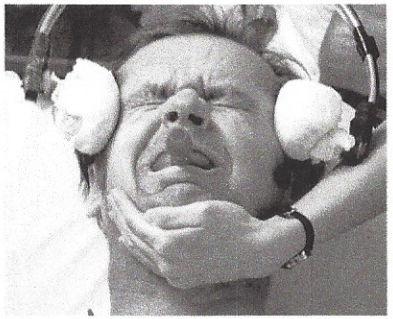
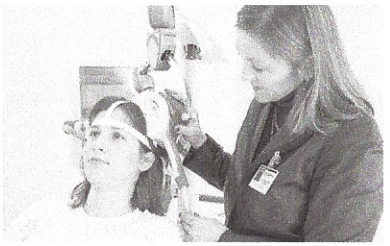
History of Brain Stimulation Therapies

- Electroconvulsive Therapy (ECT) 1938



- Cranial Electrotherapy (CES) 1972

- Transcranial Magnetic Stimulation (TMS) 1985



Electroconvulsive Therapy (ECT)

- Electroconvulsive Therapy (ECT)- developed in 1938
- Used to treat major depressive disorder (MDD), mania, often as a last line of intervention.
- Anesthesia is delivered, electrodes are placed on the scalp (unilateral or bilateral)
- Electrical stimulus delivered at 1.5 times seizure threshold for bilateral and up to 12 times for unilateral
- Efficacy: Meta-analysis in 2012 indicated that overall remission rate for patients given a round of ECT treatment was 51.5% for unipolar depression, and 50.9% for bipolar depression
- MDD – mixed results:

  50% of patients relapse after ECT treatment followed by antidepressants, and twice as many relapse if only given ECT treatment

- ECT is viewed as the gold standard for catatonia

Dierckx et al., PMID 2012; 14(2):146-150; Jelovac et al. Neuropsychopharmacology 2013; 38(12):2467-74. Micallef-Trigona, Depress Res Treat 2014.

ECT Efficacy

- Highest response/remission rates of any depression treatment
- Best data are for acute treatment
- Response often occurs after a few sessions
- High relapse rates following remission
- No clear evidence to support any particular medicine for maintaining response after ECT
- Best research suggests nortriptyline, lithium, venlafaxine

Sackeim HA et al. Arch Gen Psychiatry 2009;66(7):729-37;
Sackeim HA et al. JAMA 2001;285(10):1299-307;
Kellner CH et al. Arch Gen Psychiatry 2006;63(12):1337-44.

ECT in Practice

- Acute course: typically 6–12 treatments; maximum generally 20
- Treatment should continue for 3 sessions after symptoms remit or plateau; relapse rates are higher if ECT is discontinued prematurely
- Frequency can influence memory effects; patients may not have sufficient time to recover prior to the next session
- Right unilateral may have fewer memory effects than bilateral
- Urgent situations (e.g., suicidality): bitemporal ECT
- Less severe situations: high-dose right unilateral ECT

Husain MM et al. J Clin Psychiatry 2004;65(4):485-91;
Gelenberg AJ et al. APA; 2010. Available at http://psychiatryonline.org/guidelines.aspx;
Blumberger DM et al. Curr Psychiatry Rep 2013;15(7):368.

ECT: Mechanism of Action

- 80–95% of electrical activity is shunted by the skull and conducted by the CSF → widespread cortical and subcortical stimulation
- Small proportion of the electrical current is focused toward frontal cortex (therapeutic effects)
- Majority of the electrical current results in non-focal activation (adverse cognitive effects)
- Involves induction of generalized seizures with electrical current

Blumberger DM et al. Curr Psychiatry Rep 2013;15(7):368;
Sackeim HA et al. Convulsive Ther 1994;10(2):93-123.

Cranial Electrotherapy (CES)

- A noninvasive brain stimulation that applies a small, pulsed electric current across a person's head for the treatment of a variety of mental health conditions
- Low intensity electrical stimulation originated in studies of galvanic currents as early as 1794
- In 1972, a specific form of CES was developed by Dr. Margaret Patterson and called NeuroElectric Therapy (NET)
- Approved by the Food and Drug Administration (FDA) in 1976
- Electrodes placed on the ear lobes, maxilla-occipital junction, mastoid processes, or temples
- CES stimulation of 1mA (milliampere) has shown to reach the thalamic area at a radius of 13.30 mm.

Kirsch et al. Psychiatr Clin N Am. 2013.36:169-176.

Cranial Electrotherapy (CES)

- Induces changes in EEG: Increases alpha relative power and decreases relative power in delta and beta frequencies
- In electromagnetic tomography and functional magnetic resonance imaging (fMRI) studies, CES has shown to reach cortical and subcortical areas of the brain
- CES treatments have been found to induce changes in neurohormones and neurotransmitters that have been implicated in psychiatric diseases
- Substantial increases in beta-endorphins, adrenocorticotrophic hormone, and serotonin
- Moderate increases in melatonin and norepinephrine
- Modest increases in cholinesterase, GABA, DHEA, and modest decreases in cortisol

Kirsch et al. Psychiatr Clin N Am. 2013.36:169-176.

After One 20-minute CES Session: Mean Changes in Blood Plasma Levels

Neurochemical	Change	Implications
Beta endorphin	↑ 98%	Decreases pain
Adrenocorticotrophic hormone	↑ 75%	Promotes homeostasis
Serotonin (5HT)	↑ 50%	Improves mood Increases pain tolerance Decreases insomnia
Melatonin	↑ 25%	Induces sleep
Norepinephrine	↑ 24%	Increases pleasure Increases arousal
Cortisol	↑ 18%	Reduces stress response
Cholinesterase	↑ 8%	Increases relaxation
gamma-Aminobutyric acid	↑ * (percentage increase not stated)	Decreases spasticity
Dehydroepiandrosterone	↑* (percentage increase not stated)	Improves immune system functioning

Kirsch et al. Psychiatr Clin N Am. 2013.36:169-176.

