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Psychiatry and Addictions Case Conference
UW Medicine | Psychiatry and Behavioral Sciences

TRANSCRANIAL MAGNETIC STIMULATION

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UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?
  - ✓ No relevant financial relationships to disclose
    - ✓ I work at a clinic that offers TMS.
    - ✓ I also am on the Board of the Clinical TMS Society and serve as its Treasurer and Chair of the Insurance Committee.

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WHAT IS "INTERVENTIONAL PSYCHIATRY?"

- "…an emerging subspecialty that utilizes neurotechnologies to identify dysfunctional brain circuitry underlying psychiatric disorders and apply brain stimulation techniques to modulate that circuitry." (Williams, 2014)
- Treatment modalities include (* = FDA approved)
  - TMS*
    - cTBS
    - iTBS*
    - dTMS*
  - ECT*
  - Ketamine infusions
  - Esketamine (Spravato) nasal spray*
  - VNS*
  - DBS
  - tDCS
  - . . . others

Williams N. Interventional Psychiatry: Why Now? J Clin Psychiatry. 2014 Aug; 75(8): 895-897

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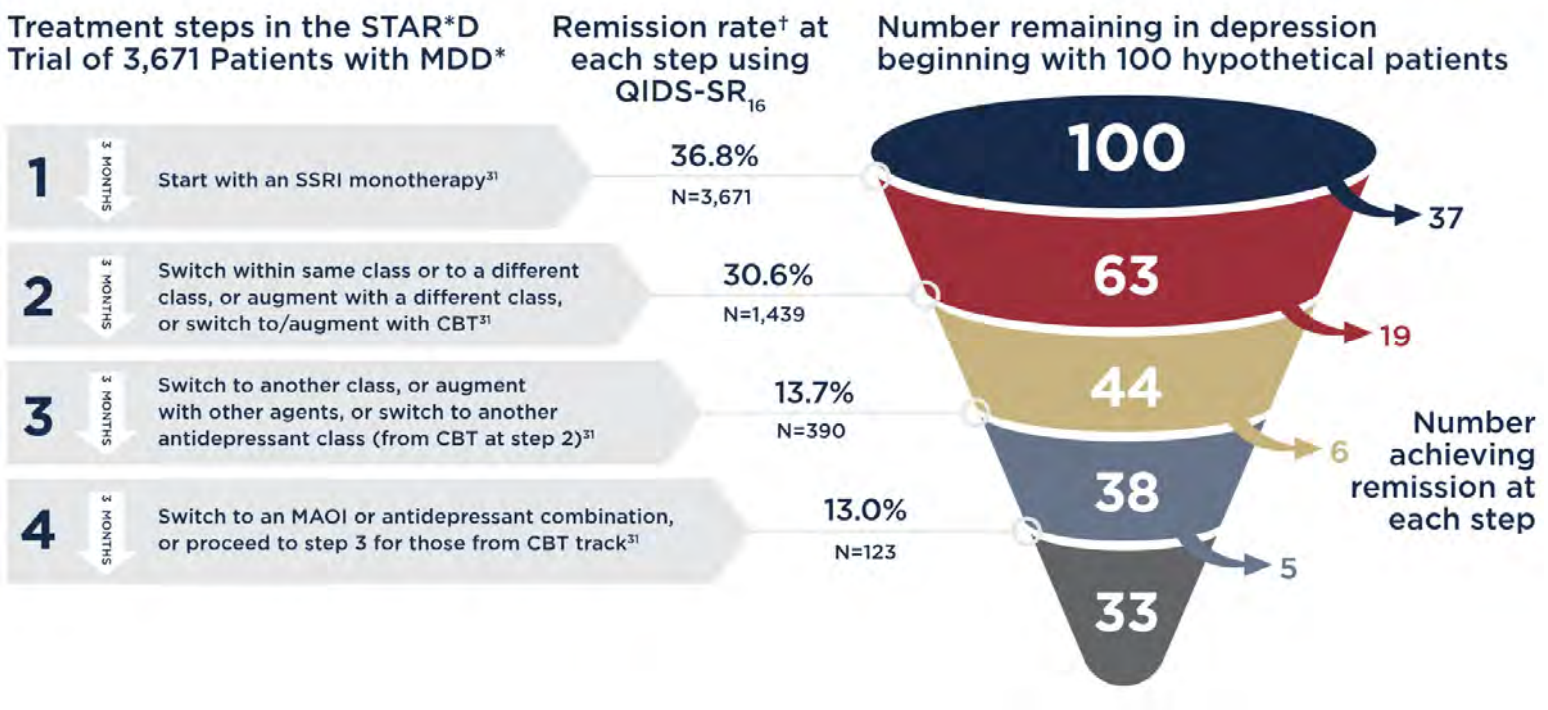
STAR*D

STUDY: Sequenced Treatment Alternatives To Relieve Depression



Only 2/3 achieved remission after four medications

https://www.unlockingdepression.com/images/topic-9-funnel.svg

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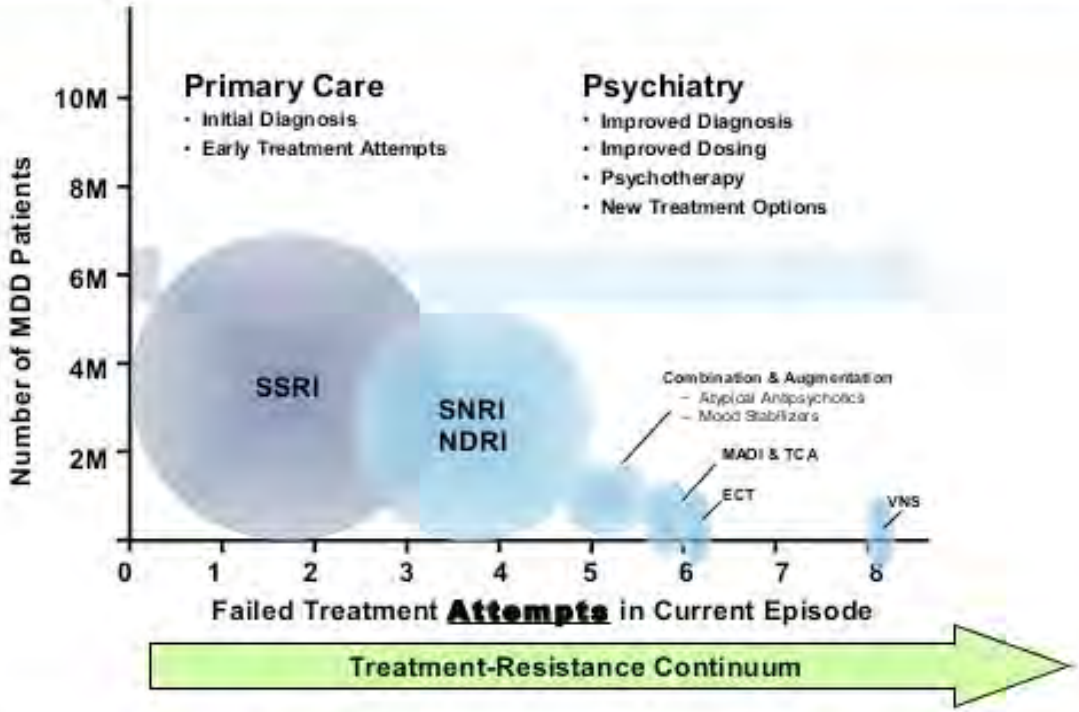
~~Current~~ Treatment Practices in MDD

2003 (note the absence of TMS on this graph)



Kessler RC et al. *Arch Gen Psychiatry*. 2005;62(6):617-627; Kessler RC et al. *JAMA*. 2003;289(23):3095-3105; Hermann RC et al. *Am J Psychiatry*. 1995;152(6):869-875.

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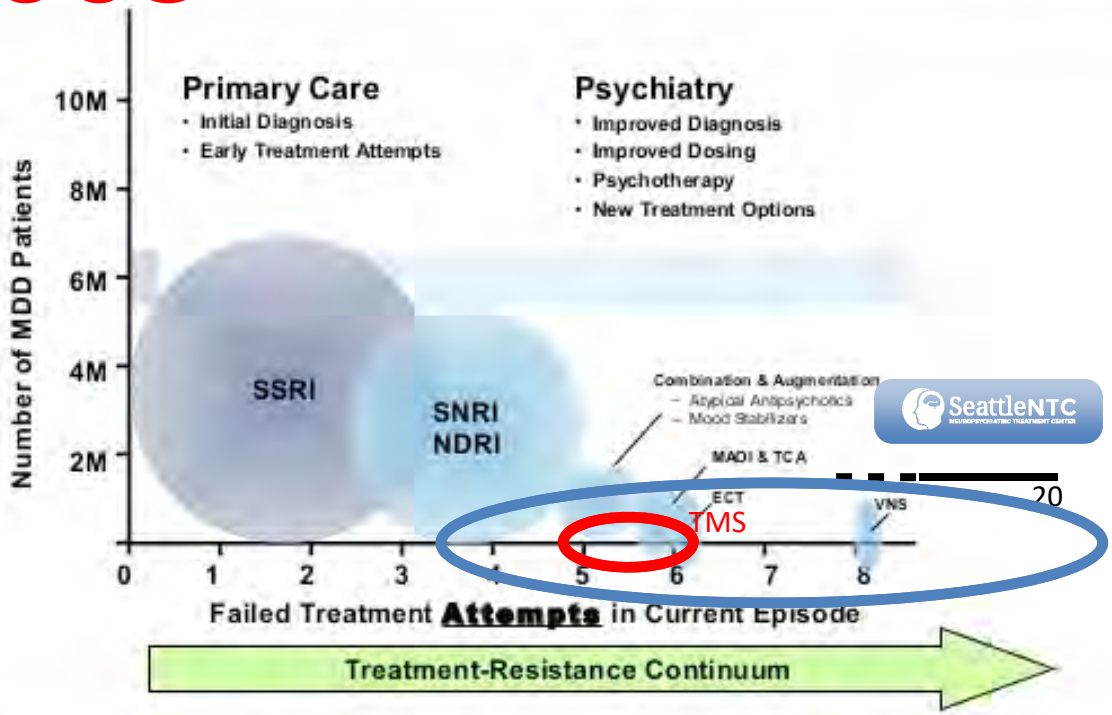
~~Current~~ Treatment Practices in MDD

2003



Kessler RC et al. *Arch Gen Psychiatry*. 2005;62(6):617-627; Kessler RC et al. *JAMA*. 2003;289(23):3095-3105; Hermann RC et al. *Am J Psychiatry*. 1995;152(6):869-875.

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TRANSCRANIAL MAGNETIC STIMULATION (TMS)

- Delivery of focused magnetic field pulses of 1.0-2.5 T through a coil placed over the scalp
- Induces an electric current when it reaches the brain
- Modulates the activity of dysfunctional cortical regions that are stimulated and other brain regions functionally connected to the stimulation site

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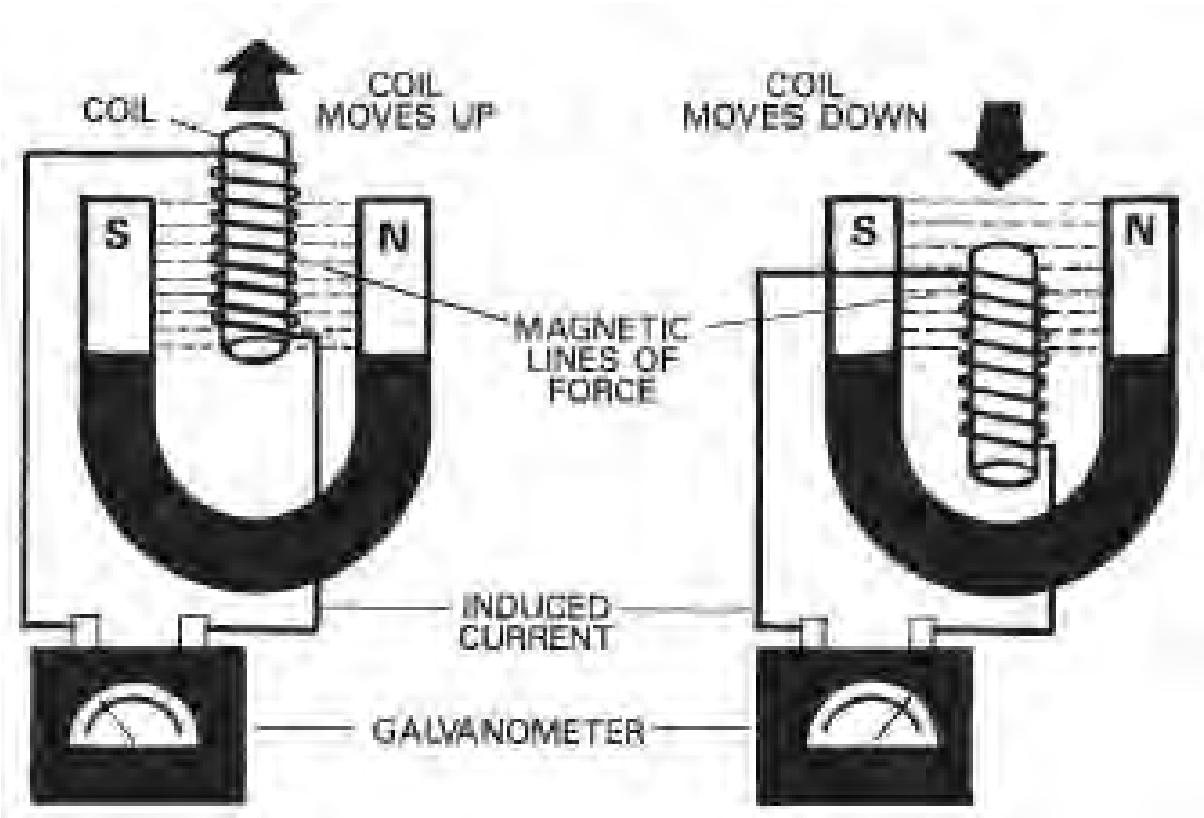
Faraday's Law



