Transcranial Magnetic Stimulation: a novel treatment for depression and other neuropsychiatric disorders

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Disclosures

- CEO of Contemporary TMS
- Past President Clinical TMS Society
- Commercial relationship
  - Neuronetics Corporation
- Speaker Bureau
  - Sunovian Pharamaceuticals
  - Otsuka Corporation

CME Study Goals

- What is Depression?
- TMS and other forms of Neuromodulation
- TMS applications in Psychiatry and Neurology

What is Depression?

Major Depression

- Affects 22 million US residents and 380 million worldwide[1] (17.1% lifetime risk)[2]

The National Institute of Mental Health **(NIMH) (e**stimates that 6.7% of American adults have had depressive illness during the last 12 months, and 30.4% of these cases (2% of the whole adult population) have severe symptoms.

While the NIMH says women are 70% more likely to develop MDD during their lifetime, an article published in *JAMA Psychiatry* (August 2013 issue) showed that depression affects 30.6% of men and 33.3% of women

- Second most disabling condition in developed countries and 4th most disabling worldwide[3]

- Increased morbidity of comorbid general medical conditions[1] and increased rate of suicide as percent of total mortality[4]

1. Greden JF. *J Clin Psychiatry.* 2001;62(suppl 22):5-9. 2. Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51:8-19. 3. Murray CJL, Lopez AD, eds. *The Global Burden of Disease.* Cambridge, Mass: Harvard University Press; 1996. 4. Fawcett J. *Int Clin Psychopharmacol.* 1993;8:217-220. 5. Thase ME, Rush AJ. In: Bloom FE, Kupfer DF, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press, Ltd.; 1995:1082-1097.

Definition of Depression

Mourning and Melancholia

Sigmund Freud *(1917)*

Mourning or sadness is recognized as a healthy and normal process that is necessary for the recovery of the loss.

Melancholia, which is an abnormal pathology and a dangerous illness due to its suicidal tendency with additional features that are absent in mourning.

Core symptoms

1. **ANHEDONIA and AMOTIVATION**

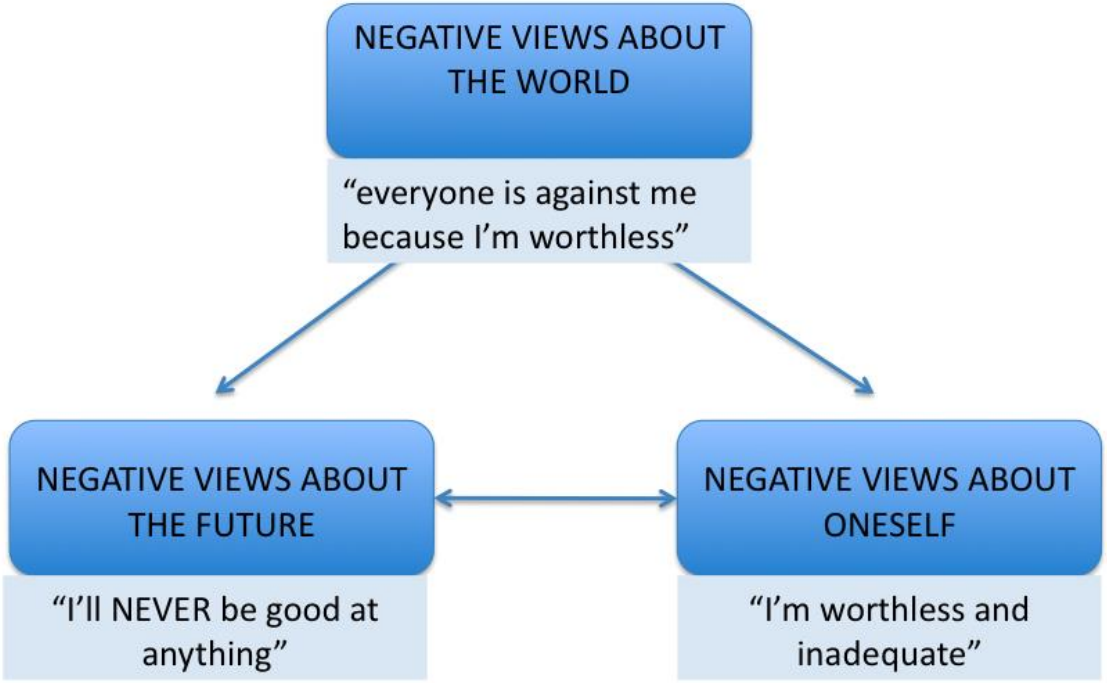
2. **NEGATIVE RUMINATIONS**

Cognitive Model of Depression

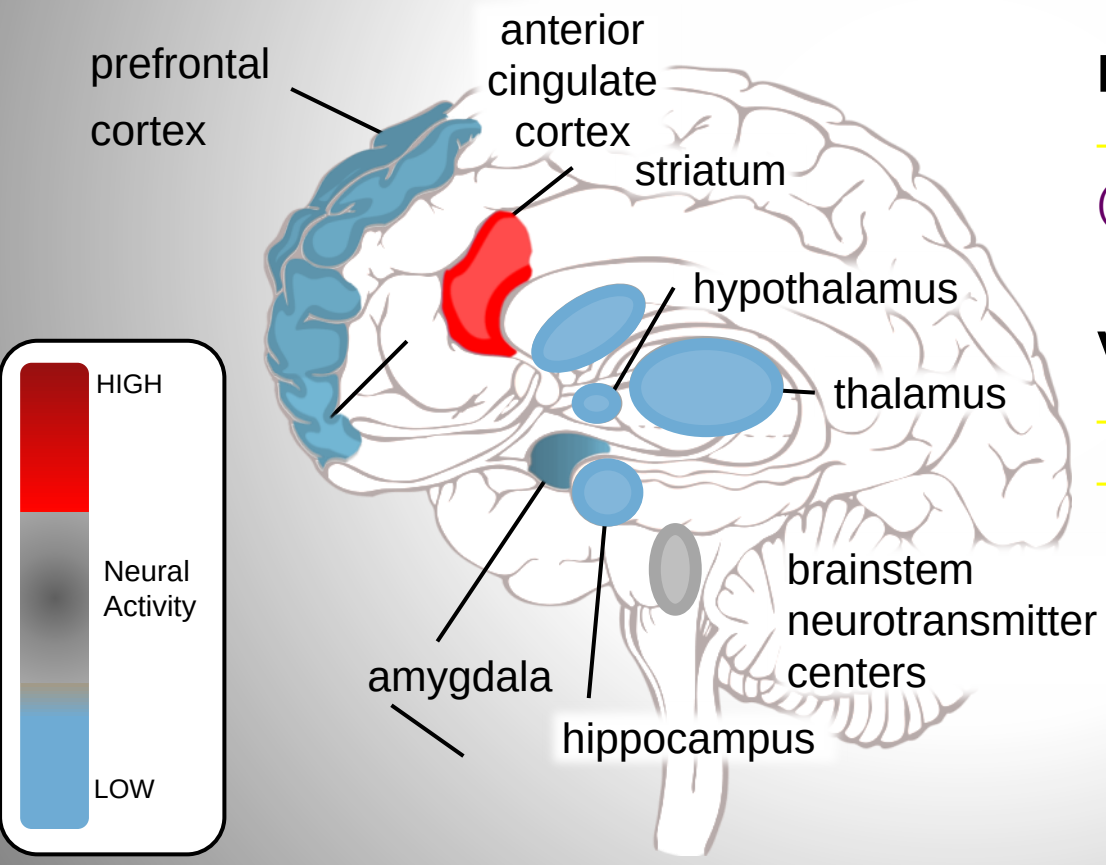
- **Aaron Beck's cognitive model of depression 1967**
  - Early life stress + genetic vulnerability leads to…
  - Negative information processing biases in attention, memory, and cognition that results in…
  - Cognitive Distortions associated with MDD described by Beck

COGNITIVE TRIAD & ERRORS IN LOGIC

(Beck, 1967)



Neuroimaging hypothesis of depression



Left DLPFC Hypoactivity

- Inability to recognize positive cues
- Anhedonia (negative cost benefit analysis)
- Negative expectations/hopelessness
- Poor Concentration

