Modern Electroconvulsive Therapy:
Vastly Improved Yet Greatly Underused

On the 80th Anniversary of ECT
Nordic Association for Convulsive Therapy
Tallinn, Estonia
May 23, 2018

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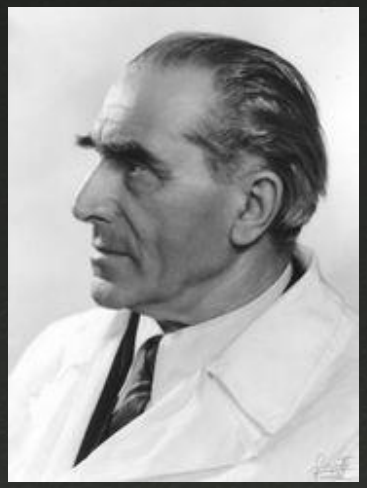
DISCLOSURES

- 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)

80th Anniversary of ECT: The Beginning

Ladislas Meduna

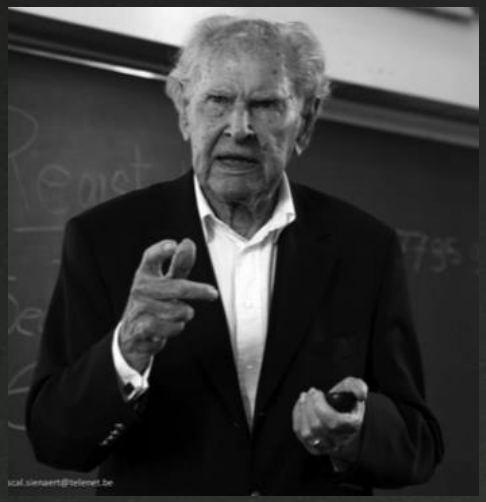


Ugo Cerletti

Lucio Bini

Lothar Kalinowsky

80th Anniversary of ECT: The Nordic Influence



Jan-Otto Ottosson

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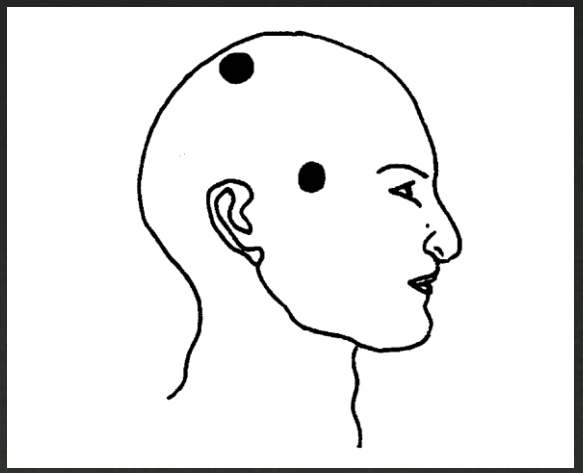


Giacomo d'Elia

Lizzie Sand Strömgren

Present Practice of Electroconvulsive Therapy in Scandinavia

Giacomo d'Elia, MD; Jan-Otto Ottosson, MD; Lizzie Sand Strömgren, MD

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

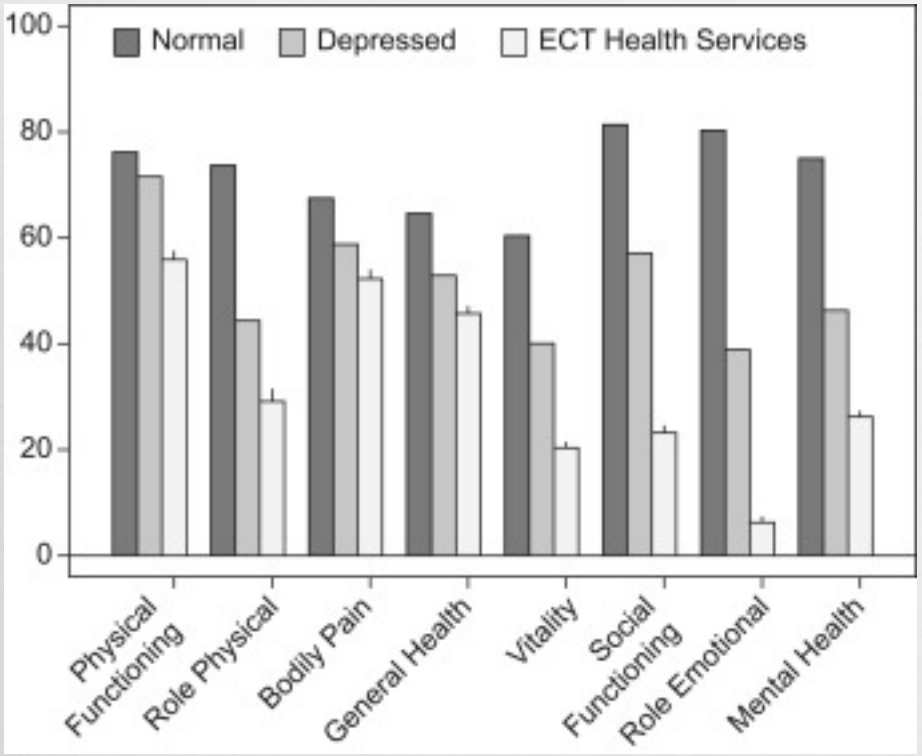
• ECT samples could be studied medication free

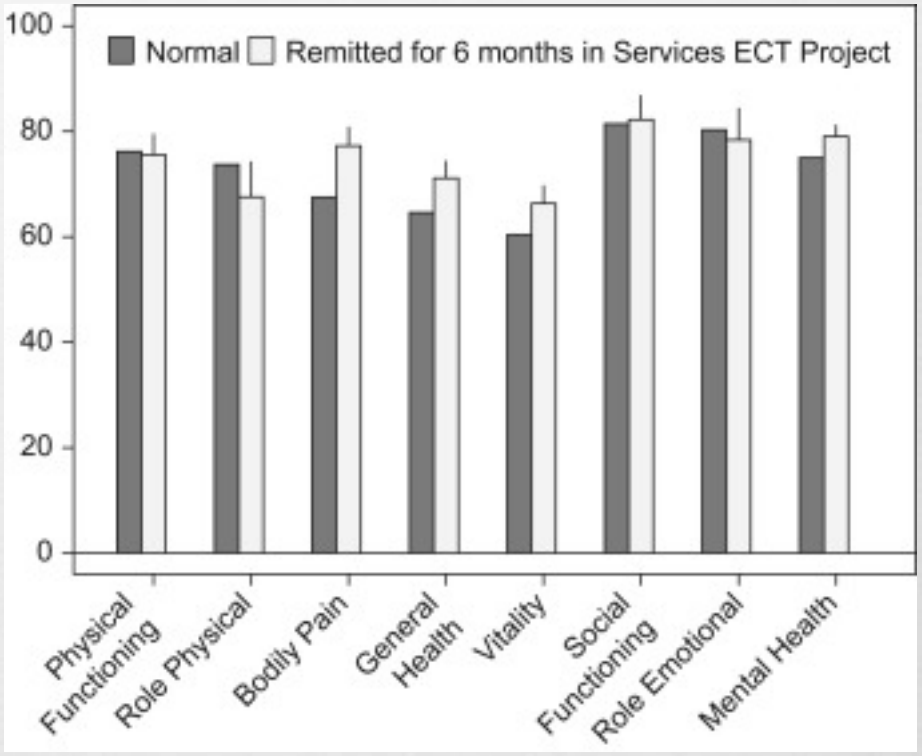
• ECT can be spatially targeted; unilateral ECT as good as the Wada test to identify hemispheric specialization for language

