MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

New Neuromodulation Treatments for Mood Disorders

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Harvard Medical School

Disclosures: Dr. Camprodon

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- Funding: NIMH, NIDA, NIAAA, NIA, NIH Brain Initiative, Harvard Players Health Study, Harvard Brain Initiative, Gerstner Foundation, AE Foundation, Solinsky Foundation.
- Scientific Advisory Board: Feelmore Labs, Hyka Therapeutics
- Consultant: Neuronetics

Disclosures: Dr. Henry

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Spouse Salary: Roche Pharmaceuticals

Lifetime Disclosures: Dr. Henry

- Eli Lilly: Honoraria, Travel, Research Grants
- Jansen Pharmaceuticals: Honoraria, Travel, Research Grants
- Glaxo Smith Kline: Honoraria, Travel, Research Grants
- Forest: Research Grants
- Bristol Myers Squibb: Honoraria
- Sunovian (Sepracor): Honoraria, Research Grants
- Pfizer (Wyeth Ayerst): Honoraria, Research Grants
- Bracco Diagnostics: Research Grants
- Biomedical Research Models: Stock ownership
- General Electric: Stock Ownership
- Abbott Labs: Former employee
- Roche Pharmaceuticals: wife is an employee

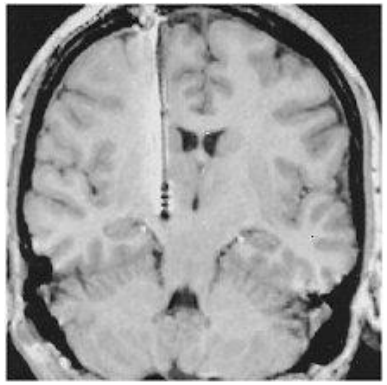
Brain Stimulation – Neuromodulation

Invasive

Deep Brain Stimulation (DBS)

Vagal Nerve Stimulation (VNS)

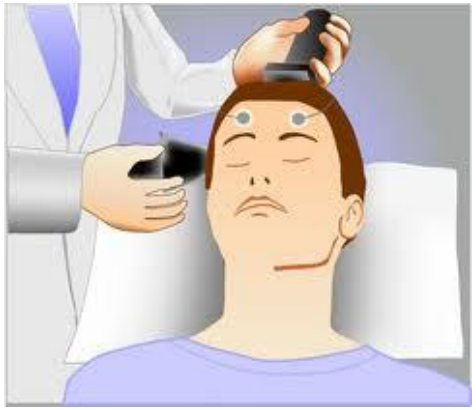
Epidural Stimulation (ES)



Convulsive

Electroconvulsive Therapy (ECT)

Magnetic Seizure Therapy (MST)

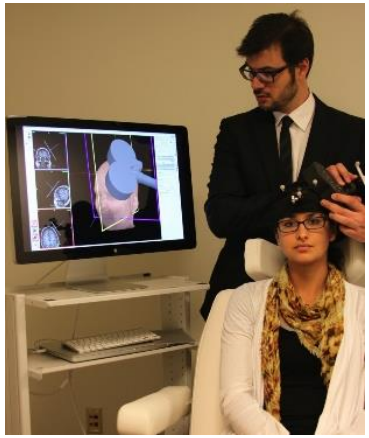


Noninvasive

Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

Transcranial Photobiomodulation (tPBM)

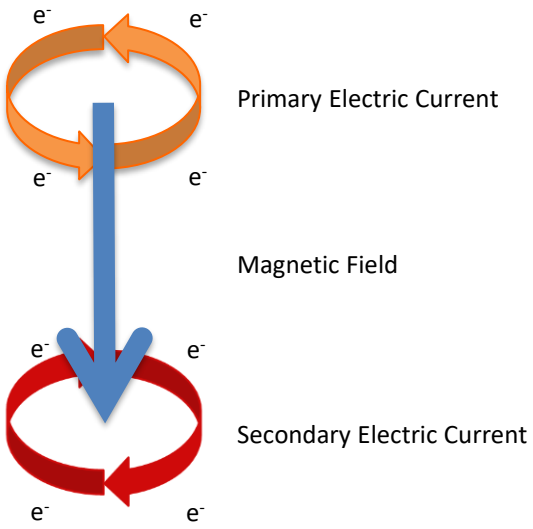


(Therapeutic) Neuromodulation and the FDA

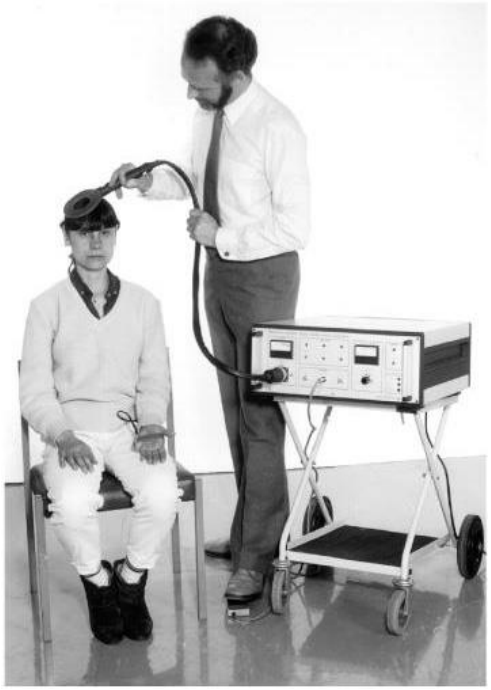
DEVICE	CONDITION	FDA STATUS
Deep Brain Stimulation	Chronic Pain	First indication, now revoked
	Parkinson´s Disease	General Approval
	Essential Tremor	General Approval
	Dystonia	Humanitarian Device Exception
	Obsessive Compulsive Disorder	Humanitarian Device Exception
	Major Depressive Disorder	Experimental
Vagus Nerve Stimulation	Epilepsy	General Approval
	Major Depressive Disorder	General Approval
Transcranial Magnetic Stimulation	Major Depressive Disorder	General Approval
	Migraines: acute management	General Approval
	Obsessive Compulsive Disorder	General Approval
	Smoking Cessation	General Approval
Transcranial Current Stimulation	MDD, ADHD, Alzheimer, Epilepsy…	Experimental

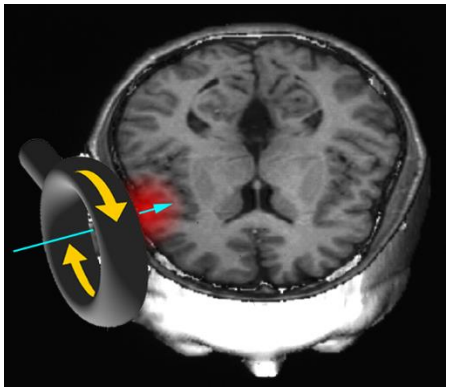
Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction



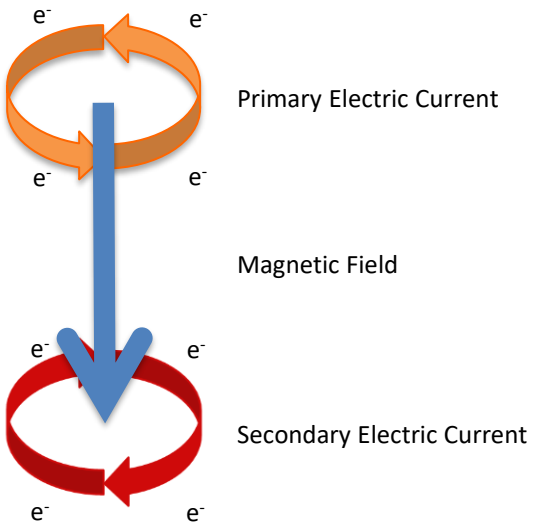
Anthony Barker 1984



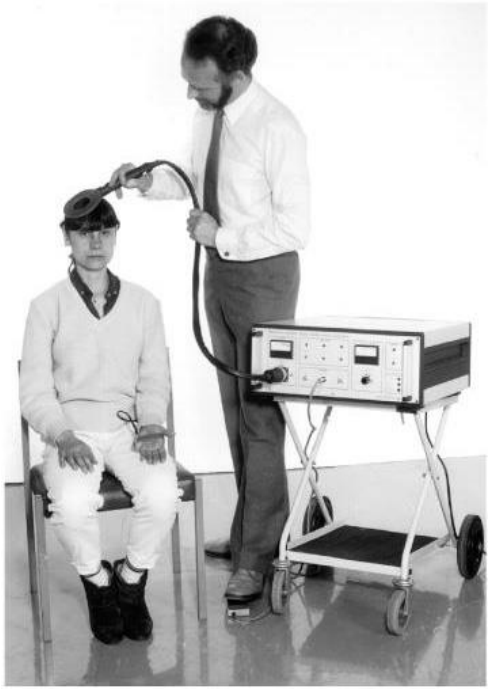


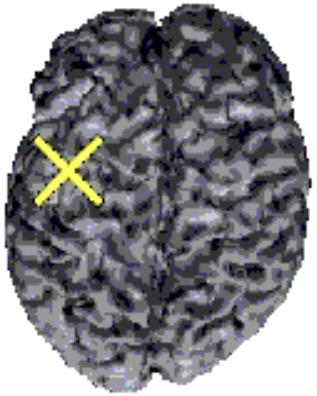
Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction



