rTMS in MDD & OCD

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Neuromodualtion
Deep TMS

1. **MDD** (Major Depressive Disorder)
2. **OCD** (Obsessive Compulsive Disorder)

1. Pharmacotherapy is the main stay

2. Psychological Therapies(CBT….)

3. Interventional Strategies: (NIBS)

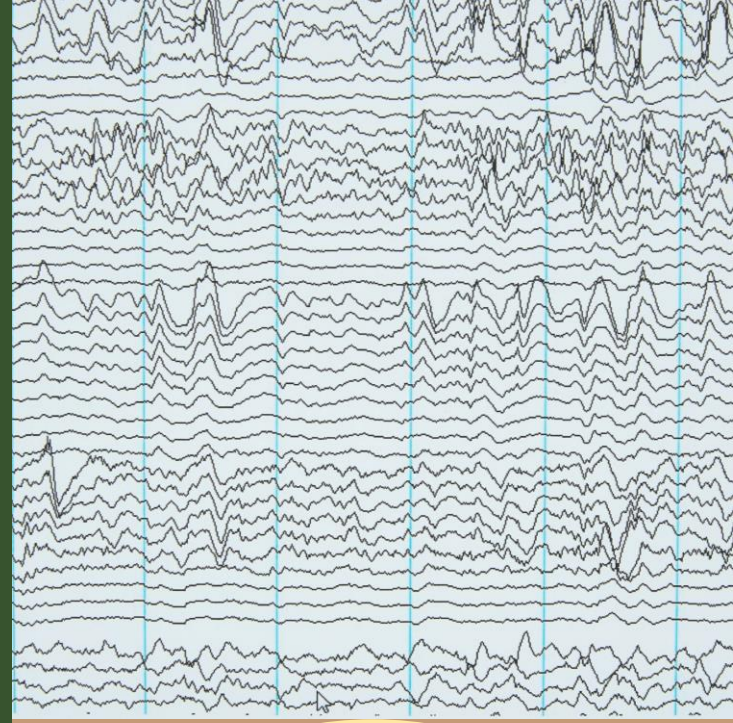
The Third Augmenting or Third Alternative Intervention

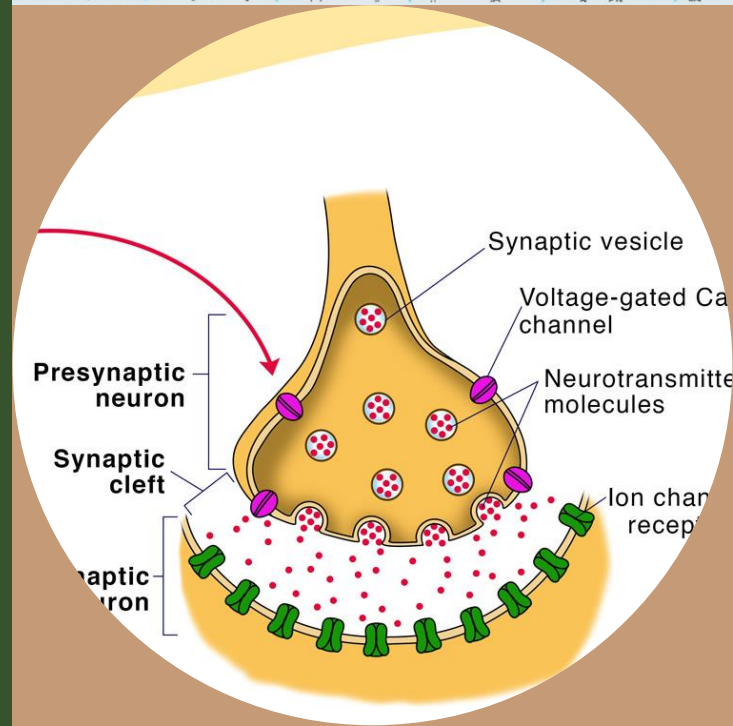
Brain is an Electro Chemical Organ

- **Electrical – EEG**
- **Chemical – NE, DA, AcH, 5HT, GABA…**

- **Parkinsonism Treatment**
- 1. Dopaminergic, Anticholinergic
- 2. Deep Brain Stimulation – Invasive Neuromodulation

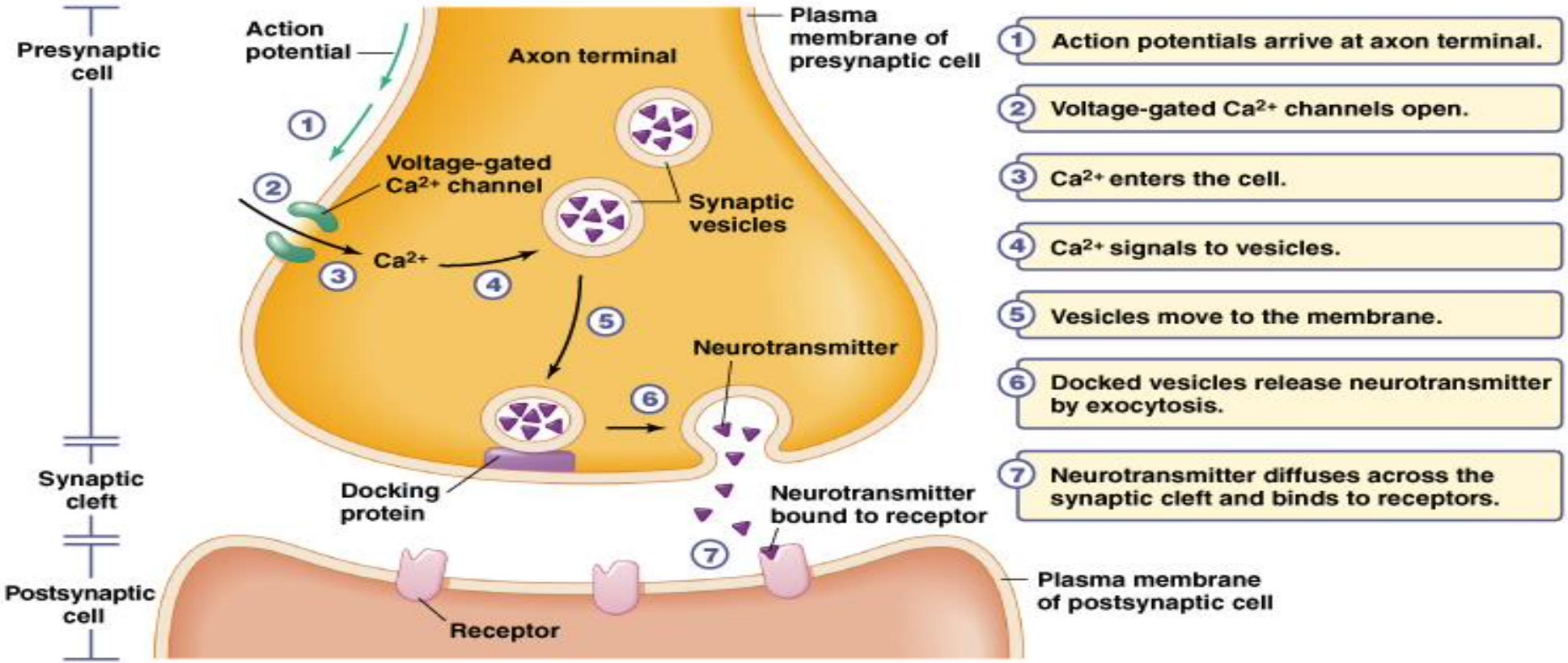
- **MDD / OCD Treatment**
- 1. Serotonergic …..
- 2. **Noninvasive Neuromodulation – Augment / Alternate**






AMERRA

(excitatory/inhibitory)



Historically in Psychiatry…..

