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Focal Electrically Administered Seizure Therapy: A Novel form of ECT Illustrates the Roles of Current Directionality, Polarity, and Electrode Configuration in Seizure Induction

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Electroconvulsive therapy (ECT) is a mainstay in the treatment of severe, medication-resistant depression. The antidepressant efficacy and cognitive side effects of ECT are influenced by the position of the electrodes on the head and by the degree to which the electrical stimulus exceeds the threshold for seizure induction. However, surprisingly little is known about the effects of other key electrical parameters such as current directionality, polarity, and electrode configuration. Understanding these relationships may inform the optimization of therapeutic interventions to improve their risk/benefit ratio. To elucidate these relationships, we evaluated a novel form of ECT (focal electrically administered seizure therapy, FEAST) that combines unidirectional stimulation, control of polarity, and an asymmetrical electrode configuration, and contrasted it with conventional ECT in a nonhuman primate model. Rhesus monkeys had their seizure thresholds determined on separate days with ECT conditions that crossed the factors of current directionality (unidirectional or bidirectional), electrode configuration (standard bilateral or FEAST (small anterior and large posterior electrode)), and polarity (assignment of anode and cathode in unidirectional stimulation). Ictal expression and post-ictal suppression were quantified through scalp EEG. Findings were replicated and extended in a second experiment with the same subjects. Seizures were induced in each of the 75 trials, including 42 FEAST procedures. Seizure thresholds were lower with unidirectional than with bidirectional stimulation ($p<0.0001$), and lower in FEAST than in bilateral ECS ($p=0.0294$). Ictal power was greatest in posterior-anode unidirectional FEAST, and post-ictal suppression was strongest in anterior-anode FEAST ($p=0.0008$ and $p=0.0024$, respectively). EEG power was higher in the stimulated hemisphere in posterior-anode FEAST ($p=0.0246$), consistent with the anode being the site of strongest activation. These findings suggest that current directionality, polarity, and electrode configuration influence the efficiency of seizure induction with ECT. Unidirectional stimulation and novel electrode configurations such as FEAST are two approaches to lowering seizure threshold. Furthermore, the impact of FEAST on ictal and post-ictal expression appeared to be polarity dependent. Future studies may examine whether these differences in seizure threshold and expression have clinical significance for patients receiving ECT.
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Keywords: electroconvulsive therapy; ECT; FEAST; unidirectional; seizure threshold; polarity

INTRODUCTION

The history of electroconvulsive therapy (ECT) has been characterized by a series of attempts to reduce its side effects while maintaining its superior antidepressant efficacy (Shorter and Healy, 2007). These attempts have included innovations in: (1) pulse shape, with the shift from sine wave to rectangular pulses (Squire and Zouzounis, 1986; Weiner, 1980) and the shift from brief to ultrabrief pulse width (Cronholm and Ottoson, 1963a; Cronholm and Ottoson, 1963b); (2) electrode placement, with the introduction of right unilateral (RUL) (Squire, 1977; Squire and Slater, 1978) and bifrontal (Abrams and Taylor, 1973) ECT; and (3) electrical dosage, with stimulus titration and dosing relative to individual seizure threshold (Sackeim *et al*, 1987). Randomized controlled trials have demonstrated that each of these innovations (pulse width (Sackeim *et al*, 2008), electrode placement (Sackeim *et al*, 1993), and electrical dosage (Sackeim *et al*, 2000)) plays a significant role in determining the clinical effects of ECT. However, other potentially important parameters of stimulation have been relatively unexplored. For example, aside from several early studies on unidirectional stimulation (Epstein and Wender, 1956; Friedman, 1942; Friedman and Wilcox, 1942), the impact of current directionality on ECT is

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relatively untested. The use of a unidirectional stimulus enables one to separately apply anodal and cathodal stimulation, and this issue of site-specific electrode polarity has never been examined in ECT. Furthermore, the potential value of altering the size and shape of the ECT electrodes has not been systematically studied. Electrode size and shape will alter the strength and spatial distribution of the induced electric field, and thus may be expected to influence the resultant seizure. Here we evaluated a novel form of ECT, focal electrically administered seizure therapy (FEAST) (Berman *et al*, 2005; Peterchev *et al*, 2007; Sackeim, 2004), which combines unidirectional stimulation with a novel electrode configuration in an attempt to enhance the efficiency and focality of seizure initiation. Contrasting FEAST with conventional ECT, we examined the contributions of current directionality (unidirectional *vs* bidirectional), polarity (anode *vs* cathode), and electrode configuration (conventional bilateral symmetrically sized electrodes *vs* unilateral anterior–posterior asymmetrically sized electrodes) in the efficiency of seizure induction in a primate model of ECT.

