An Update on TMS for Depression: 20+ Years Since Proof of Concept & 8 Years After FDA Approval

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Brain Stimulation: Basic, Translational and Clinical Research in Neuromodulation

NARSAD lecture
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  - NIMH, NINDS, NIDA, NIAAA, NASA, DARPA, DOD, VA
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- **Disclosures -**
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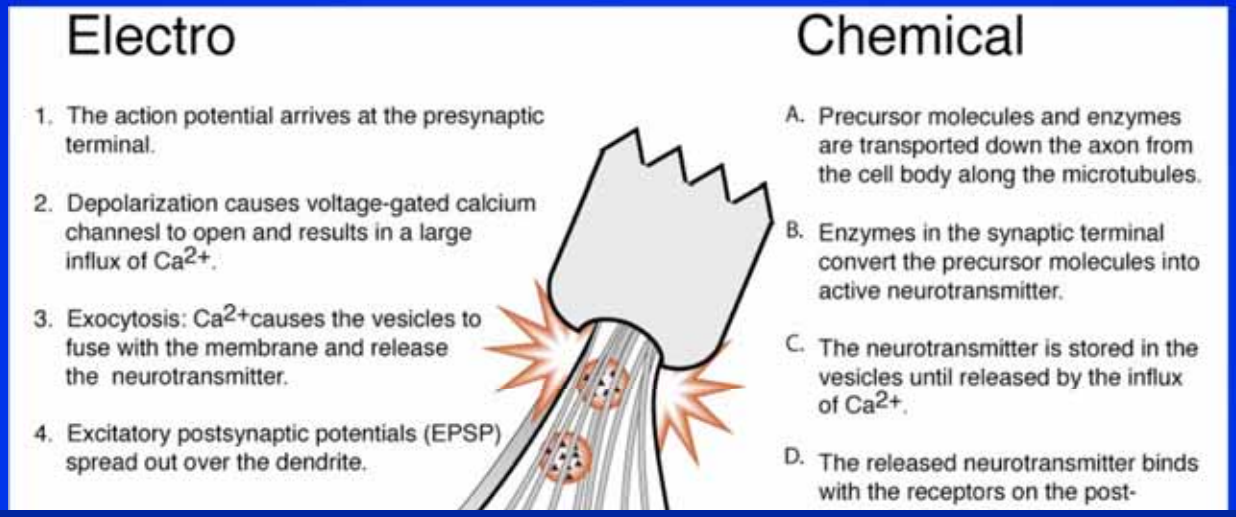
  - Editor-in-Chief, Brain Stimulation, Elsevier

The forgotten half of the truth

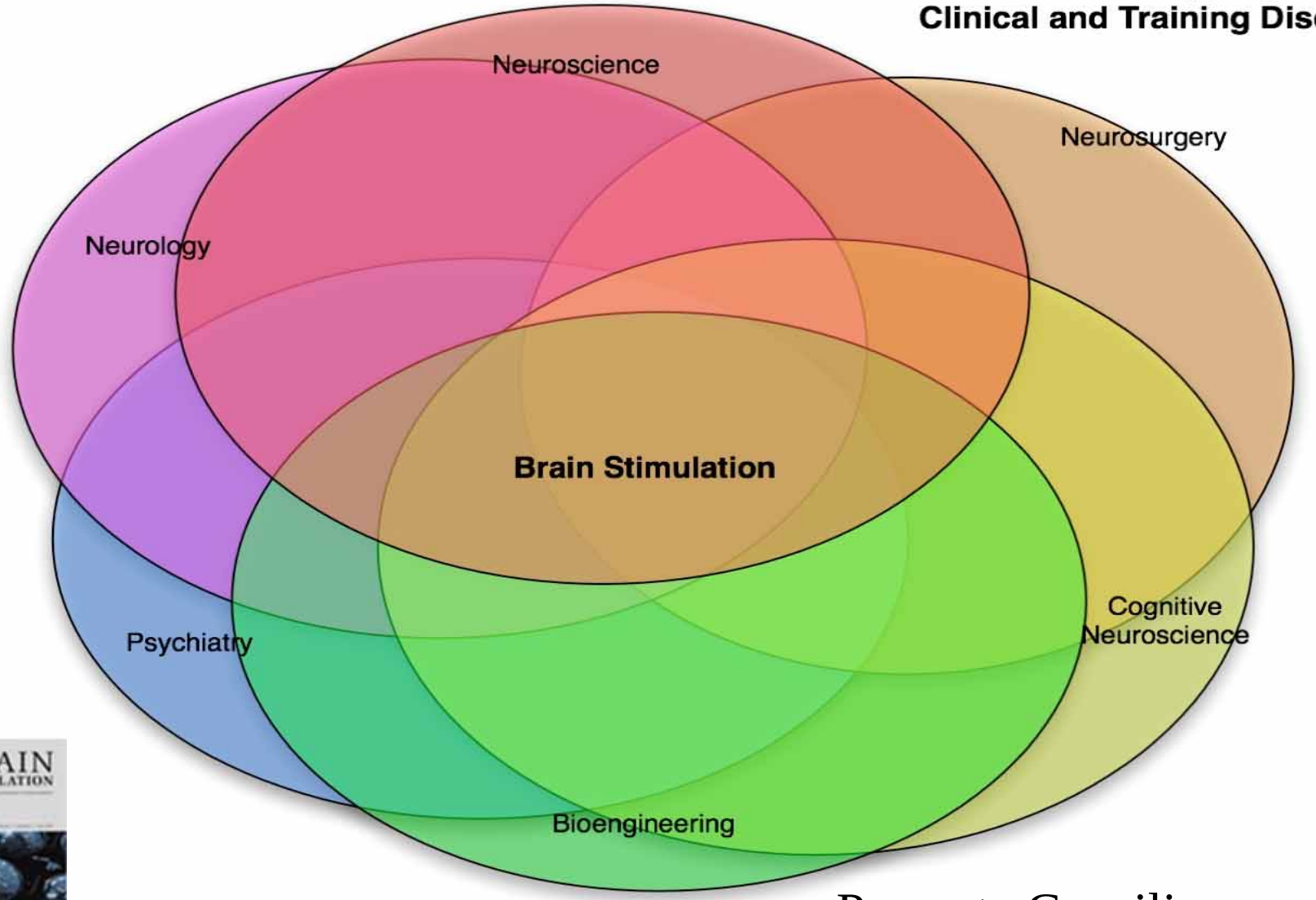


Electricity is the Currency of the Brain

All of synaptic pharmacology simply serves to transmit electrical signals to the next neuron

Figure 3.12 This is an example of the electro-chemical signaling from a dopamine neuron.

The Brain is an Electrochemical Organ



Promote Consilience

Main Brain Stimulation Techniques

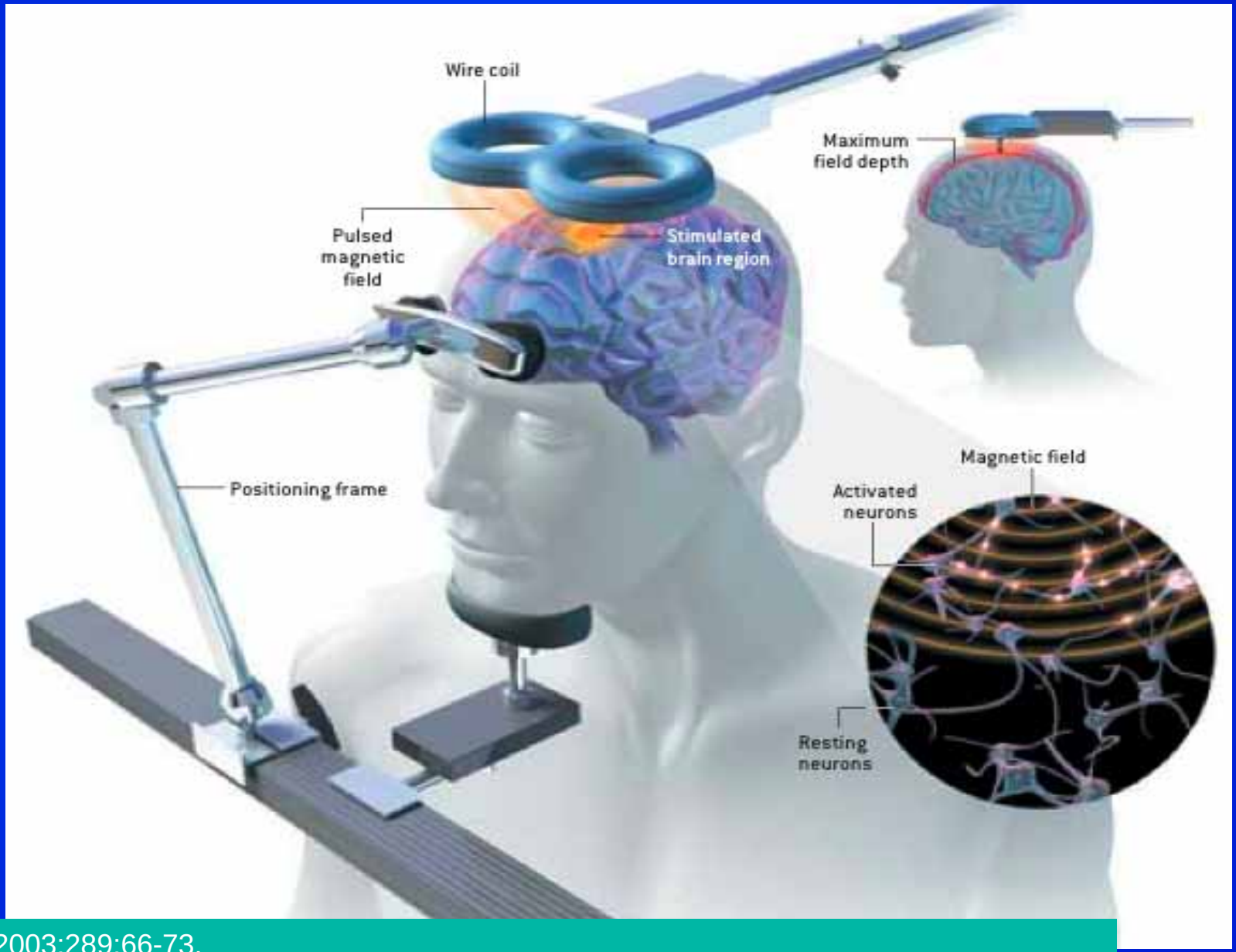
US FDA Approved

- **ECT - Electroconvulsive Therapy**
  - FEAST
- **rTMS - repeated Transcranial Magnetic Stimulation**
- **DBS - Deep Brain Stimulation – PD, dystonia, OCD**
  - RST - Responsive Stimulation Therapy, epilepsy
  - Epidural Cortical Stimulation
- **VNS - Vagus Nerve Stimulation – Epilepsy, Depression, Morbid Obesity**

Not FDA Approved

- **MST - Magnetic Seizure Therapy**
- **tDCS - transcranial Direct Current Stimulation**
- **TENS - transcutaneous Electrical Nerve Stimulation**
  - Cranial Electrical Stimulation (CES) Alpha-stim, Fisher Wallace
- **EPI-fMRI - echoplanar fMRI (LFMS)**
- **Transcranial alternating current (tACS)** Thync
- **Transcranial pulsed ultrasound**

How TMS Works



George MS. *Sci Am.* 2003;289:66-73.

Ways to use TMS

- As a neurophysiological research tool to ‘ping’ the brain and measure response
- As an interruption tool to temporarily disrupt a brain region (temporary lesion)
- As a way to measure brain plasticity paired associative stimulation (PAS)
- As a potential treatment tool, usually with multiple stimuli over several days

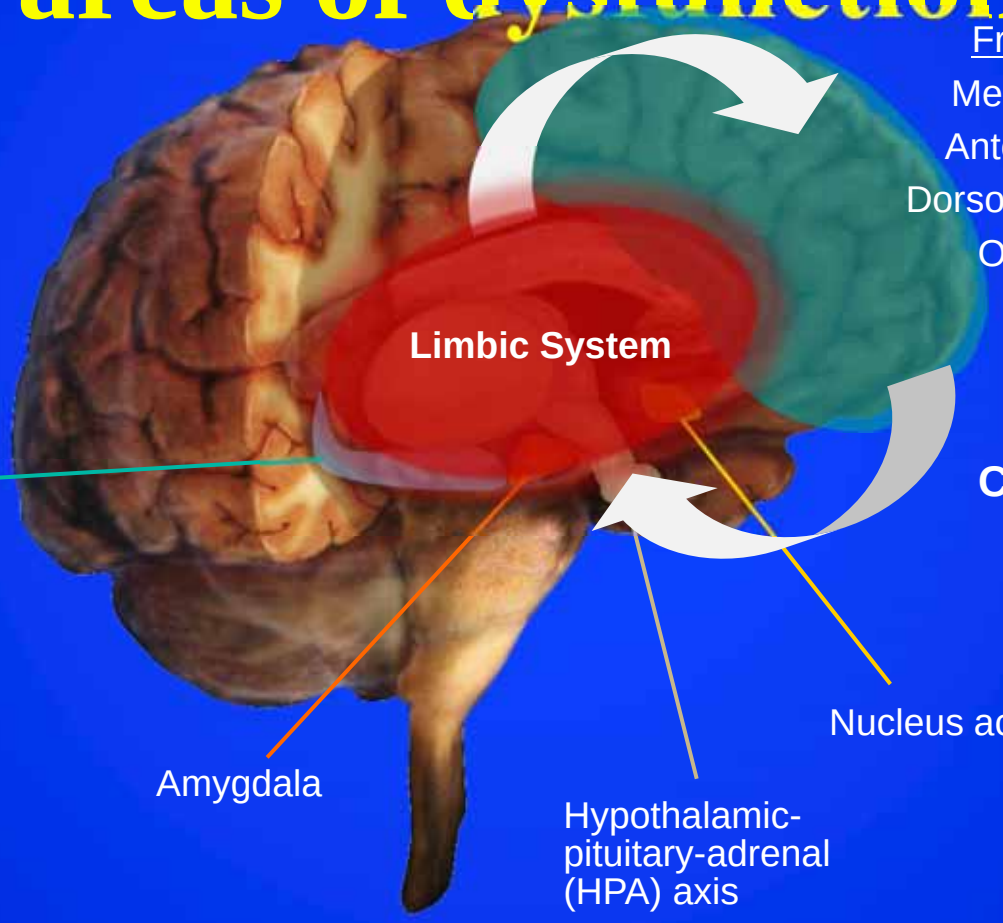
Does rTMS Work in the Treatment of Depression ?