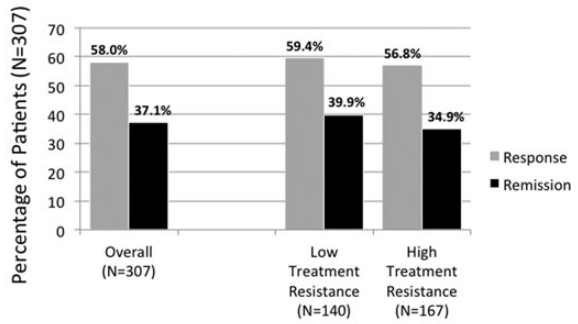
Anthony Barker 1984





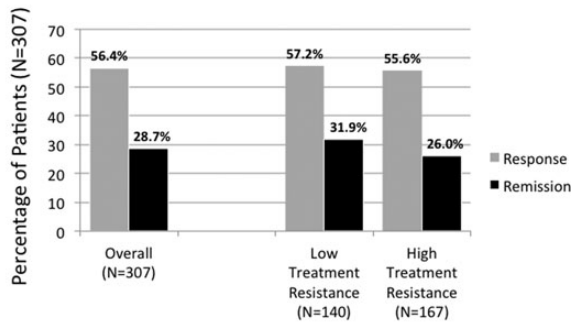
Effectiveness Naturalistic Studies in MDD

CGI-S Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

PHQ-9 Outcomes

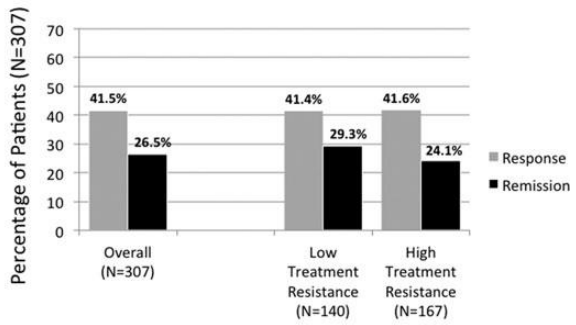


LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Carpenter et al. 2012

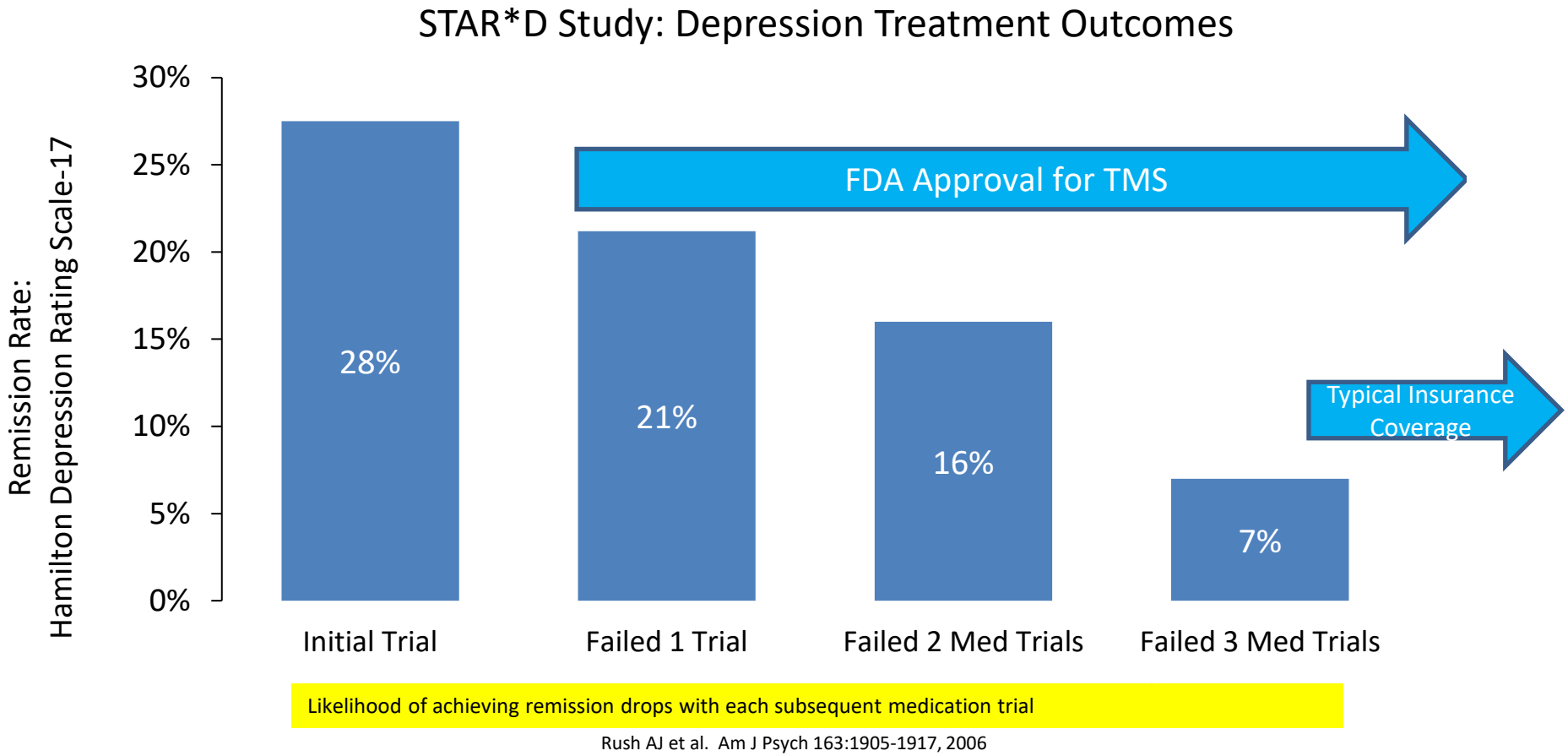
- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor

IDS-SR Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Why Consider TMS treatment for Depression?



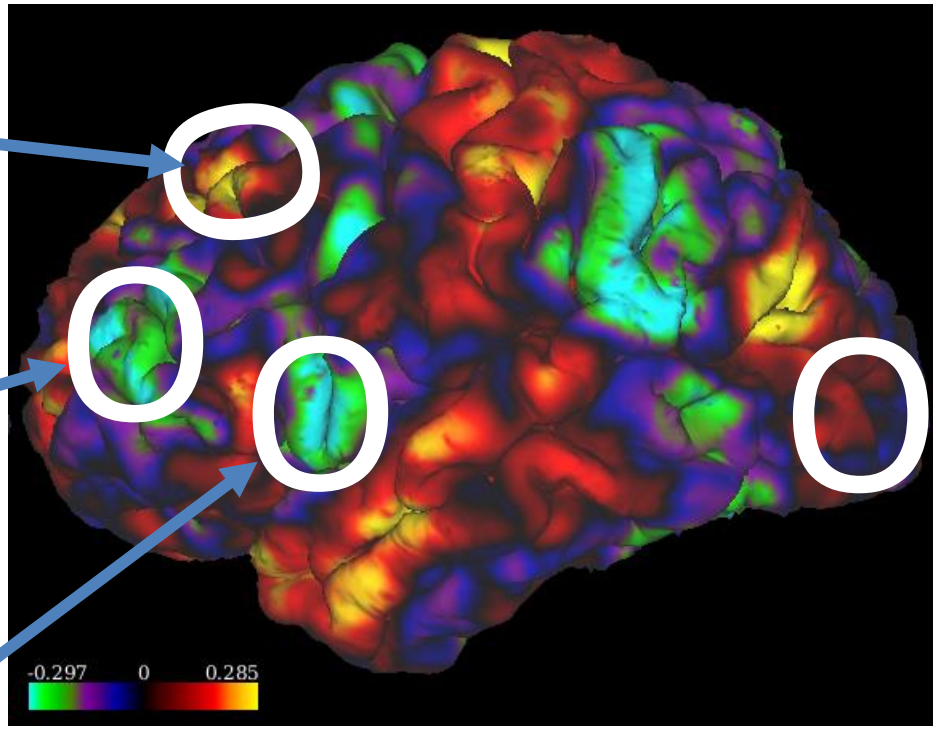
Rush AJ et al. Am J Psych 163:1905-1917, 2006