I. Asylums – Living dead……failed, Deinstitutionalization

II. 20th Century first half Two Disruptive Events happened

1. **Freud & Watson**

2. **Neuromodualtion – ECT (1938), Psychosurgery(1930)**

III. 20th Century 2nd Half: Pharmacotherapy

3. CPZ, IMI – Disruptive innovation, IP Stay, Exhaustion

4. **SSRI** & SGA

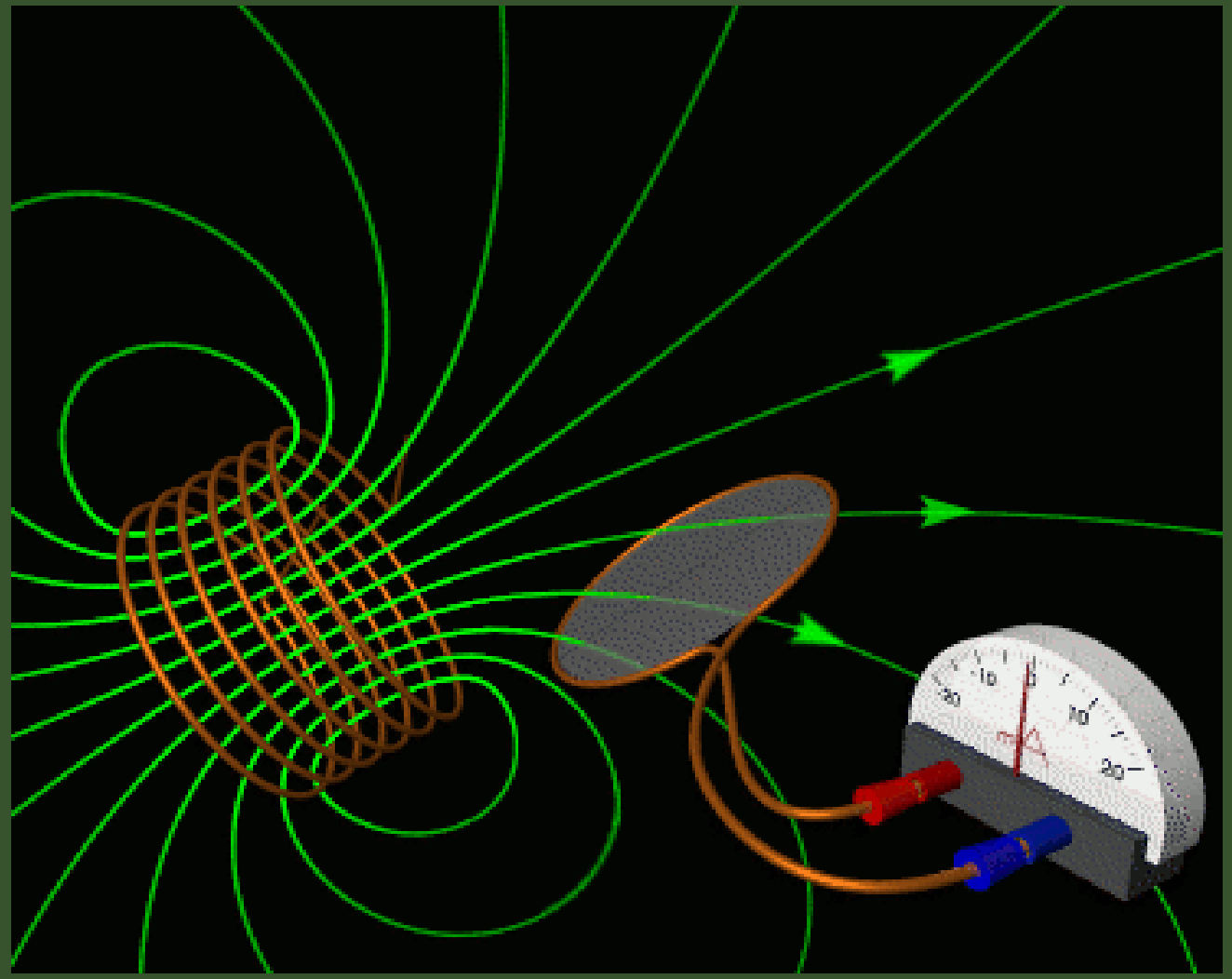
IV. 21st Century:

1. Neuromodualtion (Revisited) – Neurobiology, Decade of Brain, Connectivity……

2. Telepsychiatry – Science and Technological advance of digitalization. WWW FF by Pandemic….

Electric current flows through the solenoid producing a changing **magnetic field**.

Magnetic field causes an **Electric current** to flow in a wire loop



H1-Coil
for Major Depressive Disorder (MDD)

H7-Coil
for Obsessive-Compulsive Disorder (OCD)

H4-Coil
for Smoking Cessation

Traditional TMS Coil
for Major Depressive Disorder (MDD)

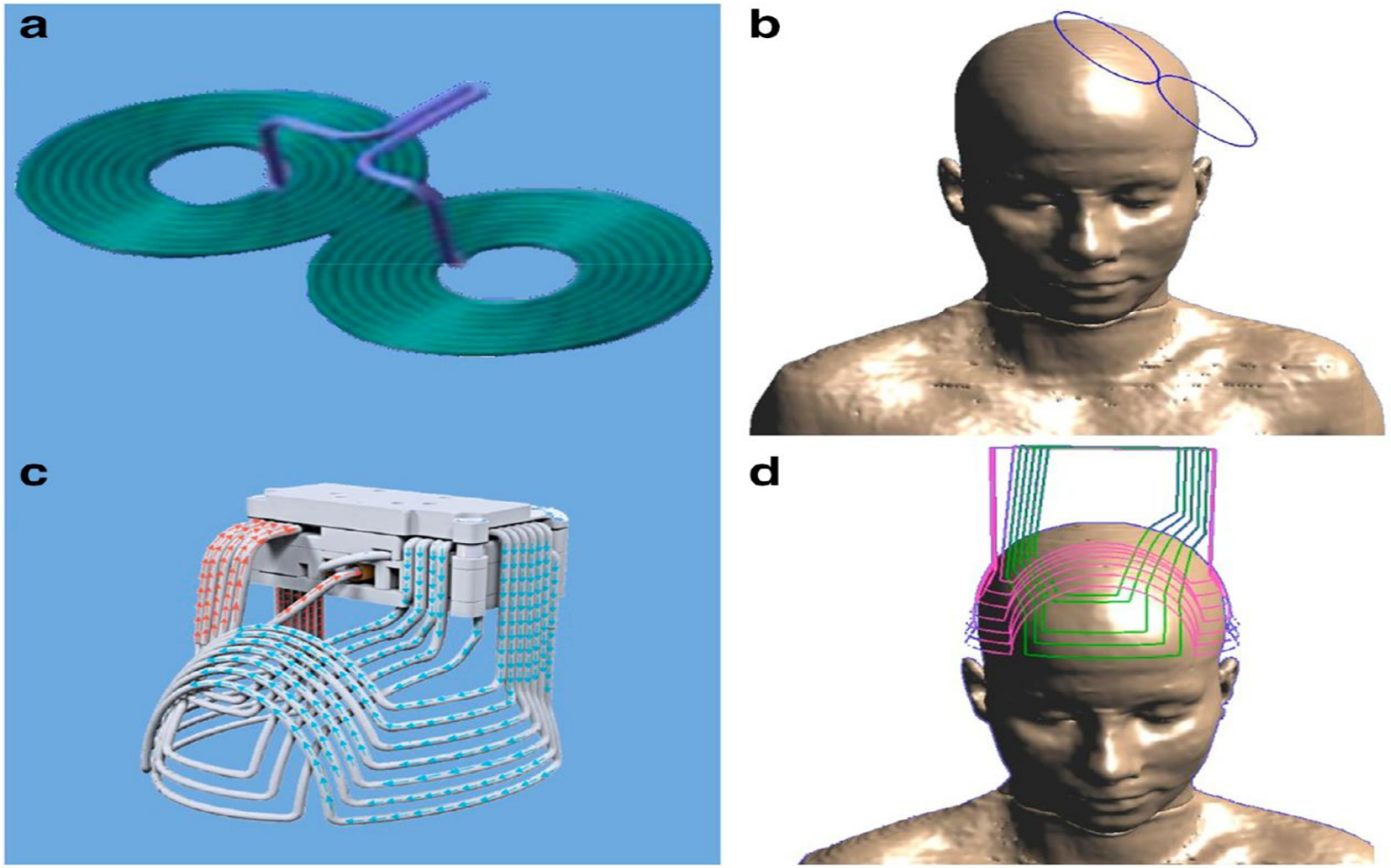
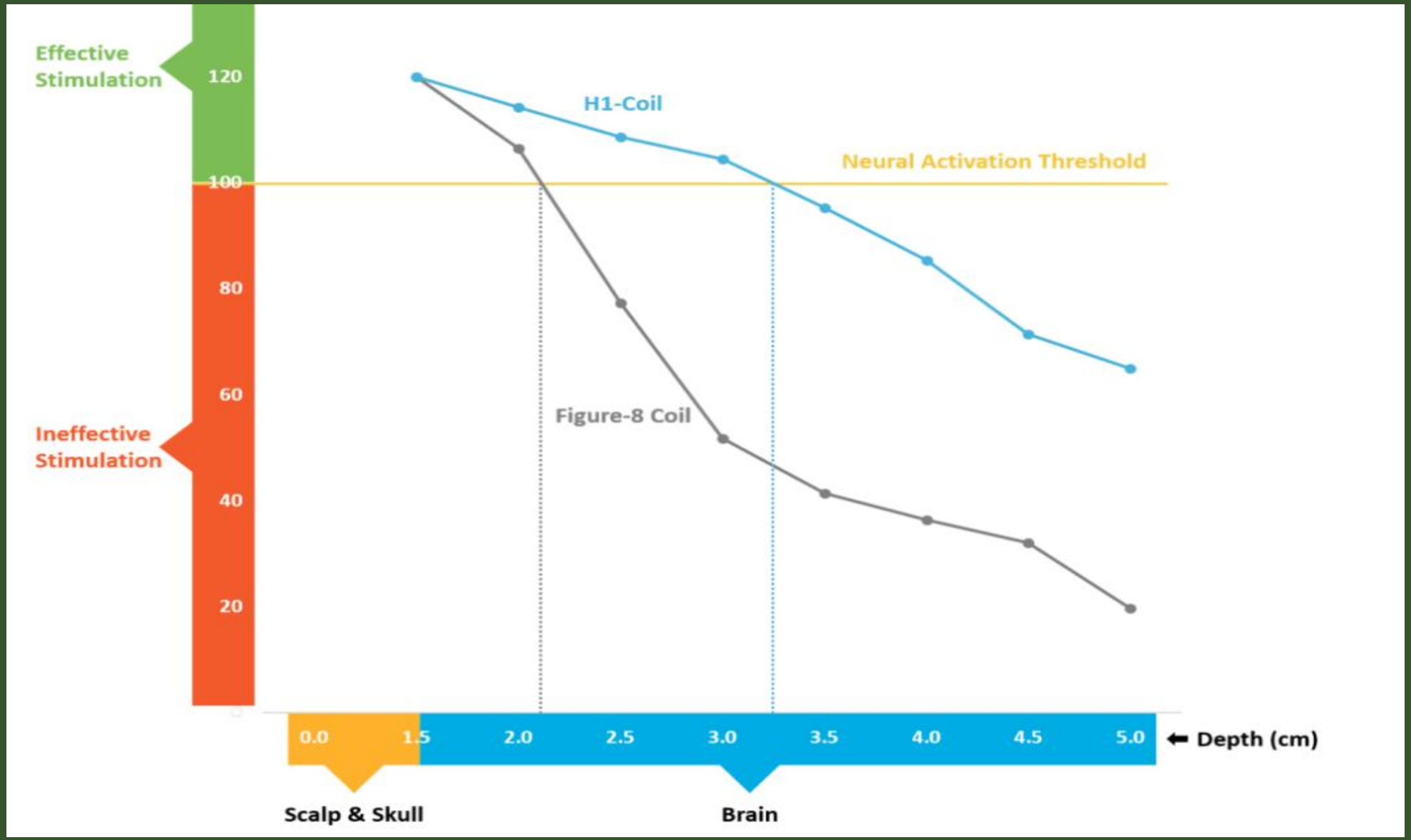
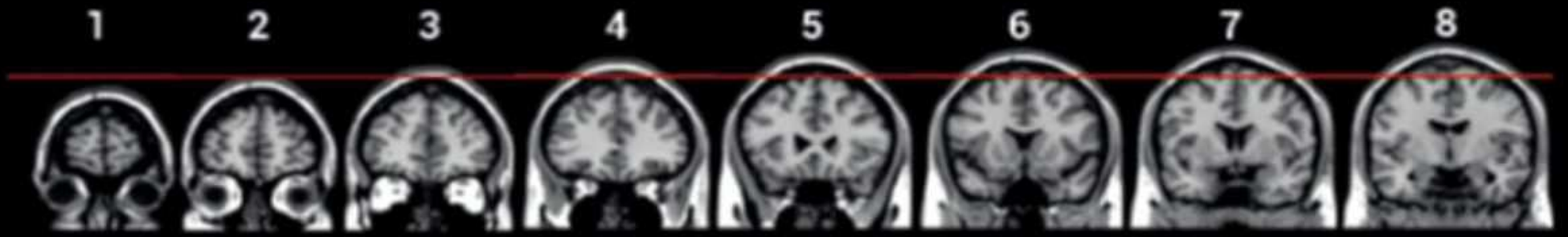


