A Practical Guide to Brain Stimulation: Therapeutic Options and Recent Advances

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Disclosures

- Labatt Family Professorship in Depression Biology
  - A University Named Professorship at the University of Toronto
- Research Support held from:
  - CIHR
  - CAMH
  - Centre for Mental Health at UHN
  - Department of Psychiatry at U of T
- No Biomedical COI

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

UHN Centre for Mental Health

camh
mental health is health

Psychiatry
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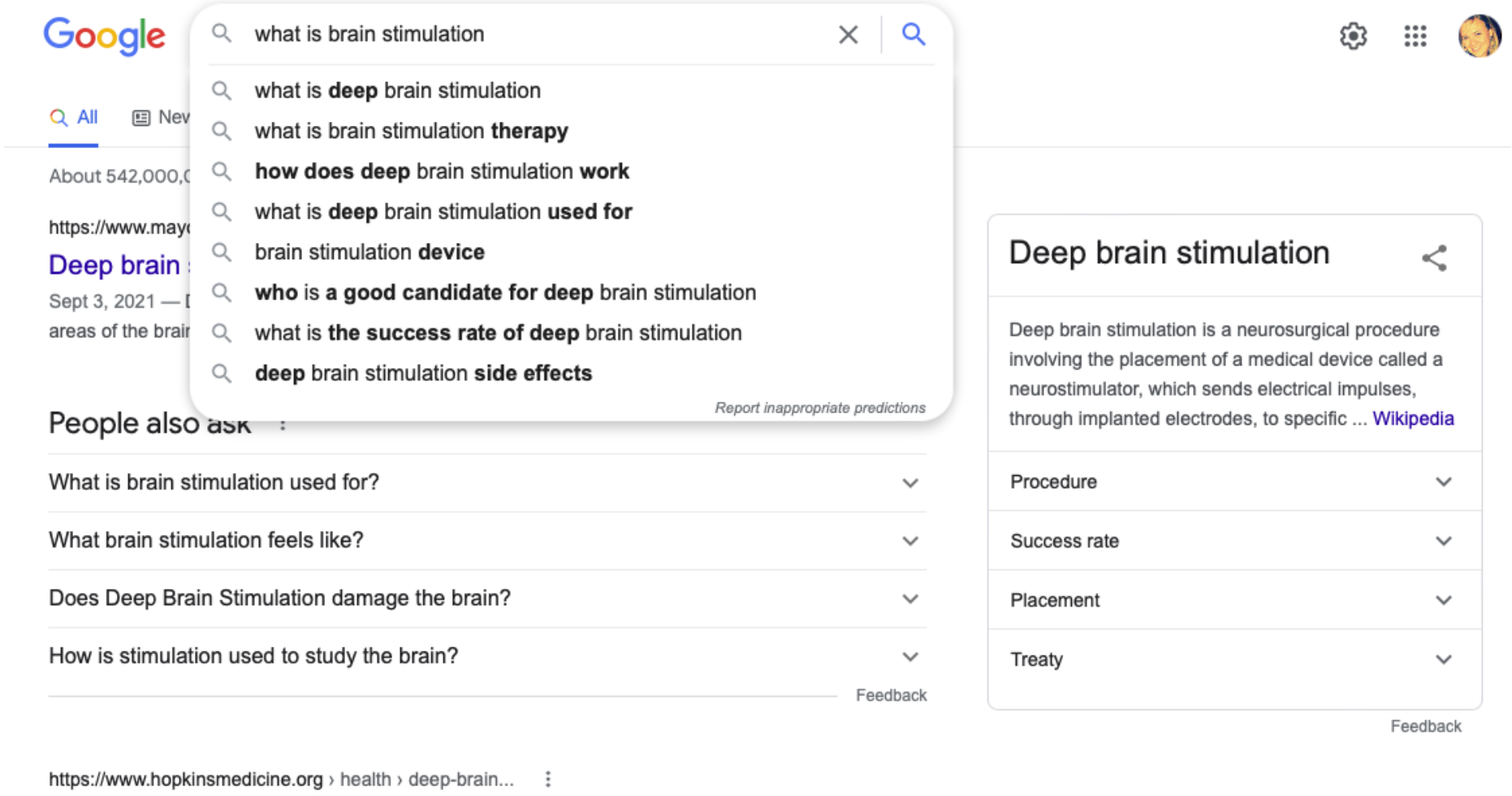
Objectives

1. List the available Brain Stimulation therapies and their indications
2. Describe recent advances in the field of Brain Stimulation
3. Understand how Brain Stimulation options may be applicable for patients in clinical practice

What is brain stimulation?



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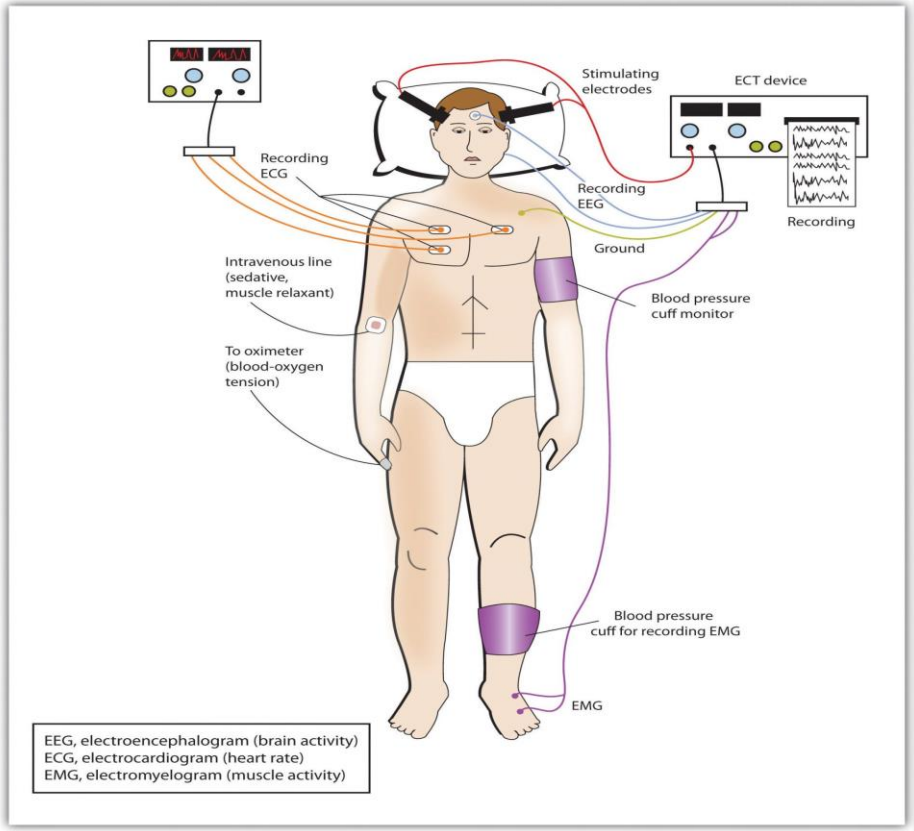
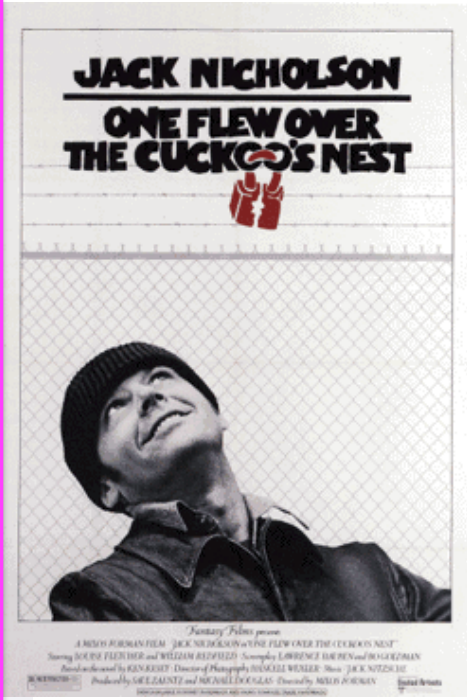
Therapeutic Brain Stimulation

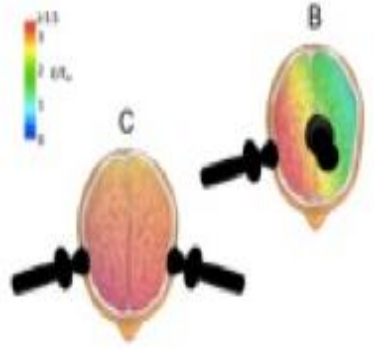
	tDCS	rTMS	MST	ECT	DBS
Type of Stimulation	Electrical	Magnetic	Magnetic	Electrical	Electrical
Convulsive	✘	✘	✓	✓	✘
GA	✘	✘	✓	✓	✓ (Surgical implantation)
Mechanism of action	Subthreshold modulation of membrane potential	Activation of inhibitory interneurons	Focal activation of inhibitory interneurons	General activation of pyramidal neurons	Activation of local circuit

Electroconvulsive therapy (ECT)

	ECT
Type of Stimulation	Electrical
Convulsive	✓
GA	✓
Mechanism of action	General activation of pyramidal neurons







Only 1% of patients receive ECT

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Indications for ECT

- Treatment-refractory conditions
- Severe or life-threatening psychiatric illness
- Most often used for the treatment of medication-resistant depression (MDD)

Indications for ECT

- Resistant MDE with or without psychosis, Unipolar or Bipolar
- Refractory Mania
- Resistant Psychosis (Schizophrenia, SCZA)
- Refractory OCD
- Catatonia
- Parkinson’s Disease
- Refractory Status Epilepticus

Contraindications to ECT

- There are no absolute contraindications to ECT

- Relative contraindications do exist
  - When should we wait?
  - When should we proceed with caution?

Relative Contraindications to ECT

- Intracranial lesion with mass effect
- Recent stroke (less than 1 month)
- Recent MI (less than 1 month)
- Unstable aneurysm or vascular malformation
- Recent orthopedic injury with unstable fracture/dislocation (less than 1 month)

(APA Guidelines 2001, Tess et al. 2009)

Morbidity & Mortality

- Mortality – 2.1 per 100,000 *(Torring et al, European Psychiatry, 2017)*
  - Meta-analysis of 14 studies, 757,662 ECT treatments
  - Risk of death associated with GA+surgical procedure = 3.4/100,000

- May induce manic state
  - 5-6% patients with bipolar disorder
  - Continue to treat with ECT

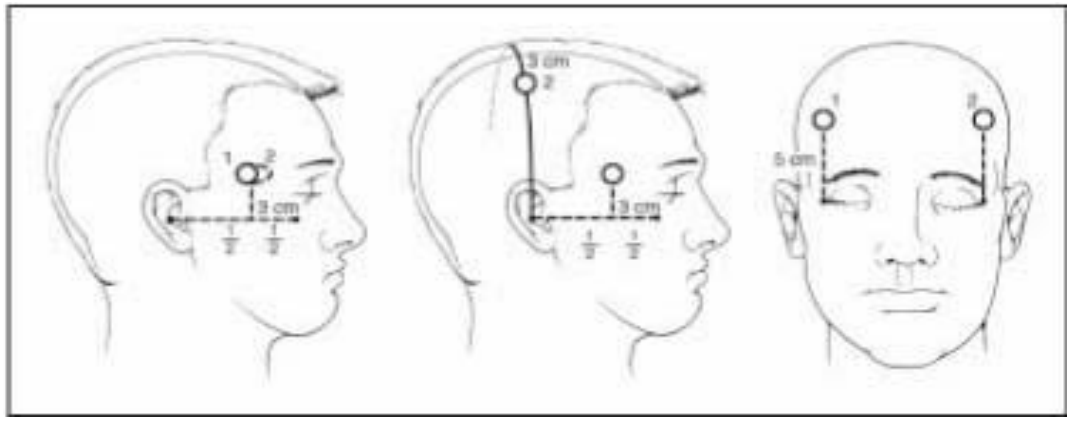
- Risks of general anesthesia
  - Mortality
  - Malignant hyperthermia/Allergic reaction
  - Cardiovascular event
  - Aspiration

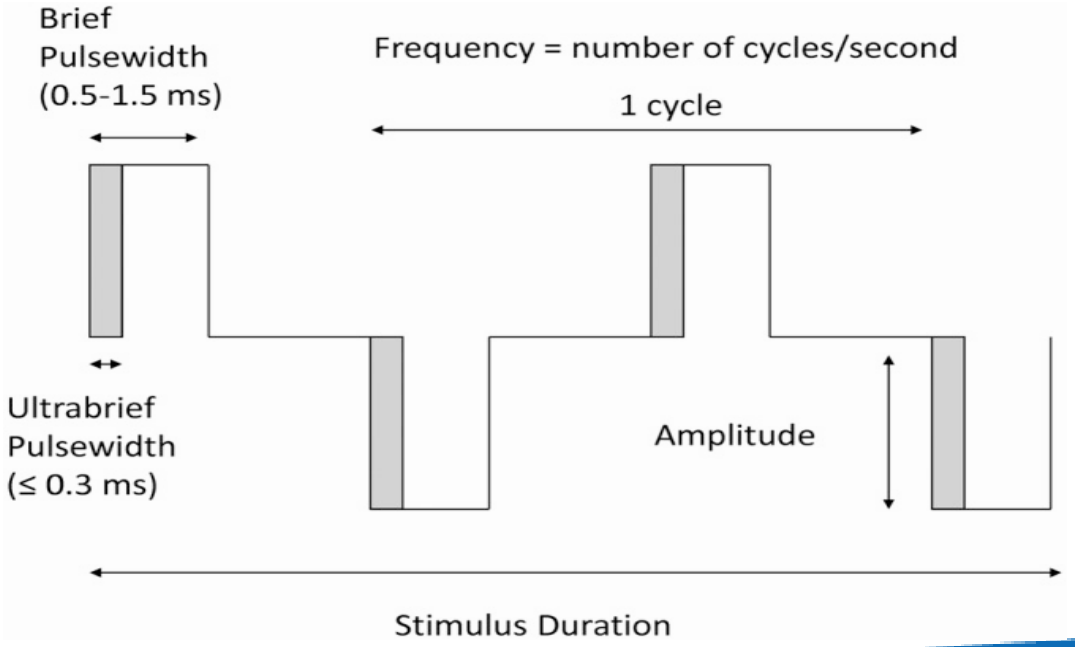
Side Effects

1. Post-ictal confusion
2. Transient hypertension
3. Cardiac changes
    a. Bradycardia → asystole (transient)
    b. Ectopy/ST changes
4. Headache
5. Muscle pains (jaw pain)
6. Nausea
7. Anterograde and retrograde amnesia**

Minimizing Cognitive S/E

1. Electrode position
   - Bitemporal vs. Unilateral
2. Pulse Width
   - Standard vs. Ultrabrief
3. Concomitant medications
4. Anaesthetic doses
5. Stimulus intensity
   - Barely suprathreshold vs. Above threshold
6. Frequency of treatment
   - 2x/wk vs 3x/wk





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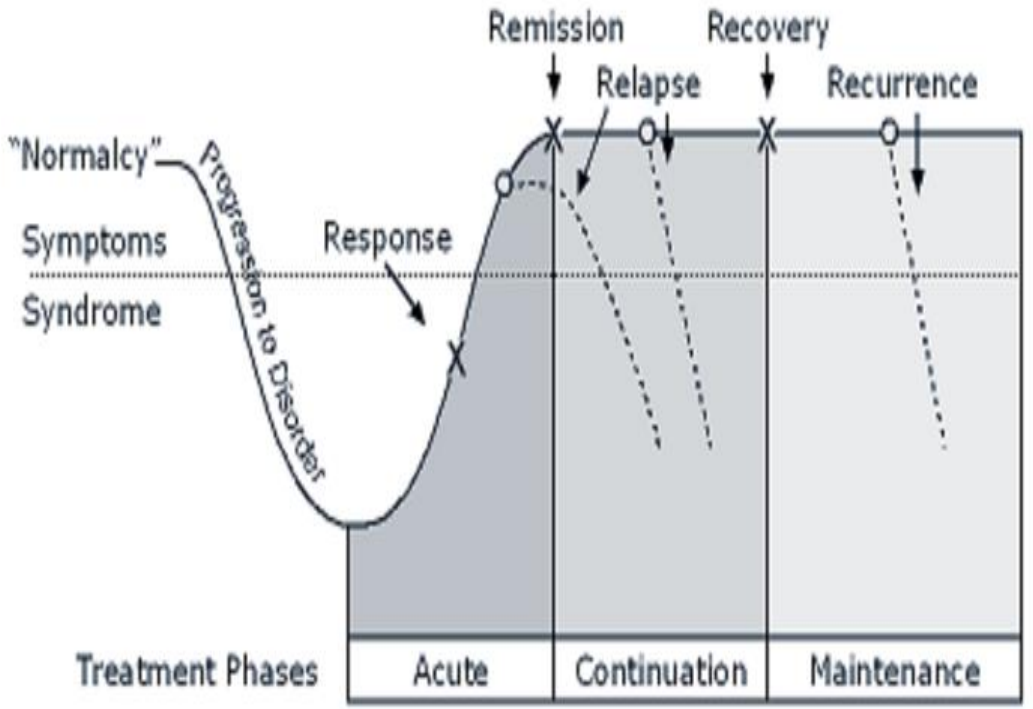
(APA Guidelines 2001, Bundy et al. 2010, Shapira et al. 1998, Kellner 2010)

A typical course of ECT

- Acute Course
  - 6-18 treatments
  - 2-3 x per week
- Continuation Course
  - To prevent relapse
  - Fixed schedule vs. Symptom Titration (STABLE)
- Maintenance Course
  - Unlikely in depression
  - Little evidence to stretch ECT session interval past q4 weeks
  - In rare cases can be helpful to maintain mood.