- **Yes**
- **But we can likely make it work better by**
  - Understanding where to stimulate
  - Manipulating and combining with brain state
  - Refining frequencies and patterns
  - Understanding durability and repeated doses for maintaining remission

Does rTMS Work in the Treatment of Other Neuropsychiatric Disorders?

- **Maybe**
- **Largest body of evidence in**
  - Pain syndromes
- **Pivotal Studies Underway in**
  - OCD
  - PTSD
  - Smoking Cessation

The depressed brain: major areas of dysfunction



Frontal Cortex
Medial prefrontal
Anterior cingulate
Dorsolateral prefrontal
Orbital frontal

Hippocampus

Amygdala

Hypothalamic-pituitary-adrenal (HPA) axis

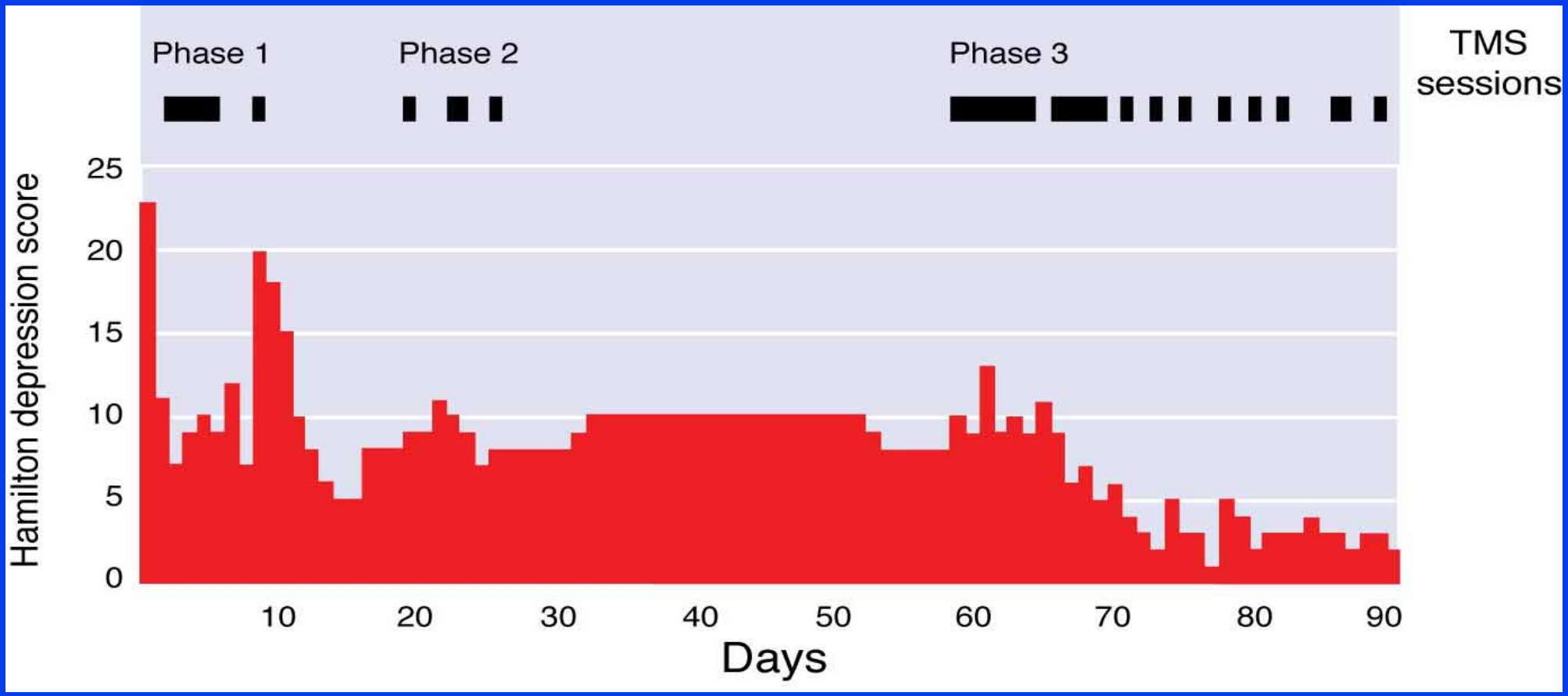
Nucleus accumbens

Cortico-limbic dysfunction : a hypothetical view

Higgins and George. Chapter 18, Neuroscience for Clinical Psychiatry, 2007

Basic Hypothesis and Reasoning

- If MDE results from an abnormal cortico-limbic governance, and ECT and talking therapy reset this
- Then, perhaps repeated subconvulsive stimulation might result in the same final rebalance, and treat MDE episodes
- TMS might be a useful first technology to test this idea of resetting or rebalancing cortico-limbic governance

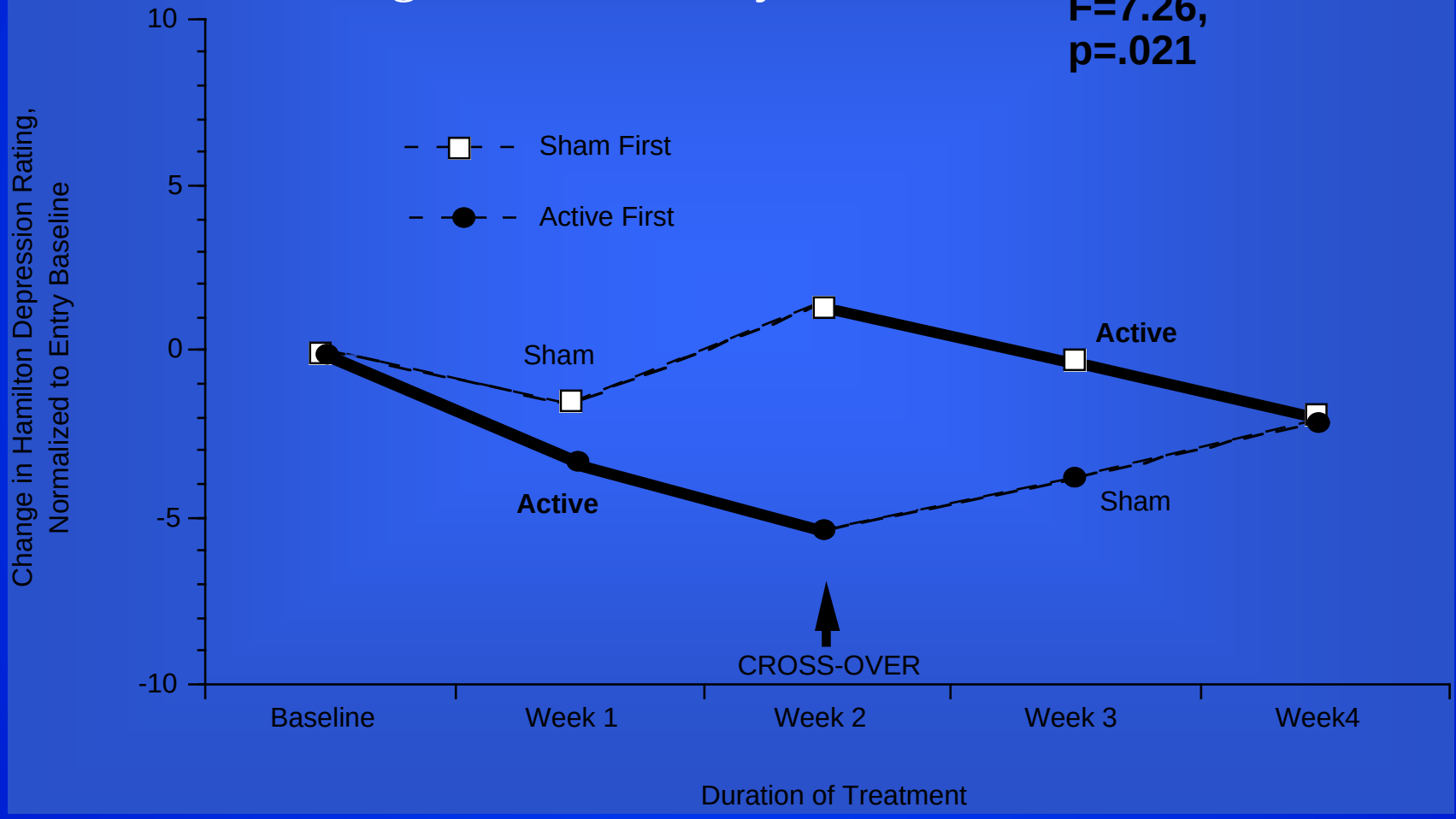


George et al, Neuroreport, 1995

Changes in Hamilton Depression Score with Active and Sham Left Prefrontal rTMS

George et al, Am J Psych 1997

ANOVA
F=7.26,
p=.021

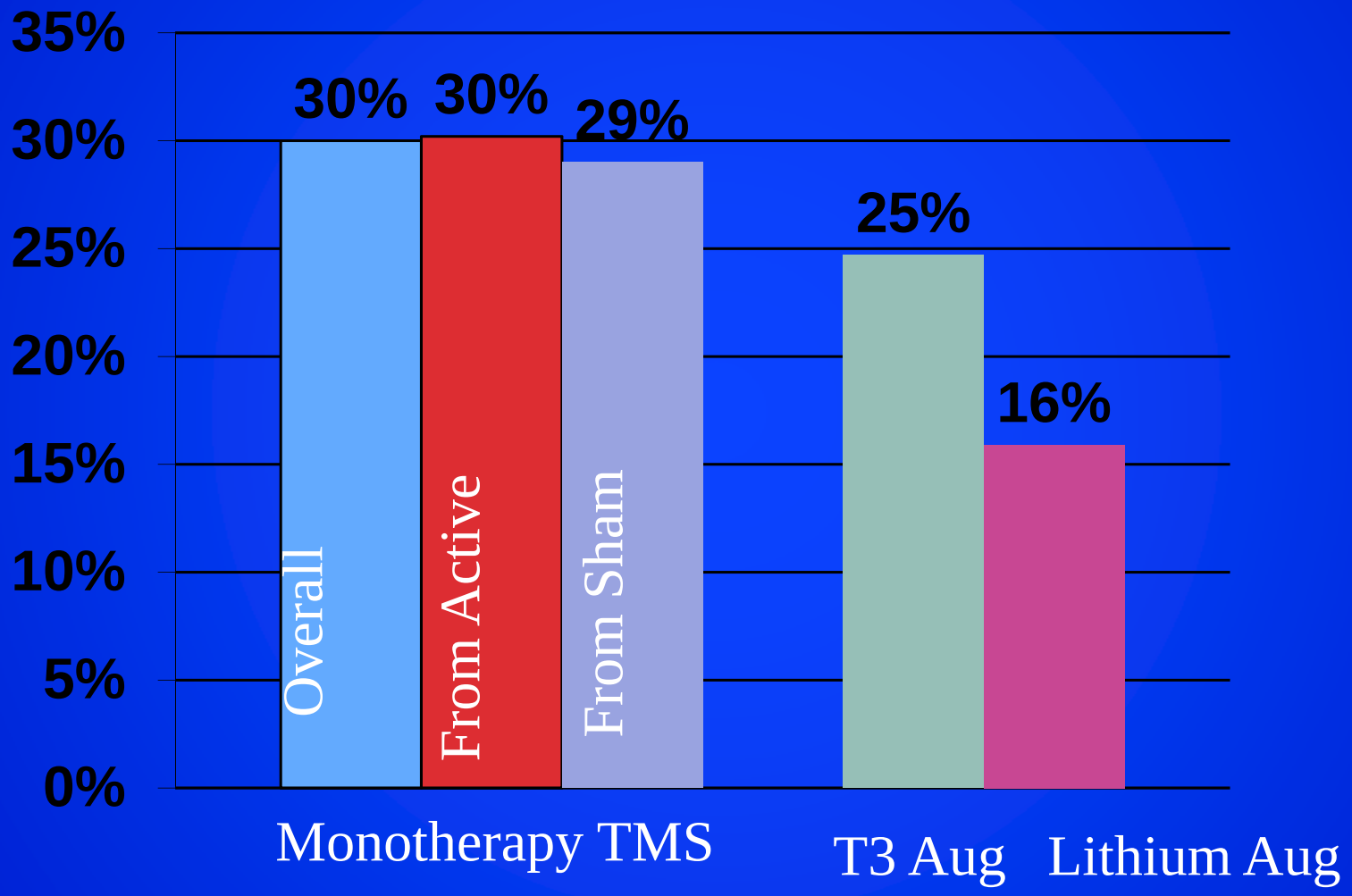


Keys to Successful Evolution of a brain stimulation technology to market

- Know the target (brain region)
- Know which patients to enroll
- Understand the placebo effect
- Know the dose and time of effect
- Conduct multi-site trials that are adequately powered to find the effect
- Have a business plan that makes money for someon

NARSAD funded many of these small trials, when other sources would not

Clinical Effect in Open-Label Compared to STAR-D Medication Options



George et al, *Arch Gen Psychiatry*, May, 2010
Nierenberg AA, et al. *Am J Psychiatry*. 2006;163:1519-1530.