Anatomy of Therapeutic Targets

OCD Target:
DMPFC/pre-SMA

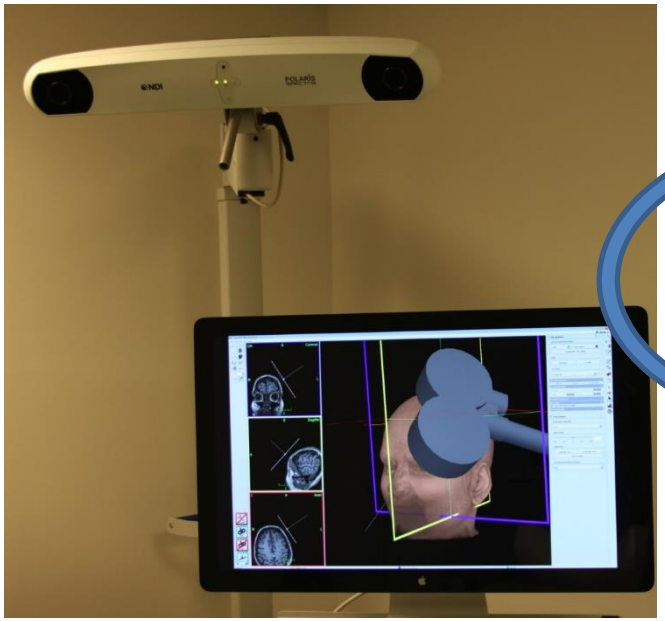
MDD Target:
DLPFC

Smoking Cessation:
VLPFC/Insula

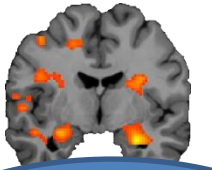


Migraine Target:
Occipital pole

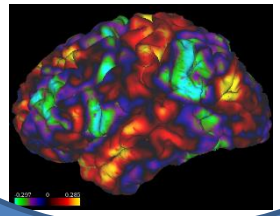
Localization: Neuronavigation

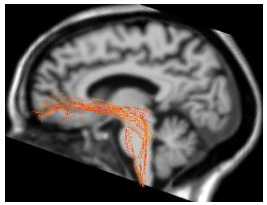


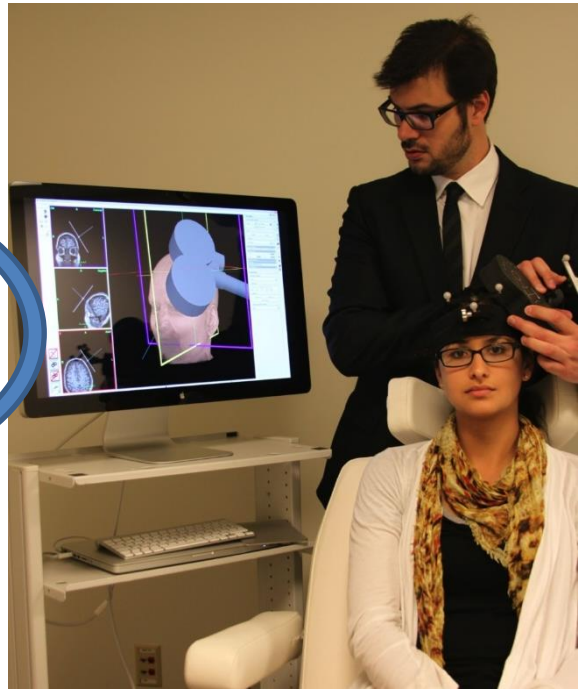
Task fMRI



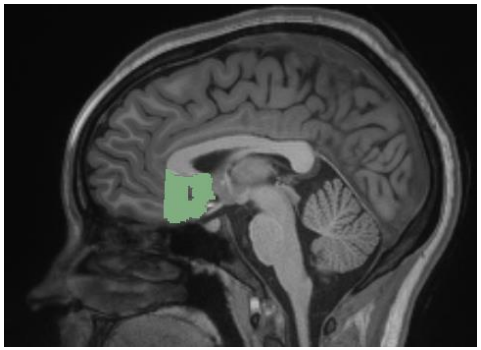
fcMRI

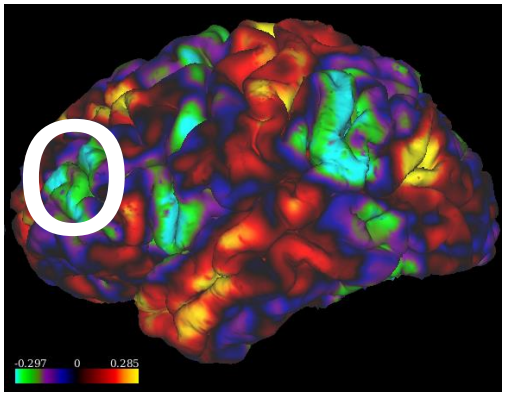


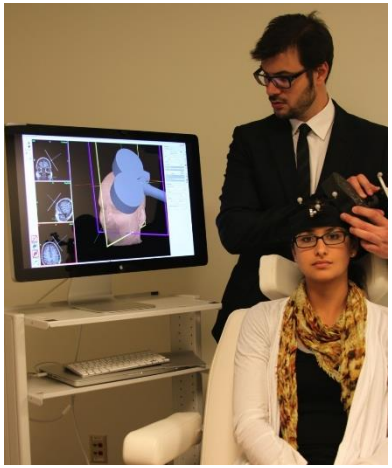




Individualized fcMRI-guided TMS

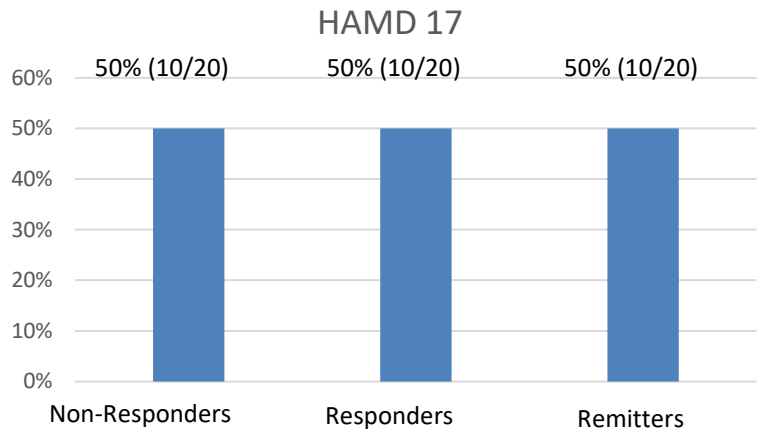


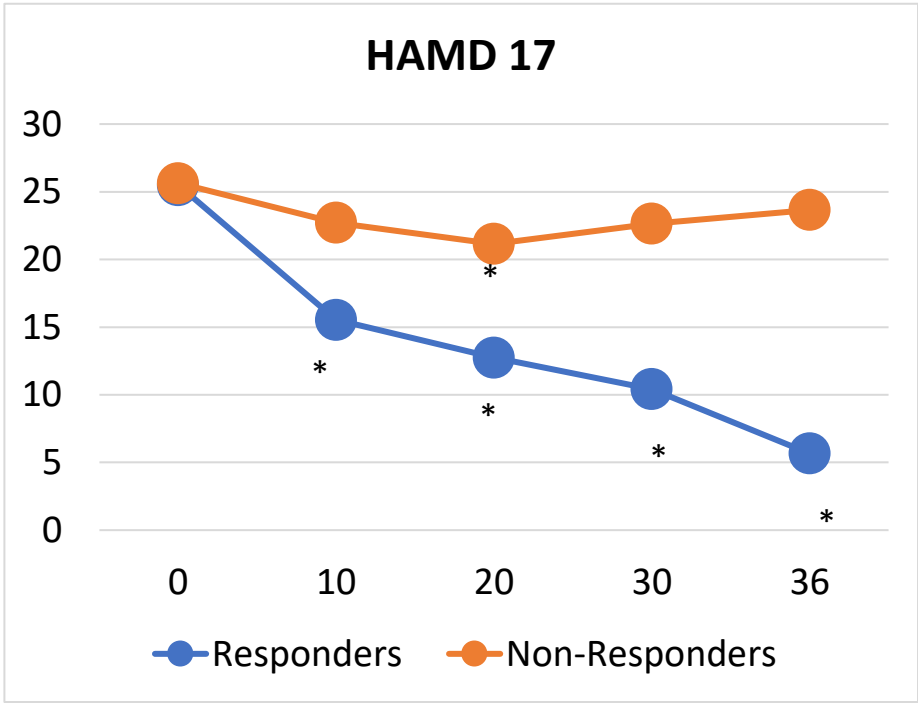




Clinical Response

(20 patients, open-label)

