ELECTROCONVULSIVE THERAPY (ECT): PAST, PRESENT, AND FUTURE

NACT MEETING
Nordic Association for Convulsive Therapy
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Disclosures

Consultant: Cyberonics Inc., Eli Lilly, Magstim Corp., Neuronetics Inc., NeuroPace, Novaritis Inc, Pfizer Inc.

MECTA Corp.

Brain Stimulation Interventions 2011

Intervention	Convulsive	Implanted	Magnetic	Responsive	Continuous
Transcranial Magnetic Stimulation (TMS)			✓		
Focal Electrically Applied Therapy (FEAT)					
Transcranial Direct Current Stimulation (tDCS)					
Vagus Nerve Stimulation (VNS)		✓			✓
Deep Brain Stimulation (DBS)		✓			✓
NeuroPace (Responsive Stimulation)		✓		✓	
Electroconvulsive Therapy (ECT)	✓				
Magnetic Seizure Therapy (MST)	✓		✓		
Focal Electrically Applied Seizure Therapy (FEAST)	✓				

Roadmap of Topics

- The past and how best to administer ECT (present)
- Should ECT and antidepressants be mixed (present)
- Durability of benefit and relapse prevention (present)
- The FUTURE:
  Optimization of ECT Stimulus: Titration in the Current Domain

  Optimization of Spatial Targeting: FEAST: Focal Electrically-Administered Seizure Therapy

Origins of ECT: Fundamental Principles

- For decades fundamental view was that the generalized seizure provided the necessary and sufficient conditions for efficacy, while electrical intensity contributed to cognitive side effects
- No rational dosing strategy
- Introduction of empirical dose titration revolutionized the field

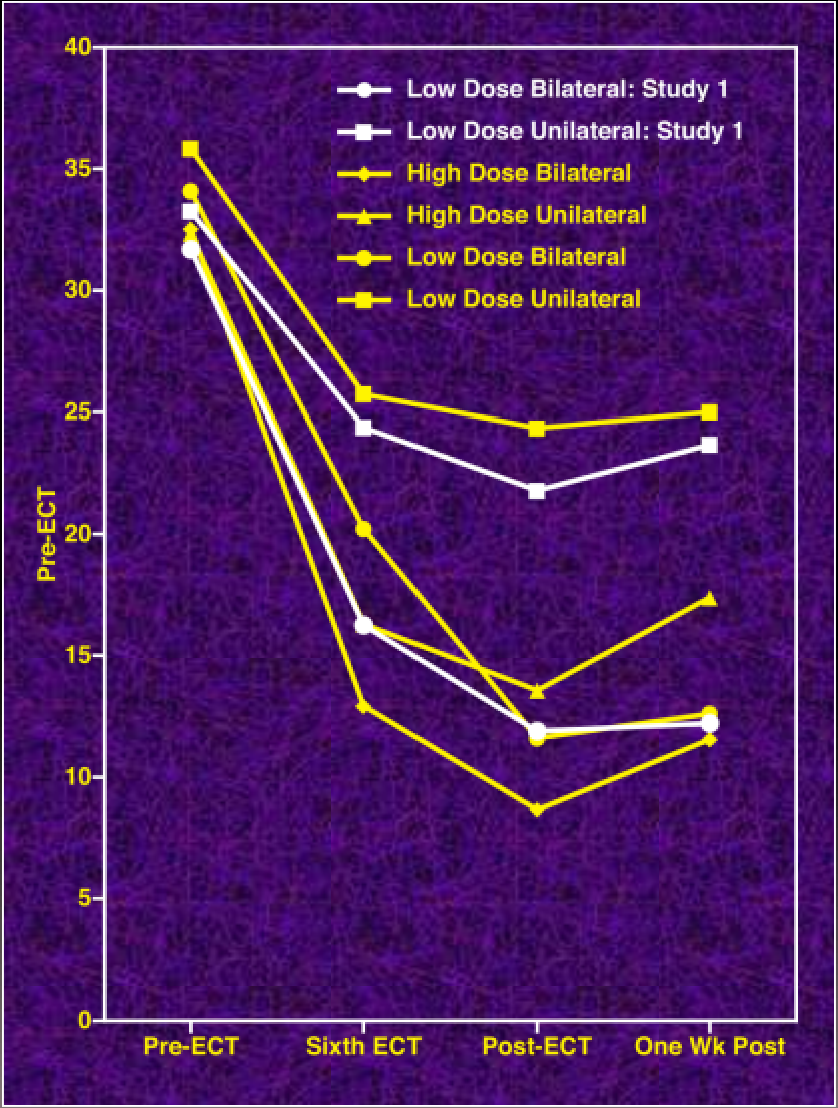
Quantification of Seizure Threshold

- Large individual differences in seizure threshold (largely anatomically driven)
- Consistent sex difference, age effect, and effect of electrode placement (anatomic positioning)
- Sensitive to pharmacological effects
- Threshold is dynamic, massive increase over ECT course, consistent with metabolic and EEG effects

Determinants of Efficacy and Cognitive Side Effects

- Seizures can be reliably elicited that lack efficacy
- Current paths and current density determine efficacy and side effects
  - Efficacy of right unilateral ECT highly dosage sensitive
  - Electrode placement key to magnitude of long-term amnesia
- Ultra-brief stimulation radically reduces cognitive effects while maintaining efficacy

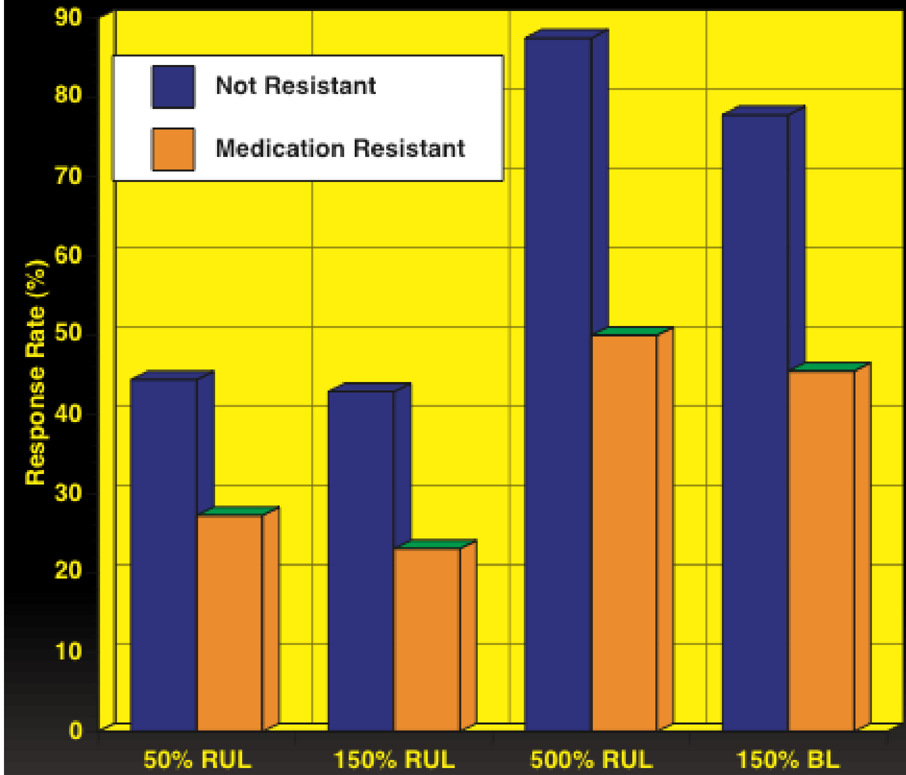
Generalized Seizures Can Be Reliably Produced that Lack Efficacy (Study 1 & 2)



- At low stimulus intensity, RUL ECT lacks efficacy
- Antidepressant effects of RUL ECT increase linearly with dosage relative to ST
- Efficacy of BL ECT can also be undone

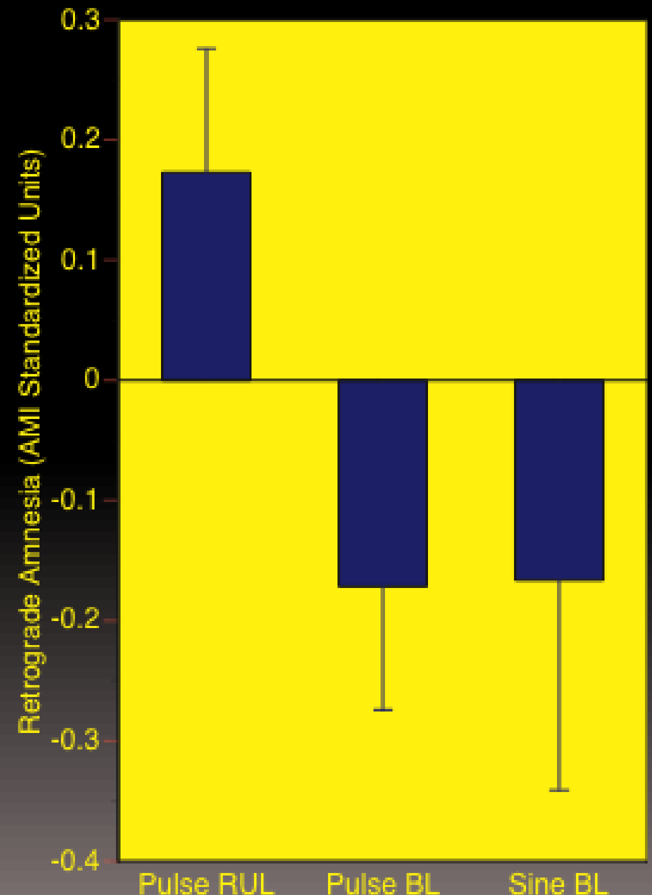
Sackeim et al. *Am J Psychiatry* (1987)
Sackeim et al. *N Eng J Med* (1993)

Electrode Placement: Efficacy and Long-term Amnesia



Dosage and the Efficacy of RUL ECT
Sackeim et al. *Arch Gen Psychiatry* (2000)

Amnesia for Autobiographical Information 6-Months PostECT (Community Study: Sackeim et al. 2007)



Rationale for Ultrabrief Stimulation

- Severity of cognitive side effects inversely related to the efficiency of electrical stimulus
  - Sine wave stimulus resulted in dramatically greater cognitive side effects than brief pulse
  - No difference in efficacy between sine wave and brief pulse stimulation

The ECT Waveform: Why is Sine Wave So Toxic

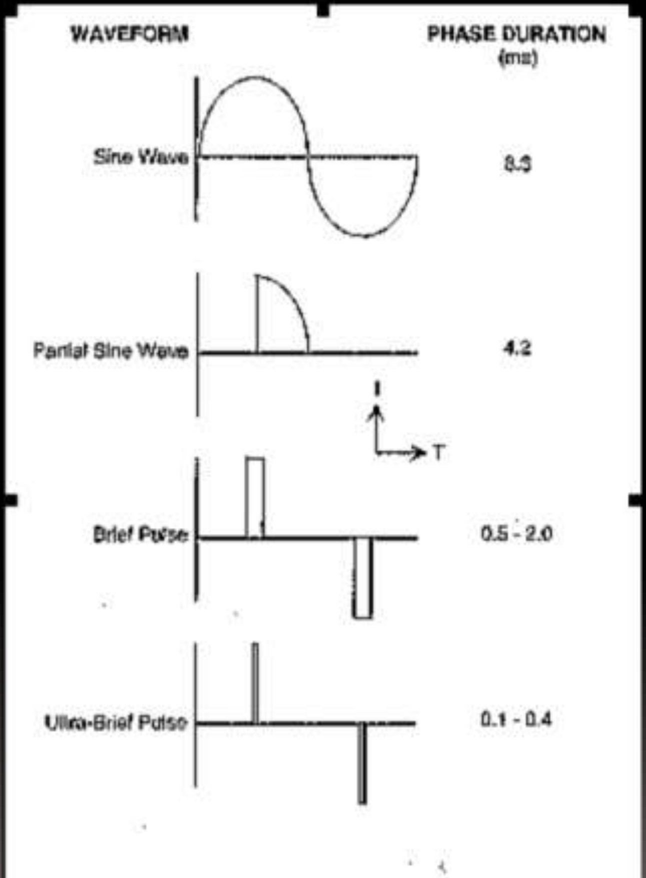


FIGURE 1

- Period of sine wave in US (60 Hz) is 8.333 ms
- Slow rise to peak (4.167 ms) which raises the ST through principle of accommodation
- Slow offset (4.167 ms), resulting in most of the stimulation delivered during neuronal refractory and relative refractory periods

