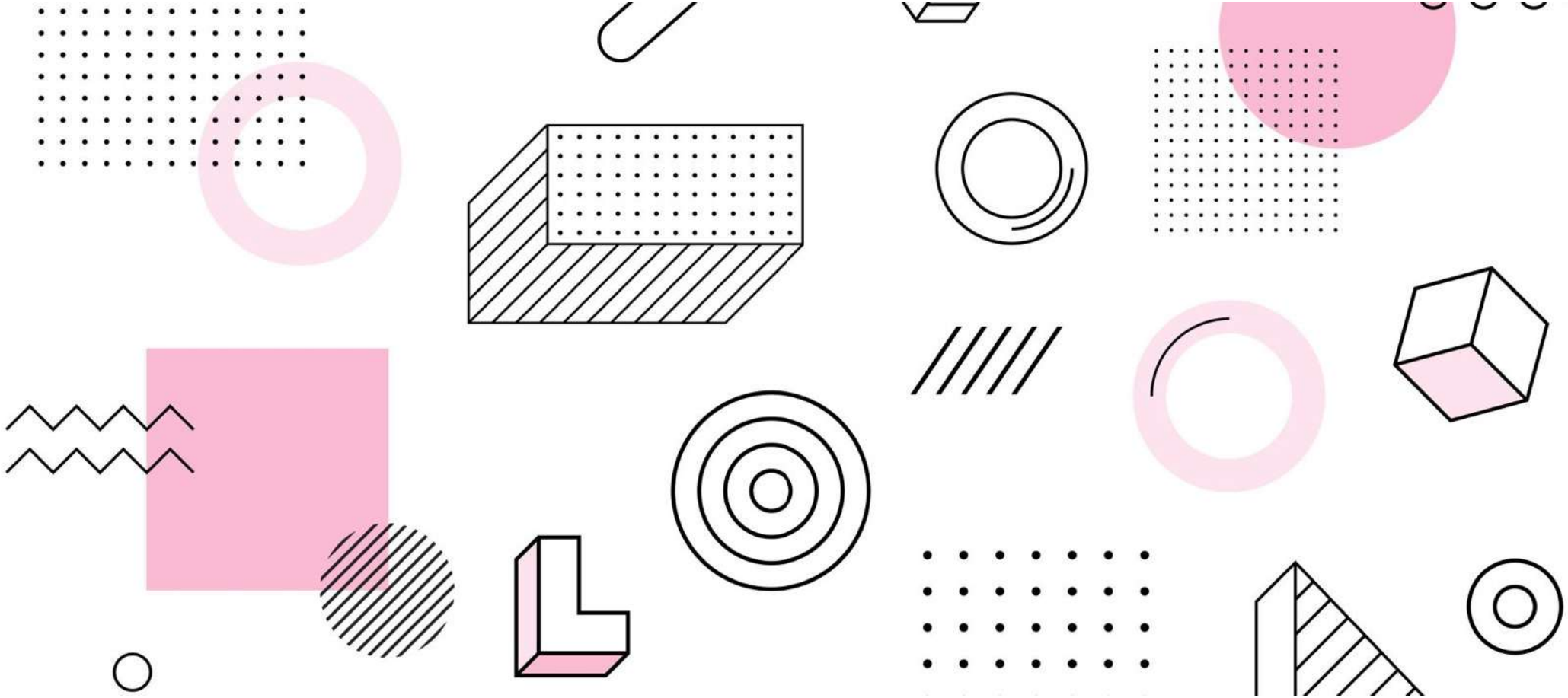
Indications	Precautions
1. Major depressive disorder 2. Persistent auditory hallucinations in schizophrenia. Possibly for positive and negative symptoms. 3. Craving in alcohol dependance and tobacco smoking: Relapse prevention 4. Obsessive-compulsive disorder 5. Mild cognitive impairment and dementia	a. Structural head injury b. Epilepsy in patient/family c. Scalp injury/skin lesions d. Implanted medical devices e. Foreign body in head/eyes f. Past history of adversities with tDCS/rTMS