The efficiency of seizure induction, as gauged through a lower seizure threshold, has been augmented by a variety of means, such as the use of: (1) RUL ECT that stimulates over the primary motor cortex, the cortical area with the lowest seizure threshold; (2) ultrabrief pulse ECT, which is closer to the chronaxie than brief pulse or sine wave ECT (Asanuma *et al*, 1976; Nowak and Bullier, 1998; Sackeim *et al*, 2008); and (3) magnetic seizure therapy (MST), which can induce seizures with much lower cortical electric field strengths than conventional ECT (Lisanby *et al*, 2003b). Each of these techniques has also been reported to be associated with less amnesia than conventional ECT (RUL < BL (Sackeim *et al*, 1993, 2000), ultrabrief < brief pulse width (Sackeim *et al*, 2008), and MST < ECT (Lisanby *et al*, 2003a; Moscrip *et al*, 2006; Spellman *et al*, 2008)). These findings suggest that other means to reduce the stimulus dosage required to induce a seizure (such as current directionality, polarity, and electrode configuration) might be explored to improve the tolerability of ECT.

Current Directionality

Conventional ECT delivers current that is bidirectional (alternating direction with each successive pulse within the train). However, there is evidence that unidirectional stimulation is more efficient in modulating cortical excitability and in seizure induction. In the 1940s and 1950s, Friedman reported lower seizure thresholds with unidirectional half wave rectified sinusoidal pulses relative to bidirectional sinusoidal pulses (Friedman, 1942; Friedman and Wilcox, 1942). In a retrospective analysis of outcomes from more than 800 patients, Epstein found unidirectional ECT to be as clinically efficacious but with significantly less memory deficits compared with bidirectional ECT (Epstein and Wender, 1956). Several uncontrolled studies reported ‘amplitude modulated unidirectional’ currents to be highly efficient in seizure induction and to have less impact on cognition (Impastato and Berg, 1956). Interest in unidirectional stimulation was renewed in several review papers in the 1980s (Hyrman *et al*, 1985; Varghese and Singh, 1985), but in the subsequent two decades, there was a notable lack of research on the potential benefits of unidirectional ECT. Modern commercially available ECT devices are bidirectional.

More recently, studies of repetitive transcranial magnetic stimulation (rTMS) have re-examined the relative efficiency of unidirectional and bidirectional stimulation. rTMS is typically given with devices that induce biphasic current pulses. Monophasic TMS devices exist that induce larger current amplitude in one direction but are typically limited to giving single pulses or very low pulse repetition rates. However, recent findings indicate that monophasic rTMS is more efficient than biphasic rTMS at both inducing motor-evoked potentials and inhibiting cortical excitation when given at low frequencies (Antal *et al*, 2002; Arai and Okabe, 2005; Taylor and Loo, 2007; Tings *et al*, 2005). These findings support a re-examination of unidirectional stimulation in ECT.

Current Polarity

The use of unidirectional stimulation enables one to spatially separate the anode from the cathode, whereas in conventional bidirectional ECT, the two electrodes alternate between serving as the anode and the cathode during the stimulation train. Work with transcranial direct current stimulation (tDCS), which stimulates below threshold for action potentials, suggests that the anode potentiates while the cathode inhibits activity and responses to stimulation (Lang *et al*, 2003; Nitsche *et al*, 2005). Studies of transcranial electrical stimulation (TES) have found lower thresholds for motor response when motor cortex is stimulated with the anode than with the cathode (Marsden *et al*, 1982; Rothwell *et al*, 1987). Direct stimulation of motor and somatosensory cortex has revealed lower thresholds with anodal than with cathodal stimulation (Libet *et al*, 1964). These findings suggest that control of polarity should be explored as a means to enhance the focality and efficiency of ECT.