Rationale for Ultrabrief Stimulation

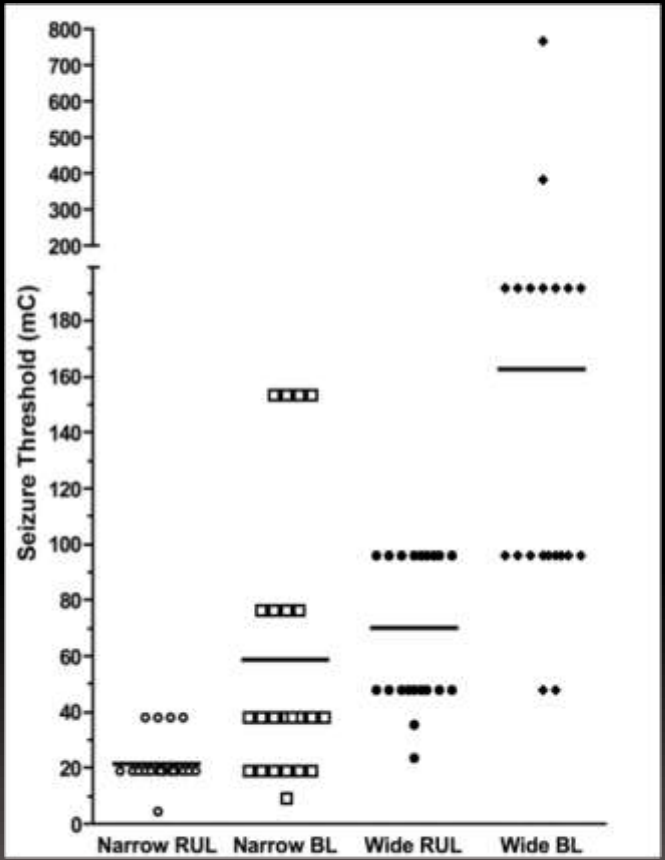
- Traditional ECT pulse width is inefficient;
  - Optimal pulse width to produce depolarization is at most 0.2 ms
  - Typical brief pulse is between 1.0-2.0 ms

Titration Schedule

PW 0.3 ms			PW 1.5 ms	
Stimulus 1*	**Charge**		**Stimulus 1***	**Charge**
20Hz			20Hz	
0.5 Dur	4.8		0.5 Dur	24
Stimulus 2**			**Stimulus 2****	
20Hz			20Hz	
1.00 Dur	9.6		1.00 Dur	48
Stimulus 3			**Stimulus 3**	
20Hz			20Hz	
2.00 Dur	19.2		2.00 Dur	96
Stimulus 4			**Stimulus 4**	
20Hz			20Hz	
4.00 Dur	38.4		4.00 Dur	192
Stimulus 5			**Stimulus 5**	
20Hz			20Hz	
8.00 Dur	76.8		8.00 Dur	384
Stimulus 6			**Stimulus 6**	
40Hz			40Hz	
8 s Train	153.6		8 Dur	768

Sackeim et al. *Brain Stimulation* (2008)

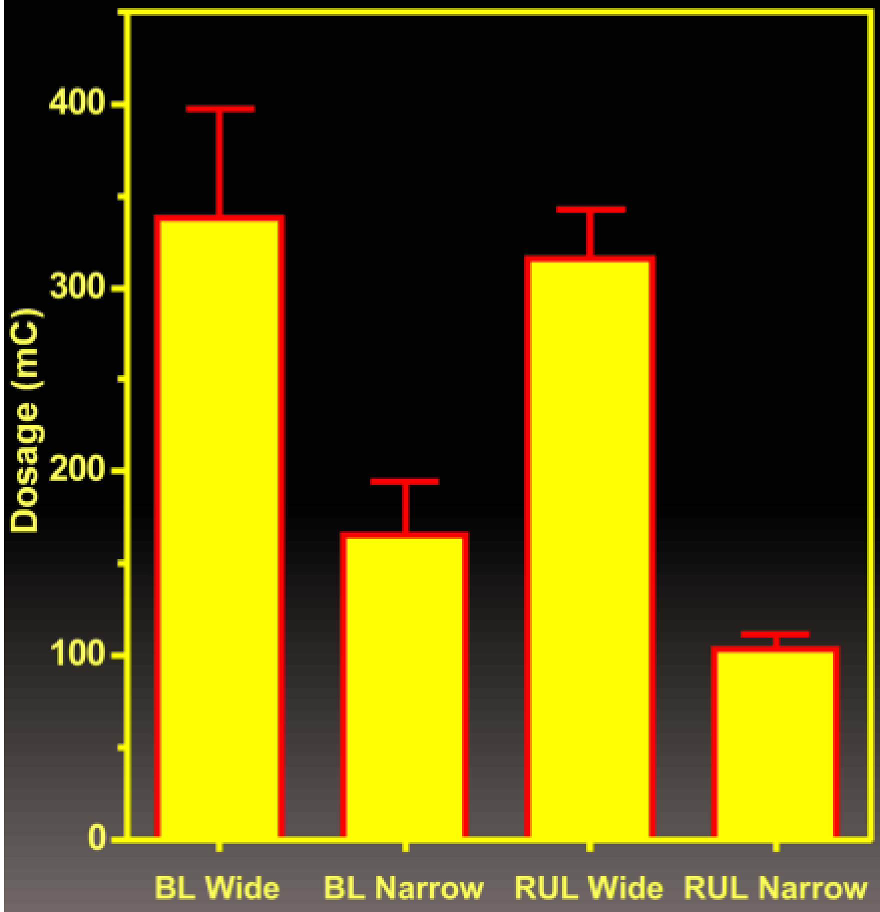
Effects of Pulse Width and Electrode Placement on Seizure Threshold: Electrical Efficiency



- Seizure threshold 3-4 times lower with ultrabrief stimulation
- Larger effect than electrode placement

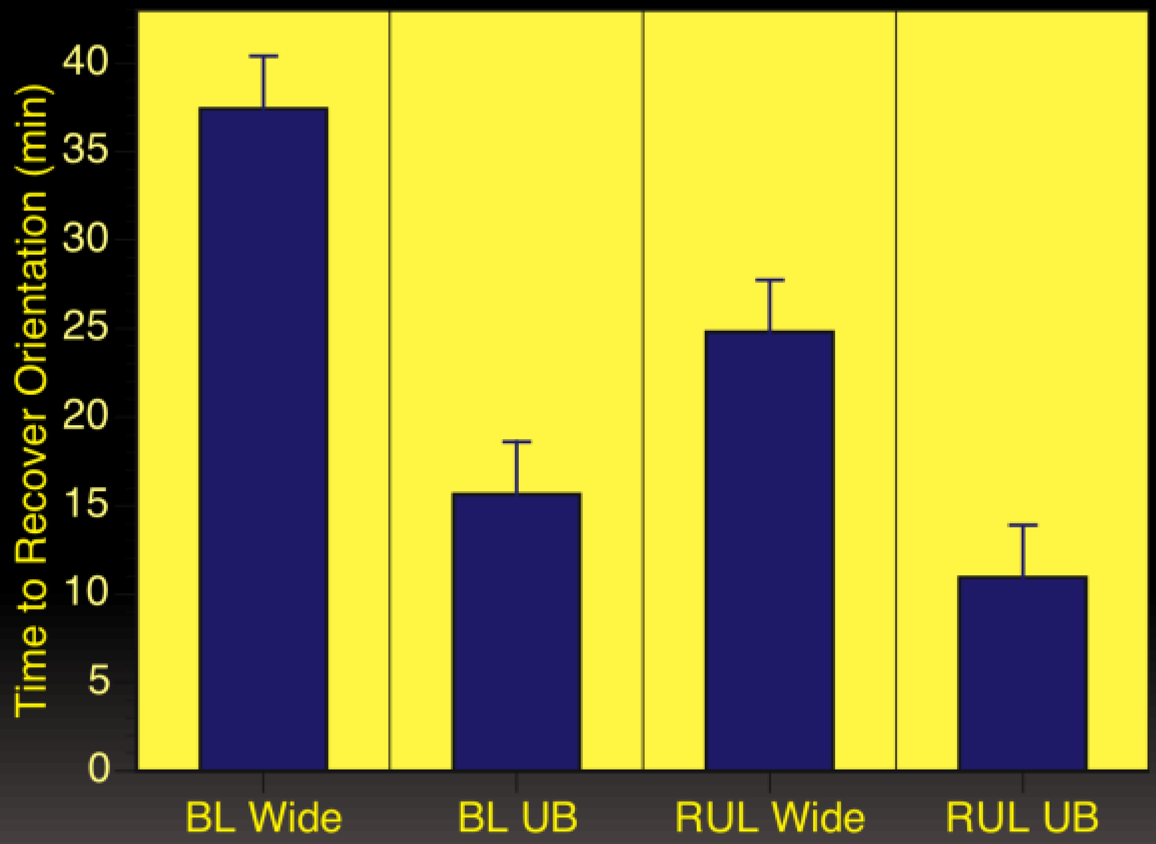
Factor	df	F	*P*
Electrode Placement (EP)	1	32.5	<0.0001
Pulse Width (PW)	1	85.8	<0.0001
EPxPW	1	0.3	NS
Age	1	3.3	0.07