Acute/Continuation/Maintenance



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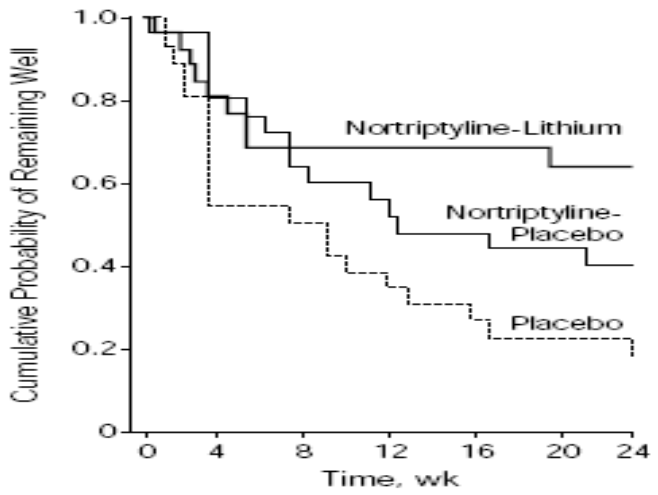
(Kupfer DJ., J Clin Psychiatry. 1991; 52:28)

Relapse following Response to ECT

Figure 2. Kaplan-Meier Estimates



No. at Risk							
Placebo	29	14	13	9	6	5	4
Nortriptyline-Placebo	27	20	15	13	12	11	10
Nortriptyline-Lithium	28	18	15	15	15	14	14

Proportion of patients who remained well during the continuation trial, for patients randomized to treatment with placebo (n=29), nortriptyline alone (n=27), and combination nortriptyline and lithium carbonate (n=28).

"…almost universal relapse should be expected without effective continuation therapy…"

Relapse rates over 24-week trial:

- Placebo - 84%
- Nortriptyline - 60%
- Nortriptyline + Lithium - 39%

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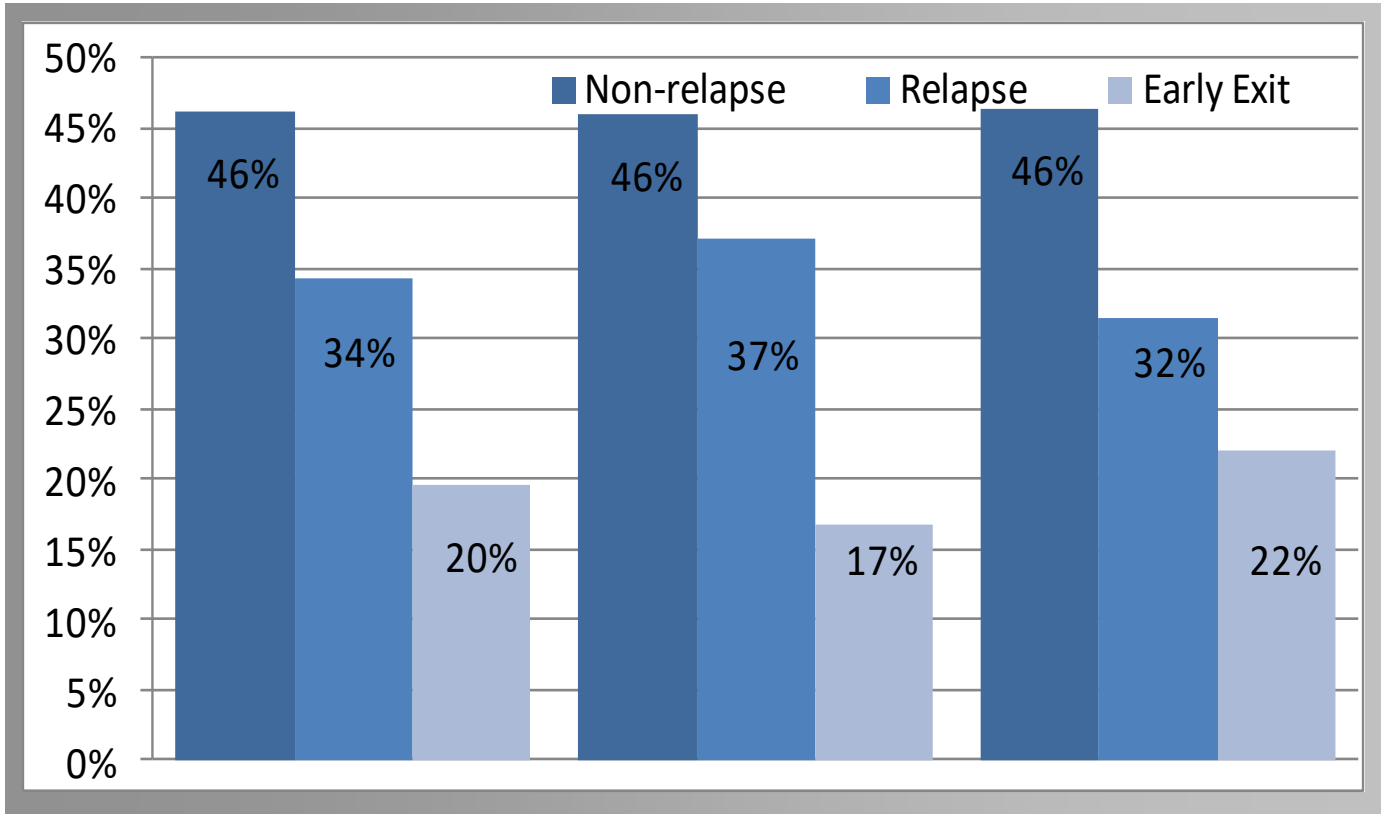
(Sackeim et al 2001, Prudic et al 2004)

CORE I: Relapse Status at 6 Months



Total (n=184) **C-ECT** (n=89) **C-Pharm** (n=95)

- Relapse-free Survival at 2yrs:
  - Continuation ECT + Meds - 93%
  - Meds alone - 52%
- Relapse-free Survival at 5 yrs:
  - Continuation ECT + Meds - 73%
  - Meds alone - 18%

(Gagne GG et al. Am J Psychiatry, 2000)

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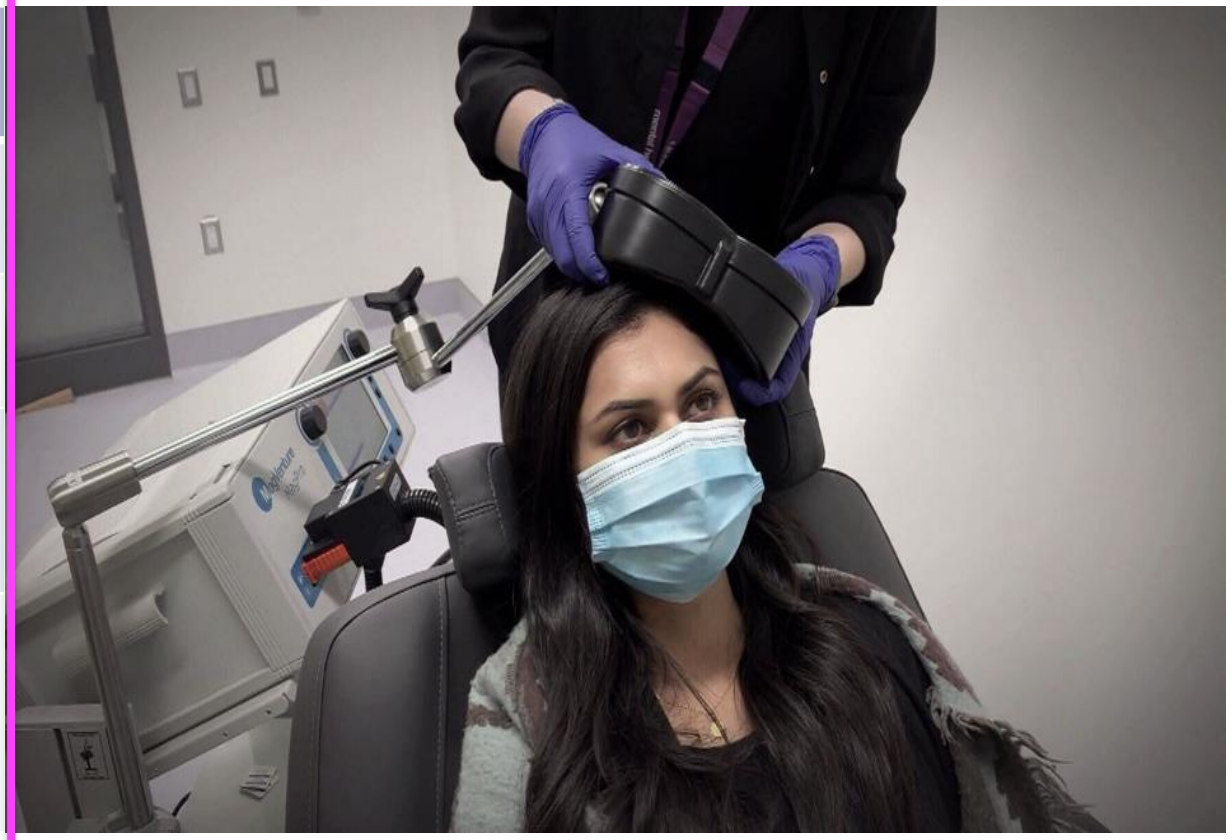
(Kellner CH, et al., Arch Gen Psychiatry. 2006)

Repetitive Transcranial Magnetic Stimulation (rTMS)

	tDCS	rTMS
Type of Stimulation	Electrical	Magnetic
Convulsive	✘	✘
GA	✘	✘
Mechanism of action	Subthreshold modulation of membrane potential	Activation of inhibitory interneurons



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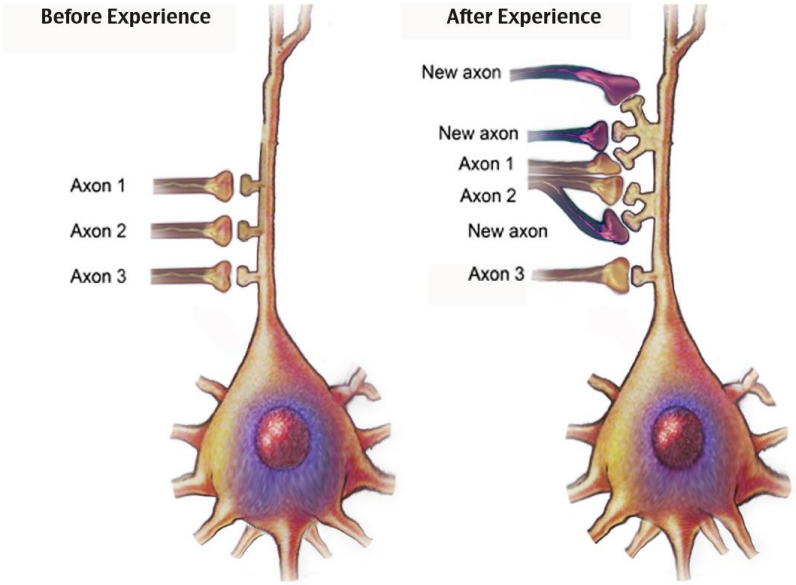
Neural Plasticity



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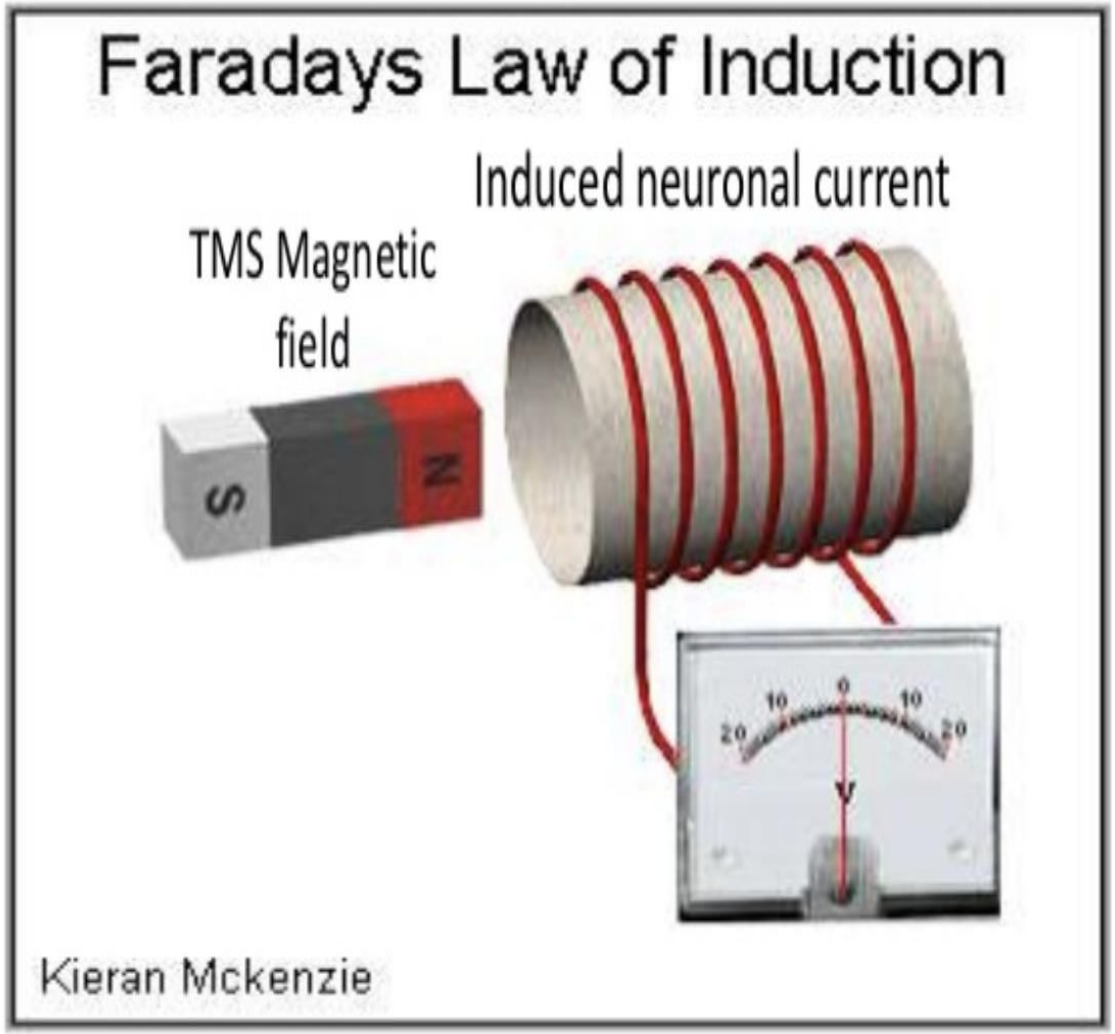
Mechanisms of rTMS



1. A paddle with loops capable of carrying electric current is held on the head

2. A current travels through the loops, generating a magnetic field perpendicular to the paddle. The field is strongest where the coils meet

3. Bursts of current cause changes in the magnetic field

4. Changes in the magnetic field induce an electric current in the brain that stimulates neurons

5. Moving the paddle changes the location of the induced current

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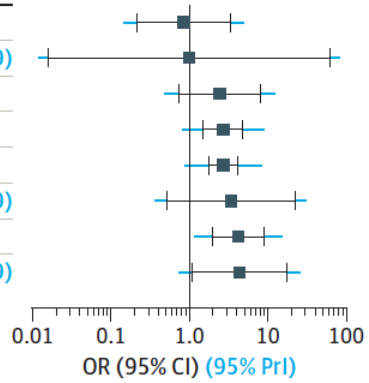
rTMS for Major Depressive Disorder

- Health Canada approved treatment for MDD
- Well established efficacy

Figure 3. Forest Plot Showing the Network Relative Odds Ratios (ORs) With Their 95% CIs and Predictive Intervals (PrI)

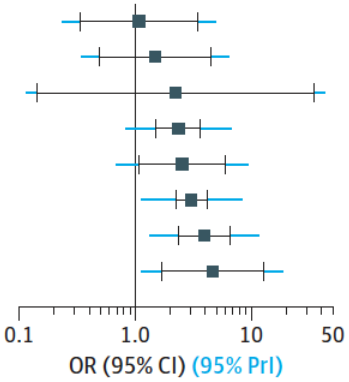
A Response

Active Device	OR (95% CI) (95% PrI)
sTMS	0.85 (0.22-3.35) (0.15-4.94)
aTMS	1.00 (0.02-62.31) (0.01-83.19)
dTMS	2.45 (0.74-8.07) (0.49-12.28)
LF-rTMS	2.70 (1.51-4.82) (0.82-8.89)
HF-rTMS	2.73 (1.78-4.20) (0.89-8.40)
TBS	3.37 (0.52-22.05) (0.37-30.69)
Bilateral rTMS	4.22 (1.96-9.05) (1.15-15.47)
pTMS	4.37 (1.10-17.47) (0.74-25.69)



B Remission

Active Device	OR (95% CI) (95% PrI)
sTMS	1.08 (0.34-3.49) (0.24-4.98)
dTMS	1.49 (0.50-4.47) (0.34-6.48)
aTMS	2.25 (0.14-35.03) (0.12-43.39)
LF-rTMS	2.37 (1.52-3.68) (0.83-6.78)
TBS	2.54 (1.07-6.05) (0.70-9.32)
HF-rTMS	3.07 (2.24-4.21) (1.12-8.37)
Bilateral rTMS	3.96 (2.37-6.60) (1.34-11.70)
pTMS	4.66 (1.70-12.77) (1.15-18.91)



aTMS indicates accelerated TMS; dTMS, "deep" (H-coil) TMS; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation.