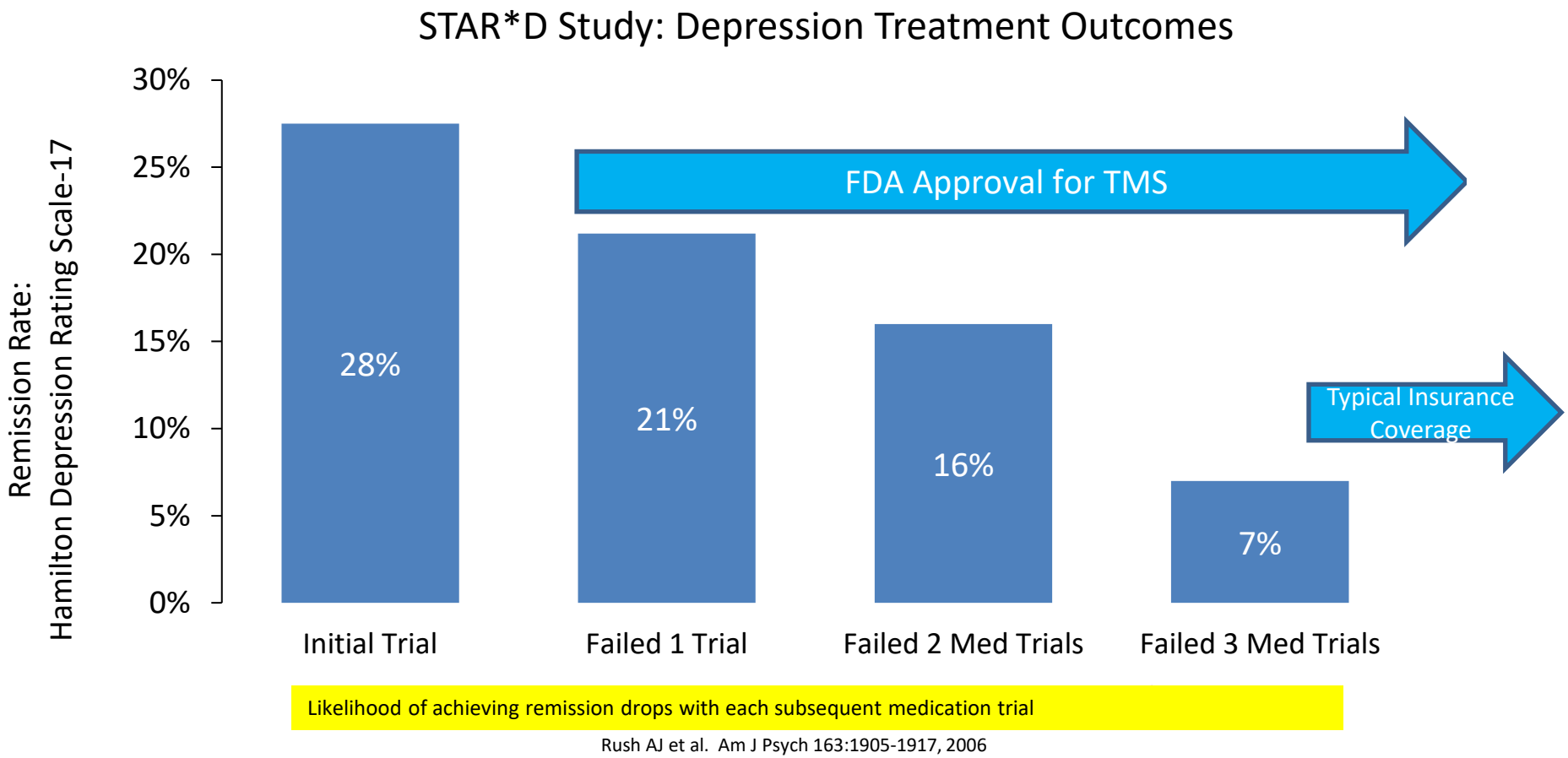




*p<.05 from baseline

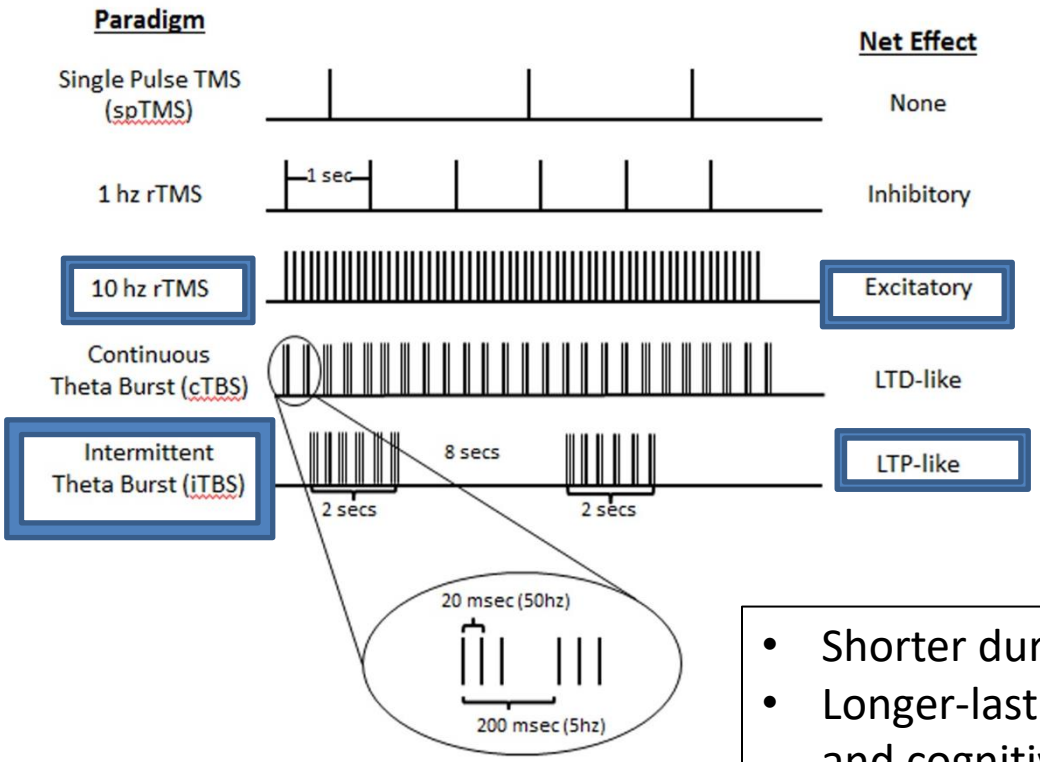
Failed medications in current episode: 7.06 (range 5-12)

In perspective…



Rush AJ et al. Am J Psych 163:1905-1917, 2006

Theta Burst Stimulation (TBS)



- Shorter duration
- Longer-lasting physiological and cognitive effects are established in mechanistic studies

FDA-cleared: TBS for MDD

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

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonathan Downar

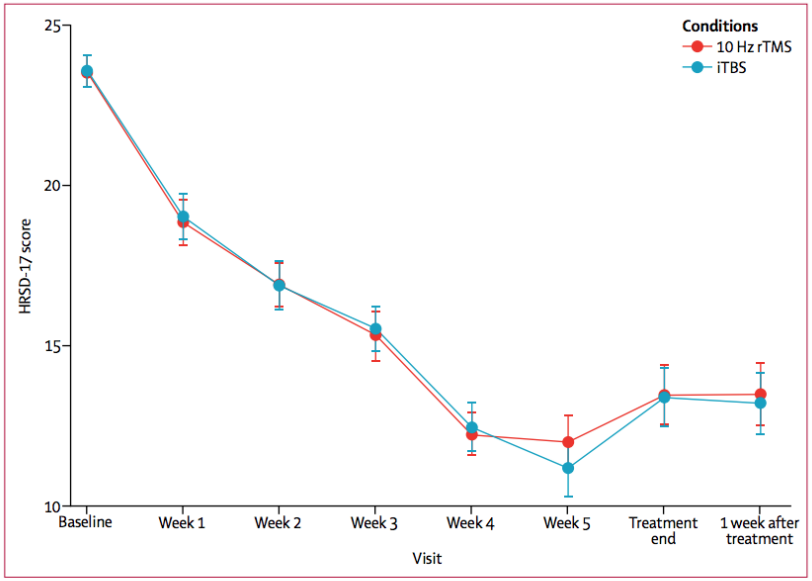


Figure 3: **Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

Response Rate: 39%-49%
Remission Rate: 20%-32%

FDA cleared in 2018

Accelerated TBS Protocol

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

Accelerated TBS for MDD

The American Journal of Psychiatry

Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression (SAINT-TRD)