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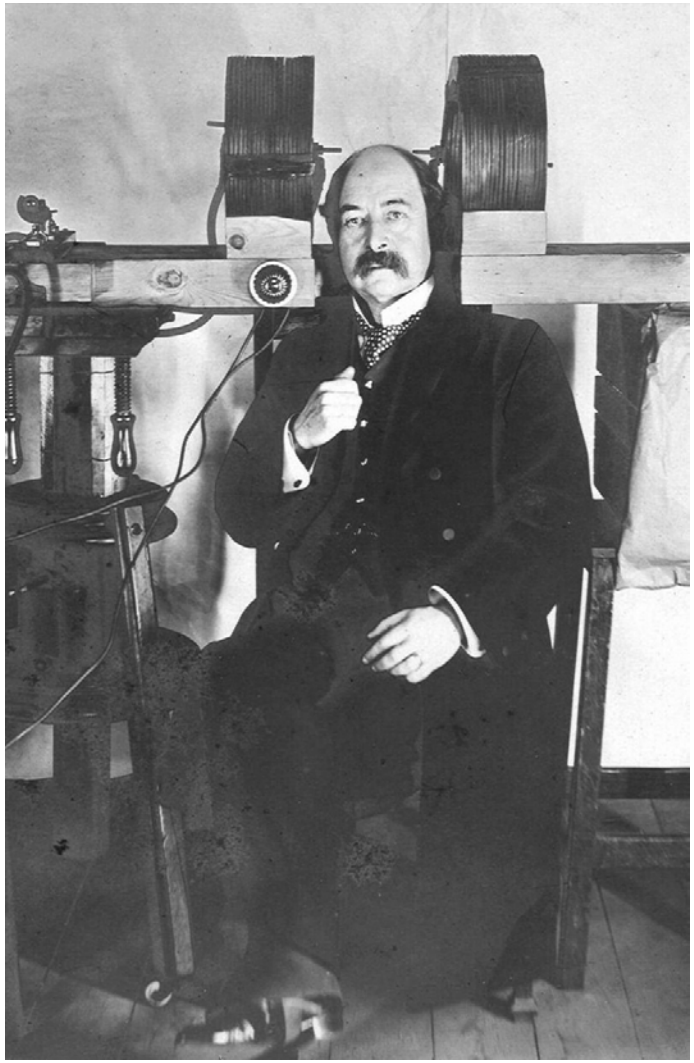

1910 photograph

Silvanus Thompson testing the physiological effect of a large alternating magnetic field.

Induced phosphenes.

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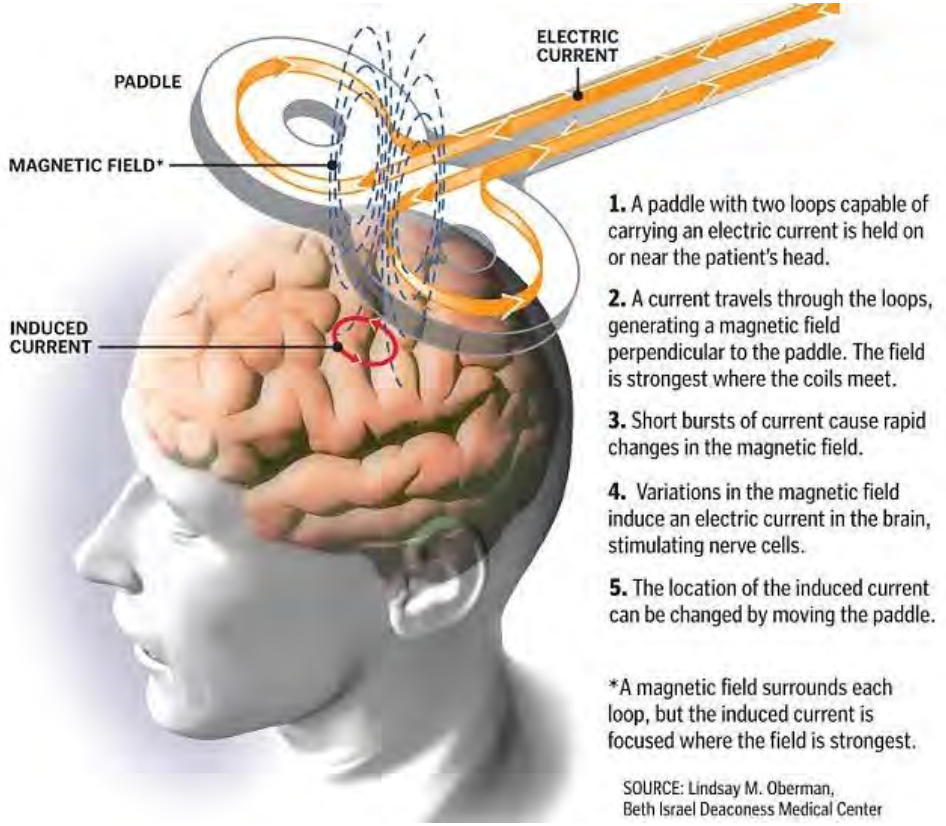
HOW DOES TMS WORK?

- Faraday's Law
  - Changing magnetic field induces electric current in a wire
- Brain is the "wire"
- Modulates activity and connectivity in **both**
  - Target area
  - Distant interconnected areas
- May alter brain oscillatory activity



Keck, M.E. 2007. Repetitive transcranial magnetic stimulation effects in vitro and in animal models. Transcranial Brain Stimulation for Treatment of Psychiatric Disorders, Marcolina, M.A. and Padberg, F. (Eds.) Advances in Biological Psychiatry, Vol. 23, Karger, Basel, Switzerland, pp. 18-34.
Leuchter, A. F., Cook, I. A., Jin, Y. & Phillips, B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Frontiers in Human Neuroscience 7, (2013).

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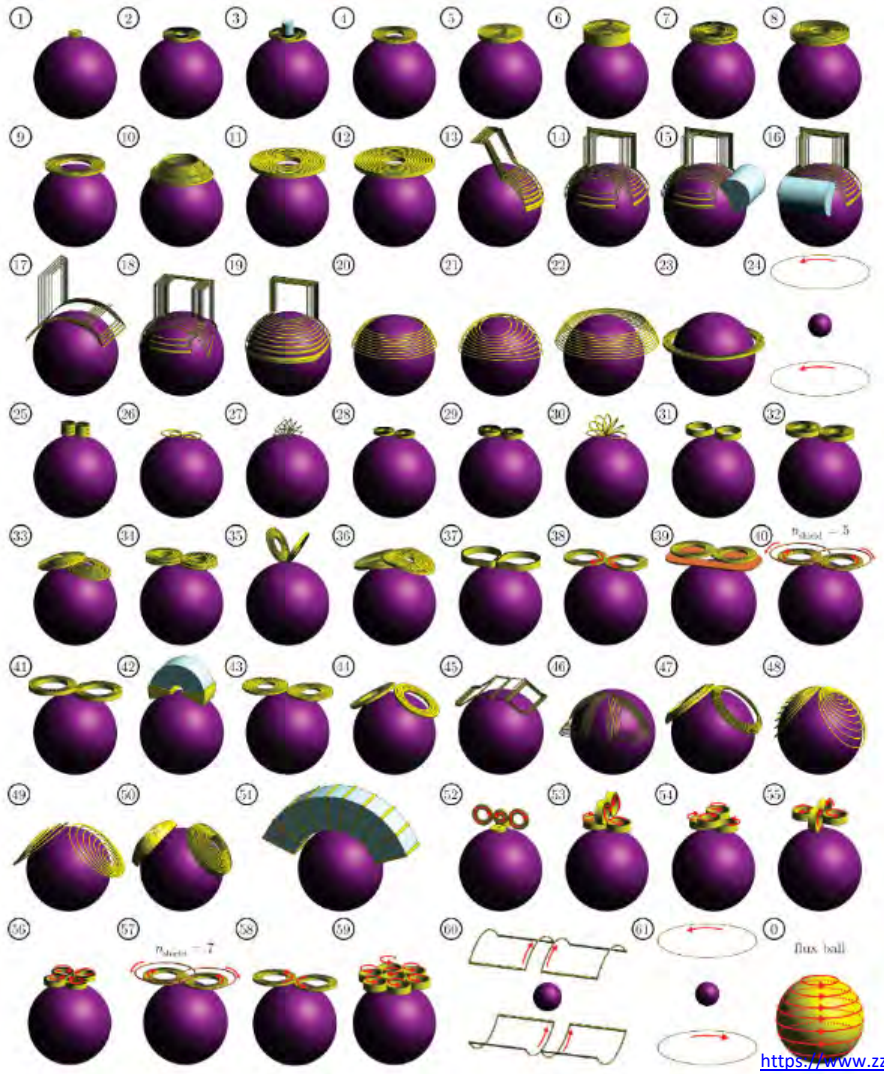
WHAT KINDS OF COILS ARE THERE?

Oh So Many Coils!

Not many are used often.

Very few FDA approved/cleared.



https://www.zzzdeng.net

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COIL SHAPE MATTERS

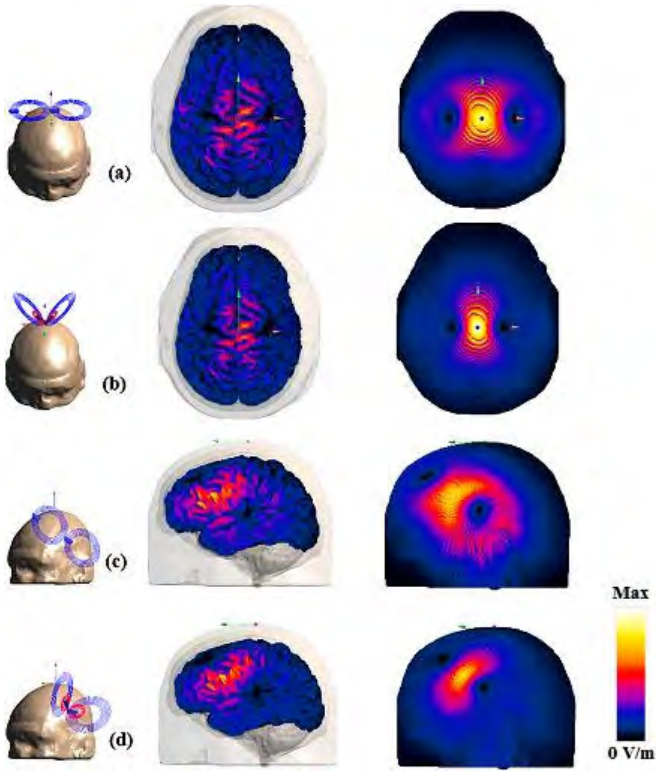

FIG. 2. Induced electric field on the grey matter and scalp due to (a) Figure-8 coil on the vertex (b) Quadruple Butterfly Coil on vertex (c) Figure-8 coil on dorsolateral prefrontal cortex (d) Quadruple Butterfly Coil on dorsolateral prefrontal cortex.