Right DLPFC Hyperactivity

- Hyper-focus on negative experiences

(due to input from the Hippocampus

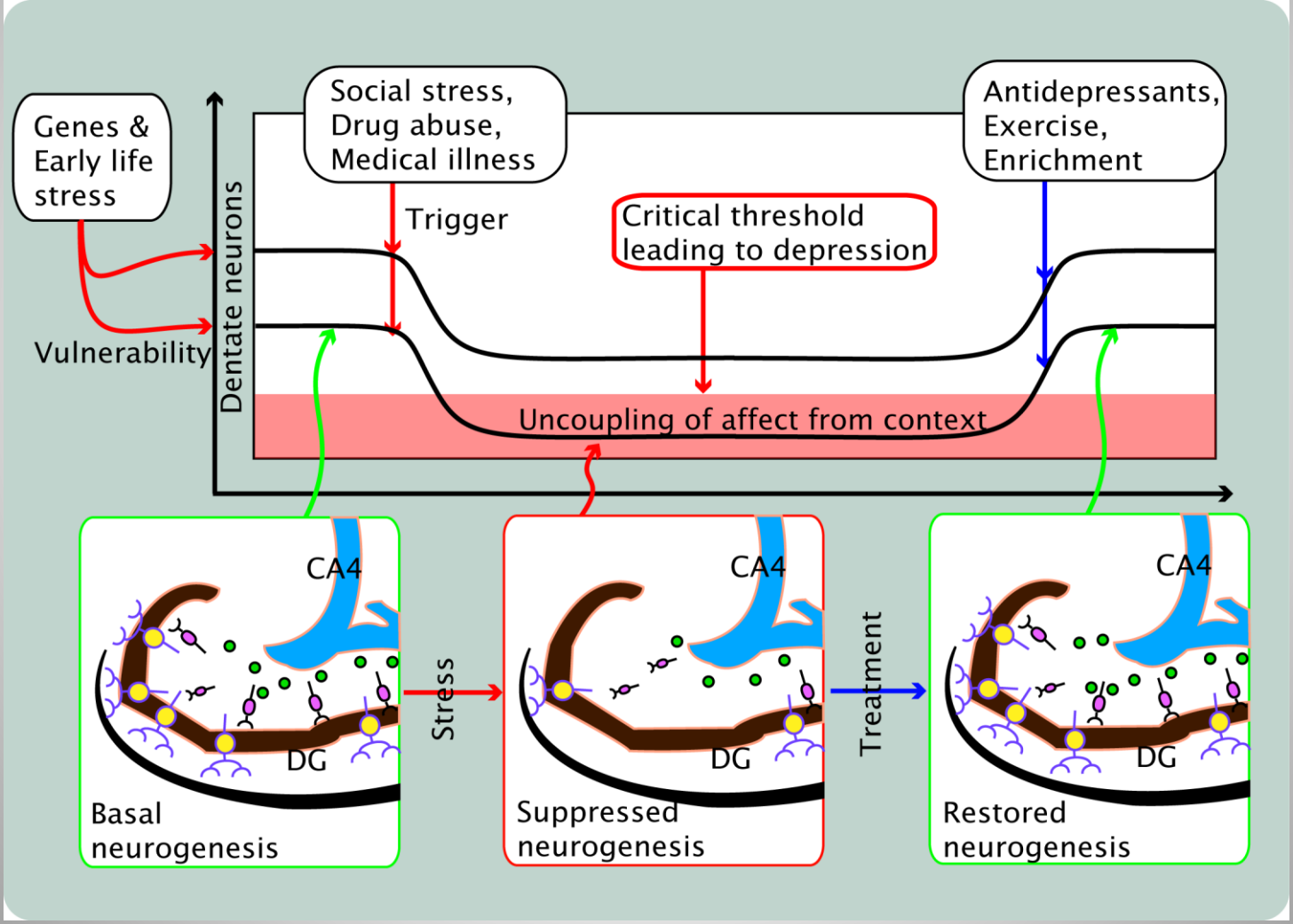
Ventro-mPFC Hyperactivity

- Anxious Ruminations
- Anhedonia (reduced sense of pleasure)
- Guilt, worthlessness

(Drevets et al 1998' Keedwell et al 2005, Philips et al 2003, Mayberg et al 2003, Grimm 2008, Keedwell 2005)

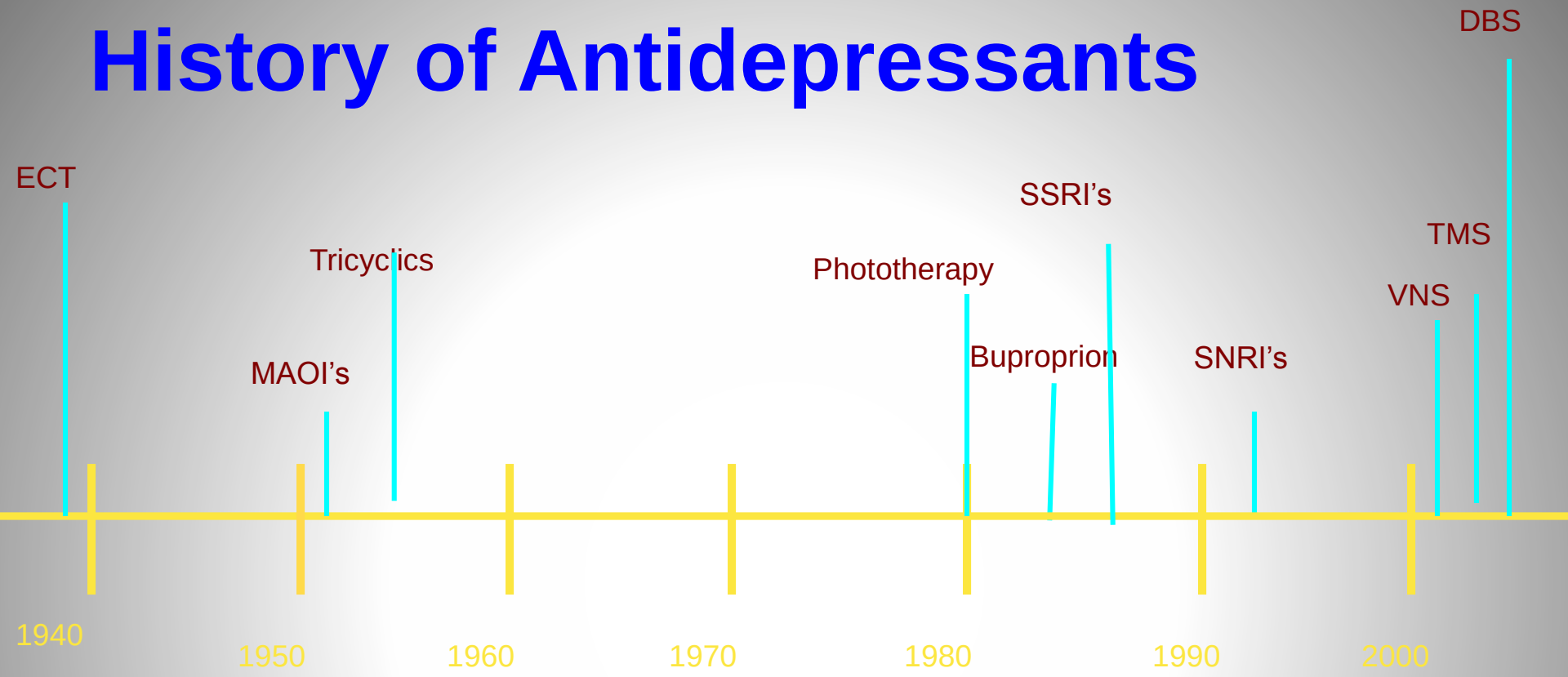
Neurogenesis Hypothesis

Perera 2008



Treating Depression

History of Antidepressants



- **1. Behavioral Interventions**
  - **Psychotherapy**
  - **Exercise**
  - **Cognitive stimulation**
- **2. Pharmacology**
  - **Antidepressants**
  - **Mood stabilizers**
  - **Atypical antipsychotics**
  - **Other: Stimulants, Thyroid, Glutamate antagonists etc.**
- **3. Neuromodulation**
  - **ECT**
  - **VNS**
  - **Other: DBS, TMS etc.**

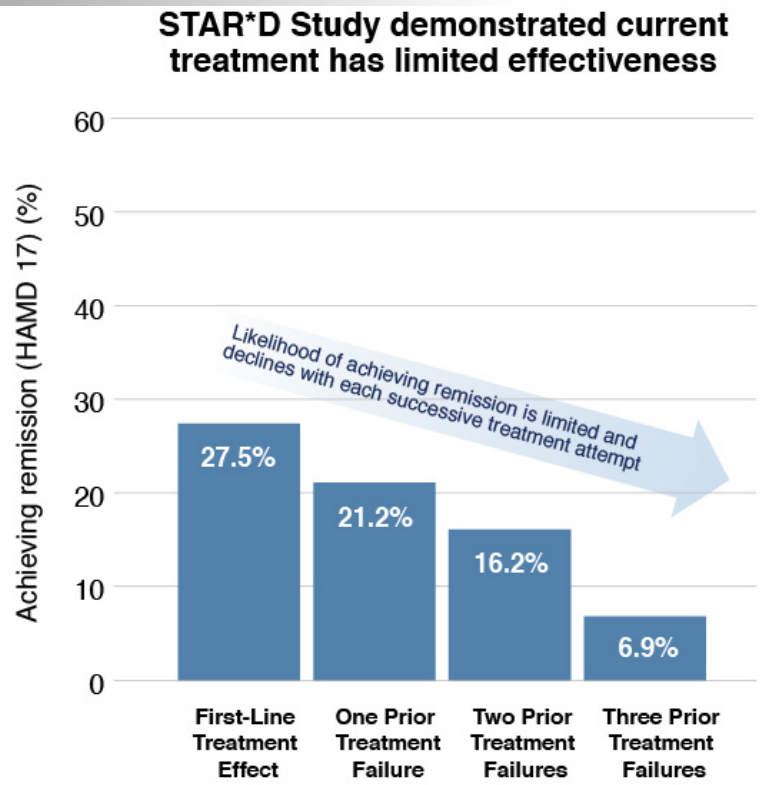
Precision of Antidepressants

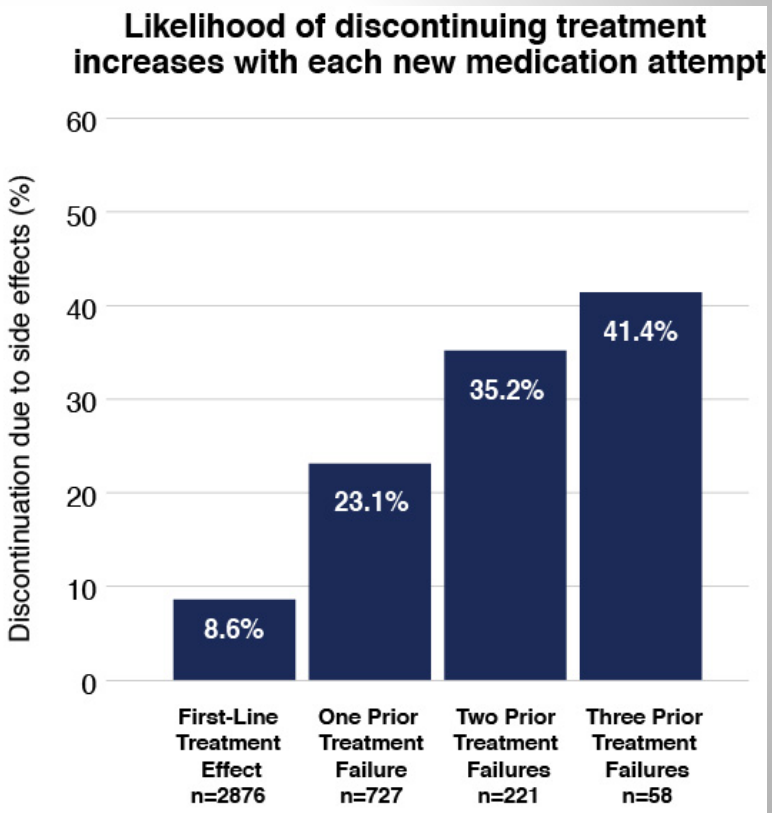
- **Nonspecific treatments**
  - Therapy (non-invasive)
  - Medications (outpatient therapy)
  - ECT (involves general anesthesia and paralysis)

- **Specific/rational/ treatments**
  - TMS (outpatient treatment)
  - VNS (involves surgery)
  - DBS (involves surgery and is experimental)

Medications

Star D Data



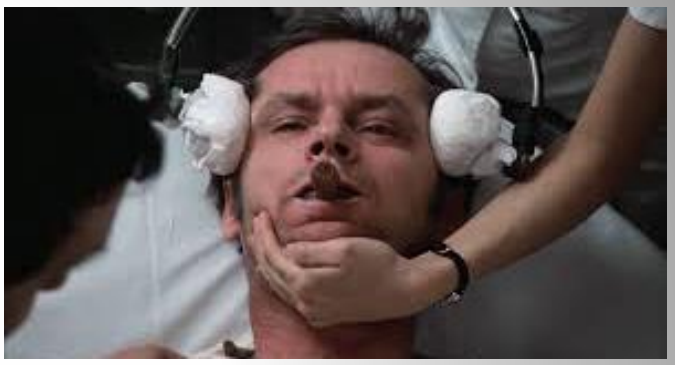


Neuromodulation

- ECT
- DCT
- CES
- DBS
- VNS
- MST
- TMS

Electro Convulsive Therapy

Most effective Antidepressant with response rates of 50-83% in Treatment Resistant Depression



But….

