Brain Stimulation and the Future of Electroconvulsive Therapy

Minnesota Psychiatric Association
Fall Scientific Meeting:
Technology and Transformative Psychiatric Practice
November 17, 2018

Harold A. Sackeim, PhD
Professor, Departments of Psychiatry and Radiology
College of Physicians and Surgeons, Columbia University

Chief Emeritus, Department of Biological Psychiatry
New York State Psychiatric Institute

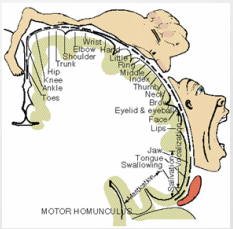
Founding Editor, *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*

DISCLOSURES

- Consultant to and/or grants from Brain Stimulation Industry: Brainsway Ltd., Cervel Neurotech Inc./NeoStim Inc., LivaNova PLC (Cyberonics Inc.), Magstim Ltd., MECTA Corp, NeoSync Inc., Neuronetics Inc., and NeuroPace Inc.
- Consultant to and/or grants from Pharmaceutical Industry: Cambridge Neuroscience Inc., Eli Lilly & Co., Forest Laboratories, Hoffman-La Roche AG, Interneuron Pharmaceuticals Inc., Novartis International AG, Pfizer Inc., Warner-Lambert, Inc., and Wyeth-Ayerst, Inc.
- Inventor of Magnetic Seizure Therapy (MST)
- Inventor and a non-remunerative patent for Focal Electrically-Administered Seizure Therapy (FEAST) (MECTA Corporation)
- Inventor and a non-remunerative patent for Titration in the Current Domain in ECT (MECTA Corporation)

Brain Stimulation:
A New Field of Neuroscience and Therapeutics

Wilder Penfield, M.D.

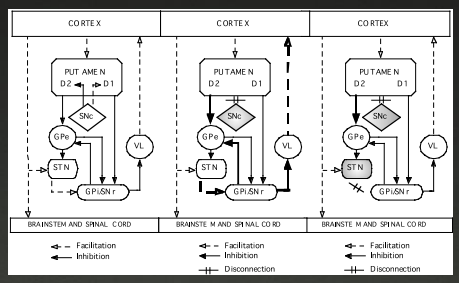


Therapeutic Power of DBS in PD

STN DBS OFF

STN DBS ON

Capacity to Modulate Networks at Multiple Nodes: We Don't (Necessarily) Fix What's Broken



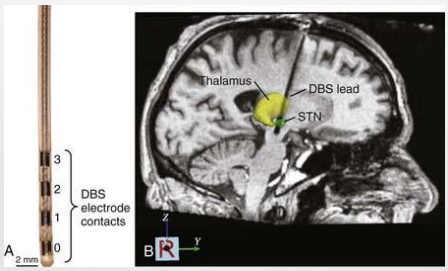
Normal | Parkinson's Disease | DBS

2014 Lasker Awardees for STN DBS for PD

Mahlon R. Delong

Alim-Louis Benabid

DBS Lead Placement in the STN



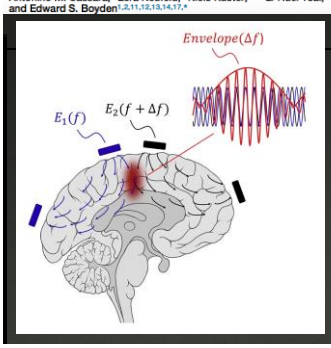
- Electrode diameter of 1.27 mm (Medtronic Model 3387); 4 contacts each 1.5 mm high, spaced 1.5 mm apart; electrodes on left and right
- We lack exact maps of pathways, let alone individual differences; Millimeter resolution key in PD; stimulation parameters determined by response

Activating Specific Neurons in mdPFC Turns Wimps into Bullies: The Tiger Mom Effect

Tingting Zhou et al. Science 2017;357:162-168
History of winning remodels thalamo-PFC circuit to reinforce social dominance

Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Nir Grossman,[1,2,3,4] David Bono,[5] Nina Dedic,[7,16] Suhasa B. Kodandaramaiah,[1,6,16] Andrii Rudenko,[7,8] Ho-Jun Suk,[2,15] Antonino M. Cassara,[9] Esra Neufeld,[9] Niels Kuster,[9,10] Li-Huei Tsai,[7,11] Alvaro Pascual-Leone,[3] and Edward S. Boyden[1,2,11,12,13,14,17,*]