Table 5: tDCS protocols for psychiatric disorders with promising evidence from RCTs

Diagnosis	Anode	Cathode	Duration	Sessions
Schizophrenia	Left DLPFC	Left TPJ	20 min	2 per day × 5 days
OCD*	Pre SMA	Right supraorbital	20 min	2 per day × 5 days
Craving (substance-use disorder)	Right DLPFC	Left DLPFC	20 min	1 per day × 5 days
Depression	Left DLPFC	Right DLPFC	30 min	1 per day × 10 days^
Dementia/MCI[$]	Left DLPFC	Right supraorbital	20 min	1 per day × 5 days

*In OCD three types of montages: SMA/Pre-SMA anode, SMA/Pre-SMA cathode, and right cerebellar anode are found to be effective. ^20-30 days of stimulation are attempted in a few large RCT. [$]In dementia, one RCT has used 10 days daily sessions every month for 8 months. OCD: Obsessive compulsive disorder; SUD: Substance use disorder; DLPFC: Dorsolateral prefrontal cortex; SMA: Supplementary motor area; TPJ: Temporoparietal junction; MCI: Mild cognitive impairment

Hybrid Stimulation



EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

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NEUROSYSTEMS

Combined transcranial alternating current stimulation and continuous theta burst stimulation: a novel approach for neuroplasticity induction

Mitchell R. Goldsworthy,[1] Ann-Maree Vallence,[1,2] Ruiting Yang,[1] Julia B. Pitcher[1] and Michael C. Ridding[1]

ORIGINAL STUDY

Transcranial Direct Current Stimulation Priming of Therapeutic Repetitive Transcranial Magnetic Stimulation

A Pilot Study

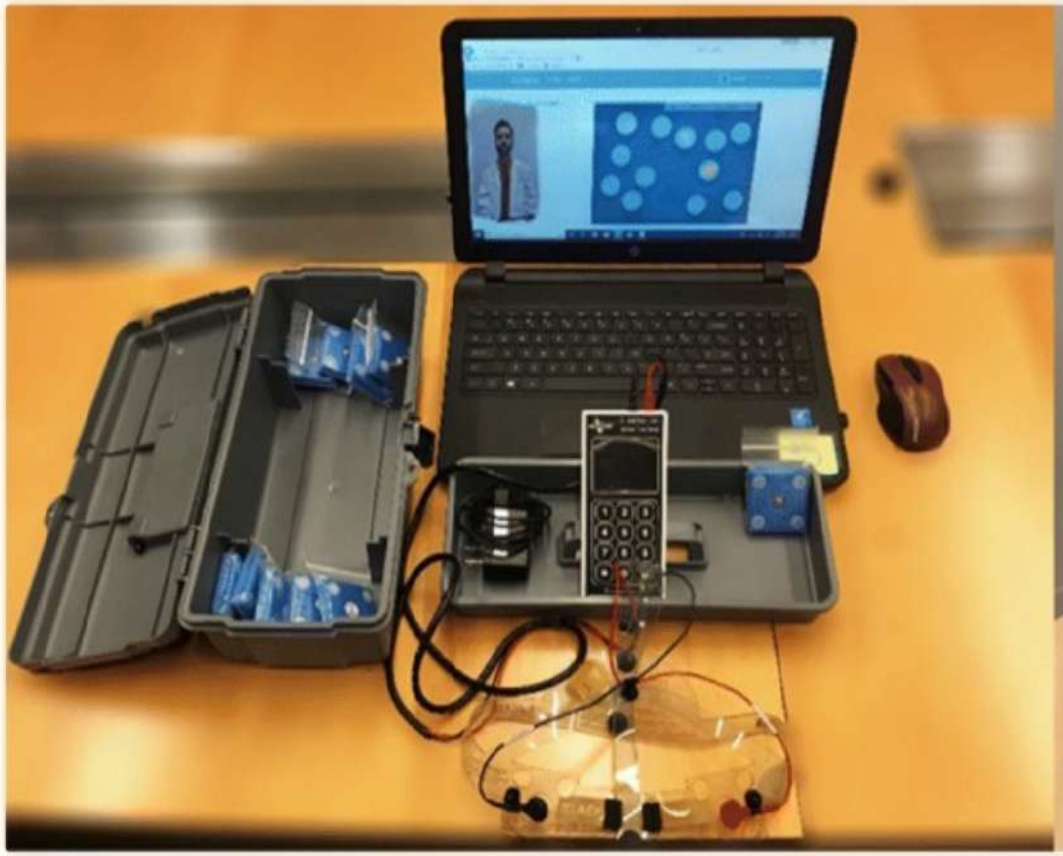
Colleen Loo, MBBS, FRANZCP, MD,†‡ Donel Martin, BSocSc (Hons), PhD,*†*
Melissa Pigot, BPsych (Hons),† Patrick Arul-Anandam,**
Philip Mitchell, MBBS, MD, FRANZCP, FRCPsych,† and Perminder Sachdev, MD, PhD, FRANZCP,*§*