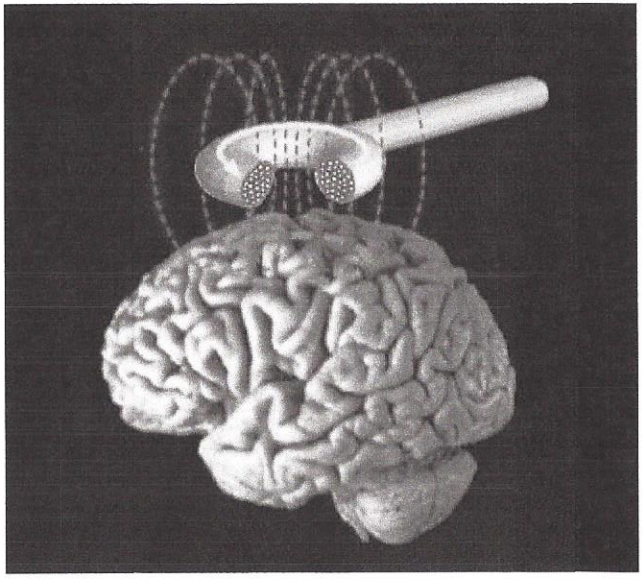
CES Efficacy

- CES treatments are cumulative; however, most patients show some improvement after the first treatment
- Depression can take up to 3 weeks for initial response
- Insomnia varies widely (immediately–2 months into treatment)
- CES can also be used in conjunction with psychotherapy, medications, hypnosis, and biofeedback
- Side effects are mild and self-limiting: vertigo, skin irritation at electrode sites, and headaches

Kirsch et al. Psychiatr Clin N Am. 2013.36:169-176.

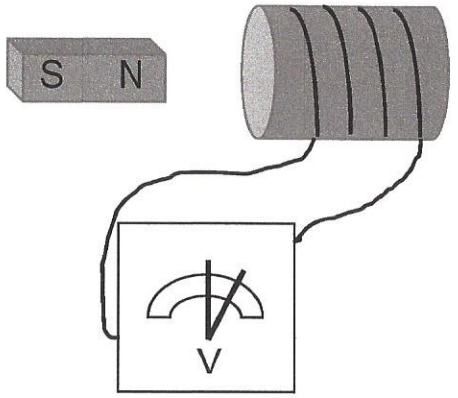
Transcranial Magnetic Stimulation (TMS)

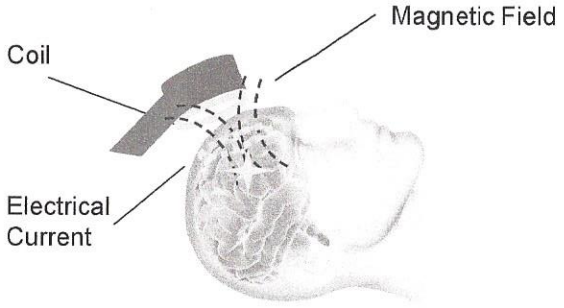
- TMS is a neurophysiological technique that allows for non-invasive stimulation of the human brain
- Can be combined with brain mapping methods (EEG, fMRI) to study brain plasticity
- Trains of TMS pulses, known as repetitive TMS (rTMS) transiently disrupt neuronal activity for periods exceeding stimulation duration
- Used to treat a variety of neuropsychiatric illnesses



History of TMS

- Physical principles of TMS discovered in 1831 by Faraday
- Observed that a pulse of electric current passing through a wire coil generates a magnetic field
- The rate of change of this magnetic field determines the induction of a secondary current in a nearby conductor
- During TMS, the stimulating coil is held over the patient's head and produces an electrical current in the brain through electromagnetic induction





TMS

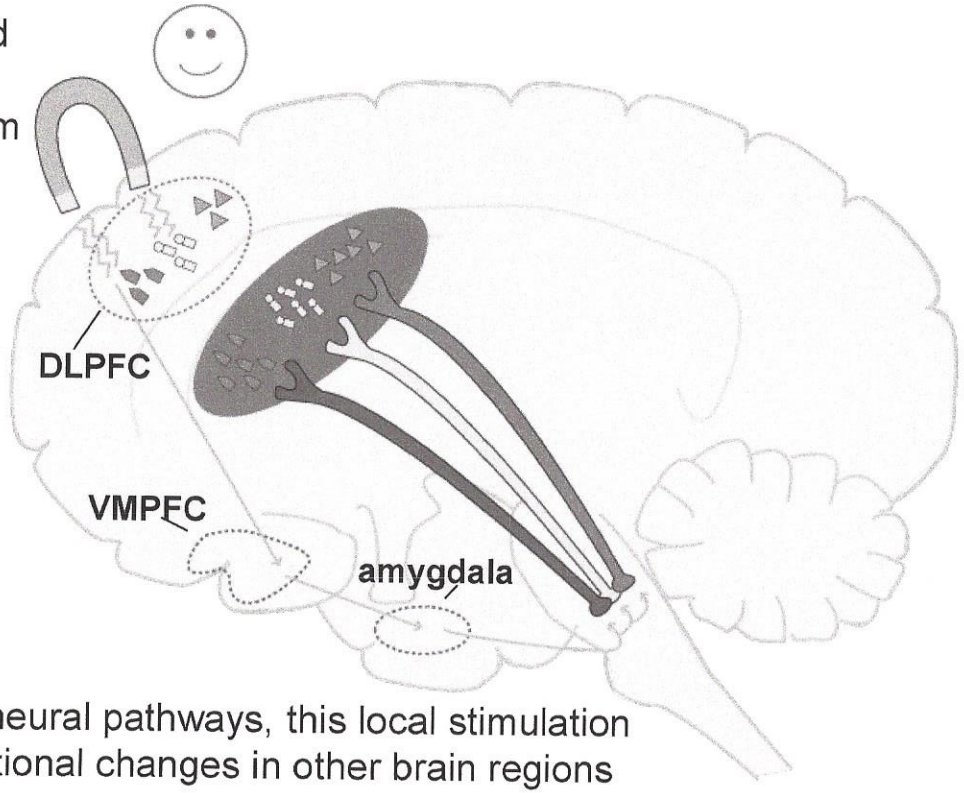
- TMS can induce relatively large currents in targeted cortical areas because magnetic fields can pass through the skull with almost no resistance
- The peak discharge current needs to be several thousand amperes to induce currents in the brain large enough to depolarize neural elements (about 10 mA/cm^2)
- The depolarized neurons can generate various physiological/ behavioral effects depending on the targeted brain region
- The precise mechanisms underlying TMS are largely unknown
- Intensity of stimulation is largely dictated by baseline excitability of the cortex
- This can be measured by the minimum stimulation required to bring about a motor evoked potential (MEP)
- Observation of muscle movement in subject after stimulation is called resting motor threshold (RMT)

Sauvé et al. Psychiatric annals. 2014, 44(6):279-283.