Published in: P. Rastogi; E. G. Lee; R. L. Hadimani; D. C. Jiles; *AIP Advances* **7,** 056705 (2017)
DOI: 10.1063/1.4973604

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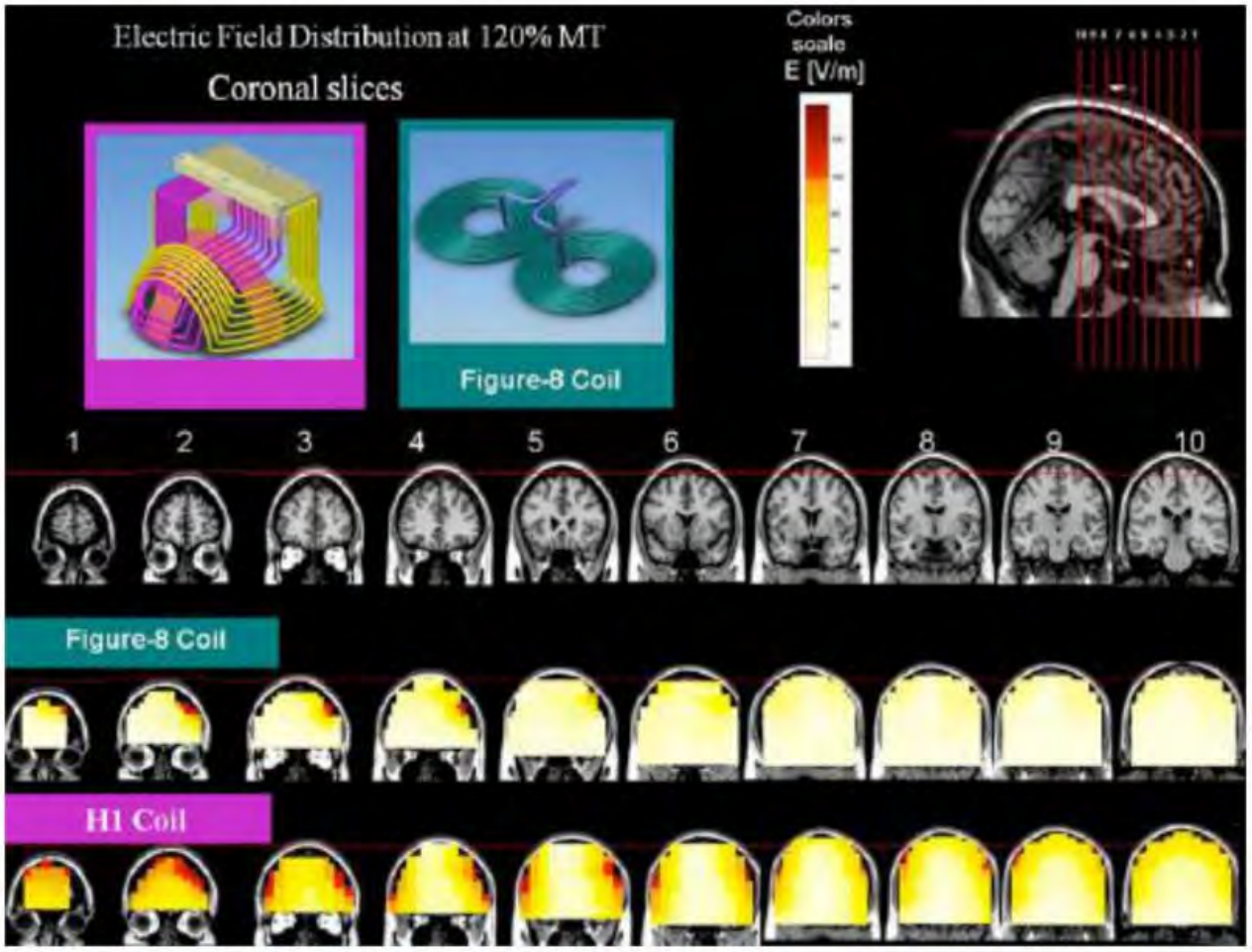
Coil Shape Matters

FIGURE-OF-8

VERSUS

H-COIL



Feifel, David & Pappas, Katherine. (2016). Treating Clinical Depression with Repetitive Deep Transcranial Magnetic Stimulation Using the Brainsway H1-coil. Journal of Visualized Experiments. 2016. 10.3791/53858.

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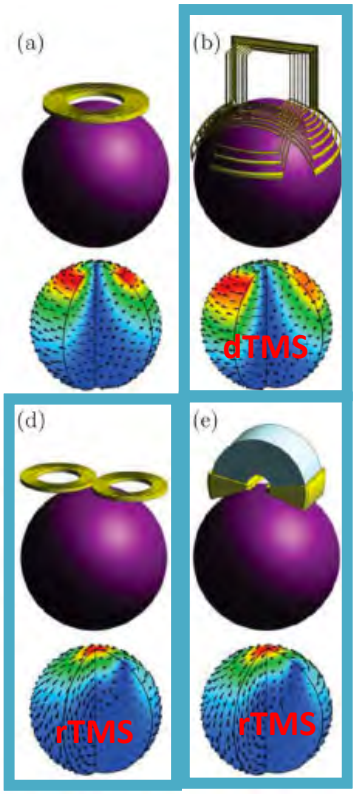
APPROVED/CLEARED TMS COILS

rTMS = repetitive TMS, usually figure-of-8 coil

dTMS = "deep TMS"

rTMS



Deng, Z.-D., Lisanby, S. H. & Peterchev, A. V. Coil design considerations for deep transcranial magnetic stimulation. Clinical Neurophysiology 125, 1202–1212 (2014).

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APPROVED/CLEARED TMS COILS

Cool D-B80
2020

SpringTMS Migraine
2014

H4 Smoking Cessation
2020

https://www.medgadget.com/2014/05/springtms-transcranial-magnetic-stimulator-for-treatment-of-migraines-fda-cleared-video.html
https://www.tandfonline.com/doi/pdf/10.1080/17434440.2016.1233812
https://www.magventure.com/media/k2/items/cache/aa5045f13216477abf2a0e16a08acd59_XL.jpg

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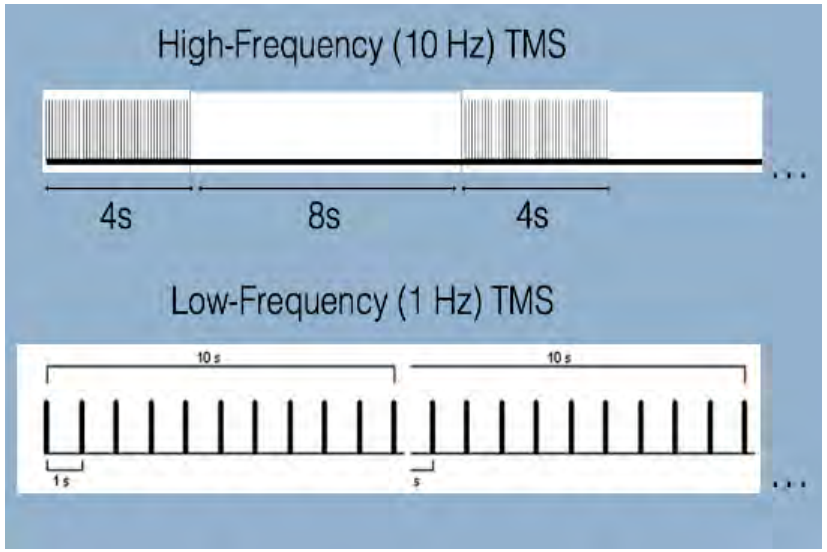
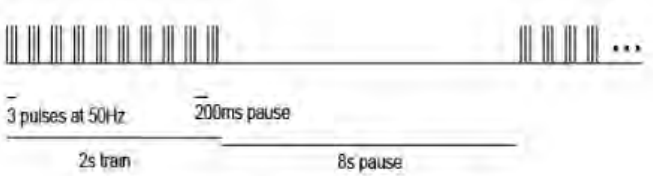
HOW DO YOU DELIVER THE PULSES?





Intermittent theta burst stimulation

Continuous theta burst stimulation

Types:

- Repetitive transcranial magnetic stimulation (rTMS)*
  - Deep transcranial magnetic stimulation (dTMS) (type of rTMS)*
- Intermittent theta-burst stimulation (iTBS)*
- Continuous theta-burst stimulation (cTBS)

*FDA Approved

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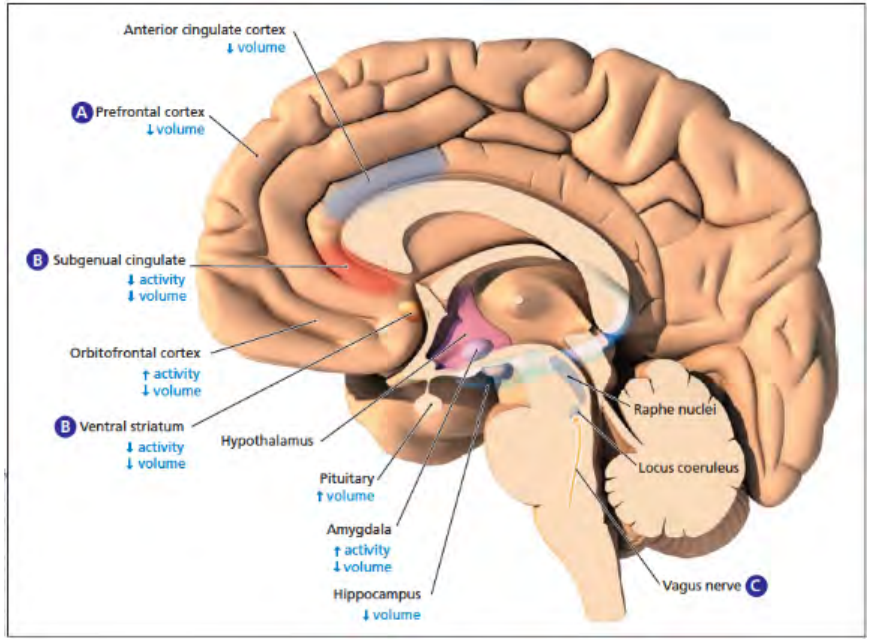
WHERE DO YOU PUT THE COIL?

- Left dorsolateral prefrontal cortex (L DLPFC)
  - Mood & anxiety disorders
- Supplementary motor area (SMA)
  - superficial target for Obsessive Compulsive Disorder (OCD)
- Anterior cingulate cortex (ACC)
  - deep target for OCD (dTMS)
- Many others have been studied for a variety of disorders



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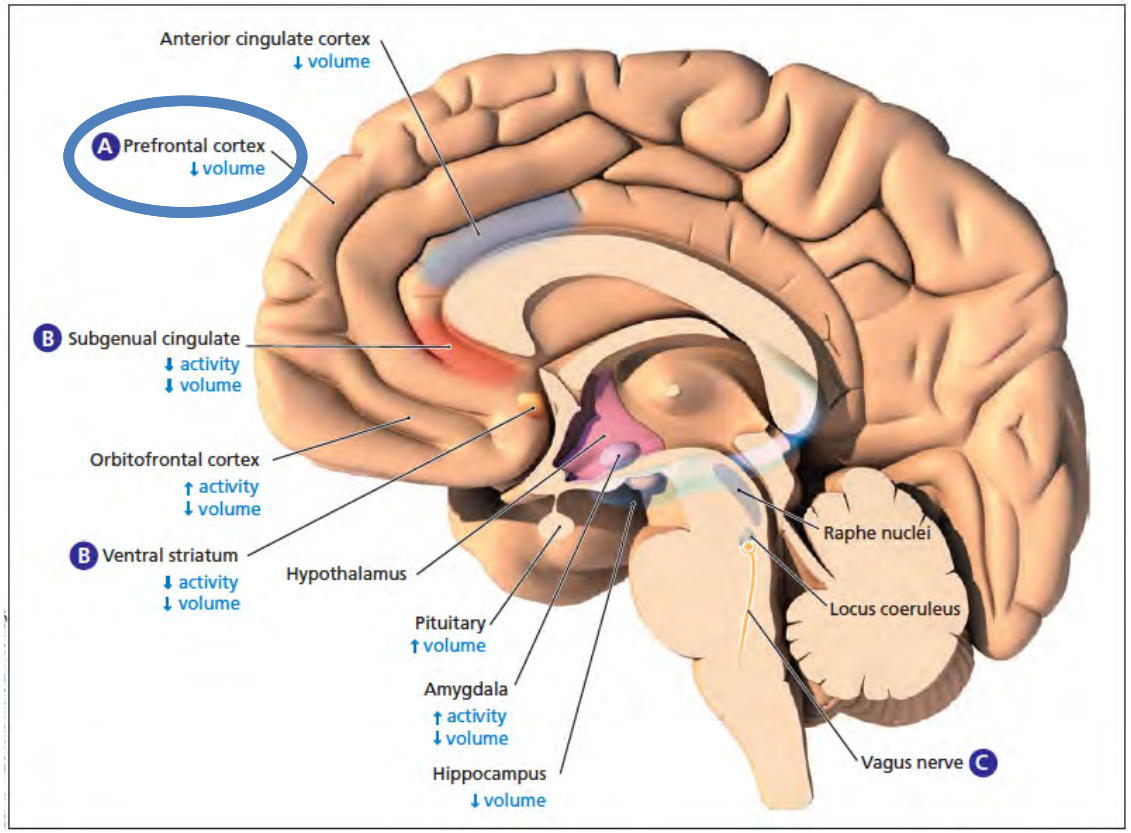
Brain Regions Altered by Depression



aan het Rot, M., Mathew, S. J. & Charney, D. S. Neurobiological mechanisms in major depressive disorder. Canadian Medical Association Journal 180, 305–313 (2009).

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TMS SIDE EFFECTS

- Considered a **minimal risk** procedure
- Headaches – 10-15%
- Less common (<5%)
  - Tenderness/discomfort at stimulation site
  - Muscle twitching (face, forehead)
  - Trigeminal pain (typically avoidable)
  - Lightheadedness

- Mania? in patients at risk (data mixed on whether this is a real concern)
- Extremely rare – seizure (fewer than 1 seizure per 60,000 sessions)
- **NO** cognitive effects or restrictions
- Precautions
  - ***Ear protection*** required to prevent risk of hearing loss
  - Magnet can move or heat up metal within 30cm

Lerner, Adam J., Eric M. Wassermann, and Diana I. Tamir. "Seizures from Transcranial Magnetic Stimulation 2012–2016: Results of a Survey of Active Laboratories and Clinics." *Clinical Neurophysiology* 130, no. 8 (August 1, 2019): 1409–16. https://doi.org/10.1016/j.clinph.2019.03.016.