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(Brunoni et al., JAMA, 2016)

Benefits and Challenges of rTMS

Benefits

- Less invasive than ECT
- Minimal side effects
- No anesthesia (can continue daily activities as normal – encouraged)

Challenges

- Commitment
- Daily travel, accessibility
- Side Effects
- Pain
- Headaches
- Fatigue

Spontaneous Adverse Events with rTMS

	Patients Reporting, No (%)	
	Active rTMS group (n = 92)	**Sham rTMS Group (n = 98)**
Headache	29 (32)	23 (23)
Discomfort at the stimulation site	17 (18)	10 (10)
Insomnia	7 (7.6)	10 (10)
Worsening of depression or anxiety	6 (7)	8 (8)
Gastrointestinal	6(7)	3 (3)
Fatigue	5 (5)	4 (4)
Muscle aches	4(4)	4 (4)
Vertigo	2(2)	2 (2)
Skin pain	1 (1)	1 (1)
Facial muscle twitching	0	1 (1)
Other	18 (20)	15 (15)

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Who might benefit from rTMS?

More likely

- Previous euthymia
- No chronic anhedonia
- Mild to moderate symptoms
- No evidence of psychosis
- Fewer treatment trials
- Not on benzodiazepines
- Not on anticonvulsants

Less likely

- Dysthymia without depression
- Chronically anhedonic
- Previous non-response to rTMS or ECT
- Ambivalent commitment to rTMS
- Active and un-minimized stressors
- On benzodiazepines or anticonvulsants

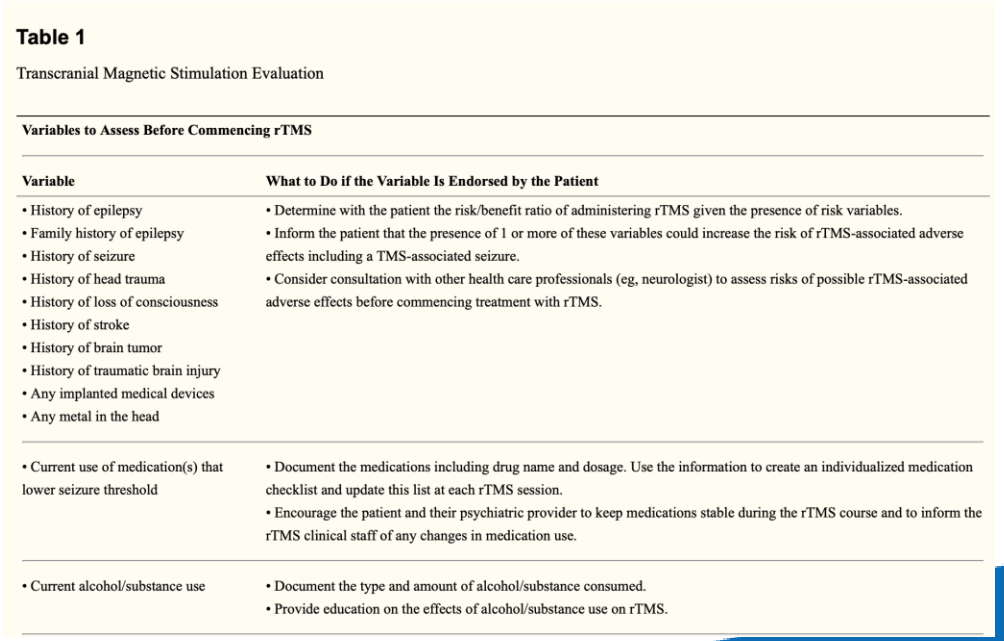

Table 1

Transcranial Magnetic Stimulation Evaluation

Variables to Assess Before Commencing rTMS	
Variable	**What to Do if the Variable Is Endorsed by the Patient**
• History of epilepsy • Family history of epilepsy • History of seizure • History of head trauma • History of loss of consciousness • History of stroke • History of brain tumor • History of traumatic brain injury • Any implanted medical devices • Any metal in the head	• Determine with the patient the risk/benefit ratio of administering rTMS given the presence of risk variables. • Inform the patient that the presence of 1 or more of these variables could increase the risk of rTMS-associated adverse effects including a TMS-associated seizure. • Consider consultation with other health care professionals (eg, neurologist) to assess risks of possible rTMS-associated adverse effects before commencing treatment with rTMS.
• Current use of medication(s) that lower seizure threshold	• Document the medications including drug name and dosage. Use the information to create an individualized medication checklist and update this list at each rTMS session. • Encourage the patient and their psychiatric provider to keep medications stable during the rTMS course and to inform the rTMS clinical staff of any changes in medication use.
• Current alcohol/substance use	• Document the type and amount of alcohol/substance consumed. • Provide education on the effects of alcohol/substance use on rTMS.

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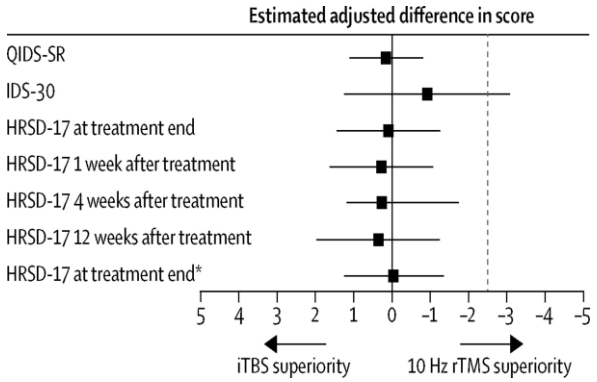
(McClintock, J Clin Psychiatry, 2018)

Recent Developments – Theta Burst Stimulation (TBS)

- Mimics endogenous theta rhythms which induces neuroplasticity in the brain
- 1/10th of the time (3min) compared to standard rTMS



THE LANCET
Volume 391, Issue 10131, 28 April–4 May 2018, Pages 1683-1692

Articles

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Daniel M Blumberger MD [a, b, c], Fidel Vila-Rodriguez MD [e, f], Kevin E Thorpe MMath [d, g, h], Kfir Feffer MD [i, j], Yoshihiro Noda MD [k], Peter Giacobbe MD [b, l, m], Yuliya Knyahnytska MD [a, b], Prof Sidney H Kennedy MD [b, c, h, o], Prof Raymond W Lam [f], Prof Zafiris J Daskalakis MD [a, b, c], Jonathan Downar MD [b, c, m, n, o]

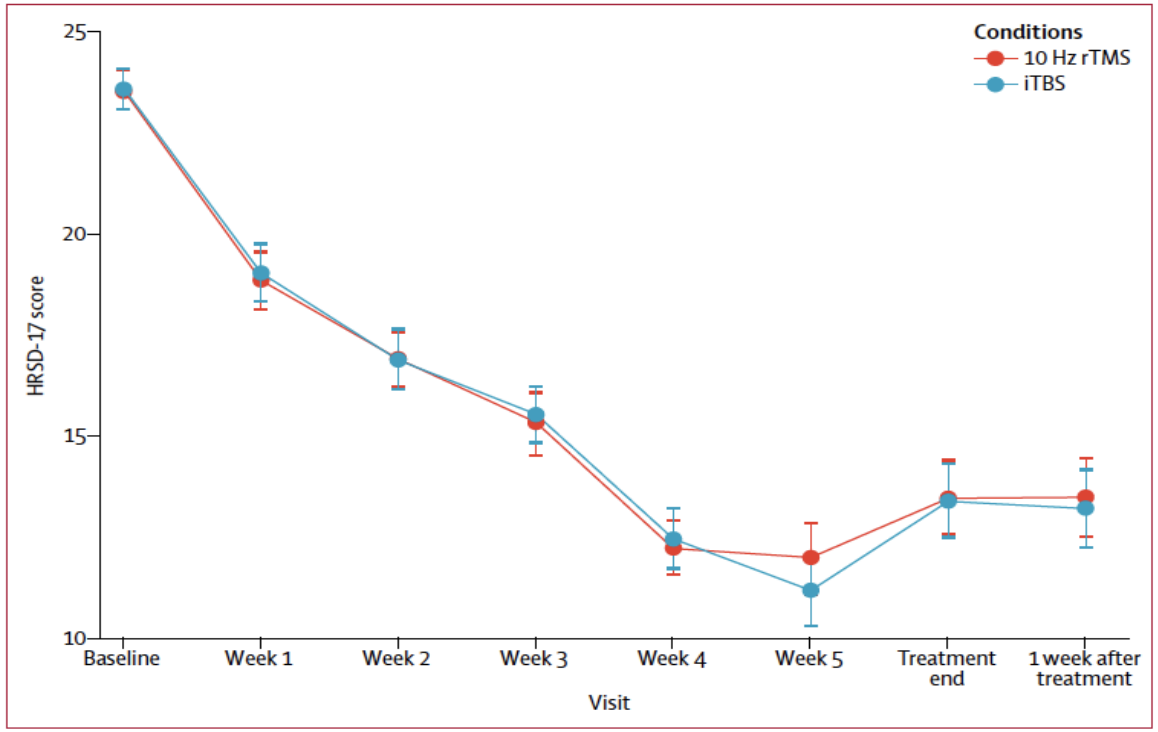


Figure 3: **Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

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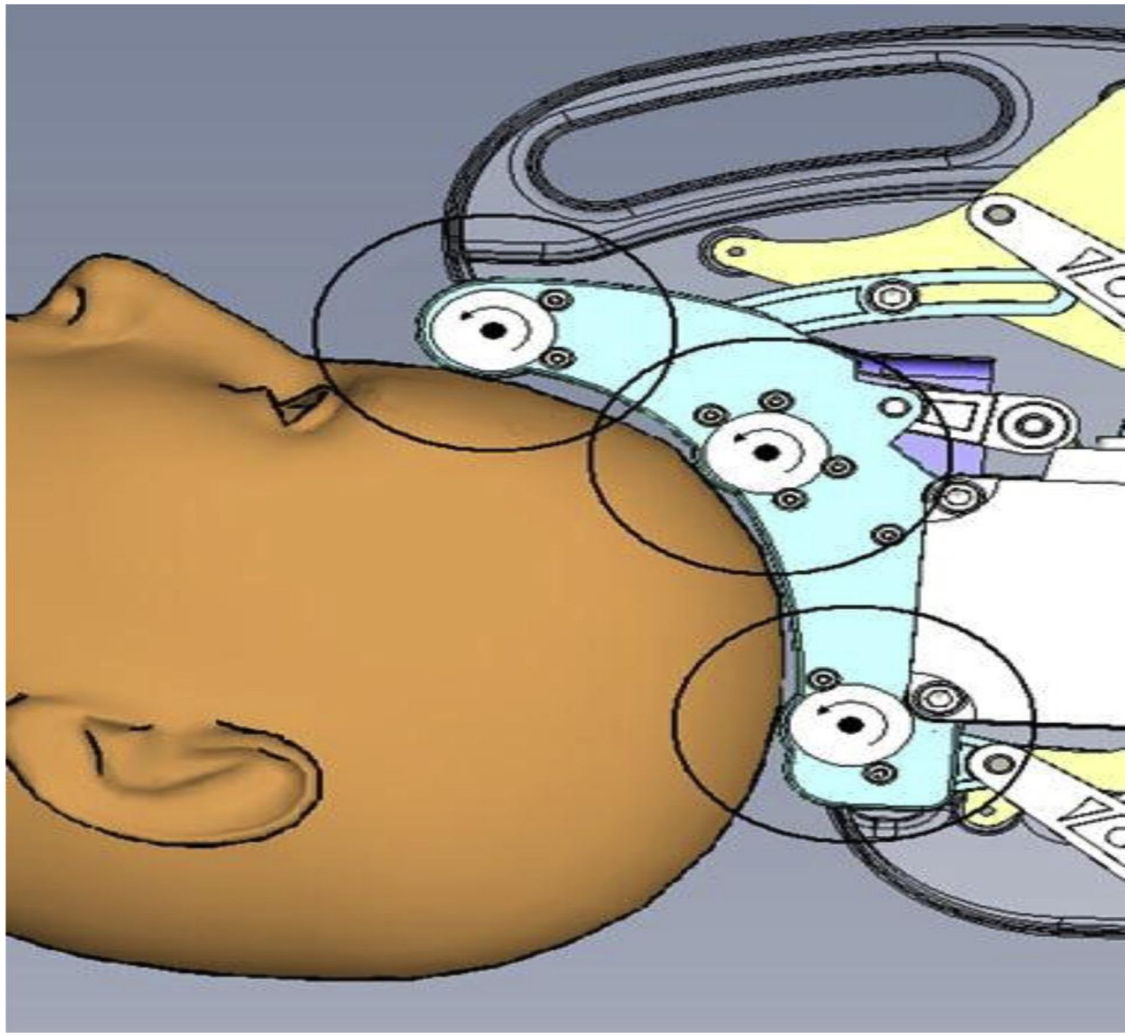
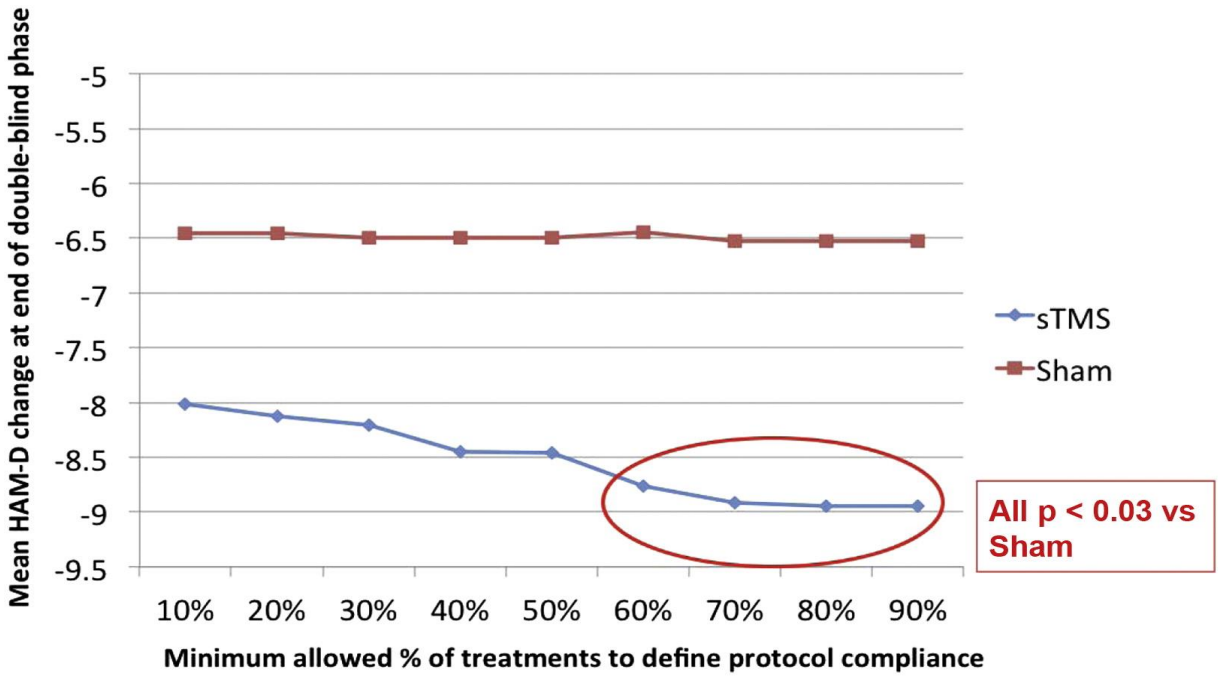
Recent Developments - Synchronized TMS (sTMS)