TMS: A Monoamine Booster?

1. Magnetic field penetrates the skull by a few cm

2. Depolarizes neurons in superficial cortex

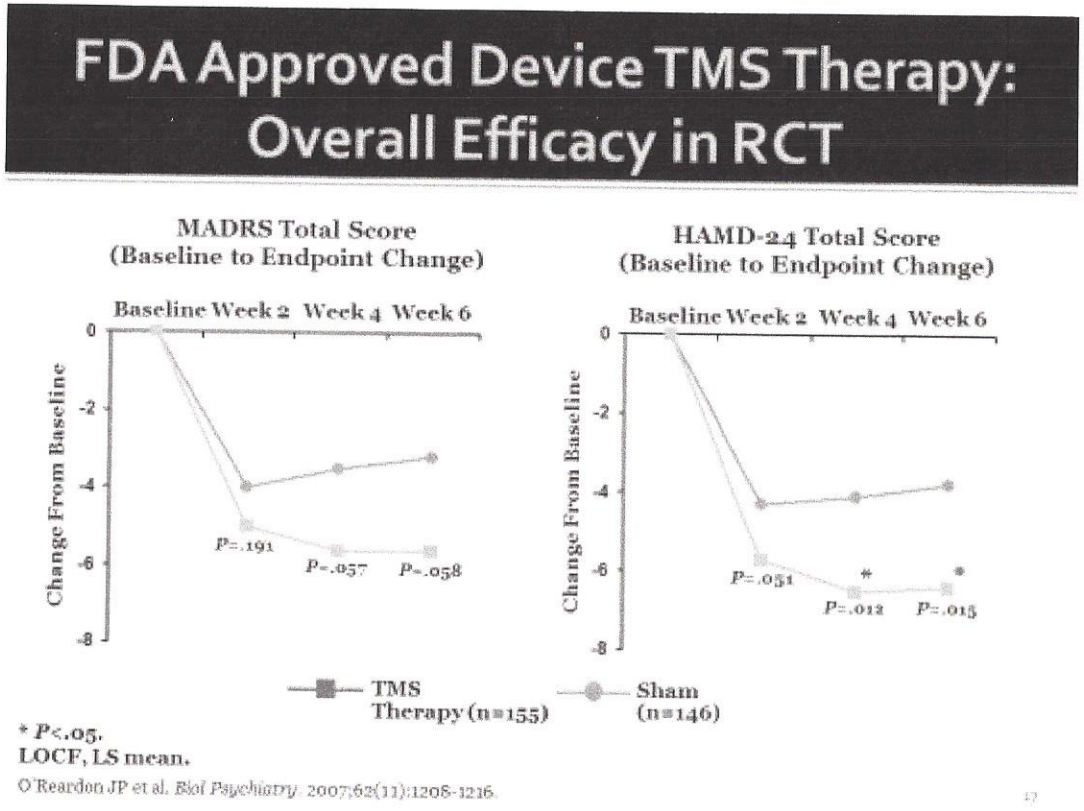


3. Through neural pathways, this local stimulation causes functional changes in other brain regions

Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.

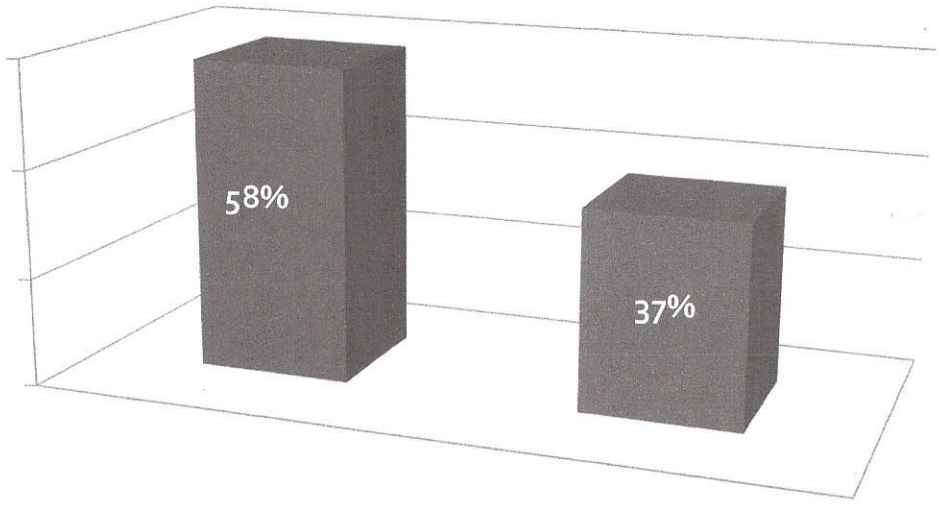
History of TMS

- Efficacy
- FDA approved in 2008



O'Reardon et al. Biol Psychiatry. 2007; 62(11):1208-1216.

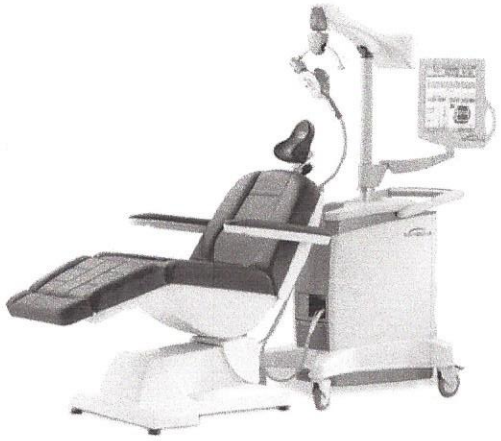
Real World Efficacy (Open Label)



Carpenter et al, Depress Anxiety, July 2012 9(7):587-96 2

TMS: The Procedure

- Electromagnetic coil is placed against the scalp and delivers pulses of the magnetic field in 30-s intervals
  - 4 s each, 10 pulses/s, with 26-s rest intervals
  - Or 2s each, 18 pulses/s with 20-s rest intervals
  - Feels/sounds like light tapping on the scalp (patient and staff should wear protective earplugs)
- Therapeutic dose: 90–120% of resting motor threshold (RMT)
  - Motor threshold: magnetic field strength that results in movement of right thumb
- Session length: typically 30–50 minutes
- Treatment duration: typically 5 treatments/week for 4–6 weeks



Long-term Efficacy of TMS

- Open label durability study published in 2014
- 42 practices, 257 patients, 120 obtained response/remission
- At 52 weeks, 62.5% still meeting criteria for response/remission
- 36.2% with return/worsening of symptoms, most reobtained response with additional treatments

Dunner DL et al. J Clin Psychiatry. 2014;75(12):1394-1401.