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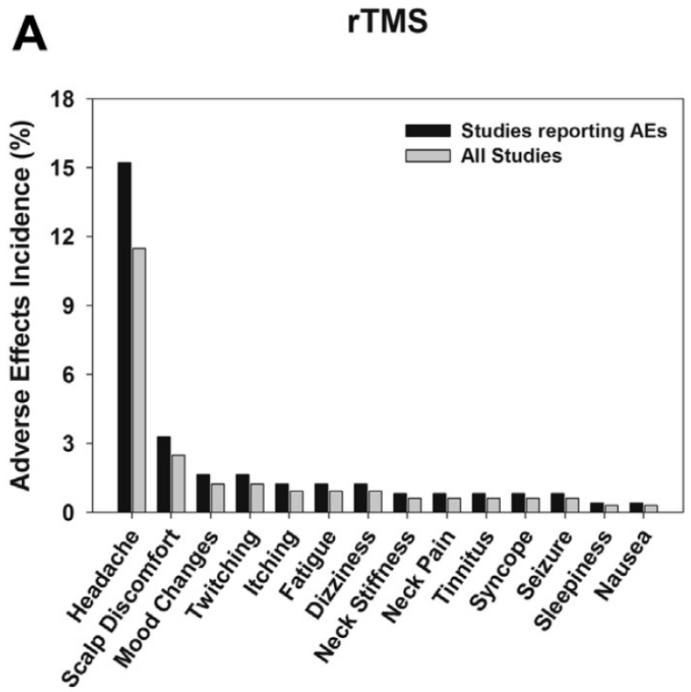
WHAT ABOUT SIDE EFFECTS IN ADOLESCENTS?

- N=322 receiving rTMS, many with neurologic conditions
  - Headache: 11.5%
  - Scalp discomfort: 2.5%
  - Twitching: 1.2%
  - Mood changes: 1.2%
  - Fatigue: 0.9%
  - Tinnitus: 0.6%
  - Generally resolve within 24 hours
- **4 (1.2%) had major side effects**
  - **2 (0.62%) seizures**
  - **2 (0.62%) syncope**



Krishnan, Santos, Peterson, & Ehinger. (2015). Safety of Noninvasive Brain Stimulation in Children and Adolescents. *Brain Stimulation, 8*(1), 76-87.

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WHO CANNOT HAVE TMS?

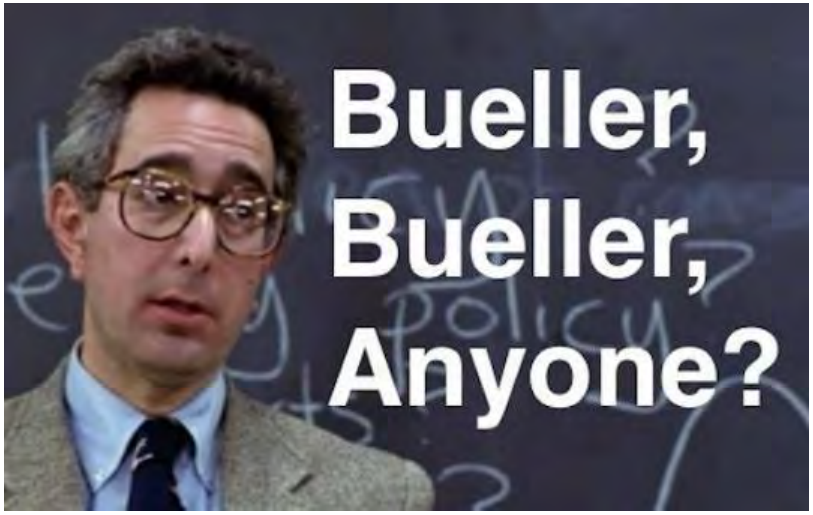
- Absolute
  - Magnetic metal within 30cm of the coil (most dental work OK; not all!)
- "Absolute"
  - Epilepsy that is active and not controlled
  - We have successfully and safely treated some patients with a remote history of epilepsy or well-controlled for years
- Relative
  - Pacemaker/AICD (would want to turn the device "off" during the treatment, e.g., with a magnet)
  - History of significant head trauma or brain surgery (due to relatively higher risk of seizure)
  - Recent stroke (due to relatively higher risk of seizure; BUT some studies on using TMS to aid stroke recovery)
  - Active substance abuse (most studies using TMS to treat substance abuse have required some period of abstinence prior to TMS)

WHAT DO WE USE TMS FOR?

FDA APPROVALS

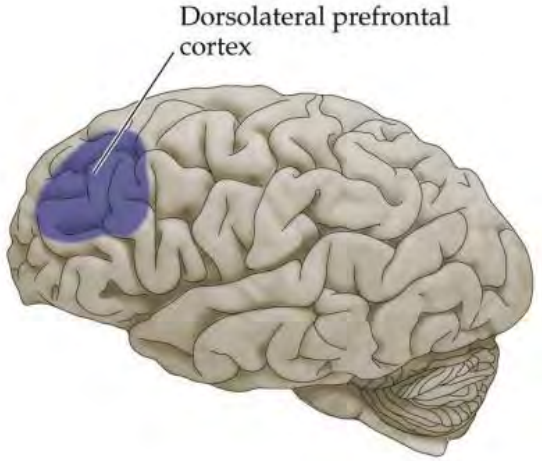
- Children/teens

- Adults
  - Major depressive disorder (after **one** failed antidepressant trial)
    - Of “adequate dose and duration”
  - Adjunctive therapy for Obsessive Compulsive Disorder (dTMS H7 or Cool-D-B80 only)
  - Intermittent Theta-Burst stimulation (iTBS) for depression



FDA-APPROVED TMS *DEPRESSION* TREATMENT PROTOCOL

- TARGET: ***left dorsolateral prefrontal cortex*** (L DLPFC)
- High frequency
  - 10 Hz or 18 Hz (depending on coil)
  - 1800-3000 pulses per session (depending on the coil)
- Stimulus is "dosed" to brain's sensitivity
  - "motor threshold" (see upcoming slide)
- Treatment Course for Standard Depression Protocol
  - **30** treatments
  - **5 days** per week
  - **15-20 minutes** per treatment (varies by treatment site – 'optimal' protocol not known)
  - +6 treatment taper



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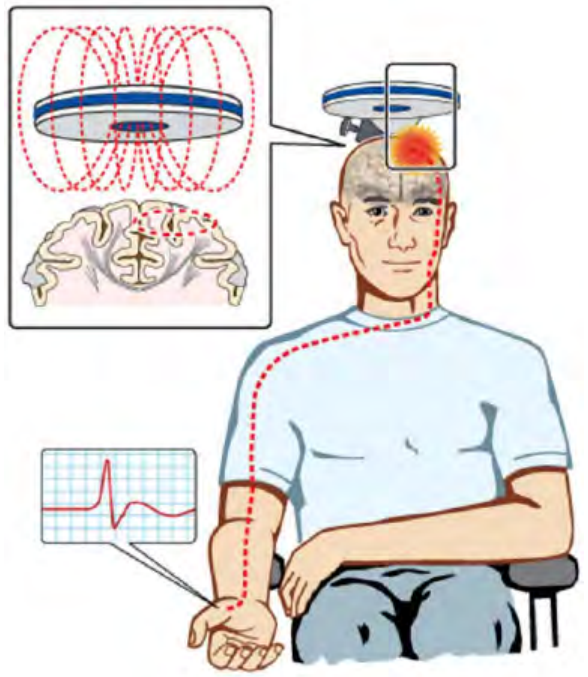
HOW DO YOU FIND THE RIGHT DOSE?

MOTOR THRESHOLD

- Titration of the stimulus “dose” to the sensitivity of the brain
- Based on elicited motor response (i.e., twitching) with stimulation of thumb/finger motor area
- “Motor threshold” = Lowest pulse strength which elicits 50% thumb twitch (out of 10 pulses, thumb twitches 5 times)
- Treatment dose expressed as %MT (typically 120%)



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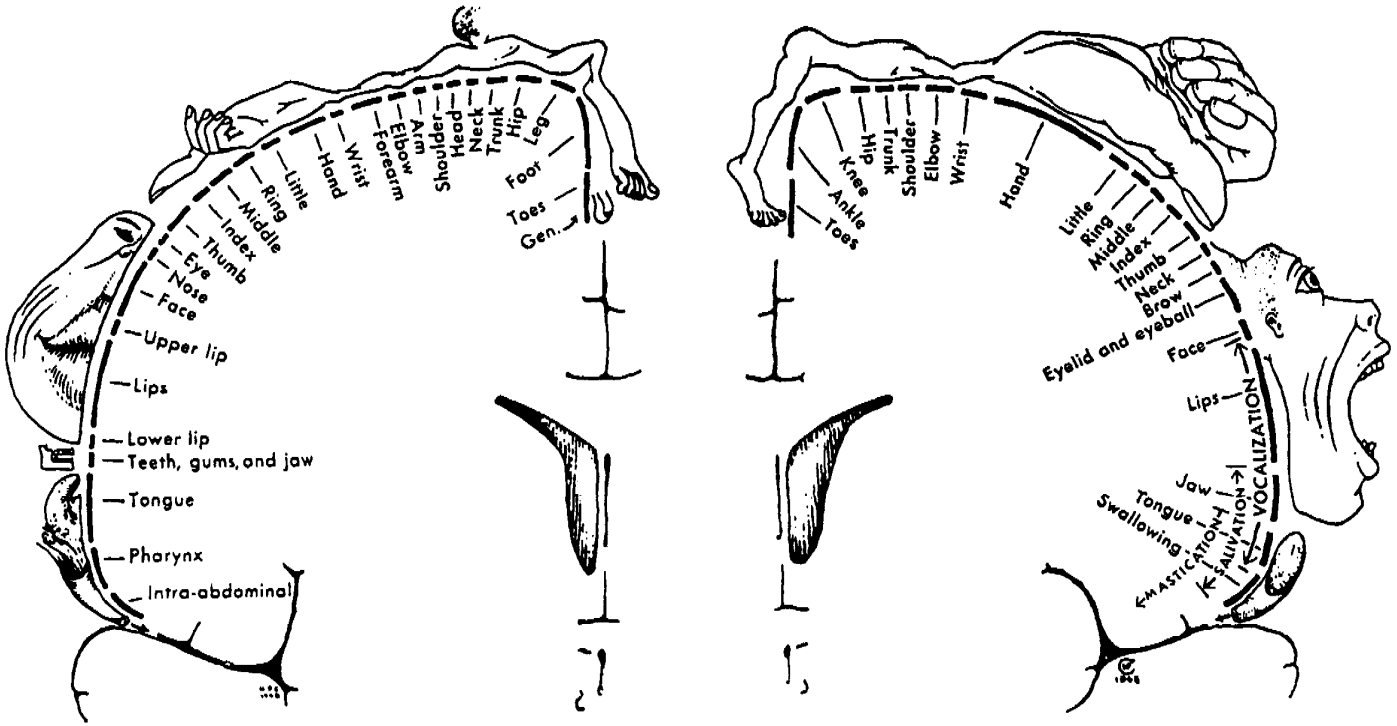
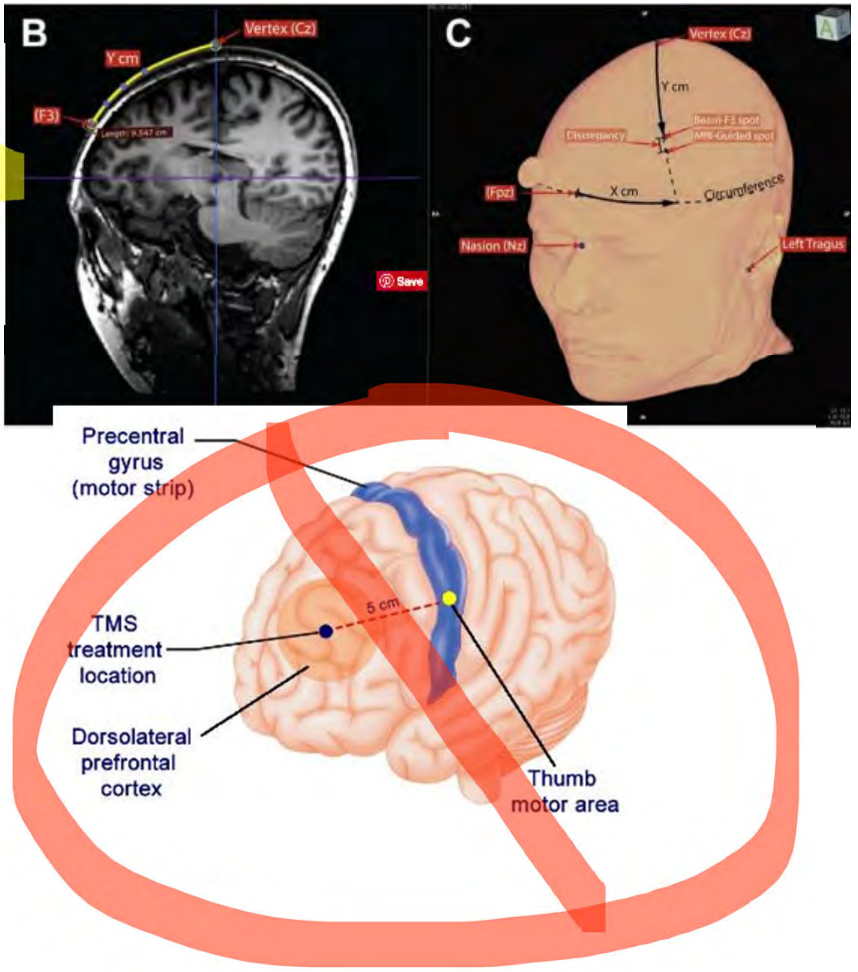


HOW DO YOU FIND THE DORSOLATERAL PREFRONTAL CORTEX??