Efficiency of Ultra-Brief Stimulation



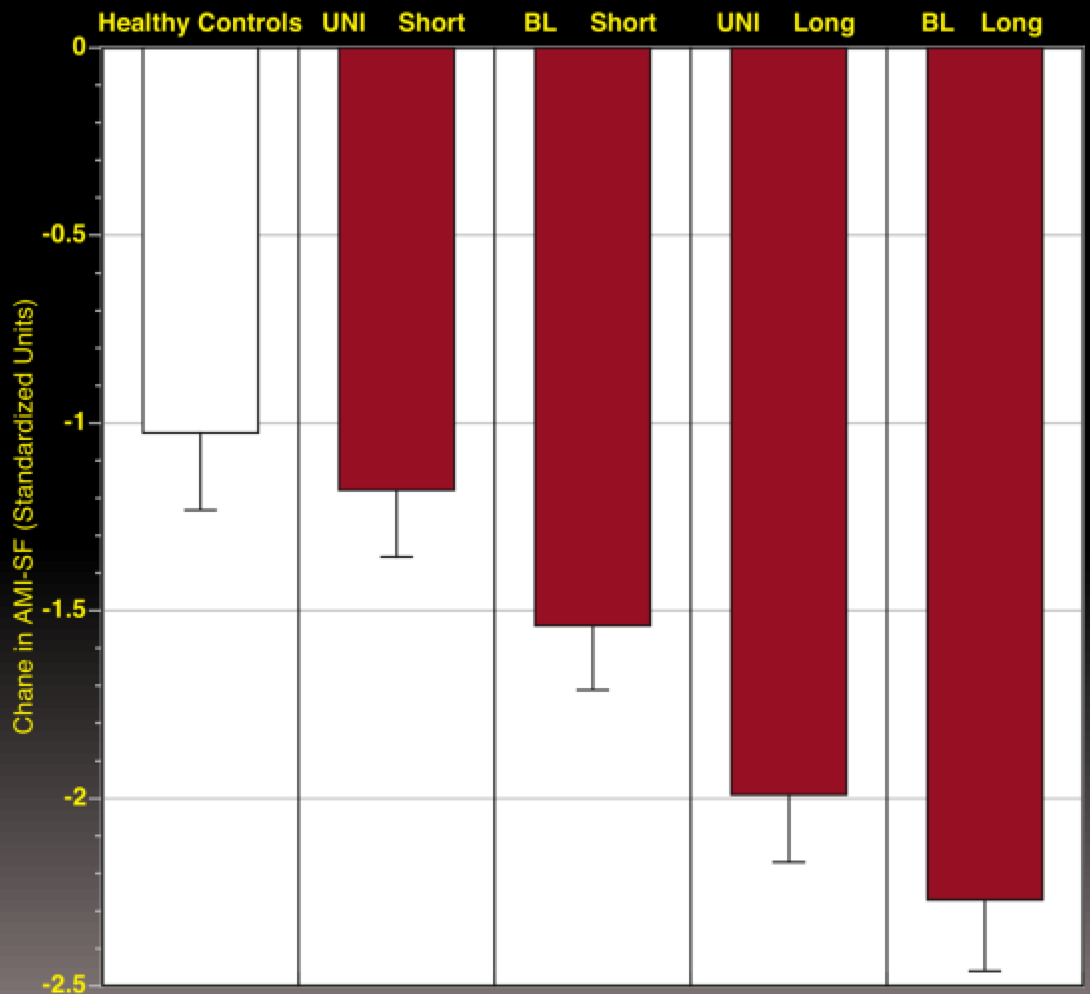
- Ultra-brief stimulation was 3-4 times as efficient as the wide pulse width stimulation.
- Majority of patients could receive high dosage RUL ECT at 6xST yet have an absolute dose of approximately 100 mC.

Cognitive Advantages are Greater for UB Stimuli than Choice of RUL



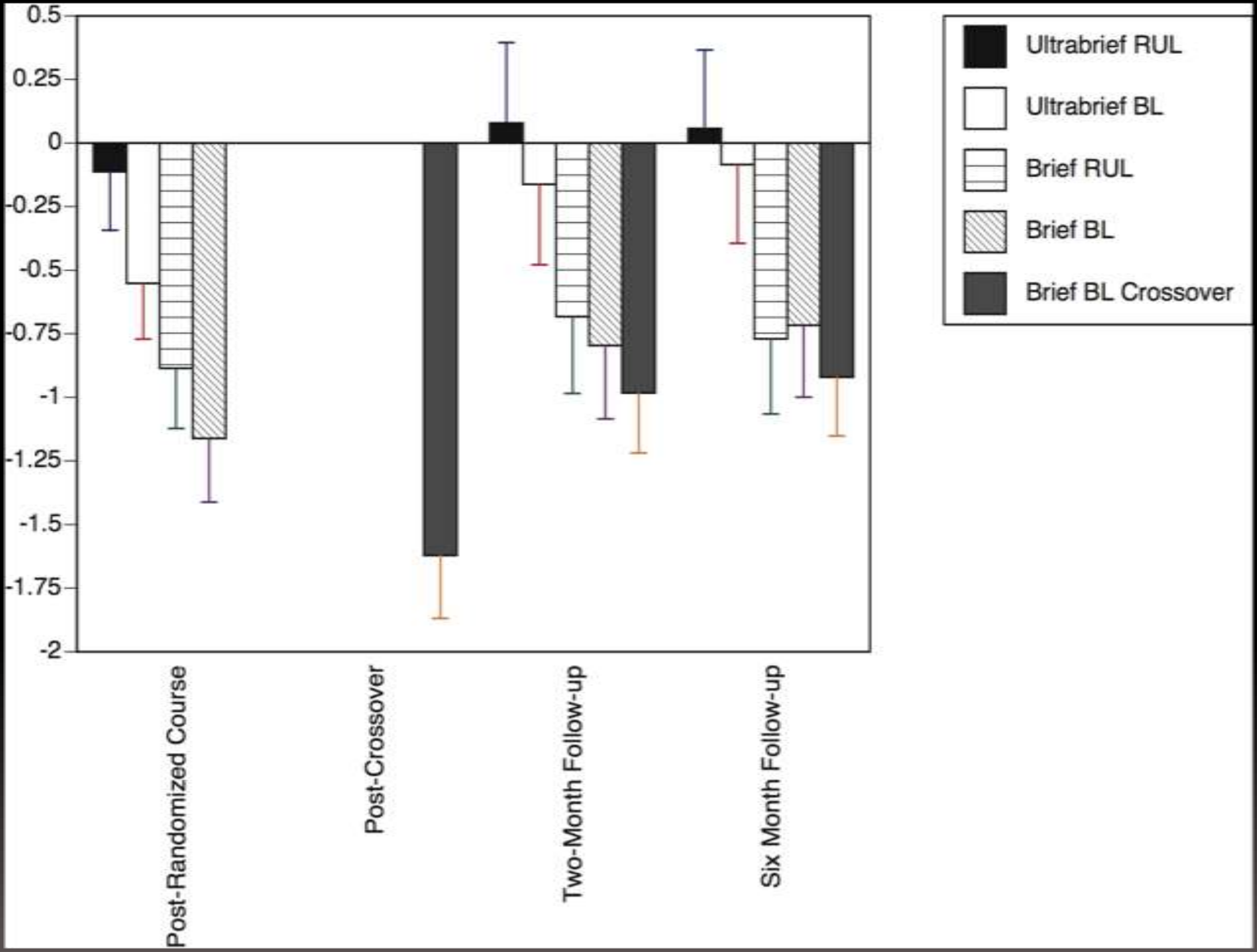
At all time points effect sizes for PW greater than for electrode placement

Retrograde Amnesia for Autobiographical Information



- Memory loss for autobiographical information highly sensitive to ECT technique
- No difference between RUL UB group and super normals in memory loss over period of ECT

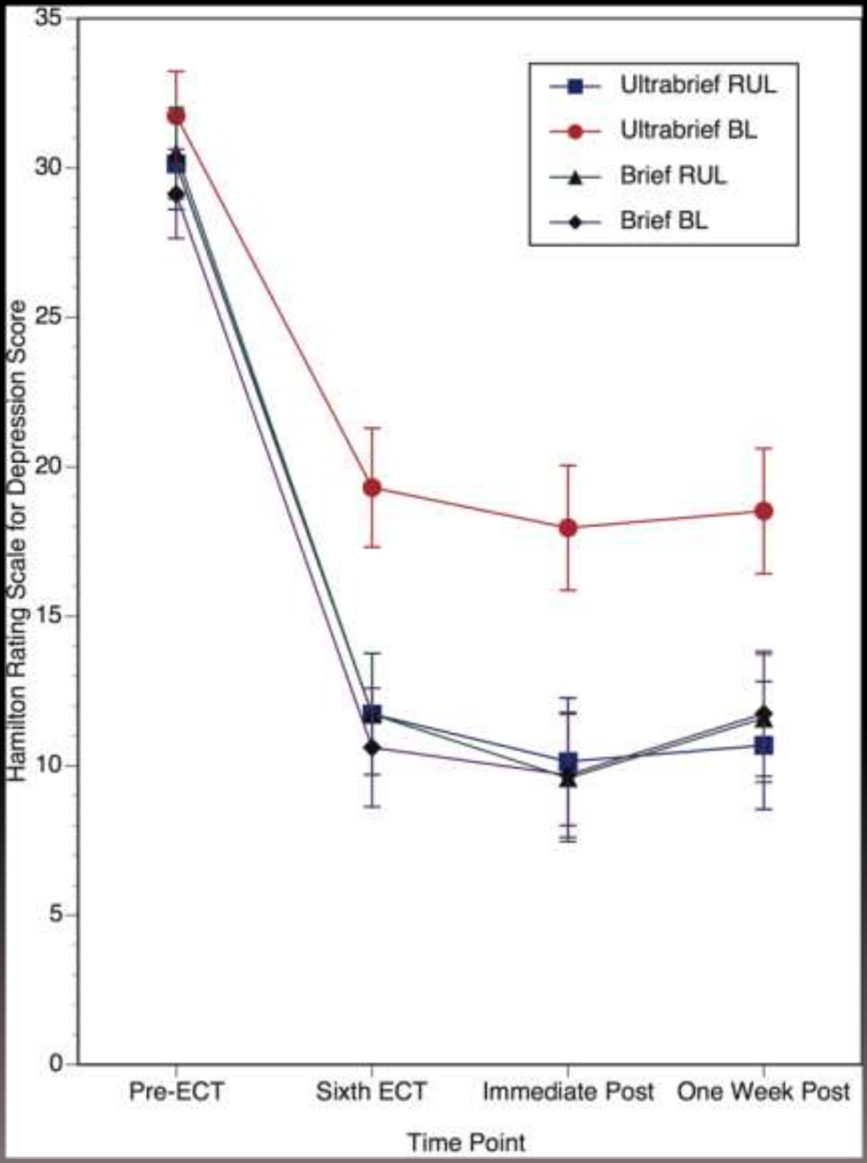
Long-term Retrograde Amnesia: Ultra-brief Advantage



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

Sackeim et al. *Brain Stimulation* (2008)

Efficacy: Ultra-brief by Electrode Placement Interaction



- UB RUL ECT (6 X ST) has strong efficacy
- UB BL ECT (2.5 x ST) has weak antidepressant effects
- First demonstration of BL inferior efficacy
- Likely due to a dose-response effect

Sackeim et al. *Brain Stimulation* (2008)

Ultrabrief Stimulation: Conclusions

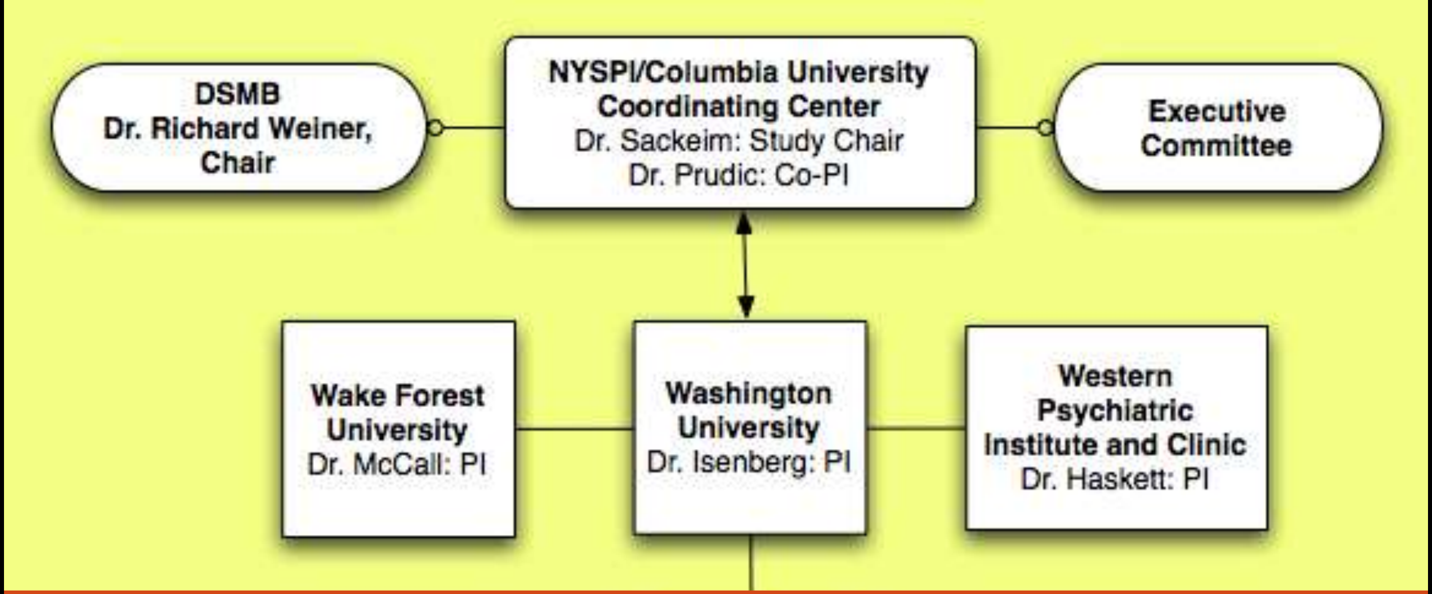
- Use of ultrabrief stimulation results in marked savings in a variety of cognitive measures
- Extends the range of devices, due to greater efficiency
- Contradicts views regarding utility of EEG analysis
- Creates dissociation between side effects and efficacy
- RUL UB ECT appears optimal first ECT exposure