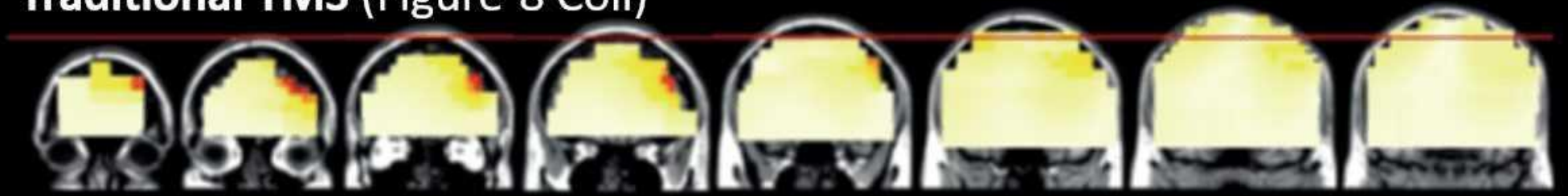
Fig. 1 Coil Designs of the figure-8 coil (a,b) and H1 coil (c,d). Schematic of the figure-8 coil (a) and its placement on the head targeting the left dlPFC (b); adapted with permission from (Parazzini et al., 2017b). Schematic of the H1 coil (c) and its placement on the head targeting the left dlPFC (d); adapted with permission from (Parazzini et al., 2017b).


Effective Stimulation
120
100
80
60
Ineffective Stimulation
40
20
H1-Coil
Neural Activation Threshold
Figure-8 Coil
0.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Depth (cm)
Scalp & Skull
Brain

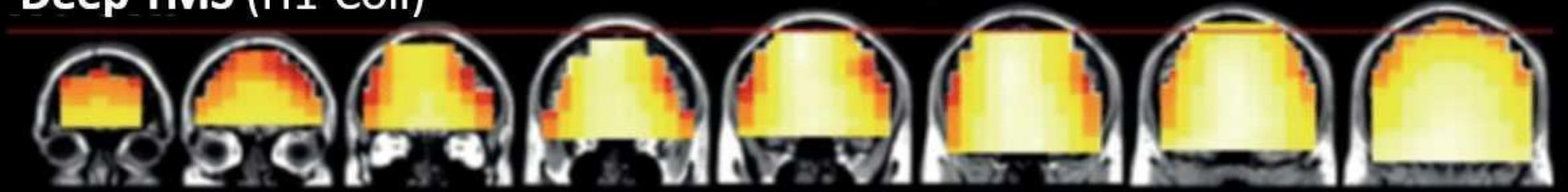
Electric Field Distribution Maps

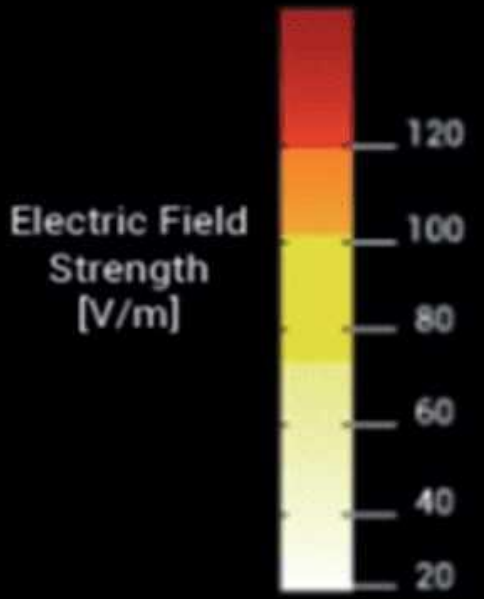


Traditional TMS (Figure-8 Coil)



Deep TMS (H1-Coil)