Highly invasive, requires general anesthesia and paralysis and involves grandmal seizures

Causes dense anterograde amnesia that often resolves in 6 weeks

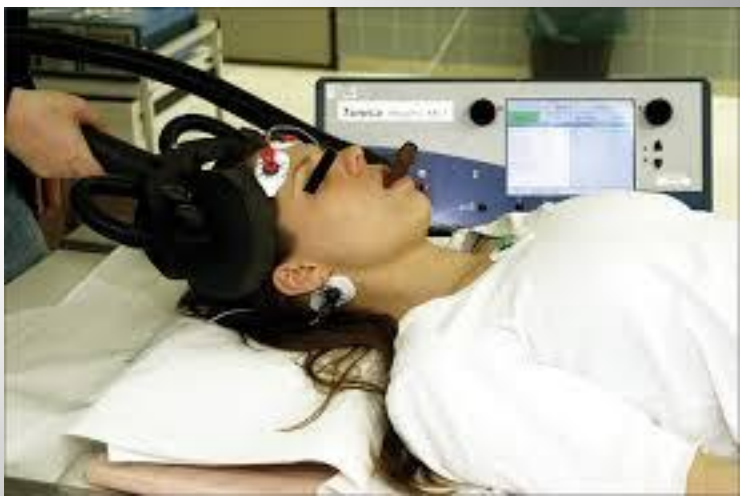
Causes severe, permanent, retrograde amnesia in 1/200 patients

High relapse rates (89%) over 6-months in the OPT ECT study

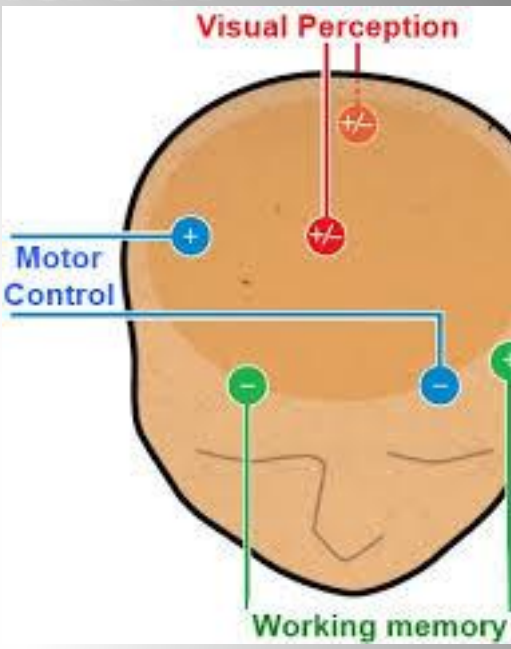
Magnetic Seizure Therapy

- Involves seizures caused by magnetic energy
- Less side effects than ECT

- But….
- Invasive, requires general anesthesia and paralysis
- Causes memory problems
- Less effective than ECT
- Experimental, not FDA approved



Direct Current Stimulation



Electrodes placed on scalp

Non-invasive

No side effects

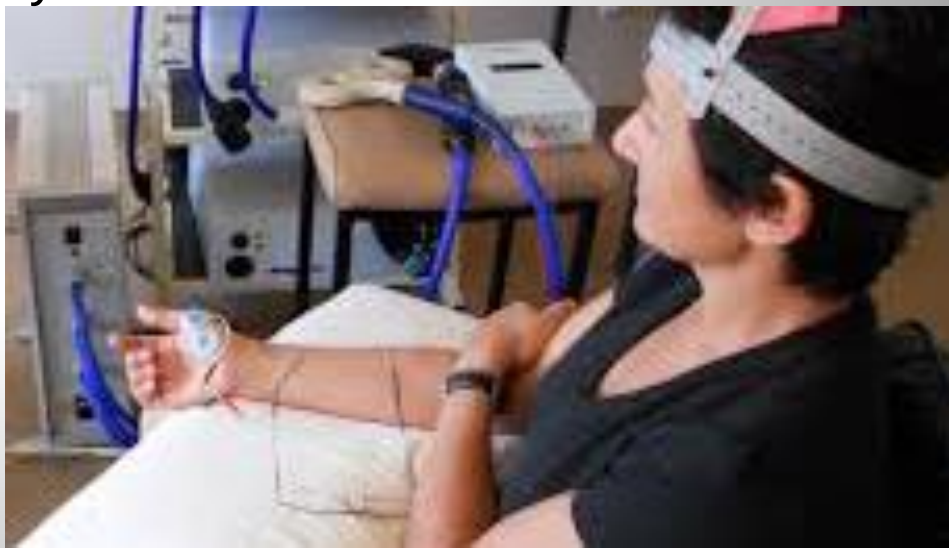
But….

Non-specific

More effective for treating working memory

Less effective in depression

Experimental, not FDA approved



Cranial Electrotherapy

Alpha Stim

Mild current applied to scalp

Safe, non-invasive

Also used for pain, anxiety, and insomnia

FDA approved for depression

But….

Fisher Wallace

Approval was gained because it was considered form of ECT

There are no multicenter trials proving efficacy

Non-specific

Unknown mechanism since electrical stimulus too weak to reach brain tissue

Deep Brain Stimulation

Most precise treatment for depression, electrodes neurosurgically placed in mPFC under MRI guidance

Established treatment for Parkinson's

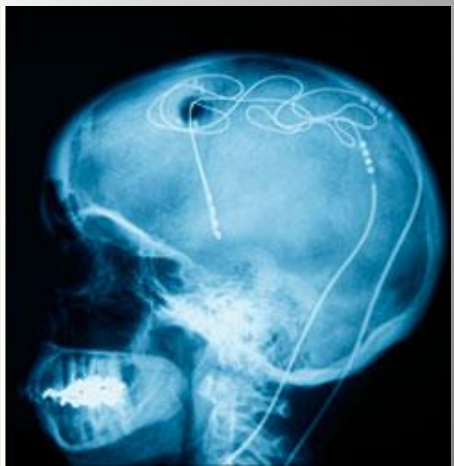
Rapid initial response in 50% of patients with Treatment Resistant Depression

But…

Highly invasive, requires neurosurgery that has ~1% mortality

Requires constant stimulation to maintain efficacy, and batteries need to be replaced in 5yrs

Experimental, not FDA approved



Vagus Nerve Stimulation

Involve targeted stimulation of vagus nerve that increases norepinephrine

FDA approved for depression

Used to treat epilepsy

But…

Invasive, surgical implantation of vagus nerve stimulator

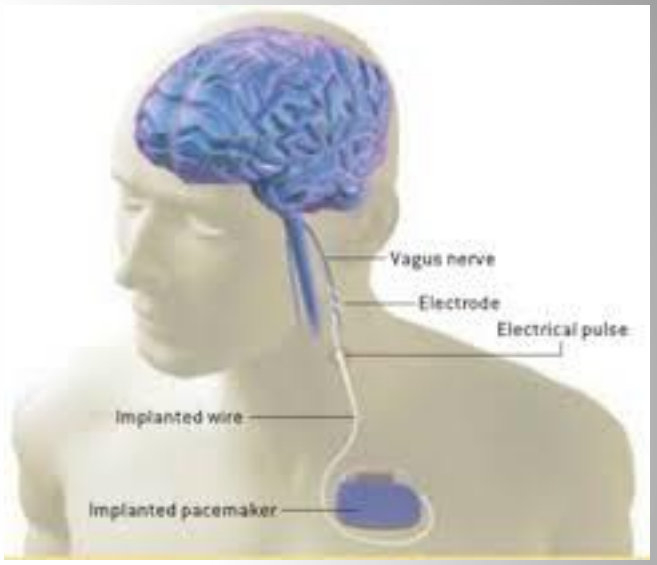
Requires constant stimulation

Batteries need replacing after 5yrs

Low response rate (~30%)

Long time to response (~6-12 weeks)

Poor Insurance coverage



Transcranial Magnetic Stimulation

a Paradigm shift in Psychiatry

Scientifically based, precisely targets depression circuits

Non invasive, outpatient treatment

Minimal side effects

Possibly, safest antidepressant

Rapidly acting (only ECT works faster)

High efficacy (only ECT and MAOIs have higher efficacy)

Durable benefits (possibly lowest relapse rate among all antidepressants)

Excellent Insurance coverage, including Medicare

FDA Approved Coils

Neuronetics Coil

First FDA approved coil 2008 for unipolar depression in adults

Solid, ferromagnetically active material (i.e., the so-called ‘solid-core’ design).

Solid core coil design result in a more efficient transfer of electrical energy into a magnetic field, with a substantially reduced amount of energy dissipated as heat, and so can be operated without treatment interruption due to heat accumulation.

Standard depth of 1.5-2.5 cm.