• 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

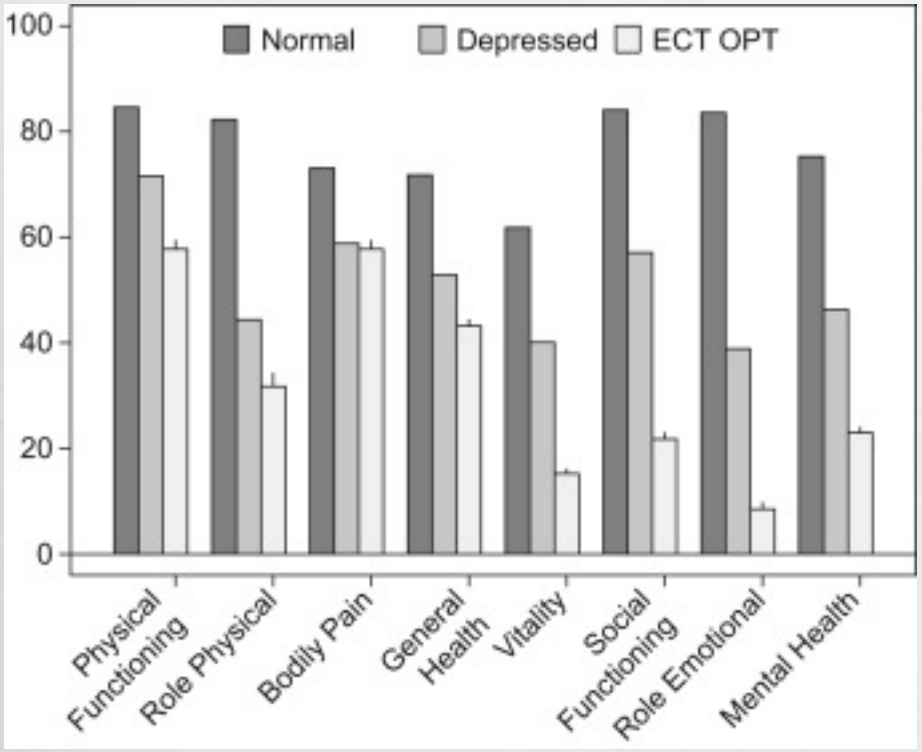


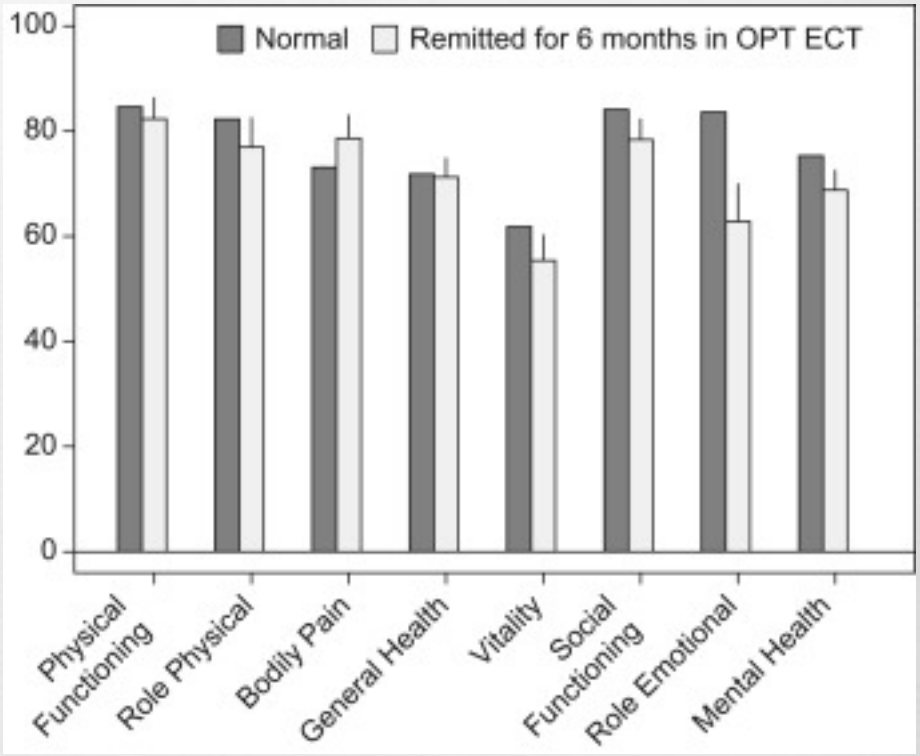


McCall et al. Journal of Affective Disorders, 2013

Quality of Life: OPT ECT Study

Sackeim et al. Archives of General Psychiatry, 2009



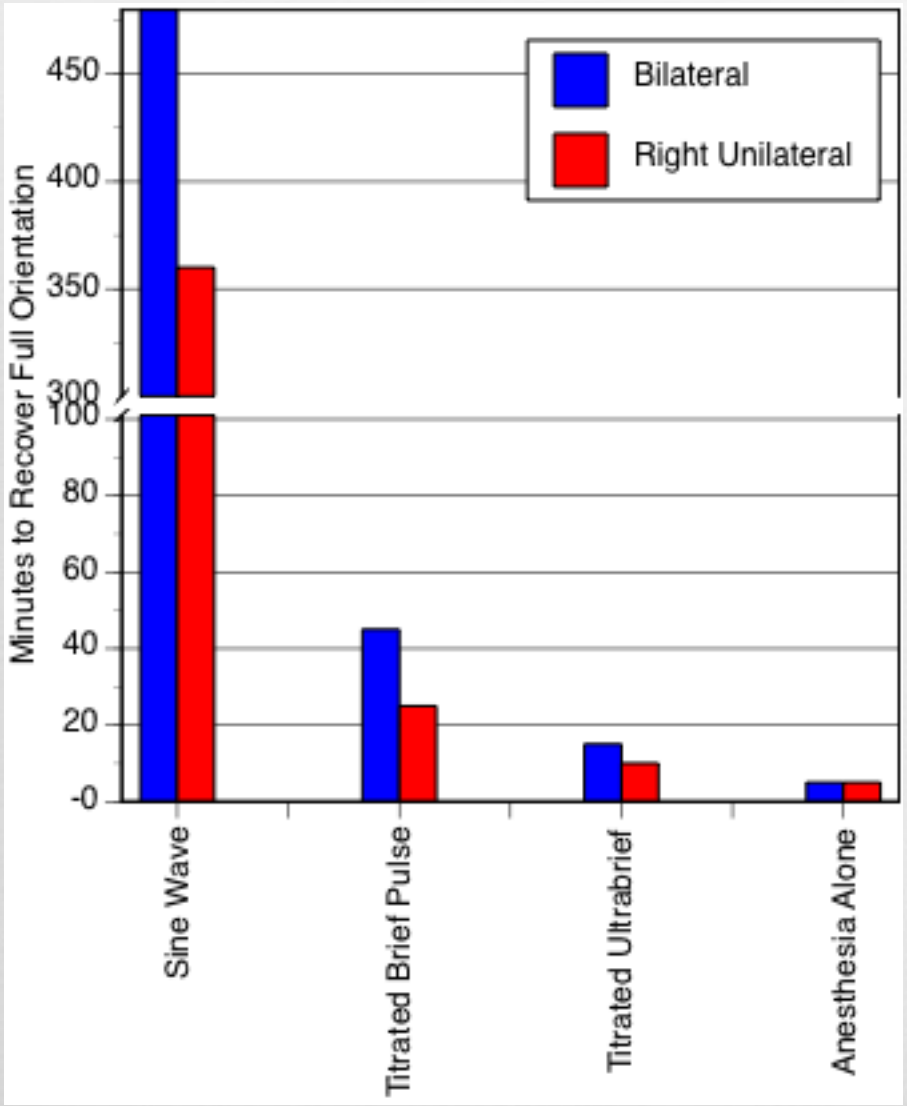


McCall et al. Journal of Affective Disorders, 2013

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



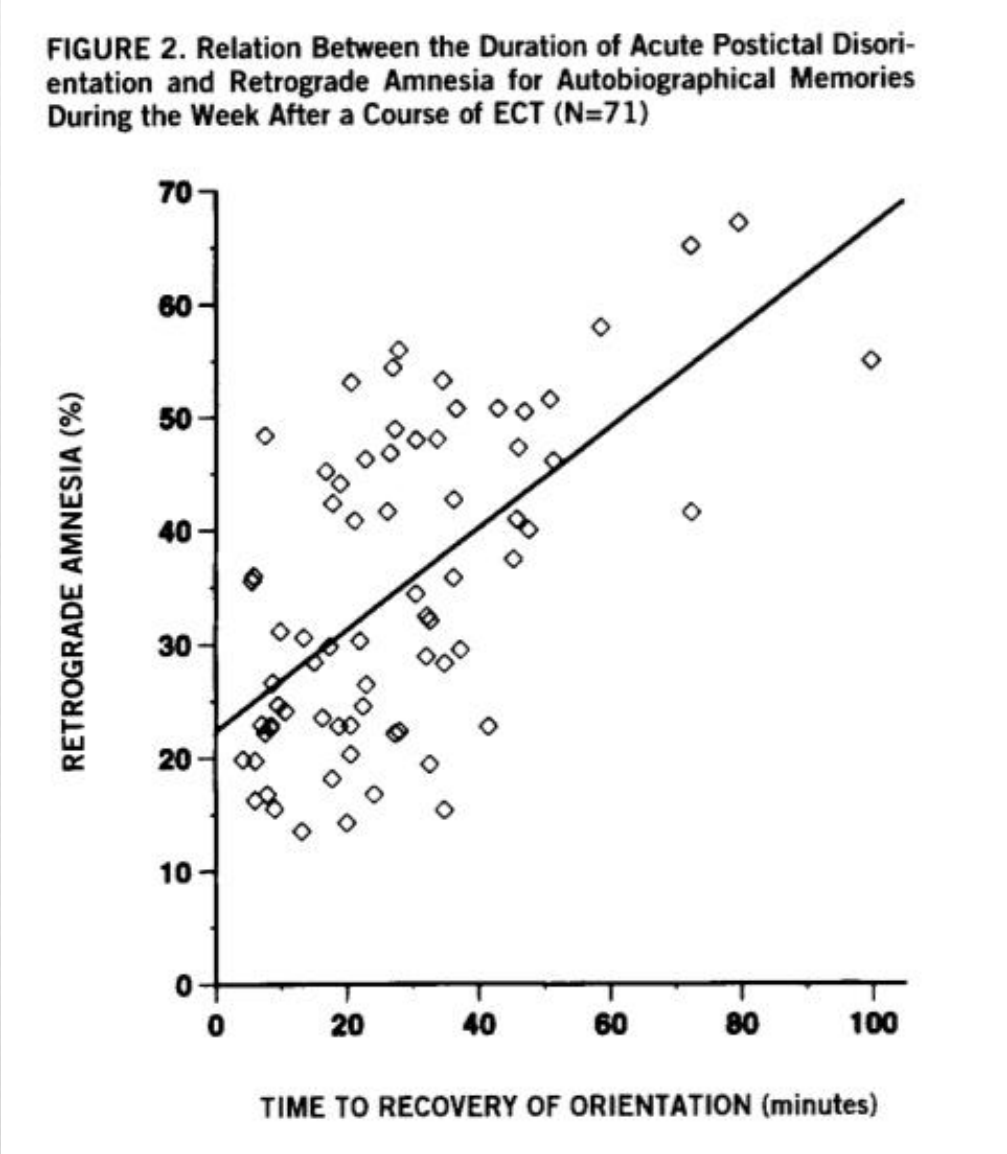
- Postictal recovery of orientation highly sensitive to ECT parameters
- Fantastic improvement in recovery time with progress in ECT stimulation

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

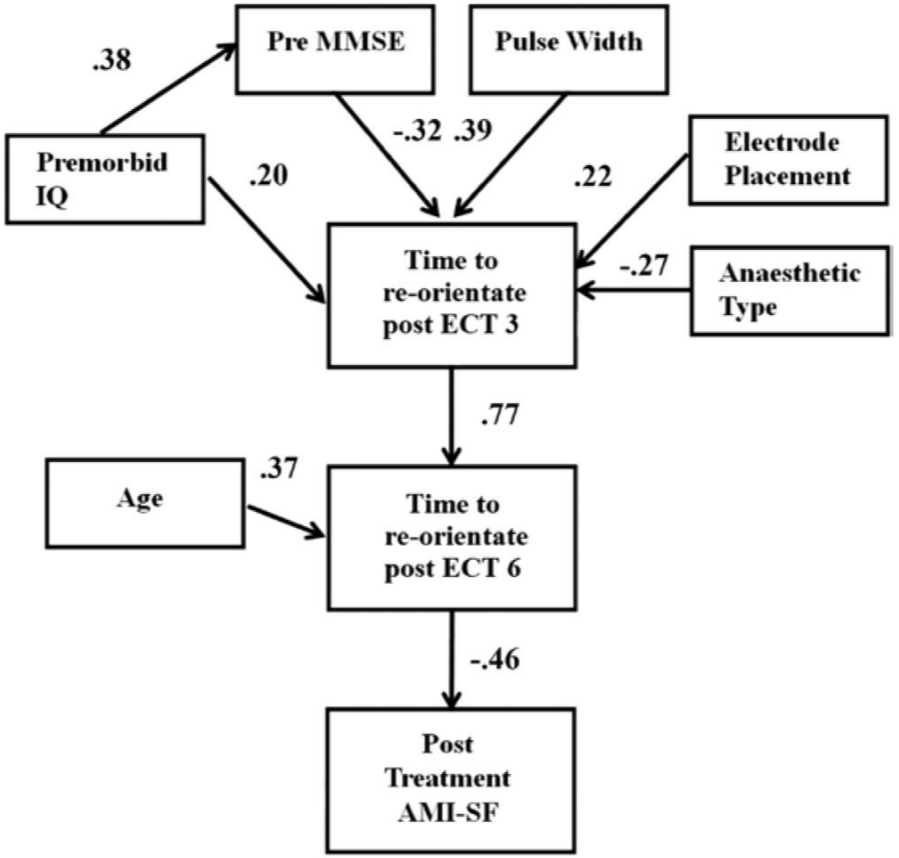


Figure 1. Hypothesized path model. Solid lines indicate statistically significant paths. AMI-SF, Columbia Autobiographical Memory Interview-Short Form; MMSE, Mini Mental State Examination.