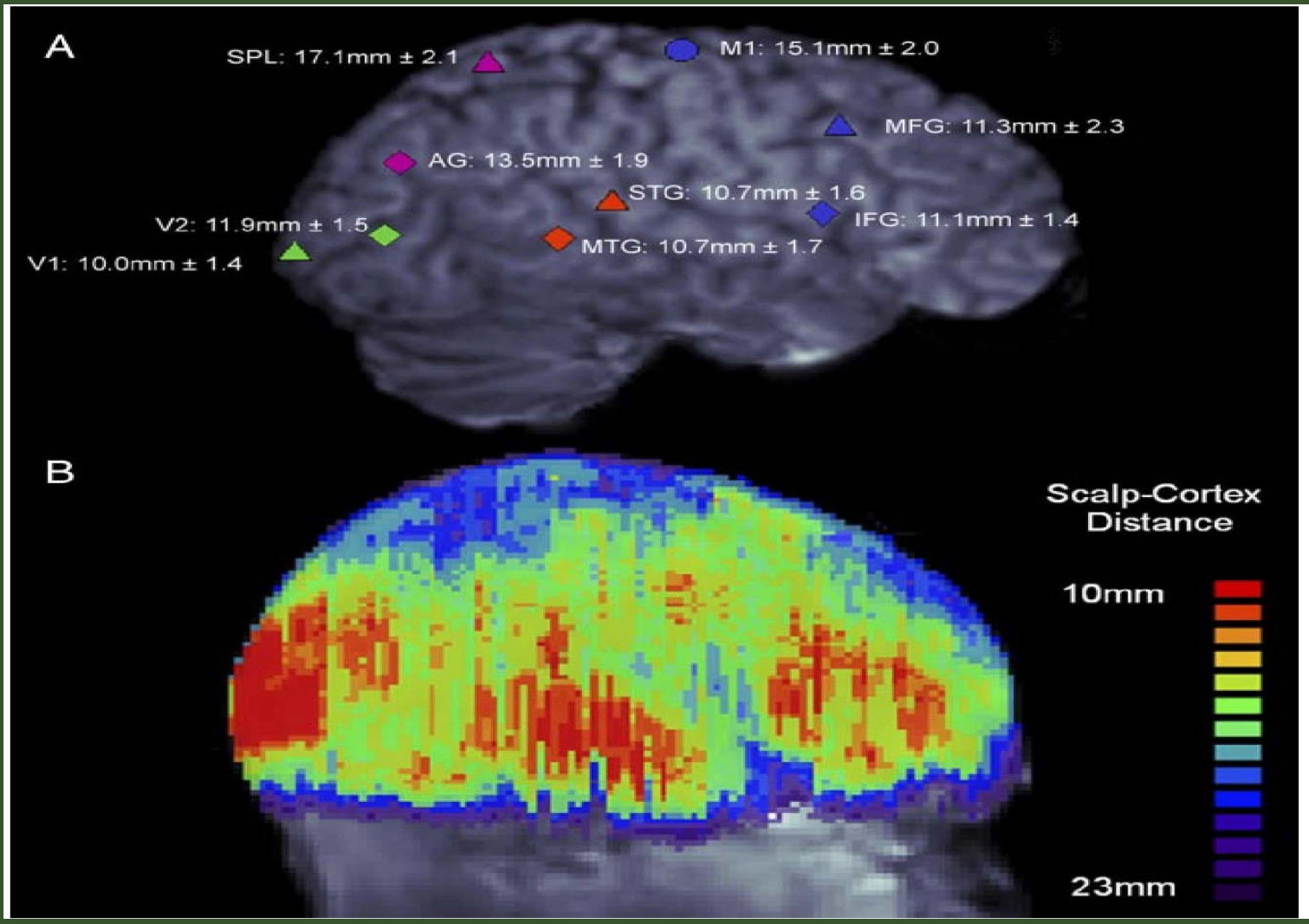


FIG. 3. The depth of underlying cortex varies across the surface of the scalp. *A*: scalp-cortex distance was measured across a range of brain regions. Mean ± SD of the distances between scalp and cortex are shown for each site. Frontal sites (blue): primary motor cortex (M1/BA4: circle), middle frontal gyrus (MFG/BA9: triangle), inferior frontal gyrus (IFG/BA45, diamond). Temporal sites (red): superior temporal gyrus (STG/BA22: triangle), middle temporal gyrus (MTG/BA 21: diamond). Parietal sites (purple): superior parietal lobule (SPL/BA7: triangle) and angular gyrus (AG/BA39: diamond). Occipital lobe sites (green): primary visual cortex (V1/BA17: triangle) and secondary visual cortex (V2/BA18: diamond). [B] Scalp-cortex distances for each voxel representing the scalp surface, shown in the right hemisphere of one participant. Distance is color-coded, with red representing small distances, and blue/purple representing large distances.

Stokes et al. J Neurophysiol, 94 (2005) 4520-7

Jean-Pascal Lefaucheur, Evidence-based guidelines on the therapeutic use of rTMS: An update (2014–2018) Clinical Neurophysiology 131 (2020) 474–528

- A group of European experts reappraised the guidelines

TMS can produce significant clinical improvement in various neurological and psychiatric disorders.

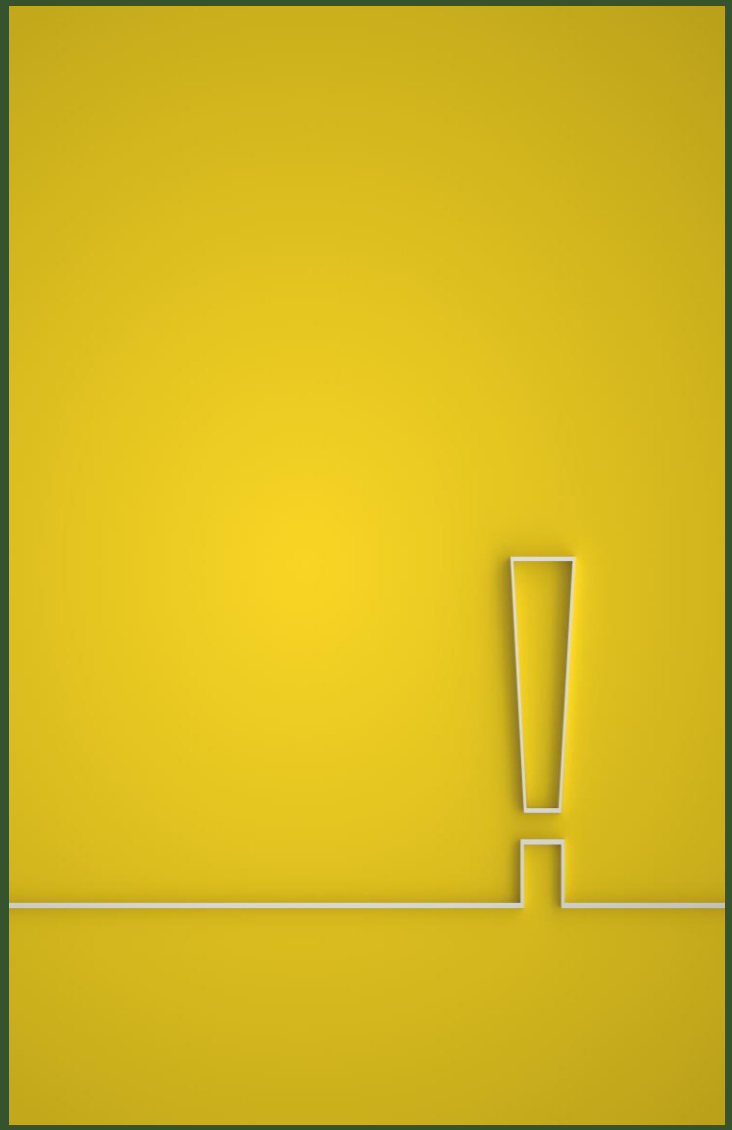
Updated guidelines on the therapeutic use of rTMS are presented, including 2014–2018 publications.

Higher evidence of efficacy is present in the areas of

Depression

Pain

Post Acute Motor Stroke



S. Rossi, A. Antal, S. Bestmann et al.,

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues:

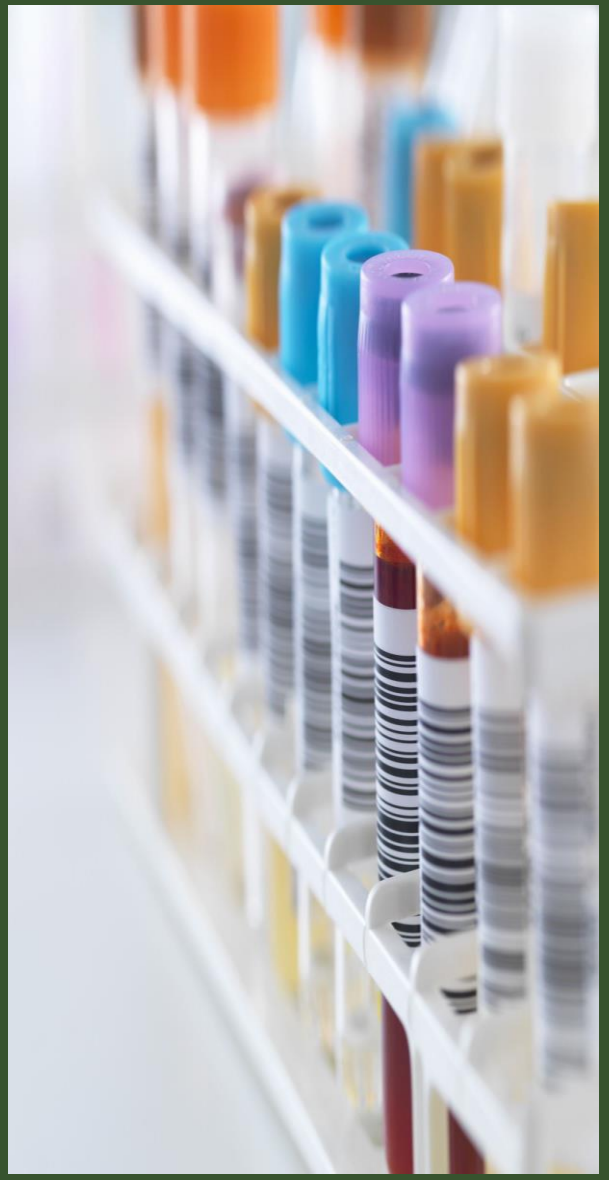
Expert Guidelines, **Clinical Neurophysiology, https://doi.org/10.1016/j.clinph.2020.10.003**

International Federation of Clinical Neurophysiology (IFCN)

- This is the **THIRD** article on safety of use of repetitive Transcranial Magnetic Stimulation (rTMS) in clinical practice and research following by eleven years the