No Efficacy/Effectiveness Gap

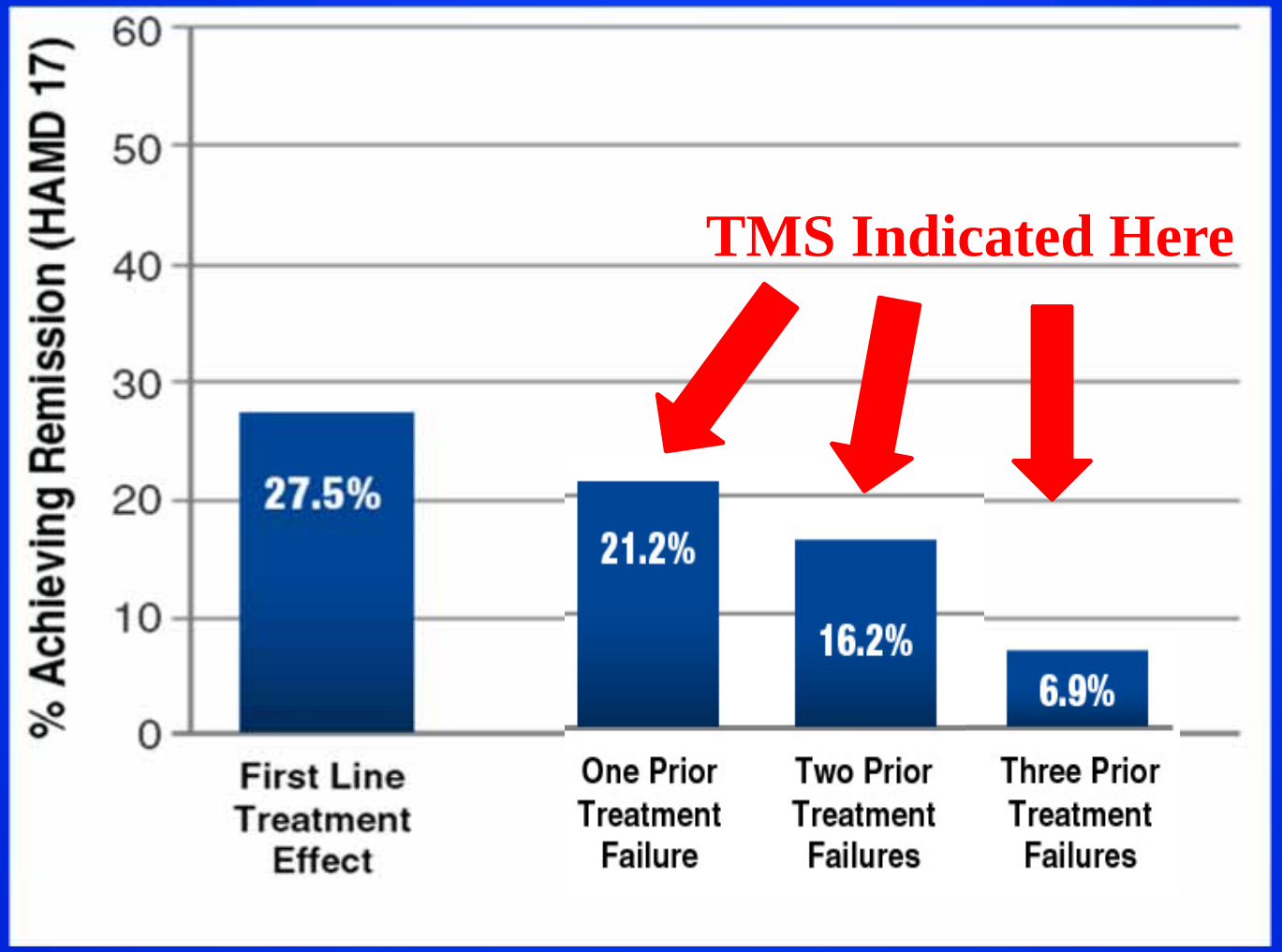
- **307 real world US patients, on medication, Neuronetics sponsored, 58% response, 37% remission, average 28 sessions (Carpenter et al, 2012)**

- **100 patients, U Penn practice model, 50% response, 25% remission (Connelly et al, 2012)**

Summary of TMS Acute Unipolar Depression Trials

- **3 Large Prospective RCT support TMS for treating acute moderately treatment resistant depression (3-6 weeks)**
- **Remission rates from 15%-30% in the double-blind phase, and 30% or more in open-label**
- **Safe, tolerable, but inefficient**
- **Modest clinical adoption**
  - In US all major insurance, VA
  - Most major countries cover, even the UK NHS

STAR*D Study Demonstrated Decreased Remission With Each Treatment Failure



Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

Antidepressant Medications

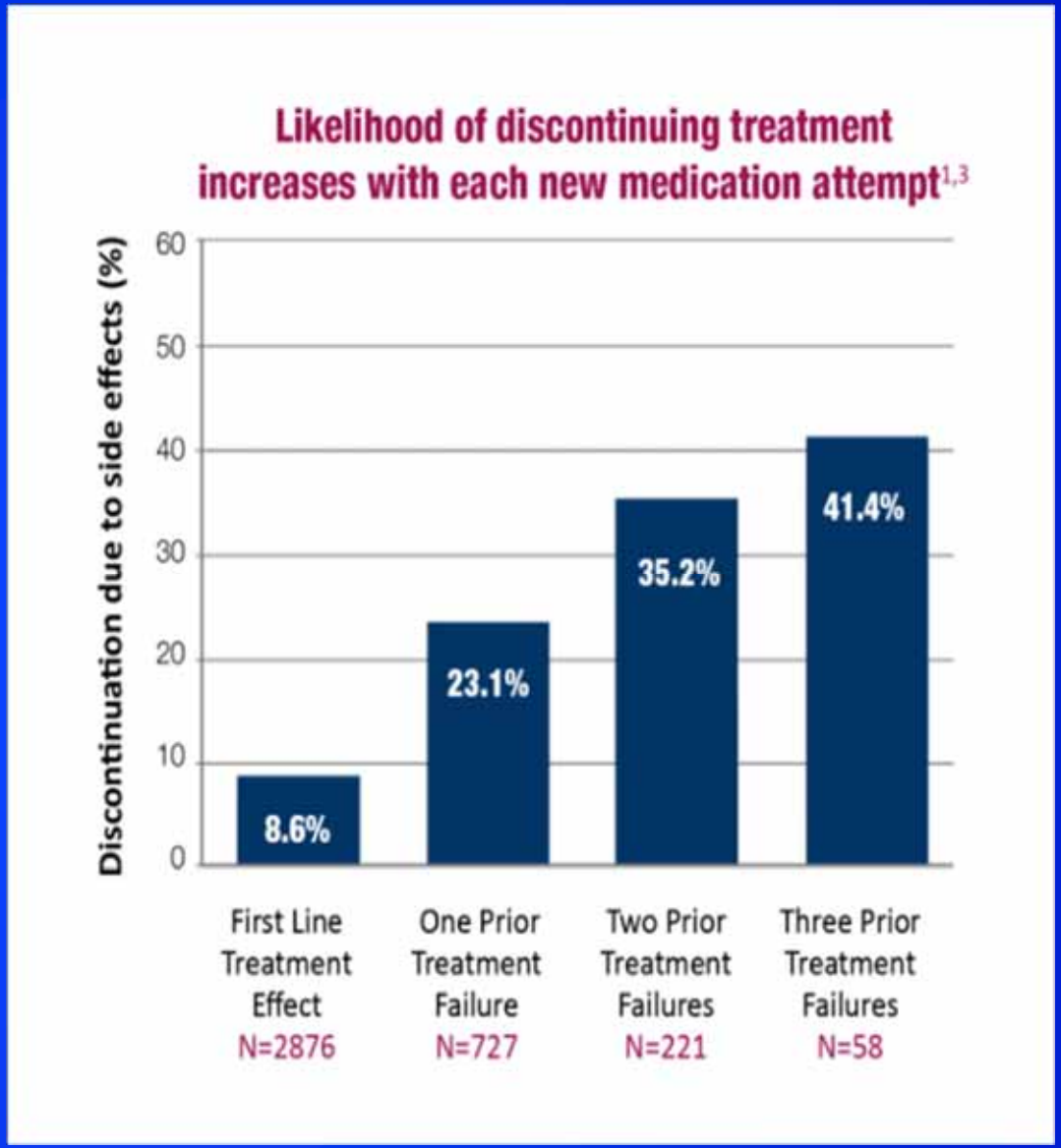
- Antidepressants get patients to remission about a third of the time
- Most recent meta-analysis shows that antidepressants have an Effect size approximately 0.31[1]
- We understand that different medications have different mechanisms of actions which can be beneficial for some patients.
- With medication combinations and the development of pharmacogenomic testing we are likely improving these outcomes.
- Unfortunately, many patients still do not respond to medications or do not tolerate the side effects associated with the medications.

[1] Cipriani, et al. Lancet Feb 2018

Typical Medication side effects:

- Increased or decreased sleep
- Changes in energy and fatigue
- Blurred vision
- Dry mouth
- Weight changes
- Appetite changes
- Sexual dysfunction
- Vital sign changes: Blood pressure and pulse
- Gastrointestinal distress: nausea, vomiting, diarrhea, constipation

STAR-D Data Support Need for Other Treatment Options



Trivedi et al. (2006) *Am J Psychiatry*
Fava et al. (2006) *Am J Psychiatry*

TMS is NOT ECT

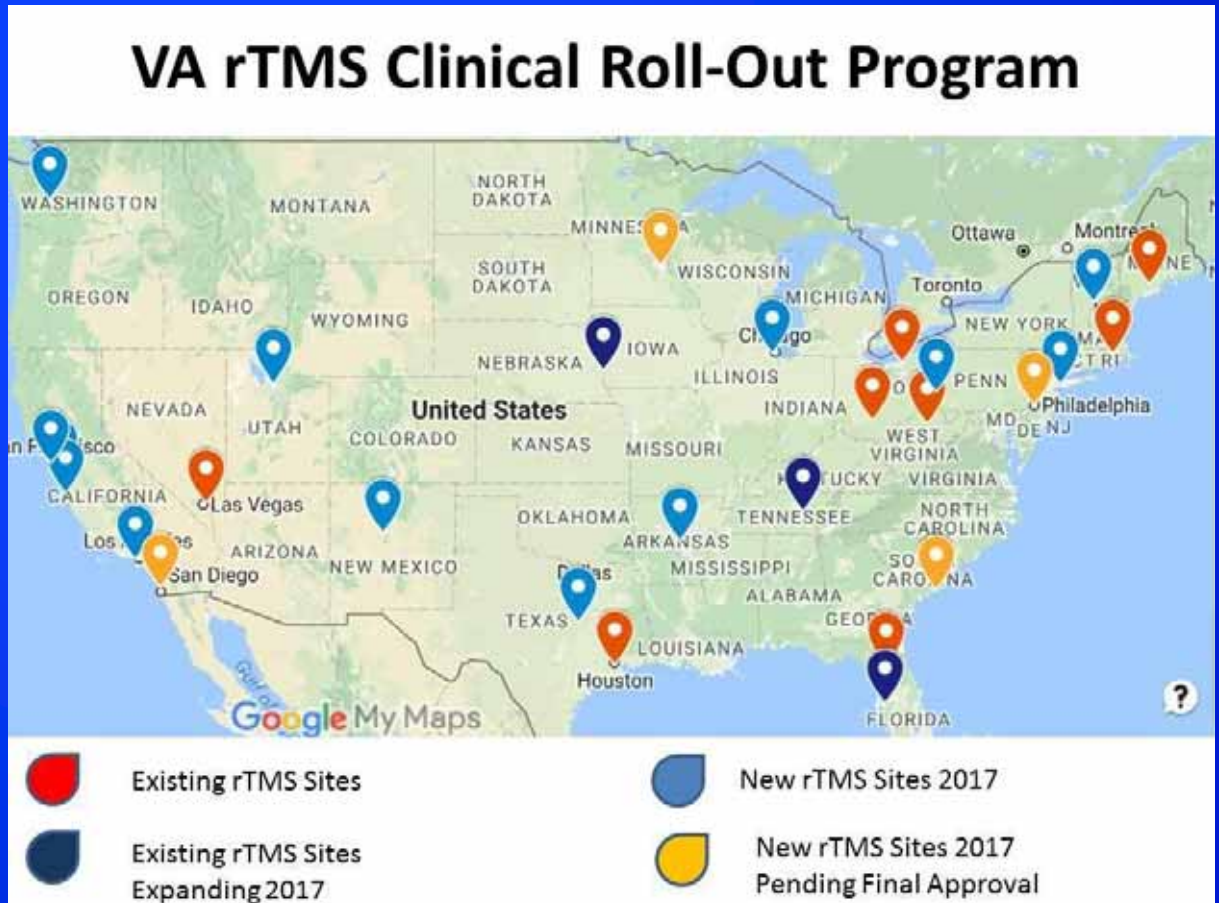
- TMS is not a replacement for ECT, but is a different modality and should likely be used earlier in course of care.
- ECT is still best for MDD with psychotic features, acute suicidality, or catatonia
- Some patients who fail ECT respond to TMS and vice versa [1]
- Head-to-head trials comparing ECT and TMS have not been completed with double blind due to the challenge of creating "double-dummy" sham design
- "It has been well established that, regardless of continuation treatment, relapse following ECT concentrates heavily in the weeks immediately following ECT termination, indicating that ECT has little intrinsic durability of benefit." [2]