Sackeim et al. *Brain Stimulation*, 2008

Key Issues: Impact of Concurrent Pharmacotherapy on Efficacy and Side Effects

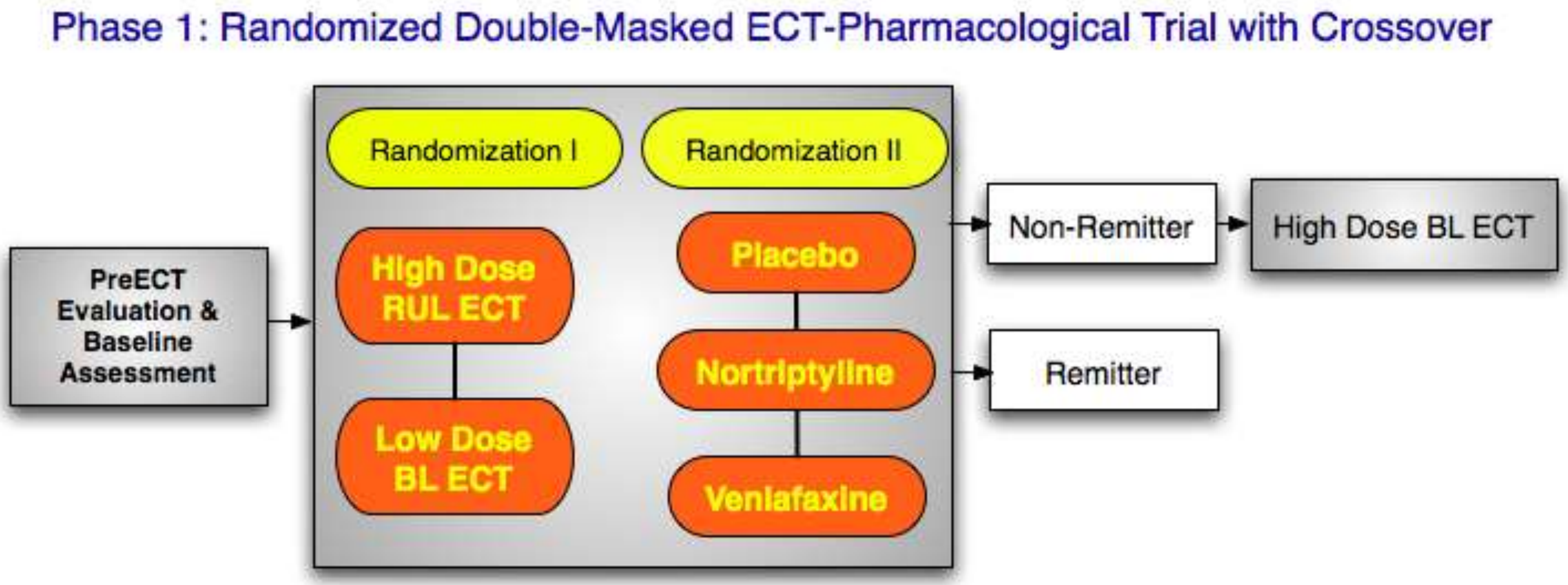
- Should antidepressant medication be co-administered during ECT
  - Impact on efficacy
  - Concern about aggravation of side effects
  - A method to prevent early relapse?

Organization of Opt-ECT



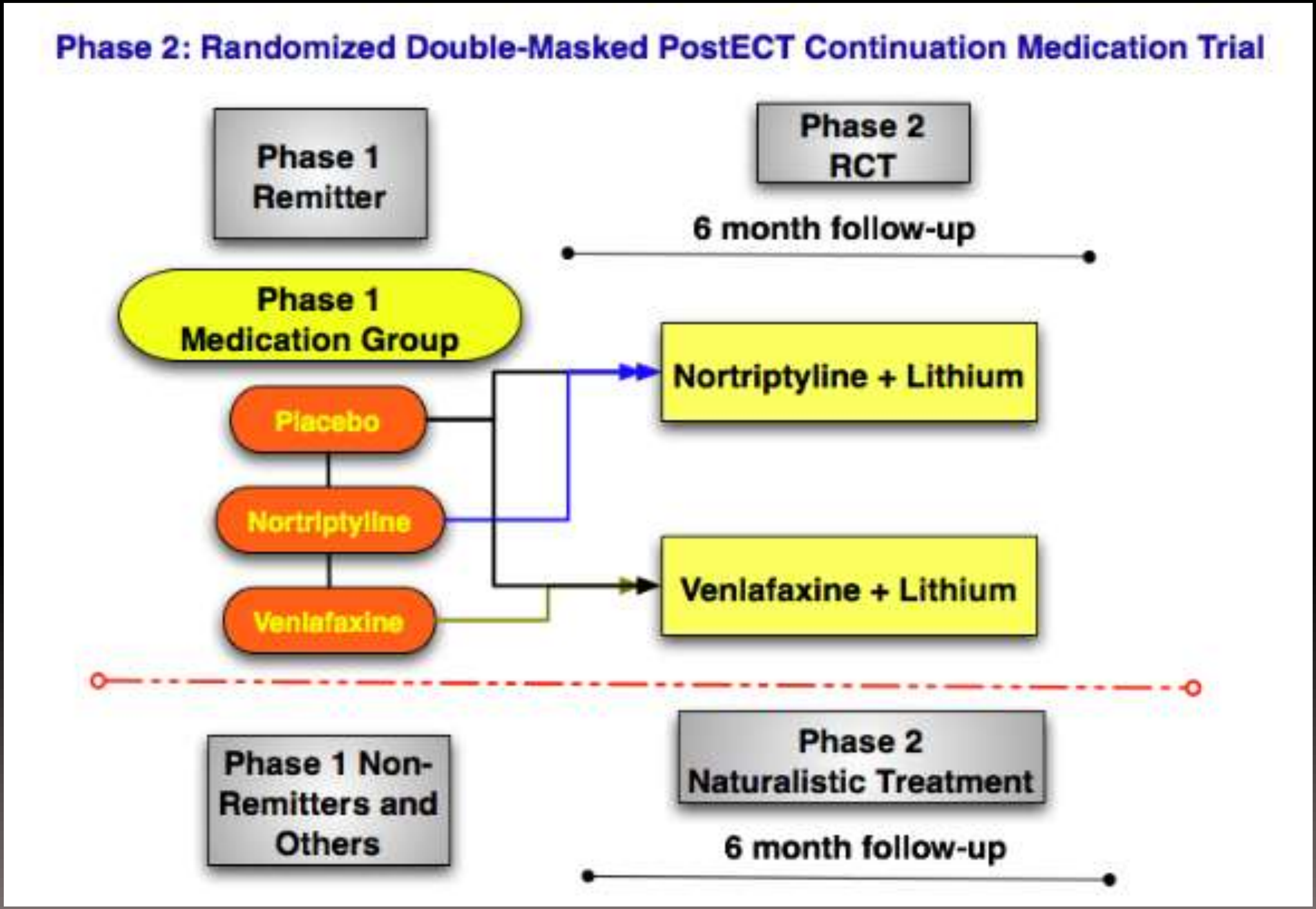
Sackeim et al. *Archives of General Psychiatry*, 2009

Study Design — Phase 1 OPT-ECT



Sackeim et al. *Archives of General Psychiatry*, 2009

Study Design —OPT-ECT

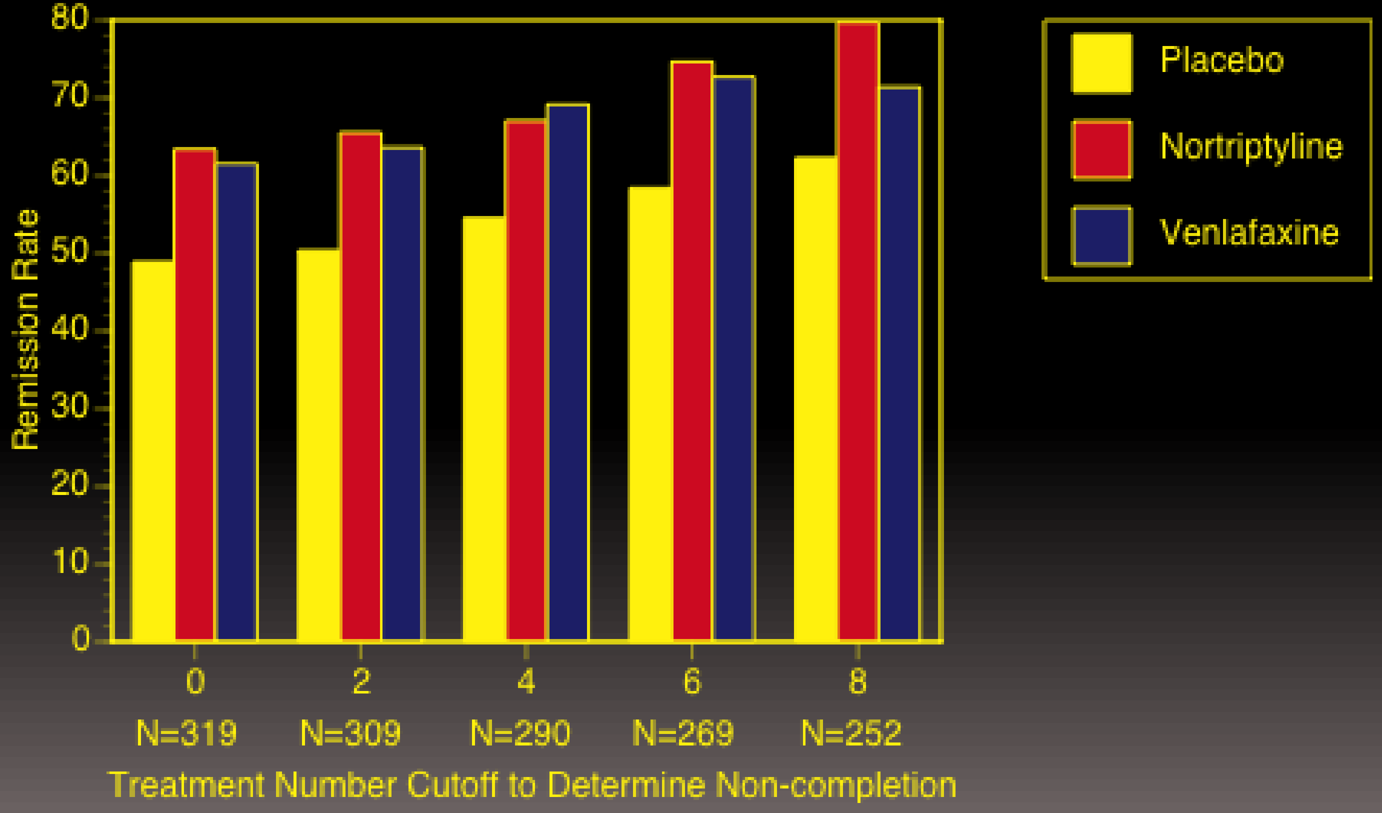


Phase 1 Demographics and Clinical Characteristics (N = 319)