- Using electrical field frequency cancellation, Grossman et al. could induce activation of specific hippocampal fields without impacting on overlying cortex
- They also stimulated individual whiskers in motor cortex

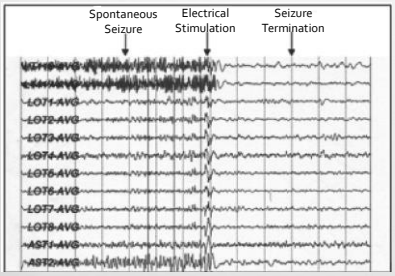
Brain Stimulation Human Interventions 2018

Intervention	Convulsive	Implanted	Magnetic	Responsive	Continuous
Transcranial Magnetic Stimulation (TMS)			✓		
Transcranial Electrical Stimulation (tDCS, tACS, tRNS)					
Transcranial Pulsed Ultrasound Stimulation (tPUS)					
Vagus Nerve Stimulation (VNS)		✓			✓
Deep Brain Stimulation (DBS)		✓			✓
Closed-Loop or Responsive DBS		✓		✓	
Electroconvulsive Therapy (ECT)	✓				
Magnetic Seizure Therapy (MST)	✓		✓		
Focal Electrically Applied Seizure Therapy (FEAST)	✓				

Key Features of Brain Stimulation

- Spatial targeting of neurocircuitry subserving therapeutic or basic motor/affective/cognitive processes; As a discovery tool, BS is key in revealing this circuitry
- Capacity to (1) reveal patterns of connectivity and (2) to modulate networks at multiple nodes
- Capacity to modulate brain functional activity independently in different brain regions, e.g., altering transmitter levels or plasticity measures in opposite directions
- Capacity to modulate brain activity with responsive stimulation
- Electrical stimulation is ephemeral; Any persistent behavioral or physiological effect reflects an endogenous adaptive response of the brain to BS; only one type of electricity vs. infinite artificial molecules
- BS can have distinct therapeutic properties (symptoms vs. syndromes; unusual durability)
- Capacity to design interventions to match stimulation parameters to the pathophysiology of the individual

Closed-Loop or Responsive Stimulation: Stopping Seizures



- Responsive stimulation is context-dependent; state of the brain (or behavior) triggers or shapes stimulation
- NeuroPace detects a paroxysmal event, and stimulates locally to terminate seizure

Bergey et al. *Epilepsia* (2002)

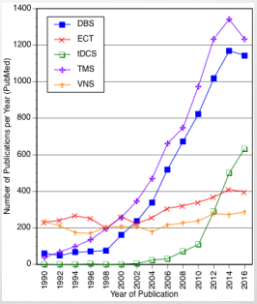
The Field of Brain Stimulation is Undergoing Explosive Growth!!

•Data for 2016 incomplete

•TMS, DBS, and tDCS have similar slopes; showing remarkable and continuing growth

•ECT (nearly 80 years old) doubled in publications

•VNS shows some recent growth

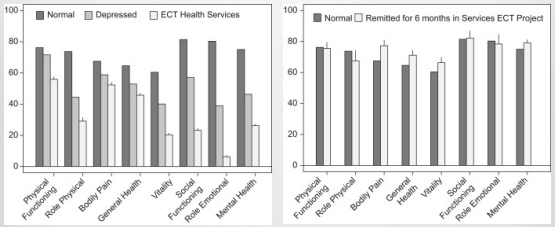


Electroconvulsive Therapy: Clinical Neuroscience of Mood Disorders

- ECT depressed samples among the most ill in terms of symptom severity, functional disability, and suicidality
- Extent of clinical improvement, speed of improvement, and percentage who benefit superior to any other psychological or biological therapy
- ECT samples could be studied medication free
- ECT can be spatially targeted; unilateral ECT as good as the Wada test to identify hemispheric specialization for language
- ECT has characteristic cognitive effects; a laboratory for the neuropsychology and neurobiology of learning and memory

Quality of Life: Services Study

Sackeim et al. Neuropsychopharmacology, 2007

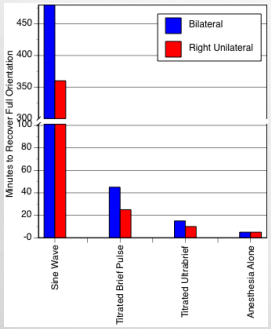


McCall et al. Journal of Affective Disorders, 2013

Major Factors Limiting the Use of ECT

- Cognitive Side Effects — Retrograde Amnesia
- Durability of Benefit — High Rates of Relapse
- Financial burden — Pills cost much less
- Lack of understanding of mechanisms
- Stigma — Distorted and negative perceptions (patients, professionals, and the public)