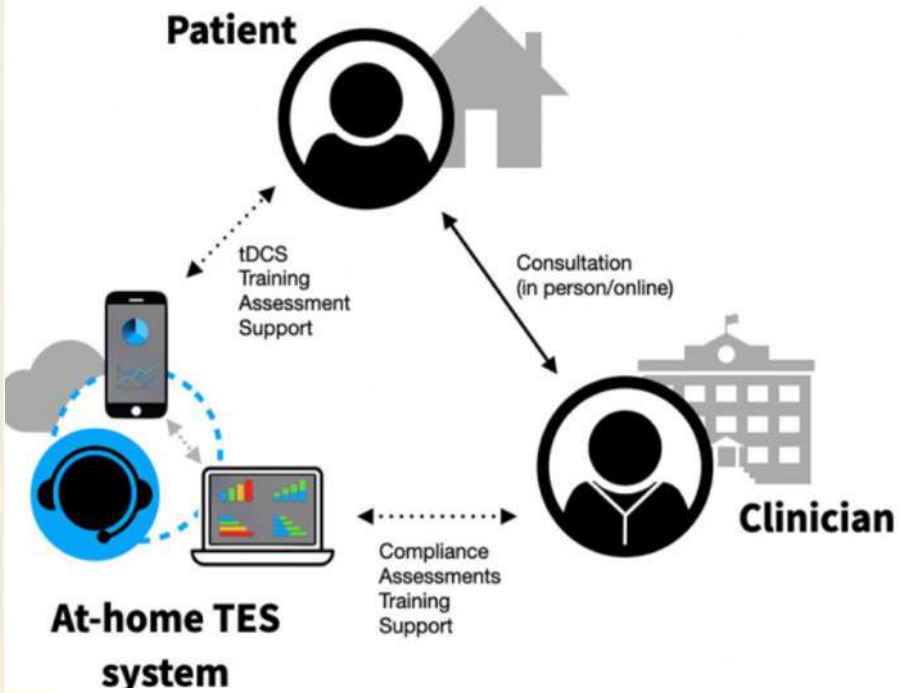
Other emerging or experimental methods

- Deep Brain Stimulation (DBS)
- Transcranial Electrical Stimulation (TENS)
- Transcranial Alternating Current Stimulation (tACS)
- Random Noise Stimulation
- Transcranial Laser Stimulation using Functional Infrared Spectroscopy
- External Trigeminal Nerve Stimulation