- 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

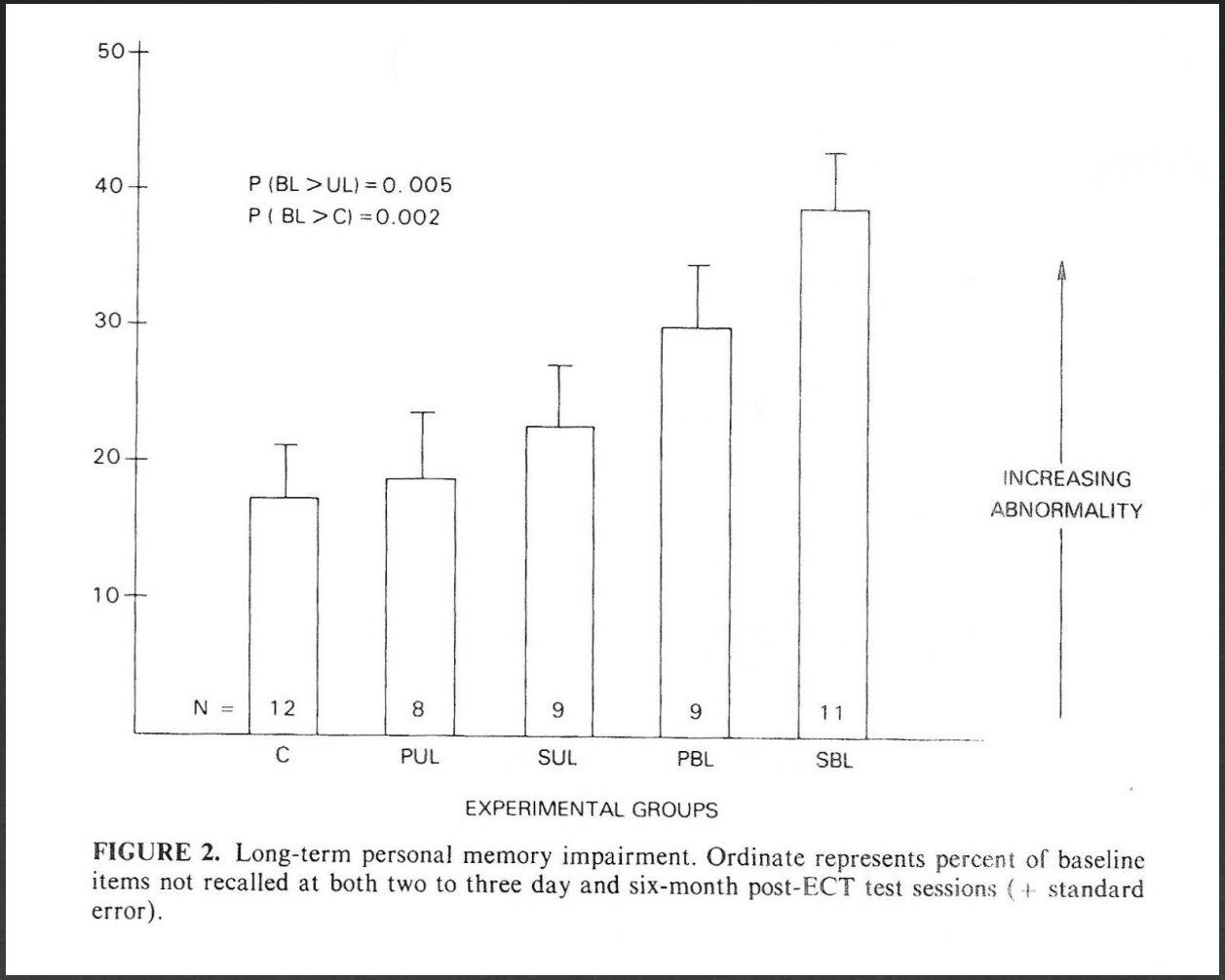
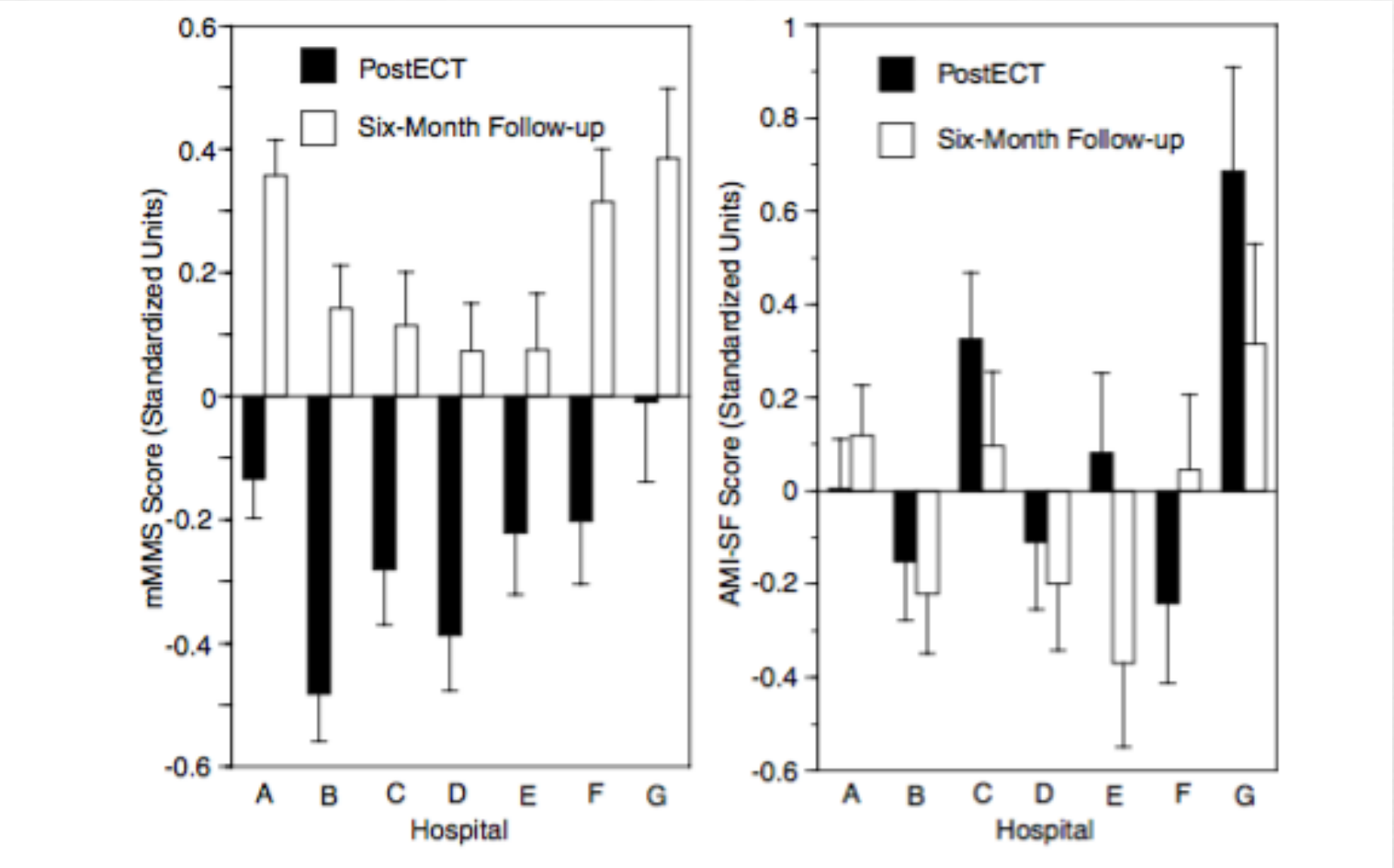


FIGURE 2. Long-term personal memory impairment. Ordinate represents percent of baseline items not recalled at both two to three day and six-month post-ECT test sessions (+ standard error).

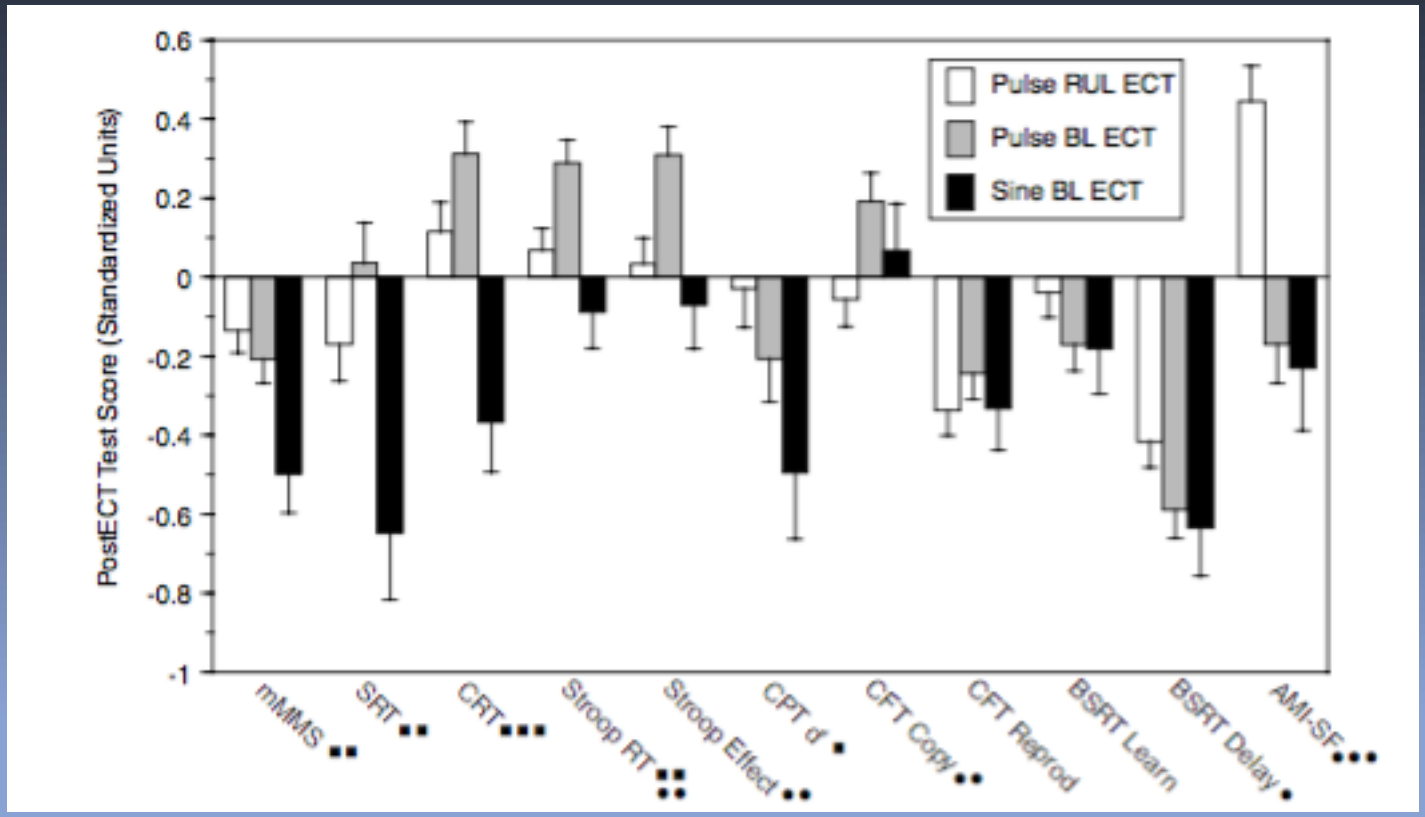
Weiner, Squire et al. Ann NY Acad Sci, 1986

The Cognitive Effects of Electroconvulsive Therapy in Community Settings



Sackeim et al. Neuropsychopharmacology, 2007

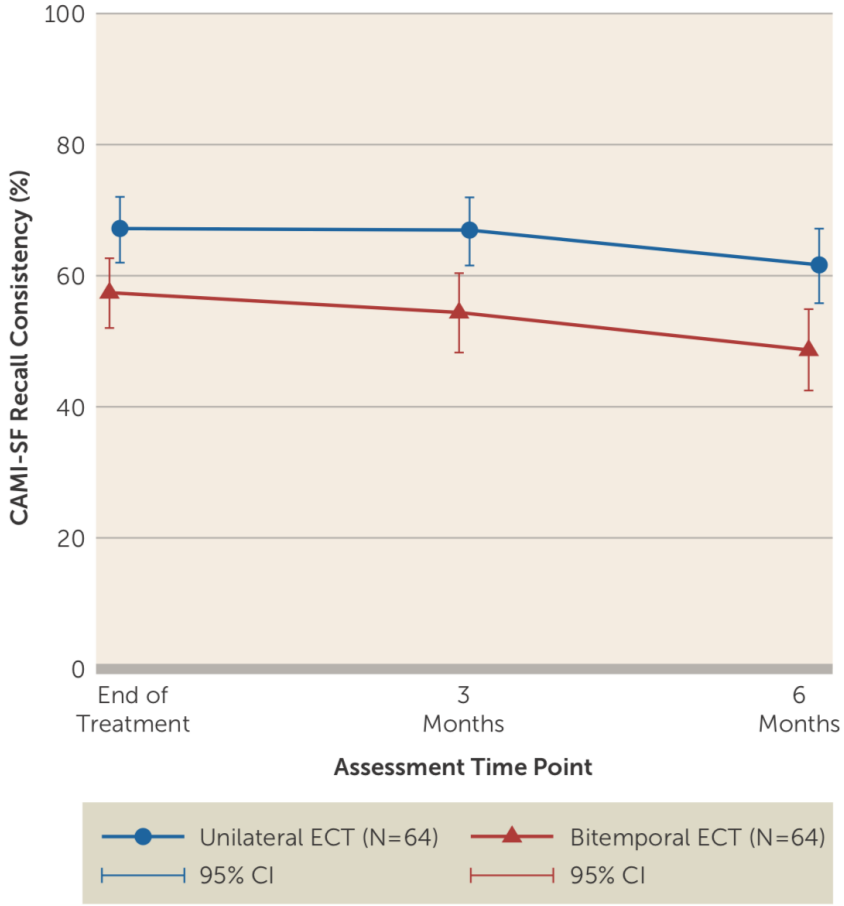
The Cognitive Effects of Electroconvulsive Therapy in Community Settings



Sackeim et al. *Neuropsychopharmacology*, 2007

Long-term Retrograde Amnesia: The EFFECT-Dep Trial

FIGURE 3. Autobiographical Memory Following ECT: Recall Consistency (%) With Baseline Scores for Unilateral and Bitemporal ECT Groups[a]