Average treatment duration 37 minutes

Requires Disposable (Senstar)

Brainsway coil

FDA approved coil 2013

H1 Coil design that fits head and treats deeper regions but over a larger brain area

Standard depth of > 2.5 cm and hence called Deep TMS

Average treatment duration 20 minutes

Requires Disposable (PPU)

Being studied for several other indications including Bipolar Depression

Magstim and Magventure

FDA approved coil 2015

Air Coil design that requires cooling apparatus since it used more current

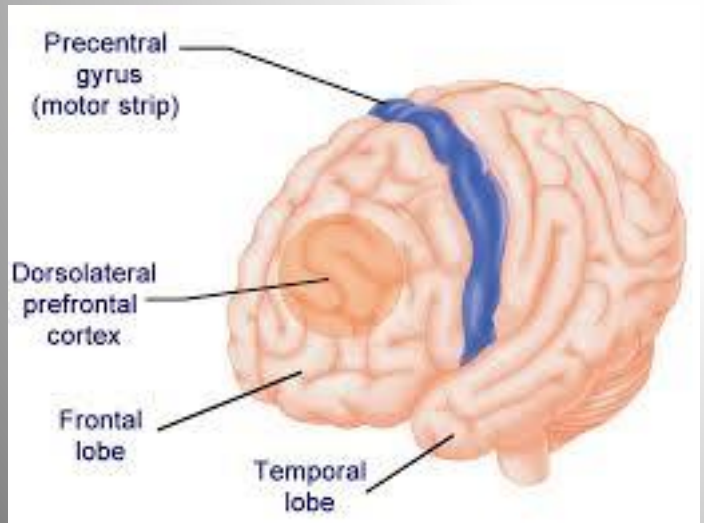
Has no disposable

No multi center randomized clinical trials using this device

Typical TMS Course

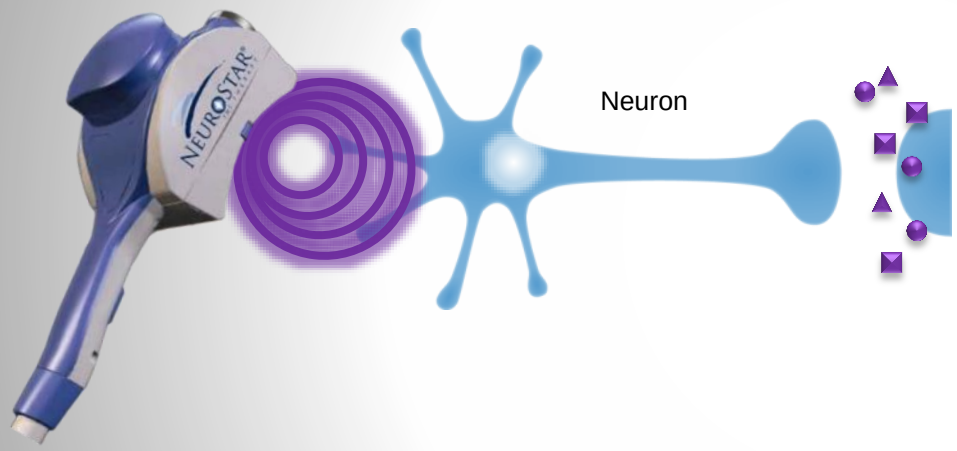
- Non-invasive
- No anesthesia or sedation
- Outpatient procedure
- 37-minute daily procedure (3000 pulses)
- 6-8 week treatment course
- Antidepressant medication monotherapy may be used for maintenance

Finding DLPFC and dose



Mechanism of action of TMS

TMS effects on Neurons



Neurons are “electrochemical cells” and respond to either electrical or chemical stimulation

Fast TMS

10-20Hz

Depolarizes Neurons

Activates Glutamate as well as serotonin, noreepinephrine, and dopamine

Causes Longterm-potentiation (LTP)

Activates hypoactive brain regions

Slow TMS

1Hz

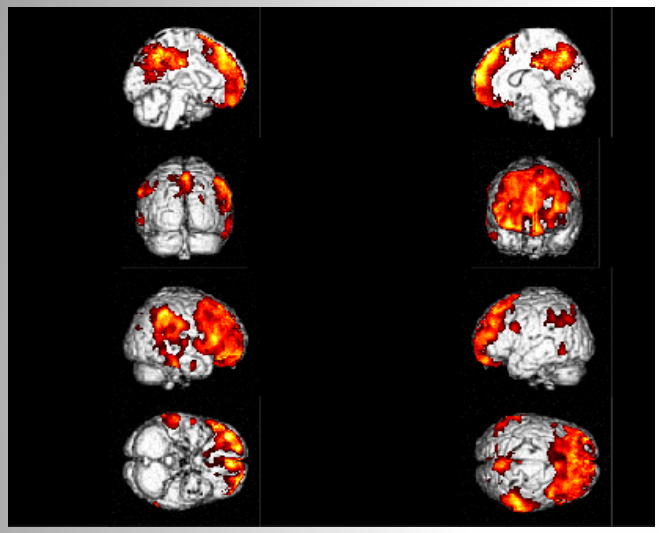
Hyperpolraizes neurons

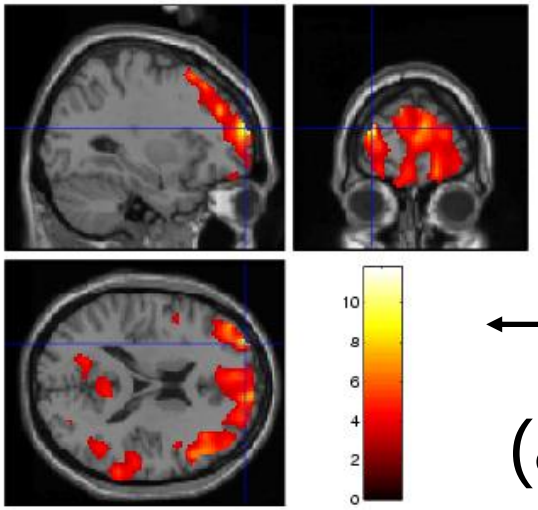
Activates GABA

Causes longterm Depression (LTD)

Suppresses hypeeractive brain regions

Why does TMS target the left DLPFC?

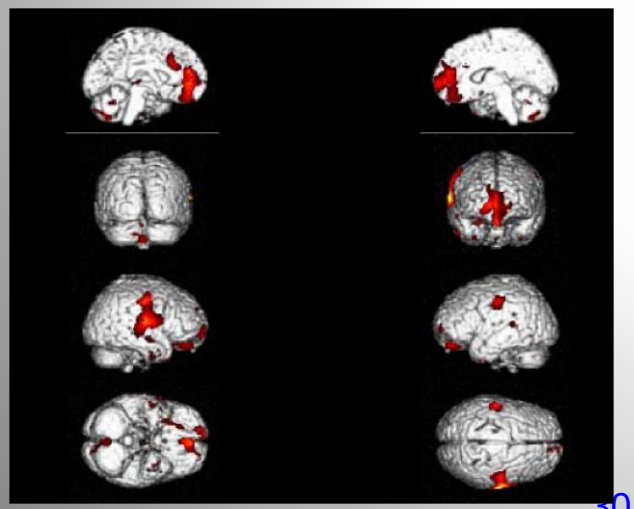




← ECT

(acute 20 min)

Nobler et al.



← Zoloft

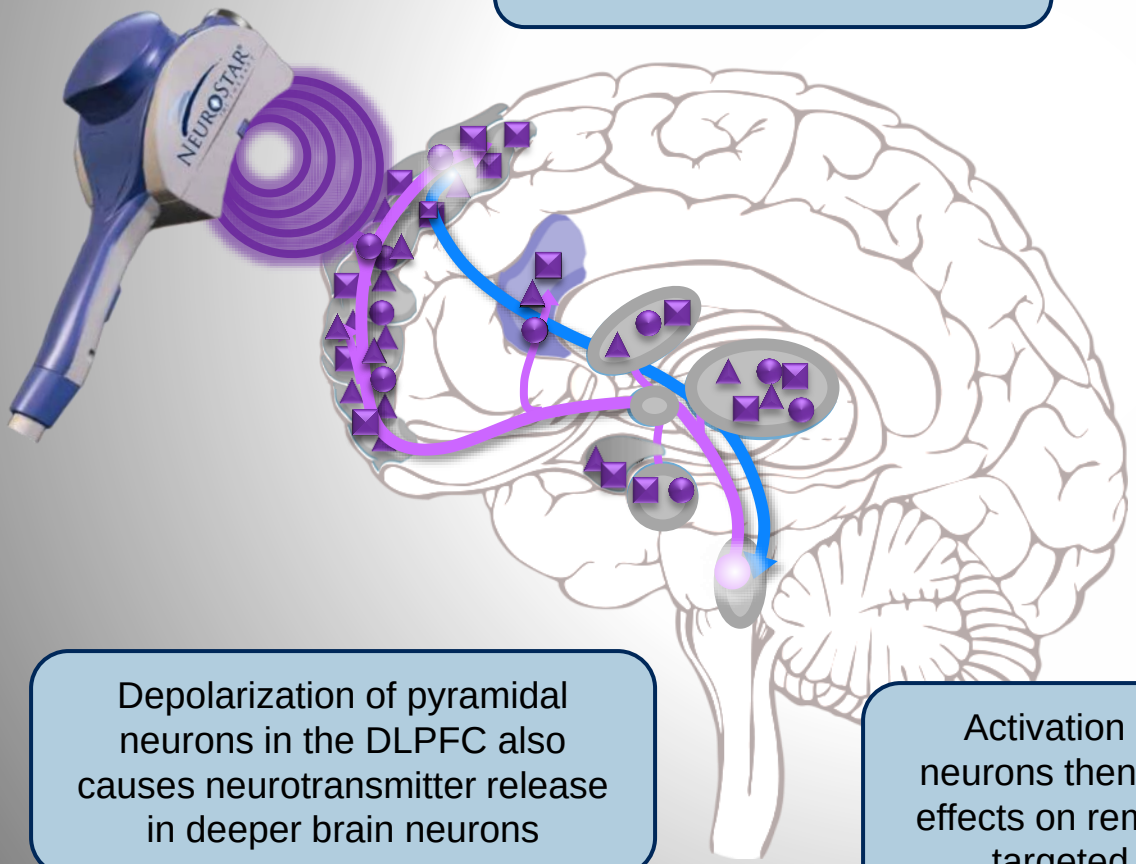
(8 wk)

Sackeim et al.