Are We Ready for TMS Maintenance?

- What should we offer to patients after they complete an acute course of TMS treatment, particularly if they responded?
- Current standard is to return patient to outpatient providers for pharmacological/psychotherapeutic treatment
- If symptoms relapse, a new course of TMS is considered
- What about relapse-prevention maintenance?
- Recent study: clustered maintenance (5 sessions over two days, once a month) prevented relapse better than no maintenance
- Also effective: 1 session/wk for 2 wks, 1 session every 2 wks for 2 months, 1 session/month for 2 months
- Once monthly for medication-free patients with MDD may not be sufficient
- Appropriately powered clinical trials are needed
- In the meantime, clinicians need to make decisions about the most effective course for individual patients

Dunner et al., J Clin Psychiatry. 2014;75(12):1394-401; Fitzgerald et al., Brain Stimulation. 2013;6(3):292-7; Richieri et al., J Affect Disord. 2013;151(1):129-35.

Monitoring Efficacy of TMS: Neuroimaging

- Technical feasibility for the combination of TMS and functional magnetic resonance imaging (fMRI) was first demonstrated in 1998
- Investigated brain responses to TMS over motor cortex (M1)
- Found that TMS affected the BOLD signal not only at the stimulation site, but in remote brain structures interconnected with M1
- Applying TMS to one region can affect the activity in remote cortical areas with high spatial specificity
- TMS may influence interconnected brain regions not just diffusely, but via topographically organized anatomical tracts (e.g., visual field studies)
- Concurrent TMS-fMRI makes it possible to investigate context-dependence of functional interactions within extended networks of remote but interconnected brain areas, while varying stimulation or task-state
- fMRI can be helpful in monitoring the efficacy of TMS on behavior

Ruff et al. Cortex 2009;45(9):1043-1049.

Repetitive TMS (rTMS) and Major Depression

- Repetitive TMS (rTMS) has been shown to disrupt neuronal activity for periods exceeding stimulation duration for the treatment of a variety of neuropsychiatric illnesses
- Current rTMS treatment for Major Depressive Disorder (MDD) has frequently followed one of the two most common protocols

  High-frequency rTMS (HF-rTMS,>1.0Hz) to the **left** dorsolateral prefrontal cortex (DLPFC)

  Low-frequency rTMS (LF-rTMS,<1.0 Hz) to the **right** DLPFC
- High-frequency stimulation activates, while low-frequency stimulation inhibits neural activities (when intensity is > MT)
- Altered cortical activity modulates interactions of different brain regions
- Meta-analysis: Both rTMS methods have been equally effective therapies for MDD

Teng et al., Eur Psychiatry. 2017;41:75-84; Brasil-Neto et al., Arq Neuropsiquiatr 2003;61(1):83-6.

Repetitive TMS and Major Depression

- Recent meta-analysis examined HF-rTMS on MDD
- Thirty RCTs with a total of 1754 subjects (1136 TMS; 618 sham)
- For groups: 5, 10, 15, 20 sessions
- rTMS had a significant overall therapeutic effect on depression severity scores
- Subgroups examined number of pulses: less than or equal to 100 pulses, 1200-1500, 1600-1800, or 2000-3000 pulses
- The higher the number of rTMS sessions, the greater the improvement

  Across the groups, the maximal mean effect size overall was obtained in the subgroup of 1200-1500 pulses per day ($p<0.05$)
- This pulse range may produce the best antidepressant effects, regardless of session numbers

Teng et al., Eur Psychiatry. 2017;41:75-84; Brasil-Neto et al., Arq Neuropsiquiatr 2003;61(1): 83-6.

TMS for Treatment of Depression in Special Populations

Traumatic Brain Injury (TBI): 

- Recent study: treatment-resistant depressed patients with multiple TBIs: 20 daily sessions of bilateral rTMS treatment (4000 left-sided excitatory pulses, 1000 right-sided inhibitory pulses)
- Improvements in clinician-assessed mood ratings, self-report emotional scores (mood, anger, anxiety, and behavioral dyscontrol), fluid cognition, and headaches (Hacker et al., unpublished)

Bipolar: 

- 20 sessions of active or sham deep TMS (dTMS) administered to the left DLPFC (H1-coil, 55 18 Hz 2-sec 120% MT trains)
- Active dTMS was superior to sham in reducing scores on the Hamilton Depression Rating Scale (HDRS-17)

Diego et al. Neuropsychopharmacology. doi: 10.1038/npp.2017.26; Hacker et al. (Abstract, not published)

TMS for the Treatment of Depression in Special Populations

Parkinson's 

- rTMS over the DLPFC resulted in significant reductions in scores of depressive symptoms and improved cognitive performance in patients with Parkinson's

Post Stroke Depression (PSD): 

- Meta-analysis of RCTs of rTMS for the treatment of PSD
- rTMS was beneficial on PSD using three different scales (HAMD, NIHSS, and MARDE)
- Findings should be treated with caution because of the heterogeneity and potential bias

Dinkelbach et al. Neuroscience and Behavioral Reviews. 2017;75:407-418; Shen et al. Journal of Affective Disorders. 2017;65-74.