[1,2]

Sackeim, H. *Brain Stimulation* 2016 (9) 313-319.

VA Purchased 40 Machines, coordinating a national network

- **J. Yesavage, Palo Alto VA**



2018 TMS Depression Update

- **6 Devices now FDA cleared for depression**
  - Neuronetics, Brainsway, Magventure, Magstim, Neurosoft, Nexstim
- **No New Large RCT's**
- **VA CSP 556 data**
- **Two Guidelines Manuscripts published.**

Brain Stimul. 2016 May-Jun;9(3):336-46. doi: 10.1016/j.brs.2016.03.010. Epub 2016 Mar 16.

The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder.

Perera T[1], George MS[2], Grammer G[3], Janicak PG[4], Pascual-Leone A[5], Wirecki TS[6].

NeuroStar TMS Therapy System

Coil

Capacitors

Nexstim TMS Device

Coil

Capacitors

Brainsway TMS Device

Coil

Capacitors

Cloud TMS NeuoSoft System

Capacitors

Magventure

Coil

Capacit ors

Coil

Coil

Capacitors

Magstim

Ongoing Refinements and Improvements

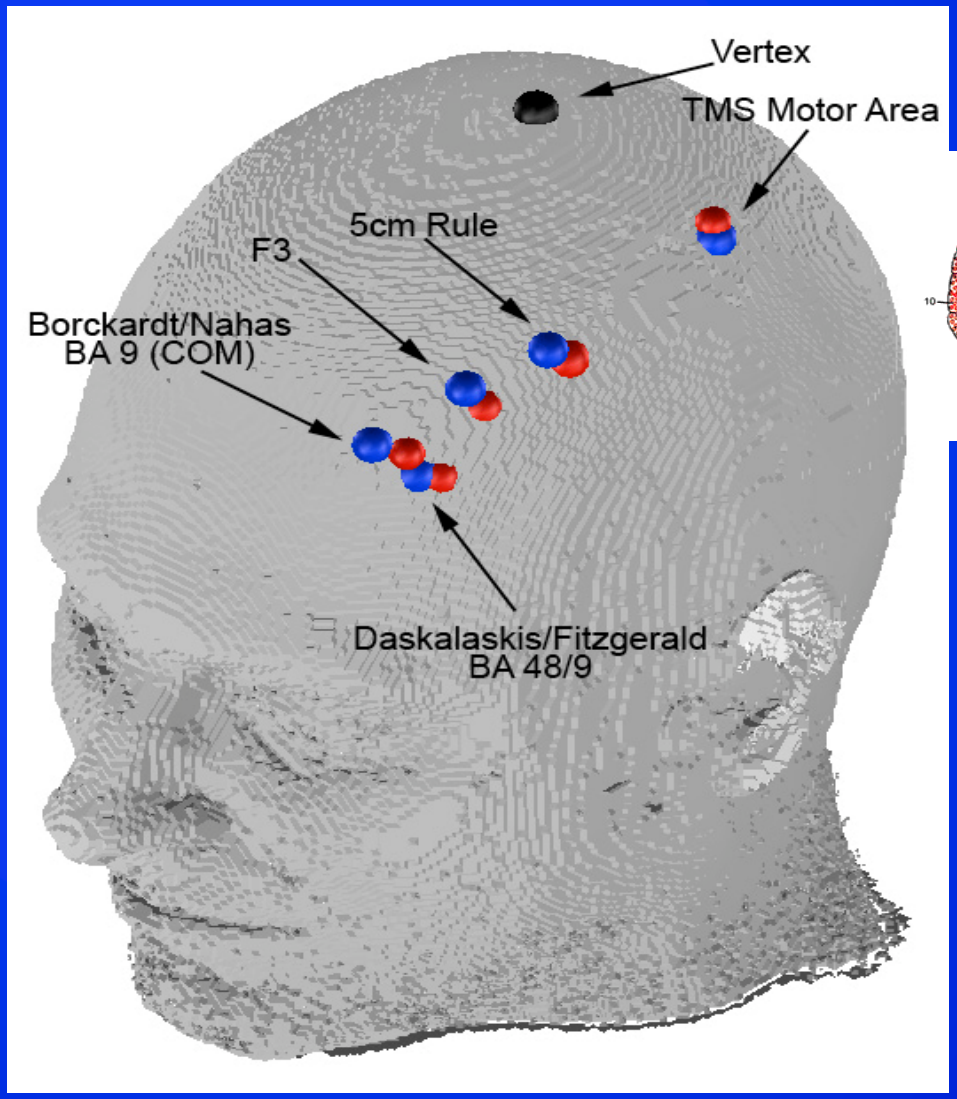
- Understanding where to stimulate
- Manipulating and combining with brain state
- Refining frequencies and patterns
- Understanding durability and repeated doses for maintaining remission

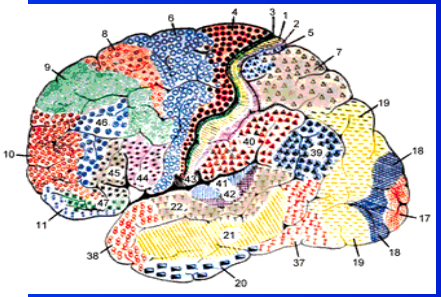
Best Prefrontal Positioning?

Comparison of F3, 5 cm and other rules for positioning

Borckardt, in blue

Anderson, in red





MUSC BSL Lab Testing Jan 24, 2008

Intelligent targeting with TMS for Depression

- Are we just missing the target in non-remitters?

- If cortical TMS causes circuit changes, why not image the circuit and then locate the correct cortical target?

- Resting state functional connectivity, find deep target, and correlated or anti-correlated location for that person?

- So far, works for group, not yet for individual..

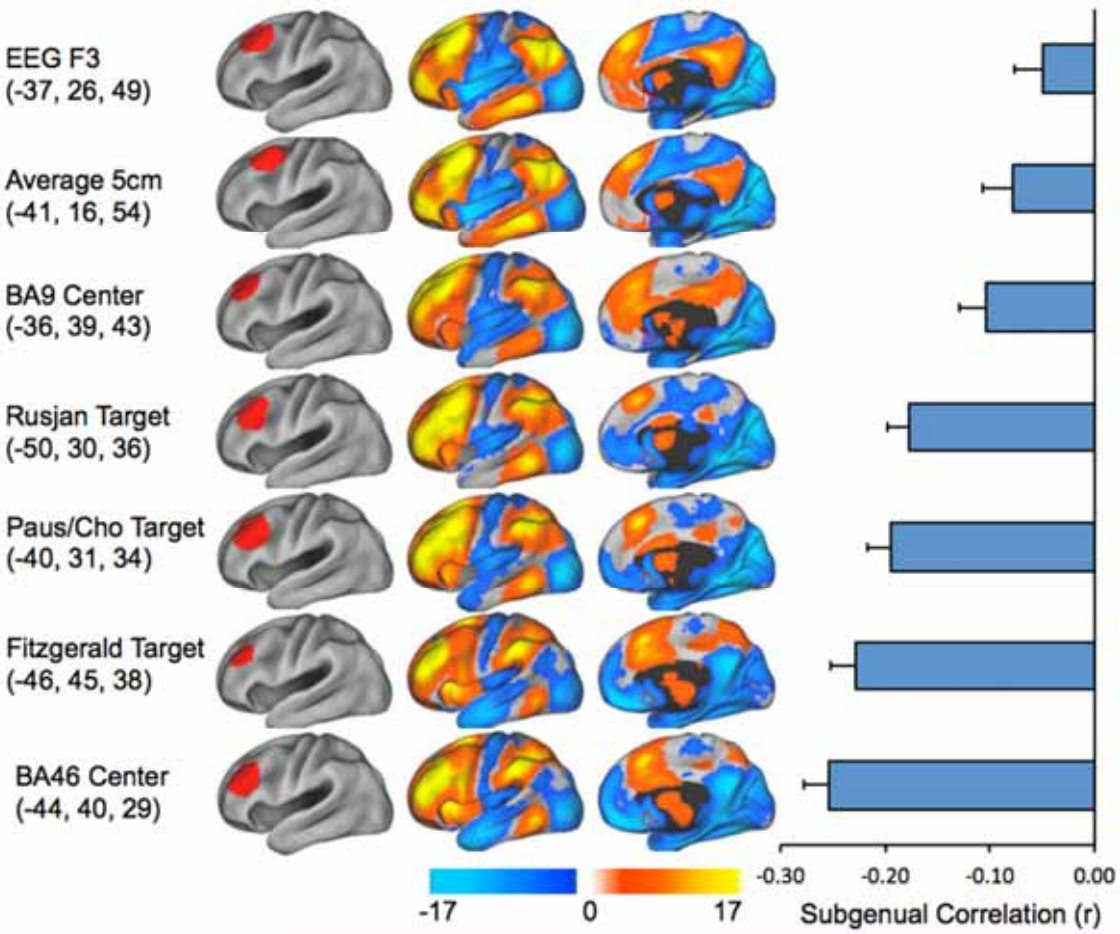
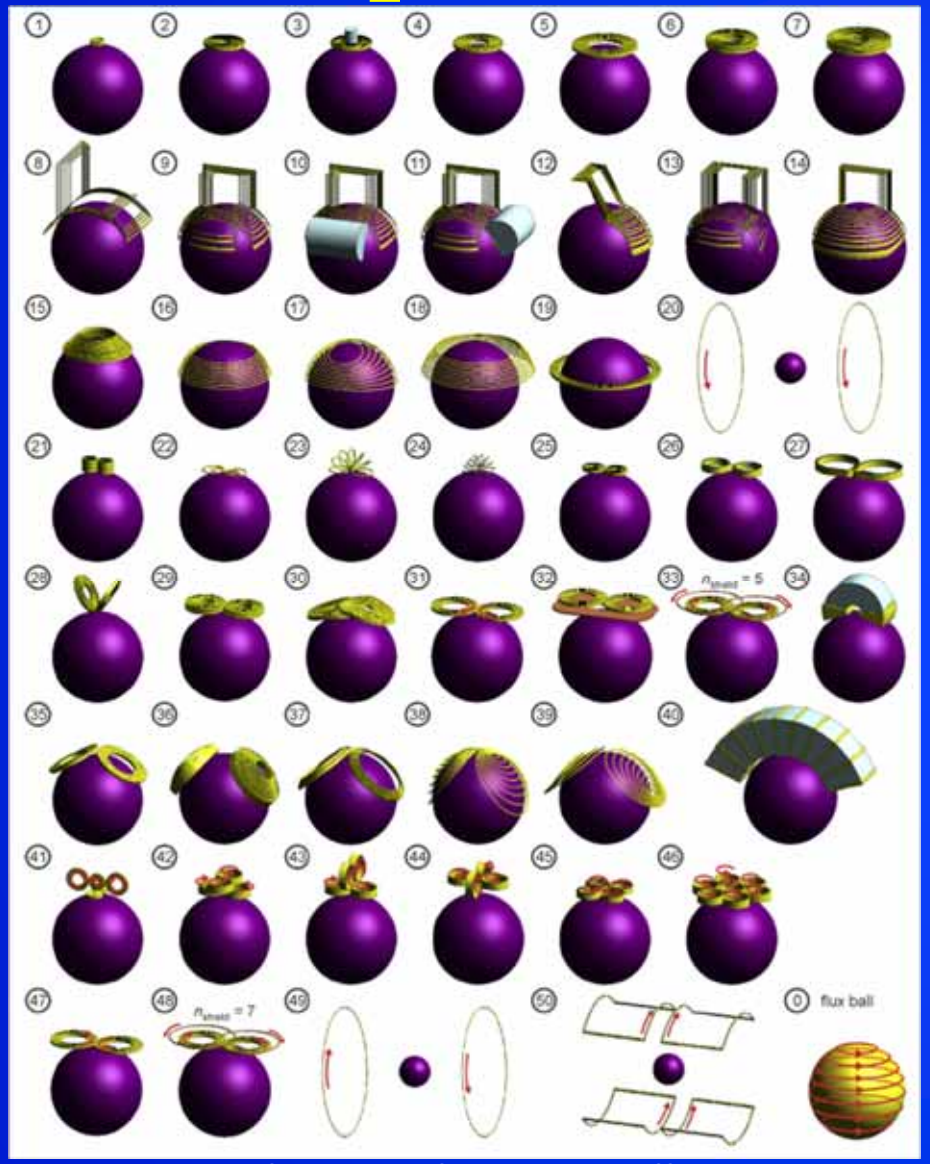
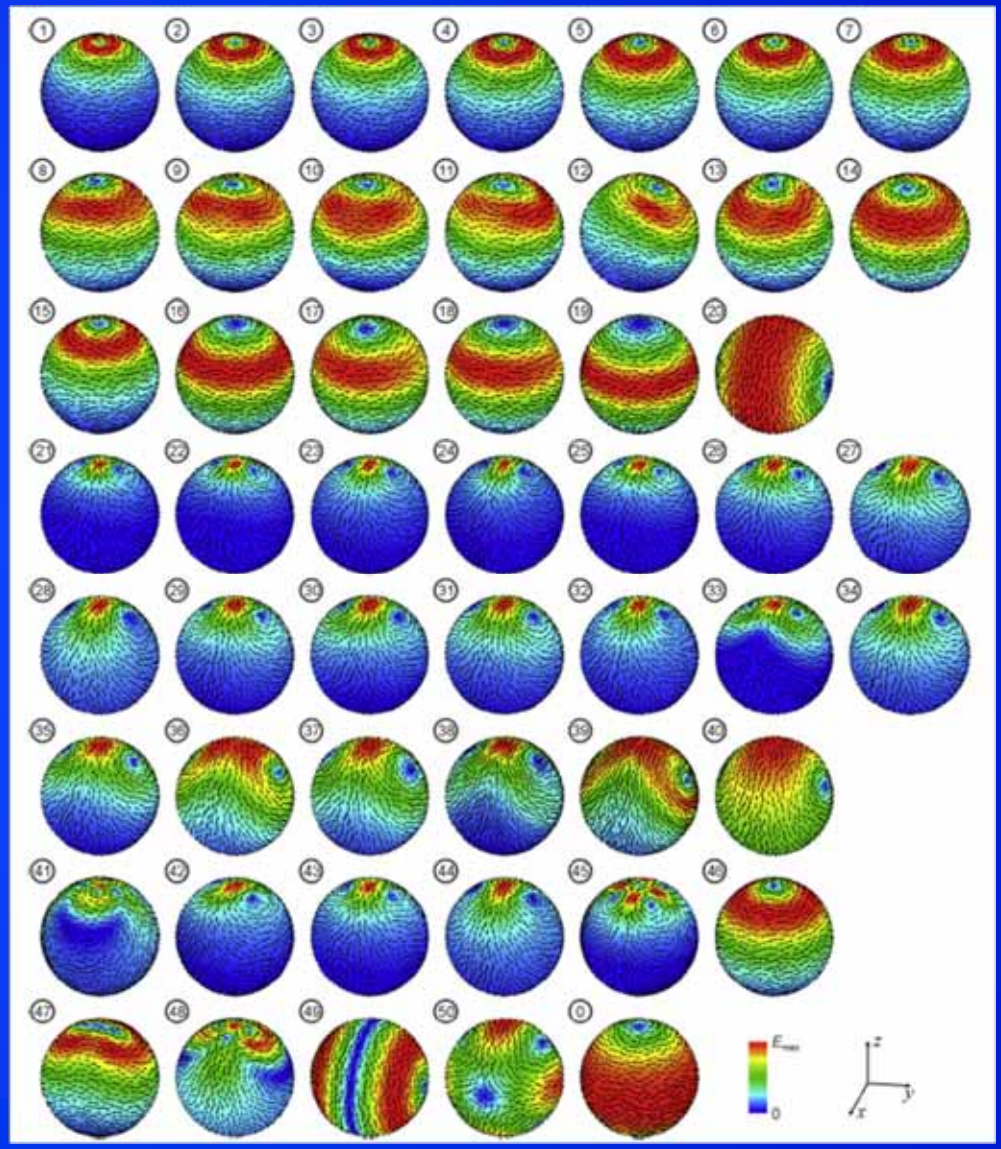