↑ TMS (2 wk) George et al. 1998

Consequence of DLPFC stimulation

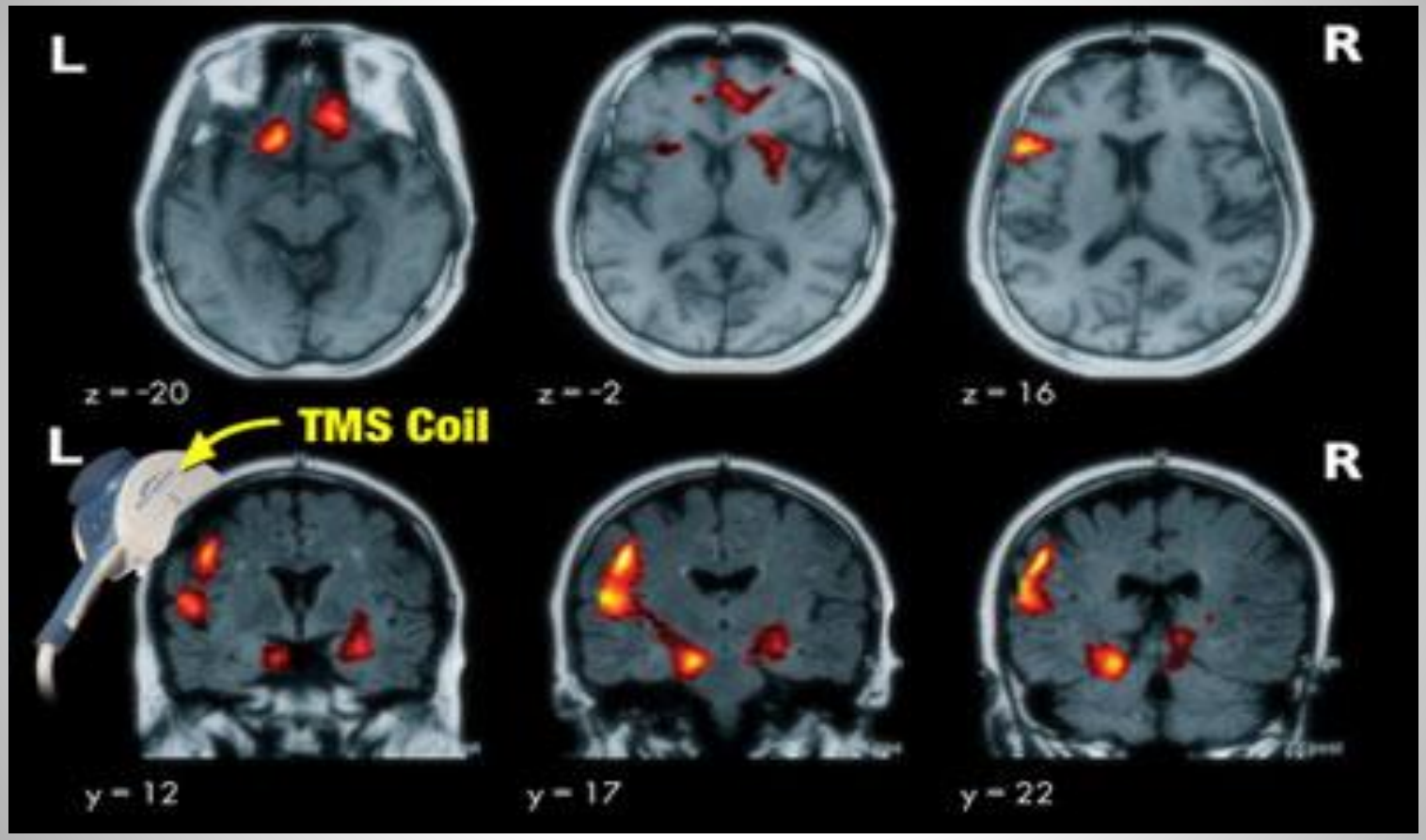
Depolarization of neurons in the DLPFC causes local neurotransmitter release



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

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

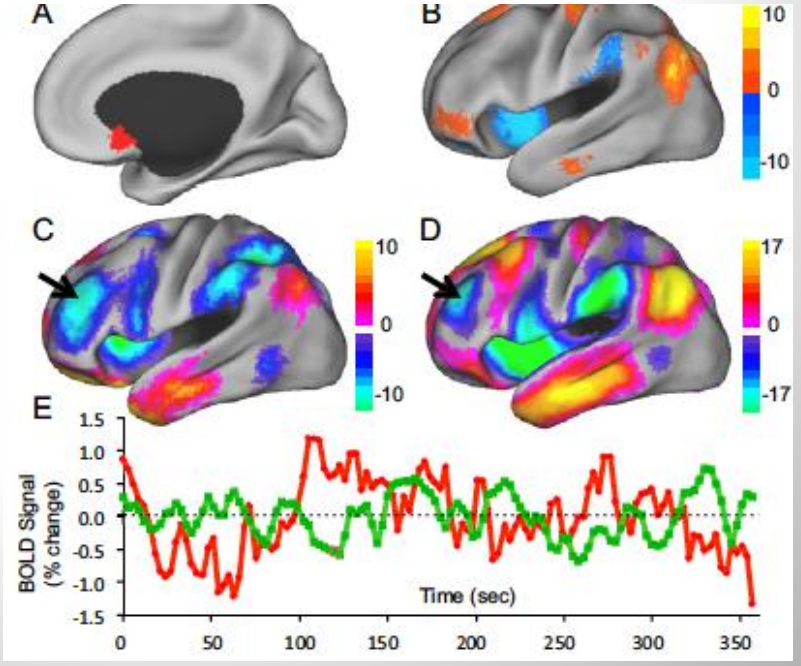
TMS treats deeper structures



- Depolarization of neurons in the DLPFC causes activation of deeper brain neurons then exerts secondary effects on remaining portions of targeted mood circuits

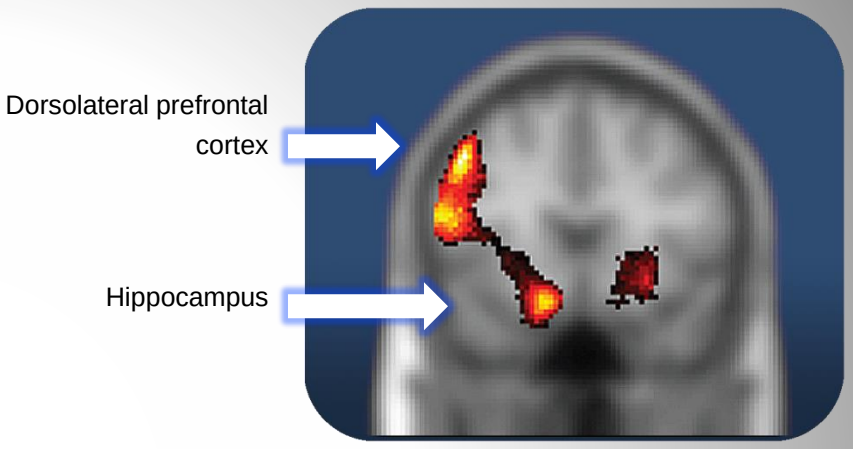
TMS stimulation of DLPFC suppresses mPFC

- More effective rTMS therapy was associated with greater anticorrelation between DLPFC (increased activity) and subgenual cingulate in mPFC (decreased activity) (Fox et al 2012)

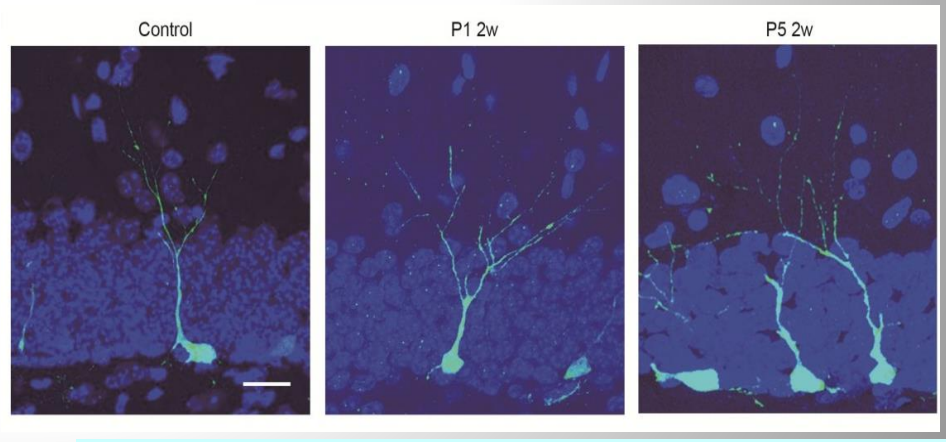


rTMS on DLPFC increases Hippocampal activity

Functional brain imaging shows that rTMS over prefrontal cortex (PFC) influences hippocampus activity in humans (Kimbrell et al 2002; Speer, Post et al 2000; Li, George et al 2004, Eldaief, Pascual-Leone et al, 2011)