Variable	Mean	SD
Age	49.0	15.7
Sex (% female)	63.6	
Education (yrs)	13.6	2.9
PreECT HRSD	31.1	6.5
PostECT HRSD	13.0	10.4
Polarity (% bipolar)	20.7	
Psychotic depression (%)	19.7	
No. of Treatments	8.1	4.3

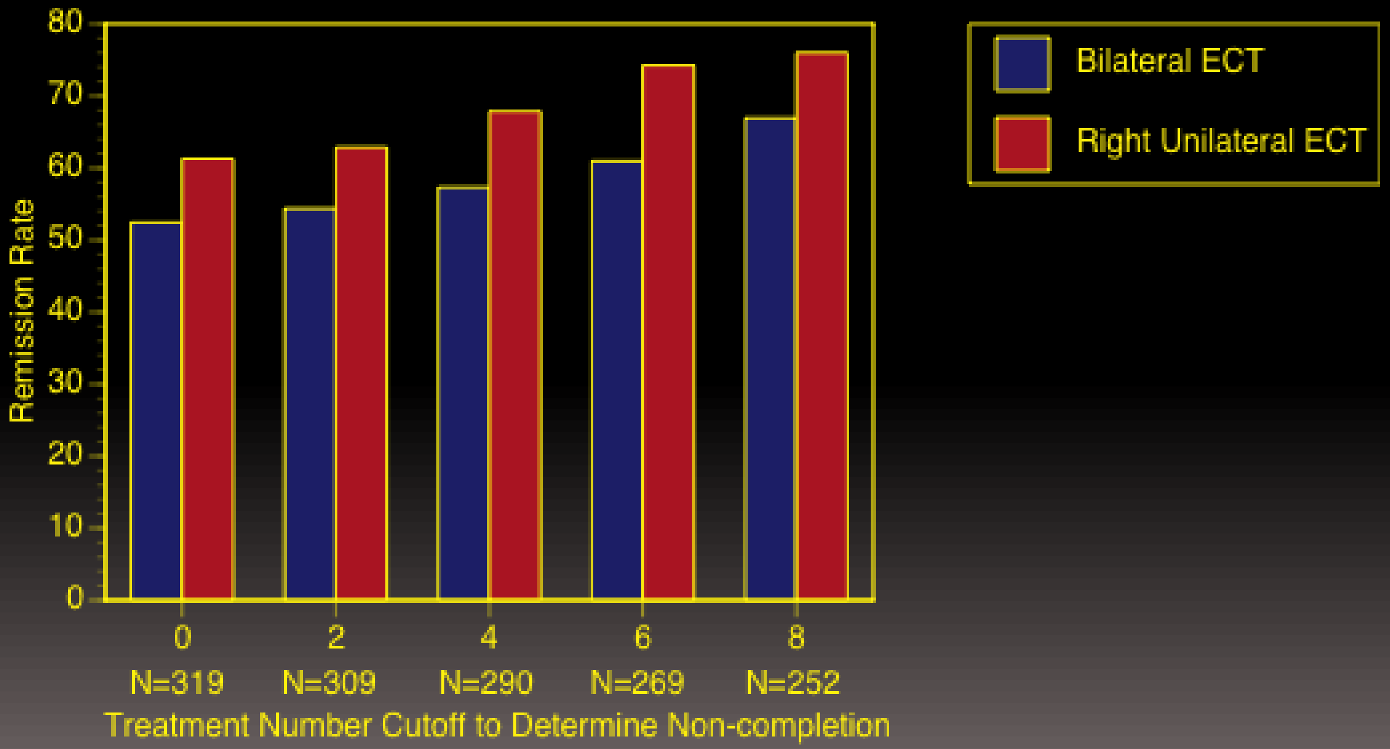
Remission Rate as a Function of Pharmacological Conditions: ITT and Completer Samples

- Advantage of NT over PL maintained at all cutoffs
- Improvement in remission is about 15%



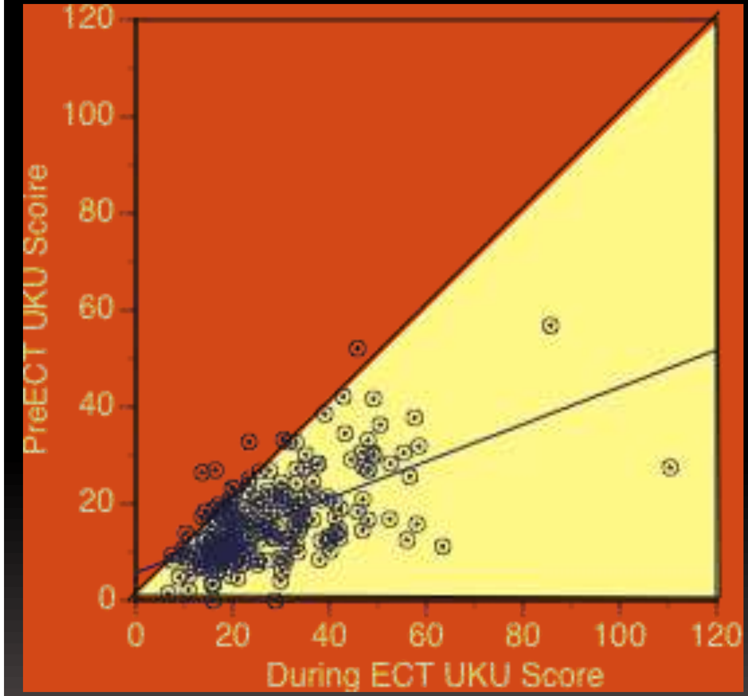
Remission Rate as a Function of ECT Conditions: ITT and Completer Samples

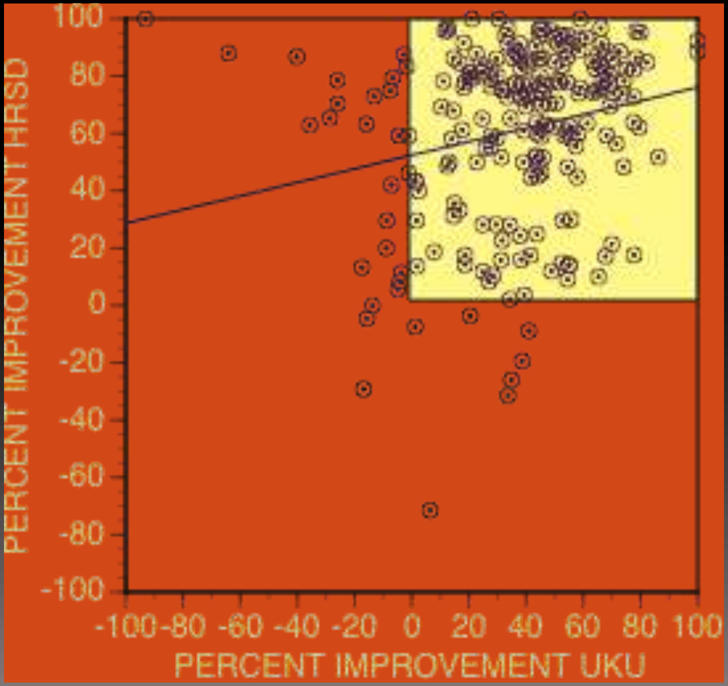
- Smaller advantage of RUL over BL ECT seen at all cutoffs
- Significant only for ITT and low cutoffs



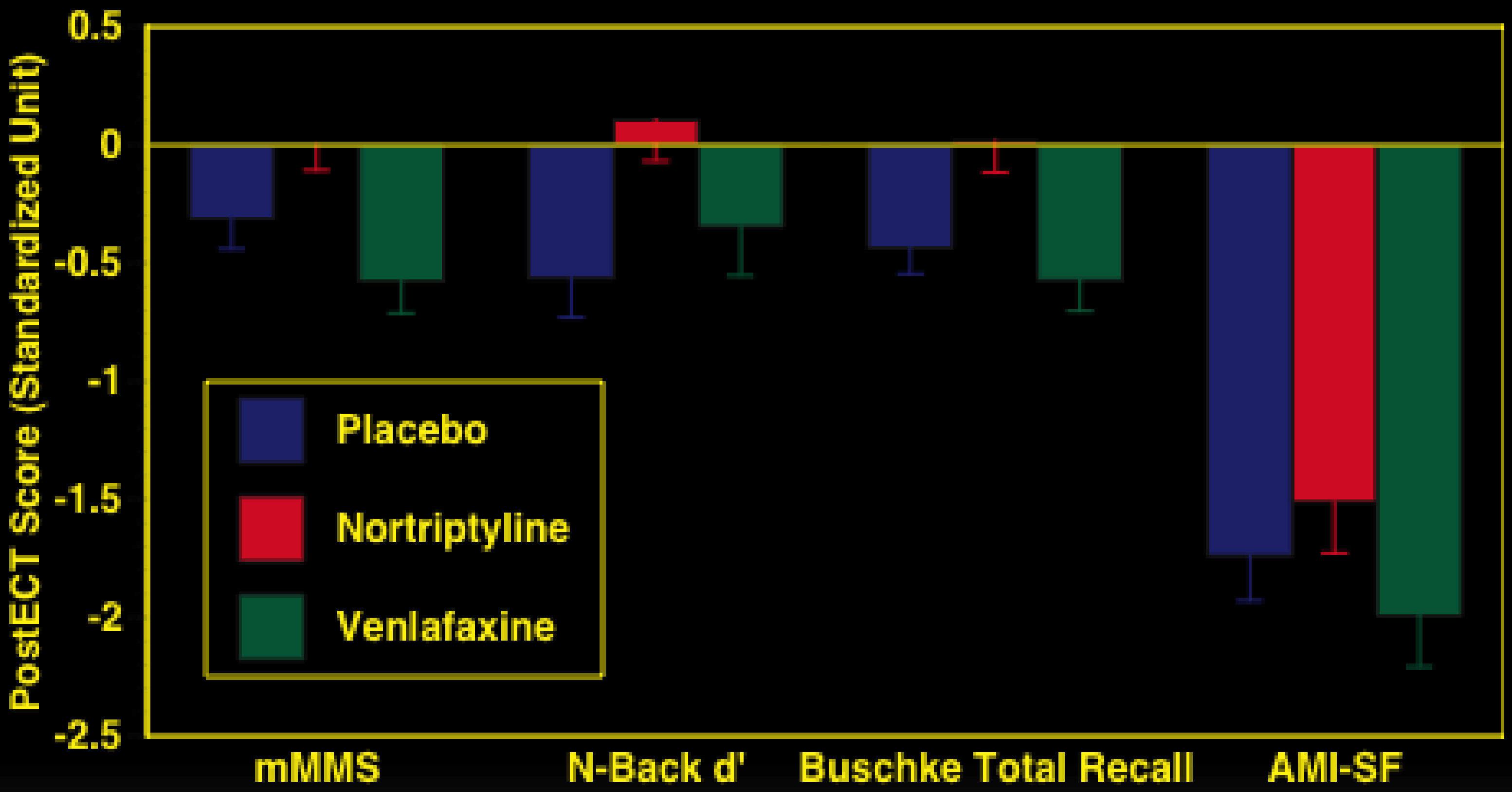
Systemic Side Effects

- No differences among groups in number of AEs or SAEs or UKU scores.
- Profound improvement in UKU scores from pre to during ECT
- Pre Mean ± SE = 27.2 ± 0.89
  During ECT = 16.0 ± 0.50
- Change in UKU strongly related to clinical improvement