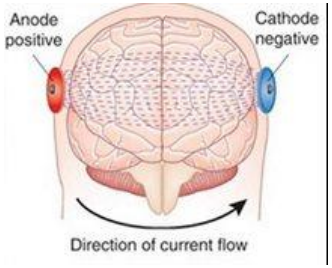
Protocol
- iTBS (excitatory) to left DLPFC
- Pulse intensity: 90% vs 120% RMT
- 1800 pulses/session (**3x** 600pulses)
- **10** sessions per day (50min pause)
  - = 6 weeks of daily TBS
- 5 consecutive days (inpatient)
  - = 5 courses of TBS

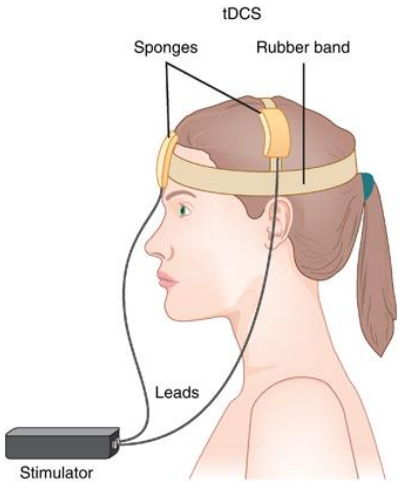
22 patients (DBS candidates)
1 did not complete
19 remitters after 5 days (86.36% ITT)

TMS for Bipolar Depression

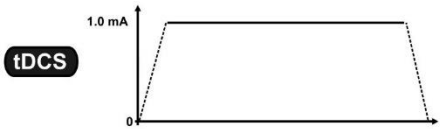
- FDA In 2020, the FDA granted **breakthrough device designation** to TMS for treating bipolar depression
- Traditional 10Hz protocols to the left DLPFC seem effective, but unclear TBS is.
  - What is the right anatomical target for BD?
  - What is the right frequency of stimulation?

Transcranial Electrical Stimulation

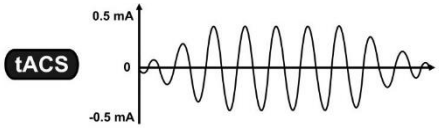




transcranial Direct Current Stimulation (tDCS)



transcranial Alternating Current Stimulation



transcranial Random Noise Stimulation

tDCS for MDD

BJPsych The British Journal of Psychiatry (2012) 200, 52–59. doi: 10.1192/bjp.bp.111.097634

Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial†

Colleen K. Loo, Angelo Alonzo, Donel Martin, Philip B. Mitchell, Veronica Galvez and Perminder Sachdev

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Continuation transcranial direct current stimulation for the prevention of relapse in major depression

Donel M. Martin [a], Angelo Alonzo [a], Kerrie-Anne Ho [a], Michael Player [a], Philip B. Mitchell [a], Perminder Sachdev [a,b], Colleen K. Loo [a,c,*]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

Results From a Factorial, Randomized, Controlled Trial

Andre R. Brunoni, MD, PhD; Leandro Valiengo, MD; Alessandra Baccaro, BA; Tamires A. Zanão, BS; Janaina F. de Oliveira, BS; Alessandra Goulart, MD, PhD; Paulo S. Boggio, PhD; Paulo A. Lotufo, MD, PhD; Isabela M. Benseñor, MD, PhD; Felipe Fregni, MD, PhD

ORIGINAL ARTICLE

Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression

A.R. Brunoni, A.H. Moffa, B. Sampaio-Junior, L. Borrione, M.L. Moreno, R.A. Fernandes, B.P. Veronezi, B.S. Nogueira, L.V.M. Aparicio, L.B. Razza, R. Chamorro, L.C. Tort, R. Fraguas, P.A. Lotufo, W.F. Gattaz, F. Fregni, and I.M. Benseñor, for the ELECT-TDCS Investigators*

tDCS for MDD

ORIGINAL ARTICLE

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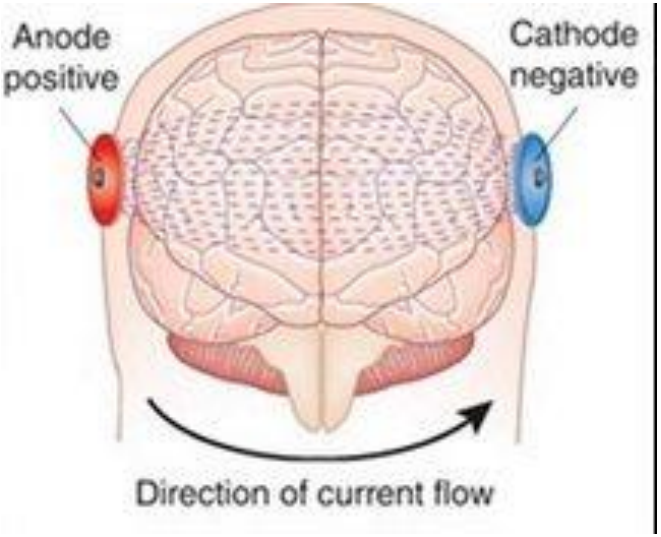
Table 2. Response and Remission Rates According to Montgomery-Asberg Depression Rating Scale Scores[a]

	No. (%)					
	Week 2		Week 4		Week 6	
Group	Response	Remission	Response	Remission	Response	Remission
Sham tDCS and placebo	11 (36.7)	6 (20.0)	9 (30.0)	3 (10.0)	5 (16.7)	4 (13.3)
Sham tDCS and sertraline	10 (33.3)	5 (16.7)	8 (26.7)	4 (13.3)	10 (33.3)	9 (30.0)
Active tDCS and placebo	9 (30.0)	4 (13.3)	12 (40.0)	7 (23.3)	13 (43.3)	12 (40.0)
Active tDCS and sertraline	16 (53.3)	6 (20.0)	16 (53.3)	7 (23.3)	19 (63.3)	14 (46.7)
P value	.25	.89	.14	.40	<.001	.03

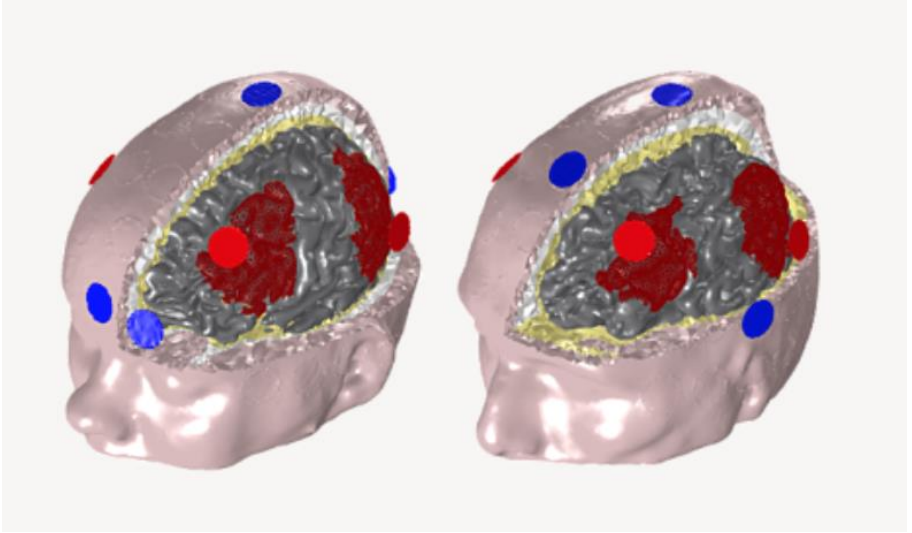
Home-based tDCS for MDD

- CE approved
- FDA granted IDE: pivotal trial launching

Standard vs Optimized Montage



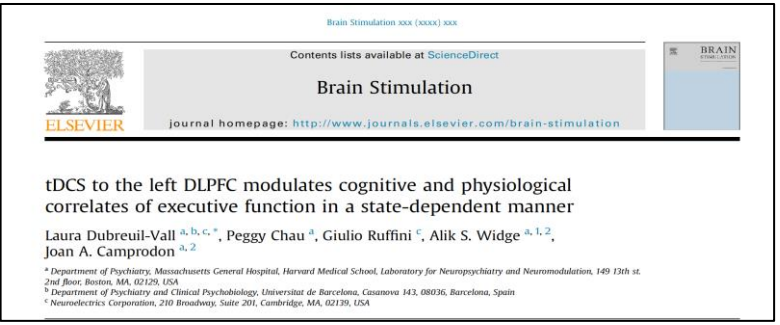
Traditional Bipolar
Montage: L+ - R-



Individualized multielectrode
High Definition tDCS

Beyond Mood in MDD: Cognition

Established pro-cognitive effects of tDCS



Brain Stimulation xxx (xxxx) xxx

Contents lists available at ScienceDirect

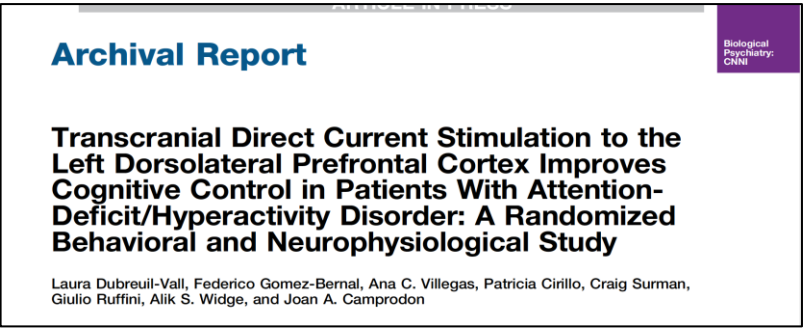
Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

tDCS to the left DLPFC modulates cognitive and physiological correlates of executive function in a state-dependent manner