Focal Electrically Administered Seizure Therapy

FEAST combines unidirectional stimulation with a novel electrode configuration in which the anode and cathode are of asymmetrical shapes, with a small anteriorly placed electrode in midline prefrontal cortex and a large posteriorly placed electrode over lateral motor cortex (Berman *et al*, 2005; Peterchev *et al*, 2007; Sackeim, 2004). The concept for FEAST, introduced by Sackeim (2004), was based on earlier work illustrating the utility of a small, focal anode and large, diffuse cathode in enhancing the focality of TES (Amassian *et al*, 1990; Cracco *et al*, 1989). Previously, we piloted FEAST in four rhesus monkeys, showing feasibility of seizure induction in 12 of 12 trials and finding suggestions that FEAST triggered seizures were more lateralized than conventional bilateral (BL) ECT (Berman *et al*, 2005; Sackeim, 2004). We also recorded intracerebral voltages and seizure expression in a monkey chronically implanted with 30 intracerebral recording sites and found that FEAST induces electric field strengths in depth ranging from 1.7 to 6.2 V/cm, compared with 3.0–4.6 V/cm in BL ECT, and mean ictal power ranging from 0.6 to 3.6 mV^2 compared with 0.5–2.4 mV^2 for BL ECT. We also noted

FEAST to induce a different pattern of intracerebral electric field compared with RUL, BL, and bifrontal ECT and MST (Peterchev *et al*, 2007). FEAST is predicated on the hypothesis that improving the focality of the treatment may reduce its side effects while retaining antidepressant efficacy. If focal seizures retain antidepressant benefit, this would argue against the hypothesis that seizures must generalize to deeper brain structures to be therapeutic. If, however, focal seizures are found to lack antidepressant effects that result would support the deep-generalization hypothesis.

Present Study

Using a nonhuman primate model of ECT (Moscrip *et al*, 2004, 2006; Spellman *et al*, 2008), we examined the effects of current directionality, polarity, and electrode configuration on efficiency of seizure induction and strength of seizure expression. In two experiments, monkeys underwent seizure threshold titration on separate days with ECT conditions that crossed the factors of current directionality (unidirectional or bidirectional), electrode configuration (standard BL or FEAST (small anterior and large posterior electrode)), and polarity (assignment of anode and cathode in unidirectional stimulation) (Figure 1). We tested the hypothesis that unidirectional stimulation and the FEAST electrode configuration would be more efficient in eliciting seizures. We also hypothesized that unidirectional stimulation would be more lateralized in its ictal expression (consistent with greater focality).

METHODS

Subjects

This study was approved by the Institutional Animal Care and Use Committee of the New York State Psychiatric Institute and Columbia University. Subjects were two pathogen-free male Macaca mulatta monkeys obtained from the same NIH breeding colony. At the start of the study, Subject 1 was 13 years old and 14.2 kg, and Subject 2 was 7 years old and 7.9 kg. Both subjects were past sexual maturity and their approximate ages in human years were 39 and 21, respectively (Gavan and Swindler, 1996; Tigges *et al*, 1988).

Electroconvulsive Shock

Details of the nonhuman primate model of ECT, including anesthesia, seizure monitoring, and vital sign monitoring are reported elsewhere (Moscrip *et al*, 2004). Briefly, pre-procedure sedation was achieved with i.m. ketamine