Effects of Medication Conditions on Cognition



- Retrograde memory for autobiographical information most severely affected
- NT exerts protective effects on 3 of 4 measures

Conclusions: Concurrent Pharmacotherapy

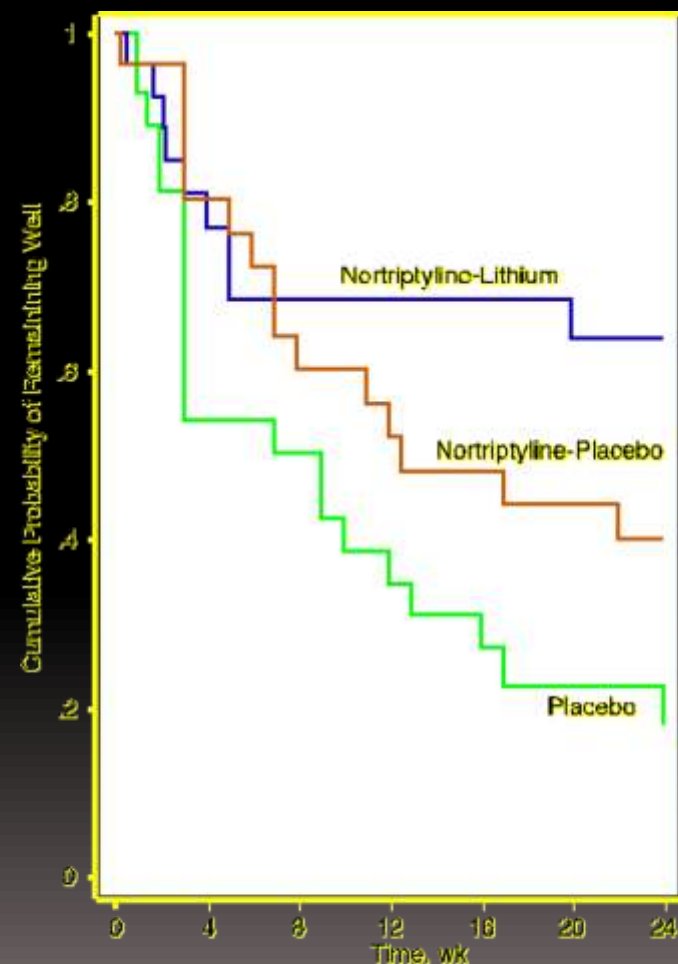
- Antidepressant pharmacotherapy may enhance efficacy of ECT
- Favorable efficacy and side effect profile for nortriptyline (and high dosage RUL ECT)
- May lead to altered recommendations by APA

Key Issues: Relapse Following ECT

- Without continuation therapy virtually all patients will relapse within 6 months of achieving remission with ECT
- Relapse reduced by treatment with nortriptyline and lithium
- Relapse rate comparable with continuation ECT
- Does starting nortriptyline (or venlafaxine) during ECT reduce postECT relapse?

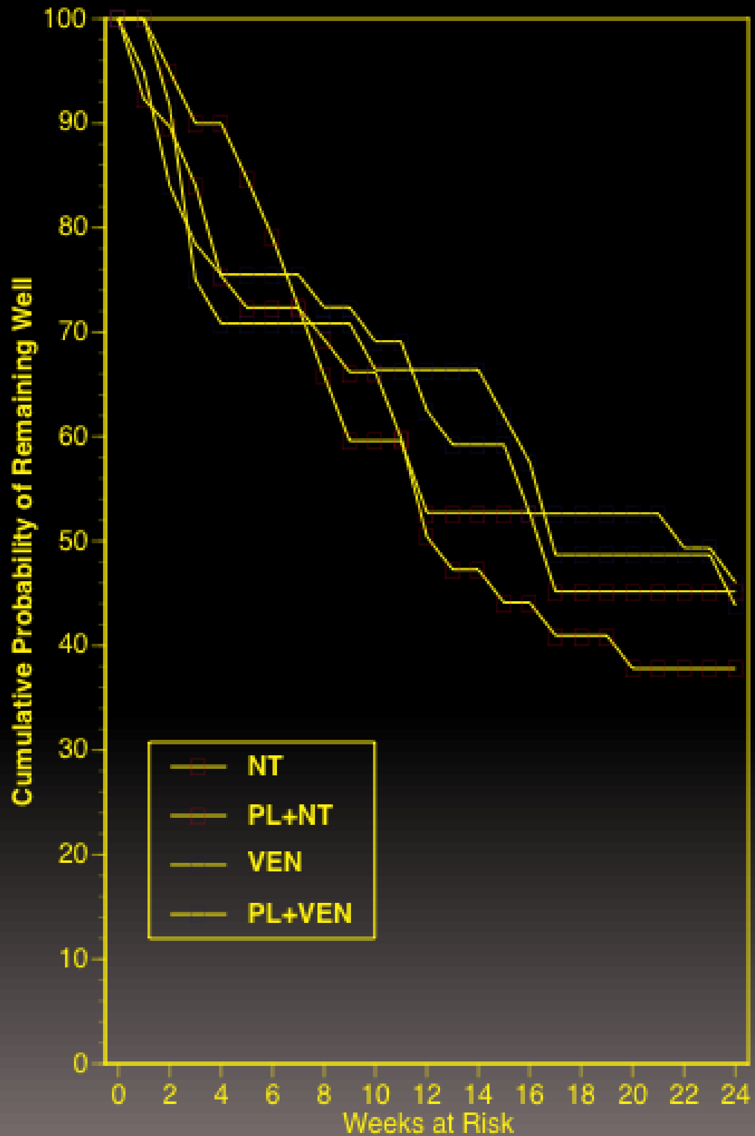
Reconsidering the Role of Pharmacology in ECT: Relapse Prevention

- Relapse rates following ECT are unacceptable. In Prudic et al. (2004) study of ECT in community settings, 61% of 162 ECT remitters relapsed within 6 months.
- No strategy appears effective in preventing early relapse (including continuation ECT)
- (1) Abrupt termination of ECT and (2) starting continuation pharmacotherapy only at ECT termination may both contribute to relapse. Does starting an antidepressant at the start of ECT reduce rates of early relapse?



Sackeim et al., *JAMA*, 2001

Relapse Rate by Pharmacological Condition



- Starting the antidepressant medication (vs. placebo) during ECT had no impact on postECT relapse
- Relapse rates comparable for NT-Li and VEN-Li

The (Immediate) Future of ECT

- All focal brain stimulation technologies are characterized by the key issues: “where” and “how”
- The major “how” question facing ECT is how to further improve the efficiency of stimulation
- The major “where” questions require improved capacity for focal target selection

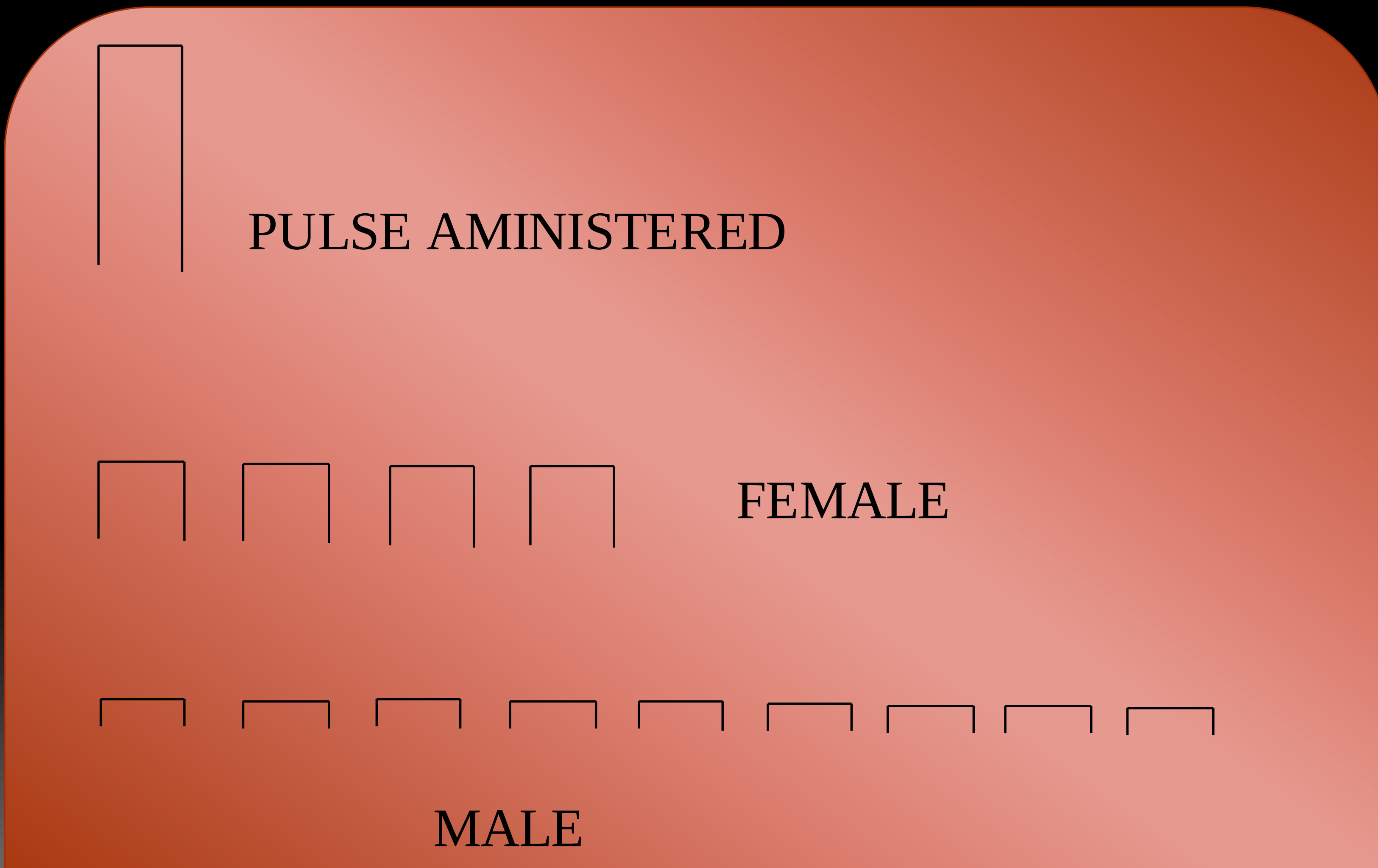
Parameters of the ECT stimulus: Contributions to efficiency of stimulation

- Pulse width (minimize)
- Train duration (maximize)
- Pulse frequency (can maximize, but keep low)
- Current (the next challenge)
- Directionality (bidirectional vs. unidirectional)

Titration in the Current Domain: Rationale

- Vast individual differences in seizure threshold are mainly due to anatomic factors influencing the amount of current entering brain
- Intracerebral current level determines depth and breadth of biological effects
- Despite this, we fix current and vary how many pulses patients receive
  - Patients with low thresholds receive high intracerebral current levels and fewer pulses
  - Patients with high thresholds receive low intracerebral current levels and many pulses