- Pulses delivered in conjunction with EEG
- Synchronized with alpha rhythm
- Low intensity sinusoidal waveform

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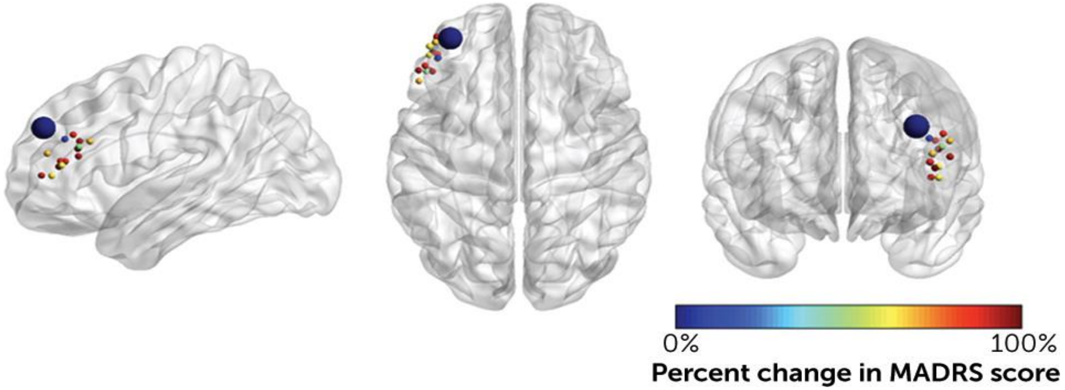
(Leuchter et al, Brain Stimulation, 2015)

Recent Developments – SNT Protocol

- 10 iTBS sessions/day x 5 days
- 18,000 pulses/day
  - 3x dose of FDA approved iTBS protocol
- fMRI guided individualized neuronavigational target
- 85.7% response, 78.6% remission



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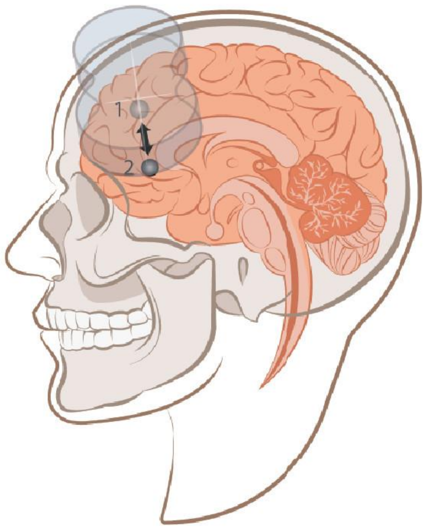

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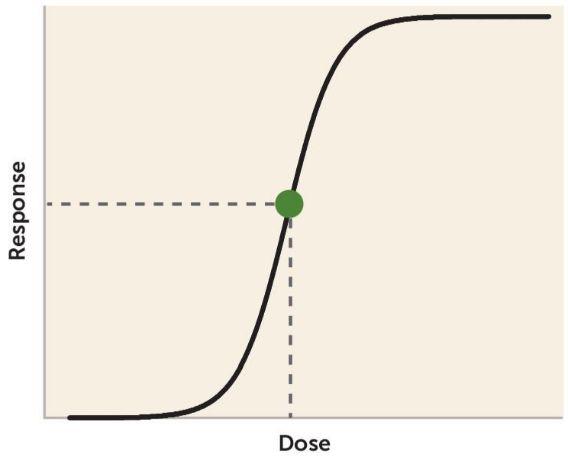

B

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
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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
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(Cole et al, AJP, 2019, Cole et al, AJP, 2021)

rTMS for Late-Life Depression

JAMA Psychiatry

RCT: Effectiveness of Standard Sequential Bilateral Repetitive Transcranial Magnetic Stimulation vs Bilateral Theta Burst Stimulation in Older Adults With Depression

POPULATION

80 Men, 92 Women

Older adults with treatment-resistant depression

Mean age (range), 67.1 (60-74) y

INTERVENTION

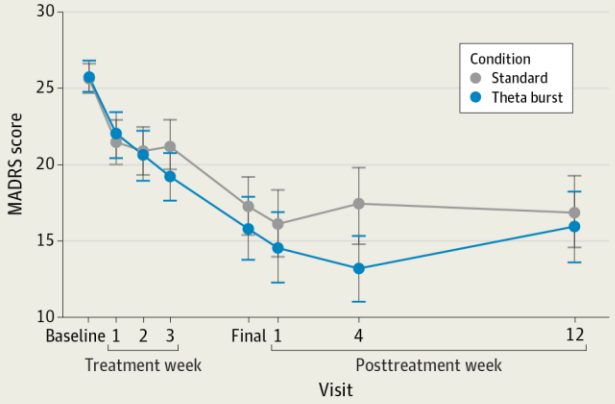
172 Patients randomized

87 Standard repetitive transcranial magnetic stimulation (rTMS)
Standard sequential bilateral rTMS for 47.5 min

85 Theta burst stimulation (TBS)
Bilateral TBS for 4 min

FINDINGS

The estimated adjusted difference in MADRS change was 1.55 points in favor of TBS. This was lower than the a priori margin of 2.75 in favor of standard rTMS, establishing noninferiority.



Mean (SD) MADRS total score improvement
rTMS from 25.6 (4.0) to 17.3 (8.9)
TBS from 25.7 (4.7) to 15.8 (9.1)

SETTINGS / LOCATIONS

1 Tertiary psychiatric hospital in Canada

PRIMARY OUTCOME

Change in the Montgomery-Åsberg Depression Rating Scale (MADRS) (range, 0-50) was the primary outcome measure from baseline to end of treatment in those who completed the majority of the 4-wk treatment.

Blumberger DM, Mulsant BH, Thorpe KE, et al. Effectiveness of standard sequential bilateral repetitive transcranial magnetic stimulation vs bilateral theta burst stimulation in older adults with depression: the FOUR-D randomized noninferiority clinical trial. *JAMA Psychiatry.* Published online September 21, 2022. doi:10.1001/jamapsychiatry.2022.2862

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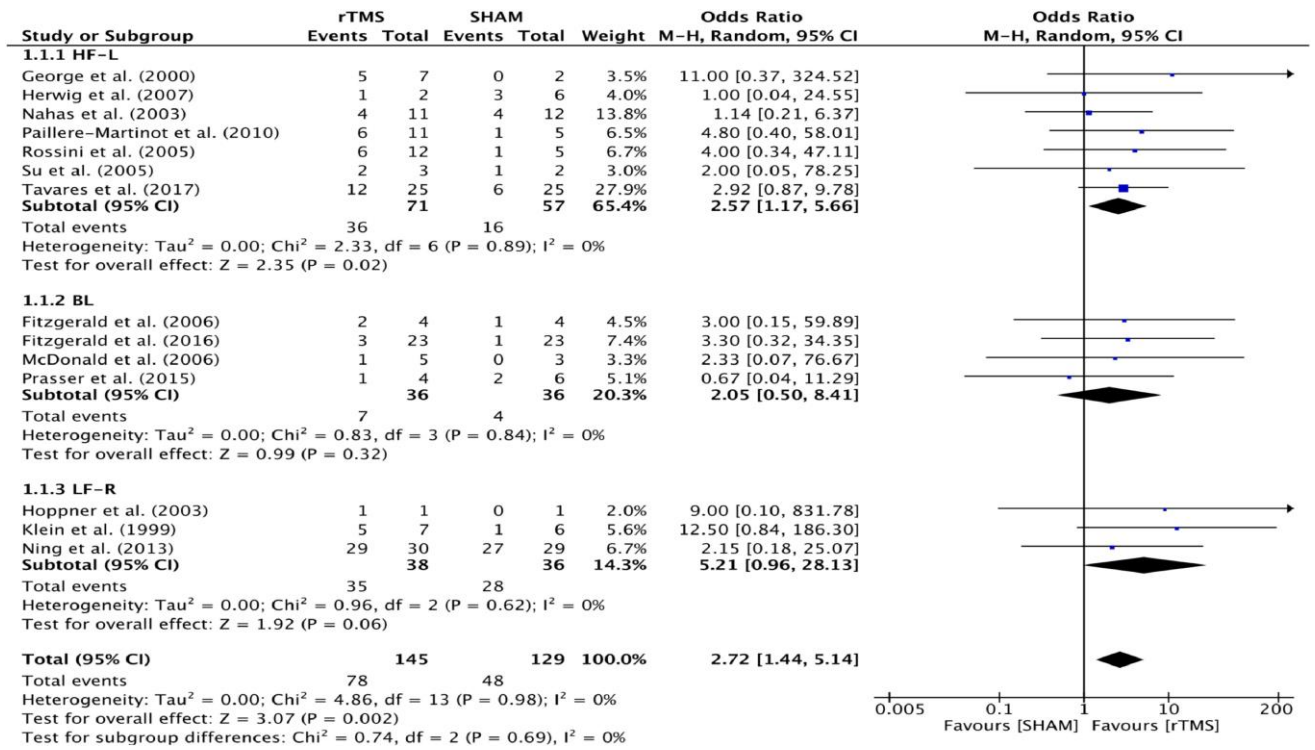
(Blumberger et al, JAMA Psychiatry, 2022)

rTMS for Bipolar Depression

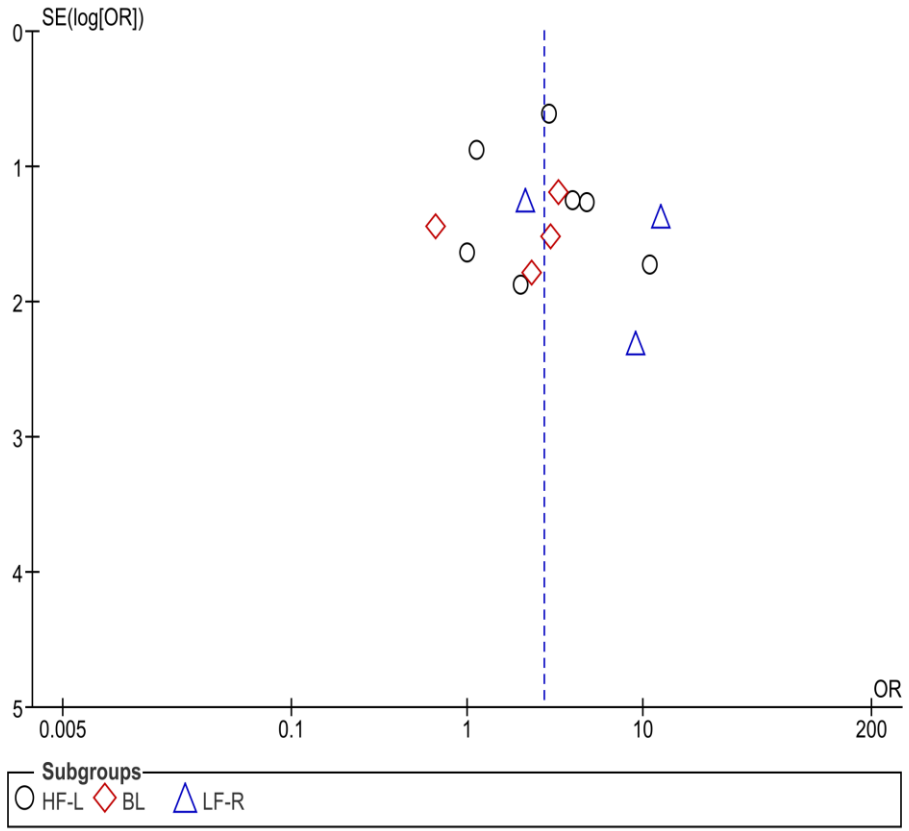


Study or Subgroup	rTMS Events	rTMS Total	SHAM Events	SHAM Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 HF-L						
George et al. (2000)	5	7	0	2	3.5%	11.00 [0.37, 324.52]
Herwig et al. (2007)	1	2	3	6	4.0%	1.00 [0.04, 24.55]
Nahas et al. (2003)	4	11	4	12	13.8%	1.14 [0.21, 6.37]
Paillere-Martinot et al. (2010)	6	11	1	5	6.5%	4.80 [0.40, 58.01]
Rossini et al. (2005)	6	12	1	5	6.7%	4.00 [0.34, 47.11]
Su et al. (2005)	2	3	1	2	3.0%	2.00 [0.05, 78.25]
Tavares et al. (2017)	12	25	6	25	27.9%	2.92 [0.87, 9.78]
Subtotal (95% CI)		**71**		**57**	**65.4%**	**2.57 [1.17, 5.66]**
Total events	36		16			
Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 6 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
1.1.2 BL						
Fitzgerald et al. (2006)	2	4	1	4	4.5%	3.00 [0.15, 59.89]
Fitzgerald et al. (2016)	3	23	1	23	7.4%	3.30 [0.32, 34.35]
McDonald et al. (2006)	1	5	0	3	3.3%	2.33 [0.07, 76.67]
Prasser et al. (2015)	1	4	2	6	5.1%	0.67 [0.04, 11.29]
Subtotal (95% CI)		**36**		**36**	**20.3%**	**2.05 [0.50, 8.41]**
Total events	7		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.1.3 LF-R						
Hoppner et al. (2003)	1	1	0	1	2.0%	9.00 [0.10, 831.78]
Klein et al. (1999)	5	7	1	6	5.6%	12.50 [0.84, 186.30]
Ning et al. (2013)	29	30	27	29	6.7%	2.15 [0.18, 25.07]
Subtotal (95% CI)		**38**		**36**	**14.3%**	**5.21 [0.96, 28.13]**
Total events	35		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.06)						
Total (95% CI)		**145**		**129**	**100.0%**	**2.72 [1.44, 5.14]**
Total events	78		48			
Heterogeneity: Tau² = 0.00; Chi² = 4.86, df = 13 (P = 0.98); I² = 0%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Chi² = 0.74, df = 2 (P = 0.69), I² = 0%						

Odds Ratio M-H, Random, 95% CI

0.005 0.1 1 10 200

Favours [SHAM] Favours [rTMS]



- rTMS is better than sham
- No consensus on optimal paradigm or parameters

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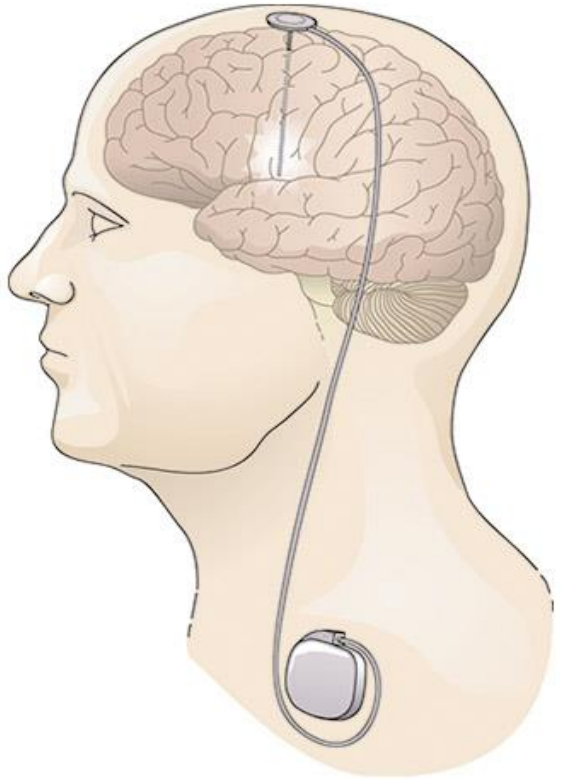
(Nguyen et al, Journal of Affective Disorders, 2021)

Deep Brain Stimulation (DBS)

	DBS
Type of Stimulation	Electrical
Convulsive	✘
GA	✓ (Surgical implantation)
Mechanism of action	Activation of local circuit