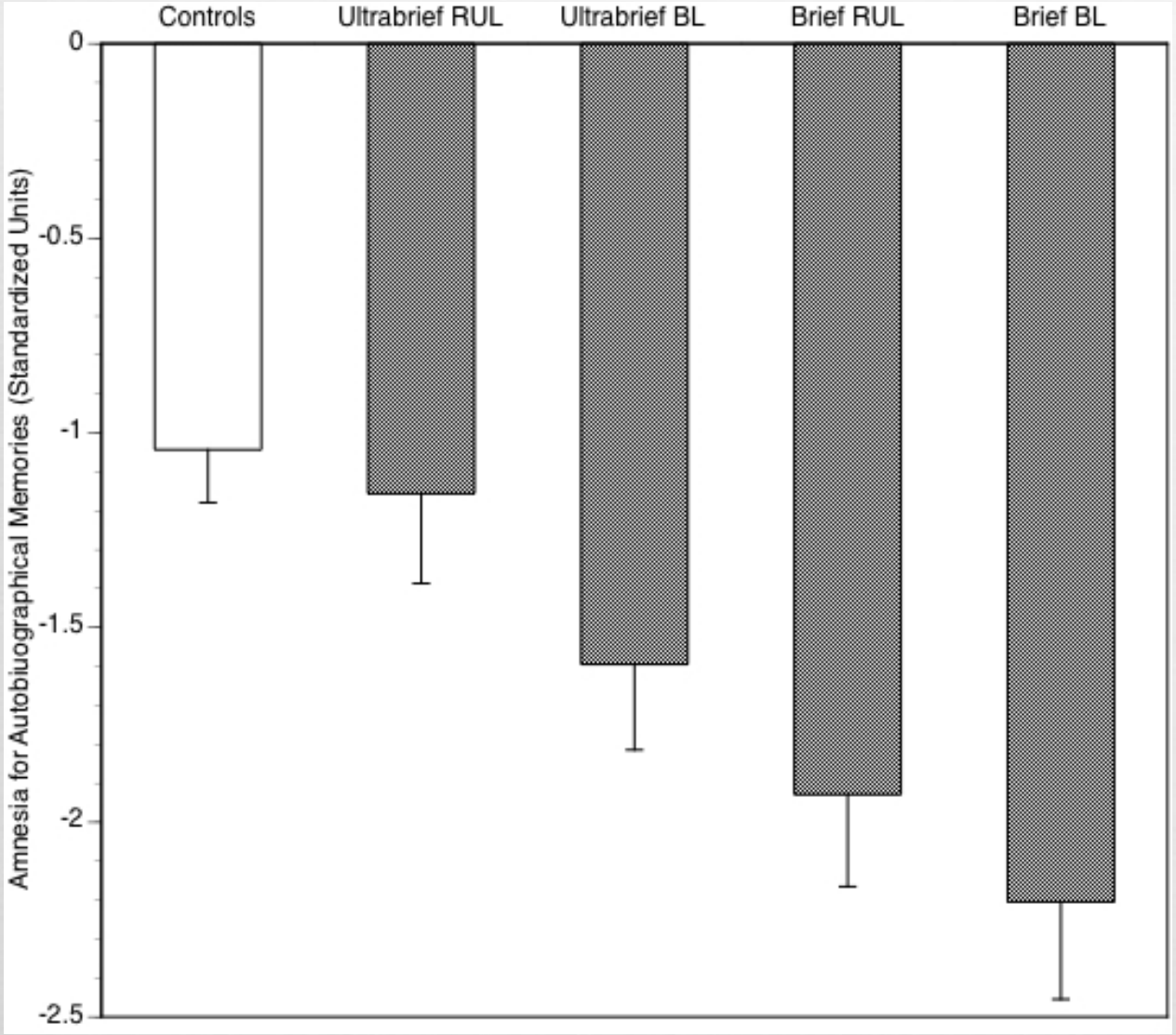


[a] CAMI-SF=Columbia Autobiographical Memory Interview-Short Form.

- 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

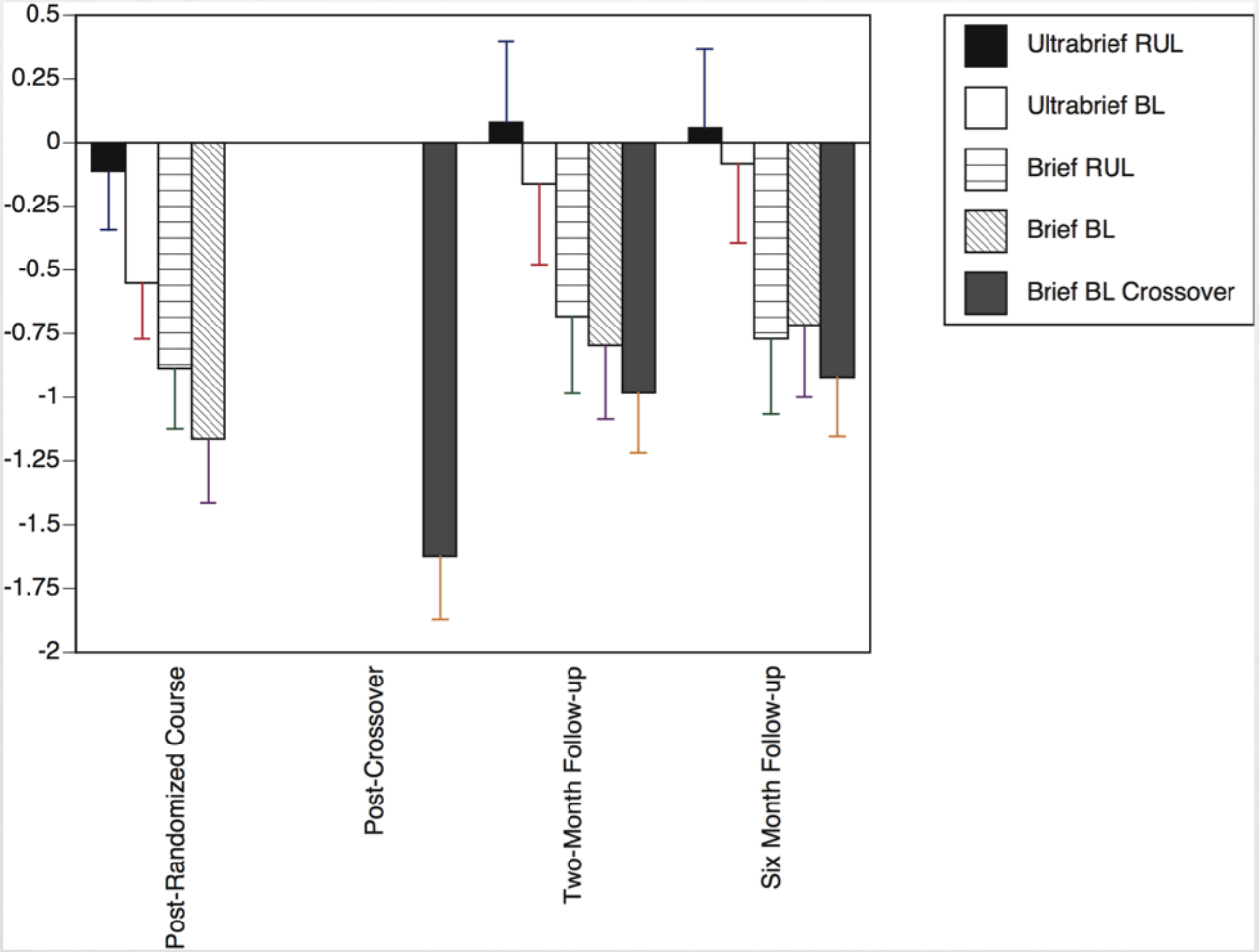
Retrograde Amnesia for Autobiographical Information Immediately Following the ECT Course



- 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



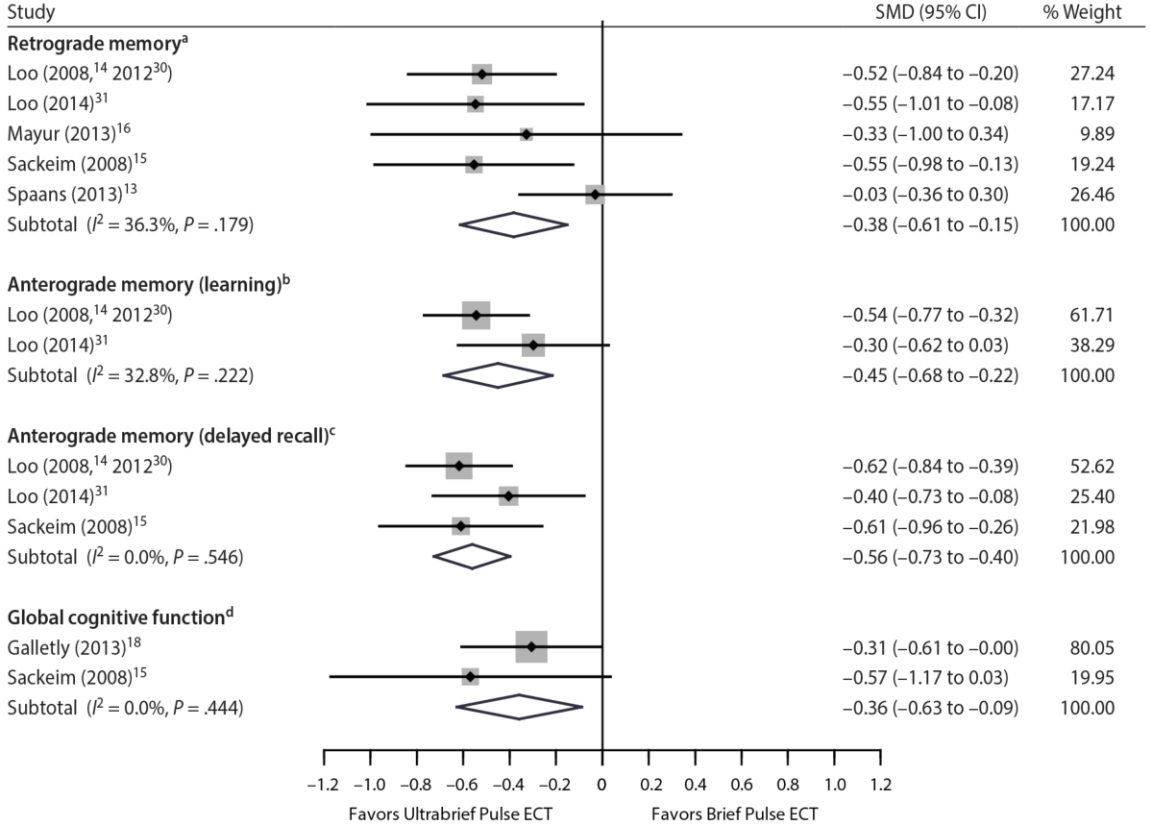
Effects of pulse width on amnesia maintained through 6-month follow-up

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

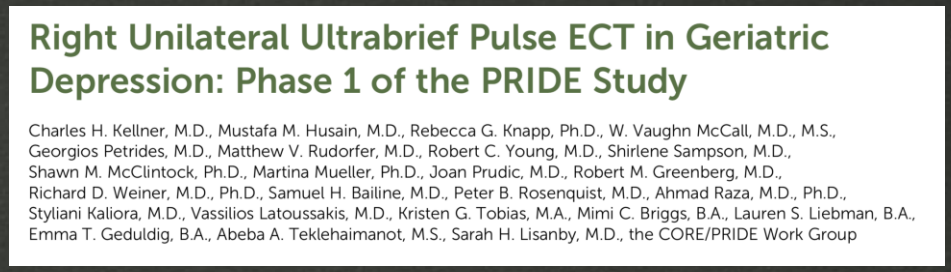
- UB RUL ECT superior to brief pulse RUL ECT in postECT cognitive measures
- In randomized trials, no difference in efficacy
- UB RUL patients received ~ 1 additional treatment. Likely due to superior cognitive effects

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



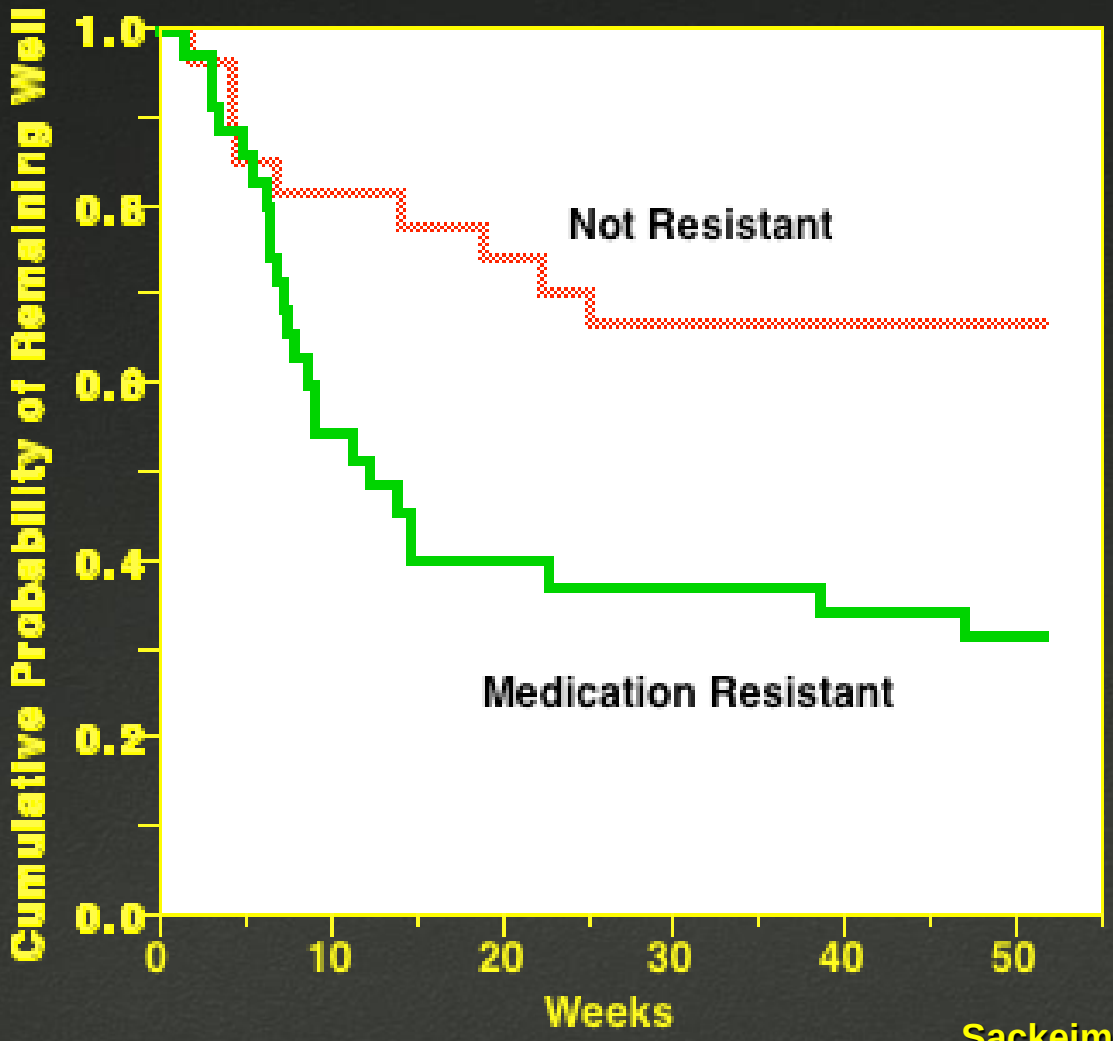
Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study