Titration in the Current Domain: Illustration



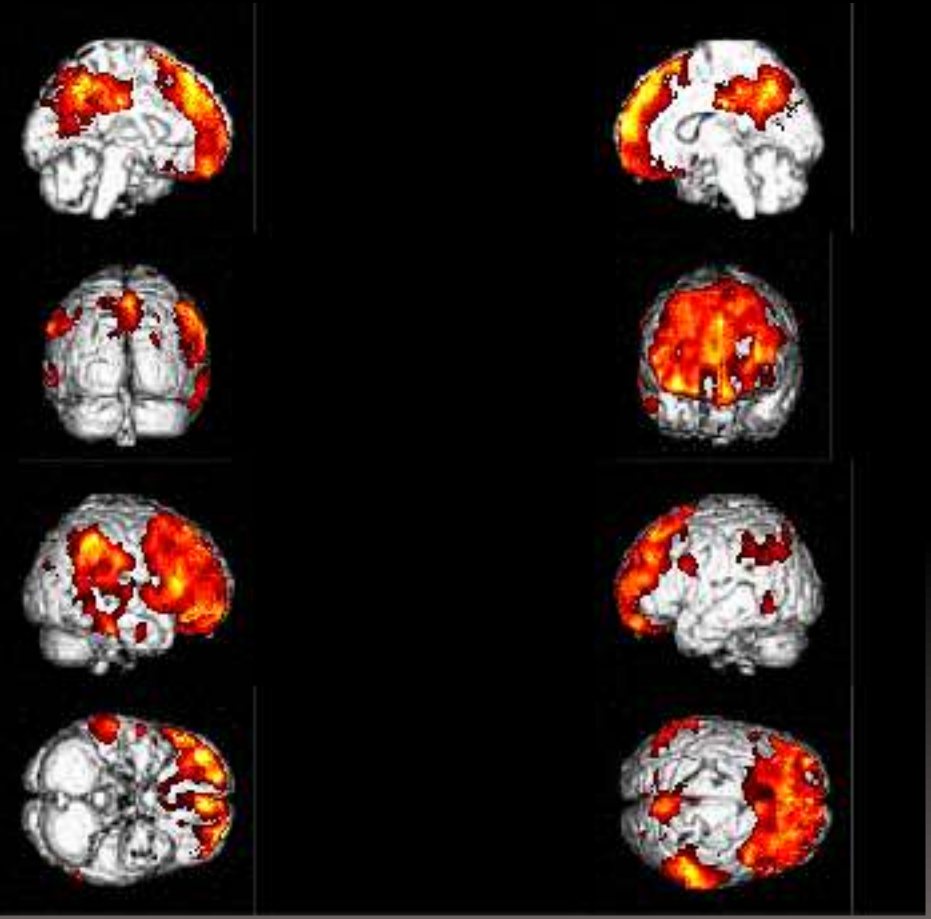
Optimizing Current: The Next Challenge

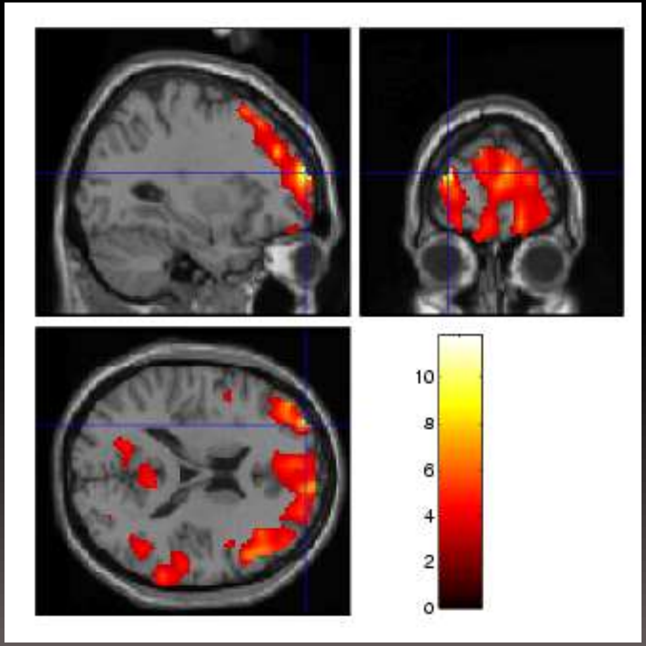
- Titration in current domain is feasible and improves the extent to which all patients receive the same intracerebral pattern of stimulation
  - New MECTA offers 500-900 mA range in 50 mA steps
- We have little information on prior question: What is the optimal level of current?
  - Efficiency may increase at higher levels of current
  - Practical limits to use of higher pulse amplitude

The Future of ECT
Spatial Targeting: Refining the "Where"

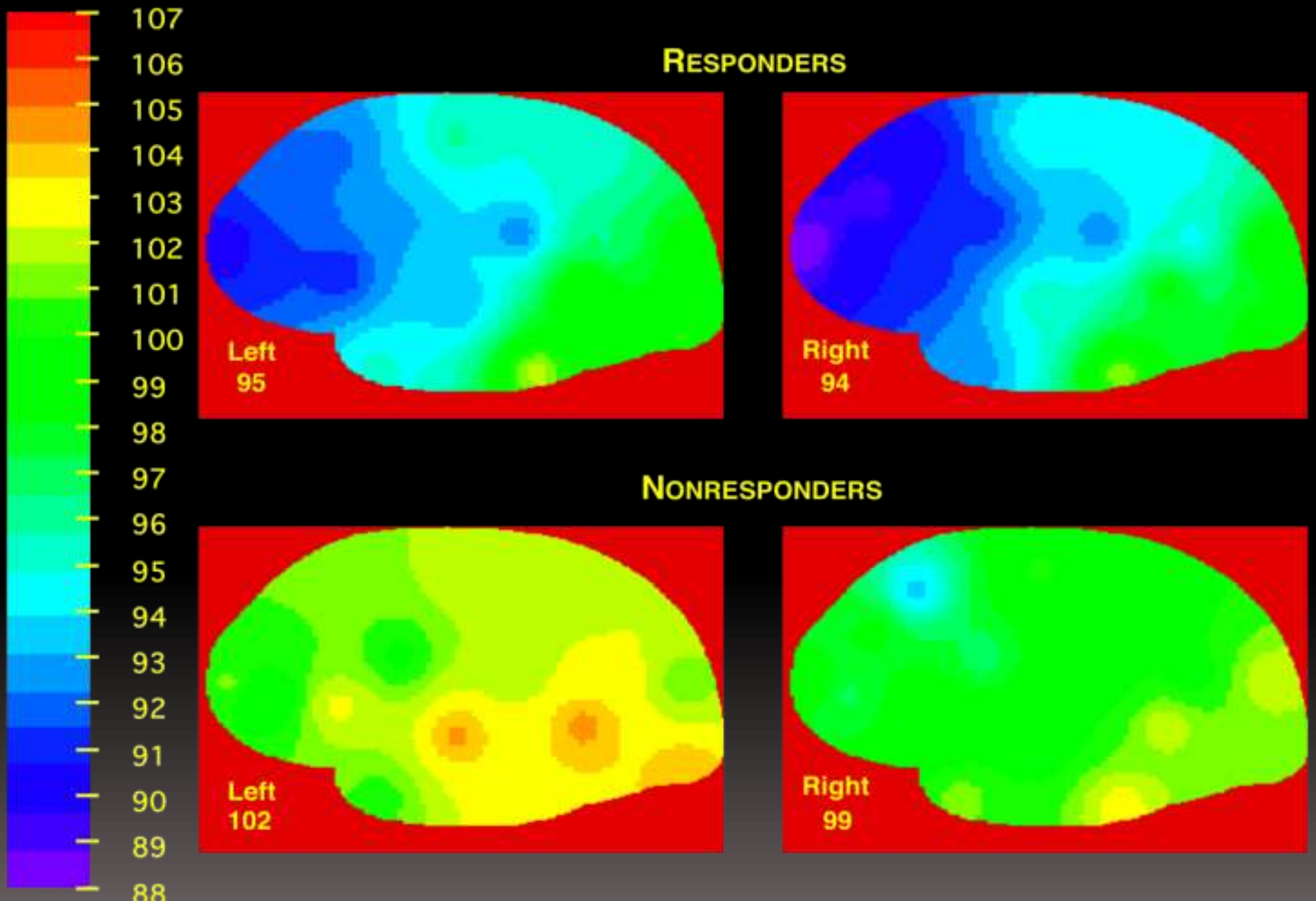
- Traditional ECT has relatively poor control over intracerebral current path and dosage within the path
- Anatomic circuitry identified by functional imaging
- New physical capabilities to shape current density paths to target particular neural regions

Effects of ECT on rCBF: 20 min Postictal



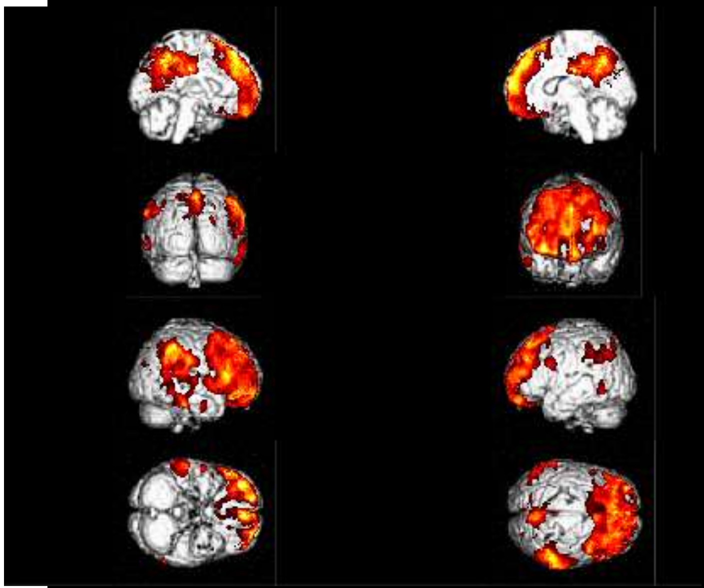


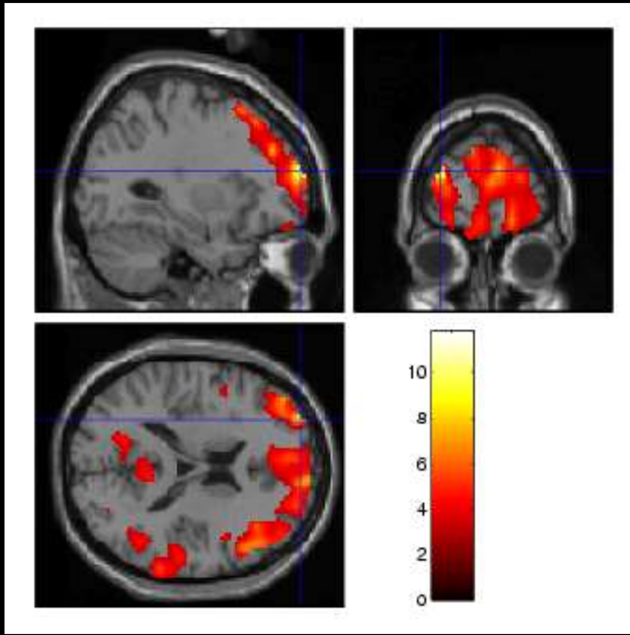
Acute rCBF Changes and Clinical Outcome



Nobler et al. *Arch Gen Psychiatry* (1994)

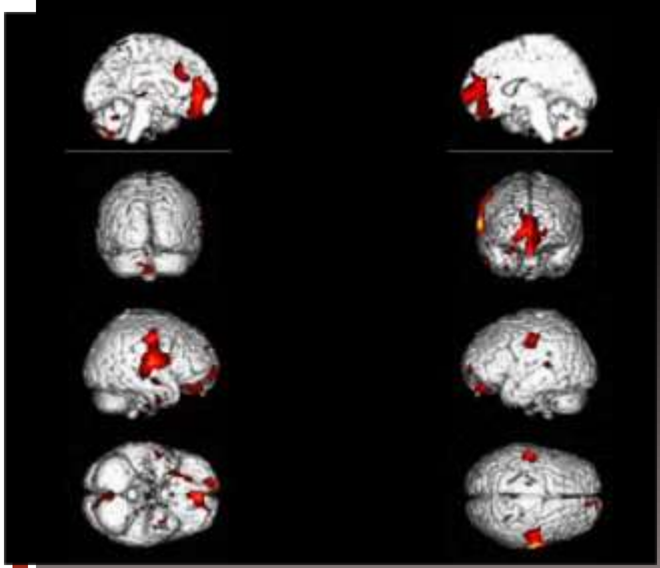
Targets for Neuromodulation Circuitry Linked to Antidepressant Response