- **last IFCN guidelines (Rossi et al., 2009),** which itself followed the

- **first guidelines by eleven years (Wassermann, 1998)**



SEIZURES

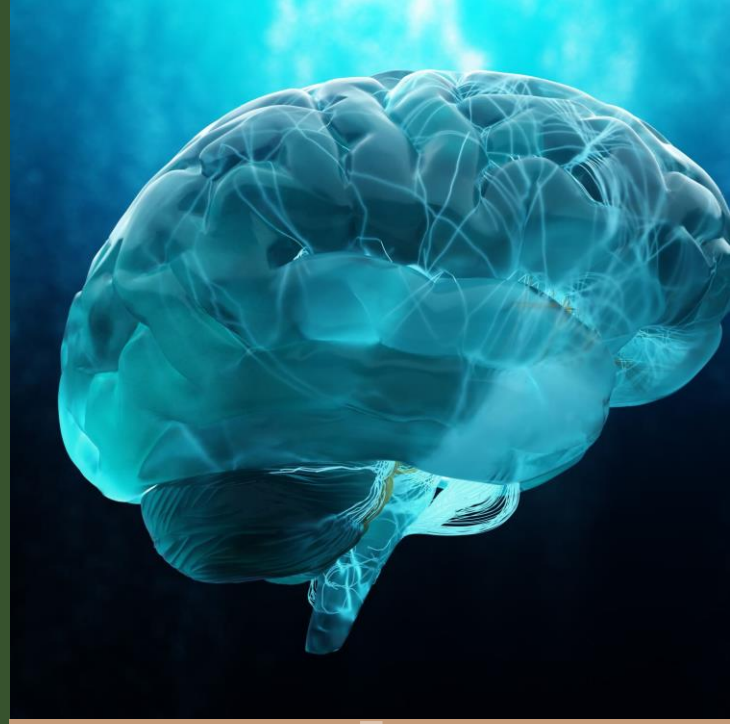
- Stultz et al, TMS Safety with Respect to Seizures: A Literature Review, Neuropsychiatric Disease and Treatment 2020:16 2989–3000

- The risk of TMS-related seizures is **0.00037%**

- TMS has successfully been used in patients with epilepsy, traumatic brain injuries, and those with a prior TMS-related seizure.

- **Over 62% of seizures occurred on the first exposure to TMS**

- 75% occurred within the first three exposures.



The combined use of TMS with MRI or magnetic resonance spectroscopy (MRS) has great clinical and neuroscientific potential.

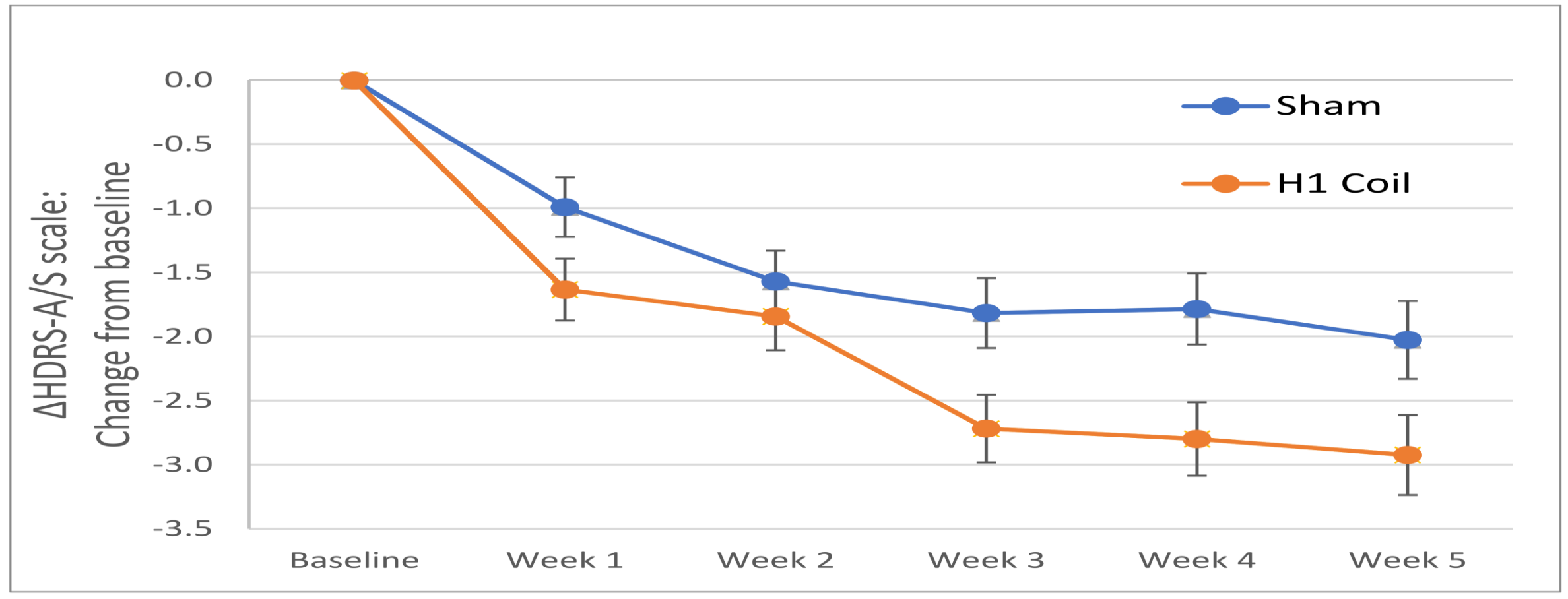
it can capture TMS- induced changes in tissue concentrations of relevant molecules such as glutamate or GABA in brain regions of interest

Diffusion weighted imaging **(DWI)** can help to link TMS-induced plasticity to regional changes in brain microstructure and to derive information about the structural connectivity of the targeted brain region.

TMS can also be combined with functional MRI **(fMRI)** to delineate immediate and longer lasting effects of the TMS intervention on regional brain activity as well as functional connectivity within and among brain networks (Bestmann et al., 2008; Ruff et al., 2009).

fMRI can be used as **functional localizer** to identify the optimal cortical target. DWI and fMRI can also reveal brain **regions that are indirectly stimulated by TMS** through spread of excitation along pre-existing neuronal connections.

Gaby S Pell et al, **Efficacy of Deep TMS with the H1 Coil for Anxious Depression**
J Clin Med. 2022 Feb 15;11(4):1015.



Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Real-world efficacy of deep TMS for obsessive-compulsive disorder: Post-marketing data collected from twenty-two clinical sites

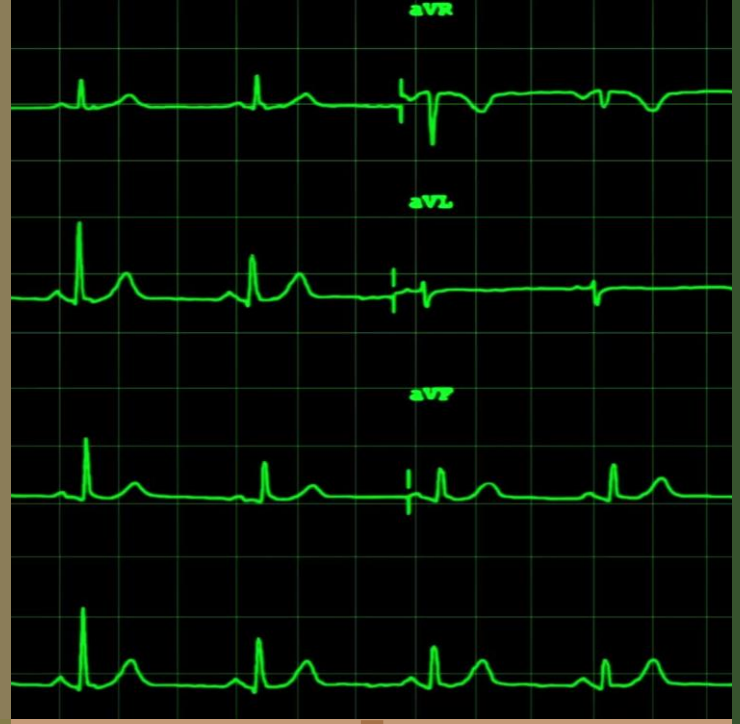
Yiftach Roth [a,b,*], Aron Tendler [a,b,c], Mehmet Kemal Arikan [d], Ryan Vidrine [e], David Kent [f], Owen Muir [g], Carlene MacMillan [h], Leah Casuto [i], Geoffrey Grammer [j], William Sauve [j], Kellie Tolin [k], Steven Harvey [l], Misty Borst [m], Robert Rifkin [l], Manish Sheth [n], Brandon Cornejo [o], Raul Rodriguez [p], Saad Shakir [q], Taylor Porter [r], Deborah Kim [s], Brent Peterson [t], Julia Swofford [u], Brendan Roe [u], Rebecca Sinclair [g], Tal Harmelech [b], Abraham Zangen [a]

- 22 clinical sites with H7-coils provided data on details of treatment and outcome (YBOCS) measures from a total of 219 patients

- 167 patients who had at least one post-baseline YBOCS measure were included in the main analyses

- Overall first and sustained response rates were 72.6% and 52.4%, respectively
- The response rate was 57.9% in patients who had YBOCS scores after 29 dTMS sessions

- First response was achieved in average after 18.5 sessions (SD = 9.4) or 31.6 days (SD = 25.2)
- Onset of sustained one-month response was achieved in average after 20 sessions (SD = 9.8) or 32.1 days (SD = 20.5)
- Average YBOCS scores demonstrated continuous reduction with increasing numbers of dTMS sessions



- Reddy S, Shreekantiah U, Goyal N, and Roy C (2022). Brain activation alterations with adjunctive deep TMS in OCD: an fMRI study. CNS Spectrum

- 15 OCD patients received 10 sessions of high-frequency dTMS using the H7 coil

- fMRI was used to measure the activation of brain regions while performing the Stroop task in additio0n to YBOCS & HAM D

- significant improvement in the obsessive-compulsive, anxiety, and depressive symptoms after the 2 weeks of the dTMS treatment.