Tremendous Progress in Reducing Cognitive Effects: Little Room for Improvement

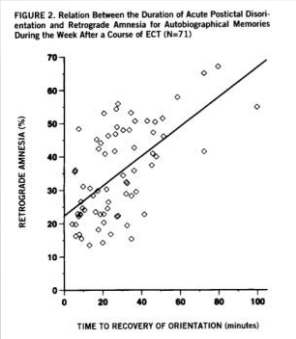


- Postictal recovery of orientation highly sensitive to ECT parameters
- Fantastic improvement in recovery time with progress in ECT stimulation

Miller, Siris, & Gabriel:
Treatment Delays in the Course of ECT
Hosp Community Psychiatry 1986

Electroconvulsive therapy (ECT) is often delayed because the patient develops cognitive disturbances. The authors reviewed the charts of 45 depressed patients who received ECT and found that 25 patients (56%) developed cognitive dysfunctions severe enough to cause a delay in treatment. The development of organic symptoms causing delays in treatment was positively correlated with increased age and the presence of preexisting cognitive dysfunction, and the treatment delays led to longer periods of hospitalization. The authors emphasize the need for early identification of the causes of cognitive dysfunction after ECT and for careful selection of the treatment strategy for each patient to reduce the risk of adverse effects.

Time to Recover Orientation Predicts Magnitude of PostECT Retrograde Amnesia



- Orientation recovery time predicts long-term retrograde amnesia for autobiographical information
- This effect holds both immediately and months following ECT
- Replicated by Martin, Galvez, & Loo et al. (2015)

Sobin et al. *Am J Psychiatry*, 1995

Path Model: Age, PreECT MMSE, Pulse Width, Electrode Placement and Time to Recover Orientation Predict Magnitude of PostECT Retrograde Amnesia

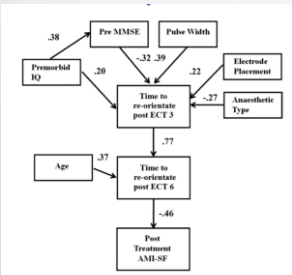


Figure 1. Hypothesized path model. Solid lines indicate statistically significant paths. AMI-SF, Columbia Autobiographical Memory Interview-Short Form; MMSE, Mini Mental State Examination.

- Orientation recovery time again predicts postECT retrograde amnesia for autobiographical information
- Other factors include age, pre-existing cognitive impairment, pulse width, and electrode placement

Martin, Galvez, & Loo *Int J of Neuropsychopharm*, 2015

First Demonstration of Impact of Treatment Parameters on Long-term Retrograde Amnesia for Autobiographical Information

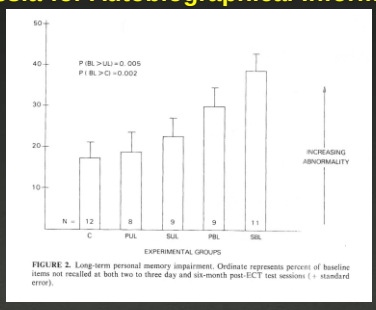
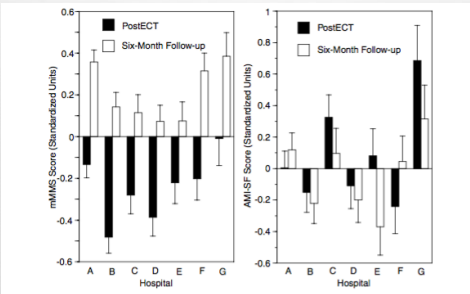


FIGURE 2. Long-term personal memory impairment. Ordinate represents percent of baseline items not recalled at both two to three day and six-month post-ECT test sessions (± standard error).