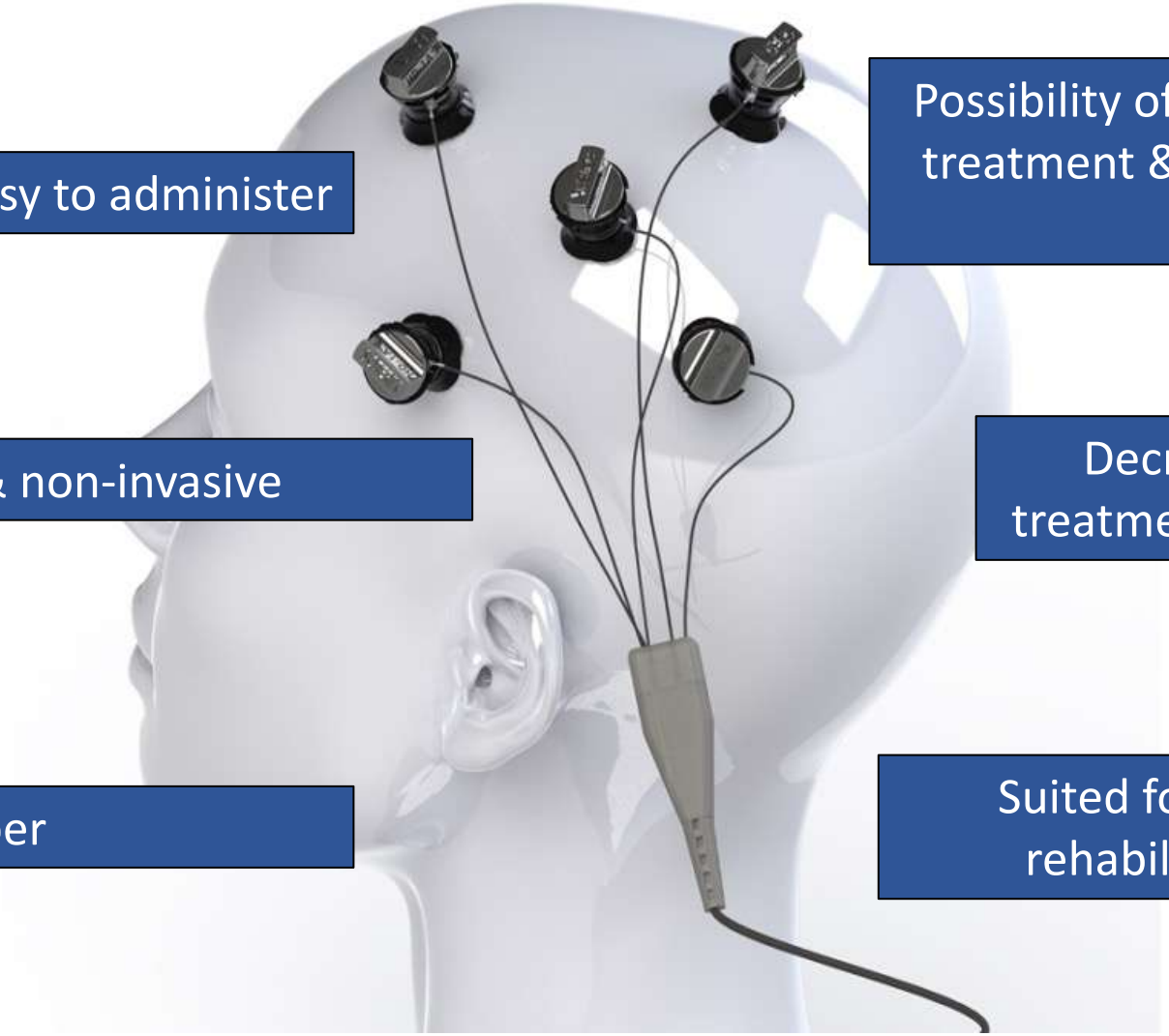
What Future Beholds??

Tele-tECS




Patient
tDCS
Training
Assessment
Support
Consultation
(in person/online)
Clinician
Compliance
Assessments
Training
Support
At-home TES
system

Tele-tECS



Easily portable & Easy to administer

Possibility of remotely supervised treatment & resolve accessibility barriers

Safe & non-invasive

Decreases visits to clinic for treatment & increases compliance

Cheaper

Suited for long term use & rehabilitation in old age

Ethics of Brain Stimulation

Although the risk is small, it is always present, we have to see:

- How can you **minimize risk** & discomfort?
- What is the **minimal stimulation** necessary?
- Is the TMS information **clear and consent informed**?
- Are subjects *always* **screened**?
- Is the practitioner safety **trained**?
- Are **emergency procedures** clear & in place?