Laura Dubreuil-Vall [a, b, c, *], Peggy Chau [a], Giulio Ruffini [c], Alik S. Widge [a, 1, 2], Joan A. Camprodon [a, 2]

[a] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Laboratory for Neuropsychiatry and Neuromodulation, 149 13th st. 2nd floor, Boston, MA, 02129, USA
[b] Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona, Casanova 143, 08036, Barcelona, Spain
[c] Neuroelectrics Corporation, 210 Broadway, Suite 201, Cambridge, MA, 02139, USA



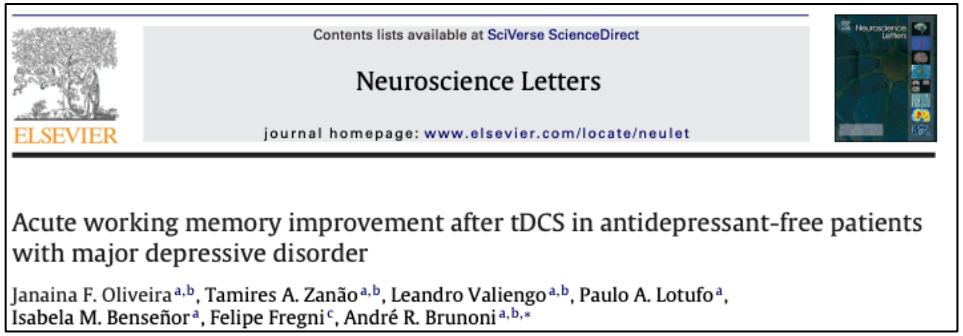
Archival Report

Biological Psychiatry: CNNI

Transcranial Direct Current Stimulation to the Left Dorsolateral Prefrontal Cortex Improves Cognitive Control in Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Behavioral and Neurophysiological Study

Laura Dubreuil-Vall, Federico Gomez-Bernal, Ana C. Villegas, Patricia Cirillo, Craig Surman, Giulio Ruffini, Alik S. Widge, and Joan A. Camprodon

Also for patients with MDD



Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

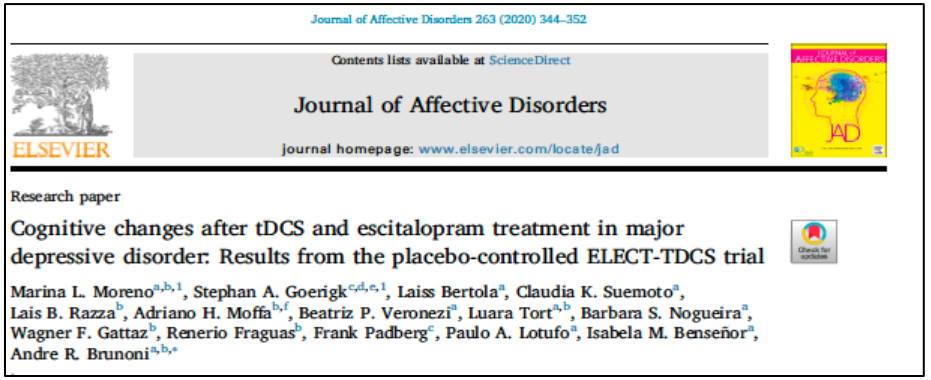
Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder

Janaina F. Oliveira [a,b], Tamires A. Zanão [a,b], Leandro Valiengo [a,b], Paulo A. Lotufo [a], Isabela M. Benseñor [a], Felipe Fregni [c], André R. Brunoni [a,b,*]

ARCHIVAL REPORT

Amelioration of Cognitive Control in Depression by Transcranial Direct Current Stimulation

Larissa Wolkenstein and Christian Plewnia



Journal of Affective Disorders 263 (2020) 344–352

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Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Cognitive changes after tDCS and escitalopram treatment in major depressive disorder: Results from the placebo-controlled ELECT-TDCS trial

Marina L. Moreno [a,b,1], Stephan A. Goerigk [c,d,e,1], Laiss Bertola [a], Claudia K. Suemoto [a], Lais B. Razza [b], Adriano H. Moffa [b,f], Beatriz P. Veronezi [a], Luara Tort [a,b], Barbara S. Nogueira [a], Wagner F. Gattaz [b], Renerio Fraguas [b], Frank Padberg [c], Paulo A. Lotufo [a], Isabela M. Benseñor [a], Andre R. Brunoni [a,b,*]

ECT Utilization in U.S. 2014

- General Population
  - 2014 Marketscan database (N=47,258,528)
  - 5.56 ECT patients per 100,000.
  - 0.25% of patients with a mood disorder.
  - Co-morbid psychiatric disorder (RR = 5.70)
  - Multiple Psychotropic Medications (d = 0.77)
  - Substance use disorder (RR = 1.97)

Wilkinson ST et al., Psychiatr Serv 2018 69:542-8

QUESTIONS

1. What is current clinical use of ECT?
   - A. MDD
   - B. Catatonia
   - C. Psychosis
   - D. Adolescents
   - E. COVID
2. What is the “Best Way” to do ECT?
   - A. Brief vs Ultra-Brief Pulse
   - B. FEAST
3. What do you do after ECT?
   - A. Medication Management
   - B. Maintenance ECT

Clinical Indications for ECT

Disease Responsive to ECT	Clinical Circumstances
Major Depression	Need for rapid, definitive clinical response (severity, safety)
Mania	Treatment Resistance Intolerance to medications/therapy
Catatonia/Trisomy 21 Disintegrative Disorder	History of positive response to ECT
Psychosis: Schizophrenia/schizoaffective disorder	Patient's Preference
Parkinson's Disease (on-off) NMS Intractable Seizures	

Weiner, R, 2001
Rudorfer et al.1997

Clinical Predictors of Response to ECT

	Depression	Mania	Psychosis	Catatonia
Positive	-Psychomotor retardation -psychotic symptoms -Age	-Severe mania (+/- psychosis) -Mixed states	- Good prognosis signs	
Negative	- Antidepressant Medication failure - Chronicity of episode	-Irritability		

Rudorfer MV et al., 1997
Pinna M et al., 2016

COVID

- Limited Availability
  -- Resources diverted to COVID pts and other procedures.
  -- Dosing paradigm more definitive.
  -- PPE for providers
- Bag mask ventilation increases droplets
  -- Ventilation changes

BEST WAY TO DO ECT?

- **Efficacy without side effects**
- Electrode Placement
- Stimulus
- Dose
- Anesthesia