TMS for the Treatment of Anxiety Disorders

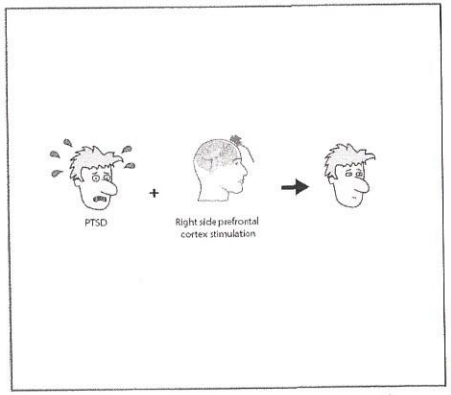
- Up to 50% of patients with generalized anxiety disorder (GAD) fail to respond to first-line pharmacotherapies
- In a recent study, patients with GAD were treated with HF-rTMS (20 Hz) applied to the right DLPFC at 110% RMT
- 25 treatments resulted in a significant reduction in the Hamilton Anxiety Scale (HARS) scores compared to sham

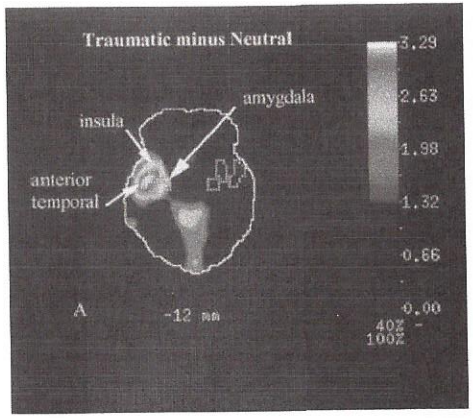
- Patients with Panic Disorder (PD): HF-rTMS to the left DLPFC has resulted in significant reduction of symptoms
- LF-rTMS *and* HF-rTMS to the right DLPFC both result in reduced symptoms in anxiety disorders
- Limitation of rTMS in anxiety disorders: not possible to stimulate distant cortical and subcortical areas that are relevant to the pathogenesis of anxiety
- Further studies should examine tDCS

Dilkov et al. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:61-65.

TMS and Post-Traumatic Stress Disorder (PTSD)

- Not all patients respond to pharmacological treatment for PTSD
- LF-rTMS applied to the right dorsolateral prefrontal cortex (DLPFC) improves symptoms
- In as few as 10 sessions, PTSD symptoms significantly improved
- LF-rTMS might decrease activity in the cortical areas of the right hemisphere
- Improve abnormalities in asymmetries associated with PTSD
- HF-rTMS activates the HPA axis, inhibiting autonomic response and suppressing amygdala activity
- Both LF *and* HF rTMS when applied to the right DLPFC reduce symptoms of PTSD





Iannone et al. Clinical use of TMS and tDCS. 2017;74(10):829-835.

TMS for the treatment of PTSD

- fMRI has identified hypo-activation of the prefrontal cortex (mPFC and DLPFC) and hyper-responsivity of the amygdala in individuals diagnosed with PTSD
- PET analysis confirmed a right-sided lateralization in individuals with PTSD by demonstrating increased blood flow in right-sided limbic and paralimbic regions when participants were presented with traumatic scripts compared to neutral scripts
- In a study, 29 patients with PTSD randomly assigned to one of 3 groups:

  Group 1: Sham

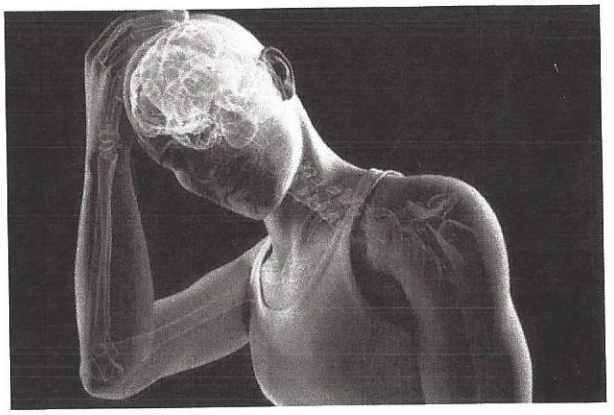
  Group 2: Low frequency (1 Hz) at 80% RMT to the right DLPFC (20 min total)

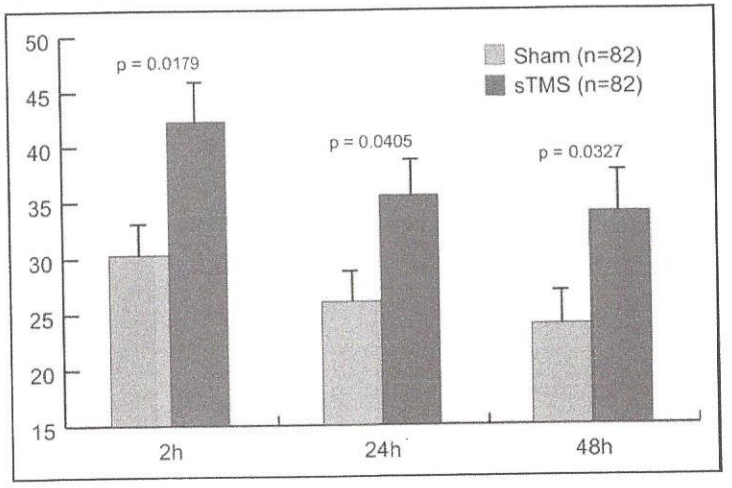
  Group 3: High frequency (10 Hz) at 80% RMT to the right DLPFC (20 min total)
- High-frequency rTMS (Group 3) significantly improved anxiety and PTSD core symptoms (avoidance and re-experiencing) in comparison to low-frequency and sham groups
- Recent study found significant improvements in PTSD symptoms (intrusions, avoidance, arousal) from deep transcranial magnetic stimulation (dTMS) to the **mPFC** at 120% RMT combined with brief exposure procedure
- Further research defining treatment delivery and pulse sequences should bring this treatment modality closer to routine clinical application

Iannone et al. Clinical use of TMS and tDCS. 2017;74(10):829-835; Isserles et al. Brain Stimul. 2013;6:377-83.

TMS for the Treatment of Headache/Migraine

- Aura has been implicated in the pathophysiology of migraine
- TMS pulses can block waves of cortical spreading depression (CSD) that underlies migrainous aura
- TMS can block waves of CSD once initiated
- Cannot prevent them
- May disrupt CSD by interrupting progression across cortex
- Single pulse TMS to the occipital lobe (two pulses administered after onset of migraine) resulted in pain-free results at 2, 24, and 48 hours post treatment

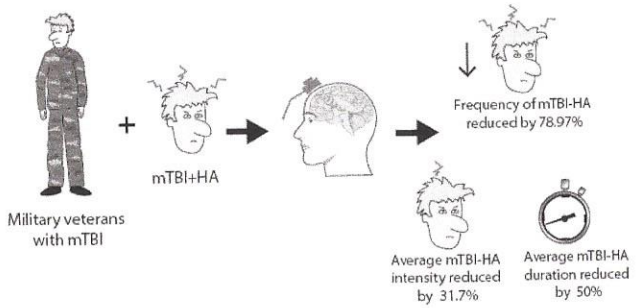




Barker et al. Headache. 2016;57(3):517-524.