- DLPFC
  - 5cm anterior to motor strip (least accurate)
    - "Unfortunately, due to anatomical variability, this method of targeting led to stimulation of premotor areas in up to 1/3 of patients, possibly accounting for the low response rates seen in some earlier studies"
  - **Beam F3**
  - MRI-guided (most accurate, but least available)



Mir-Moghtadaei, Caballero, Fried, Fox, Lee, Giacobbe, . . . Downar. (2015). Concordance Between BeamF3 and MRI-neuronavigated Target Sites for Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex. Brain Stimulation, 8(5), 965-973.

Trevizol, Alisson P., and Daniel M. Blumberger. "An Update on Repetitive Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder." *Clinical Pharmacology and Therapeutics* 106, no. 4 (October 2019): 747–62. https://doi.org/10.1002/cpt.1550.

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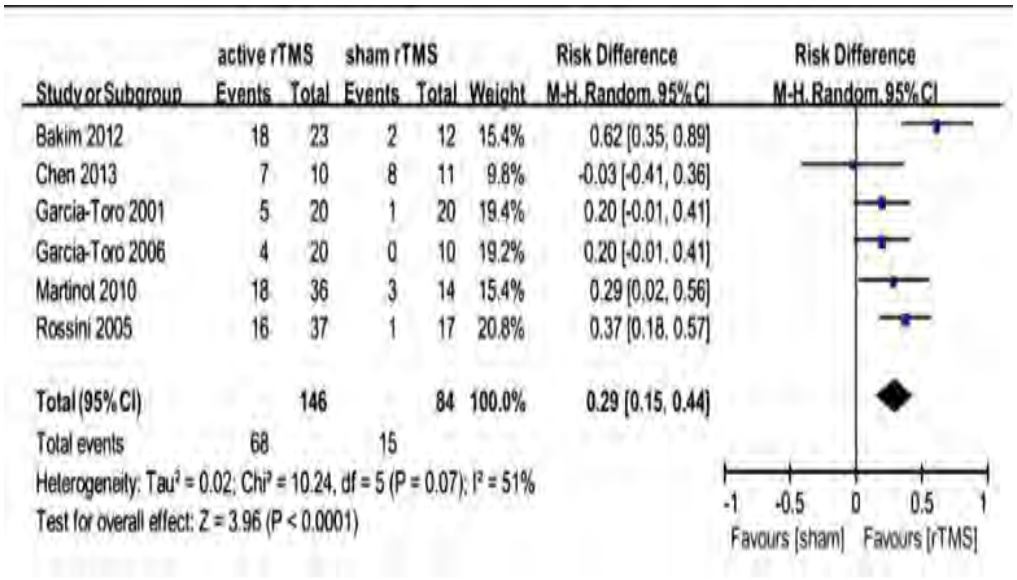
DOES TMS WORK FOR *DEPRESSION*?



Study or Subgroup	active rTMS Events	Total	sham rTMS Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Bakim 2012	18	23	2	12	15.4%	0.62 [0.35, 0.89]
Chen 2013	7	10	8	11	9.8%	-0.03 [-0.41, 0.36]
Garcia-Toro 2001	5	20	1	20	19.4%	0.20 [-0.01, 0.41]
Garcia-Toro 2006	4	20	0	10	19.2%	0.20 [-0.01, 0.41]
Martinot 2010	18	36	3	14	15.4%	0.29 [0.02, 0.56]
Rossini 2005	16	37	1	17	20.8%	0.37 [0.18, 0.57]
Total (95% CI)		146		84	100.0%	0.29 [0.15, 0.44]
Total events	68		15			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.24$, df = 5 (P = 0.07); $I^2 = 51\%$

Test for overall effect: Z = 3.96 (P < 0.0001)

Risk Difference M-H, Random, 95% CI

-1 -0.5 0 0.5 1

Favours [sham] Favours [rTMS]

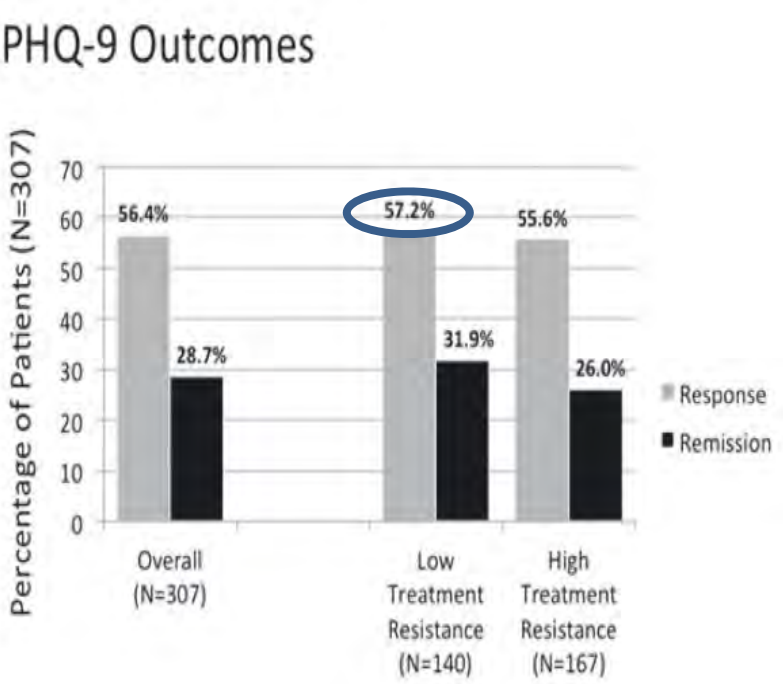
7 RCTs, N=279 (171 active, 108 sham)

Response (active) – 46.6%

Response (sham) – 22.1%

NNT = 3.4

I tell patients:
"About 5-6 out of every 10 people respond."



Multisite, open-label, observational study

N = 307 patients

Mean # failed antidepressant attempts = 3.6

Over 54% failed 2+ antidepressant trials

Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry. 2014 Nov 30;14(1):342.

Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. Transcranial Magnetic Stimulation (TMS) for Major Depression: A Multisite, Naturalistic, Observational Study of Acute Treatment Outcomes in Clinical Practice. Depression and Anxiety. 2012 Jul;29(7):587–96.

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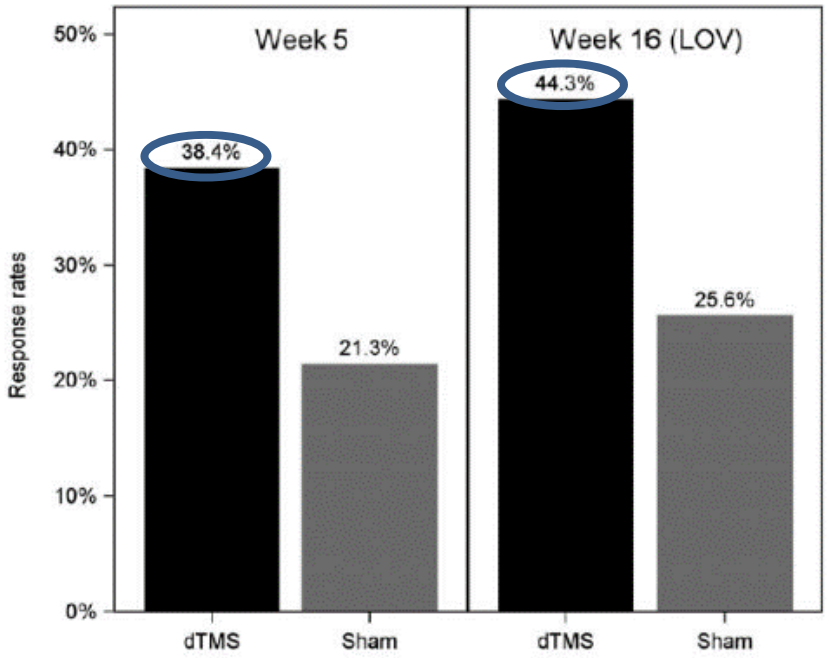
IS DTMS BETTER FOR *DEPRESSION* THAN RTMS?

(THERE ARE MANY MORE RTMS STUDIES . . . AND *ONLY ONE STUDY* COMPARING THE TWO COILS!)



Levkovitz, Y. et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 14, 64–73 (2015).

Filipčić I, Šimunović Filipčić I, Milovac Ž, et al. Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-Coil in treatment of major depressive disorder; A randomized clinical trial. *Journal of Psychiatric Research*. 2019;114:113-119. doi:10.1016/j.jpsychires.2019.04.020

Journal of Psychiatric Research 114 (2019) 113–119

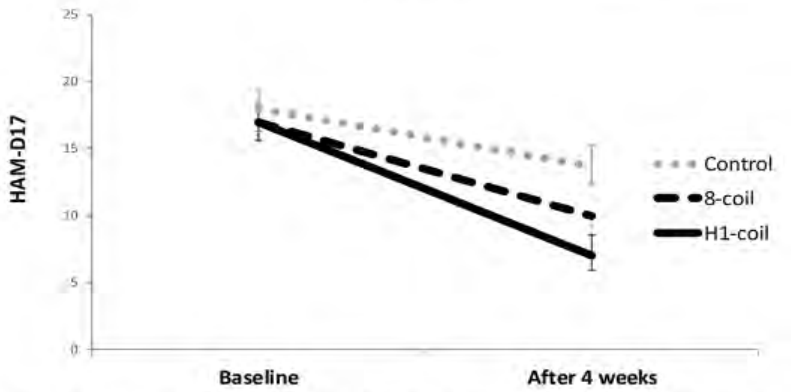


Fig. 2. HAM-D17 score at baseline and at 4th week follow up in intention-to-treat population; error bars represent 95% confidence intervals.

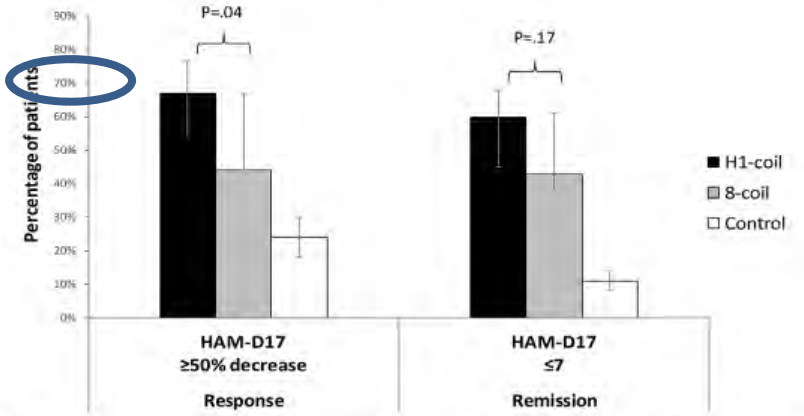


Fig. 3. Response and remission rates in intention-to-treat population; error bars represent 95% confidence intervals; star represent significant difference between H1-coil and figure-8-coil.

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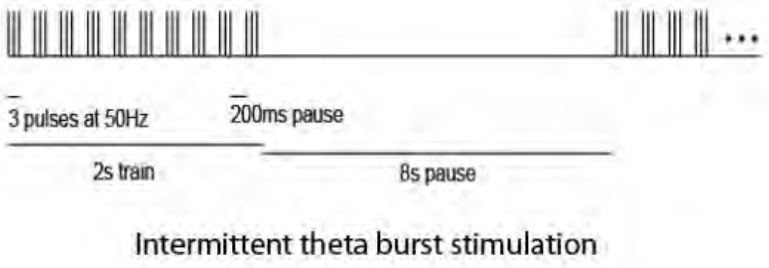
HOW LONG DOES RTMS BENEFIT LAST FOR *DEPRESSION*?