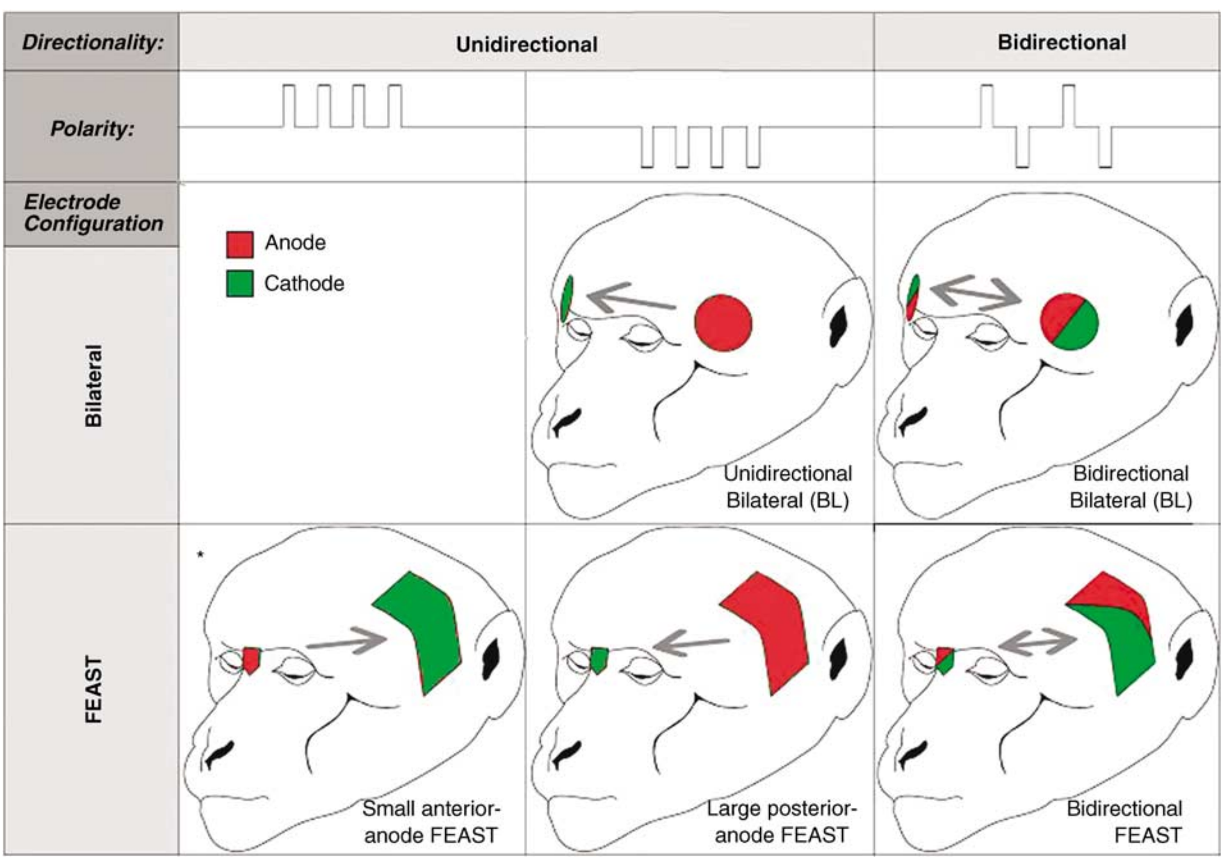

Figure 1 Study design. This figure illustrates the conditions tested. Current directionality (shown in the columns) was either unidirectional or bidirectional. Electrode configuration (depicted in the rows) was either standard bilateral (BL) or focal electrically applied seizure therapy (FEAST) with asymmetrically shaped electrodes. In bidirectional conditions (far right column), each electrode serves as both anode and cathode for alternating pulses. In unidirectional conditions (middle and left columns), one electrode serves as the anode (red) and the other serves as the cathode (green). The small anterior anode unidirectional FEAST condition (bottom left, *) was added in Study 2. The other conditions were preformed in both Study 1 and Study 2. Each condition was replicated 4 times in each of 2 subjects, for a total of 8 replications per condition per study (total of 16 replications per condition across studies).

(5 mg/kg) and xylazine (0.3 mg/kg for Subject 1 and 0.35 mg/kg for Subject 2, adjusted for anesthetic response). Anesthesia and muscle paralysis were induced with i.v. methohexitol (1 mg/kg) and succinylcholine (3.5 mg/kg), respectively. Electroconvulsive shock (ECS) was delivered with an MECTA Spectrum 5000Q ECT device that had been modified to administer unidirectional or bidirectional pulse trains (MECTA Corporation, Tualatin, OR, USA). With this device, frequency refers to total pulse pairs per second. In bidirectional mode, a pulse pair consists of one positive and one negative square wave. In unidirectional mode, a pulse pair consists of two positive square waves. Charge is expressed as the area under the rectified curve, regardless of current direction. For example, a unidirectional pulse train with the parameters 50 Hz, 800 mA, 1-s duration has the same charge (80 mC) as a bidirectional pulse train of the same parameters. However, the unidirectional pulse train will contain 100 positive pulses, whereas the bidirectional pulse train will contain 50 positive and 50 negative pulses.