- A significant decrease in the activation of left caudate nucleus and adjacent white matter was noted while performing the Stroop task after the dTMS treatment.

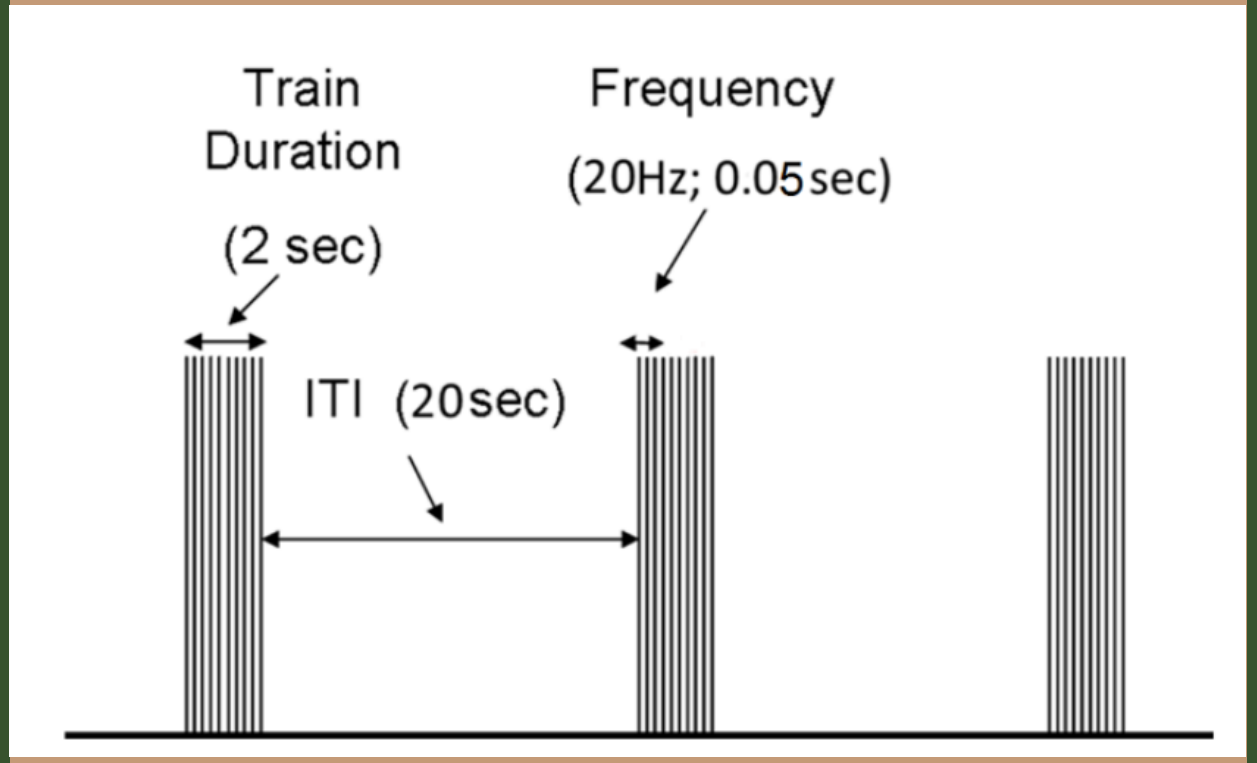
- Conclusion. The study provides preliminary evidence for functional correlates of effectiveness of dTMS as an adjunctive treatment modality for OCD.

Voigt et al. BMC Psychiatry (2019) 19:13

A systematic literature review of the clinical efficacy of rTMS in non-treatment resistant patients with MDD

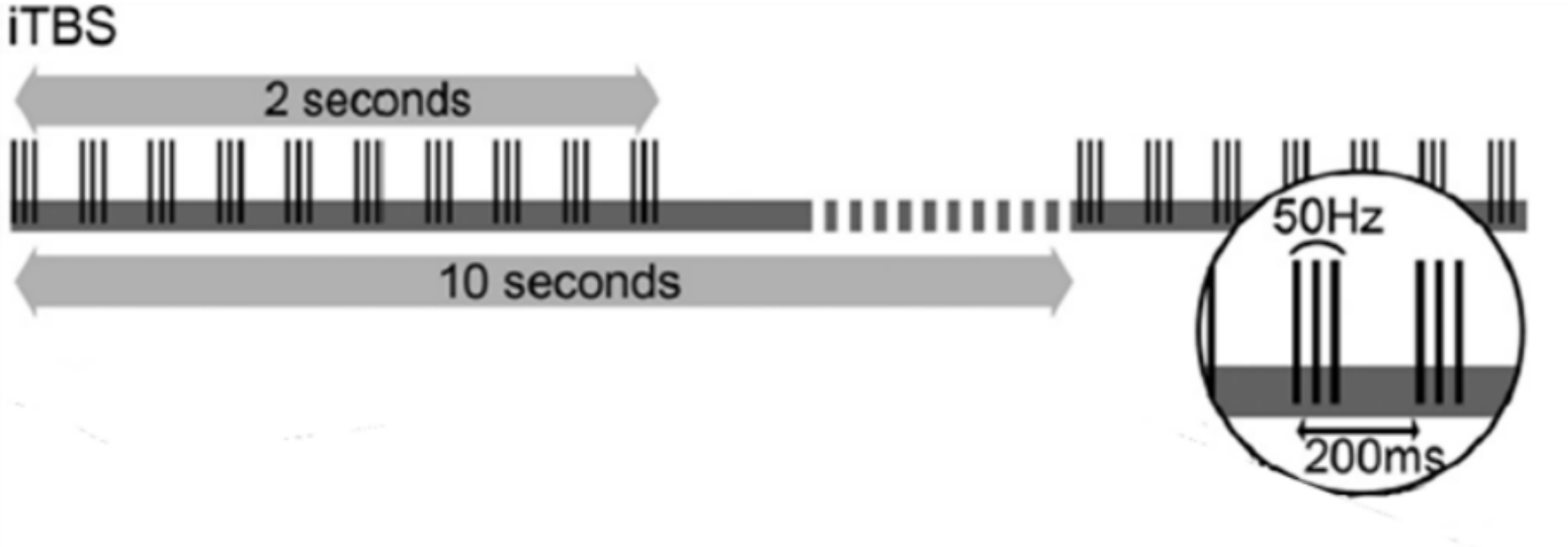
Conclusion: The use of rTMS in patients after ≤1 medication trial should be considered. US payers should consider revising their coverage policies to include the use of rTMS in these patients.

Typical
High Frequency rTMS scheme



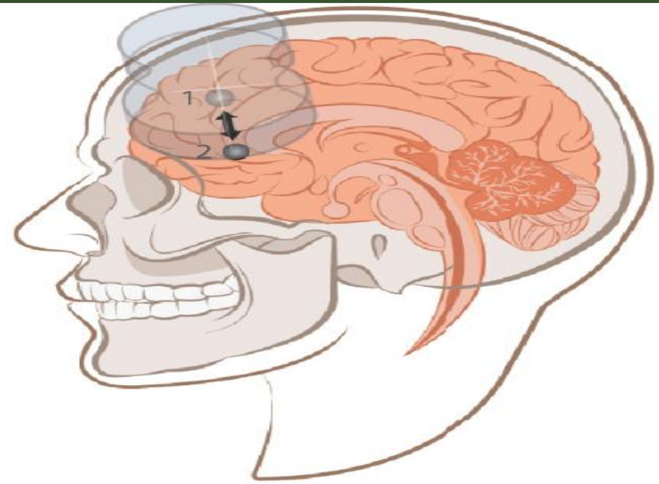
Intermittent Theta Burst (iTBS) is a 3-minute TMS protocol for MDD

- Involves intermixing of high and low frequencies:
  - Bursts of three pulses delivered at 50Hz with the bursts delivered at 5Hz
  - 10 bursts are delivered every 2 seconds, for a total of 30 pulses
  - With 20 trains per session, that equates to 600 pulses per session



This is in contr
standard high
20-minute pro

Eleanor J. Cole et al, **Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for Treatment-Resistant Depression,** American Journal of Psychiatry, 2020, Volume 177, Number 8,