- A **meta-analysis** on the length of time that rTMS effects last reported that, amongst responders:
  - 66.5% sustained response after 3 months
  - 52.9% sustained response after 6 months
  - 46.3% sustained response after 1 year (this is what I usually tell patients)
- One naturalistic study (N=204) reported relapse rates of:
  - 25% at 2 months
  - 40% at 3 months
  - 57% at 4 months
  - 77% at 6 months
- Yet another study (N=257) reported a relapse rate of <30% over the first year
  - Relapse more likely in the first 6 months
- Re-treatment tends to work (2-3 week "booster" course)
- No evidence-based guidelines for maintenance TMS treatments

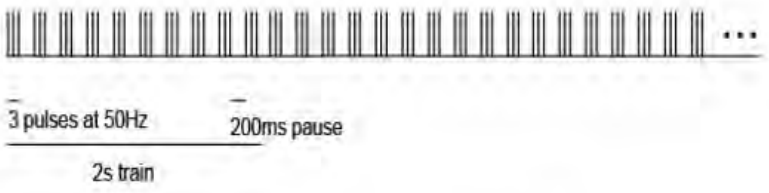
Senova, S., Cotovio, G. & Pascual-leone, A. Brain Stimulation Durability of antidepressant response to repetitive transcranial magnetic stimulation : Systematic review and meta-analysis. Brain Stimul. (2018).doi:10.1016/j.brs.2018.10.001
Cohen, R. B., Boggio, P. S. & Fregni, F. Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. Depress Anxiety 26, 682– 688 (2009).
Dunner D, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder: Durability of Benefit Over a 1-Year Follow-Up Period. Journal of Clinical Psychiatry. 2014 Dec;75(12):1394–401.

WHAT ABOUT THETA BURST STIMULATION (TBS)?

- Approved 2018 for ***depression*** (MagVita system)
- Modification of rTMS device to deliver **triplets** of pulses at theta frequency
- Mimics theta frequency of neurons in the brain
  - Theta range refers to EEG waves between 4-7Hz in humans



Intermittent theta burst stimulation

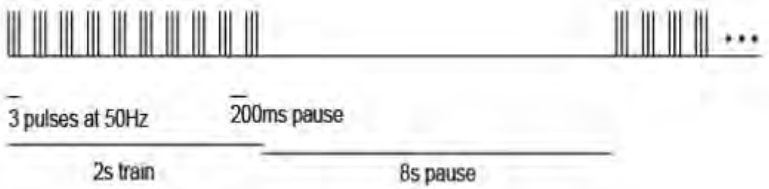


Continuous theta burst stimulation

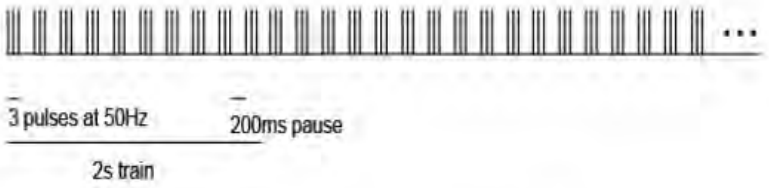
Blumberger, Daniel M, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, et al. "Effectiveness of Theta Burst versus High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Depression (THREE-D): A Randomised Non-Inferiority Trial." *The Lancet* 391, no. 10131 (April 2018): 1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.

WHAT ABOUT THETA BURST STIMULATION (TBS)?

- Intermittent (iTBS) provides a two second train of bursts (30 pulses), repeated every 10 seconds.
- iTBS has been shown to cause long-term potentiation-like (LTP) effects of cortical excitability
- **3-4 minute treatment**
- theta-burst showed essentially **identical** efficacy to standard TMS protocols for depression



Intermittent theta burst stimulation



Continuous theta burst stimulation

Blumberger, Daniel M, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, et al. "Effectiveness of Theta Burst versus High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Depression (THREE-D): A Randomised Non-Inferiority Trial." *The Lancet* 391, no. 10131 (April 2018): 1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.

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AND BY “IDENTICAL,” I MEAN…

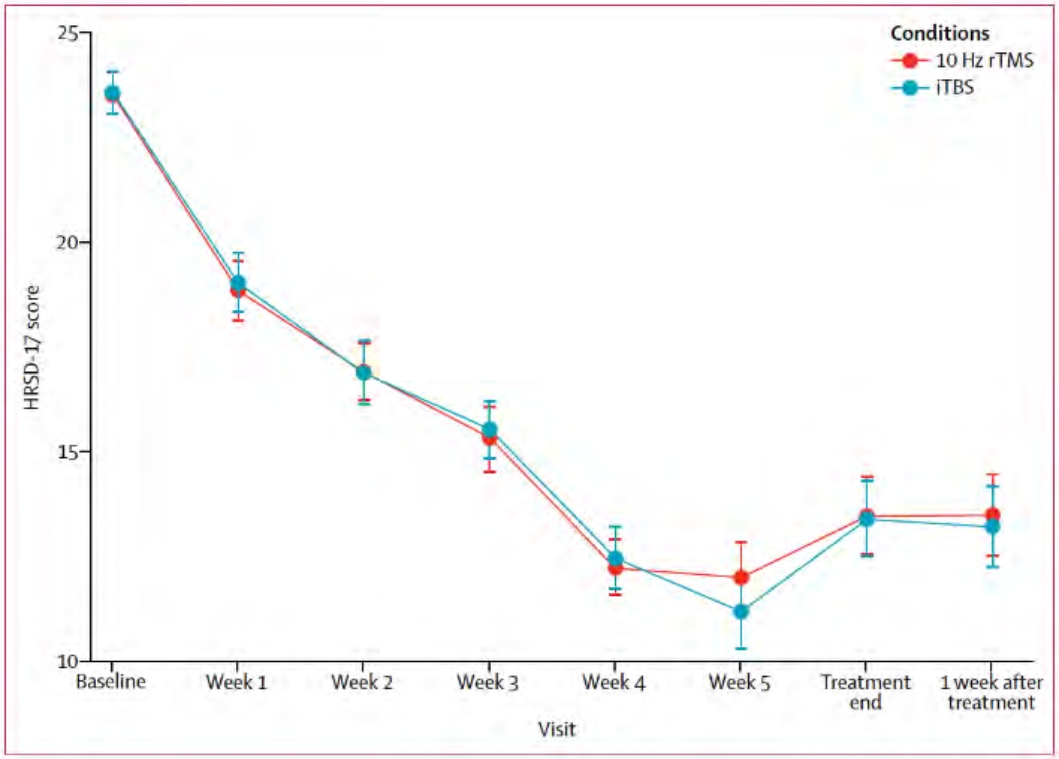

Figure 3: **Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

Intermittent Theta Burst TMS is equivalent to standard protocol for depression ***in the short term***.

No good long-term durability data available for theta burst.

Blumberger, Daniel M, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, et al. “Effectiveness of Theta Burst versus High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Depression (THREE-D): A Randomised Non-Inferiority Trial.” *The Lancet* 391, no. 10131 (April 2018): 1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.

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EFFICACY SUMMARY - DEPRESSION

- In depression, typically estimated as **50-60%** chance of **response** in patients who have failed 2+ antidepressants (inclusive of remission)
  - **20-30%** chance of **remission** in same population
  - Irrespective of # of failed treatment trials
  - Compare to STAR*D **~5-6%** likelihood of remission at 3rd-4th step
  - Many studies include both bipolar and unipolar depression
    - evidence for TMS for bipolar depression is mixed and conclusions are unclear
  - Studies are heterogeneous in their assessments and reporting of response/remission
  - Current (limited) data suggests similar efficacy in adolescents (13+)

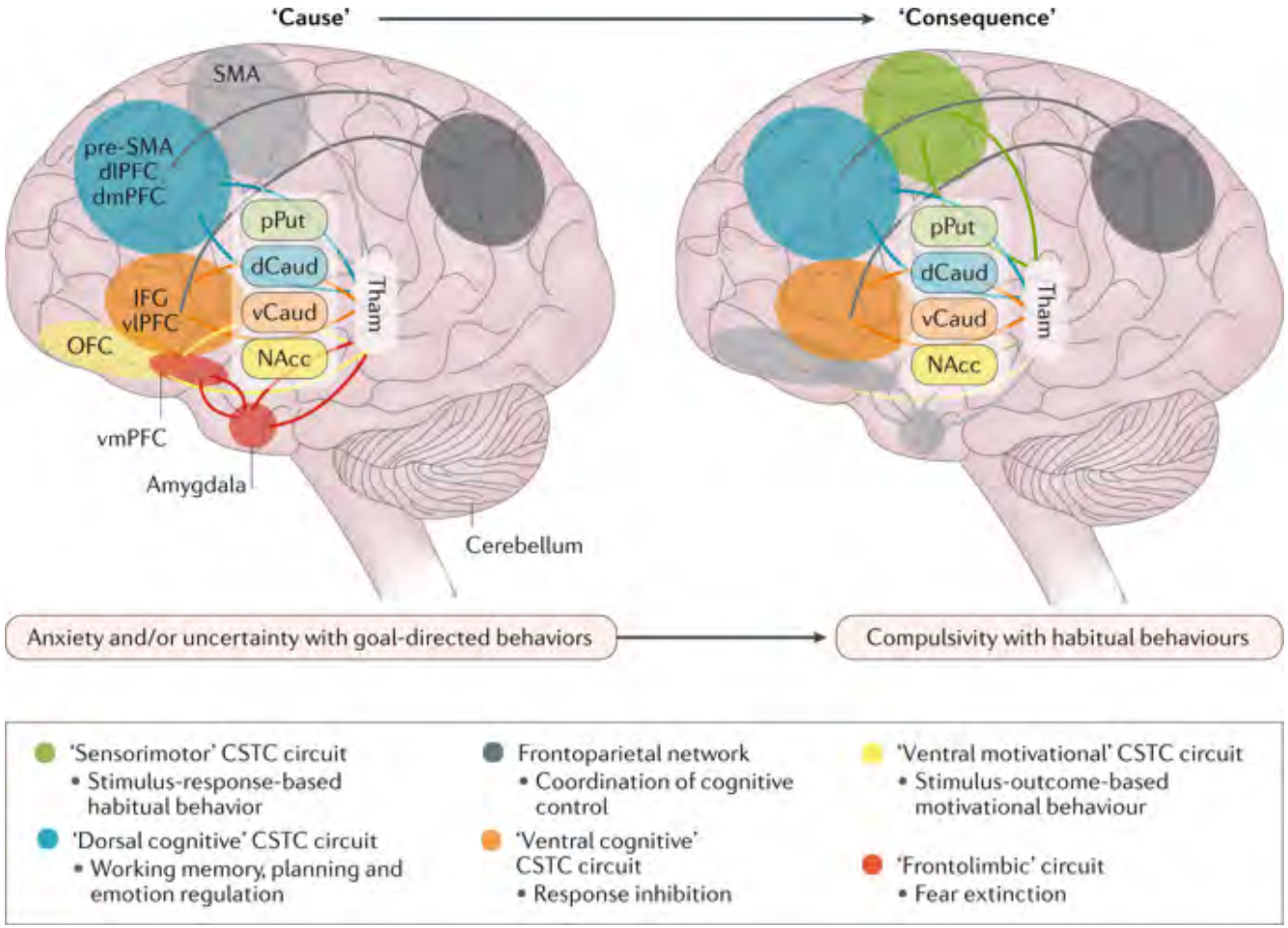
Senova S, Cotovio G, Pascual-Leone A, Oliveira Maia AJ. Durability of antidepressant response to repetitive transcranial magnetic stimulation: systematic review and meta-analysis. Brain Stimulation [Internet]. 2018 Oct [cited 2018 Oct 3]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1935861X18303206
Dunner D, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder: Durability of Benefit Over a 1-Year Follow-Up Period. Journal of Clinical Psychiatry. 2014 Dec;75(12):1394–401.

EFFICACY SUMMARY - DEPRESSION

- Durability estimates range from 46.3% (Senova et al, 2018) to ~70% (Dunner et al, 2017) at 1 year
  - A small study (Mayer, et al) showed 3-year durability of results in 8 adolescents (now in early 20s) at 3 years

Senova S, Cotovio G, Pascual-Leone A, Oliveira Maia AJ. Durability of antidepressant response to repetitive transcranial magnetic stimulation: systematic review and meta-analysis. Brain Stimulation [Internet]. 2018 Oct [cited 2018 Oct 3]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1935861X18303206
Dunner D, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder: Durability of Benefit Over a 1-Year Follow-Up Period. Journal of Clinical Psychiatry. 2014 Dec;75(12):1394–401.

TMS for Obsessive Compulsive Disorder



Stein, Dan J., Daniel L. C. Costa, Christine Lochner, Euripedes C. Miguel, Y. C. Janardhan Reddy, Roseli G. Shavitt, Odile A. van den Heuvel, and H. Blair Simpson. "Obsessive–Compulsive Disorder." *Nature Reviews Disease Primers* 5, no. 1 (August 1, 2019): 1–21. https://doi.org/10.1038/s41572-019-0102-3.