Safety

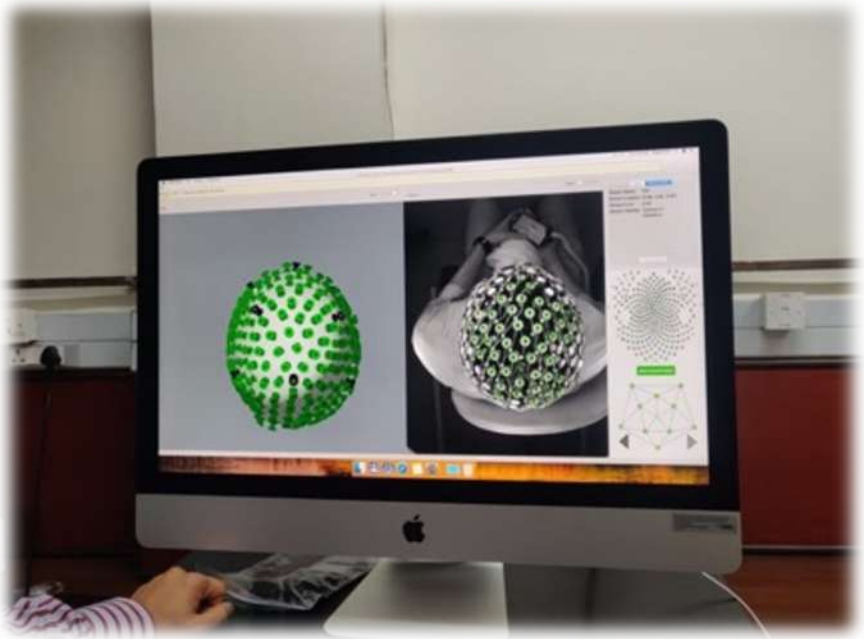
- Heating
- Magnetic field exposure
- Hearing
- Metal implants
- Seizures