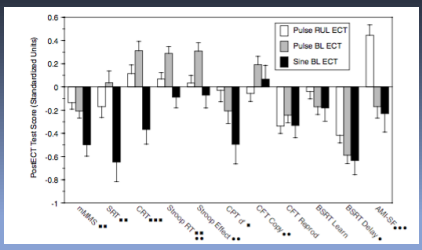
Weiner, Squire et al. Ann NY Acad Sci, 1986

The Cognitive Effects of Electroconvulsive Therapy in Community Settings



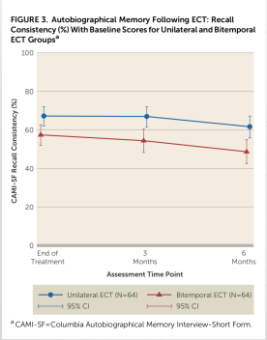
Sackeim et al. Neuropsychopharmacology, 2007

The Cognitive Effects of Electroconvulsive Therapy in Community Settings



Sackeim et al. *Neuropsychopharmacology*, 2007

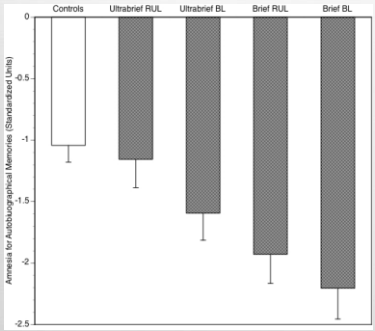
Long-term Retrograde Amnesia: The EFFECT-Dep Trial



- Large non-inferiority trial comparing twice weekly high dose (6xST) RUL ECT and moderate (1.5xST) BL ECT
- RUL and BL ECT not different in efficacy or relapse
- "Bitemporal ECT was associated with a lower percent recall of autobiographical information (odds ratio=0.66) that persisted for 6 months"
- RUL ECT also resulted in fewer subjective cognitive side effects acutely and at 6 months

Semkovska et al. *Am J Psychiatry*, 2016

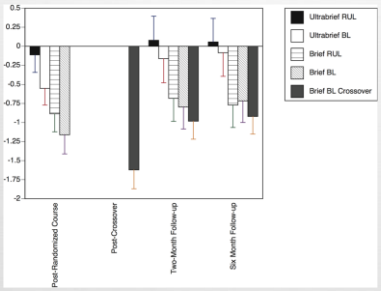
Retrograde Amnesia for Autobiographical Information Immediately Following the ECT Course



- No difference between RUL UB ECT and healthy controls
- Highly sensitive to ECT parameters
- ECT group differences persist for at least 6 months

Sackeim et al. *Brain Stimulation*, 2008

Long-term Retrograde Amnesia: The Ultrabrief Advantage



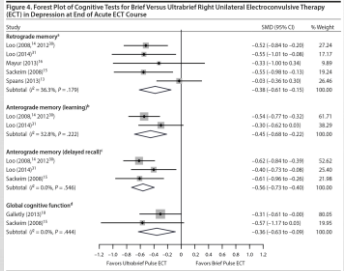
Effects of pulse width on amnesia maintained through 6-month follow-up

Sackeim et al. Brain Stimulation (2008)

A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression

Phern-Chern Tor, MBBS, DFD(CAW), MMed(Psych)[a,b]; Alison Bautovich, MBBS[a]; Min-Jung Wang, MSC[a]; Donel Martin, MClinNeuro, PhD[a]; Samuel B. Harvey, MBBS, MRCGP, MRCPsych, FRANZCP, PhD[a]; and Colleen Loo, MBBS, FRANZCP, MD[a,*]

Figure 4. Forest Plot of Cognitive Tests for Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy (ECT) in Depression at End of Acute ECT Course



[a]Retrograde memory: P < .001.
[b]Anterograde memory (learning): P < .005.
[c]Anterograde memory (delayed recall): P < .001.
[d]Global cognitive function: P = .009.
Abbreviation: SMD = standardized mean difference.

- UB RUL ECT superior to brief pulse RUL ECT in postECT cognitive measures
- In randomized trials, no difference in efficacy
- UB RUL patients received - 1 additional treatment. Likely due to superior cognitive effects

Tor et al. *J Clin Psychiatry* (2015)

Amazing Improvement in Cognitive Side Effects: Any Future Innovation Should Maintain Efficacy and Further Improve Safety

- In the PRIDE Study (Kellner et al., 2016) of 240 geriatric patients treated with venlafaxine and high dose, UB RUL ECT, 62% remitted.
- The standard in future comparisons (MST, FEAST) should be high dose (6xST), ultrabrief (UB), RUL ECT