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., Shirlene Sampson, M.D., Shawn M. McClintock, Ph.D., Martina Mueller, Ph.D., Joan Prudic, M.D., Robert M. Greenberg, M.D., Richard D. Weiner, M.D., Ph.D., Samuel H. Bailine, M.D., Peter B. Rosenquist, M.D., Ahmad Raza, M.D., Ph.D., Styliani Kaliora, M.D., Vassilios Latoussakis, M.D., Kristen G. Tobias, M.A., Mimi C. Briggs, B.A., Lauren S. Liebman, B.A., Emma T. Geduldig, B.A., Abeba A. Teklehaimanot, 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

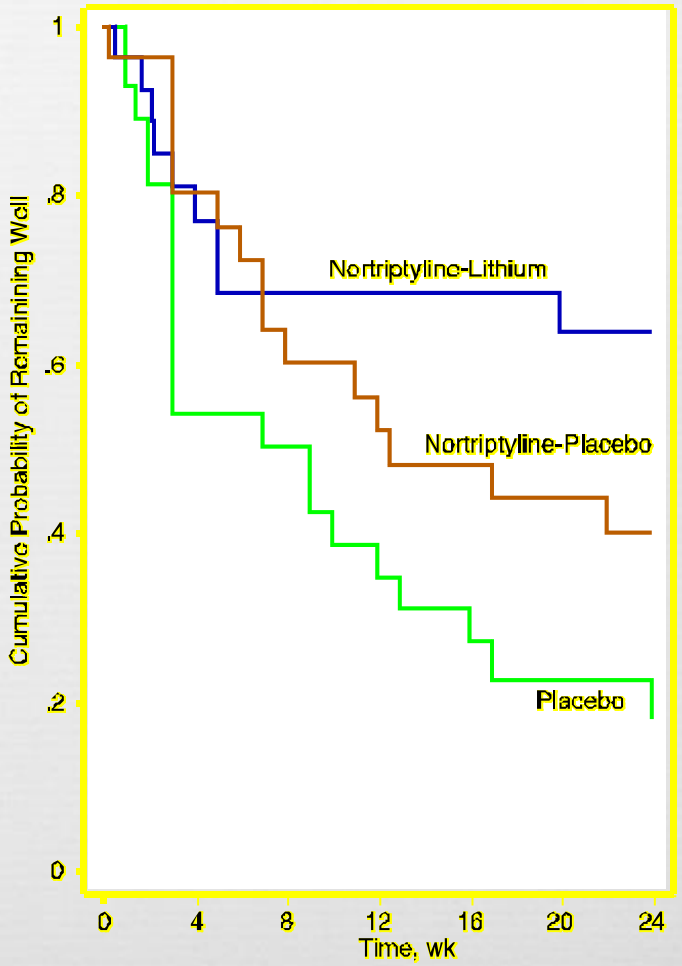


- Relapse was more than twice as likely among medication-resistant patients (68.6%) compared to patients who had not received an adequate medication trial prior to ECT (33.3%)

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

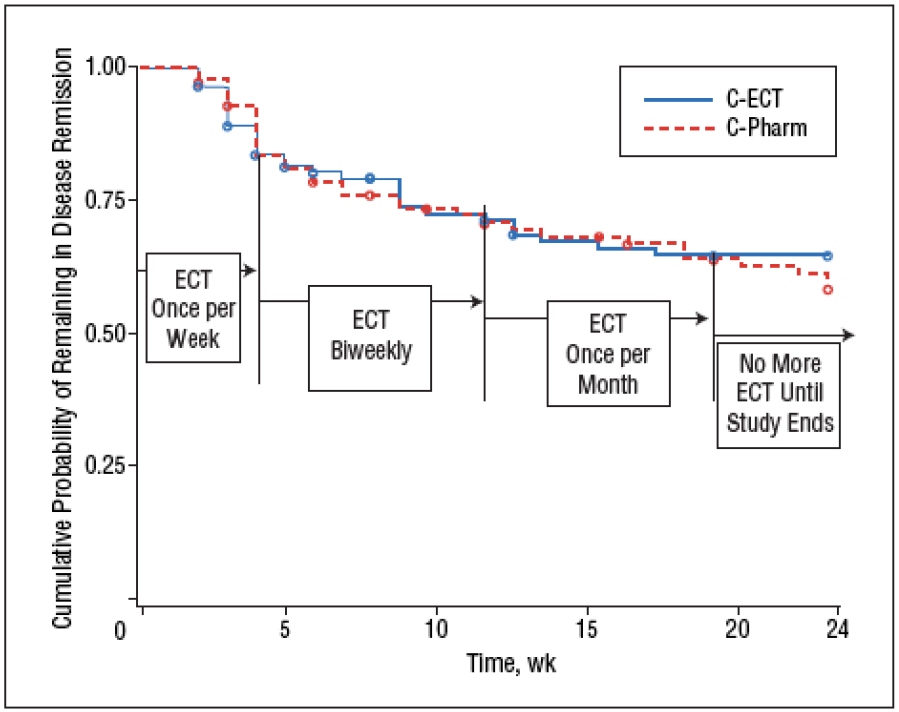


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: $\chi^2=0.30$; $P=.59$. C-ECT indicates continuation electroconvulsive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

Kellner et al. Arch Gen Psychiatry, 2006

Pharmacology During and Following ECT: OPT-ECT Study

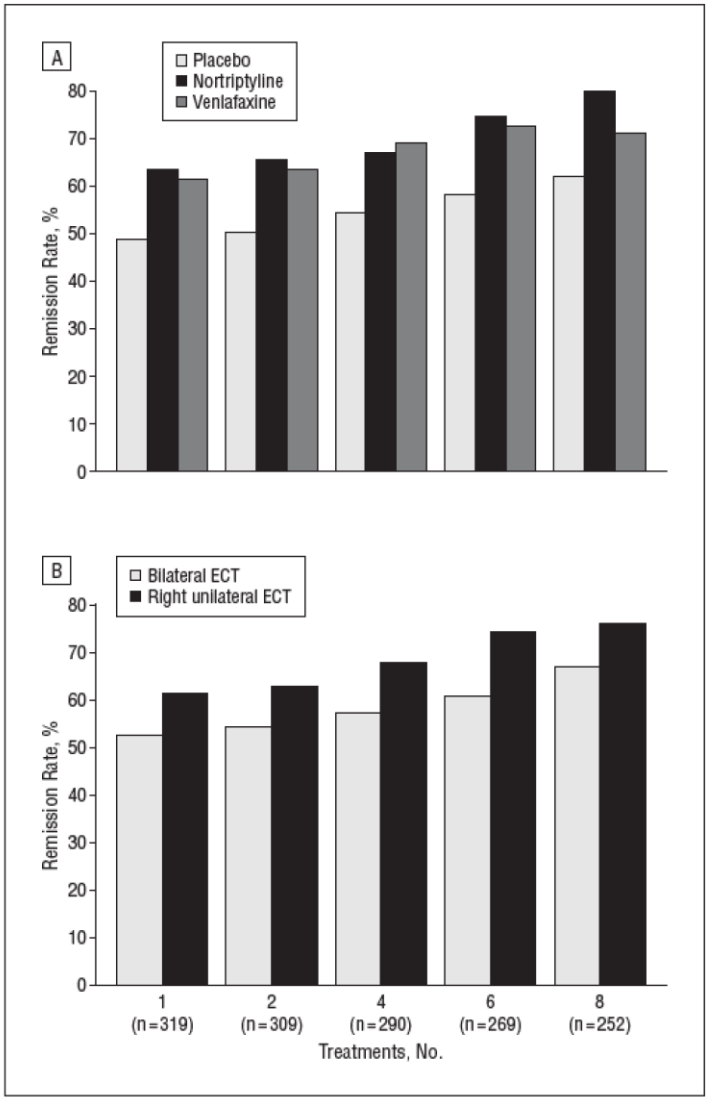


Figure 2. Remission rates for the pharmacological (A) and electroconvulsive therapy (ECT) electrode placement (B) conditions as a function of requiring a different number of treatments to be classified as a completer in the context of lack of remission. More stringent criteria result in an overall increase in remission rates, but have little effect on the differences among the pharmacological and ECT conditions.