TMS for Treatment of TBI-Related Headache

- Headache: one of the most common chronic pain conditions in patients with mild traumatic brain injury (mTBI)
- Meta-analysis: rTMS used for management of chronic pain
- In a recent pilot study (n=6), 4 treatment sessions of rTMS delivered to left DLPFC in patients with mTBI-related headaches
- 2000 pulses at 80% RMT
- Average headache frequency: ↓ 78.97%, 2 patients had complete cessation of headaches
- For those with persistent headaches, average duration: ↓ 50%, and intensity ↓ 31.7%



Lueng et al., Neuromodulation. 2017. doi: 10.1111/ner.12615

TMS for the Treatment of Obsessive-Compulsive Disorder

- OCD is associated with dysfunction in the frontostriatal circuit
- Only 40% of patients respond to pharmacological treatment and cognitive behavioral therapy
- Recent studies with rTMS: Inhibitory application at low frequency (1 Hz) on the supplementary motor area (SMA) improves symptoms and increases the motor threshold
- Increased intracortical inhibition measured by the matched magnetic pulses technique
- In recent lit reviews: Response rates to LF-rTMS on the orbitofrontal cortex or SMA varied between 13% and 35%
- Promising targets for reducing symptoms of OCD
- Recent study using H7 coil found significantly positive results in treatment of OCD, possibly by stimulating the mPFCs and ACC
- More studies needed

Iannone et al. Clinical use of TMS and tDCS. 2017;74(10):829-835.

TMS for the Treatment of Addiction

- Positive results from HF-rTMS for several types of addictions:

Methamphetamine:

- 30 MA-addicted patients received 5 sessions of 8 min sham or 10 Hz rTMS to the left DLPFC
- rTMS over the left DLPFC reduced craving significantly after 5 sessions of rTMS compared to sham stimulation
- rTMS improved verbal learning and social cognition in MA-addicted patients

Cocaine:

- 32 cocaine-addicted patients received rTMS to the left DLPFC or sham
- rTMS resulted in a significantly higher number of cocaine-free urine drug tests compared to control

Terraneo et al. Eur Neuropsychopharmacology. 2016;26(1):37-44; Su et al. Drug Alcohol Depend. 2017;175:84-91.

TMS for the Treatment of Addiction

Gambling Disorder (GD)

- 22 patients with GD received HF-rTMS to the left DLPFC or sham
- Before and after each rTMS session, participants rated their gambling craving from 0 to 100 before and after viewing a gambling video used as a cue
- A single session of HF-rTMS significantly decreased cue-induced craving; however, it did not alter gambling behavior
- Future studies are needed

Alcohol Dependence:

- Accelerated HF-rTMS at 110% RMT to the right DLPFC (15 sessions over 4 days) and fMRI
- General craving significantly decreased after 15 HF-rTMS sessions
- However, cue-induced alcohol craving was not altered
- Brain activation changes after 1 session, and 15 HF-rTMS sessions, respectively were observed in regions associated with the extended reward system and default mode network

Herremans et al. PLOS One. 2015;10(8): e0136182. doi:10.1371; Gay et al. Eur Psychiatry. 2017;41:68-74.

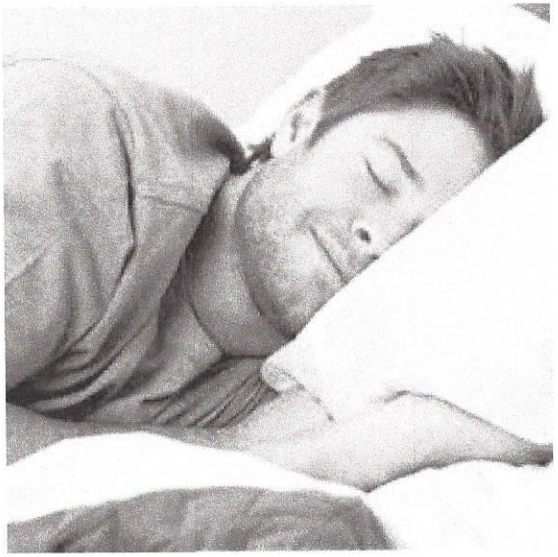
TMS for the Treatment of Epilepsy

- Recent meta-analysis examined brain stimulation techniques on frequency of seizures in patients with drug-resistant epilepsy (DRE)
- 4 studies: use of rTMS as a non-invasive antiepileptic option for patients with DRE had mixed results
- 2 studies: no significant differences in seizure frequency
- 2 studies: significant reductions in seizure frequency in patients with predetermined location of cortical seizure foci
- In contrast to the previous 2 studies, this study included patients with cortical dysplasia or superficial epilepsy origin
- A significant decrease in seizure frequency, eight weeks after stimulation
- Initial rTMS treatment had a longer-lasting effect on seizure frequency reduction after completion of treatment
- Single-blinded trial demonstrated that 35.5% of patients remained seizure free, and 22% had a complete abolishment of epileptiform discharges at the end of the blinded evaluation period

Fregni et al. Ann Neurol. 2006;60:447-455; Theodore et al. Neurology. 2002;59:560-562; Cantello et al. Epilepsia. 2007;48:366-374; Sun et al. Epilepsia. 2012;53:1782-1789.

TMS for the Treatment of Sleep Disturbances

- Recent study examined LF-rTMS on sleep pattern in patients with focal epilepsy
- 24 male patients underwent LF-rTMS (1000 pulses/ 1Hz) daily for 10 days
- Polysomnographic study was performed at baseline and after the last TMS treatment
- TMS induced significant increase in sleep efficiency and total sleep time, along with a decrease in latency and number of awakenings
- TMS may mediate therapeutic effects in the treatment of patients with focal epilepsy



Sanchez-Escandon et al., Sleep Med. 2016;20:37-40.