Figure 1. Different left dorsolateral prefrontal cortex (DLPFC) transcranial magnetic stimulation targets show variability in resting state functional connectivity, especially with the subgenual cingulate. The left hand column shows the coordinates and regions of interest for various left DLPFC transcranial magnetic stimulation targets employed in the literature. The middle columns show resting state functional connectivity maps for each DLPFC region of interest. The border of our a priori defined subgenual region of interest is shown for reference in red. The right hand column is the correlation coefficient between the time course from each DLPFC region of interest and that of the subgenual cingulate. BA, Brodmann area; EEG, electroencephalogram.

For group data, some cortical locations do connect better subcortically. Does that translate into clinical effects, or help with individual placing?

Deep Versus Focal Stimulation



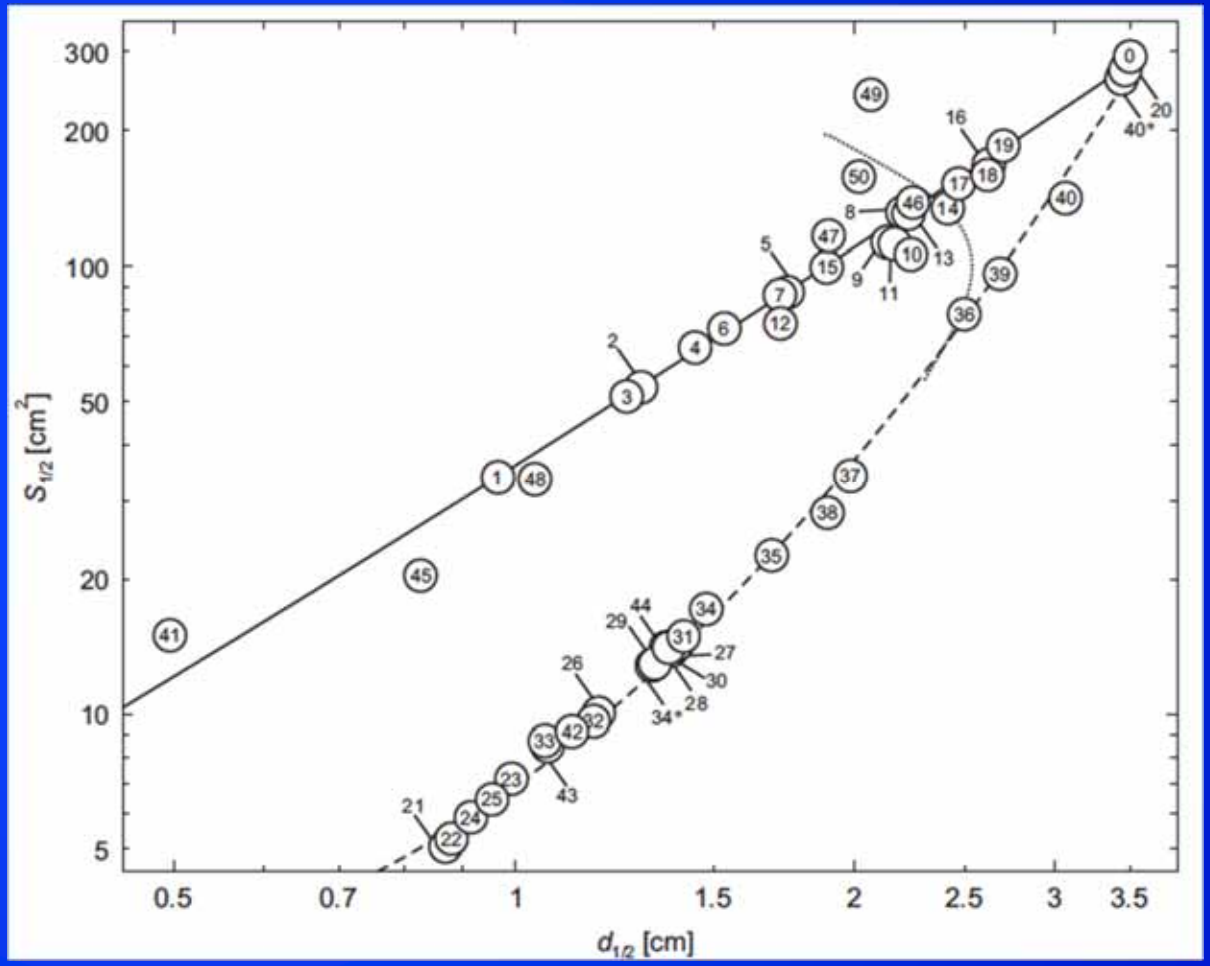


Deng et al, Electric field depth focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs *Brain Stimulation*, 2012

Depth-Focality Tradeoff

‘Among the TMS coil designs, there is a tradeoff between electric field depth of penetration and focality..’

With conventional TMS coils, to go deep in the brain you have to be broad and non-focal.



Deng et al, Electric field depth focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs *Brain Stimulation*, 2012, In Press

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Brain Stimulation xxx (2013) 1–12

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Safety and Characterization of a Novel Multi-channel TMS Stimulator

Yiftach Roth [a,d,*], Yechiel Levkovitz [b,c,1], Gaby S. Pell [a,d], Moria Ankry [d], Abraham Zangen [a,d,*]

[a] Department of Life Sciences, Ben-Gurion University, Beer Sheva, Israel
[b] The Emotion-Cognition Research Center, Shalvata Mental Health Care Center, Hod-Hasharon, Israel
[c] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[d] Brainsway Ltd, Israel

Numerous interleaved TMS-fMRI and other imaging studies show that prefrontal cortical TMS can have short term and longer term changes in mood regulating circuit excitability and function.

Perhaps not synaptic plasticity but circuit plasticity…

Prefrontal TMS causes changes in network connectivity and size

Brain Stimulation 9 (2016) 577–583

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Transcranial Magnetic Stimulation of Left Dorsolateral Prefrontal Cortex Induces Brain Morphological Changes in Regions Associated with a Treatment Resistant Major Depressive Episode: An Exploratory Analysis

Martin J. Lan [a,b,*], Binod Thapa Chhetry [a,b], Conor Liston [c,f], J. John Mann [a,b], Marc Dubin [c,d]

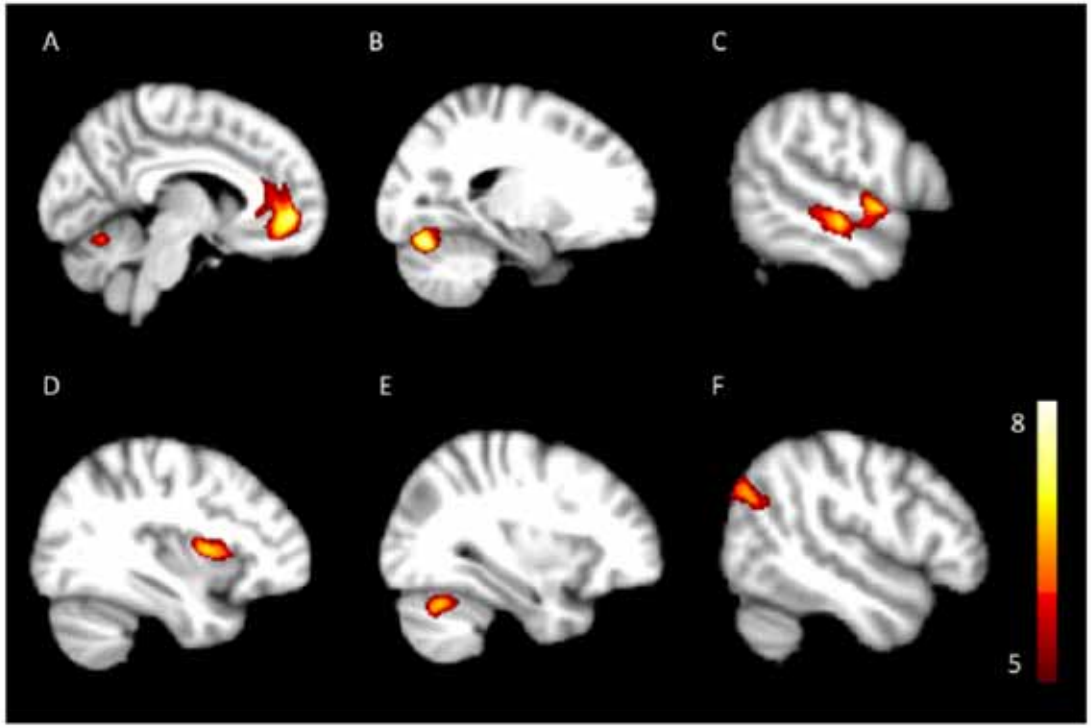


Figure 1. Regions of significant gray matter volume (GMV) changes when depressed pre-treatment MRI scans are compared to HVs, overlaid on standard space T1 image. The extent of increase in GMV is provided by the color-coded *t*-values. The color scale represents the *t*-statistics, with colored regions surviving the $P_{FWE} < 0.05$ and minimum cluster of 500 voxels.