ECT
(acute 20 min)

Nobler et al. In preparation

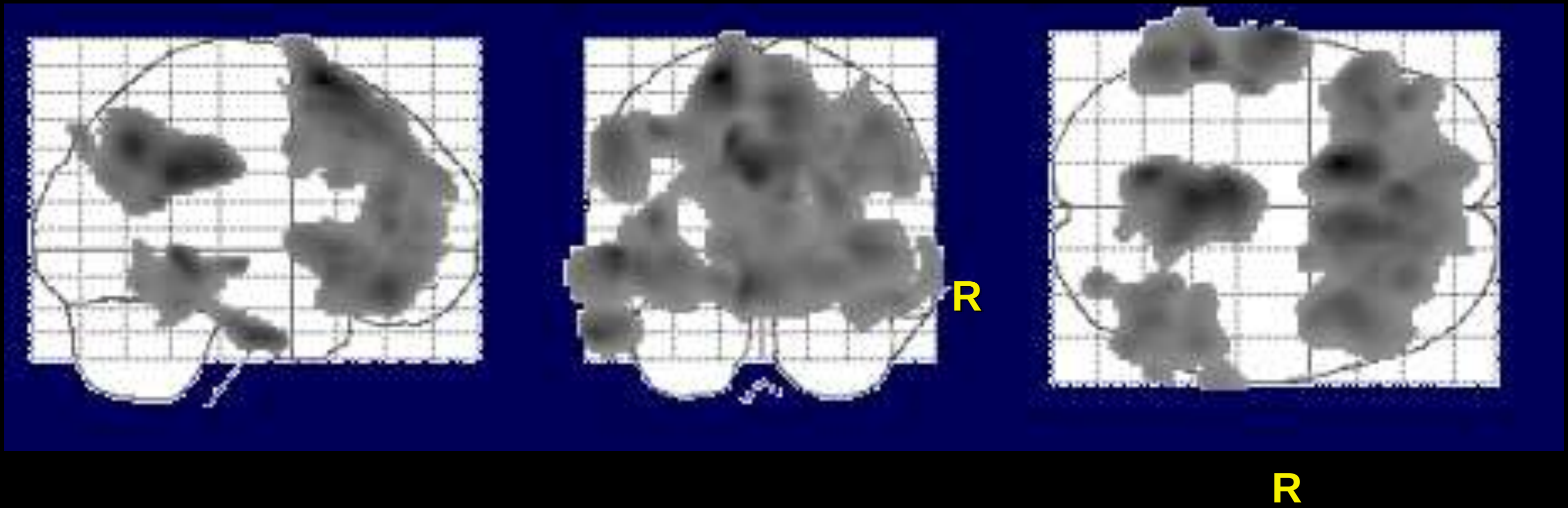


Sertraline
(8 wk)

Sackeim et al. In preparation

TMS (2 wk) George et al. 1998

Short-term Reductions in CMR_{glu}: SPM



- 10 MDE patients studied medication-free and at rest with FDG PET
- Widespread areas of reduced CMR_{glu}
- Most prominent: (1) bilateral superior frontal lobe, (2) bilateral dorsolateral and medial prefrontal cortex, (3) bilateral parietal cortex, (4) posterior cingulate, and (5) left medial and inferior temporal lobe

Nobler et al. *Am J Psychiatry*, 2001

Clues to the "Where" and Implications for the ECT Therapeutic Process

- Imaging consistently links modulation of prefrontal areas to therapeutic response
- Understanding of impact of dosage on RUL efficacy implicates right prefrontal areas
- The findings are consistent with the idea of surround inhibition with particular regional distribution as key to efficacy
- In turn, distribution of inhibition is a function of current paths and dosage, as determined by the site of seizure initiation. We can spatially direct this anticonvulsant process by selecting sites of seizure initiation?

Approaches to Spatial Targeting

- MST: Magnetic Seizure Therapy (Sackeim, 1994)
- FEAST: Focal Electrically-Administered Seizure Therapy (Sackeim, 2004)

MST

- Feasibility of deliberate magnetic seizure induction established
- Theoretically offers great control of site of seizure initiation and over consistency of intracerebral dosage
- Practical limitations raise serious doubts about clinical utility. Dosage insufficient with prefrontal stimulation, and deficit is especially in induced current.

Essentials of FEAST: Focal Electrically-Administered Seizure Therapy

UNIDIRECTIONAL STIMULATION (to permit spatial targeting and enhance efficiency of stimulation)

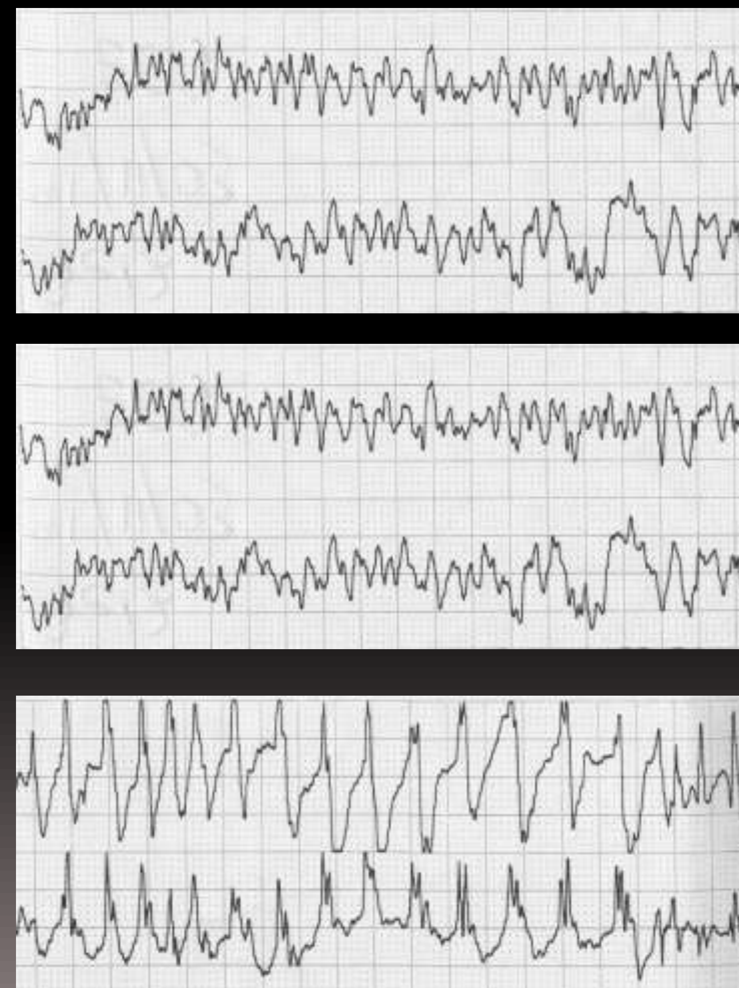
NOVEL ELECTRODE GEOMETRY (to target sites of seizure initiation and to limit seizure propagation)

FEAST promises (a) focality in induction of seizure activity to areas proximal to the small anode electrode and (b) inhibition of seizure propagation in areas proximal to the large cathode electrode.

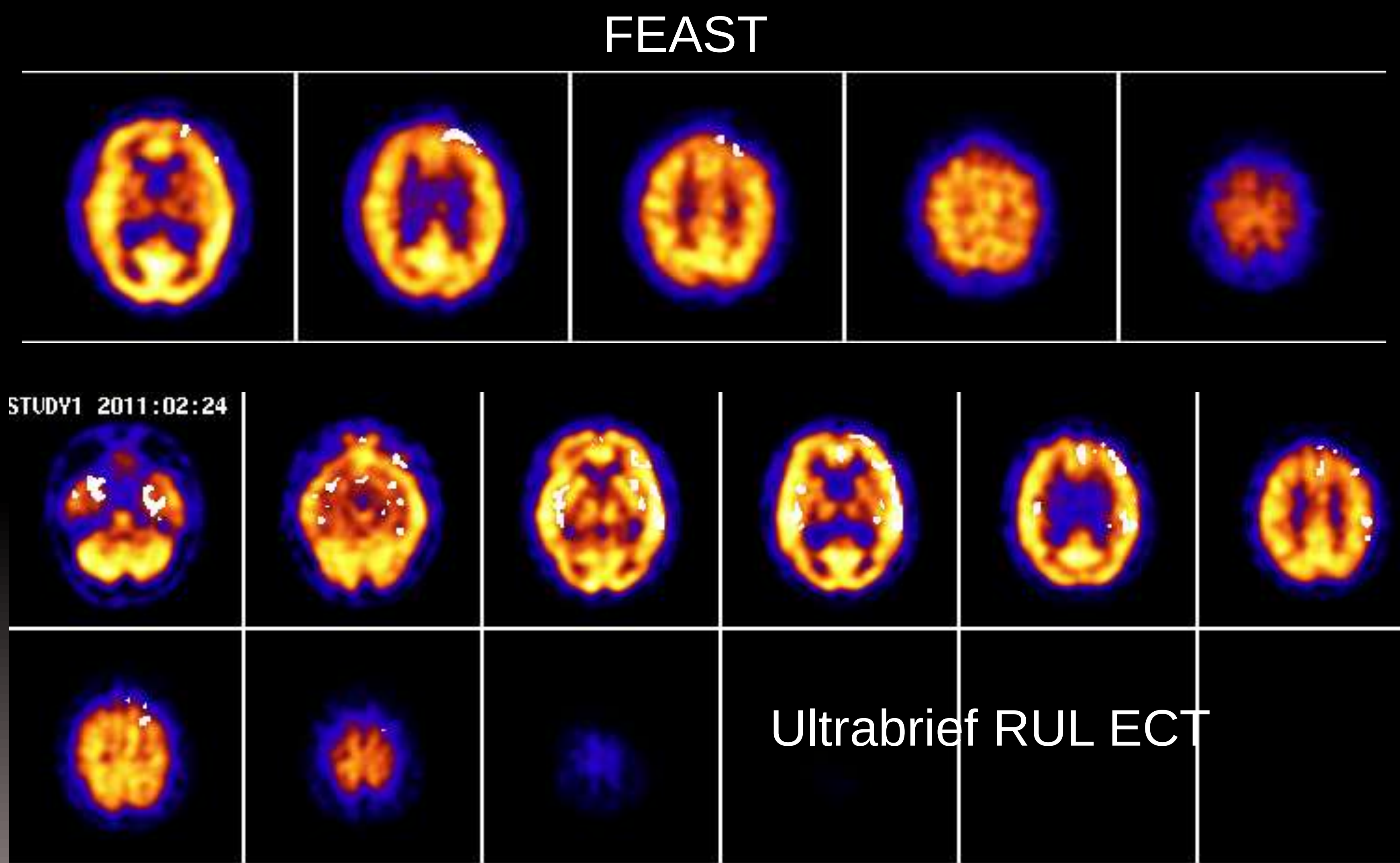
EEG during Standard ECS and FEAST

FEAST

ECS



First Ictal SPECT Scans during FEAST and Ultrabrief RUL ECT



Experience with FEAST

Repeated inductions in 4 primates at Columbia

Piloting in 7 patients at Columbia

Piloting in 10 patients at MUSC

A New York State of Mind

Columbia University Medical Center

New Building, NYSPI

Columbia University

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