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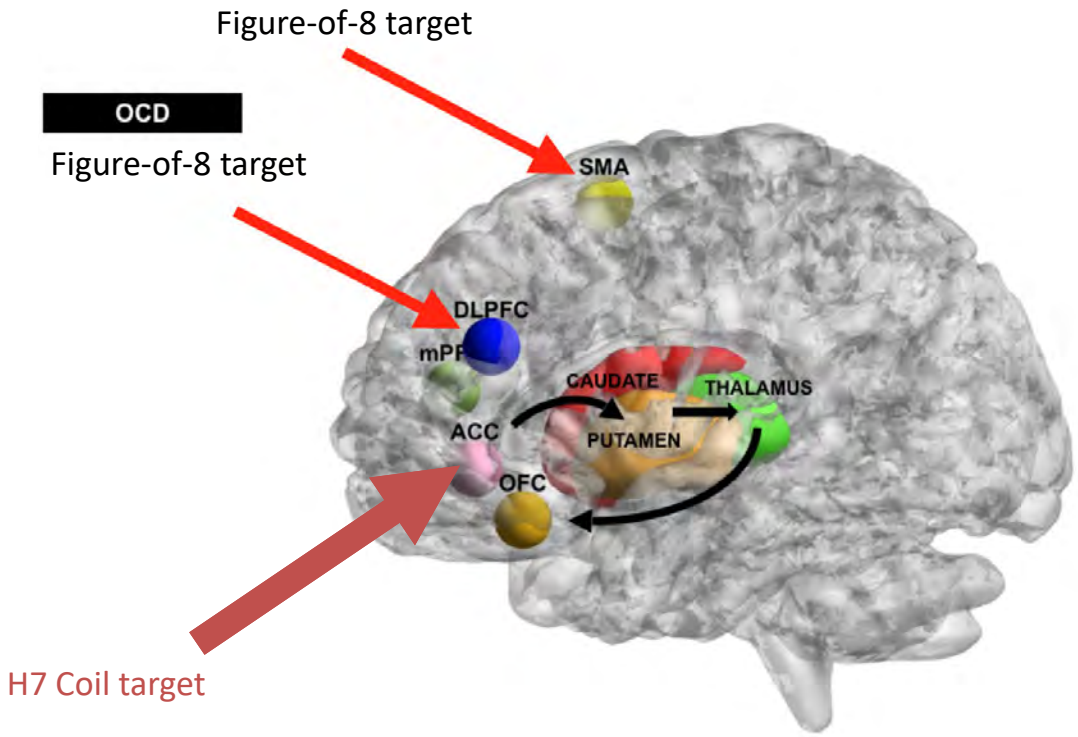
OBSESSIVE COMPULSIVE DISORDER



TMS FOR OCD

- Multiple studies using rTMS and figure-of-8 coils to treat OCD
- . . . HOWEVER the **only** current FDA approved protocol is using dTMS with a Brainsway helmet OR the same protocol using the Cool D-B80 MagVenture coil
- Brain targets from various OCD studies
  - Right dorsolateral prefrontal cortex
  - Left dorsolateral prefrontal cortex
  - Supplementary motor area
  - Right orbitofrontal cortex
  - Some combinations of the above (for example, bilateral DLPFC, or R-DLPFC plus SMA)

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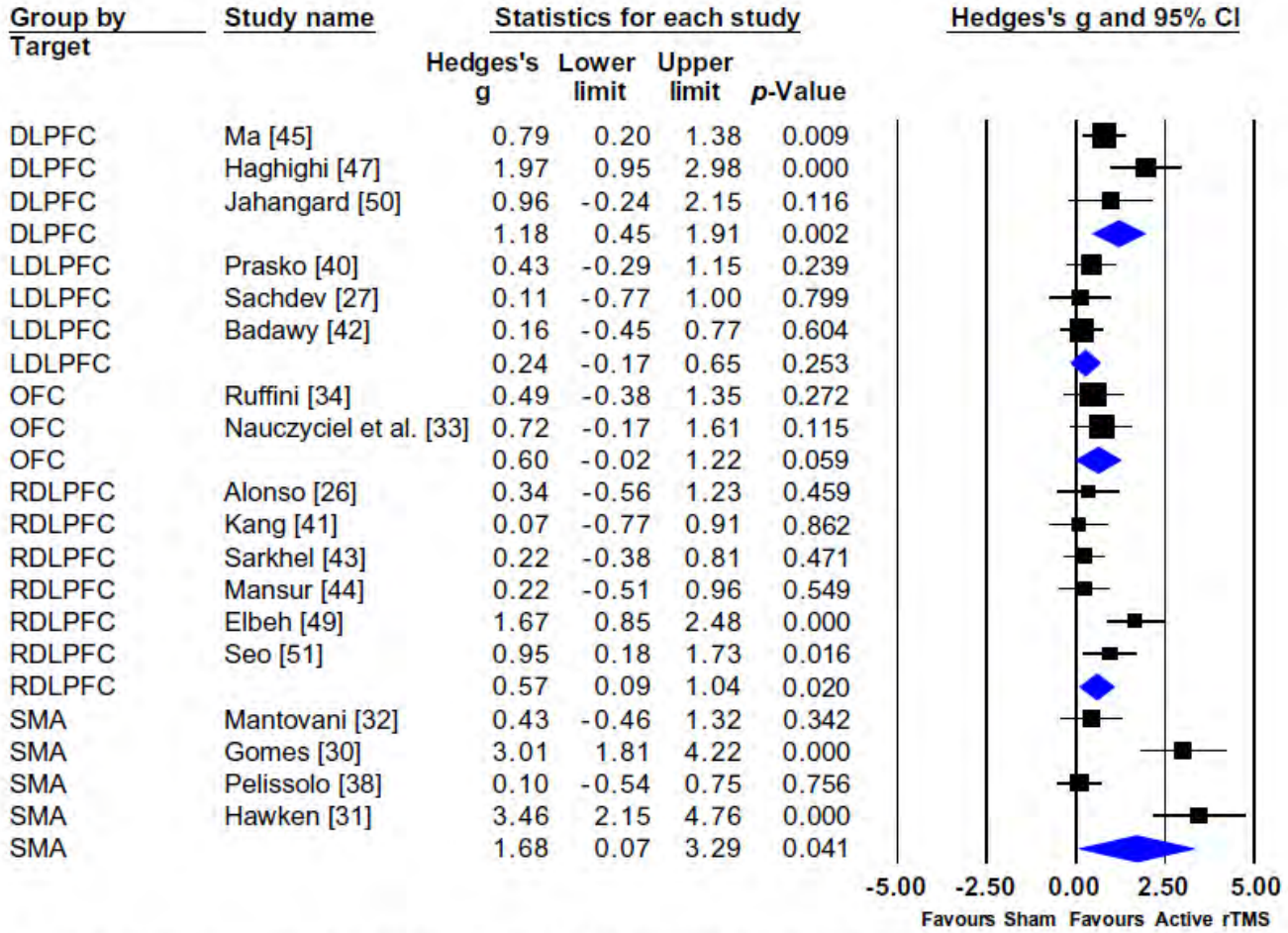
TMS FOR OCD

Many studies using figure-of-8 coils



Group by Target	Study name	Hedges's g	Lower limit	Upper limit	p-Value
DLPFC	Ma [45]	0.79	0.20	1.38	0.009
DLPFC	Haghighi [47]	1.97	0.95	2.98	0.000
DLPFC	Jahangard [50]	0.96	-0.24	2.15	0.116
DLPFC		1.18	0.45	1.91	0.002
LDLPFC	Prasko [40]	0.43	-0.29	1.15	0.239
LDLPFC	Sachdev [27]	0.11	-0.77	1.00	0.799
LDLPFC	Badawy [42]	0.16	-0.45	0.77	0.604
LDLPFC		0.24	-0.17	0.65	0.253
OFC	Ruffini [34]	0.49	-0.38	1.35	0.272
OFC	Nauczyciel et al. [33]	0.72	-0.17	1.61	0.115
OFC		0.60	-0.02	1.22	0.059
RDLPFC	Alonso [26]	0.34	-0.56	1.23	0.459
RDLPFC	Kang [41]	0.07	-0.77	0.91	0.862
RDLPFC	Sarkhel [43]	0.22	-0.38	0.81	0.471
RDLPFC	Mansur [44]	0.22	-0.51	0.96	0.549
RDLPFC	Elbeh [49]	1.67	0.85	2.48	0.000
RDLPFC	Seo [51]	0.95	0.18	1.73	0.016
RDLPFC		0.57	0.09	1.04	0.020
SMA	Mantovani [32]	0.43	-0.46	1.32	0.342
SMA	Gomes [30]	3.01	1.81	4.22	0.000
SMA	Pelissolo [38]	0.10	-0.54	0.75	0.756
SMA	Hawken [31]	3.46	2.15	4.76	0.000
SMA		1.68	0.07	3.29	0.041

Fig. 4 Subgroup analysis of Active vs. Sham rTMS by specific cortical target: pre-post Y-BOCS scores. L: left; R: right; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; SMA: supplementary motor area

Rehn, Simone, Guy D. Eslick, and Vlasios Brakoulias. "A Meta-Analysis of the Effectiveness of Different Cortical Targets Used in Repetitive Transcranial Magnetic Stimulation (RTMS) for the Treatment of Obsessive-Compulsive Disorder (OCD)." *Psychiatric Quarterly* 89, no. 3 (September 2018): 645–65. https://doi.org/10.1007/s11126-018-9566-7.

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TMS FOR OCD: BRAINSWAY PROTOCOL, FDA APPROVED

- Meta-analyses of figure-of-8 studies prior to FDA approval of Brainsway protocol were promising
- Then along came Brainsway/dTMS – FDA approval in 2018 as adjunct for OCD, over mPFC and ACC
  - And similar coil approved in 2020 for use with the same protocol: the Cool D-B80 from MagVenture
- ***dTMS/D-B80 protocol uses "PERSONALIZED SYMPTOM PROVOCATION" before treatment***
  - ***Theory: use the circuit during treatment***

Picture from: Popa, Traian, Laurel S. Morris, Rachel Hunt, Zhi-De Deng, Silvina Horovitz, Karin Mente, Hitoshi Shitara, Kwangyeol Baek, Mark Hallett, and Valerie Voon. "Modulation of Resting Connectivity Between the Mesial Frontal Cortex and Basal Ganglia." Preprint. Neuroscience, October 1, 2018. https://doi.org/10.1101/432609.

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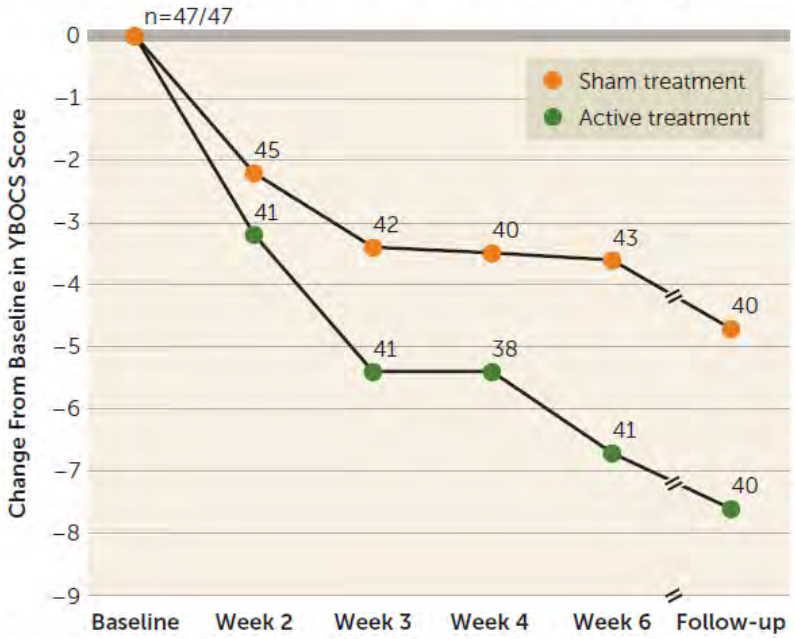
OBSESSIVE COMPULSIVE DISORDER

- 11 centers in RCT
- 99 OCD patients
- Allocated to 20 Hz or sham dTMS
- Active dTMS response was 6.0 points on YBOCS & sham dTMS response was 3.3 points
- Response rate was 38.1% in active and 11.1% in sham.
- 1-month follow up had higher response rates of 45.2% in active group and 17.8% in sham group.