Daily Prefrontal TMS in Depression Regrows the Brain in Mood Regulating Regions (dACC)

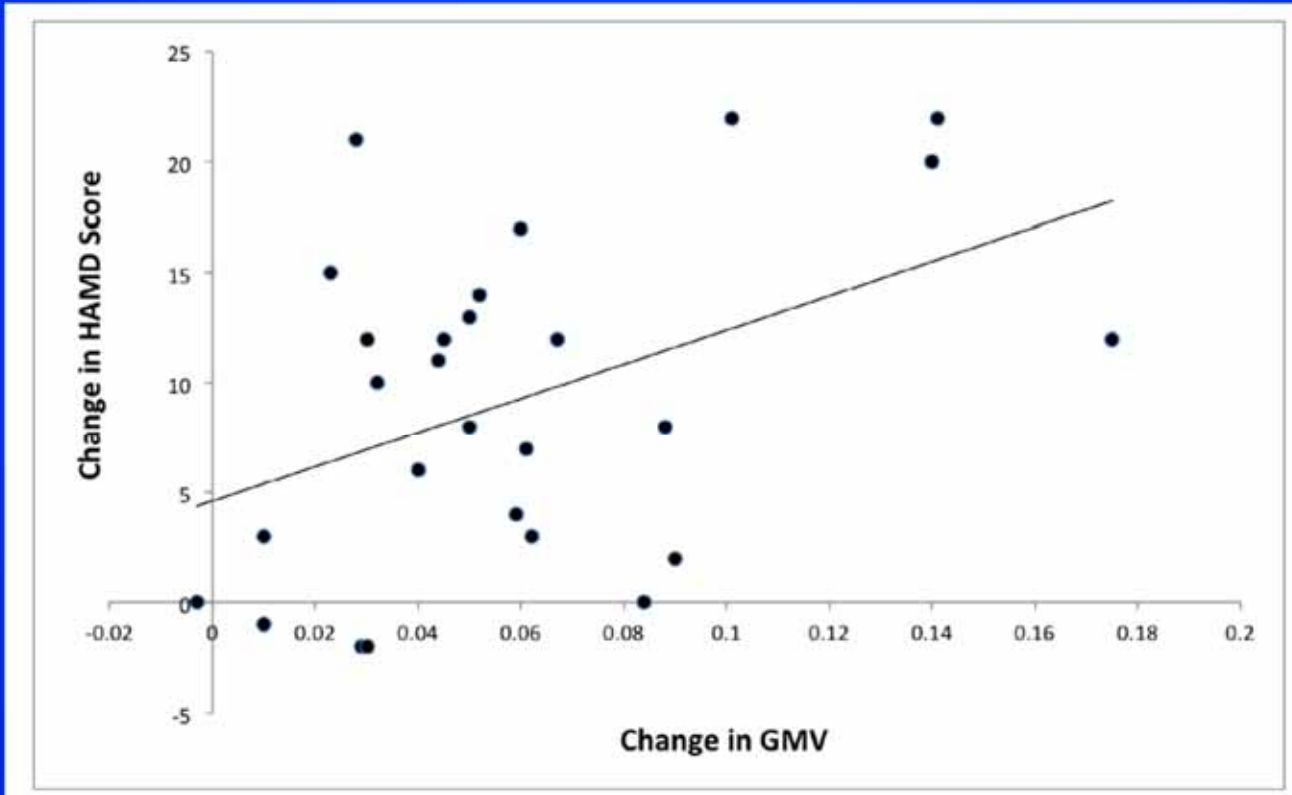


Figure 2. Correlation between the increase in mean gray matter volume in the anterior cingulate cluster with improvement in depression severity.

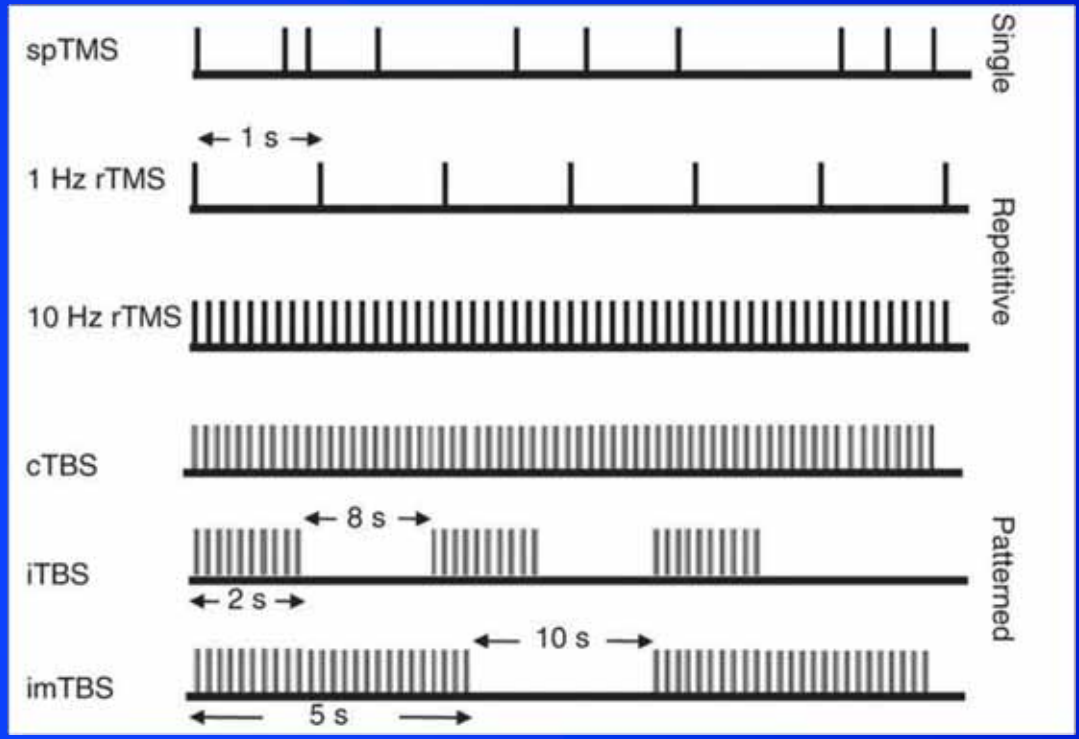
Does rTMS Work in the Treatment of Depression ?

- **Yes**
- **But we can likely make it work better by**
  - Understanding where to stimulate
  - **Manipulating and combining with brain state**
    - **CBT during depression treatment session?**
    - **OCD exposure after SMA TMS**
    - **PTSD exposure before or during TMS**
    - **Cue induced craving before or during TMS for addictions**

Does rTMS Work in the Treatment of Depression ?

- **Yes**
- **But we can likely make it work better by**
  - **Refining frequencies and patterns**
  - Understanding durability and repeated doses for maintaining remission

Theta Burst



- Theta burst is a patterned signal, generated in neurons. Triplets at 50hz, at 5Hz
- Potent at producing LTP, LTD

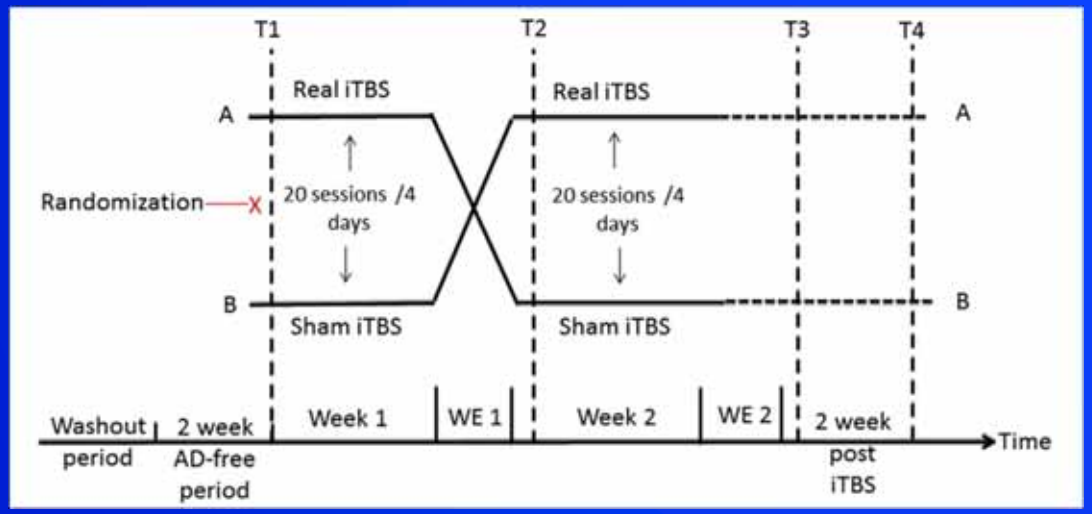
Seok et al, The efficacy and safety of accelerated rTMS in MDD.

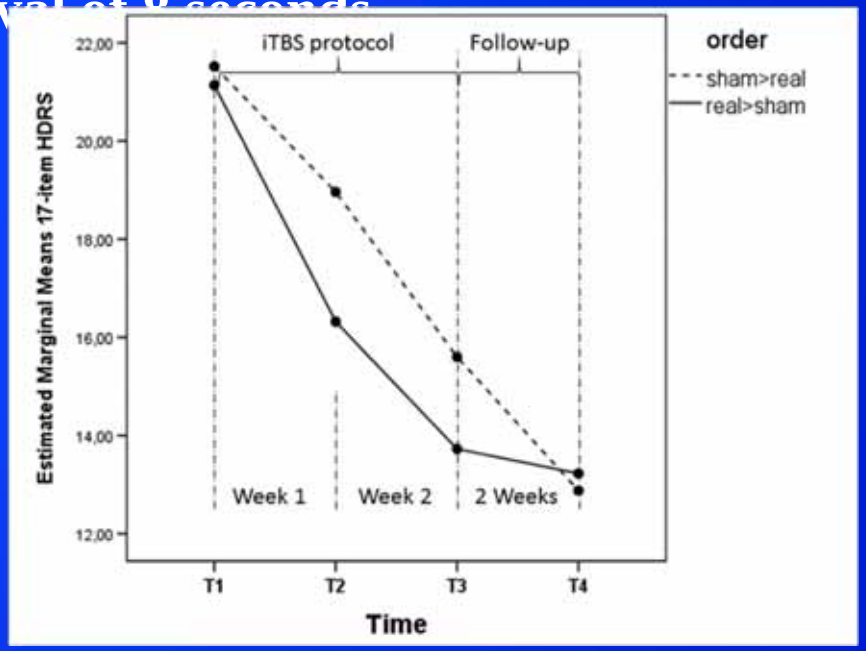
- **RCT, 10 patients daily prefrontal rTMS for 3 weeks (15 sessions)**
- **10 patients, 15 sessions in 3 days**
- **At 3 weeks, no difference between the two groups, similar efficacy and side effects**
- **More rapid response in the accelerated group**

Abstract, Brain Stimulation, 2015, presented in Singapore

Accelerated Theta Burst

- 47 TRD patients, 37% response rate
- 20 iTBS sessions spread over 4 days
- 1620 pulses per session in 54 triplet bursts with train duration of 2 seconds and an intertrain interval of 8 seconds





R. Duprat et al. / Journal of Affective Disorders 200 (2016) 6–14

Williams Study

- **7 Heavily Treatment Resistant Patients**
- **iTBS, 5 sessions/day, three days, stimuli**
- **Open label**
- **5 remitters**
- **Unfortunate quick relapse several weeks later**

High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression
Nolan R Williams, Keith D Sudheimer, Brandon S Bentzley, Jaspreet Pannu, Katy H Stimpson ...
Brain, awx379, https://doi.org/10.1093/brain/awx379
Published: 05 February 2018

Dosing pattern conclusions - soft

- **There is nothing sacred about one treatment session per weekday.**
- **It appears likely that there is a total dose (stimuli) effect, and that novel delivery patterns are possible**
  - May fit better with the logistics of patients and clinics
- **The minimum off time, and max per day, have not been fully established.**

Does rTMS Work in the Treatment of Depression ?

- **Yes**
- **But we can likely make it work better by**
  - Understanding durability and repeated doses for maintaining remission

But Depression Often Recurs

Table 1
Rate of acute remission, likelihood of completing 12-months without relapse, and probability of sustained benefit at each level of STAR*D [19].