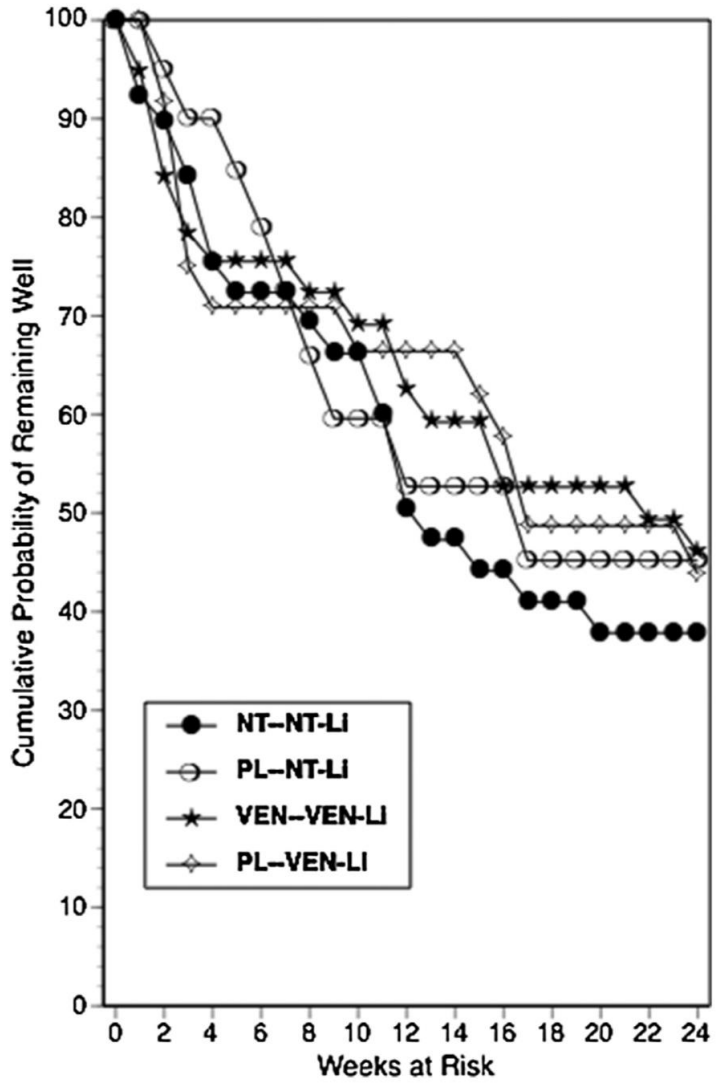
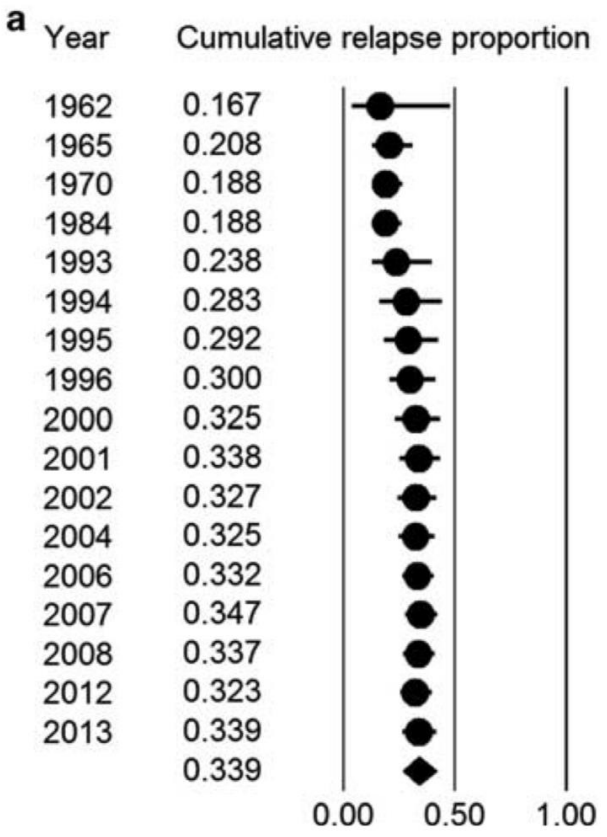
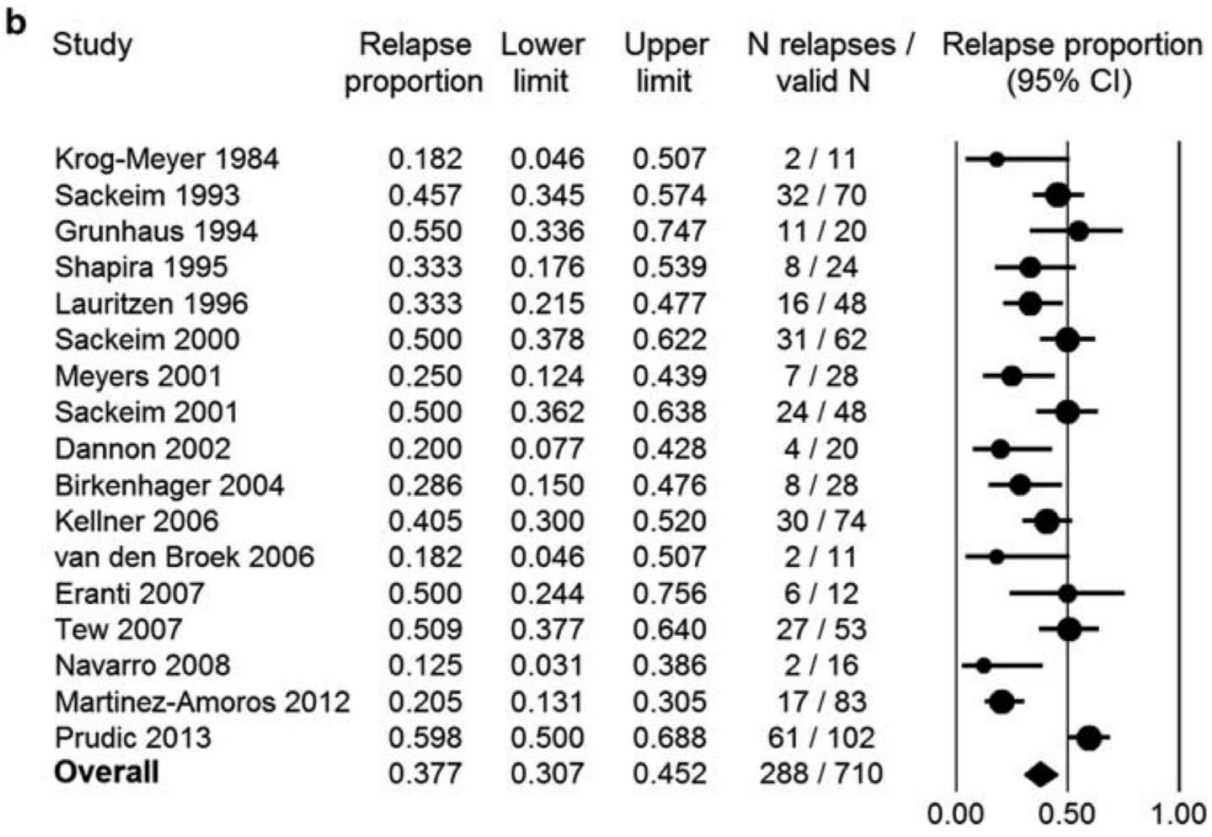


FIGURE 3. Kaplan-Meier estimates of the proportion of patients who remained well during the continuation trial for patients randomized to the 4 treatment conditions: PL or drug (NT or VEN) during ECT and, during continuation pharmacotherapy, NT-Li or VEN-Li as continuation pharmacotherapy.

Meta-analysis of Post-ECT Relapse

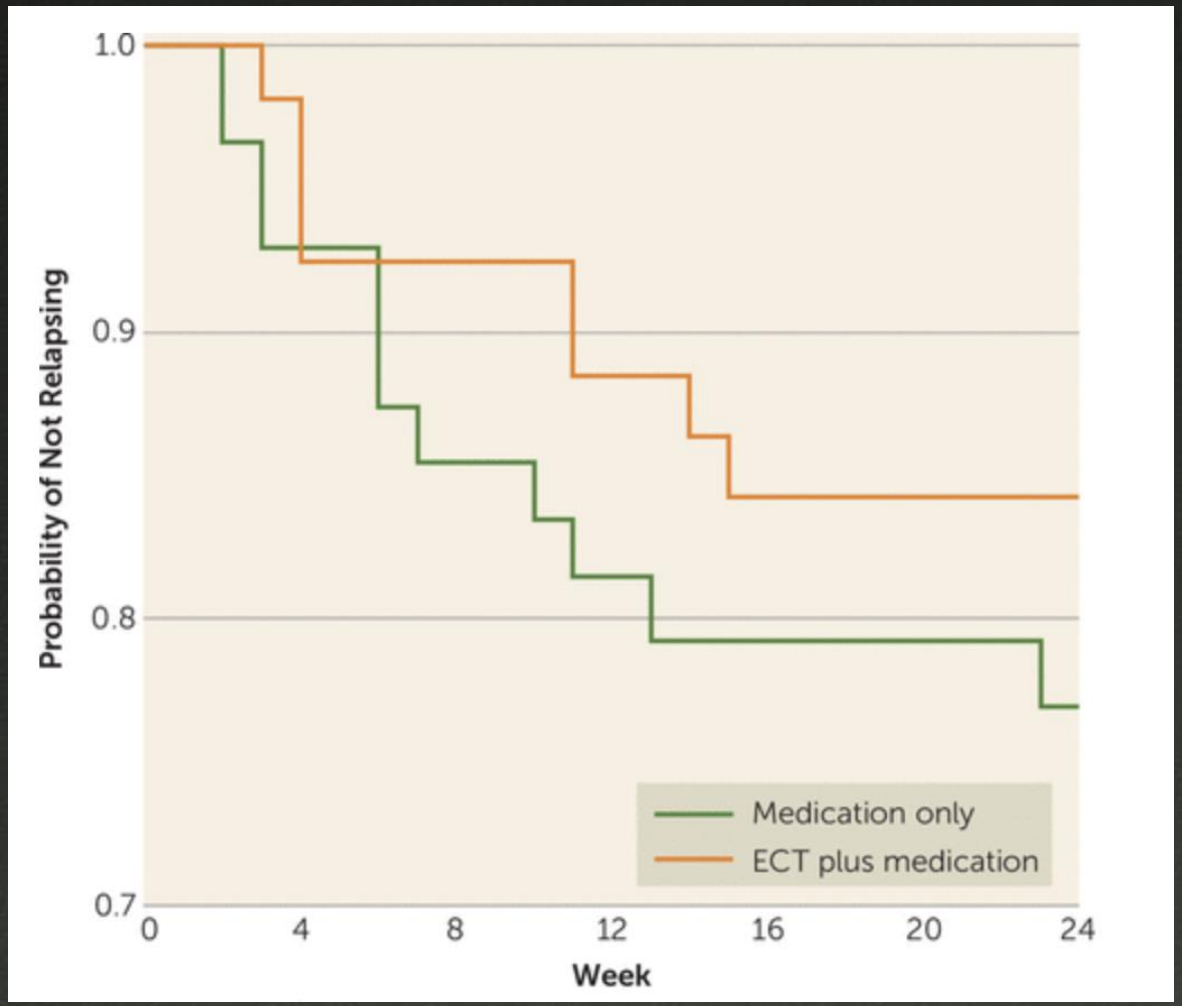




- "In present day clinical practice, nearly 40% of ECT responders can be expected to relapse in the first 6 months and roughly 50% by the end of first year."

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

Fundamental View of ECT Mechanisms

- The **generalized seizure** provides the **necessary and sufficient conditions for efficacy**. The **electricity** contributes only to **cognitive side effects**

- Supported by key experimental data (Ottosson, 1960) and the comparison of ECT with Flurothyl (chemical seizure induction) (Small et al., 1968)
- Emphasizes a Hebbian mass action view or a focus on deep brain nuclei that broadly modulate cortical and subcortical activity (e.g., thalamus, hypothalamus)
- Led to strong scientific focus on the neurobiology, especially neurochemistry, during seizures

New Understanding of ECT Mechanisms

- Both the efficacy and cognitive effects of ECT are dependent on the current path and dosage of the ECT stimulus. Generalized seizures can be reliably evoked that lack efficacy.
- There is localization to the neural systems underlying antidepressant and cognitive effects.
- Efficacy and cognitive effects are independent and dissociable. This is supported both by behavioral data and neurophysiological correlates.
- Objective cognitive effects are reflected in patients' subjective self-evaluations
- Seymour Kety's pessimism no longer applies. We need to distinguish the neurobiological effects of effective from ineffective seizures.

Advances In Theories of Mechanisms

- We know much more about what is not true. Scores of theories have been disproven.
  * ECT does not cause cell loss!! (Dwork et al. *Neuroscience,* 2009)
  * Patients do not get better because they are punch drunk or amnestic

- Diencephalic stimulation – neuroendocrine normalization
  * See Bolwig, *Canadian Journal of Psychiatry*, 2011 for an elegant review.

- Anticonvulsant Theory and Seizure Termination/Inhibitory Processes
  * Postictal suppression, EEG delta increases and CBF and metabolic suppression linked to efficacy
  * ECT effective in mania, catatonia, alcohol withdrawal (DTs), status, and intractable epilepsy

- Neurotrophic Properties
  * All effective antidepressants promote neurogenesis, ECT is especially powerful (Perera et al. *J Neurosci.* 2007). Depressogenic manipulations decrease neurogenesis
  *Manipulations that block neurogenesis (in animals) block antidepressant effects

- Circuit-based Alterations
  * ECT results in regional changes in synaptogenesis, brain structure, and functional connectivity. Stimulation induced neuroplasticity changes circuit dynamics
  * Sites of seizure initiation may be more critical to efficacy than sites of propagation

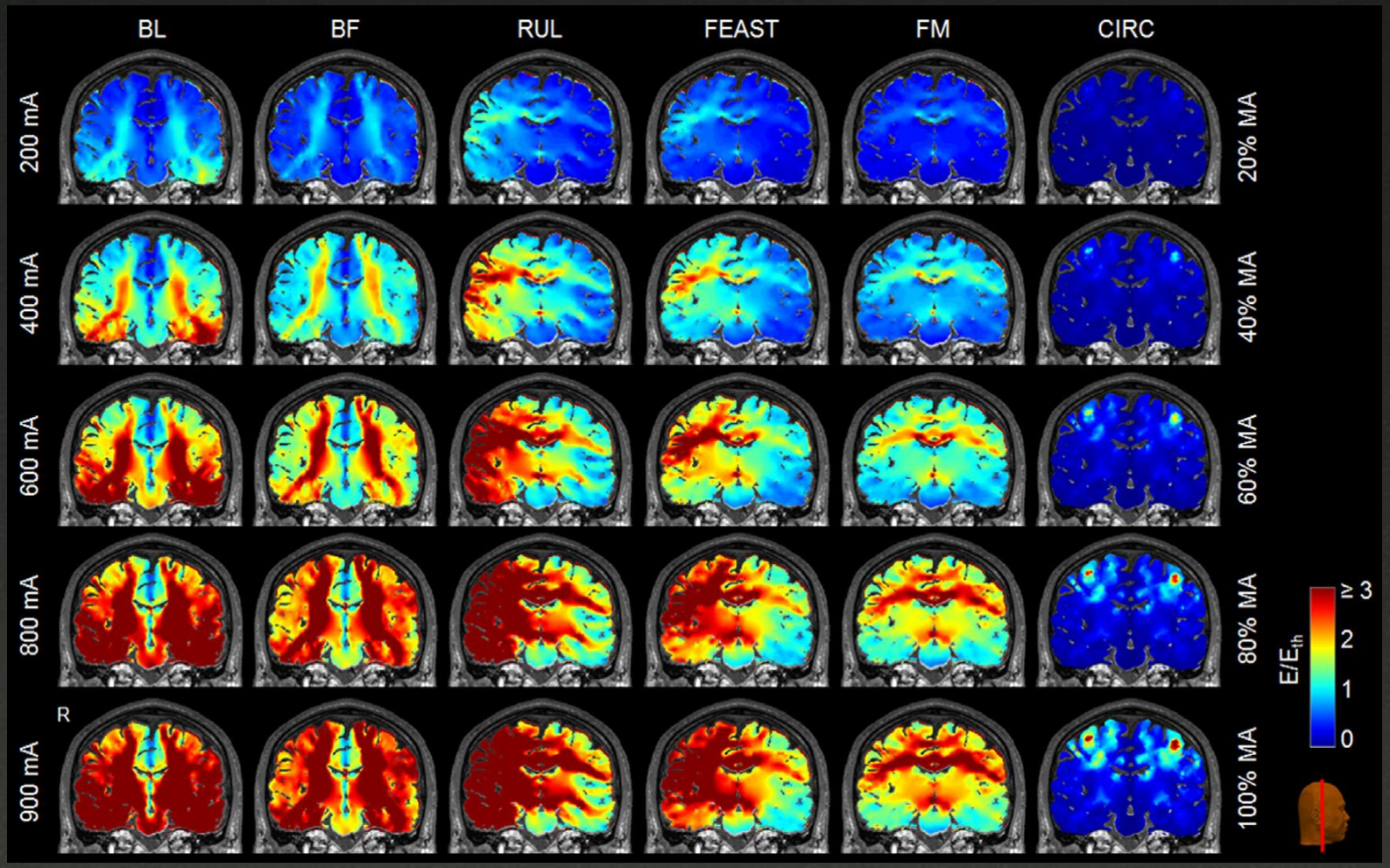
Vision of the Future

- 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 (Nordic 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