Seizure Threshold Titration

Seizure threshold was determined by an ascending method of limits procedure (Sackeim *et al*, 1987), by administering a series of progressively longer pulse trains at 20-s intervals until a seizure was induced. Current was 800 mA, frequency was 50 Hz, and pulse width was 0.5 ms. Electrical dosage in units of charge (mC) was computed from these parameters.

Electrode Configurations: FEAST and BL ECS

FEAST was administered using a custom-made curved steel plate as the large posterior electrode (1.25 × 3.43 inches, placed just above and anterior to the left ear, adjacent to the left primary motor cortex) and a custom-cut pentagonal Thymapad (Somatics Corporation, Lake Bluff, IL, USA) as the small anterior electrode (0.5 × 1.13 inches, placed at the nasion) (Berman *et al*, 2005; Peterchev *et al*, 2007). This was contrasted with our standard configuration for BL ECS in primates (two custom-cut Thymapads, 1.45 inches in diameter, placed on the temples) (Moscrip *et al*, 2004, 2006; Spellman *et al*, 2008).

Study 1: Contrasting Directionality and Electrode Configuration

Each subject received four sessions per condition, given in random order. There were four conditions (illustrated in Figure 1): unidirectional BL ECT (with anode in the left frontotemporal placement), unidirectional FEAST (with the large posteriorly placed electrode serving as the anode), bidirectional BL ECT, and bidirectional FEAST. The durations of successive stimuli were increased by 160 ms until a seizure was induced. Each subject received $\leqslant 2$ seizures per week, a frequency at which we have not found increases in seizure threshold in this model.

Once this dataset was complete, we analyzed seizure threshold and EEG power. We saw no significant condition effect on threshold, but we found that ictal power with unidirectional FEAST stimulation was higher than with bidirectional FEAST or with unidirectional BL stimulation ($df = 79$, $t = 2.81$, $p = 0.0062$; and $df = 79$, $t = 3.57$, $p = 0.0006$, respectively). We hypothesized that the steps in our titration schedule might not have been fine-grained enough to detect threshold differences between conditions. Excessively large steps in a titration schedule can overestimate seizure threshold. This might also explain the higher EEG power in FEAST seizures. Specifically, we could not rule out the possibility that the stronger seizures in the FEAST condition could have been a result of overestimating threshold in that condition resulting in stimulation well above threshold, whereas BL seizures were being induced at or slightly above threshold. We therefore designed a replication study with a finer-grained titration schedule, and also added a FEAST condition using the small anterior electrode as the anode to examine the effects of polarity on FEAST.

Study 2: Contrasting Directionality and Electrode Configuration—Finer-Grained Threshold Titration and Comparison of Polarity Effects in FEAST Condition

Beginning 2 months after the first study, and spanning the subsequent 6 months, we collected another dataset of four sessions per condition (Figure 1) per subject. Subjects received the same conditions as in Study 1, but with the addition of a fifth condition (unidirectional FEAST using the small anterior electrode as the anode). Subjects were re-titrated, starting one step lower than each subject's lowest recorded threshold, and successive stimuli were increased by 10% of the starting stimulus.

EEG Recording

Seizure activity was measured with BL fronto-mastoid EEG channels using the amplifiers of the MECTA Spectrum (gain = 5000, band passed 1.4–48 Hz, sampling rate = 100 Hz) and digitized using the MECTA Spectrum Program. Motor seizure manifestations were monitored using the cuff technique (APA, 2001).

Data Processing

EEG recordings were visually inspected to remove artifacts caused by head movement, inadvertent movement of recording electrodes and wires, and the electroconvulsive stimulus itself. The artifact-free data were subjected to fast Fourier transform, using 1-s epochs over-lapping by 0.5 s, and tapered with a Hann window. Mean absolute power (in μV^2) was computed within four frequency bands: δ (1.4–3.5 Hz), θ (3.5–7.5 Hz), α (7.5–12.5 Hz), β (12.5–29.5 Hz). This was done separately for the baseline (defined as the 30-s period immediately after administration of methohexitol), ictal period, and for a 10-s period after the end of seizure. Beginning and end of ictal activity were determined by off-line inspection of the EEG data and substantiated by comparison with the stimulation and motor convulsion time points noted during the procedure. Power values were log-transformed to normalize the distribution for statistical analysis.