Electrode Placement

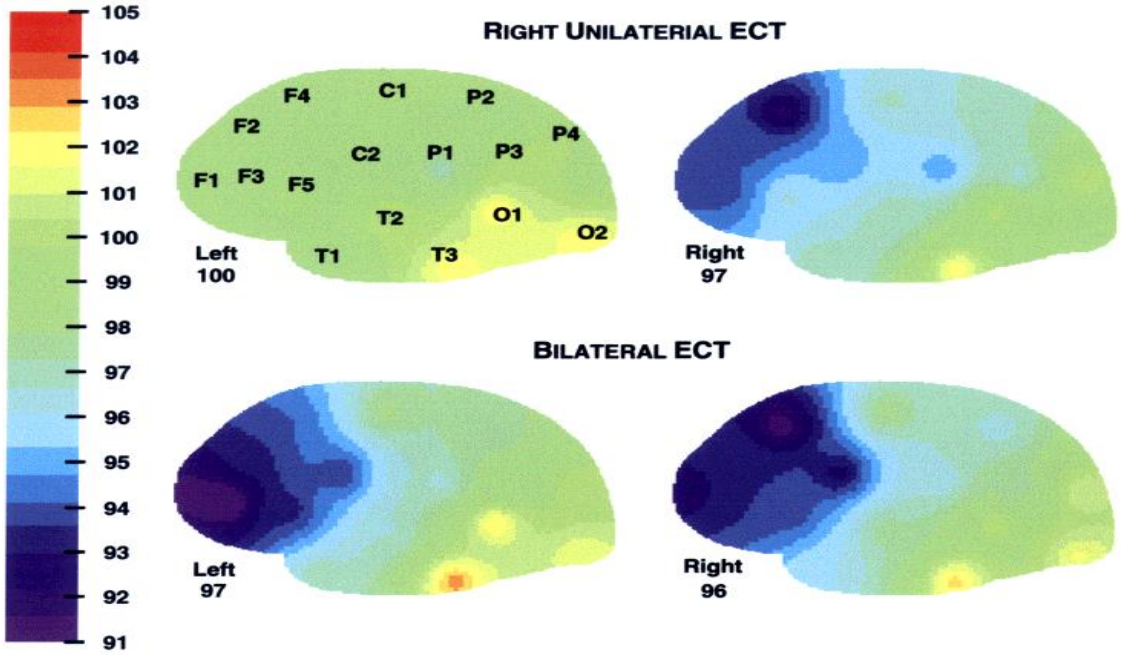
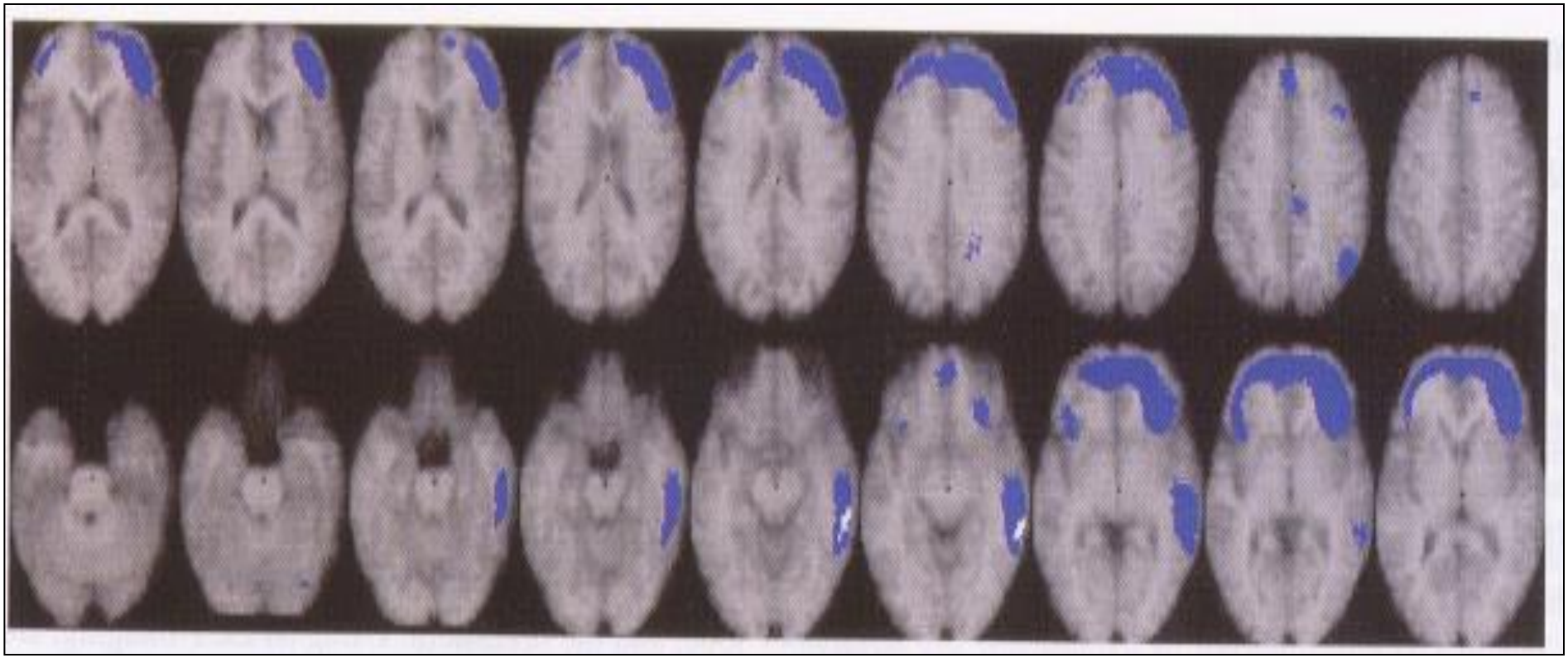


Figure 1. Changes in regional cerebral blood flow (rCBF) in depressed patients acutely after a single ECT treatment, as a function of electrode placement. CBF values at 32 brain regions were expressed as ratios of values 50 min after a treatment relative to 30 min before the treatment (post/pre × 100). Values of 100 indicate no change. The ratio scores were color coded so that purple and blue colors correspond to posticta CBF reductions, whereas orange and red colors correspond to posticta CBF increases. The brain shapes are displayed in a 185 × 112 matrix. Pixels were interpolated from all 16 detectors in each hemisphere, with each detector value multiplied by an inverse-square factor equal to $2^{18}/r^2$, and r being the distance in pixels to the center of each detector. All pixels within a radius of 5 from the center of each detector were set to the value of that detector. Changes in the left and right hemispheres are presented separately for patients treated with right unilateral ECT (n = 28) or bilateral ECT (n = 26). Relative positions of the rCBF detectors are labeled on the representation of the left hemisphere of patients treated with right unilateral ECT [Nobler et al., 1994].

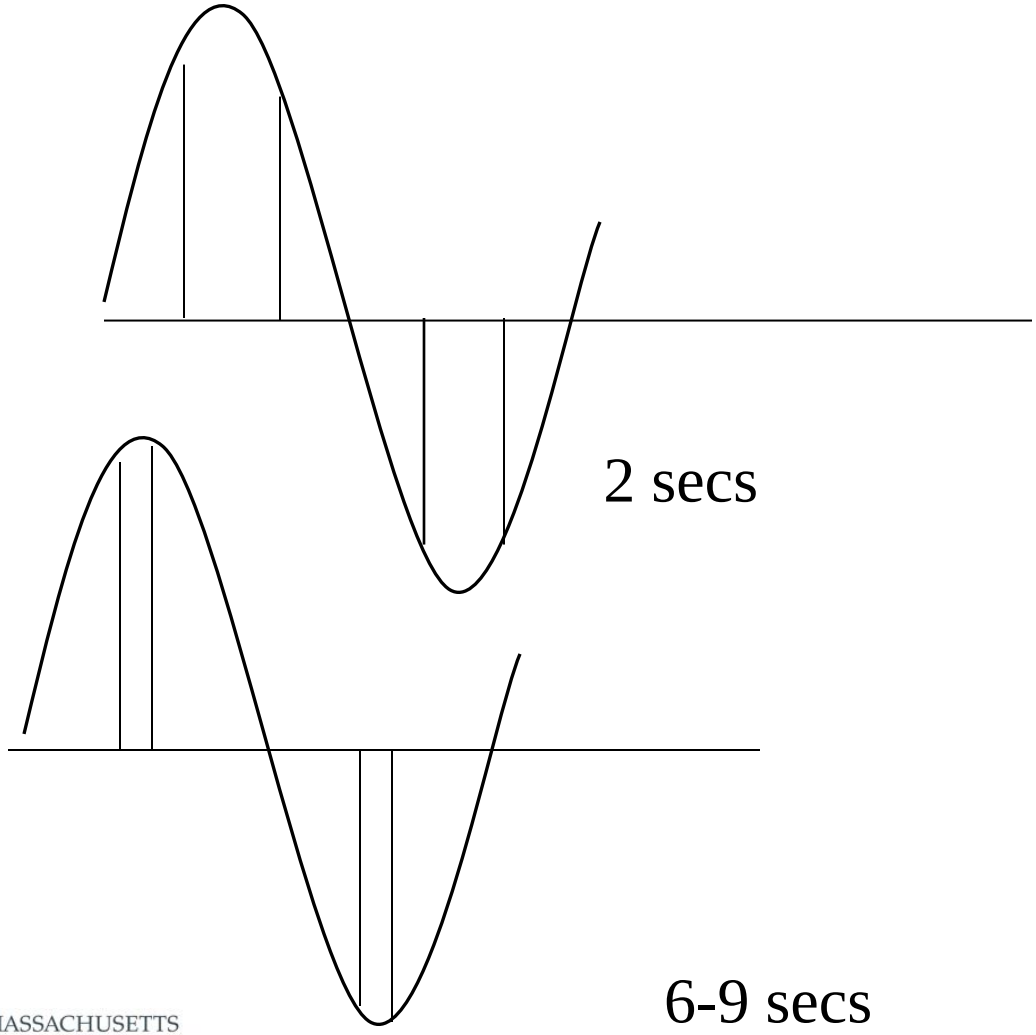
Nobler MS et al., Depression and Anxiety 2000; 12:144-156