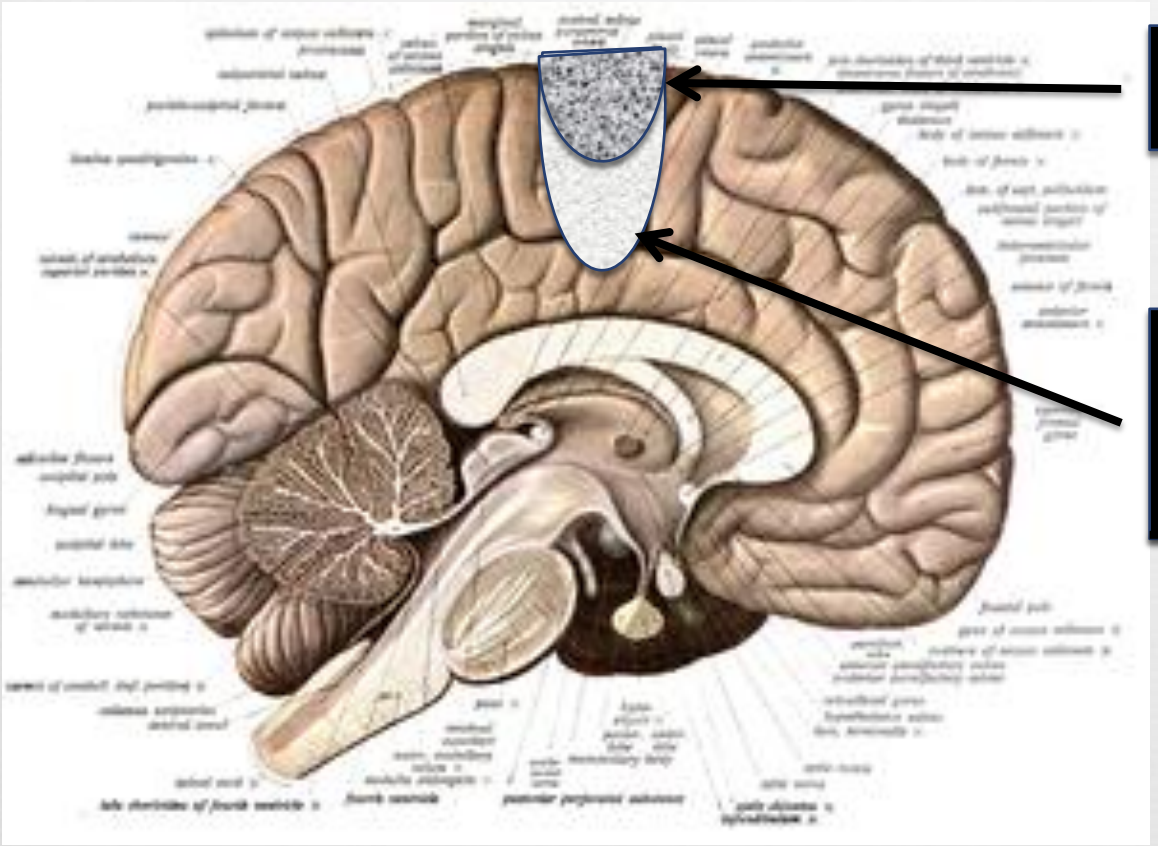
Modeling the Electrical Field of Traditional ECT, FEAST, and MST



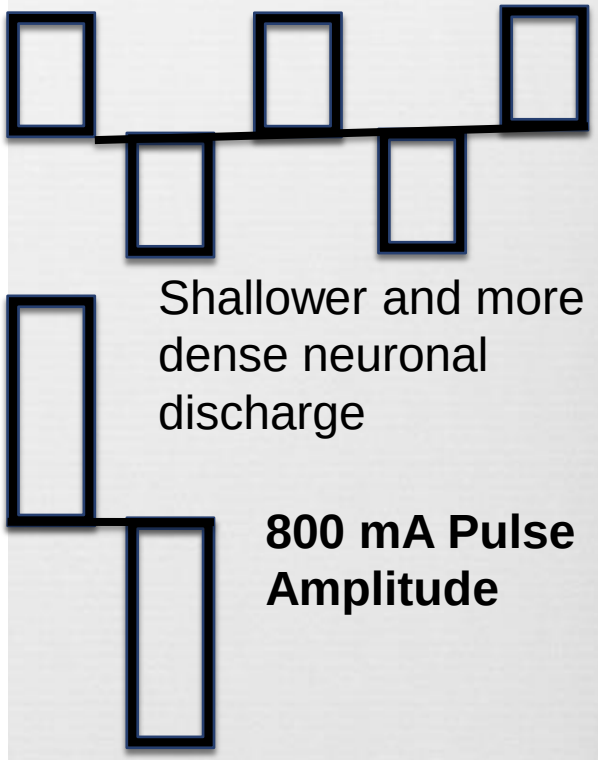
Current intensity (pulse amplitude) strongly determines focality and impacts on spatial targeting

Lee et al. *European Psychiatry* (2016)

Rationale for Titration in the Current Domain



500 mA Pulse Amplitude



Shallower and more dense neuronal discharge

800 mA Pulse Amplitude

Deeper stimulation; more sparse neuronal discharge

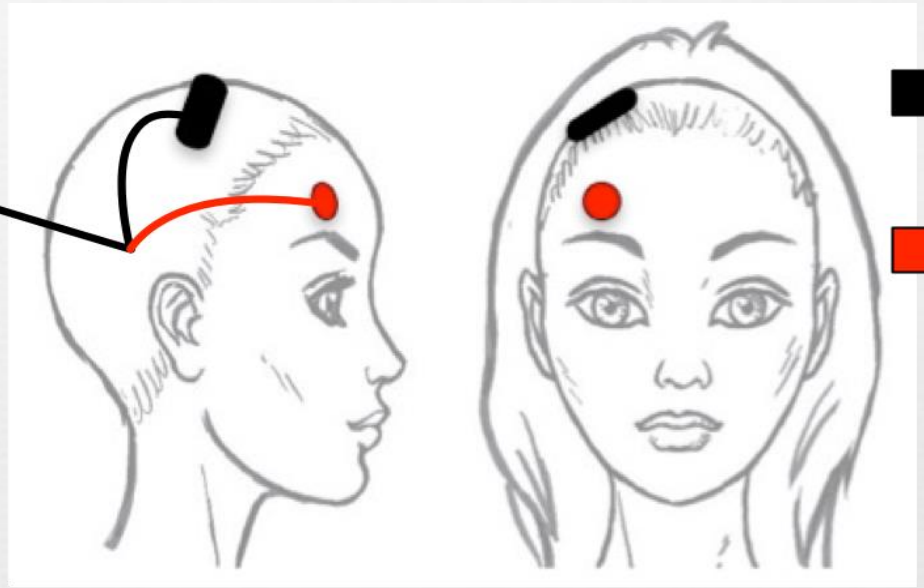
Spatial Targeting of the ECT Stimulus

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

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Clinical Neuroscience Research 4 (2004) 39–57

Clinical Neuroscience Research

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

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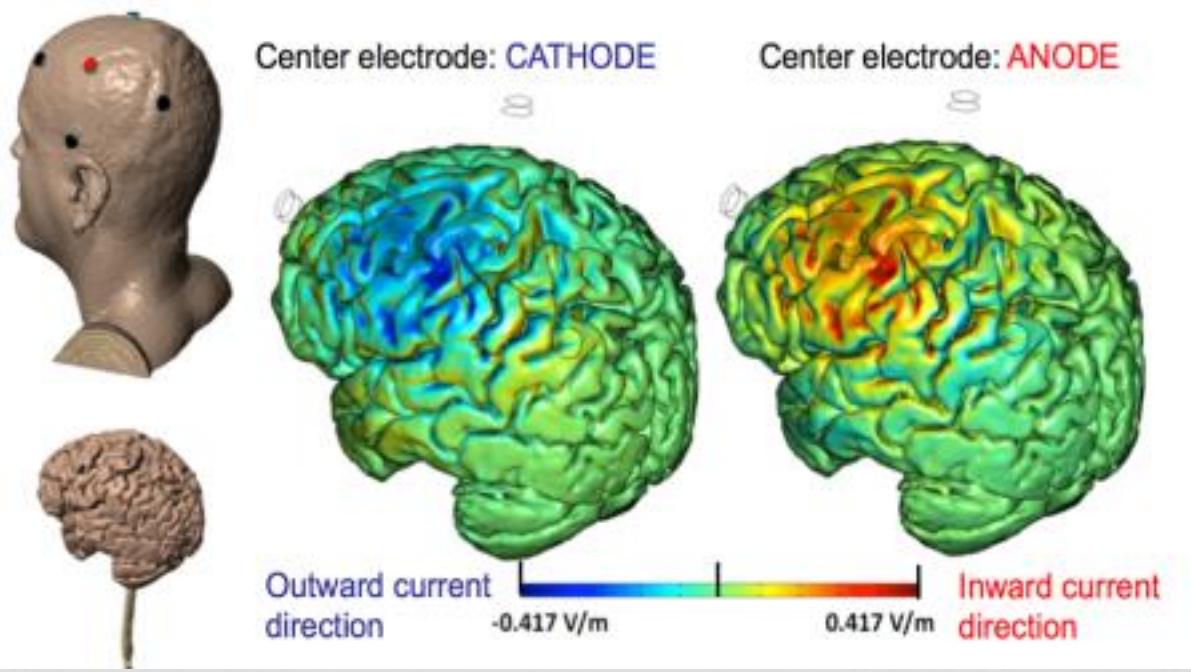
Spatial Targeting in ECT: We are at the Beginning