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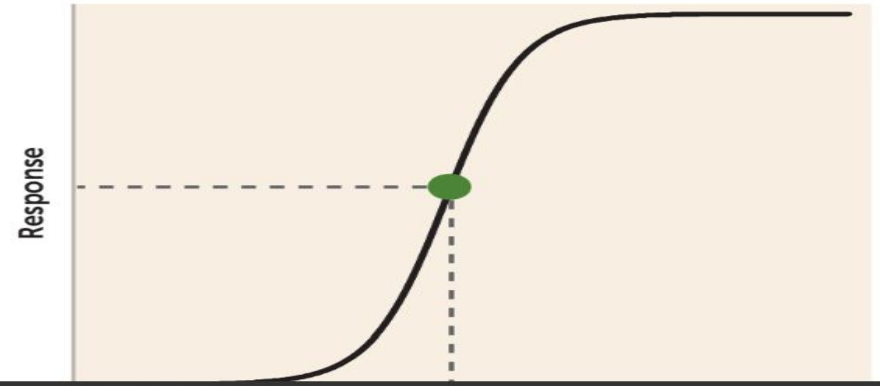

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS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

	Post-SAINT							One Month Post-SAINT						
Measure	Mean	SD	N	Response (%)	N	Remission (%)	N	Mean	SD	N	Response (%)	N	Remission (%)	N
MADRS	5.00	6.37	21	90.48	21	90.48	21	10.95	11.76	20	70.00	20	60.00	20
HAM-D, 17-item	4.29	4.43	21	90.48	21	80.95	21	8.05	8.31	20	75.00	20	65.00	20
HAM-D, 6-item	2.24	3.10	21	85.71	21	85.71	21	4.40	4.72	20	75.00	20	70.00	20
BDI-II	4.47	5.76	15	100.00	12	93.33	15	12.25	13.06	16	57.14	14	62.50	16
Suicidal ideation														
C-SSRS[b]	0.00	0.00	18	100.00	14	100.00	18	0.00	0.00	19	100.00	14	100.00	19
HAM-D, item 3	0.05	0.22	21	100.00	19	95.24	21	0.10	0.31	20	100.00	18	90.00	20
MADRS, item 10	0.10	0.44	21	95.24	21	95.24	21	0.35	0.75	20	90.00	20	80.00	20

[a] Response was defined as a reduction ≥50% in score from baseline; remission was defined as a score <8 on the 17-item HAM-D (32), a score <5 on the 6-item HAM-D (33), a score <11 on the MADRS (31), a score <13 on the BDI-II (34), and a score of zero on the C-SSRS (74). Data for the intent-to-treat sample are presented in Table S2 in the online supplement. BDI-II=Beck Depression Inventory–II; C-SSRS=Columbia-Suicide Severity Rating Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale.

[b] Suicidal ideation subscale.

Eleanor J. Cole et al, Stanford Neuromodulation Therapy (**SNT**): A Double-Blind Randomized Controlled Trial
Am J Psychiatry 2022; 179:132–141

The mean percent reduction from baseline in MADRS score 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group.

Remission and response rates, respectively, 0, 1, 2, 3, and 4 weeks after treatment in the active treatment group were 57.1% and 71.4%; 66.7% and 77.8%; 53.8% and 84. 6%; 61.5% and 69.2%; and 46.2% and 69.2%. Remission and response rates, respectively, in the sham treatment group were 0% and 13.3%; 10.0% and 20.0%; 7.1% and 7. 1%; 7.1% and 7.1%; and 0% and 7.1%. – (0 refers to the Day 6, one day after completion of SNT)

…intensity of 90%
….dysfunction in the left DLPFC- sgACC network is the predominant neural basis of depres- sive symptoms

….No severe adverse events occurred during the trial.

stimulation sessions were delivered hourly, because intersession intervals between 50 and 90 minutes have been shown to produce a cumulative effect on synaptic strengthening.
In contrast, sessions with intersession intervals of 40 minutes or less do not produce a cumulative effect

Observational data analyzed*

(until December 2023)

Diagnosis	April 2022 to December 2023	Mean difference in rating scale (HAMD-17/YBOCS)	Outcome measure	Response Rate
MDD	391	12.70±7.27	Day 6 HAM D	60.86%
OCD	239	10.59±5.98	Day 10 YBOCS	62.76%

- **Speed and Rate of RRR**
- **Drop out Rate**
- **Cost Effectiveness**
- **AE**
- **Long term maintenance of gains**
- **Health Economics**

1. dTMS vs Sham - OCD
2. dTMS vs Sham – Bipolar Depression

*Mudunuru A K, Reddy M S, Valipay K, et al. (May 23, 2024) The Clinical Efficacy of Accelerated Deep Repetitive Transcranial Magnetic Stimulation in Depression and Obsessive-Compulsive Disorder: Multi-centric Real-World Observational Data. Cureus 16(5): e60895. PMCID: PMC11148627. DOI 10.7759/cureus.60895

Asian Journal of Psychiatry
Volume 102, December 2024, 104264

Letter to the Editor

Iatrogenic Tardive Dyskinesia in a middle-aged man treated with deep repetitive transcranial magnetic stimulation using H4 coil

Balaji Sainath Annaluru [1], Chaitanya Deepak Ponangi, M.S. Reddy, Rajesh Bethala, M. Aswin Kumar

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https://doi.org/10.1016/j.ajp.2024.104264

Title:	**Efficacy and Safety of Deep Transcranial Magnetic Stimulation Versus High-Frequency Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder: A Systematic Review**
Publication & Date:	**Current Behavioral Neuroscience Reports**
Investigators:	**Nan Zhang, Yu Mo, Xian-Jun Lan, Qi-Man Liu, Wen-Xiu Li, Xing-Bing Huang, Hua-Wang Wu, Shi-Chao Xu, Shu-Yun Li, Xin-Hu Yang, Wei Zheng**
	The results of this systematic review showed that dTMS provides a more pronounced overall antidepressant response than HF-rTMS, but causes more muscle twitching/spasms or jaw pain incidences. Both RCTs had similar rates of other adverse events and discontinuation.
Conclusions:	dTMS leads to a better antidepressant response than HF-rTMS, although both interventions have favorable safety profiles. However, more RCTs using rigorous methodologies are warranted. The conclusions of this systematic review are that dTMS is associated with a better antidepressant response than HF-rTMS in adult patients with MDD, although both treatment modalities have favorable safety profiles.


BrainsWay

OCD

Age of onset is around 15 years, with about 2-3% Prevalence

OCD is a long term, **Prolonged** illness.....**Washers, Checkers, Hoarders…**

OCD is the most **Secretive** of all psychiatric disorders

OCD is **not Episodic,** like BD

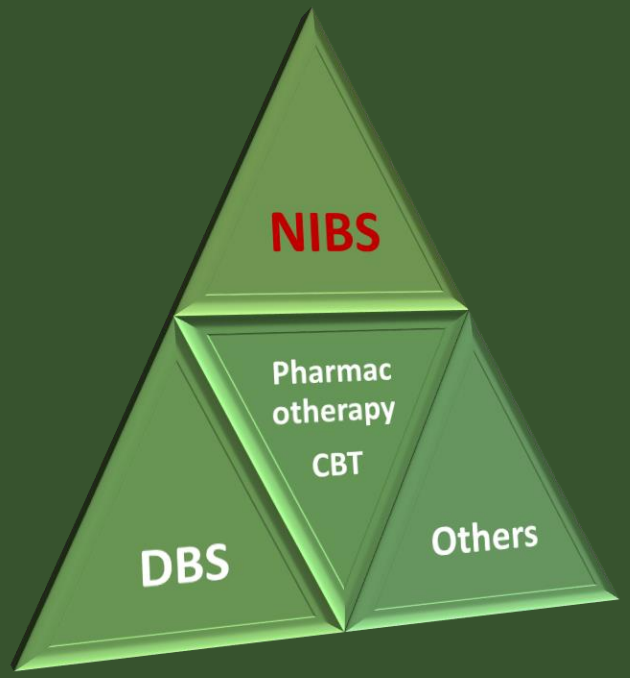
OCD, **in my opinion, causes the "The Maximum Distress"** to the patient, as it being a disorder with good **INSIGHT**, among Simple / Severe Mental Disorders

OCD, is a **Comorbid** condition in several Psychiatric disorders….**OCD+BD…Nightmarish**

OCD – Pharmacotherapy is the Mainstay, CBT supports,

Need for a **"Third" therapy** is an immediate and urgent need……

Management of OCD



1. Pharmacotherapy is the main stay - SSRI

2. Cognitive Behavior Therapy (**CBT**)

3. Interventional Strategies: (Third way)

1. **Invasive:**
   - Psychosurgery – Egas Moniz
   - Deep Brain Stimulation (DBS)
2. **Non Invasive Brain Stimulation (NIBS):**
   - **TMS**
   - **TDCS**
   - ECT ?