	Acute remission rate	Probability of remaining well for 12 months after acute remission	Probability of sustained benefit
Level 1	36.80%	69.90%	25.72%
Level 2	30.60%	44.70%	13.68%
Level 3	13.70%	35.40%	4.85%
Level 4	13.00%	28.90%	3.76%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Brain Stimulation ■■ (2016) ■■–■■

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journal homepage: www.brainstimjrnl.com

ELSEVIER

Acute Continuation and Maintenance Treatment of Major Depressive Episodes with Transcranial Magnetic Stimulation

Harold Sackeim, PhD

Relapse Prevention Study

- **6 Clinical enrolling sites in US**
- **Neuronetics Sponsored**
- **Active open 6 weeks treatment, medication free**
  - 67 enrolled, 49 later randomized after acute response – **73% acute response rate**
- **½ were treated one session per month, the other ½ just monitored**
- **All retreated if they begin to relapse**

Once Monthly rTMS, medication free, delayed relapse time
Shortened number of sessions needed for re-remission

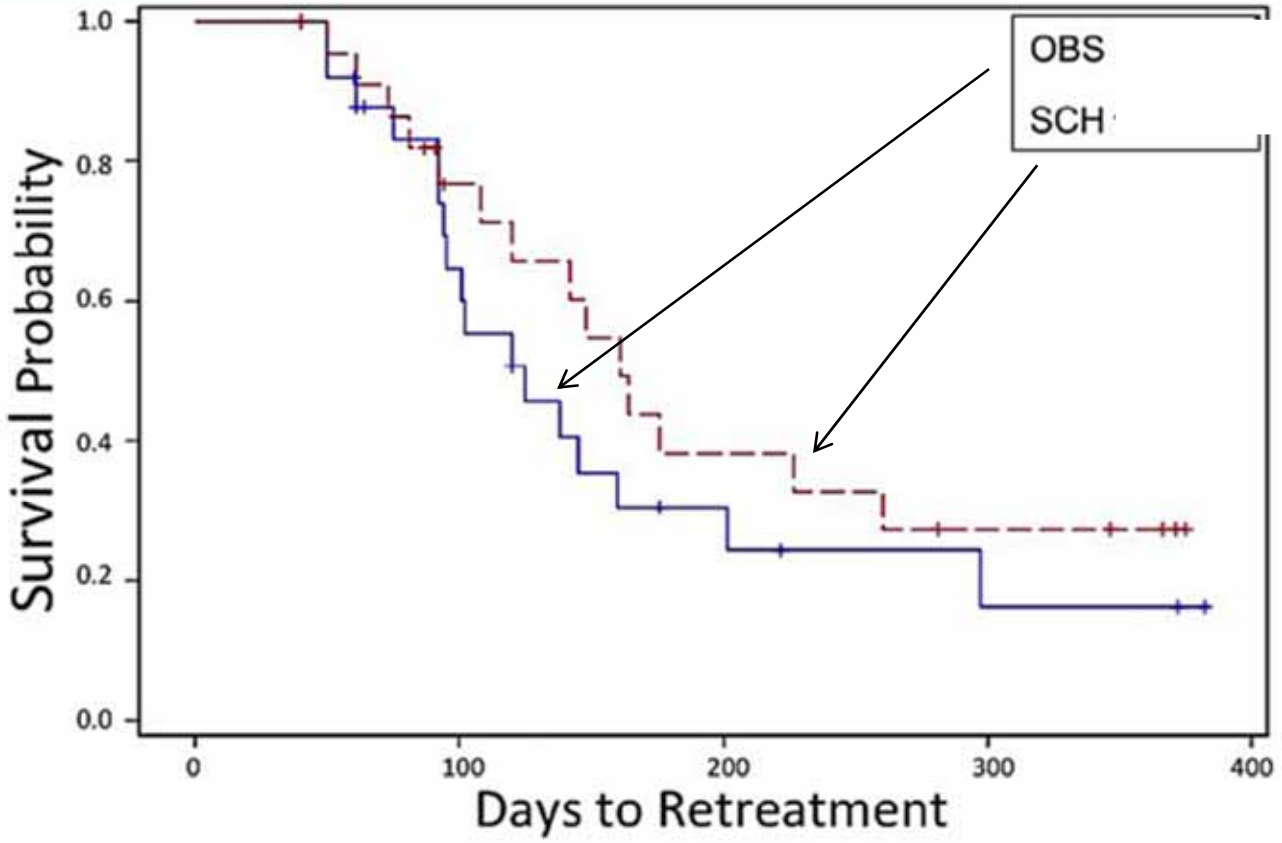


Figure 2. Survival curves for time to first retreatment. Kaplan–Meier survival curves for time to first retreatment. Log-rank $\chi^2 = 1.01$, df = 1, $p > 0.1$. Key: OBS, observation-only group; SCH, scheduled TMS group. + indicates participant drop outs.

Philips et al, Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation DOI: (10.1016/j.brs.2015.11.007)

Relapse Prevention Summary

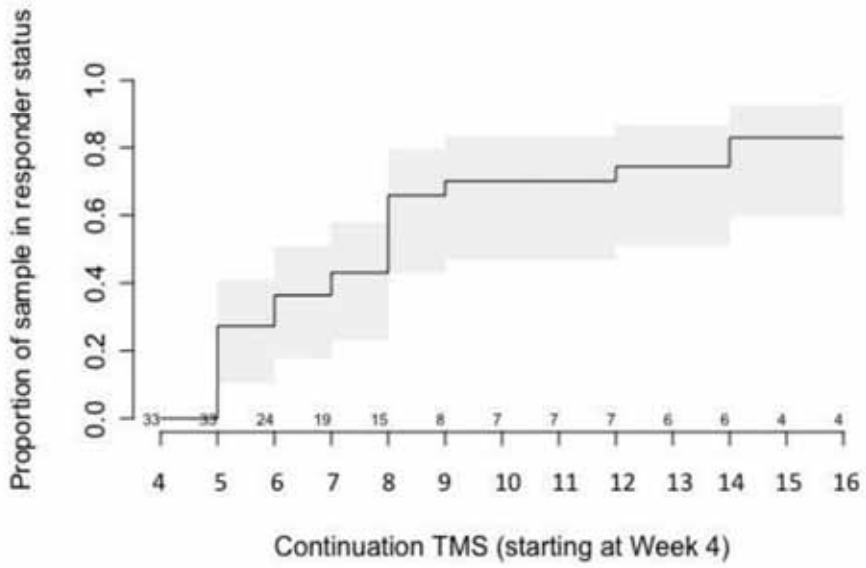
- It is possible to maintain TRD patients off antidepressants using periodic TMS
- Once a TMS responder, always a TMS responder – high rates of re-response (78% reresponse)
- The one/month schedule may have been underdosed

When to give up and try the next therapy?

- **Early TMS trials were 2,3,4, then 6 weeks in duration.**
- **Gradual improvement in remission rates with longer duration (15-30-45%)**
- **What to do with a TRD patient at the end of 6 weeks and no response?**
  - Try a different form of TMS?
  - Non – randomized, then post hoc ergo proctor hoc
  - What about just more of the same?

61% of Unmedicated Treatment Resistant Depression Patients Who Did Not Respond to Acute TMS Treatment (6 weeks) Responded After Four Weeks of Twice Weekly Blinded Deep TMS in the Brainsway Pivotal Trial

Figure 1. Cumulative incidence (1- survival) plot among non-responders to acute-phase dTMS. The event is ≥50% improvement from baseline (pre-treatment) HDRS-21 score (first occurrence of) among individuals remaining in the study at a given time point. The small numbers above the x axis indicate numbers 'at risk' for the event (i.e., those who have not achieved response and remained in the study at a particular time point). Gray area indicates 95% confidence interval.



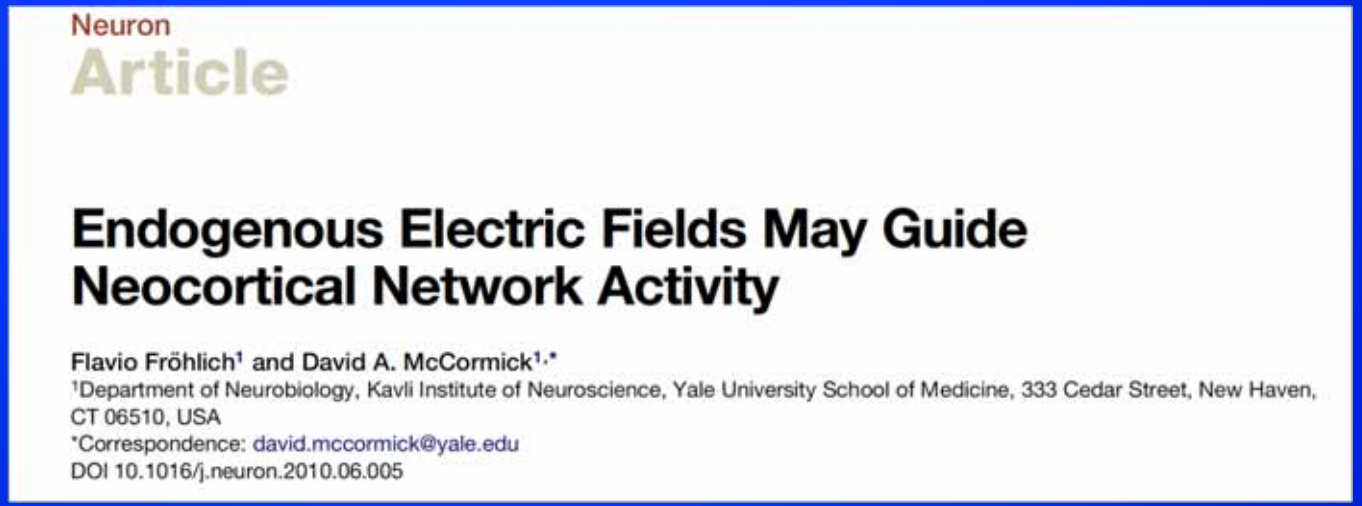
Yip, Roth, Zangen, Carpenter, George
Brain Stimulation 2018

Implications if true

- With herculean amounts of prefrontal TMS on a daily or twice weekly basis (10 weeks), we may be able to get remission rates approaching ECT (60-70% in TRD patients), with fewer side effects, and longer durability.
- But at what cost? Chair time, personnel, travel time for patient
- We thus need to understand what we are doing neurobiologically with each ‘trip to the gym’, and make TMS more efficient, less expensive

The importance of rhythm

- **Ephaptic coupling, small synchronized stimulation can have large harmonic effects (Frohlich, McCormick, 2011)**
- **Neosync – a form of weak synchronized stimulation**



Neuron

Article

Endogenous Electric Fields May Guide Neocortical Network Activity

Flavio Fröhlich[1] and David A. McCormick[1,*]
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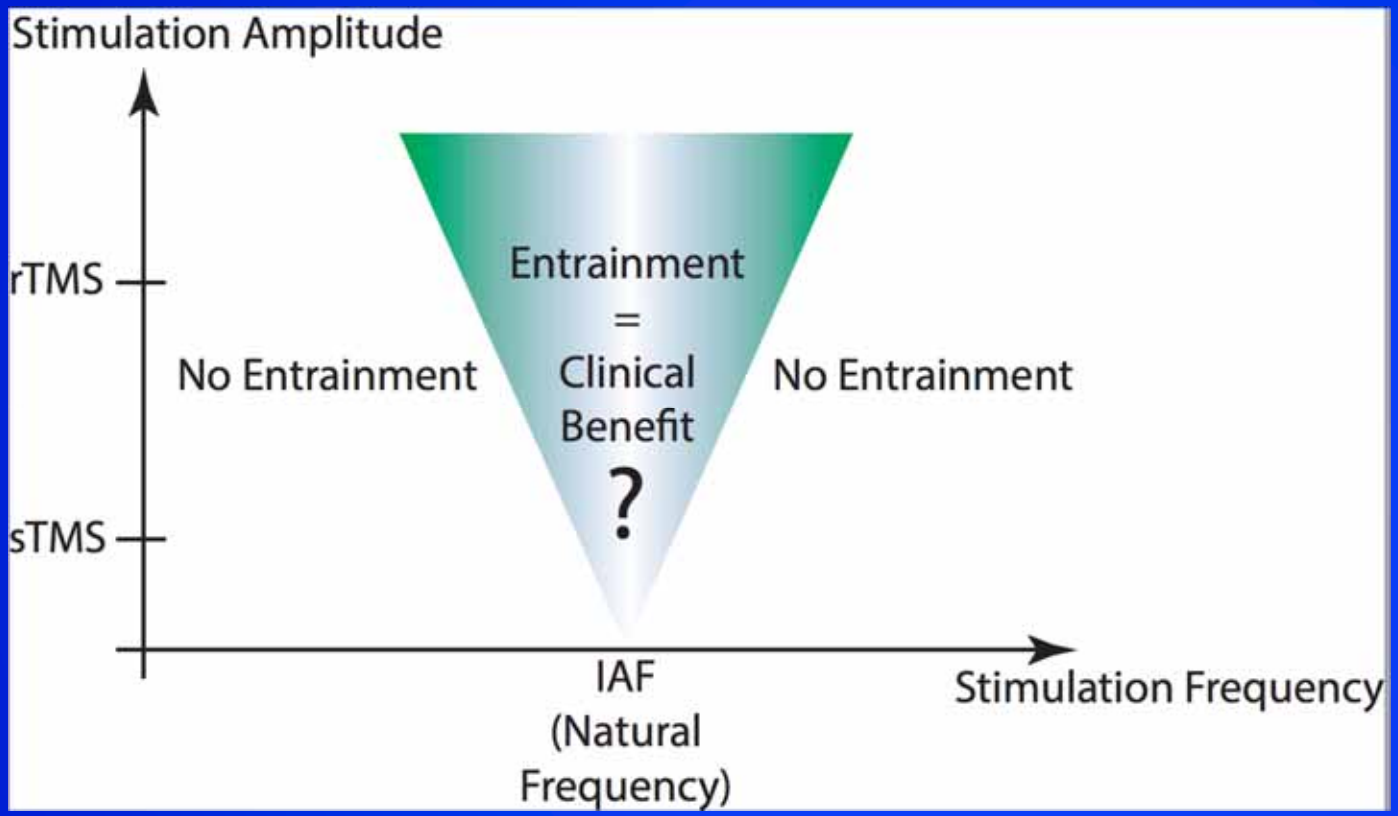
DOI 10.1016/j.neuron.2010.06.005