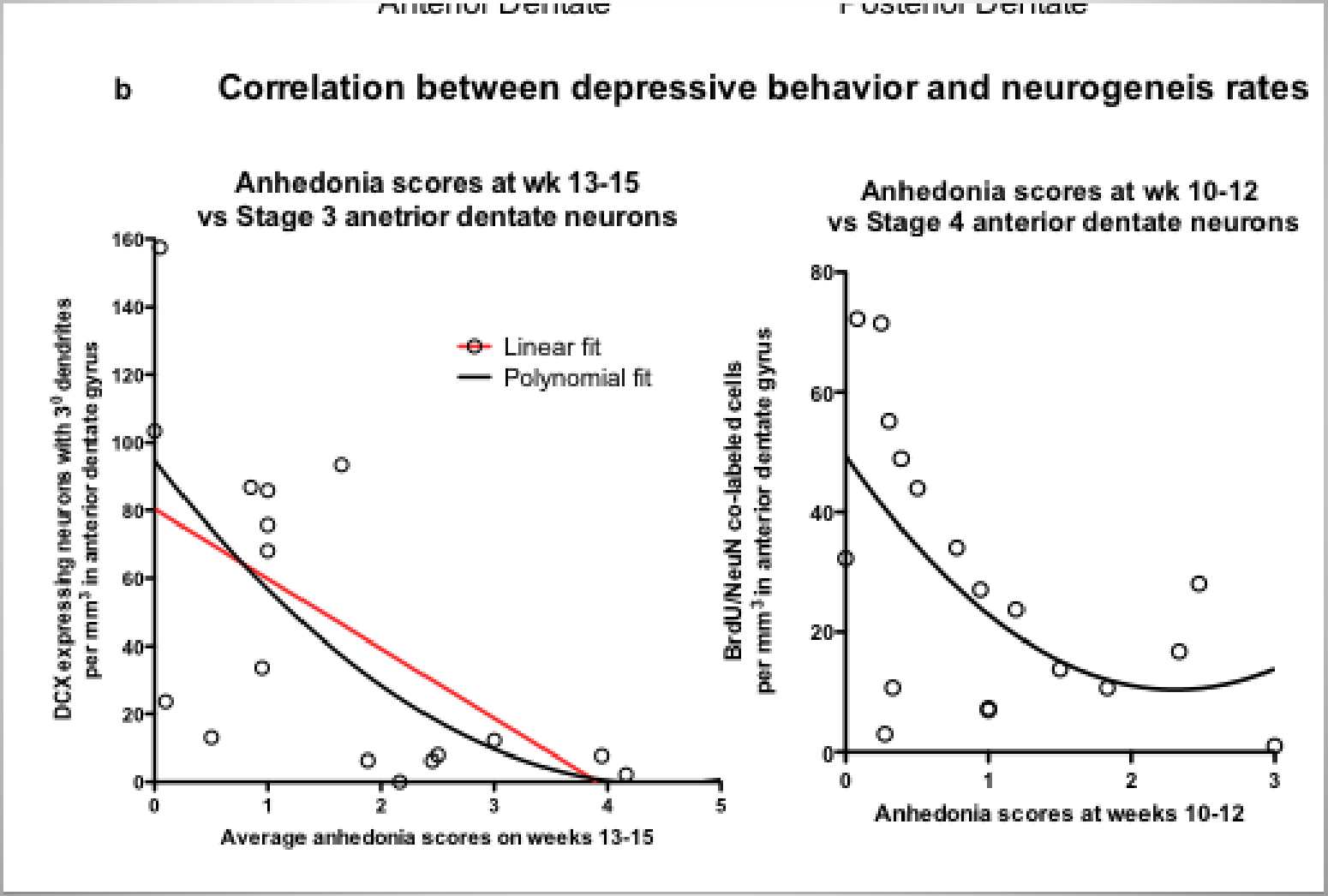
rTMS stimulates hippocampal neurogenesis



GFP immunostaining (Green) with retroviral labeled newborn neurons. Mature neurons stained in DAPI (Blue) in the hippocampus of control rat and two rats (P1 and P5) treated with 2 weeks of deep magnetic stimulation. (Zhang et al Molecular Brain 2014)

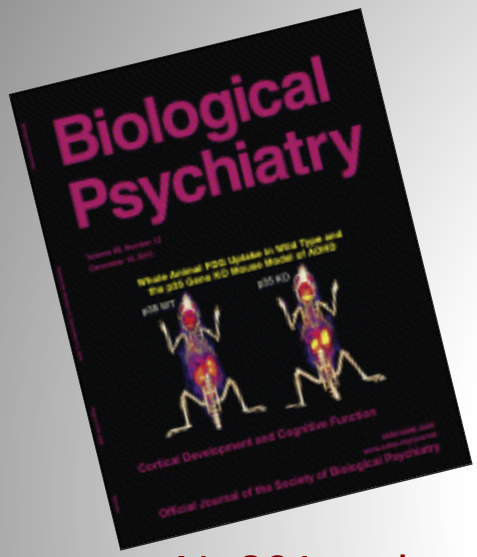
Correlation between depressive behavior and Neurogenesis in the monkey dentate gyrus

Perera et al PLOS One 2011



Clinical Studies of TMS

Neuronetics Randomized Controlled Trials



PRIORITY COMMUNICATION

Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial

John P. O'Reardon, H. Brent Sovason, Philip G. Janicak, Shirlene Sampson, Keith E. Isenberg, Ziad Nahas, William M. McDonald, David Avery, Paul B. Fitzgerald, Colleen Loo, Mark A. Demitrack, Mark S. George, and Harold A. Sackeim
BIOL PSYCHIATRY 2007;62:1208-1216

Major Findings:

- N=301 patients (ATHF 1 thru 4), 23 sites
- *22.1%* reduction in MADRS total score with active NeuroStar TMS vs *9.1%* on sham *at 4 weeks* (in ATHF = 1 population)
- Clinically meaningful effect size = *0.52* (in ATHF = 1 population)
- In open label extension study, 1 in 2 patients responded, 1 in 3 patients achieved remission *at 6 weeks*
- Safety confirmed in 6 month follow-up

Conclusion: *"Transcranial Magnetic Stimulation was effective in treating major depression with minimal side effects reported. It offers clinicians a novel alternative for the treatment of this disorder."*

Demitrack & Thase (2009) *Psychopharm Bulletin*

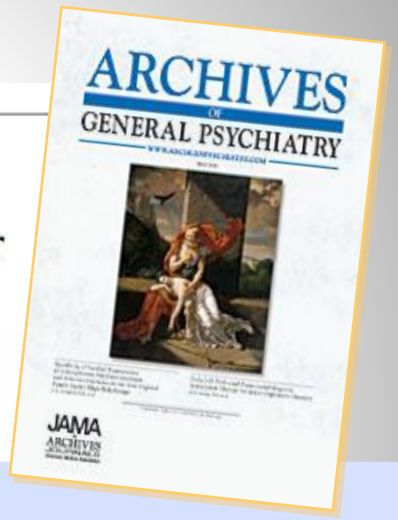
Optimization of TMS ('OPT-TMS') Study

ORIGINAL ARTICLE

Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

A Sham-Controlled Randomized Trial

Mark S. George, MD; Sarah H. Lisanby, MD; David Avery, MD; William M. McDonald, MD; Valerie Durkalski, PhD; Martina Pavlicova, Phd; Berry Anderson, Phd, RN; Ziad Nahas, MD; Peter Bulow, MD; Paul Zarkowski, MD; Paul E. Holtzheimer III, MD; Theresa Schwartz, MS; Harold A. Sackeim, PHD



Major Findings:

- **NIMH-funded, independent of industry**
- **N=190 patients, 4 premier academic sites**
- **Primary outcome measure:**
  % Remission - Active 15% vs Sham 4% (*P = 0.015*); Odds Ratio of achieving remission: *4.2* (95%CI, 1.3-13.2)
- MADRS total score decreased:16.6% (Active) vs 6.9% (Sham) p=0.01 (Effect size: 0.51)
- 30% of patients achieved remission in open-label extension phase
- Excellent safety and adherence

Conclusion: *"Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham."*

Brainsway Multicenter Study

RESEARCH REPORT

Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial

Yechiel Levkovitz[1], Moshe Isserles[2], Frank Padberg[3], Sarah H. Lisanby[4], Alexander Bystritsky[5], Guohua Xia[6], Aron Tendler[7], Zafiris J. Daskalakis[8], Jaron L. Winston[9], Pinhas Dannon[10], Hisham M. Hafez[11], Irving M. Reti[12], Oscar G. Morales[13], Thomas E. Schlaepfer[14], Eric Ho[15], Joshua A. Berman[16], Mustafa M. Husain[17], Uzi Sofer[18], Ahava Stein[19], Shmulik Adler[19], Lisa Deutsch[20], Frederic Deutsch[20], Yiftach Roth[21], Mark S. George[22], Abraham Zangen[21]

Major Findings:

- **Brainsway funded**
- **N=181 patients, 20 International sites**
- **Primary outcome measure:**
  % Remission – Active 33% vs Sham 15% (*P = 0.005*)

HAMD21 total score at week 5 6.39 point improvement active versus 3.11 points sham, p=0.008))

- **Maintenance Phase**
- Twice a week TMS until week 16
- Response rates were 44.3% for TMS versus 25.6% for sham treatment (p=0.0086)
-
- Remission rates were 31.8% for Deep TMS versus 22.2% for sham treatment (p=0.15.

Summary of Outcomes of RCT studies

- Three large, multisite, randomized controlled trials
- Aggregate number of patients 709
- Number of Antidepressant Failures 1-4
- Treatment Duration 4-6 weeks
- Response Rates 55-63%

Meta Analysis of 42 TMS trials

Meta-Analysis Results:

rTMS was significantly superior to Sham

p<0.001

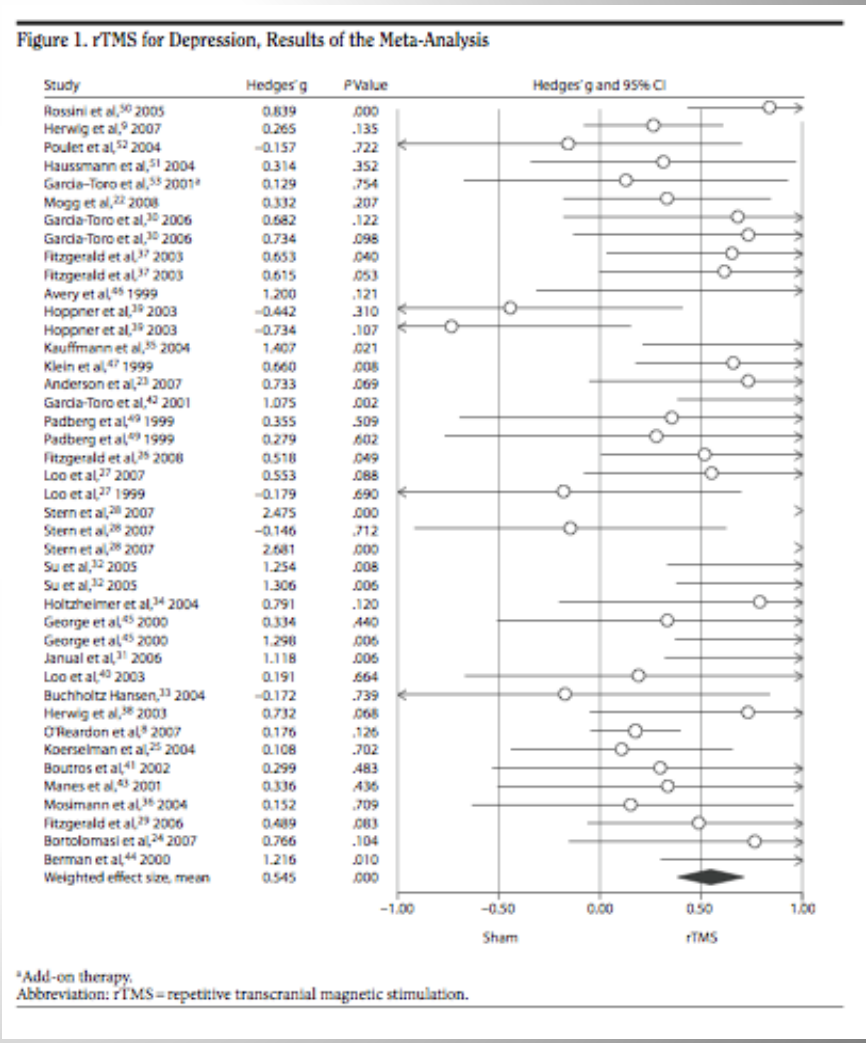


Figure 1. rTMS for Depression, Results of the Meta-Analysis

Study	Hedges' g	PValue
Rossini et al,[50] 2005	0.839	.000
Herwig et al,[9] 2007	0.265	.135
Poulet et al,[52] 2004	−0.157	.722
Haussmann et al,[51] 2004	0.314	.352
Garcia-Toro et al,[53] 2001[a]	0.129	.754
Mogg et al,[22] 2008	0.332	.207
Garcia-Toro et al,[30] 2006	0.682	.122
Garcia-Toro et al,[30] 2006	0.734	.098
Fitzgerald et al,[37] 2003	0.653	.040
Fitzgerald et al,[37] 2003	0.615	.053
Avery et al,[46] 1999	1.200	.121
Hoppner et al,[39] 2003	−0.442	.310
Hoppner et al,[39] 2003	−0.734	.107
Kauffmann et al,[35] 2004	1.407	.021
Klein et al,[47] 1999	0.660	.008
Anderson et al,[23] 2007	0.733	.069
Garcia-Toro et al,[42] 2001	1.075	.002
Padberg et al,[49] 1999	0.355	.509
Padberg et al,[49] 1999	0.279	.602
Fitzgerald et al,[26] 2008	0.518	.049
Loo et al,[27] 2007	0.553	.088
Loo et al,[27] 1999	−0.179	.690
Stern et al,[28] 2007	2.475	.000
Stern et al,[28] 2007	−0.146	.712
Stern et al,[28] 2007	2.681	.000
Su et al,[32] 2005	1.254	.008
Su et al,[32] 2005	1.306	.006
Holtzheimer et al,[34] 2004	0.791	.120
George et al,[45] 2000	0.334	.440
George et al,[45] 2000	1.298	.006
Janual et al,[31] 2006	1.118	.006
Loo et al,[40] 2003	0.191	.664
Buchholtz Hansen,[33] 2004	−0.172	.739
Herwig et al,[38] 2003	0.732	.068
O'Reardon et al,[8] 2007	0.176	.126
Koerselman et al,[25] 2004	0.108	.702
Boutros et al,[41] 2002	0.299	.483
Manes et al,[43] 2001	0.336	.436
Mosimann et al,[36] 2004	0.152	.709
Fitzgerald et al,[29] 2006	0.489	.083
Bortolomasi et al,[24] 2007	0.766	.104
Berman et al,[44] 2000	1.216	.010
Weighted effect size, mean	0.545	.000

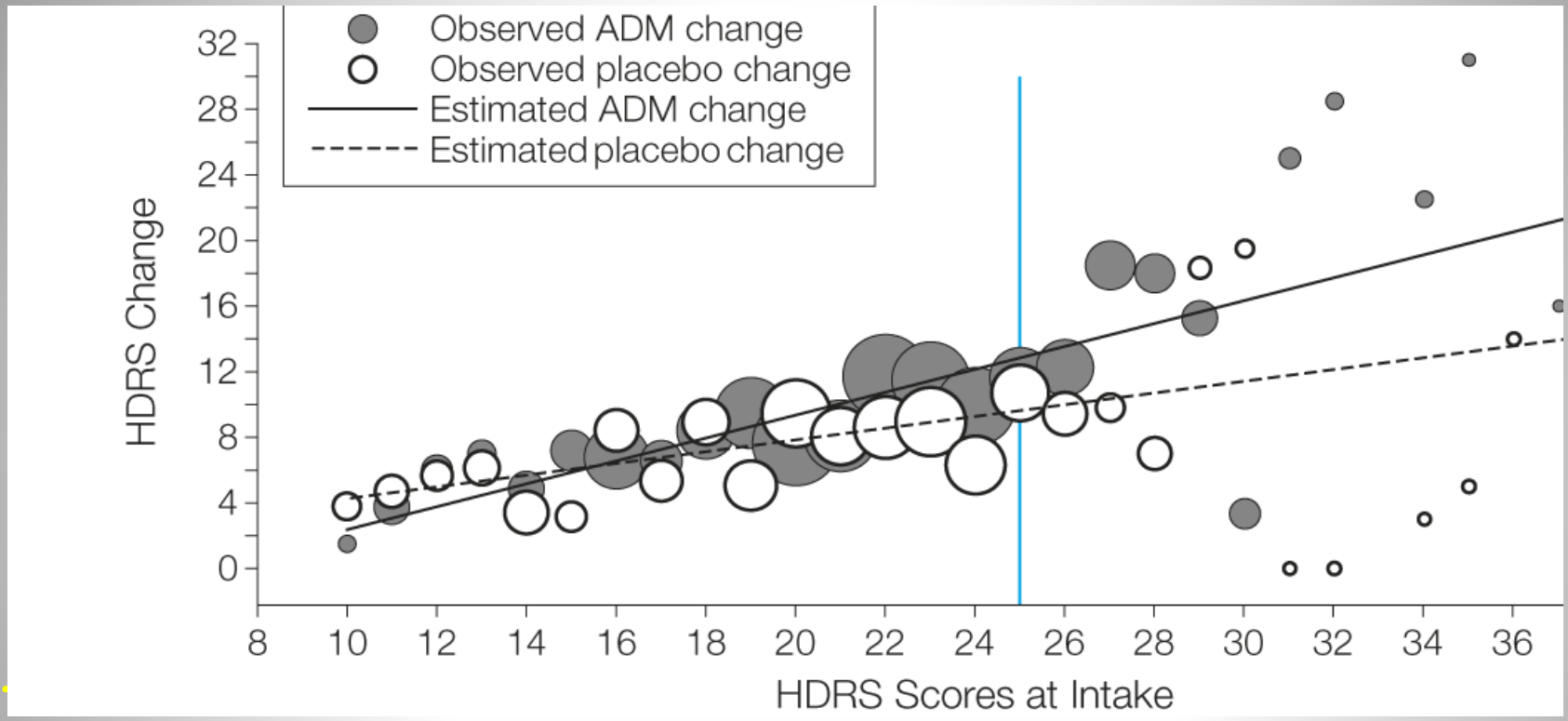
Hedges' g and 95% CI

−1.00 −0.50 0.00 0.50 1.00

Sham rTMS

[a]Add-on therapy.
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Meta analysis of 35 major antidepressant medication trials



- **Fournier et al*JAMA. 2010;303(1):47-53.***

Conclusions

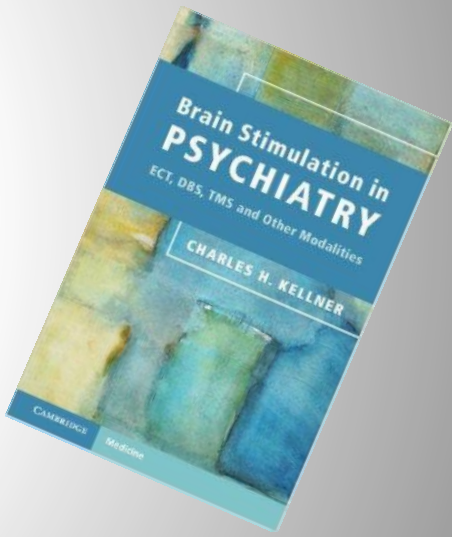
Benefit of antidepressant medication compared with placebo is nonexistent in patients with mild or moderate symptoms.

For patients with very severe depression, the benefit of medications over placebo is significant.

Durability of TMS benefits

During open-label follow up on antidepressant medication monotherapy,~37% of patients required TMS reintroduction

- Net incidence of illness relapse under 6-months of open-label follow up was: ***11%***



- ***In comparison***

  – Six-month relapse with antidepressant treatment alone in STAR*D study was 35-50% (Level 2 and 3 range)

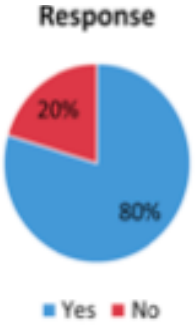
  – Six month relapse with ECT in OPT ECT trial was 89%

Our exprience at
Contemporary Care

Open Label Data from our 7 clinics

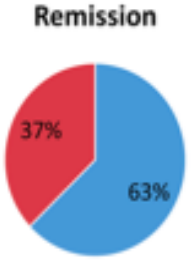
450 patients

Perera et al *Abstract* J Brain Stim 2014



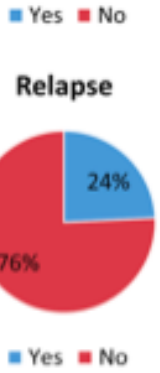
Response Rates: Response is defined as a reduction in Hamilton Depression (HAMD) Scale by 50% or greater at anytime during the initial the treatment course. HAMD scale administered during baseline, weekly throughout treatment, and at end of the treatment.

- 80% of patients responded.
- 20% showed no response.



Remission Rates: Remission is defined as a HAMD score of 9 or less.

- 63% obtained remission
- 37% did not obtain remission
  - *Response, with remission: 82.2%*
  - *Response, no remission: 17.8%*



Relapse Rates over three years

Relapse defined as a reappearance of depression with an increase in HAMD scores to 75% or greater of initial score over a three year follow up period.