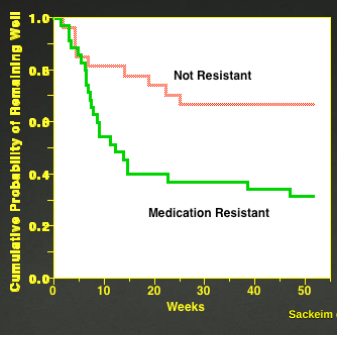
Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study

Charles H. Kellner, M.D., Mustafa M. Husain, M.D., Rebecca G. Knapp, Ph.D., W. Vaughn McCall, M.D., M.S., Georgios Petrides, M.D., Matthew V. Rudorfer, M.D., Robert C. Young, M.D., Sheleme Sampson, M.D., Shaun M. McCormack, Ph.D., Martina Mueller, Ph.D., Dian Prudic, M.D., Robert M. Greenberg, M.D., Sanjeev Kumar, M.D., Ph.D., Ashok Malhotra, M.D., Ph.D., Sanjeev Sinha, M.D., Ph.D., Sarah Ward, M.D., Ph.D., Shyhan Fahima, M.D., Vasudev Lakshmanan, M.D., Kristen G. Fobian, M.A., Mimi C. Briggs, B.A., Lauren S. Liebman, B.A., Emma T. Gedualdig, B.A., Abeba A. Tekleimanot, M.S., Sarah H. Lisanby, M.D., the CORE/PRIDE Work Group

Do the Therapeutic Effects of ECT Last?

- ECT is the only treatment in psychiatry that we stop once it works
- Research in the UK in 1960-1970's indicated that 50% relapse within six months on placebo; continuation pharmacology reduced this rate to 20%
- Continuation pharmacotherapy following ECT became the dominant approach

Relapse in the Modern Era

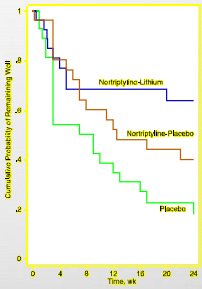


- Relapse was more than twice as likely among medication-resistant patients (68.6%) compared to patients who had not received an adequate medication trial prior to ECT (33.3%)

Sackeim et al. Arch Gen Psychiatry, 2000

Placebo-Controlled Trial of Continuation Pharmacotherapy

- Patients who responded to ECT at 3 centers randomized to placebo, nortryptyline alone or nortryptyline and lithium.
- Relapse rates (over 6 months) were 84% for placebo, 60% for nortryptyline, and 39% for the combination.



Sackeim et al. JAMA, 2001

Continuation ECT is as Effective as Continuation Psychopharmacology

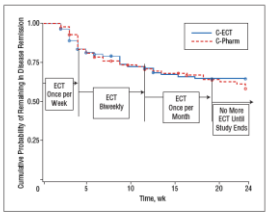
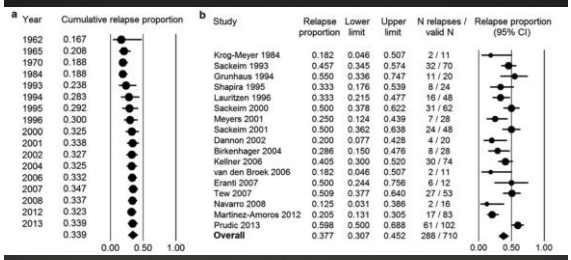


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: χ^2=0.30; P=.59. C-ECT indicates continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.

Kellner et al. Arch Gen Psychiatry, 2006

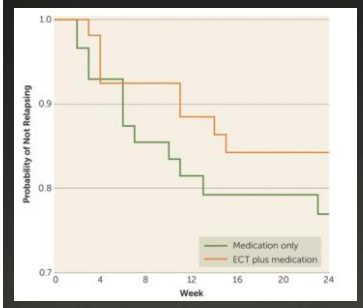
Meta-analysis of Post-ECT Relapse



- "In present day clinical practice, nearly 40% of ECT responders can be expected to relapse in the first 6 months and roughly 50% by the end of first year."

Jelovac et al. Neuropsychopharmacology, 2013

Combined Continuation ECT and Psychopharmacology Likely Most Effective



- Combined treatment superior to continuation pharmacotherapy alone in relapse prevention
- Only 15% relapse over 6 months
- UB RUL used for continuation ECT with a novel scheduling method

Kellner et al. *Am J Psychiatry*, 2016

Comparison of Outcomes: ECT and Pharmacotherapy (STAR*D)

	Acute Remission Rate	Probability of Remaining Well for 12 Months		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%**
ECT	**60.00%**	**50.00%**		**30.00%**

Sackeim, *JAMA Psychiatry*, 2017

Is ECT Cost Effective (in the US) and When Should ECT Be Used?