Adverse effects

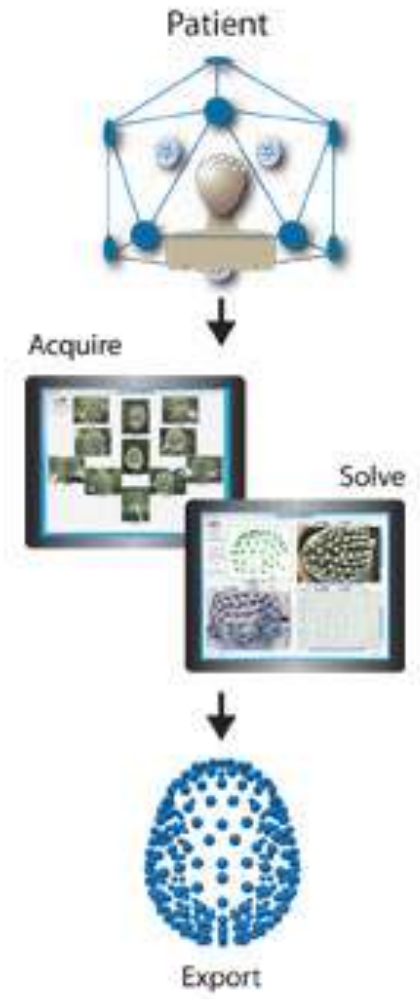
- Most serious one is **seizure**

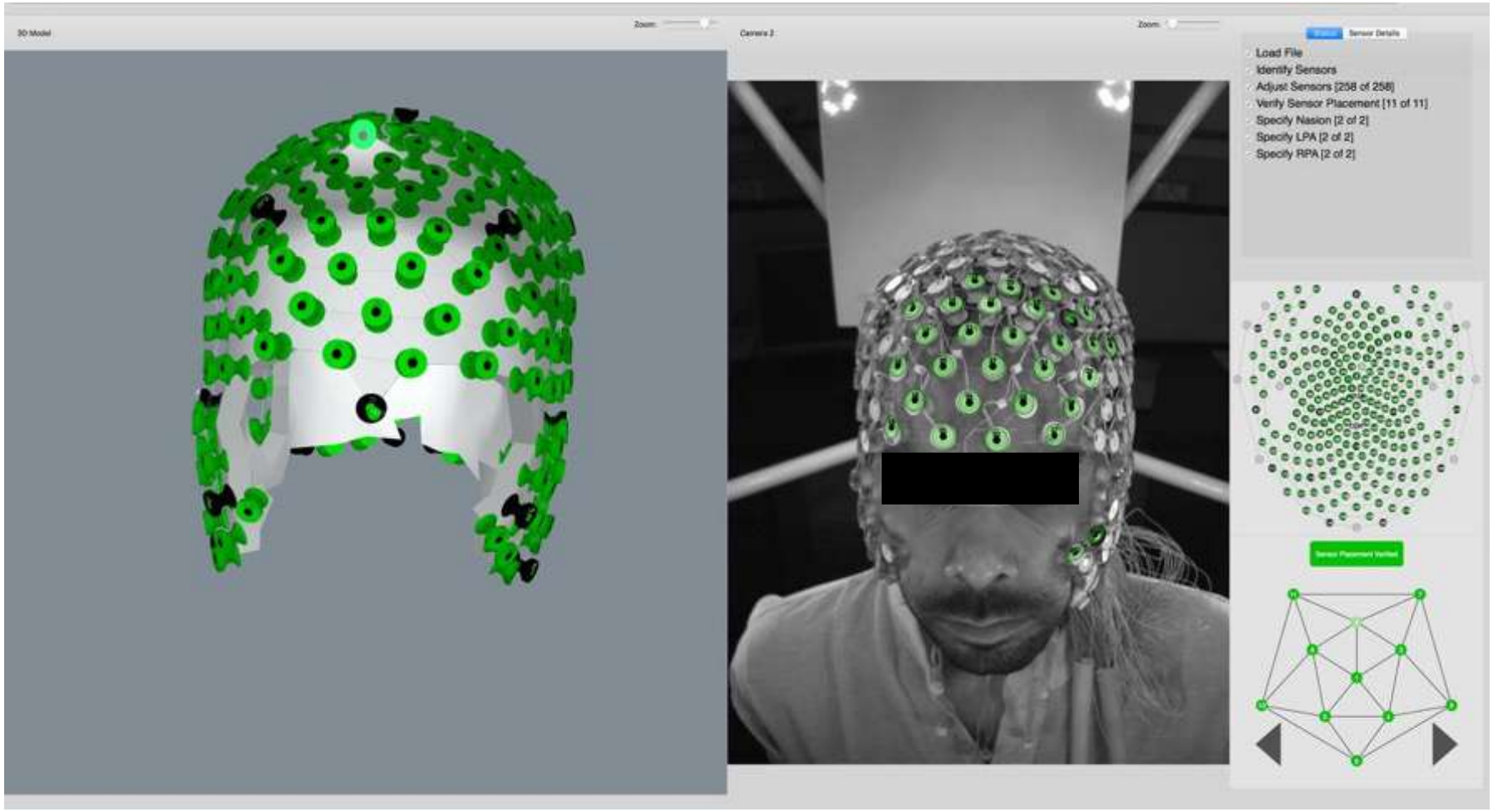
- Common side effects are
  - Scalp tenderness
  - Facial twitching
  - Acute mood changes
  - Neck pain, syncope, nausea, dizziness, erythema, sleepiness .. Short lasting and rarely require symptomatic management
  - Burning of the scalp