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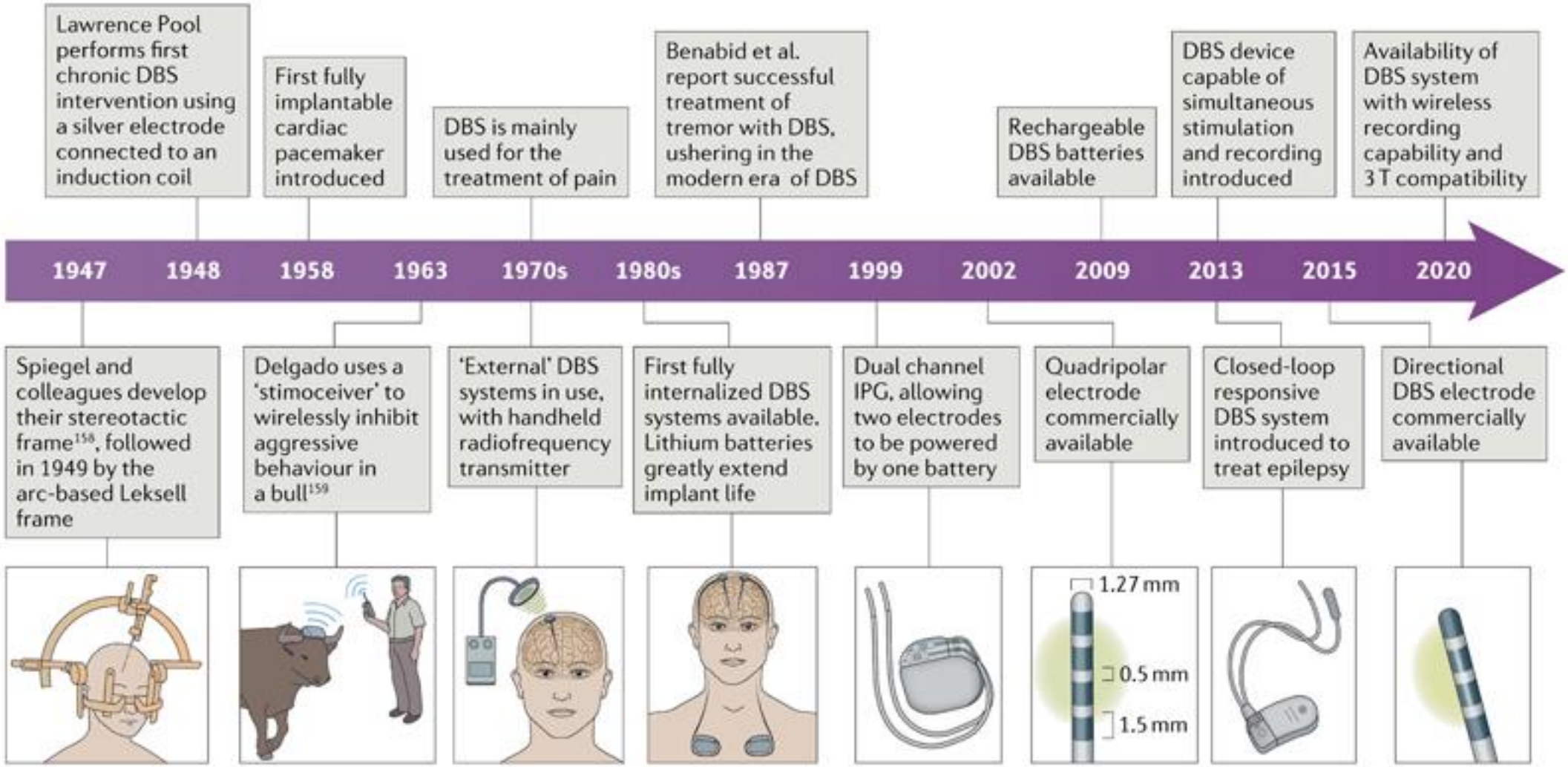

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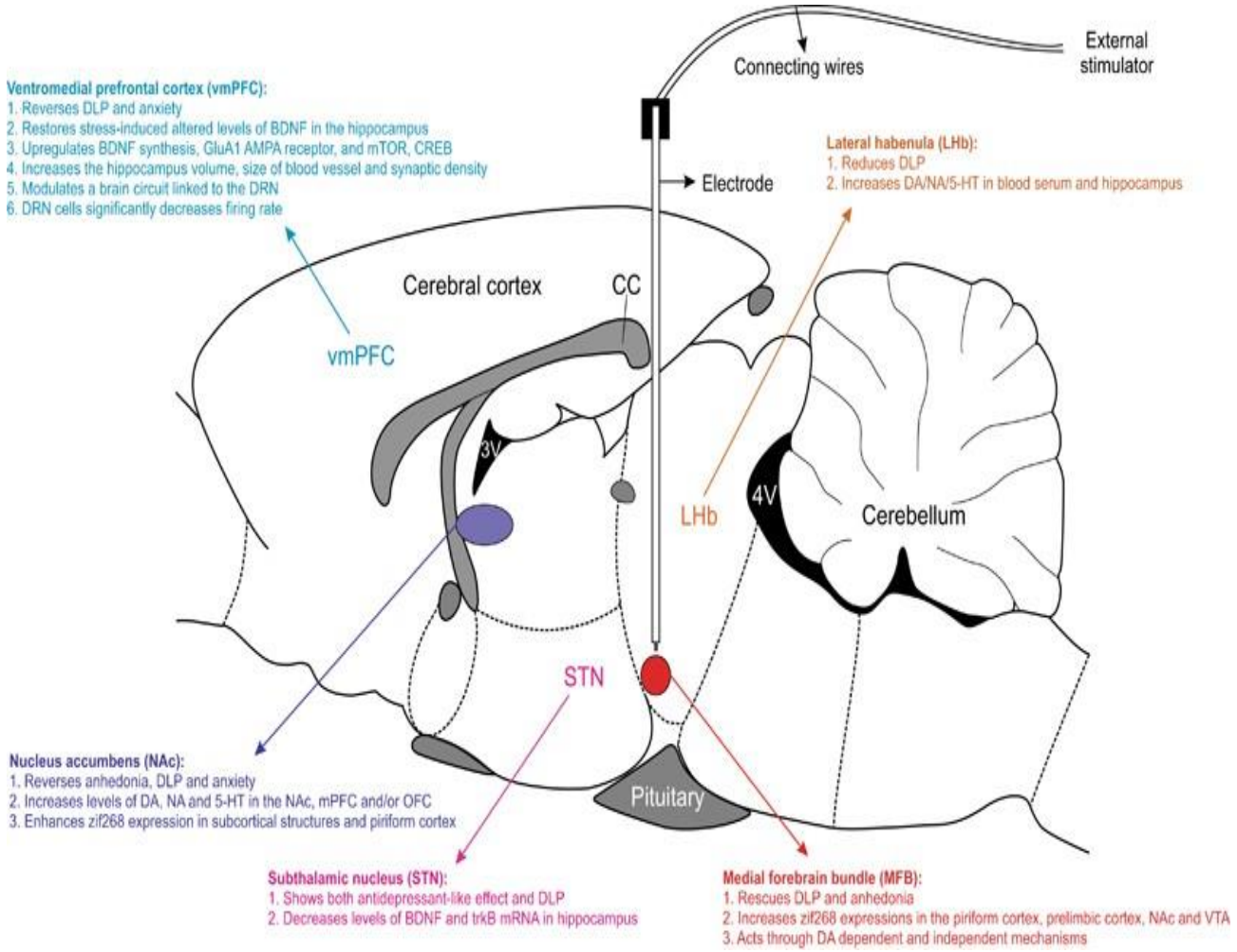
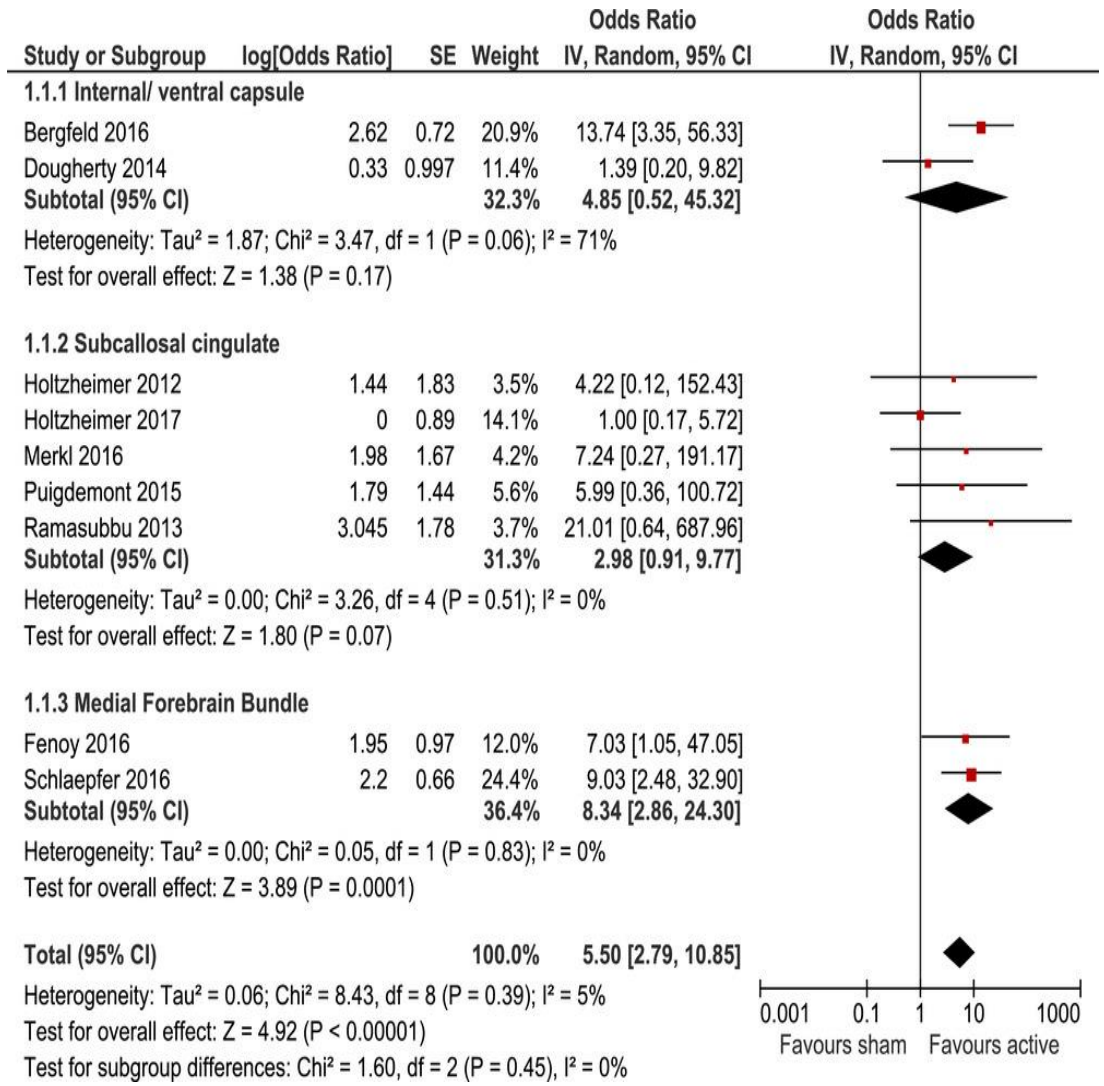
(Krauss et al, Nat Rev Neurol, 2021)

DBS for MDD





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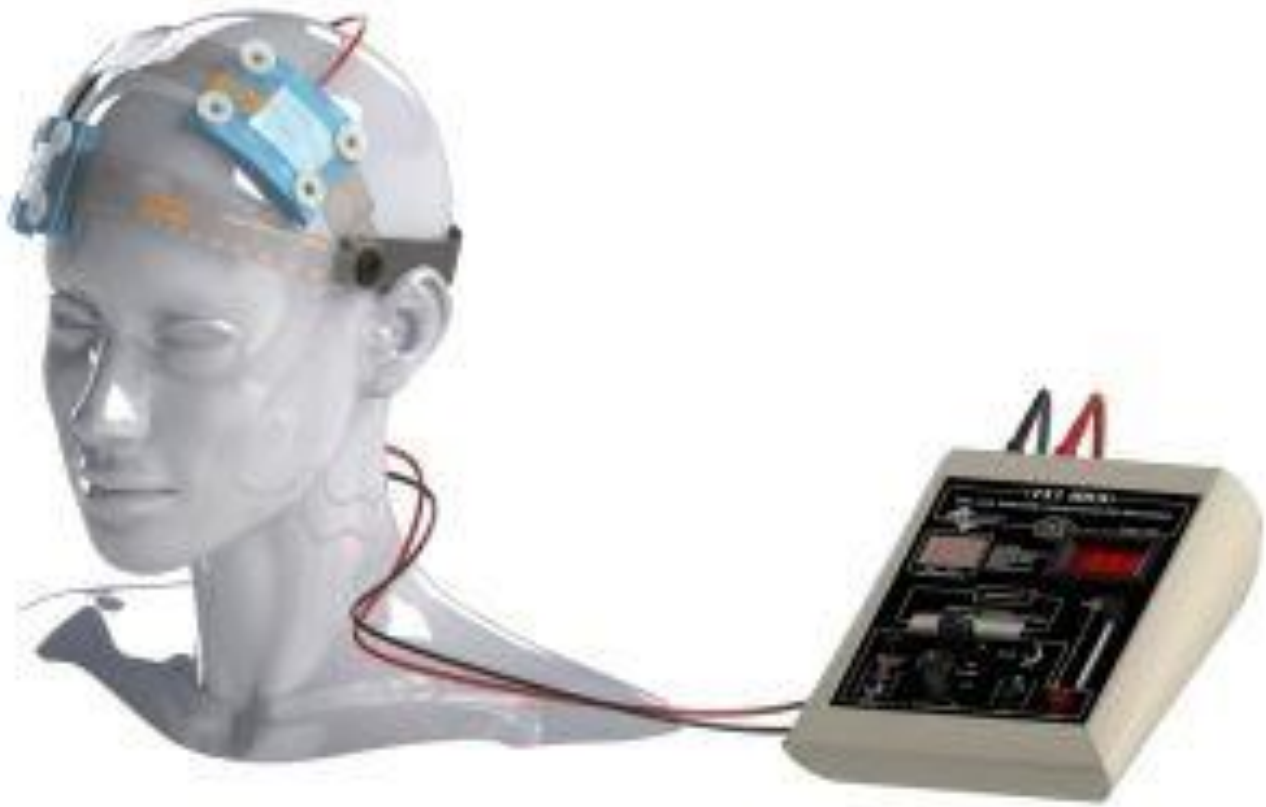
(Dandekar, Mol. Psych., 2018, Kisely et al, Dep & Anxiety, 2018)

Electrical Stimulation - tDCS & tACS

	tDCS
Type of Stimulation	Electrical
Convulsive	✘
GA	✘
Mechanism of action	Subthreshold modulation of membrane potential