JAMA Psychiatry | Original Investigation

Cost-effectiveness of Electroconvulsive Therapy vs Pharmacotherapy/Psychotherapy for Treatment-Resistant Depression in the United States

Eric L. Ross, BA; Kara Zivin, PhD; Daniel F. Maixner, MD

- "Offering ECT after 2 failed lines of pharmacotherapy/ psychotherapy is most likely to maximize its health-economic value and is concordant with recommendations from some national guidelines and ECT specialists. Increasing use of ECT by offering it earlier in the course of treatment-resistant depression could greatly improve outcomes for this difficult-to-treat patient population."

Ross et al., *JAMA Psychiatry*, 2018

Additional Areas of Marked Progress

- Characterizing ECT processes and mechanisms of action
- Vision for future advances in ECT practice

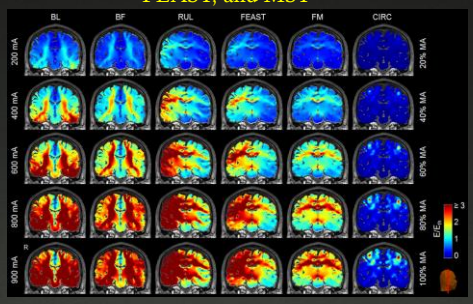
Vision of the Future

- ECT has an extraordinarily bright future in terms of further advancement
- Undoubtedly we will celebrate (I hope) ECT's 100 anniversary in 2038.
- Very few medical treatments last one hundred years!!

A Personal Perspective on the Future

- How we stimulate: Improved efficiency of stimulation
  - The role of current
  - Unidirectional stimulation
  - Grouping of pluses
- Where we stimulate: Spatial targeting
  - MST
  - FEAST
  - Multi-electrode arrays, non-invasive deep stimulation
- Conquering Individual Differences
  - Per patient computer modelling to guide dosing and targeting
- Blocking the Convulsion (Association of Nonconvulsive Therapy)
- Producing Amnesia for Therapeutic Purposes: Interfering with reconsolidation of traumatic memories in PTSD
- Therapeutic Properties of Intense Electrical Stimulation without Seizures

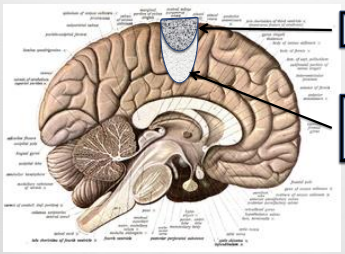
Modeling the Electrical Field of Traditional ECT, FEAST, and MST

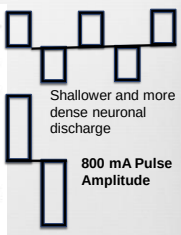


Current intensity (pulse amplitude) strongly determines focality and impacts on spatial targeting

Lee et al. *European Psychiatry* (2016)

Rationale for Titration in the Current Domain





Deeper stimulation; more sparse neuronal discharge

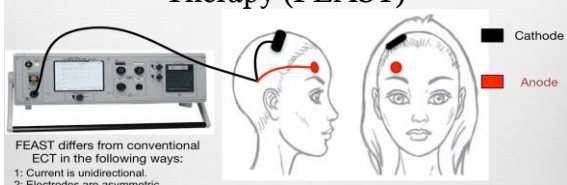
Spatial Targeting of the ECT Stimulus

1. Magnetic Seizure Therapy (MST)
2. Focal Electrically-Administered Seizure Therapy (FEAST)
3. High Definition Spatial Targeting with Novel Electrode Arrays
4. Noninvasive DBS – frequency cancellation

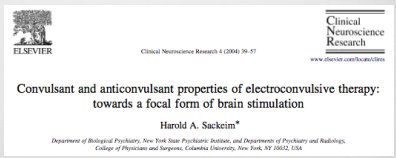
Newest MST Device

- Max 100%, 100 Hz, 10 s, biphasic waveform, pulse width 0.2 ms
- Increase in number of pulses, less change in pulse amplitude
- ≥ 2 Tesla at the coil surface
- Twin cone coil recommended over vertex