FIGURE 2. Change from baseline in mean YBOCS score through the study for the active and sham dTMS treatment groups[a]



[a] dTMS=deep repetitive transcranial magnetic stimulation; YBOCS=Yale-Brown Obsessive Compulsive Scale. Each data point includes the patients with recorded YBOCS scores at that time point.

https://doi.org/10.1176/appi.ajp.2019.18101180

TMS FOR OCD

FIGURE 3. Rates of full response and individual distribution of responders and nonresponders according to YBOCS score at week 6 in the active and sham dTMS treatment groups[a]

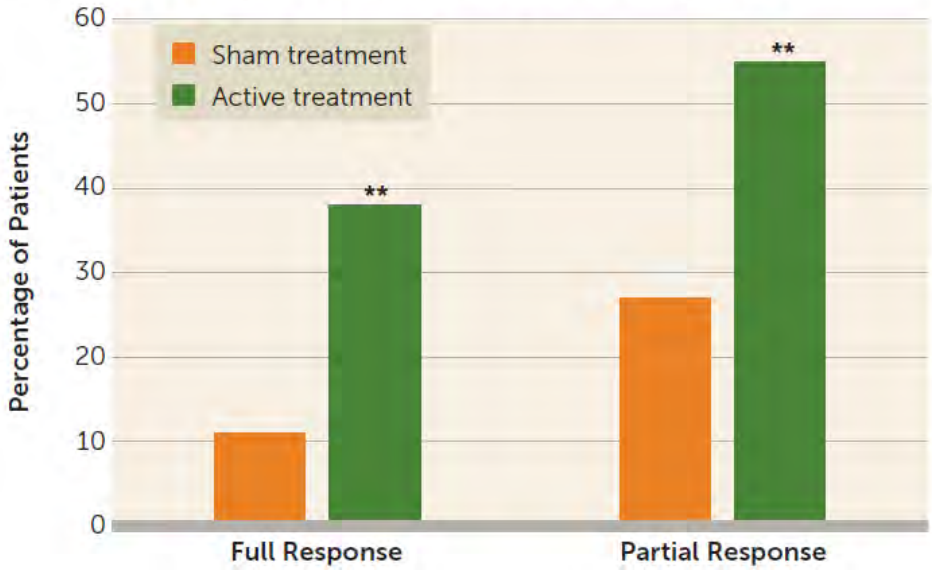
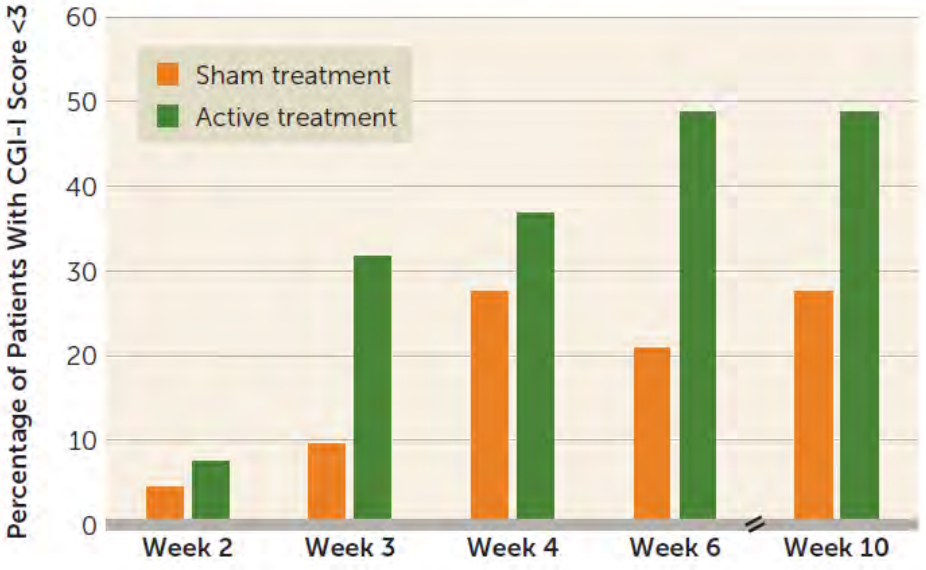


FIGURE 4. Rates of patients reported as "moderate" to "very much improved" in the active and sham dTMS treatment groups across time[a]



Carmi, Lior, Aron Tendler, Alexander Bystritsky, Eric Hollander, Daniel M. Blumberger, Jeff Daskalakis, Herbert Ward, et al. "Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial." *American Journal of Psychiatry*, May 21, 2019, appi.ajp.2019.1. https://doi.org/10.1176/appi.ajp.2019.18101180.

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EFFICACY SUMMARY - OCD

- In OCD, **30-40%** chance of **response (30% reduction),** best used as **adjunct** to exposure therapy and medications.
  - Remission is rare, as is the case with SSRI treatment
  - Effect sizes are modest (Y-BOCS reduction ~6-9), again similar to SSRI
- Large, long-term durability studies are not yet available

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INSURANCE REQUIREMENTS FOR TMS FOR DEPRESSION

- Age 18+ (<18 is case-by-case)
- **Unipolar** major depressive disorder
  - Often “severe” depression (clinically or by rating scales)
- Multiple medication failures “of adequate dose and duration”
  - Typically **4** antidepressants from **2+** classes
  - Some allow **3** antidepressants from **2+** classes **+ 2 different augmenting strategies**
  - **OR** not tolerated due to side effects/inability to take pills
  - **Medicare** requires 1 failed antidepressant in the current episode or 2 failures due to side effects
- Failed a trial of evidence-based psychotherapy (usually 12 sessions)
- Depression severe enough to warrant ECT, but ECT not feasible

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INSURANCE REQUIREMENTS FOR TMS FOR OBSESSIVE COMPULSIVE DISORDER

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THE FUTURE OF TMS

- Approaches to increase the efficacy of the standard form of rTMS include:
  - (1) combining protocols;
  - (2) improving localization of the targeted cortical regions using online neuronavigation;
  - (3) new coils, with deeper, and broader or more focal stimulation;
  - (4) new patterns of stimulation, including theta-burst stimulation (TBS) and priming TMS (pTMS);
  - (5) targeting newer cortical regions other than the DLPFC in MDD;
  - (6) and identifying clinical predictors of response.
- Extended courses (45-60 treatments) and condensed courses (2-3 treatments per day for fewer total weeks of treatment) for depression
- More indications

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ACCELERATED PROTOCOLS FOR *DEPRESSION*

- Twice-daily rTMS can achieve similar response and remission rates at the end of the course, with 35.4% and 33.8% , and 41.5% and 35.4%, response and remission rates for once-daily and twice-daily rTMS sessions, respectively
- Other studies (at least 12 total) looking at more than 1 TMS treatment per day have varied widely in the number of treatments per day. Some with 3 times per day, some with more. Highest number studied is 10 sessions per day.
- Mostly positive results; no long-term data yet on durability.

Schulze, L. et al. Brain Stimulation Number of pulses or number of sessions ? An open-label study of trajectories of improvement for once-vs . twice-daily dorsomedial prefrontal rTMS in major depression. 11, 327–336 (2018).
Sonmez, A. Irem, Deniz Doruk Camsari, Aiswarya L. Nandakumar, Jennifer L. Vande Voort, Simon Kung, Charles P. Lewis, and Paul E. Croarkin. "Accelerated TMS for Depression: A Systematic Review and Meta-Analysis." *Psychiatry Research* 273 (March 2019): 770–81. https://doi.org/10.1016/j.psychres.2018.12.041.

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DISORDERS OTHER THAN DEPRESSION

CONCLUSIONS FROM A REVIEW BY EUROPEAN EXPERTS
DATA THROUGH 2018

Level A:

- Major Depressive Disorder (previously concluded by the group)
- Neuropathic pain
- Motor stroke

Level B:

- Fibromyalgia
- Parkinson's disease
- Motor stroke
- Post-stroke aphasia
- Multiple sclerosis
- Post-traumatic Stress Disorder

Note the absence of bipolar disorder . . .

Level C:

- CRPS type 1
- Motor Stroke
- Hemispatial neglect
- Epilepsy
- Alzheimer's Disease
- Tinnitus
- Obsessive-Compulsive Disorder (FDA cleared 2019 multicenter RCT)
- Schizophrenia: auditory hallucinations
- Schizophrenia: negative symptoms
- Addiction & Craving

Lefaucheur J-P, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology*. Published online January 2020:S1388245719312799. doi:10.1016/j.clinph.2019.11.002

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SMOKING CESSATION?

- Randomized study of 262 subjects
- H4 Deep TMS coil (Insula and PFC)
- treatments were performed daily, five days a week for 3 weeks, followed by an additional 3 sessions once a week for 3 weeks (for a total of 18 sessions over the course of 6 weeks).
- four-week continuous quit rate was 28.4% in the active Deep TMS group compared to 11.7% in the sham group (p=0.0063)
- The FDA issued a 510(k) clearance in August 2020

https://www.globenewswire.com/news-release/2020/08/24/2082476/0/en/BrainsWay-Receives-FDA-Clearance-for-Smoking-Addiction-in-Adults.html

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SMOKING CESSATION?

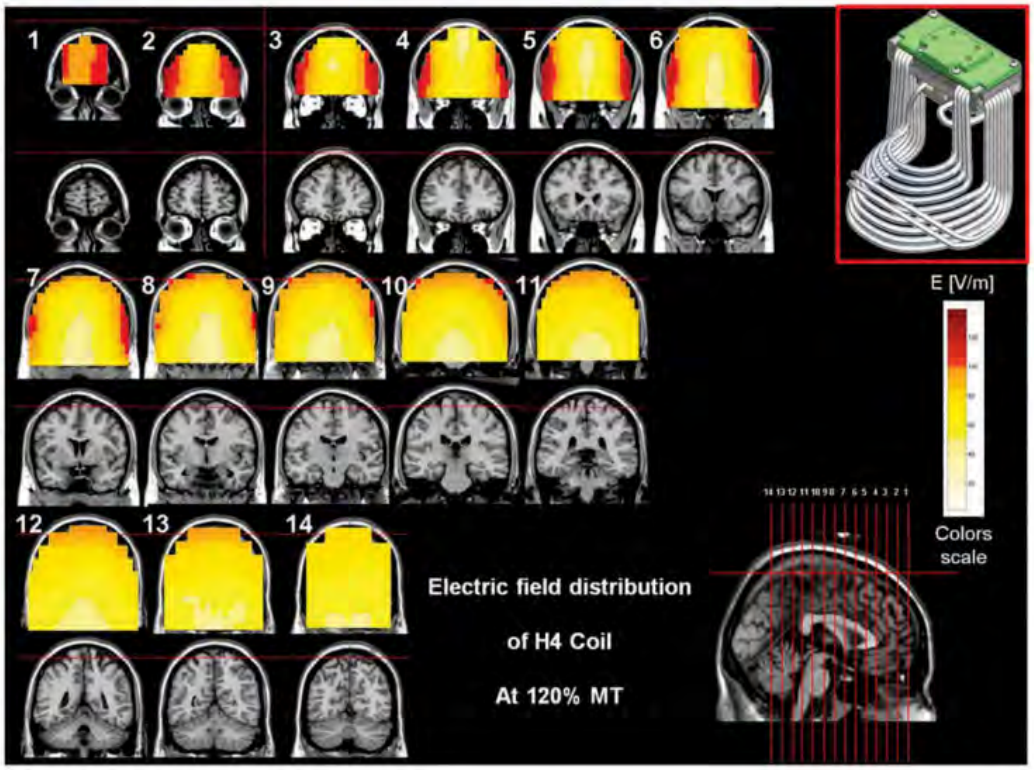

Figure 5. Colored field maps for the H4-coil indicating the absolute magnitude electrical field in each pixel at 120% of hand motor threshold, for 14 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation. Full color available online.

Tendler A, Barnea Ygael N, Roth Y, Zangen A. Deep transcranial magnetic stimulation (dTMS) – beyond depression. *Expert Review of Medical Devices*. 2016;13(10):987-1000. doi:10.1080/17434440.2016.1233812

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WHY IT IS HARD TO STUDY TMS FOR A NEW INDICATION

- ***SO MANY PROTOCOL PARAMETERS!***
  - Intensity relative to the motor threshold (MT) (for example, 120%MT)
  - Frequency (1 Hz, 10 Hz, 18 Hz)
  - Number of pulses
  - Number of sessions
  - Train and inter-train duration
  - pattern of stimulation
  - coil type and orientation
  - cortical region targeted
- Different stimulation frequencies and patterns exert different effects, not always in a consistent fashion
- "While the ability to manipulate **multiple parameters** creates a tremendous opportunity for innovation, it also poses challenges regarding understanding variability in response to the treatment"

Trevizol, Alisson P., and Daniel M. Blumberger. "An Update on Repetitive Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder." *Clinical Pharmacology and Therapeutics* 106, no. 4 (October 2019): 747–62. https://doi.org/10.1002/cpt.1550.

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TMS, IN SUMMARY

Pros

- Extremely safe, including in teens
- For MDD
  - Far more effective than 4th medication treatment trial (~50-60% vs 5%)
  - Durable effects (about 50% maintain at 1 year
  - Covered by insurance for MDD
- 30-40% chance of response in OCD
  - Not insurance covered (as of 2020)
- Some other indications with good evidence for off-label use
  - For example, PTSD

Cons

- Logistically burdensome
- Less effective than ECT (~45-60% vs ~70-80%)
- Most insurances **do not** cover non-MDD diagnoses
- Premera/BXBS cover some <18 y/o, o/w case-by-case
- Expensive if out of pocket ($9,000-$18,000 for 36 sessions; most clinics charge $250-$500 per treatment)

ACKNOWLEDGMENTS

- Thanks to all our colleagues at SeattleNTC:
  - Leigh Brown DO
  - Ki Won Nam MD
  - Steve Brogdon MD
  - Jesse Adams MD (borrowed/adapted some of his slides)
  - Rie Sharky MD
  - Laurie Arndorfer MD

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THANK YOU!

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- A patient or referring provider may contact SeattleNTC to schedule a consultation at:
  - 206-467-6300 x7 (phone)
  - 206-467-6301 (fax)
  - info@seattlentc.com
  - www.seattlentc.com
- We accept essentially all major insurance plans
- Our ECT program is performed in conjunction with Swedish Medical Centers, specifically at the Ballard & Issaquah campuses
- TMS & esketamine are provided in our office locations
  - Seattle, Bellevue, Tacoma, Bellingham