Statistical Analysis

The statistical analyses used mixed effects models (Diggle *et al*, 2002; Littell *et al*, 1996). Analyses were conducted using the PROC MIXED procedure of SAS (Cary, NC, USA). All dependent variables subjected to analysis were evaluated separately. They included EEG power, seizure threshold (measured in mC of charge), seizure duration (in seconds), as well as differences between pre- and post-ictal vital signs (CO_2, respiratory rate, heart rate, end tidal O_2, and blood pressure). For each dependent variable, two separate analyses were conducted.

One analysis included data from both the first and second studies for the four conditions that were common between the two studies (ie, excluding unidirectional FEAST with small anterior anode). In this analysis, evaluation of EEG power included six fixed variables: study (first *vs* second), directionality (unidirectional *vs* bidirectional stimulation), electrode configuration (BL *vs* FEAST stimulation), epoch (baseline, ictal, and post-ictal periods), channel (right *vs* left EEG channel), and frequency (δ, θ, α, and β frequency bands). The repeated measures ANOVA accounted for multiple epochs per session, multiple sessions per condition, and multiple conditions per subject. For evaluation of seizure threshold, seizure duration, and changes in vital signs, only study, directionality, and electrode configuration were included as fixed variables, and the repeated measures ANOVA accounted for multiple sessions and conditions per subject.

A second analysis was applied to each dependent variable, including data from the second study alone. Fixed variables for analysis of EEG power included condition (consisting of all five conditions, including unidirectional FEAST with small anterior anode), epoch, channel, and frequency. As with the cross-study analysis, the repeated measures ANOVA accounted for multiple epochs per session, sessions per condition, and conditions per subject. For the analysis of seizure threshold, duration, and changes in vital signs, only the fixed variable condition was included. As with the cross-study analysis, the repeated measures ANOVA accounted for multiple sessions per condition and conditions per subject.

Interaction effects were tested for all combinations of fixed effects, up to and including the four-way interactions. Simplification of the mean structure was sought by one-term-at-a-time backward elimination. The covariance structure selected for all models was compound symmetry. Statistical significance was judged on the basis of $\alpha = 0.05$. Parameters were estimated with the iterative maximum likelihood method.

RESULTS

Feasibility and Safety of Seizure Induction

Seizures were successfully induced in each of 75 sessions, including 42 FEAST procedures. There were no adverse events. Seizures had a mean duration of 23 s (SD = 6), which did not differ across conditions. Analysis of changes in vital signs from pre- to post-stimulation revealed that seizure induction resulted in expected increases in heart rate ($F(134) = 121.1$, $p < 0.0001$), systolic blood pressure ($F(128) = 11.95$, $p < 0.0007$), diastolic blood pressure ($F(128) = 3.4$, $p < 0.067$), but there were no effects of ECS condition.

Seizure Threshold

Analysis of the combined dataset from both studies for the four conditions (BL unidirectional, BL bidirectional, FEAST unidirectional (posterior anode), FEAST bidirectional) yielded significant main effects of directionality ($F = 16.86$, $df = 1$, $p < 0.0001$) and electrode configuration ($F = 4.97$, $df = 1$, $p = 0.0294$) on seizure thresholds, with no interaction. Seizure threshold was lower with unidirectional than bidirectional stimulation, and thresholds were lower in FEAST than in BL electrode configuration (Figure 2). *Post hoc* tests revealed that the main effect of current directionality was significant within each electrode configuration (BL ECS: $t = -2.59$, $df = 61$, $p = 0.0121$; FEAST: $t = -3.18$, $df = 61$, $p = 0.0023$). Unidirectional stimulation lowered seizure threshold relative to bidirectional stimulation by 12.8 and 8.1% (for FEAST and BL ECS, respectively).

In Study 2, we examined the role of polarity within the FEAST condition and found no difference in seizure threshold with the anode in the anterior placement (small electrode) or the posterior placement (large electrode) (14.5 ± 4.3 and 15.4 ± 3.3 mC, NS). There was, however, a main effect of *condition* ($F = 15.71$, $df = 5$, $p < 0.0001$). *Post hoc* testing revealed that the unidirectional FEAST conditions resulted in lower thresholds than the other three conditions (p's < 0.01). Threshold was highest for BL-bidirectional than for all of the other conditions (p's < 0.05).