Focal Electrically Administered Seizure Therapy (FEAST)



FEAST differs from conventional ECT in the following ways:
1: Current is unidirectional.
2: Electrodes are asymmetric
3: Novel electrode placement


ELSEVIER
Clinical Neuroscience Research 4 (2004) 39–57
Clinical Neuroscience Research
www.elsevier.com/locate/clires

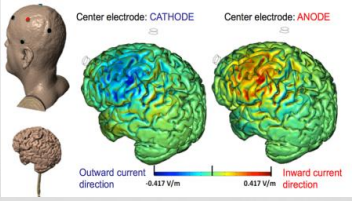
Convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation

Harold A. Sackeim*

Department of Biological Psychiatry, New York State Psychiatric Institute, and Departments of Psychiatry and Radiology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

Spatial Targeting in ECT: We are at the Beginning

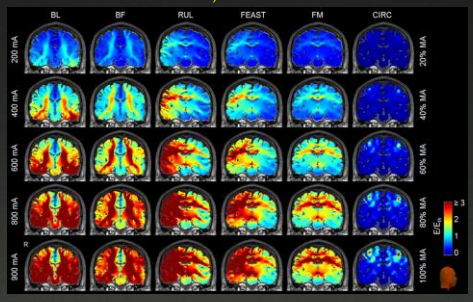
- FEAST and MST only the first iteration of focal, spatially-targeted ECT
- We need to determine optimal anatomic site and size
- Other tES technologies, particularly tDCS have developed new methods to manipulate focality and spatial targeting (Datta et al. *Brain Stimulation*, 2009)



Computational Modeling and Precision Medicine

1. Computational modelling based on high definition structural MRI will be done for every patient prior to ECT
2. Modelling will aid in dose finding, as head anatomy determines much of variance in seizure threshold
3. Modelling will determine electrode placement and geometry necessary to avoid stimulation of areas linked to side effects and concentrating stimulation in areas linked to efficacy

Modeling the Electrical Field of Traditional ECT, FEAST, and MST



Current intensity (pulse amplitude) strongly determines focality and impacts on spatial targeting

Lee et al. *European Psychiatry* (2016)

New Therapeutic Uses of ECT

1. Self-injurious behavior in autism
2. Treatment-resistant psychotic disorders
3. Post-traumatic stress disorder (PTSD)

Intense Electrical Stimulation without Seizures

1. tDCS uses very low current (1-4 mA) yet can result in significant neurobiological and behavioral change
2. Far more intense stimulation, as used in ECT, likely to have more marked biological and behavioral effects. Impact of electrical parameters on cognition a telling example
3. Stimulation-induced pharmacology a new, emerging field
4. ECT practitioners should not limit themselves to seizure-inducing procedures, but embrace non-seizure inducing, high intensity stimulation and determine new indications

Dopamine, Electricity, and Seizures

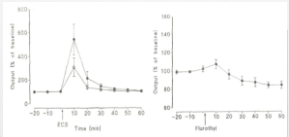


Figure 1. ECS-induced Striatal Dopamine Release
Filled Circles: ECS 170 V, 1.0 s
Open Circles: ECS 150 V, 0.75

Figure 2. Chemical Convulsive Dopamine Release

From Zis et al. (1992)

- ECS resulted in huge dopamine surge, sensitive to electrical dosage
- Flurothyl seizures did not alter dopamine release
- Barbiturate blockade of ECS seizure does not change ECS surge in dopamine release

The Accomplishments of ECT are Extraordinary

- The efficacy of the most effective treatment in psychiatry has been preserved while its adverse side effects have been virtually eliminated
- Effective strategies for relapse prevention have been established
- Probability of sustained benefit is higher with ECT than any other treatment for mood disorders
- ECT has superior cost/benefit relative to alternatives
- The behavioral, physiological, and molecular effects have been carefully documented, with viable theories of mechanisms
- There are remarkable opportunities to make further advances in the practice of ECT

ECT While Vastly Improved Is Greatly Underused

8 out of 9 general community hospitals in the US do not offer ECT

< 1% of patients with treatment-resistant depression in the US receive ECT

ECT used much more in private (academic) than public (city, state, federal) facilities

Columbia University Medical Center

Pardes Building, NYSPI

Columbia University

A New York State of Mind

Thanks to many colleagues, staff, and patients participating in these studies