Precision Neuromodulation…

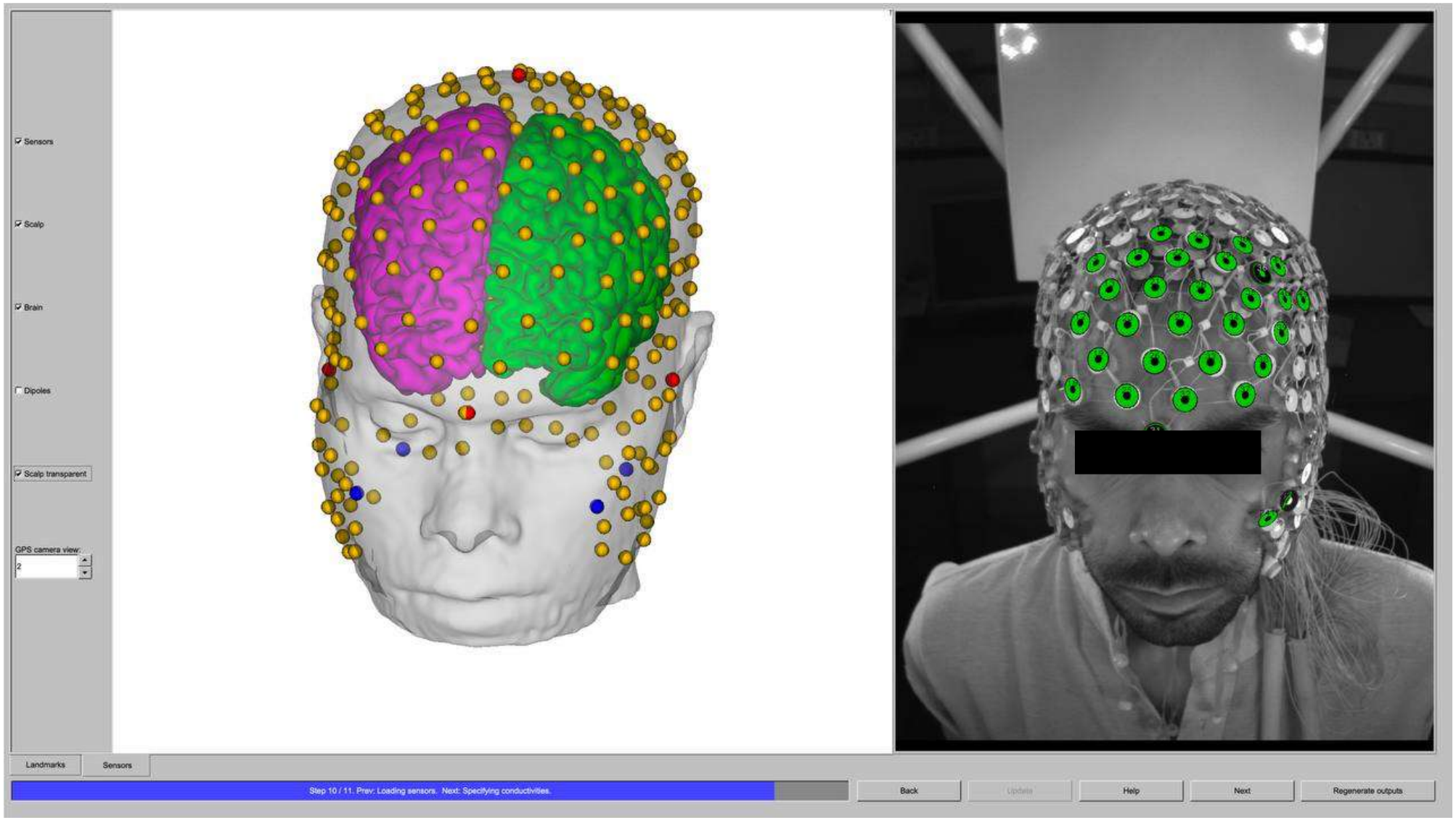


Geodesic Photogrammetry System (GPS)