Exploratory Studies with TMS

Pregnancy:
Meta-analysis (12 studies) of rTMS significantly reduced acute depressive episodes in pregnant women with no adverse consequences to offspring

Children:
LF-rTMS suppressed cortical excitability in ASD when applied to the DLPFC and results in behavioral improvements.
LF-rTMS to the SMA significantly reduced symptoms in 4 weeks for patients under 16 with Tourette's Syndrome

Elderly:
4 weeks of rTMS significantly reduced depressive symptoms and suicidal ideation.
In patients with Parkinson's Disease: Meta-analysis (22 studies) showed that rTMS significantly improved short-term upper limb fxn, short-term and long-term walking fxn

Schizophrenia:
Meta-analysis of 17 studies demonstrated that rTMS significantly reduced auditory hallucinations in patients with schizophrenia

*ASD= autism spectrum disorder; SMA =supplemental motor area

Zhang et al. Neural Regen Res. 2013;8(28):2666-76; Hameed et al. Curr Neurol Neurosci Rep. 2017;17(11):1-15; Felipe et al. Trends in Psychiatry and Psychotherapy. 2016;38(4):190-197; Chung et al. Brain Stimul. 2016;9(4):475-487.

Exploratory Studies with TMS

- Recent studies have aimed to reduce inter-individual variability and increase the efficacy of rTMS
- One factor that remains overlooked is inter-train variability (ITI)
- In early studies, ITIs were introduced to avoid overheating of stimulation coils and as a safety consideration
- Recent study: rTMS (20 Hz, 2s trains, 1200 pulses, 100% RMT) was applied to 14 healthy individuals with ITI of 4s (duration~3 min), 8s (~5min), 16s (~9min) or 32s (16.5 min)
- Sessions separated by ≥ 5 days
- Disinhibition increased with shorter ITI duration
- These findings provide the first evidence to suggest that ITI may be substantially shortened without loss of rTMS effects
- Shorter ITI results in greater disinhibitory effects, which may be desirable for accelerated treatment paradigms

Cash et al., Brain Stimulation. 2017;10:630-636.

Other Brain Stimulation Techniques

- Electroconvulsive Therapy (ECT)
- Cranial Electrotherapy (CES)
- Transcranial Direct Current Stimulation (tDCS)
- Vagus Nerve Stimulation (VNS)
- Deep Brain Stimulation

Other Brain Stimulation Techniques

- Transcranial Direct Current Stimulation (tDCS)
- Vagus Nerve Stimulation (VNS)
- Deep Brain Stimulation

Transcranial Direct Current Stimulation (tDCS)

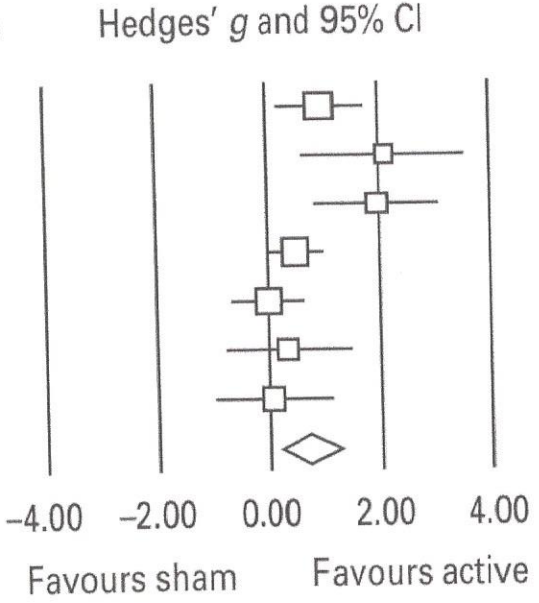
- Non-invasive, non-convulsive
- Weak direct current passes into the cerebral cortex through 2 surface scalp electrodes
- Modulates cortical excitability dependent on the polarity of the stimulation

Stimulation:	Polarization:	Neuronal firing:	Cortical excitability:
Anodal	Depolarized	↑	↑
Cathodal	Hyperpolarized	↓	↓

Blumberger DM et al. Curr Psychiatry Rep 2013;15(7):368;
Kalu UG et al. Psychol Med 2012;42(9):1791-800.

Transcranial Direct Current Stimulation: Efficacy

Study name	Statistics for each study		
	Hedges' *g*	*Z* value	*p* value
Boggio *et al.* (2008)	0.988	2.503	0.012
Fregni *et al.* (2006*a*)	2.111	2.849	0.004
Fregni *et al.* (2006*b*)	1.970	3.542	<0.001
Loo *et al.* (2012)	0.519	2.000	0.046
Loo *et al.* (2010)	0.014	0.041	0.967
Palm *et al.* (2011) (1 mA)	0.356	0.618	0.537
Palm *et al.* (2011) (2 mA)	0.084	0.157	0.875
	0.743	2.758	0.006



Kalu UG et al. Psychol Med 2012;42(9):1791-800.

Transcranial Direct Current Stimulation Procedure

- Electrode placement
  - Most studies: anodal over left DLPFC and cathodal over right DLPFC or supraorbital region
  - Based on premise that left DLPFC is hypoactive
- Current strength: 1–2 mA
- Duration: ~20 minutes/session
- Frequency: Daily for 1–4 weeks
- Side effects: headache, itchiness and redness at stimulation site, (hypo)mania

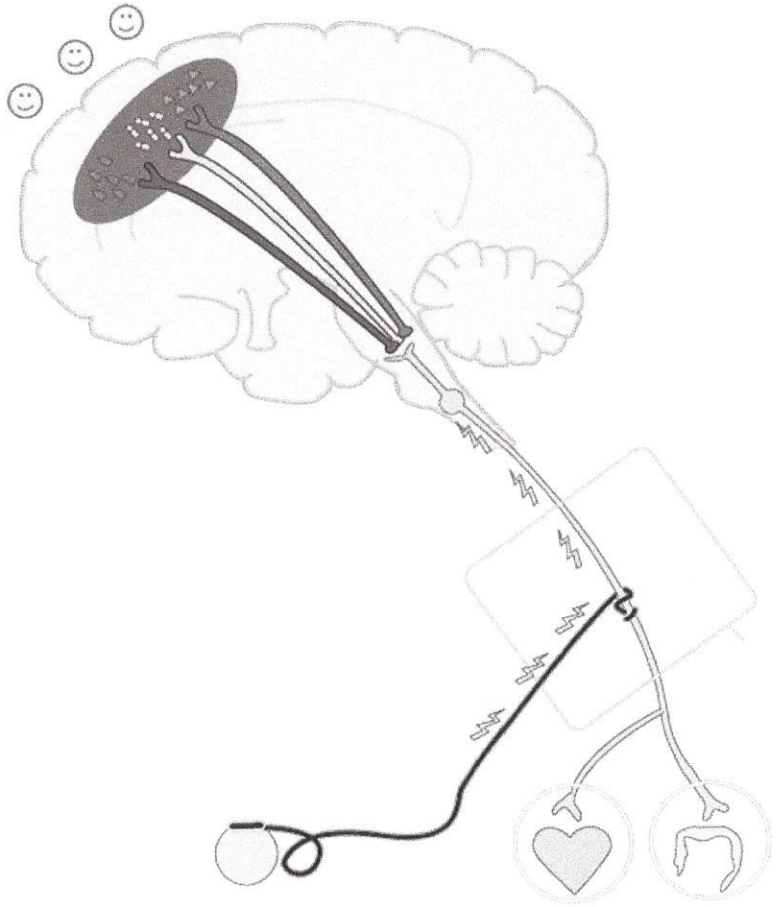
Kalu UG et al. Psychol Med 2012;42(9):1791-800.