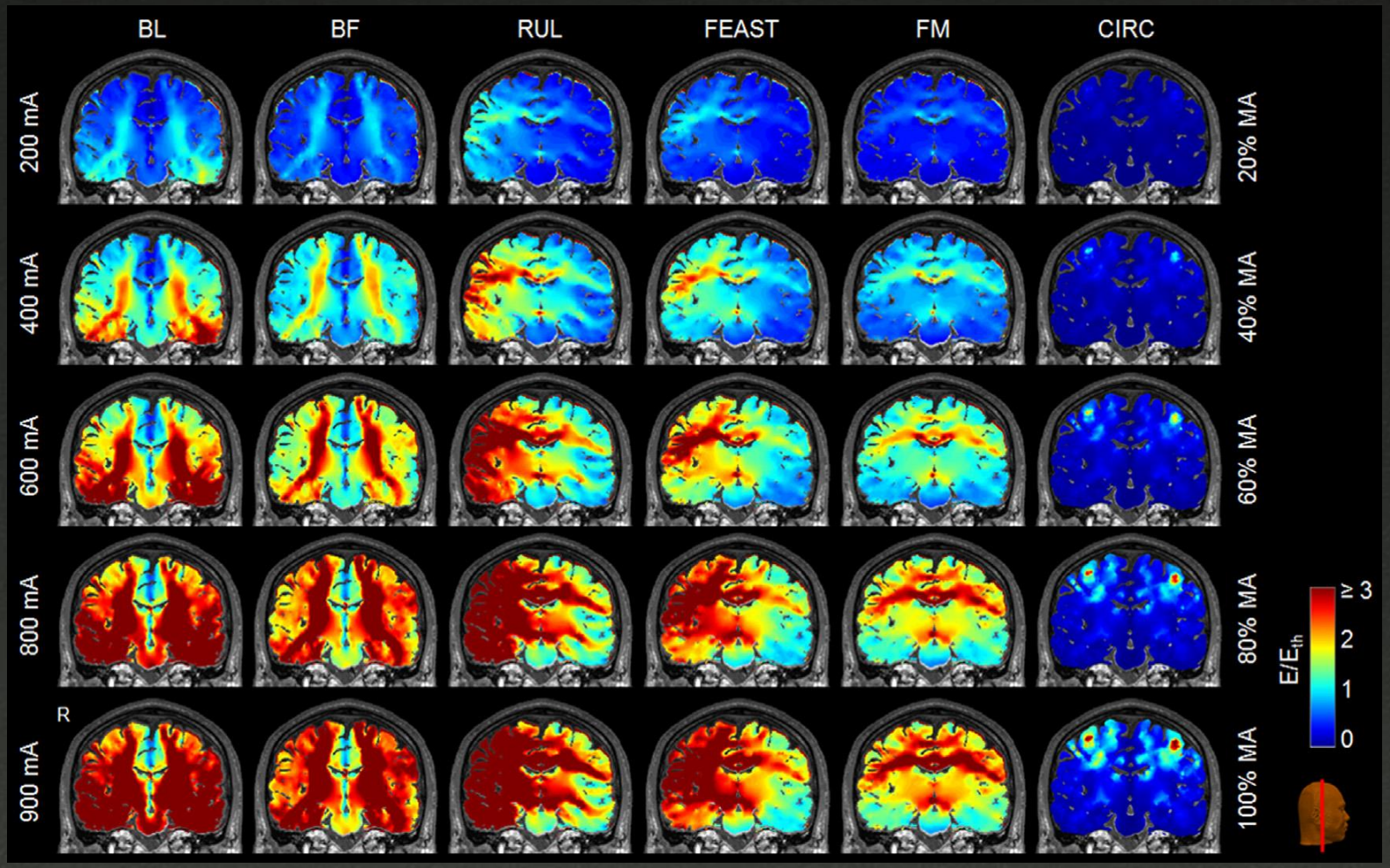
- FEAST and MST only the first iteration of focal, spatially-targeted ECT
- We need to determine optimal anatomic site and size
- Other tES technologies, particularly tDCS have developed new methods to manipulate focality and spatial targeting (Datta et al. *Brain Stimulation*, 2009)



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

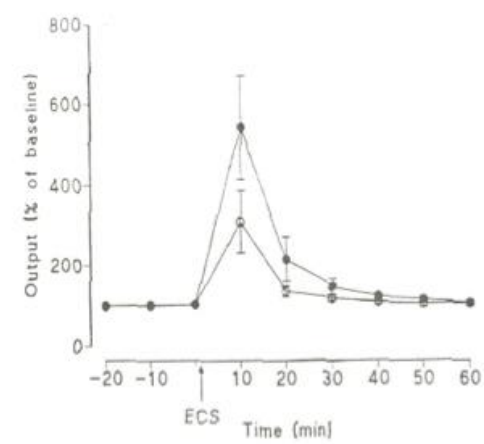


Figure 1. ECS-induced Striatal Dopamine Release
Filled Circles: ECS 170 V, 1.0 s
Open Circles: ECS 150 V, 0.75

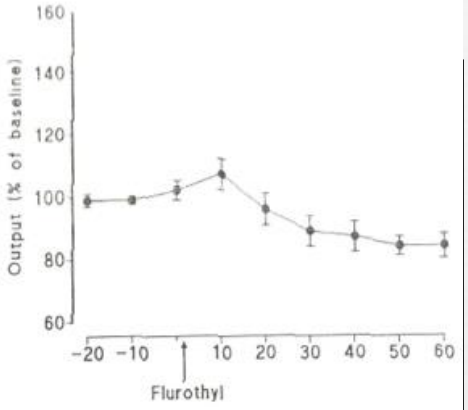


Figure 2. Chemical Convulsive Dopamine Release

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

Recent ECT use in VHA Facilities

	2013	2014	2015
Unique Veterans	863	851	870
Female	141	134	140
Male	722	717	730
Total ECT treatments*	9,777	10,490	10,034
Veterans in VHA with confirmed Major Depression**	244,025	260,577	281,975
% receiving ECT	0.34%	0.33%	0.31%

^ VHA internal data

* Most common diagnoses Major depression followed by psychotic disorders and other mood disorders

** confirmed if 2 OP visits or in-patient/ residential stay with Major depression diagnosis

Predictors of ECT Utilization in the US

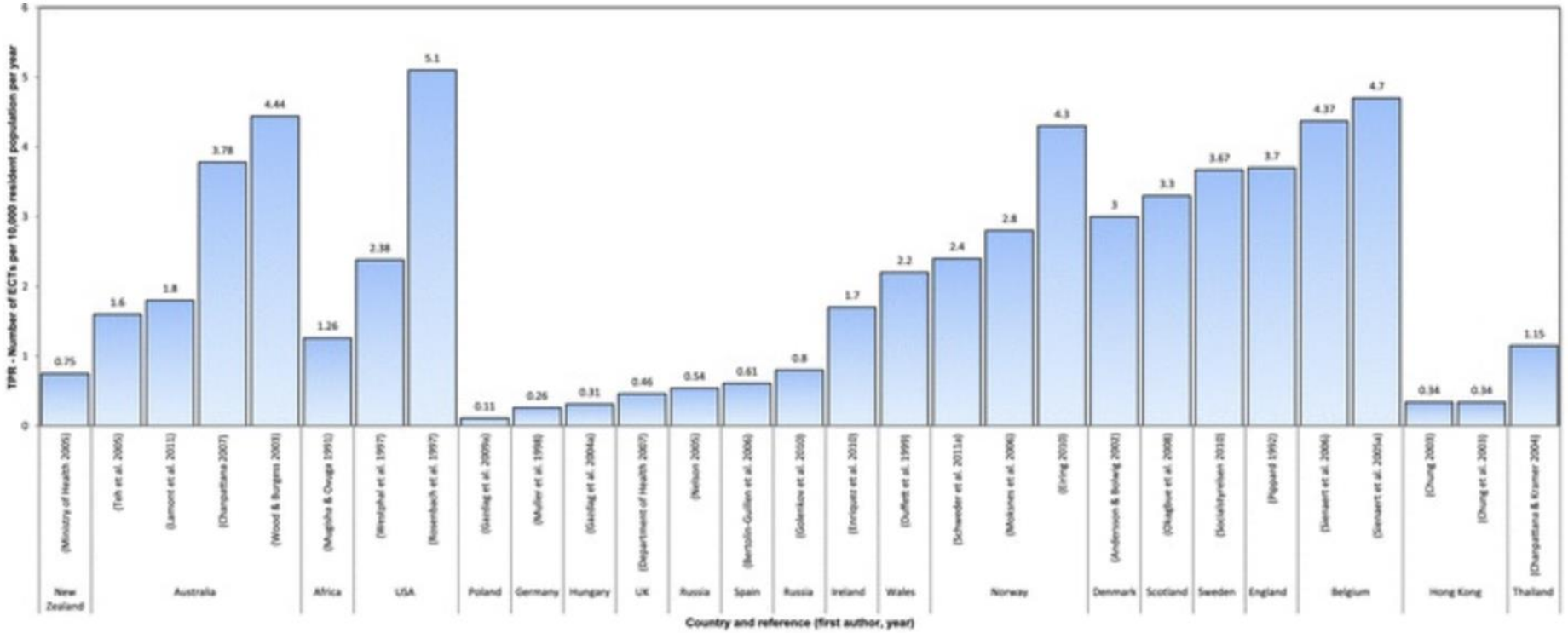
- ECT availability is characterized by marked geographic variability
- Public vs. Private Facility
- Age
- Minority Status
- Income

Olfson et al. *Am J Psychiatry* (1998)

ECT Utilization World-wide

- Marked variability across countries in ECT utilization, including the West
- Fundamental differences across societies in indications for ECT and ECT practices
- Estimates of ECT utilization world-wide are impressionistic, but use is less than anticipated. “A composite event rate of 16.9/100,000 inhabitants emerged, characterized by high heterogeneity. Across the countries assessed, the prevalence of ECT was higher in older studies.” Lesage et al. *J ECT* 2016
- Predictors: “… across the globe ECT but not antidepressant medication utilization is associated with the degree to which a nation financially invests in mental health care for its citizens.” Rajita et al. *J ECT* 2017

ECT Utilization World-wide



Leiknes et al. Brain and Behavior, 2012

Why is ECT Underused?

- Objective data indicate superior efficacy, heightened safety, and greater durability than alternatives. ECT also results in reduced long-term (all causes) mortality, and ECT is highly cost effective compared to ineffective pharmacology.

- Low utilization is tied to institutional barriers (availability) and stigma

- Stigma pertains to:
  - Psychiatric profession (referrals and providers)
  - Patients
  - Public

Defeating Stigma: Reasons for Optimism

- The field of ECT contributes to stigma due to variability in practices and guidelines. Internecine debates about ECTpractices and resistance to progress only contribute to public mistrust. Societal variation in the use of ECT must be addressed.

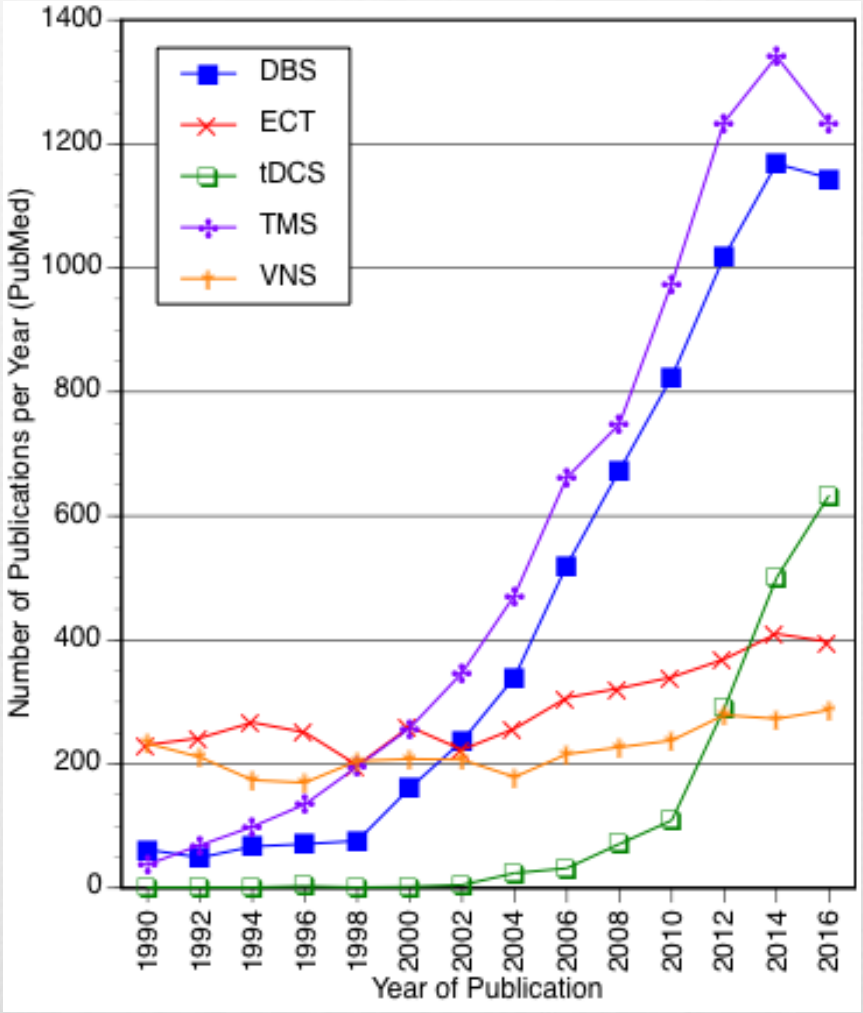
- The tremendous progress made in ECT needs to shared more widely. To survive, ECT cannot be the stepchild of psychiatry, but embraced as a beacon of hope and progress.

- The science of ECT is the greatest defense against fake news and antipsychiatry. ECT now embedded in the larger field of brain stimulation and interventional psychiatry.

- Most of all, ECT reduces suffering and saves lives. The humanistic qualities of ECT must be widely shared and appreciated.

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



Reasons for Optimism: Changing Public Perception

Reasons for Optimism: Defeating Stigma

Reasons for Celebrate:
Thank You to the ECT Community

Columbia University Medical Center

A New York State of Mind

New Building, NYSPI

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

Columbia University