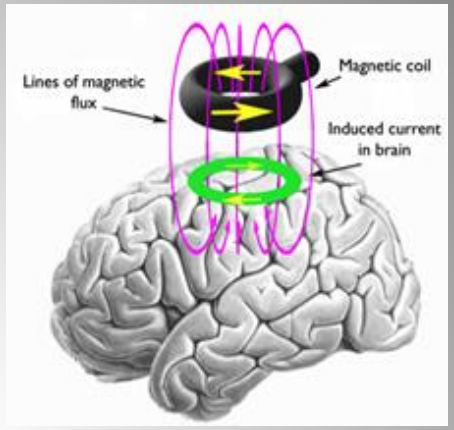
- 24% of responders relapsed.
- 76% of responders did not relapse.
- 95% of patients that relapsed responders to booster

Safety of TMS

Contraindications to TMS

- Implanted metallic devices in or around the head
- Device implants such as deep brain stimulators, cochlear implants, and vagus nerve stimulators

Side effects

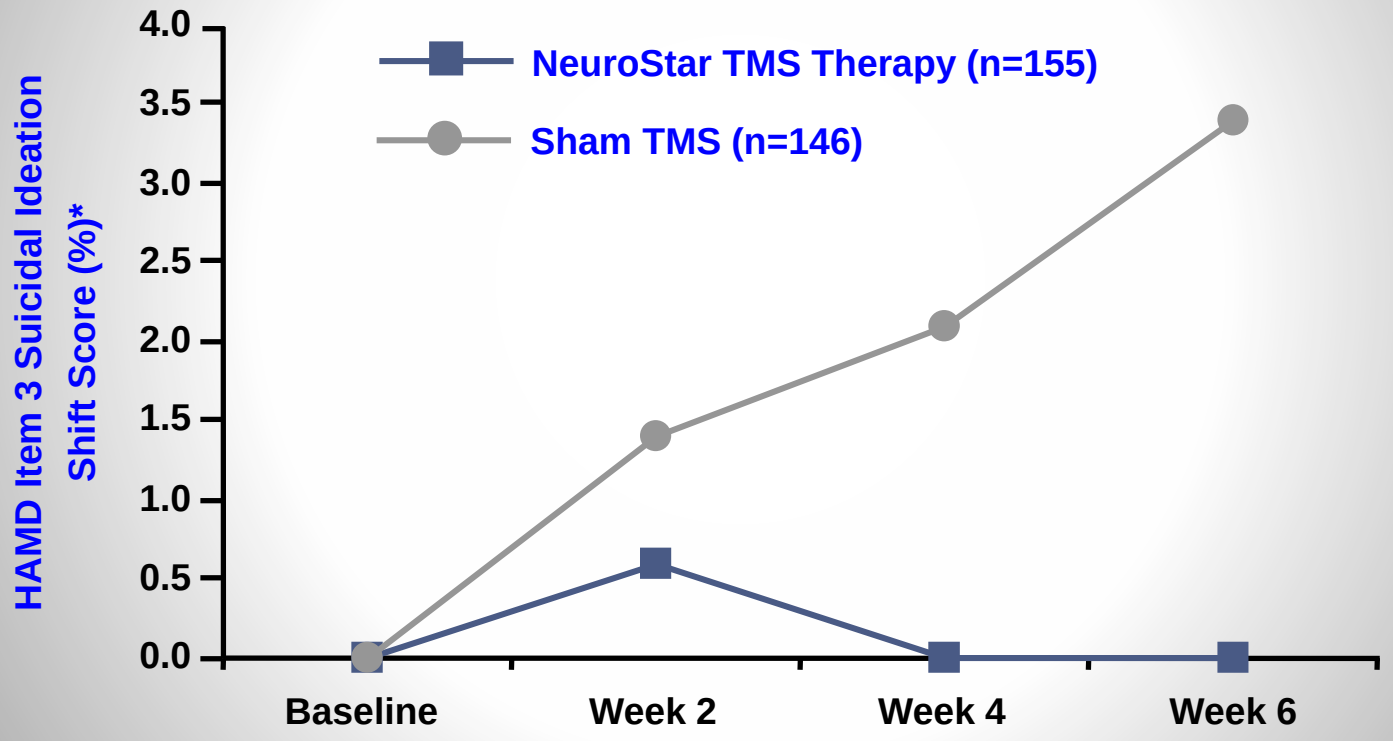


- No systemic side effects
- No adverse effect on cognition
- Most common adverse event associated with treatment was scalp pain or discomfort
  - < 5% of patients discontinued due to adverse events

Risk of Seizures

- The overall risk of seizures
  - 1 in 30,000 treatment sessions (0.003%) or less than 1 in 1000 patient exposures (<0.1%) with the Neurostar coil (NeuroStar TMS Therapy User Manual, Neuronetics, Inc., Malvern, PA, USA)
  - 6 in 5,000 patients (0.12%) with the Brainsway coil (User Manual, Brainsway Israel).

No Evidence of Emergent Suicidal Ideation



** Shift Score indicates the percent of subjects who experienced a change in HAMD Item 3 score from 0 or 1 at baseline to 3 or 4 at later point in time.*

Janicak (2008) *J Clinical Psychiatry*.

TMS in Depression

Who should get TMS?

Depressed patients who are resistant or intolerant medications

Consider TMS before prior ECT or MAOIs

Insurance coverage

Most Insurance plans and Medicare approve TMS for patients

Criteria for coverage

Criteria who have failed to respond to 4 antidepressant trials

Rationale

Probability of response with TMS = 50-80%

Probability of response to 5th antidepressant 1-4%

Future of TMS

Off-Label Applications

Psychiatry

Generalized Anxiety Disorder

Post-traumatic Stress Disorder (PTSD

Obsessive Compulsive Disorder (OCD)

Social Anxiety Disorder

Bipolar depression

Psychotic depression

Substance Abuse

Schizophrenia

Bulimia and Anorexia

Borderline Personality Disorder

Neurology

Chronic Pain

Fibromyalgia, Bone cancer, Spinal conditions

Migraines

Autistic spectrum

Tinnitus

Only in CNS etiology

Parkinson’s

Early stage

Alzheimer’s

Early stage

Traumatic Brain Injury

Including small strokes

Tourettes

Epilepsy

Slow TMS

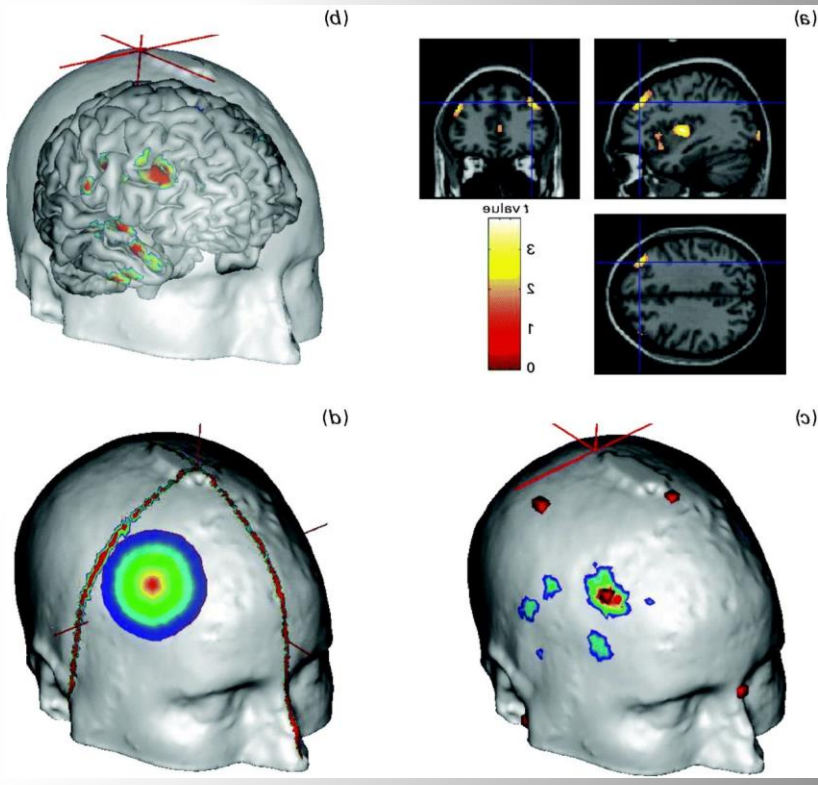
Special populations

Pregnant women

Children 8yrs and older

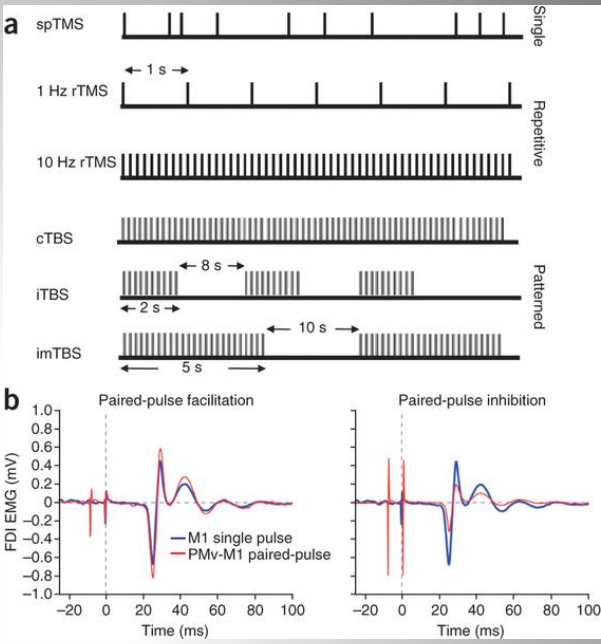
Elderly

Neuro-navigation Guided TMS

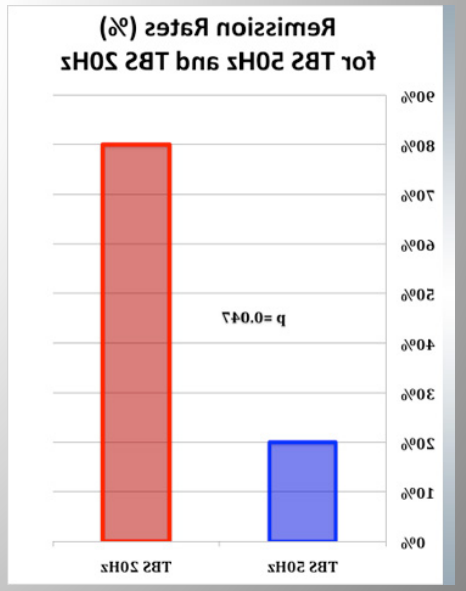


Theta burst TMS

High frequency Theta Burst TMS (TBS) is a patterned stimulation given at the theta frequency that the brain operates on when it learning new things and changing. So TBS t capitalizes on the principle of neuroplasticity.



Comparison	TBS	TMS
Session Length	3 minutes	30-40 minutes
Course	1-2 weeks	6-8 weeks
Remission rate	80%	35%



Stubbeman et al (2015). Efficacy of novel twenty hz theta burst pulse parameter in the TMS treatment of refractory depression. Brain Stimulation, 2(8), 397-398

Thank you

Efficacy of Theta Burst TMS