Absolute CMRglu Pre-Post ECT



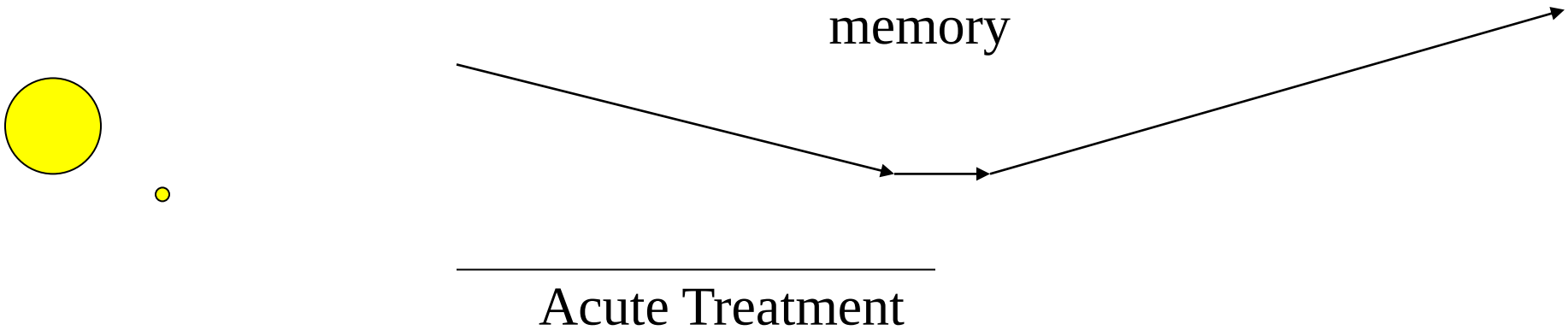
(Henry, Schmidt, Matochik, Stoddard, & Potter, 2001)

Evolution of ECT Technique



- 1938 – Sine Wave
- 1976 – Brief Pulse
- 1963, 2008 - Ultra-Brief Pulse
- 2003 - MST
- 2009 – FEAST

AVERSE EFFECTS: Memory



Ultra-Brief v Brief Pulse ECT

- Brief Pulse showed decreases in autobiographical, verbal and non-verbal memory, and processing speed.
- Ultra-brief less decline in autobiographical and anterograde memory. (Verwijk et al., 2012)
- Systematic Review of Efficacy. (Tor et al., 2015)

  - BP better than UBP (8.7 v 9.6)

  - BP more remissions than UBP (OR 0.71)

Seizure Threshold Dose

Unilateral

- 50%: 35% response rate
- 150%: 30% response rate
- 500%: 65% response rate

Bilateral

- 150%: 65% response rate

Responder = ≥ 60% reduction HRSD

(Sackeim et al., 2000)

Antidepressant Response

- 2003 – UK ECT Review Group
- **Real vs Sham ECT on Depression:**
  - 6 trials, 256 patients, 2 sine wave
  - Mean difference HDRS 9.7 (95% CI 5.7-13.5)
- **Bilateral vs Unilateral ECT:**
  - 22 trials, 1408 patients, Duration, Placement, Number varied
  - Mean difference HDRS 3.6 (95% CI 2.2- 5.2) - Bilateral
- **ECT vs Pharmacotherapy:**
  - 18 trials, 1144 patients, Duration, Placement, Number varied
  - Mean difference HDRS 5.2 (95% CI 1.4 – 8.9)
  - TCA's, MAOI's, Tryptophan, SSRI's, Li
  - Variable definitions of treatment refractoriness (4 trials).

(UK ECT Review Group, 2003)

Medication Management

- Drugs that raise seizure threshold.
  1. Benzodiazepines
  2. Antiepileptic Agents
- Drugs that lower seizure threshold.
  1. Aminophylline/caffeine
  2. Buproprion
- Lithium.

Anesthesia Options

- Pentathol
- Methohexital
- Etomidate
- Propofol
- Delayed Stimulation
- Divided Dosing Strategy

KETAMINE AUGMENTATION

- 1995-2016: 24 published articles using ketamine anesthesia/augmentation of ECT in the literature.
- Improvement early but not sustained.
- Overall clinical efficacy not different.
- Significant Limitations in study design.

Galvez V et al., 2017 World J Biol Psychiatry 18:424-444

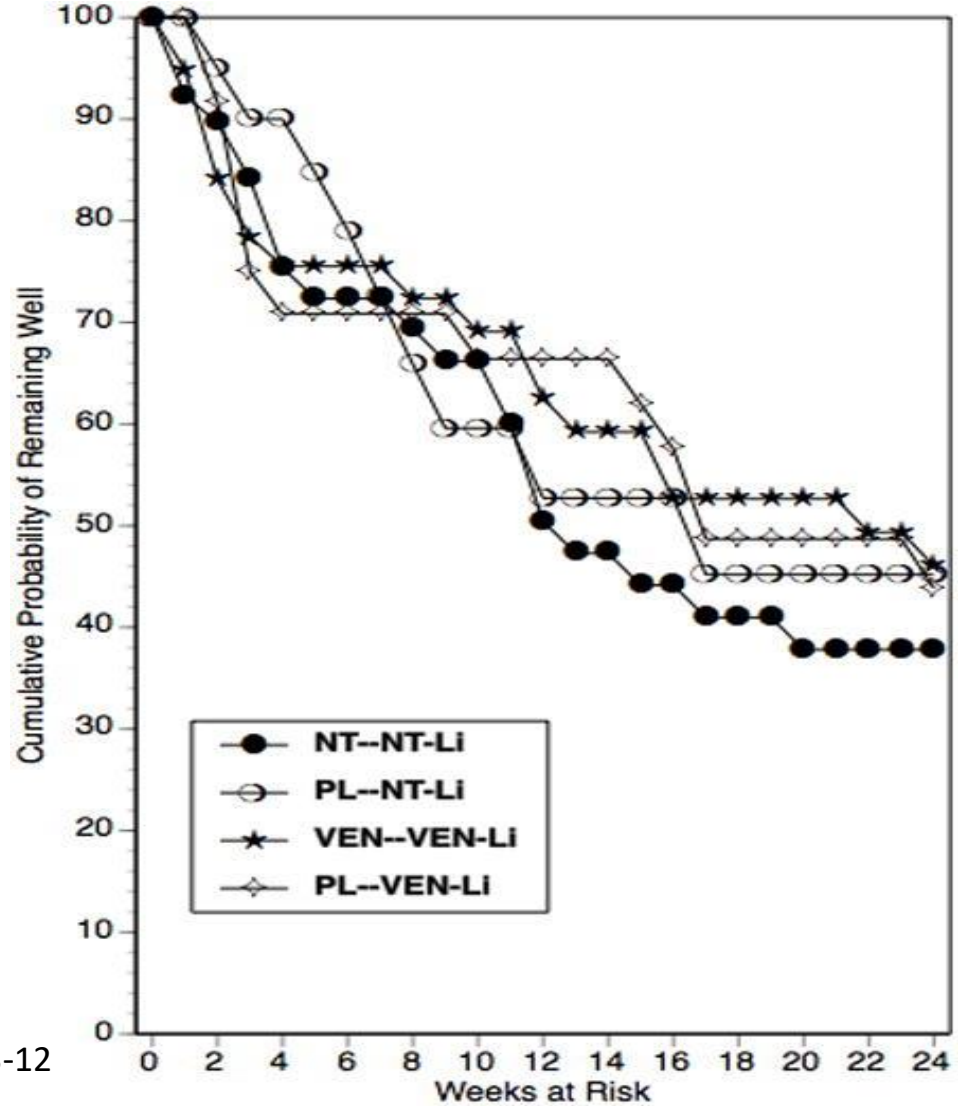
AFTER THE ACUTE COURSE OF ECT

- No Treatment
- Maintenance ECT
- Maintenance Medications/Psychotherapy

Maintenance ECT

- Rationale: Acute ECT has high relapse rate.
  Treatment resistance.
- Efficacy: 61% PT vs 32% ECT +PT relapsed 1 yr.
  Nordenskjold et al J ECT 2013; 29:86-92
- Schedule: 1x/week – 4 weeks
  1x/2 weeks
  1x/3 weeks
  1x/4 weeks – 6-12 months.

LITHIUM PLUS NT vs VEN POST ECT



Prudic J et al., J ECT. 2013; 29:3-12

CONCLUSIONS

- ECT continues to be the “gold-standard” for treatment resistant depression.
- MOA likely reflects both global and localized effects
- Major Effect is a reduction in metabolic activity: ? GABA.