Arnold's tongue



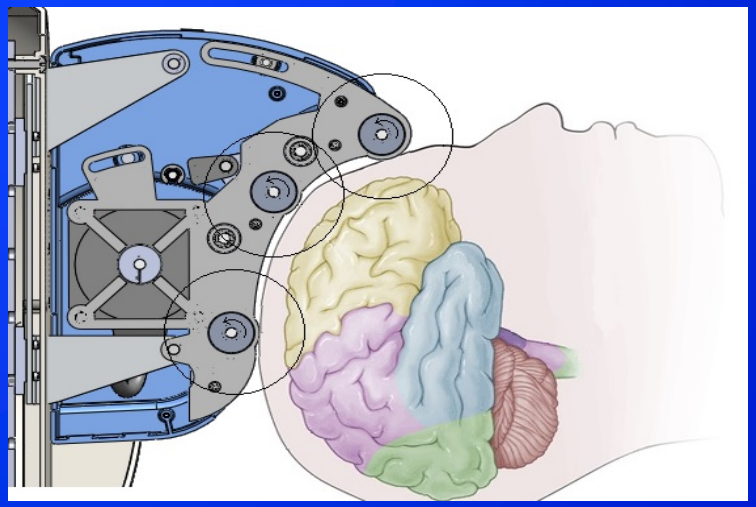
Like swinging a child on a swing, precisely timed weak pulses can have big effects.

Possibility of an at home device..

Frohlich, Brain Stimulation, 2015

NEST Device Specifications

	NeoSync® sTMS
Magnetic Field Generation	3 Rotating permanent magnets
MOA	Synchronized TMS = sTMS
Magnetic Field Strength (measured at the stimulation surface)	0.38 Tesla (1% Motor Threshold, due to low field gradient)
Target	Broad area
Pulse Frequency	Set to patient's individual alpha frequency based on EEG (8 - 13Hz)
Waveform	Continuous sine wave
Theoretical Mechanism of Action	Broad sub-threshold low energy sinusoidal waveform magnetic stimulation matched to the subjects intrinsic alpha frequency to entrain cortical neurons



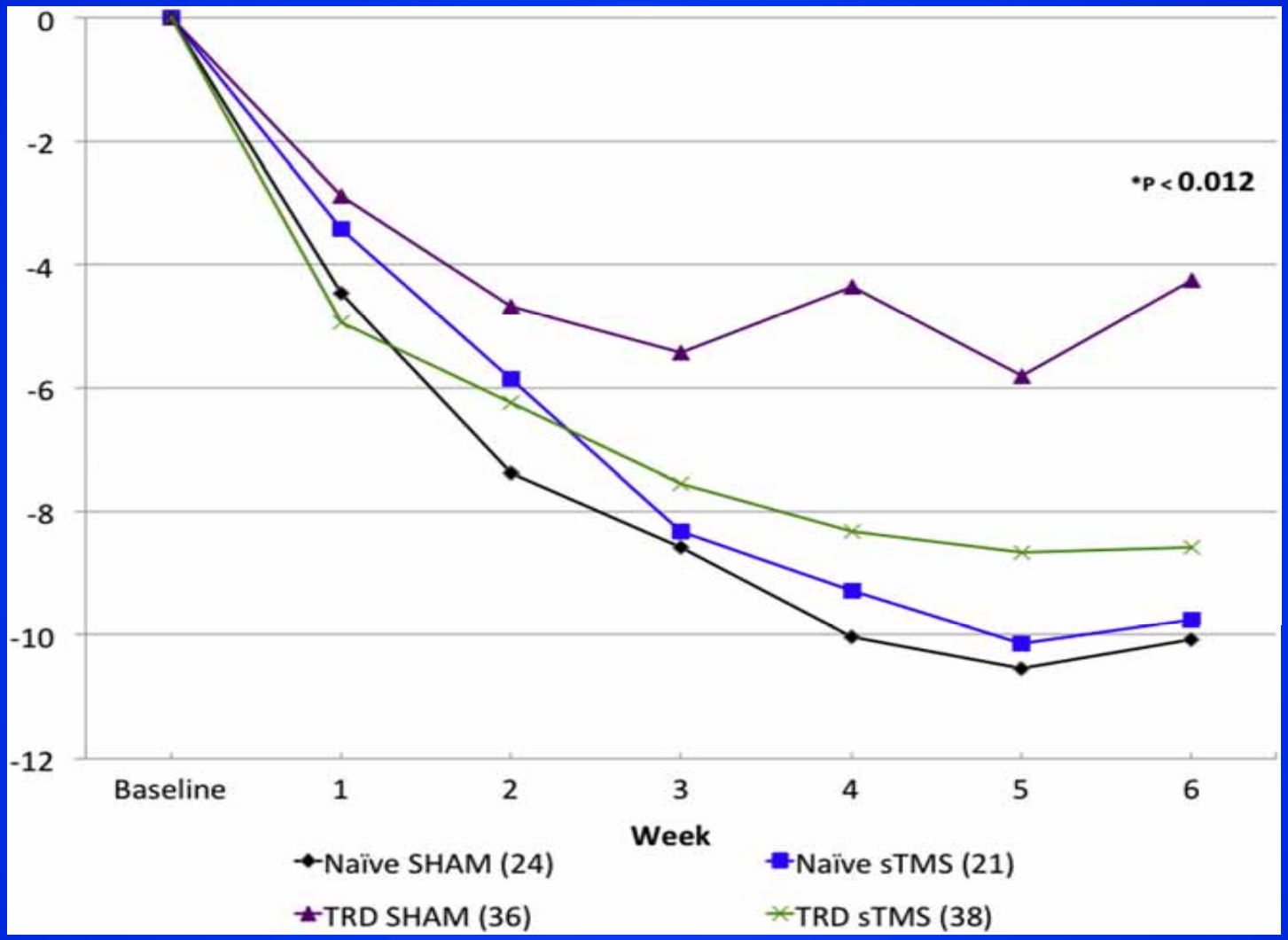
Not FDA Approved/Cleared
Leuchter, Brain Stimulation 2015

Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression

Andrew F. Leuchter, Ian A. Cook, David Feifel, John W. Goethe, Mustafa Husain, Linda L. Carpenter, Michael E. Thase, Andrew D. Krystal, Noah S. Philip, Mahendra T. Bhati, William J. Burke, Robert H. Howland, Yvette I. Sheline, Scott T. Aaronson, Dan V. Iosifescu, John P. O'Reardon, William S. Gilmer, Rakesh Jain, Karl S. Burgoyne, Bill Phillips, Paul J. Manberg, Joseph Massaro, Aimee M. Hunter, Sarah H. Lisanby, Mark S. George

Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation
Volume 8, Issue 4, Pages 787-794 (July 2015)
DOI: 10.1016/j.brs.2015.05.005

Figure 5

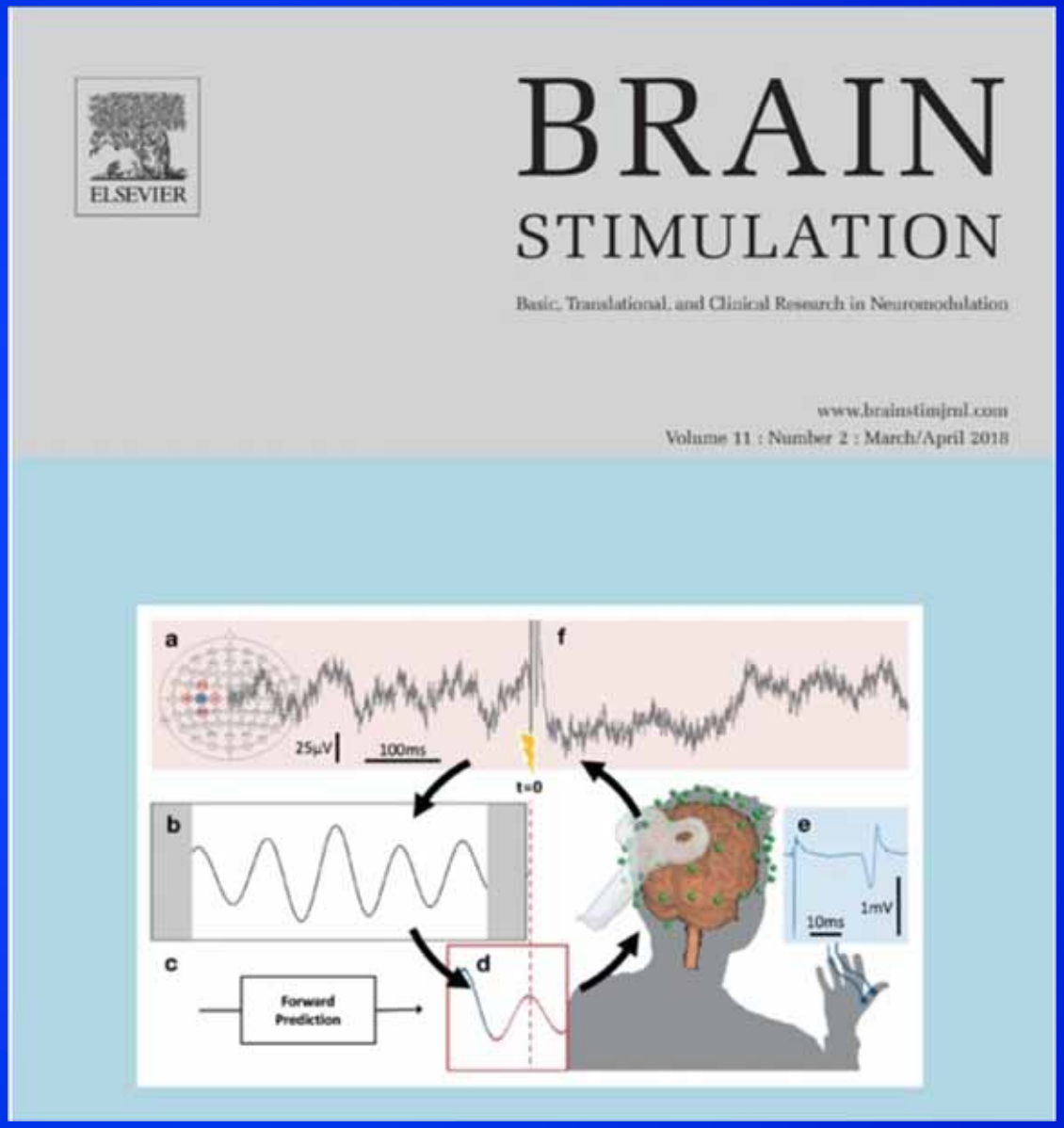


Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 2015 8, 787-794DOI: (10.1016/j.brs.2015.05.005)

Summary, Synchronized Low-Field TMS

- FDA did not grant approval, requires another study – to launch later this year
- 12 subjects were not stimulated at their alpha range – not included. No one got better – suggesting synchronization matters
- Confirmatory pivotal trial now underway
- Potential for home use with further study.

Phase Synchronized TMS Increases MEP amplitude



Does Phase Synchronization of even a single TMS pulse matter in terms of the secondary effects?

- **Possibly, perhaps probably..**
- **Interleaved TMS/fMRI/EEG with realtime analysis and closed loop feedback..**
- **Stay tuned..**

Drs. Truman Brown, Xingbao Li and subject MSG

Conclusions

- **We can likely improve TMS efficiency and efficacy by changing dose patterns, understanding rhythm, combining TMS with behavior!!**
- **We need an international community (basic and clinical and technical) in this area to understand, disrupt, transform and treat..**

ELSEVIER

3RD INTERNATIONAL
BRAIN STIMULATION
CONFERENCE

Vancouver
CANADA
24 - 27 February
2019

Should be another great meeting.
See you there!!

Thanks, Questions