EEG Power

Analysis of the cross-study EEG data revealed the expected main effect of epoch ($F = 1423.51$, $df = 2$, $p < 0.0001$) with higher power during the ictal period than baseline ($t = 47.92$, $df = 1502$, $p < 0.0001$) and post-ictal ($t = 48.19$,

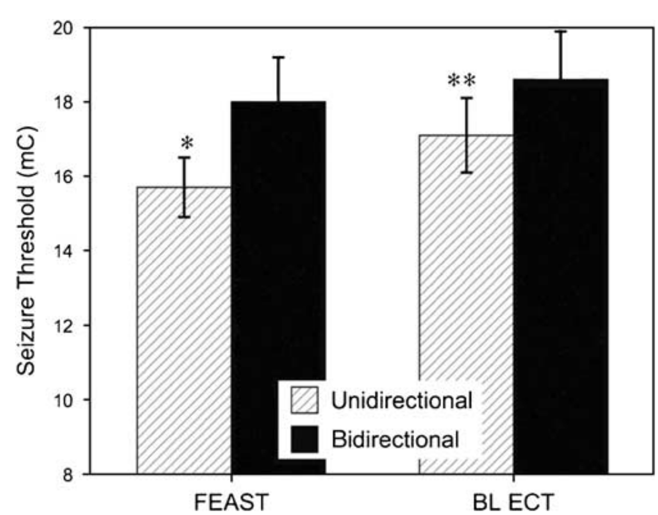

Figure 2 Seizure threshold as a function of electrode configuration and current directionality. Unidirectional had lower thresholds than bidirectional stimulation (*$p < 0.01$, **$p < 0.002$), and FEAST had lower thresholds than bilateral (BL) ECT ($p < 0.03$).

df = 1502, $p < 0.0001$) periods. There was also the expected main effect of EEG frequency band (F = 955.09, df = 3, $p < 0.0001$), with highest power in the δ band ($\delta > \theta > \alpha > \beta$, t's > 2, df = 1502, p's < 0.03). There was a main effect of study with higher power in study 1 than study 2 (F = 9.64, df = 1, $p < 0.002$), consistent with our hypothesis that the larger steps in the titration schedule in study 1 had overestimated thresholds. There were no main effects of current directionality or electrode configuration. There was, however, a significant interaction between electrode configuration and epoch (F = 7.74, df = 2, $p = 0.0005$), with higher power during the ictal phase with FEAST than BL ECS ($t = 3.28$, df = 1537, $p < 0.001$). There was also an interaction between electrode configuration and frequency band (F = 8.84, df = 3, $p < 0.0001$). As shown in Figure 3a, FEAST had more ictal power in the δ ($t = 2.78$, df = 1535, $p < 0.01$) and θ ($t = 2.36$, df = 1535, $p < 0.02$) bands specifically.

In Study 2, we examined the role of polarity within the FEAST condition. There was a significant interaction between condition and epoch (F = 4.38, df = 6, $p = 0.0002$). *Post hoc* analysis revealed that power was greater in the FEAST condition with posterior anode placement than all other conditions in both the ictal ($t = 3.35$, df = 1000, $p = 0.0008$) and post-ictal periods ($t = 2.63$, df = 1000, $p = 0.01$). As indicated by the significant interaction between condition and frequency (F = 2.21, df = 15, $p < 0.01$), the greater power in the posterior anode FEAST condition was seen primarily in the δ ($t = 2.97$, df = 995, $p = 0.003$) and θ ($t = 2.00$, df = 995, $p < 0.05$) frequency bands (Figure 3b). There was also a laterality effect, with posterior anode FEAST having greater power on the left hemisphere (which is the side of the anode) than the right hemisphere (condition × channel interaction: F = 3.04, df = 5, $p < 0.01$; left > right for posterior anode FEAST: $t = 2.25$, df = 1005, $p < 0.03$) (see Figure 4). The anterior anode FEAST condition was the only condition to show significant post-ictal suppression relative to baseline ($t = 3.05$, df = 1000, $p = 0.0024$).