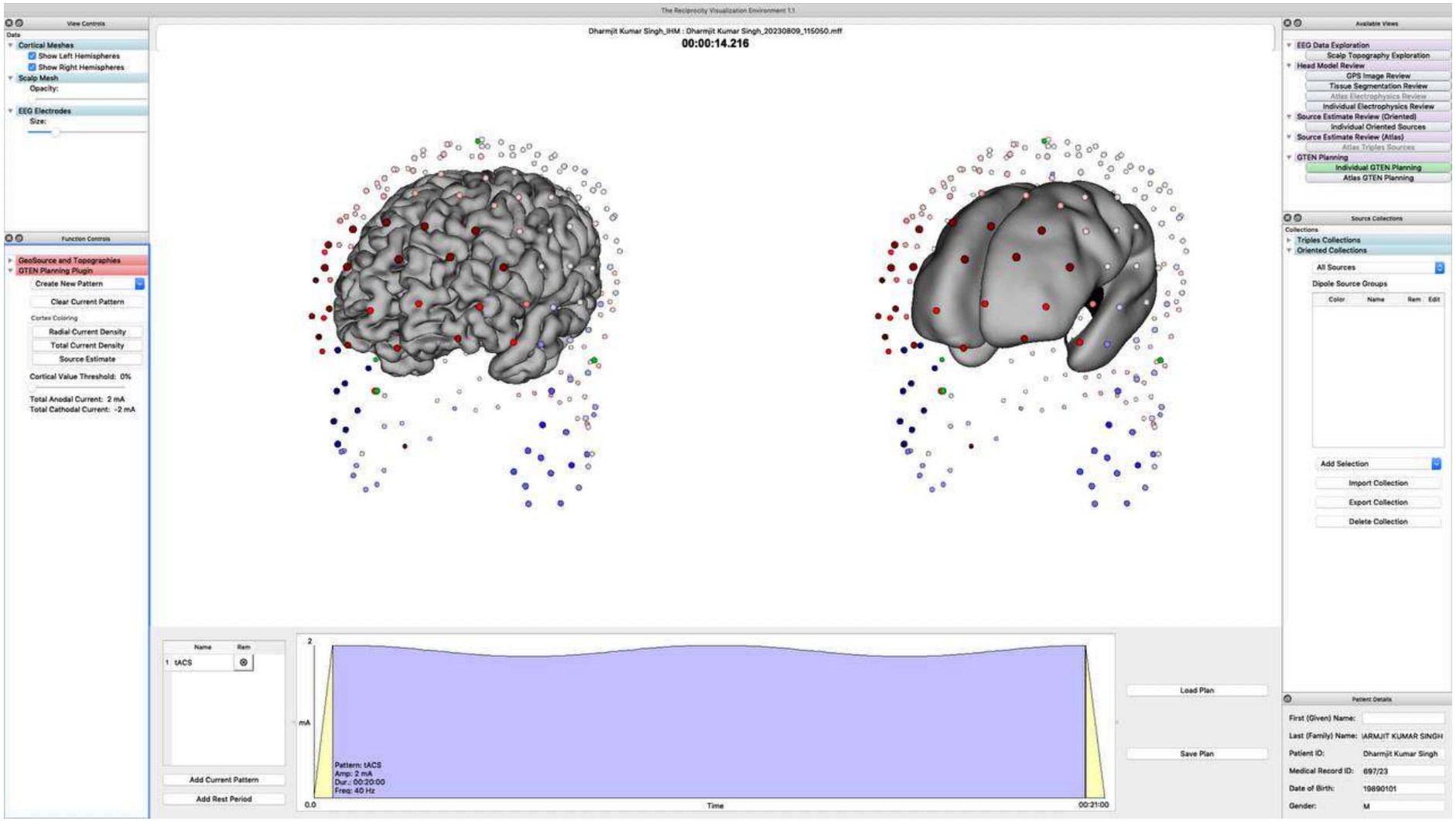




Individual Head Model via FEM



Individual GTEN Planning



Conclusion

- The **subspecialty of "interventional psychiatry"** has been proposed
- Need for **formal recognition** of interventional psychiatry as a subspecialty
- Need for **operationalized training programs** in this rapidly emerging field
- The cultivation of a properly trained cohort of interventional psychiatrists will **better meet the challenges of treatment-resistant psychiatric illness**
- **Safe and ethical practice**, while facilitating a **more informed development** and **integration of novel neuromodulation techniques**

Thank You for your kind attention!!!

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