Deep TMS with Provocational Strategies

mPFC, ACC, OFC

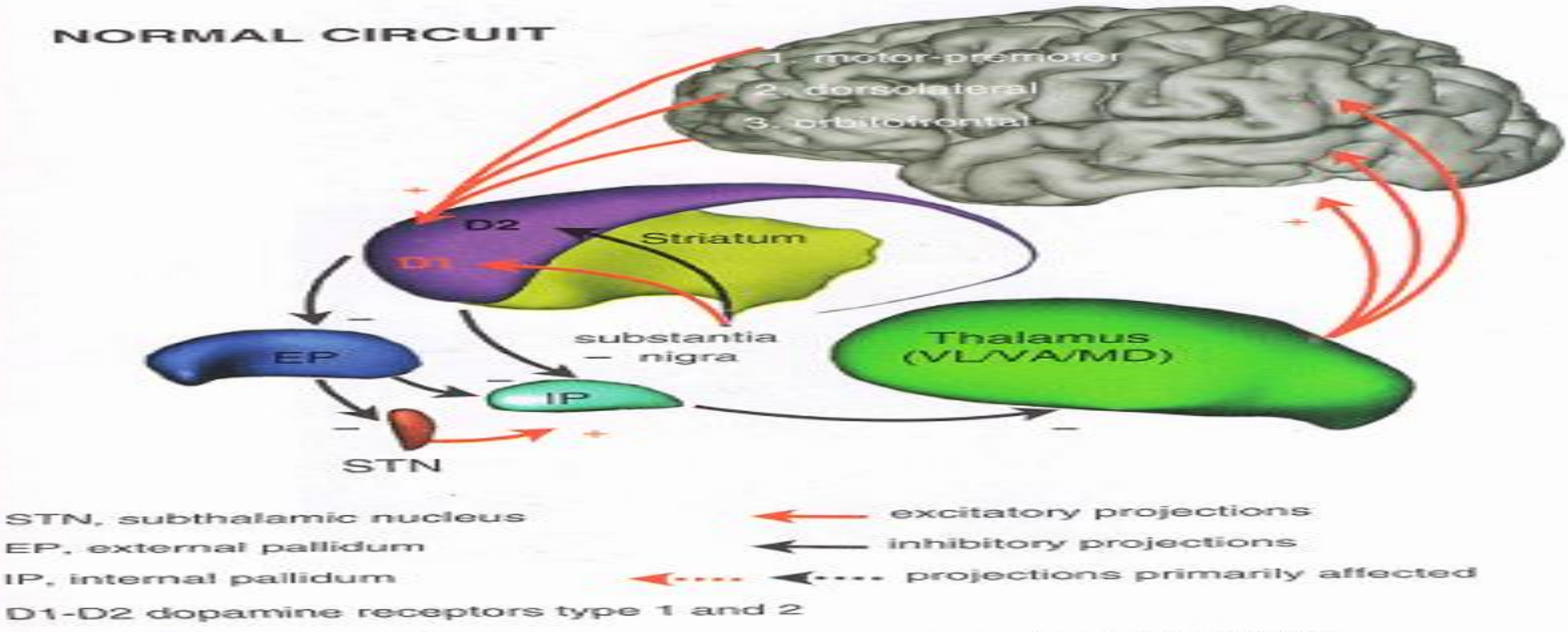


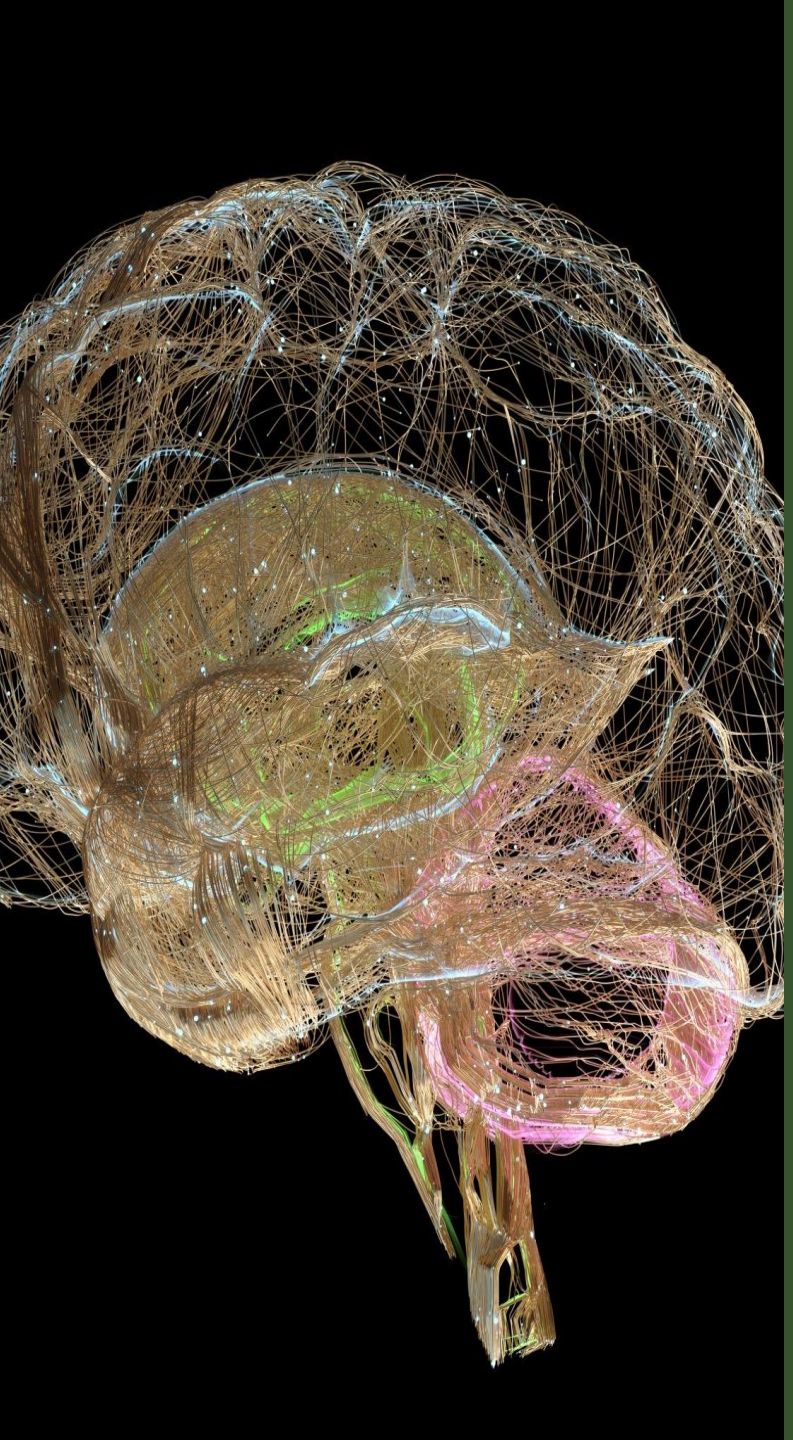
Figure 10.6 A) Diagram of the direct (cortico-striatal-pallido-thalamo-cortical) and indirect (cortico-striatal-pallido-subthalamic-pallido-thalamo-cortical) loops connecting the cerebral cortex to the basal ganglia and thalamus. The activity of the striatal neurons is regulated by dopaminergic fibres from the substantia nigra. The direct and indirect loops are part of three segregated circuits (i.e. 'motor', 'associative', and 'limbic') which originate from distinct cortical regions (i.e. motor-premotor, dorsolateral, and orbitofrontal) and relay through different thalamic nuclei (MD, mediodorsal; VA, ventroanterior; VL, ventrolateral). B, C) Models proposed to explain the neurophysiopathology of Parkinson's disease and Huntington's chorea.

1. Aron Tendler, Elyssa Sisko, Noam Barnea-Ygael, Abraham Zangen, Eric A. Storch
A Method to Provoke Obsessive Compulsive Symptoms for Basic Research and Clinical Interventions
Front Psychiatry. 2019; 10: 814.
2. Ana Maia et al, Symptom provocation for treatment of obsessive-compulsive disorder using transcranial magnetic stimulation: A step-by-step guide for professional training. Frontiers in Psychiatry, 03August2022

1. **Symptom Provocation activates Cortico-Striato-Pallido-Thalamo-Cortical circuitry**

2. **Symptom provocation activates "specific" circuits. Once a memory trace is retrieved, it becomes labile for a period of time, susceptible window period of approximately 6 hours,** (before stabilizing again during the reconsolidation process of forming long time memories). **Disrupting the Reconsolidation of a Memory by electric stimulation** has been done in both preclinical and clinical studies.

3. Advantages: preferential modulation of neural populations; specificity in TMS induced plasticity….Supposedly……



- **Neuroplasticity,** Matt Puderbaugh; Prabhu D. Emmady, Last Update: May 1, 2023.

- Neuroplasticity, also known as Neural plasticity or Brain plasticity..

  “the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by REORGANIZING its Structure, Functions, or Connections.”

- Hebbian Plasticity Rule…..

- Behavioral Timescale Synaptic Plasticity (BTSP)

OCD Protocol

Minimum of 10 Sessions….28 + Maintenance sessions
Each Session for **20 minutes**

Establishing the **Motor Threshold (MT)**
Intensity of Stimulus – 100 – 120% of MT

Stimulus Frequency – 20 Hz
Each Train – 2 seconds
Inter Train interval – 20 seconds
Number of Trains – 50
Total Impulses per session – About 2000

Thank you All