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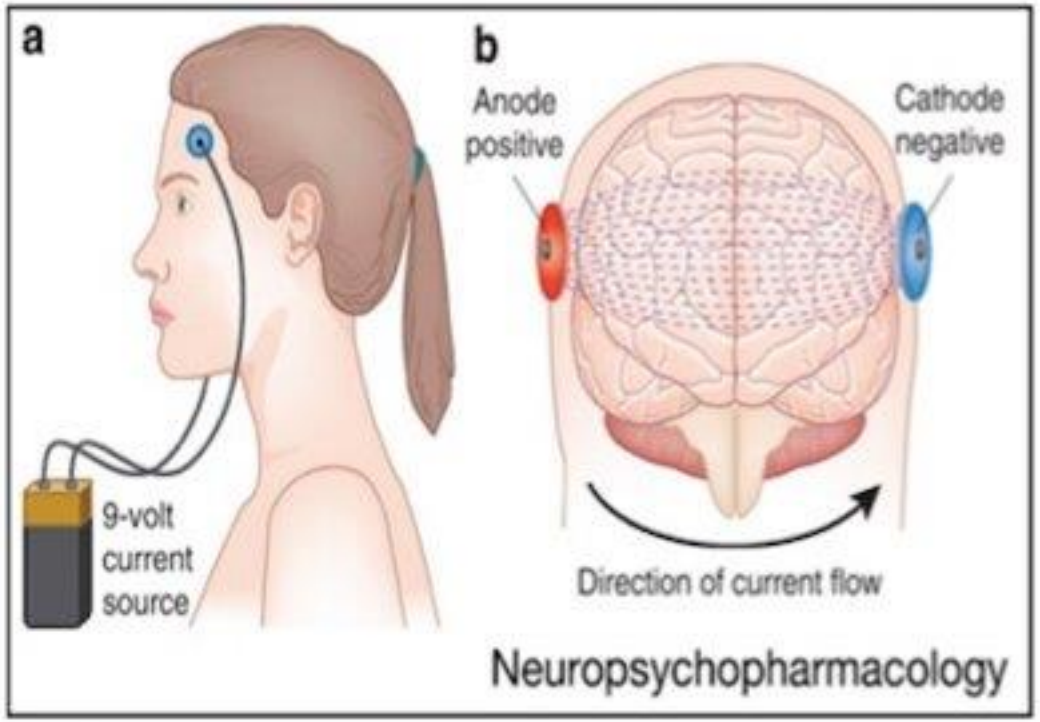
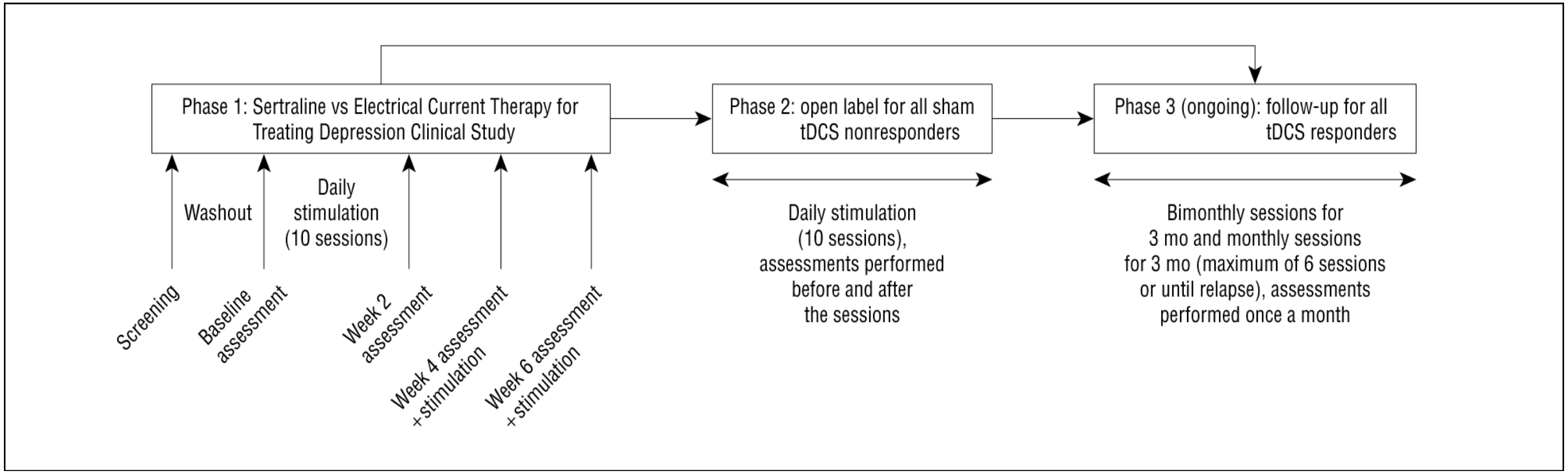
tDCS/tACS

- Noninvasive electrical stimulation applied to the scalp
- Low amplitude direct or alternating current
- Thought to induce changes in cortical excitability
- With guidance, can be used at home
- No seizures
- Minimally invasive, few side effects
  - Drowsiness, headache, skin itching at site of stimulation
- Most side effects avoided with proper technique



George & Aston-Jones, Neuropsychopharmacology, 2010

SELECT Trial



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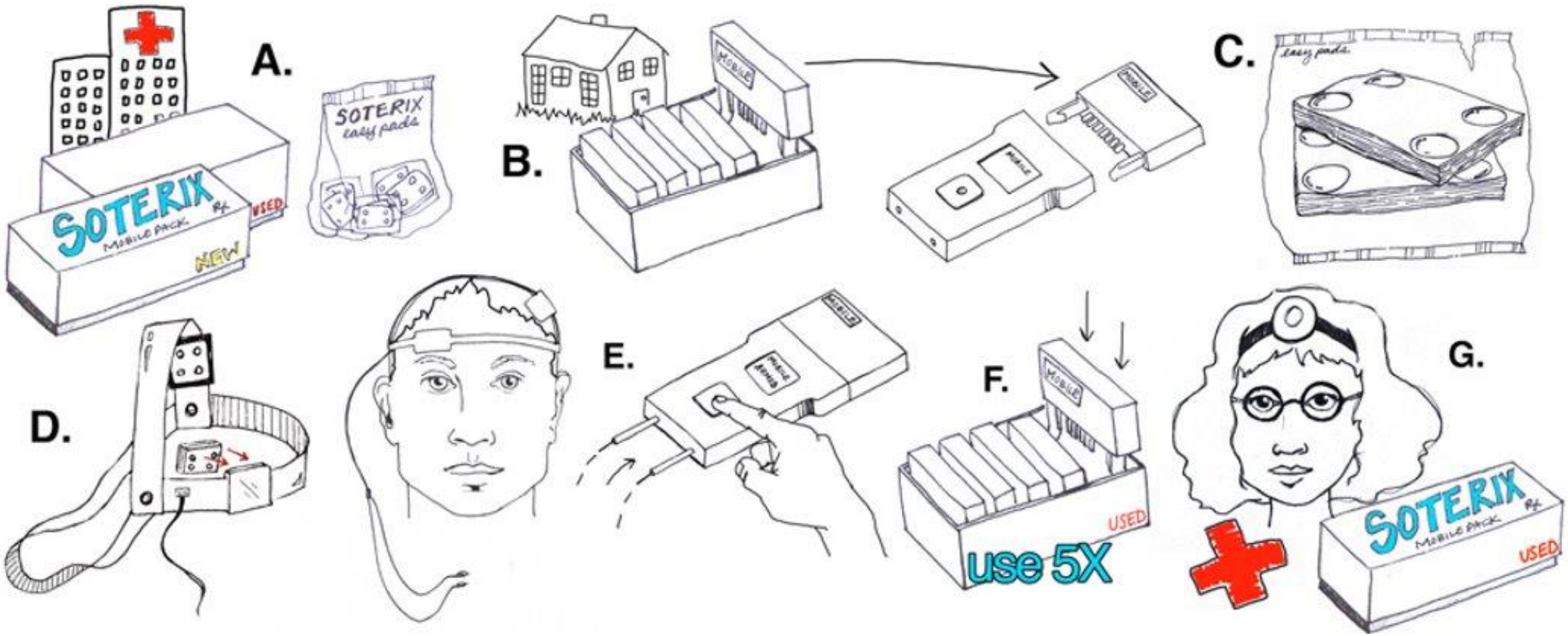
(Brunoni et al, JAMA Psych, 2013)

Opportunity for At Home Brain Stimulation



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Magnetic Seizure Therapy (MST)

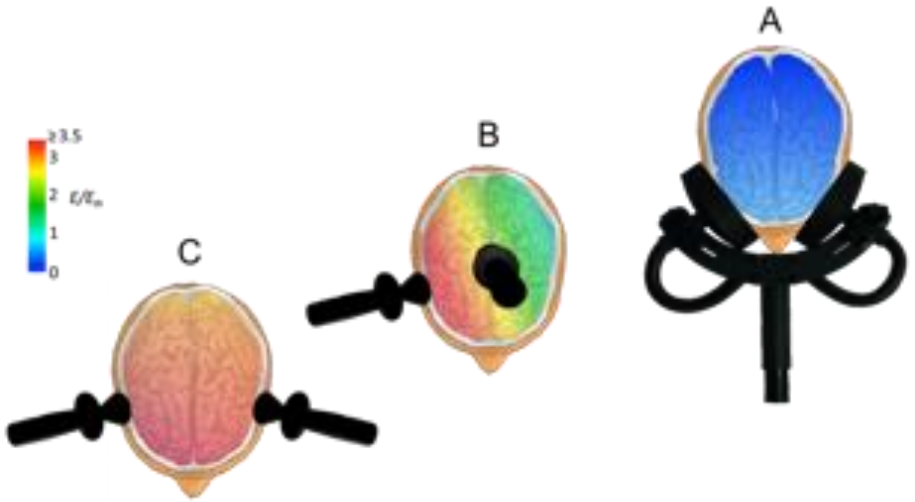

Figure 1. This figure demonstrates that (A) MST produces a seizure with much lower e-field strength (cooler colors) compared to (B) right unilateral ECT or (C) bilateral ECT which requires much higher e-field strength (hot colors) to produce an adequate seizure. Additionally, the skull shunts the electrical field making the electrical field from ECT largely non-focal. It is postulated that more focality and lower e-field strength contributes to the preservation of cognitive performance of MST compared to ECT. Modified from Fig 3, Deng et al. 2011.

MST	ECT	DBS
Magnetic	Electrical	Electrical
✓	✓	✗
✓	✓	✓ (Surgical implantation)
Focal activation of inhibitory interneurons	General activation of pyramidal neurons	Activation of local circuit

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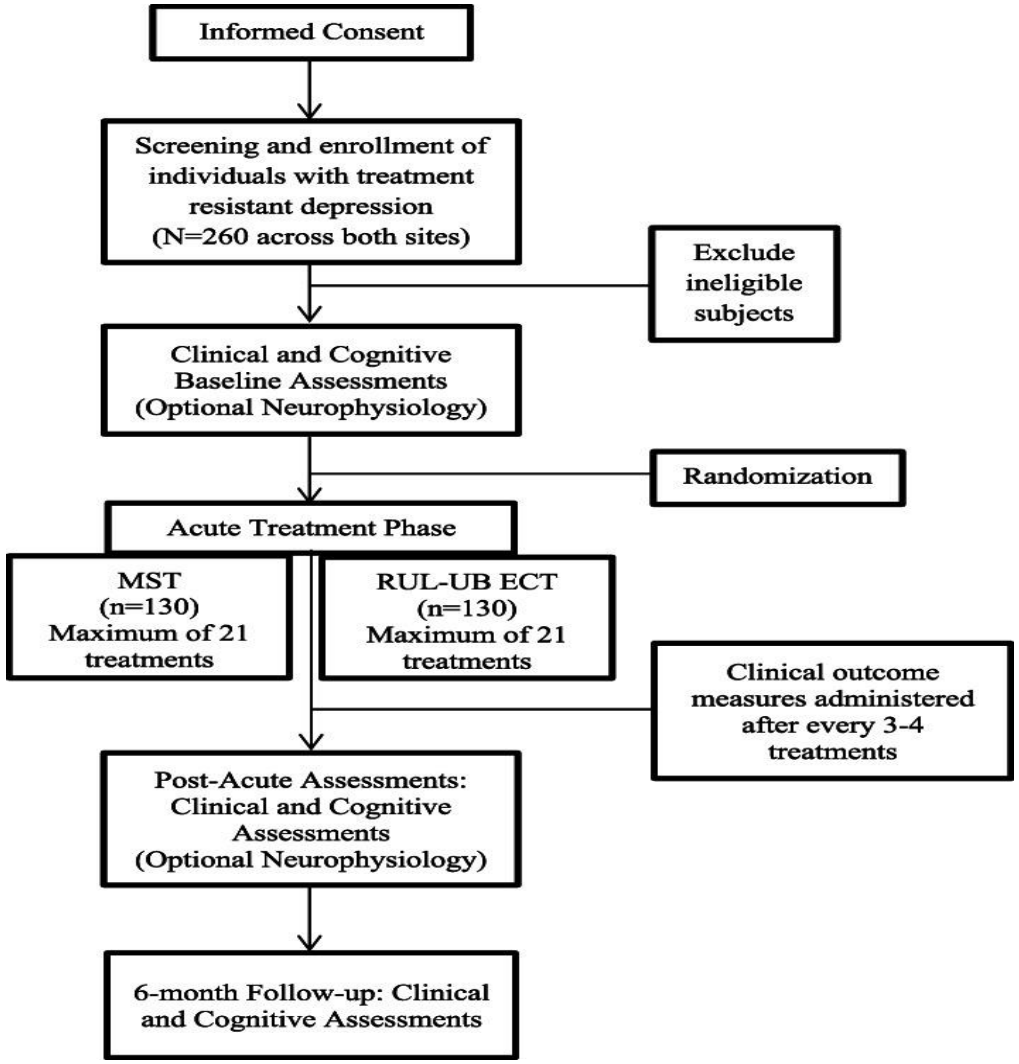
CREST Trial – Comparing MST with ECT



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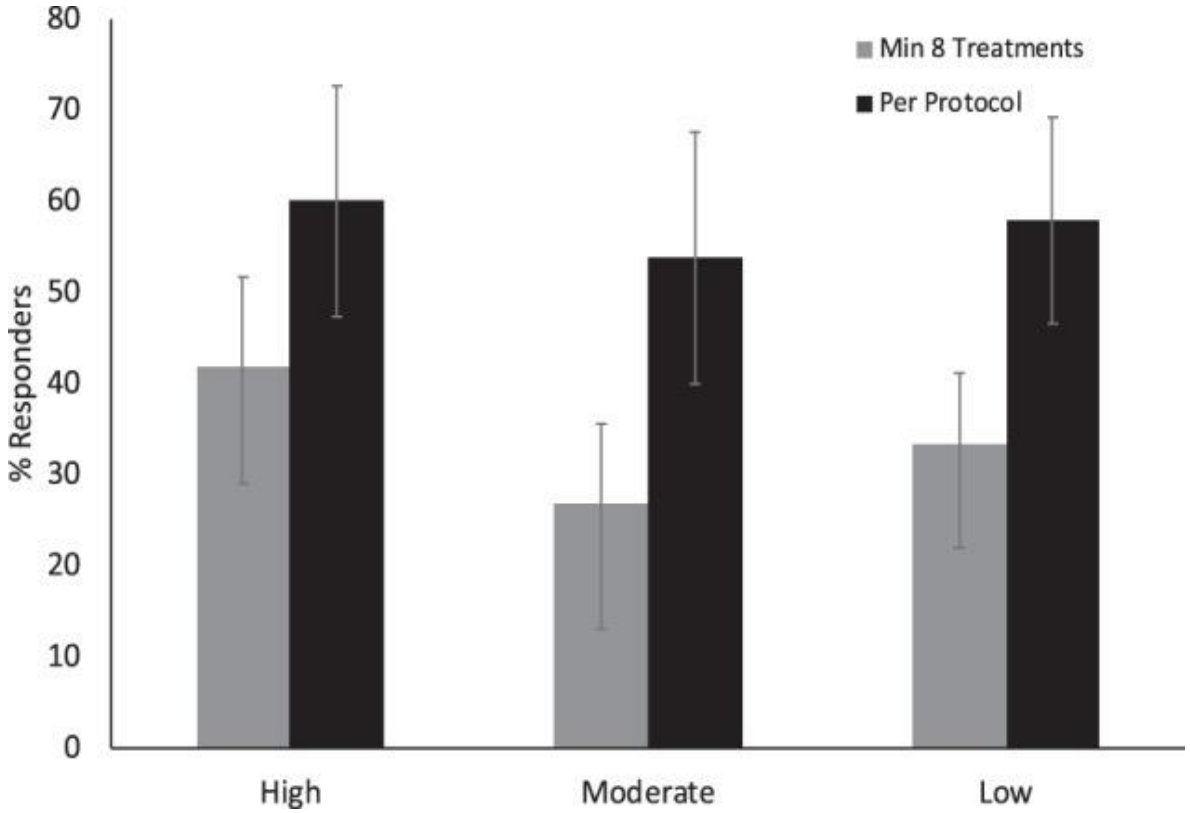
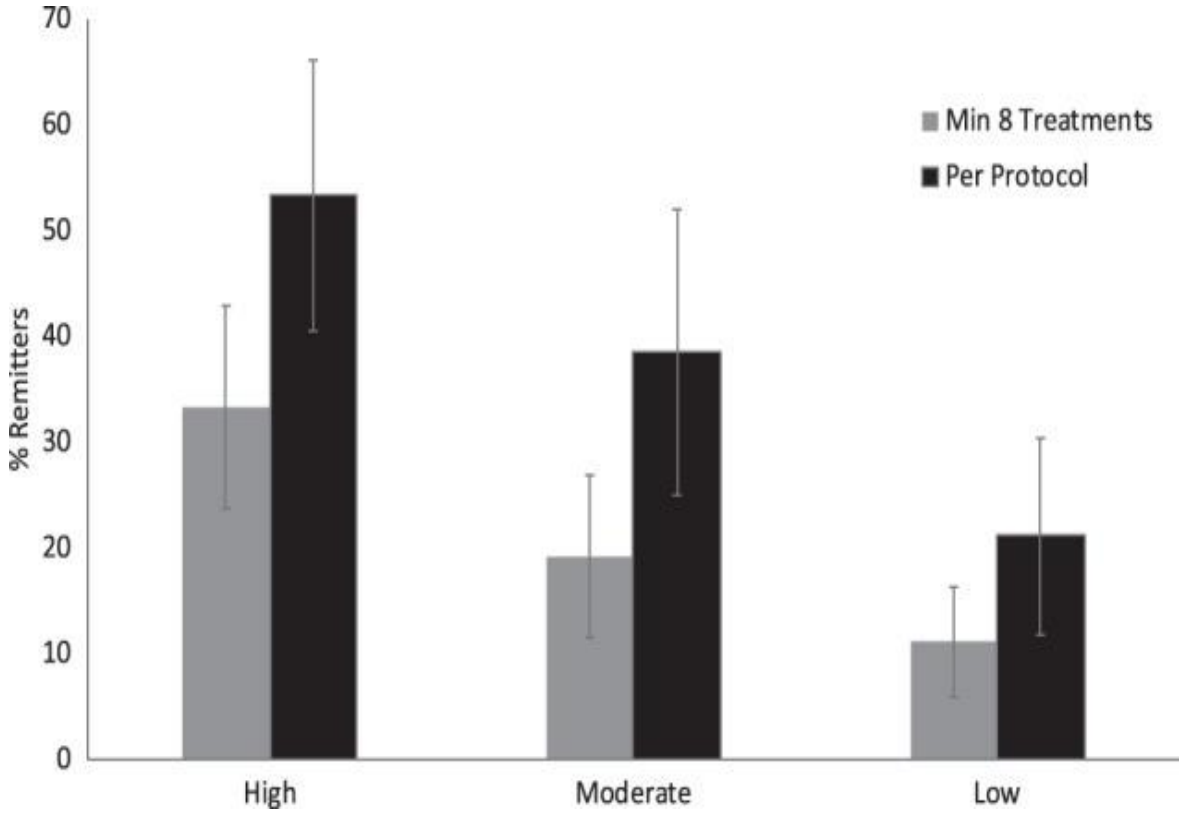
(Daskalakis et al, Trials, 2021)