Transcranial Direct Current Stimulation Current State

- Clinical trials are still in infancy
- Most studies have been in mild to moderate depression without treatment resistance
- Insufficient data for moderate to severe depression with previous treatment failure
- Minimal data but possible benefit for mild to moderate non-resistant depression

Blumberger DM et al. Curr Psychiatry Rep 2013;15(7):368;
Brunoni AR et al. Frontiers Psychiatry 2013;4(19):Epub ahead of print.

Vagus Nerve Stimulation: A Monoamine Booster?



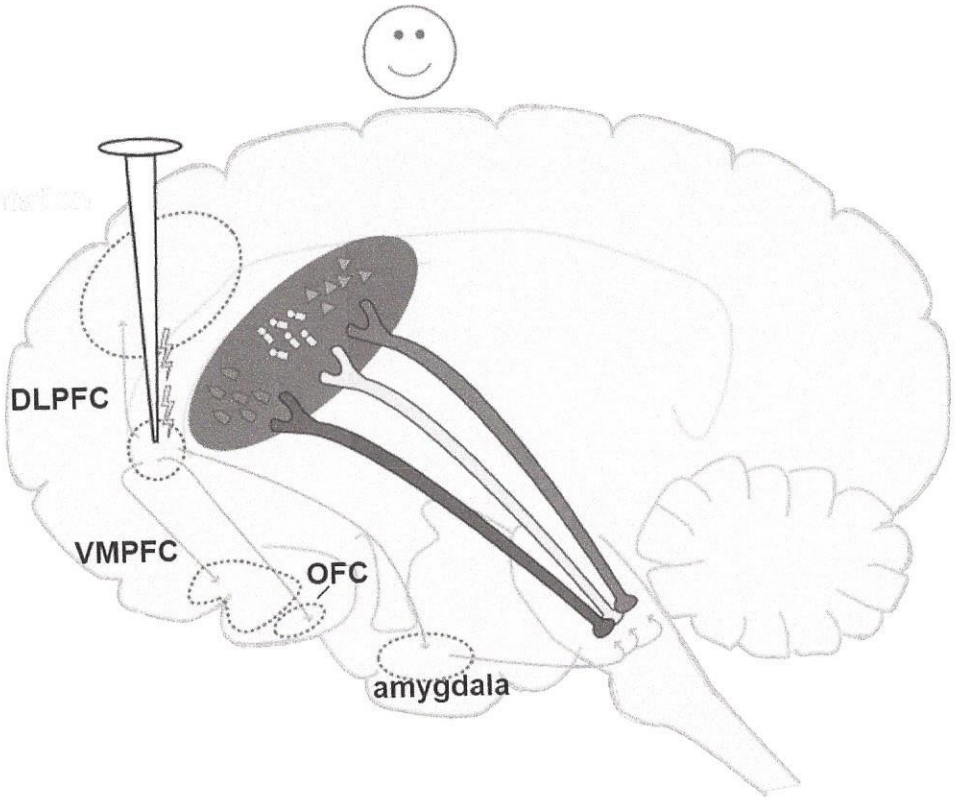
Vagus Nerve Stimulation (VNS)

- Approved to treat depression that has not responded to multiple antidepressants
- Most insurance companies do not cover
- Large controlled study did not demonstrate difference vs. placebo
- Recent meta-analysis shows superiority to treatment as usual but still low remission rates

  -Included single-arm and nonrandomized trials

Rush AJ et al. Biol Psychiatry 2005;58(5):347-54; Berry SM et al. J Med Devices 2013;6:17-35.

Deep Brain Stimulation(DBS): A Monoamine Booster?



Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.

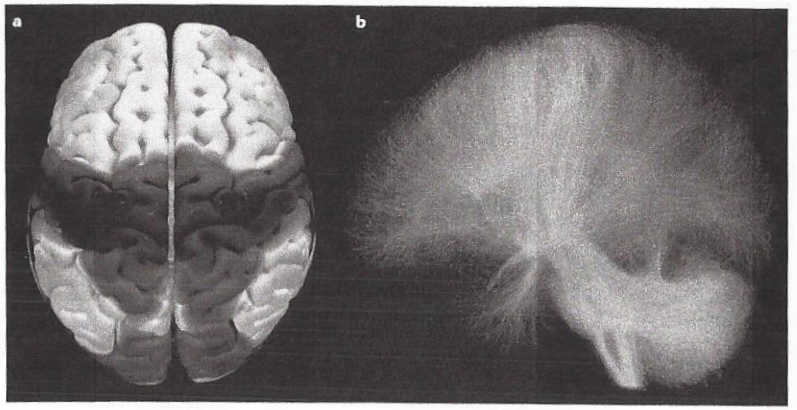
Deep Brain Stimulation (DBS)

- In trials for treatment-resistant depression
- Response to treatment appears to be rapid
- No cognitive adverse effects have been observed
- DBS is an established treatment for motor dysfunction in patients with Parkinson's Disease

Blumberger DM et al. Curr Psychiatry Rep 2013;15(7):368.

DBS in Parkinson's Disease

- Used a previously tested model to determine that certain connectivity patterns of DBS electrode placement were associated with beneficial effects on the Unified PD Rating Scale (UPDRS)
- 44 patients with PD: connectivity at the DBS electrode location could predict individual patient UPDRS scores with an average error of 15%
- Connectivity data could be used in conjunction with DBS for more accurate and effective electrode placement



Horn et al. Ann Neurol. 2017 doi: 10.1002/ana.24974