MST for Treatment Resistant Depression





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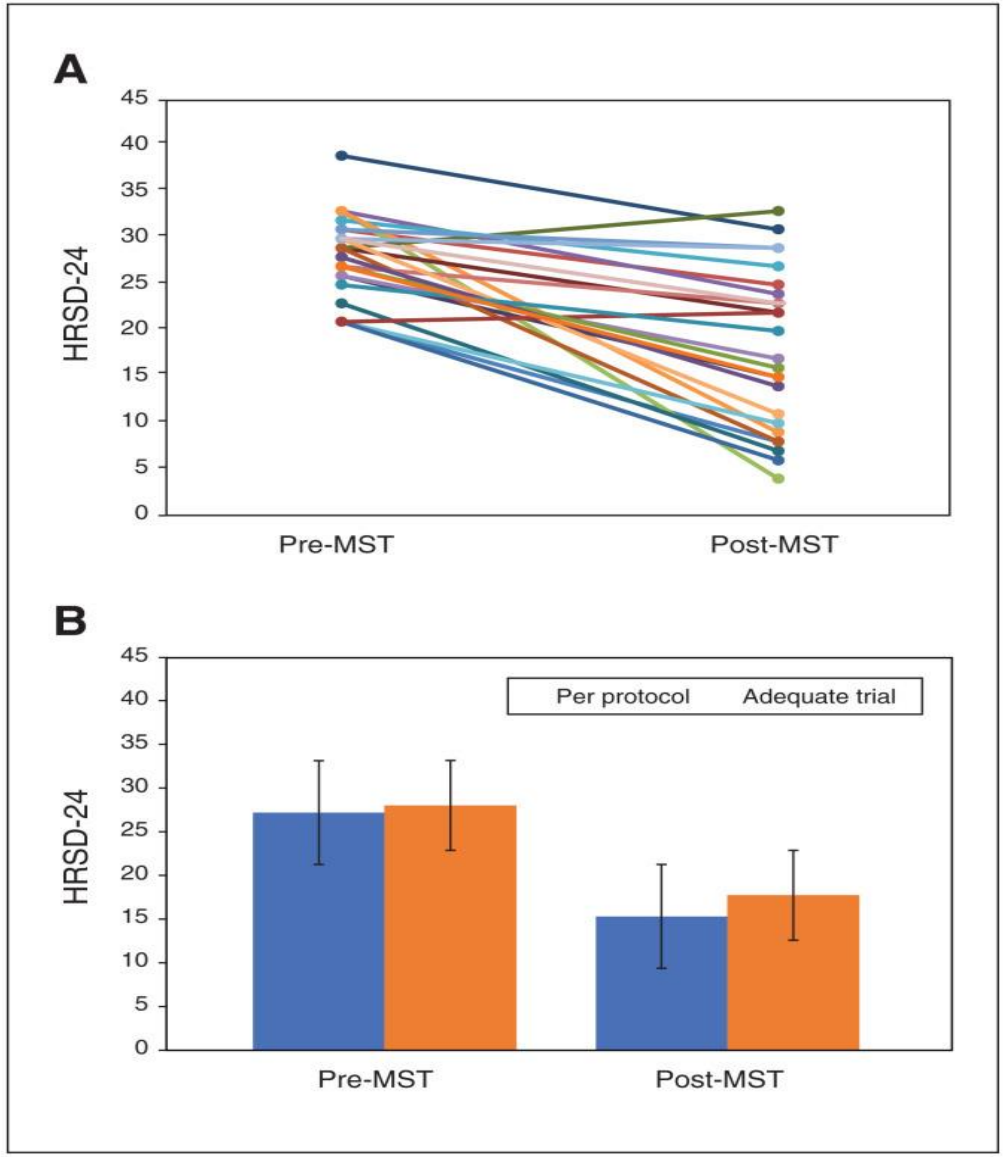
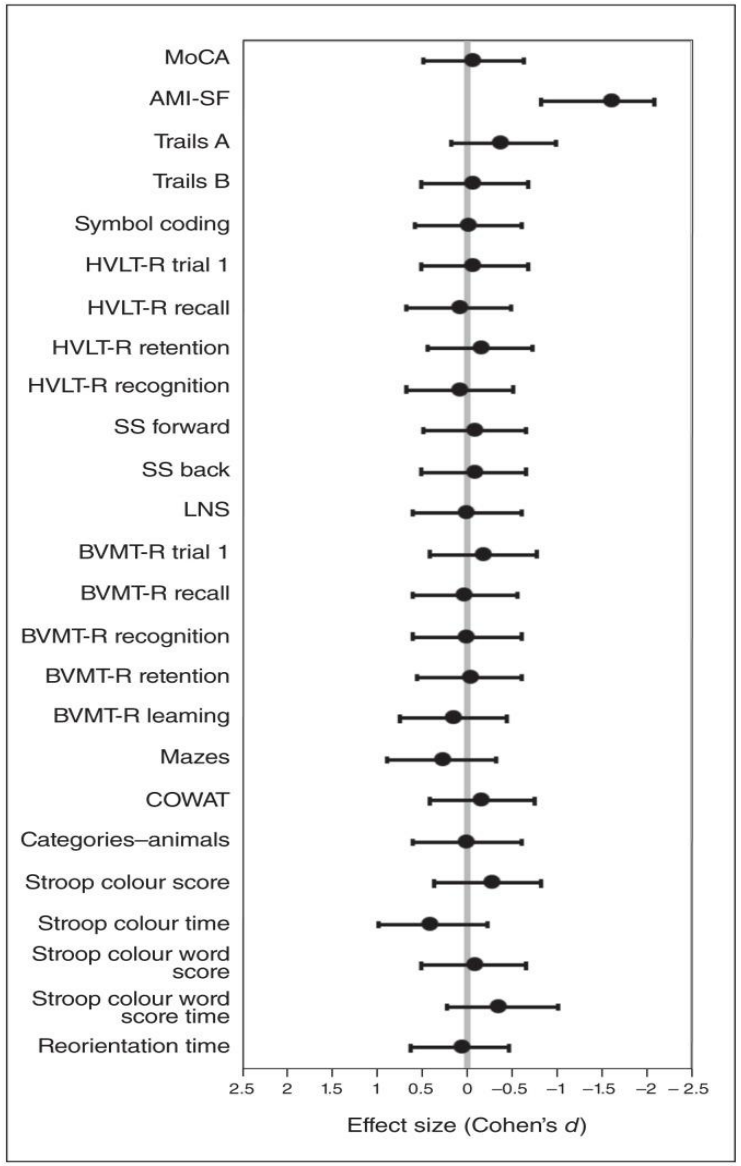
(Daskalakis et al, Neuropsychopharm, 2020)

MST for Bipolar Depression





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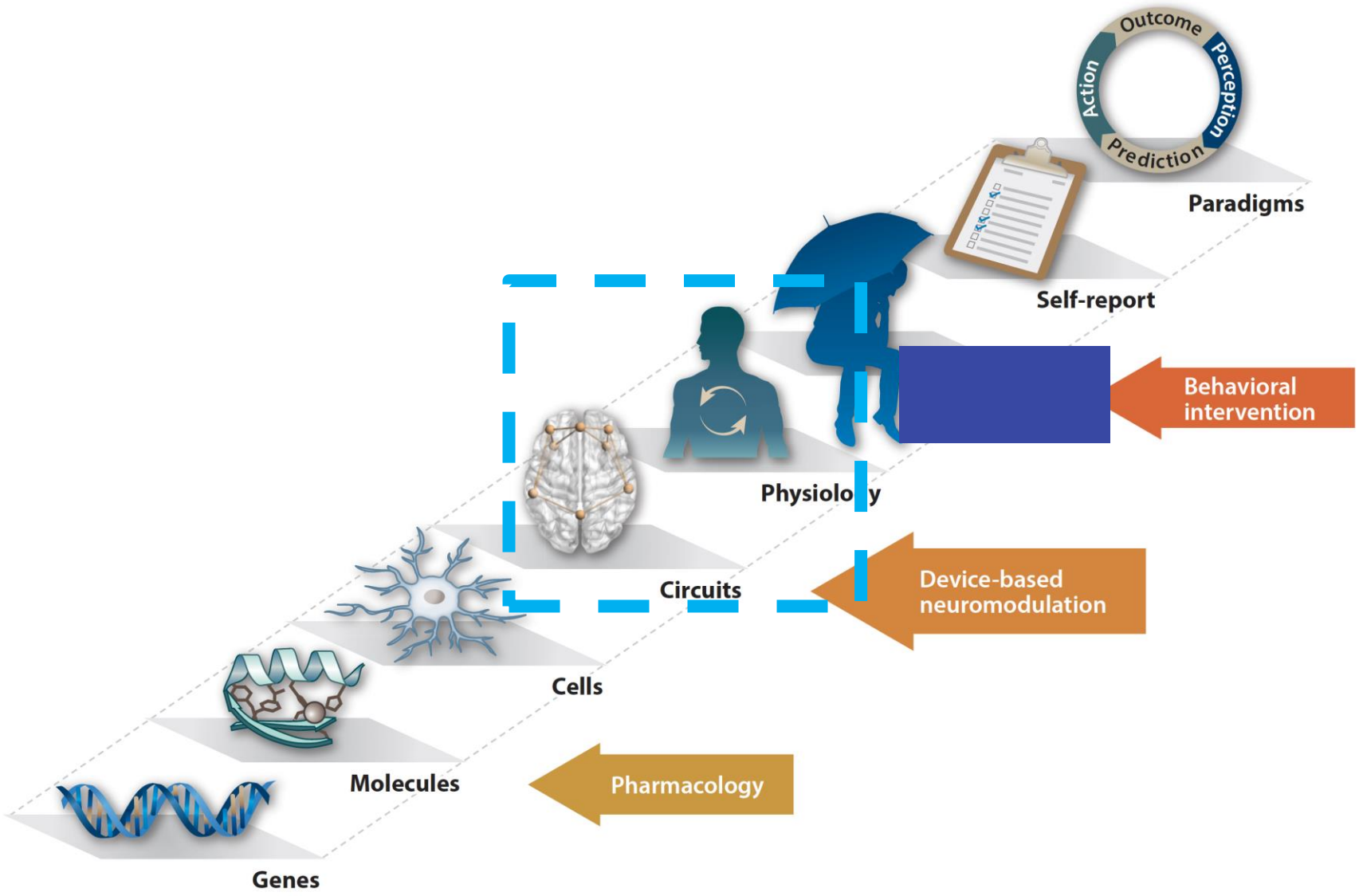
(Tang et al, Biological Psych, 2021)

Future Directions

Establishing Biomarkers to Guide Treatment



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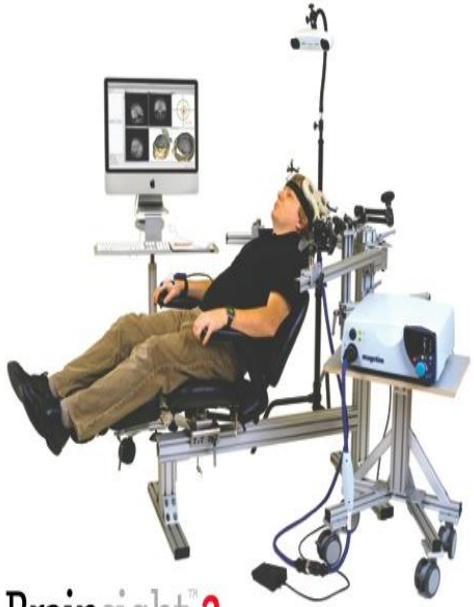
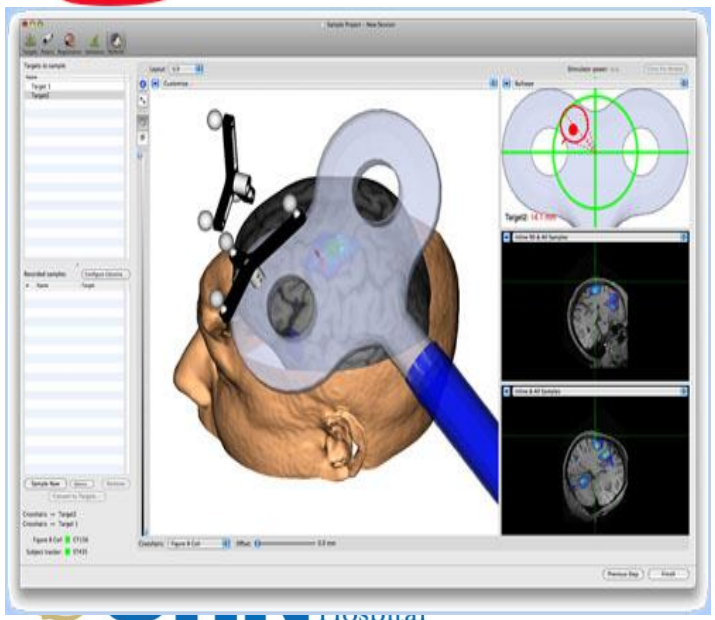
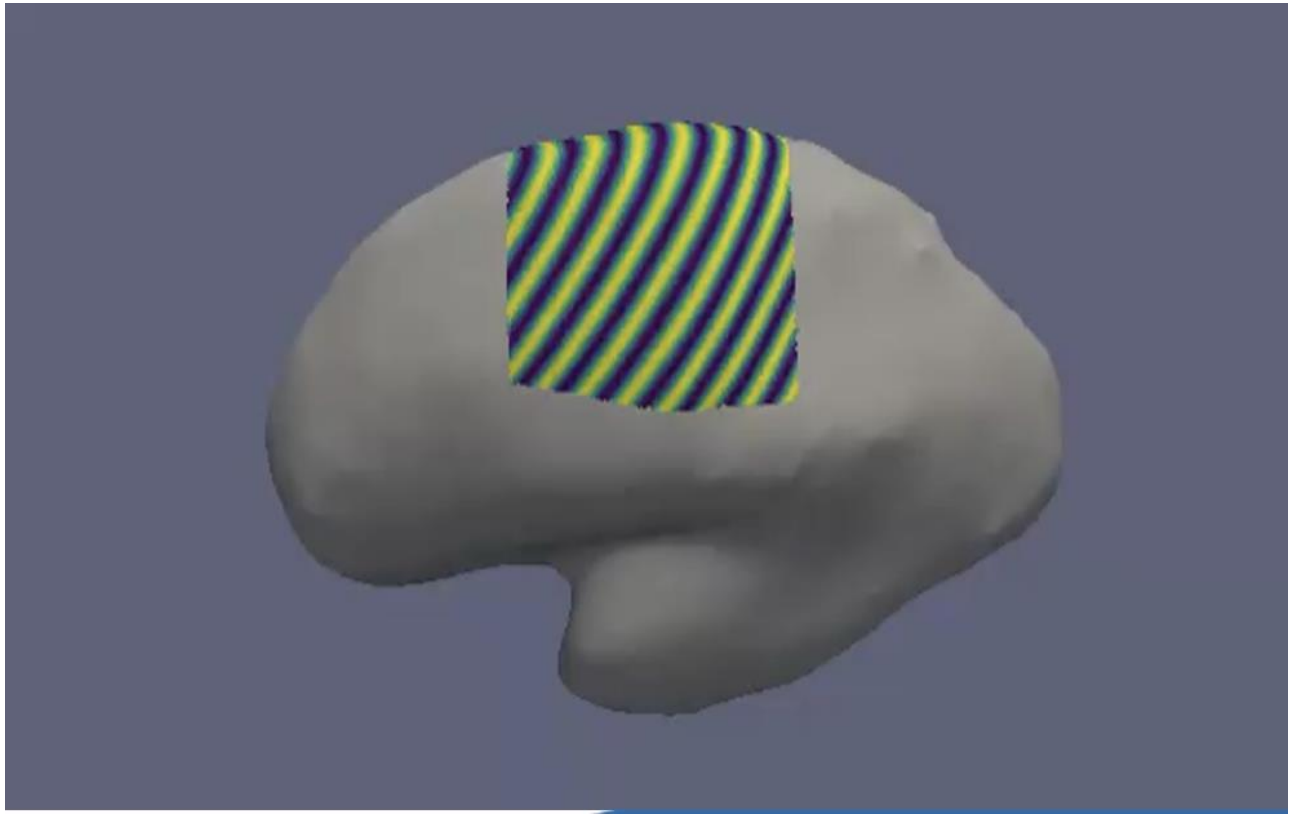
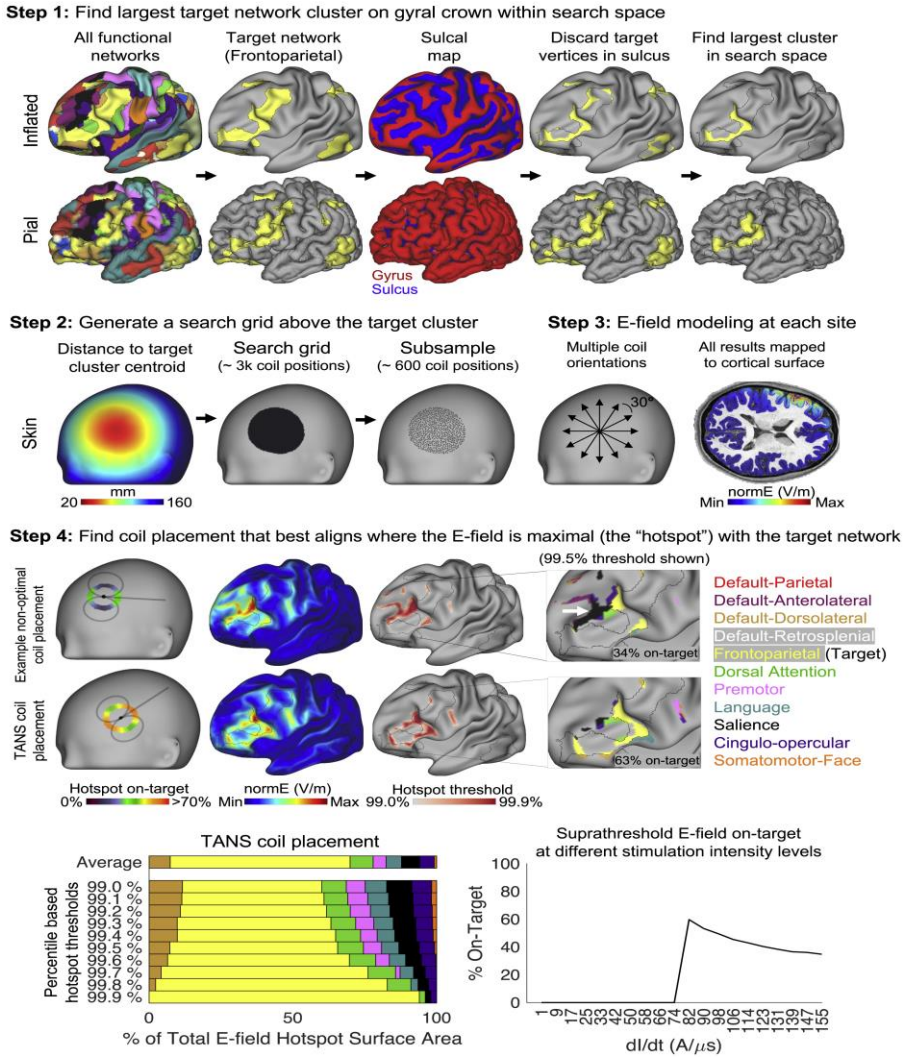
Personalizing rTMS

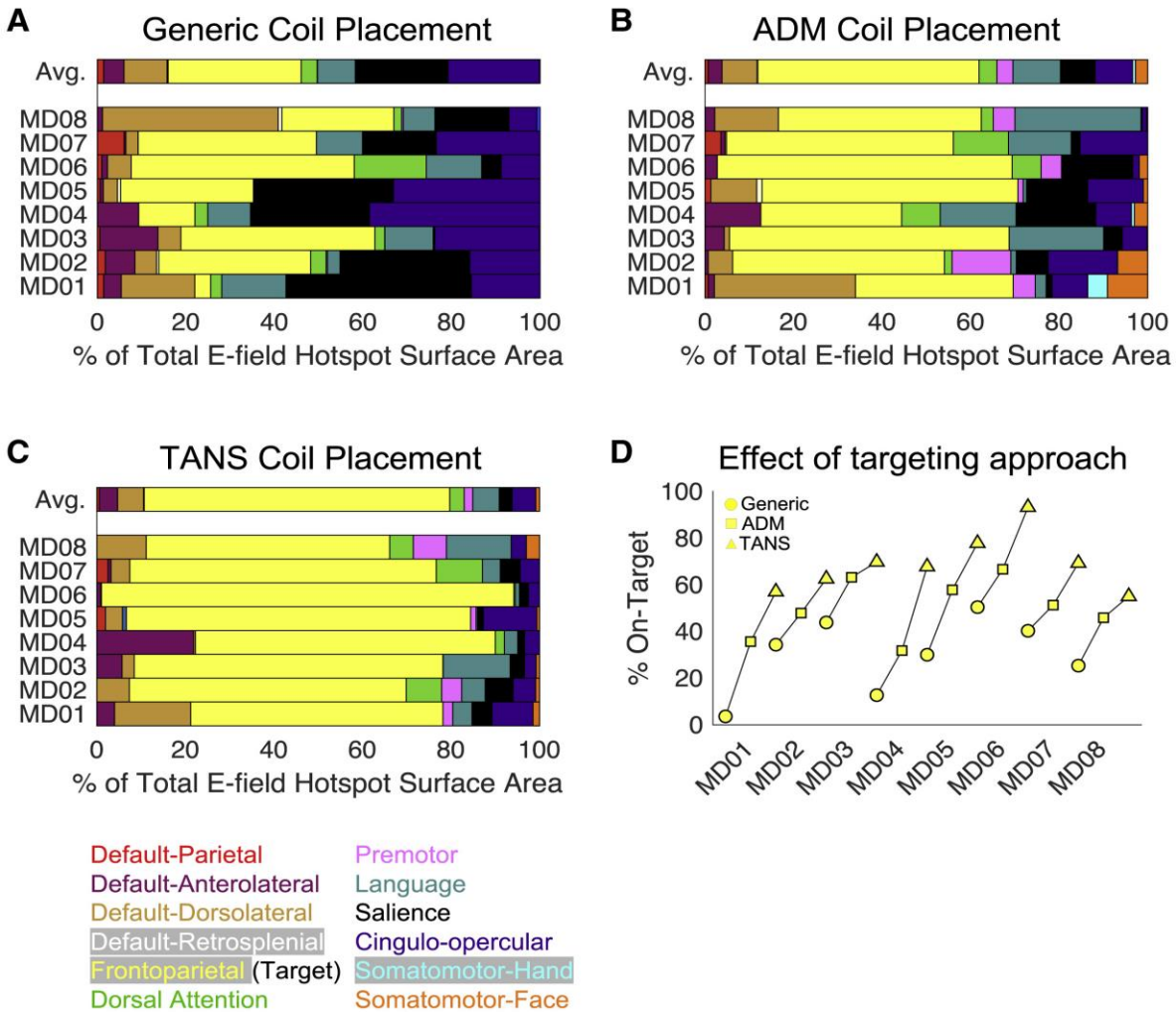






Connectivity-Based rTMS





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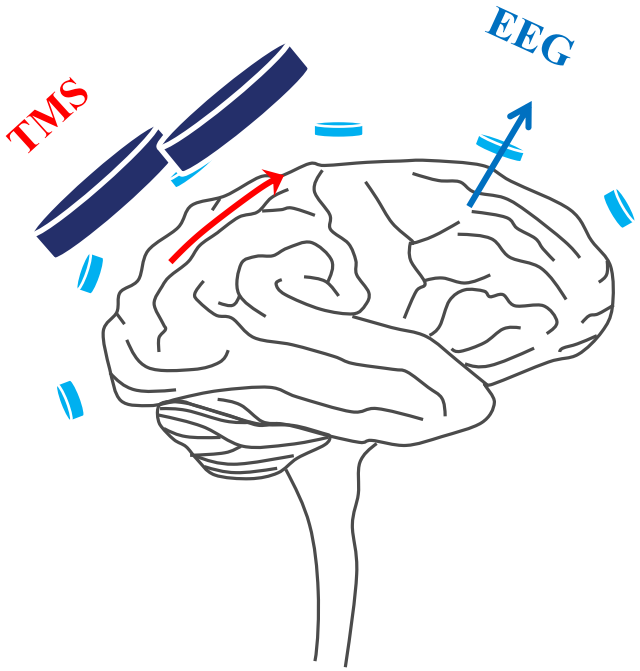
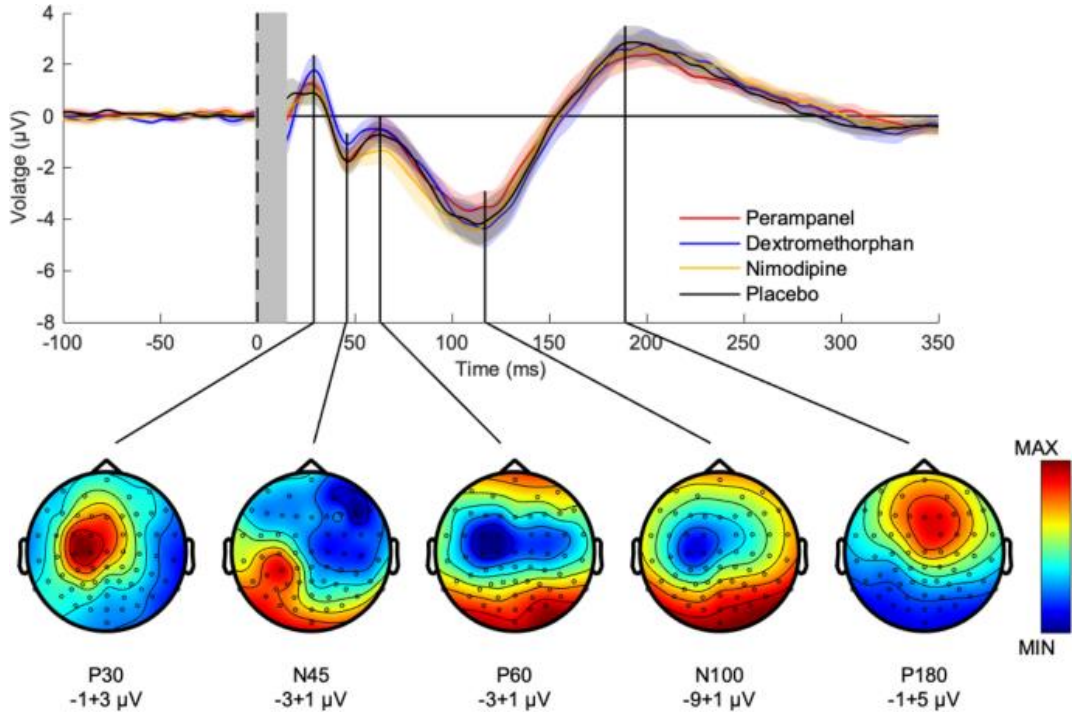
(Liston et al, Neuron, 2022)

Establishing Biomarkers to Guide Treatment





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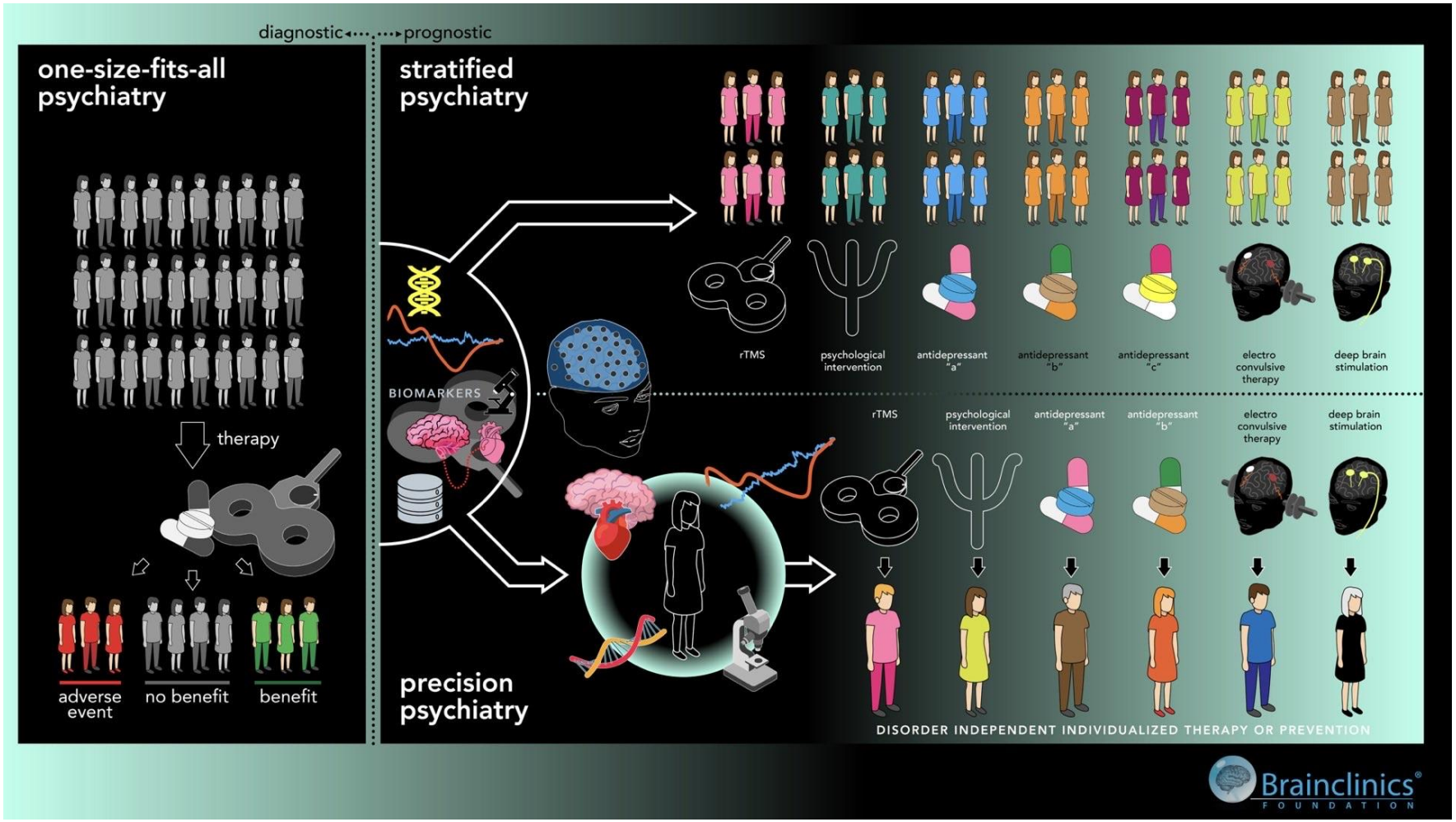
The Goal



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Questions?

Sincerest Thanks to:

The Hansen Family
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Dr. Susan Abbey
Dr. Daniel Blumberger