DISCUSSION

We present the first study contrasting FEAST with conventional ECT, and the first study of the independent contributions of current directionality, polarity, and electrode configuration in seizure induction. The key findings are (1) unidirectional current is more efficient in inducing seizures than bidirectional current, whether the electrode configuration is BL or FEAST; (2) the FEAST electrode configuration is more efficient than BL ECT; and (3) the EEG response to FEAST is polarity dependent, with higher ictal power and more lateralization when the anode is the large posterior electrode and more post-ictal suppression when the anode is the small anterior electrode. These findings may have implications for the refinement of ECT technique.

Our observed effects of current directionality and polarity on seizure induction are consistent with physiological studies, which shows that the likelihood of neuronal excitation is dependent upon the direction of current flow. When they are transcranially stimulated above the threshold for action potential, cortical neurons near the anode fire more consistently and at lower latency than those near the cathode (Amassian *et al*, 1990). Likewise, when

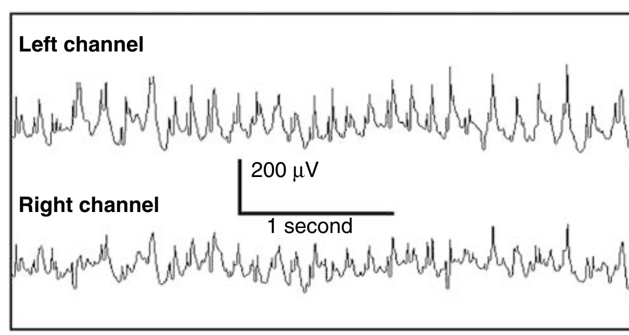

Figure 4 Representative EEG tracing illustrating higher ictal power on the left hemisphere with posterior anode unidirectional FEAST.

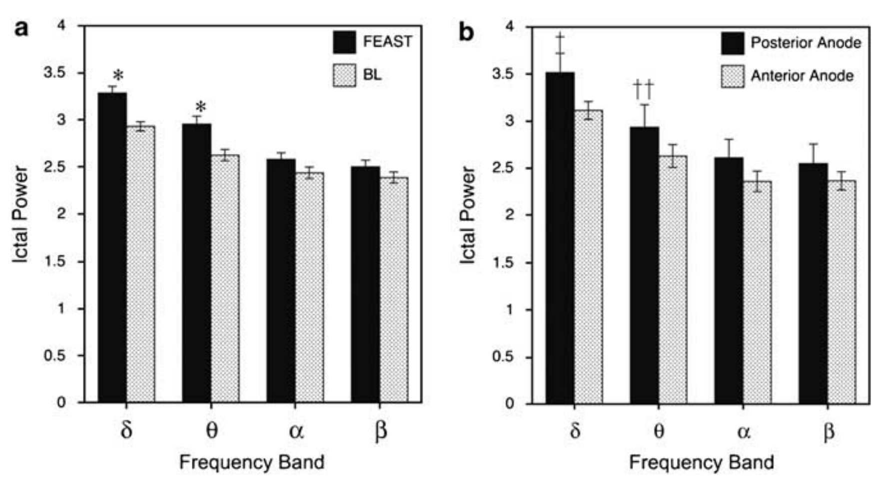

Figure 3 Ictal EEG power ($\log_{10}(\mu V^2)$) by condition and frequency band. (a) Combined data from Studies 1 and 2. FEAST had higher ictal power than BL, in the slower frequency bands (*p's < 0.01). (b) In Study 2, polarity affected ictal power with unidirectional FEAST. Ictal power was higher in the slower frequency bands with the large posterior anode in comparison with the small anterior anode placement ($^{\dagger}p < 0.003$, $^{\dagger\dagger}p < 0.05$).

stimulated below action potential threshold, as in tDCS, cortical neurons are excited by anodal stimulation and inhibited by cathodal stimulation (Nitsche *et al*, 2004, 2005). These findings may help explain the observed increased efficiency of unidirectional ECT. In unidirectional ECT, all of the anodal pulses are delivered by the same electrode, thereby facilitating seizure induction at that site. In bidirectional mode, the anodal pulses are split between the two electrodes, thus reducing the 'effective' frequency delivered by half. Furthermore, the interleaving of cathodal with anodal pulses at the same site may diminish the excitatory effect of the anodal pulses. Finally, the Amassian finding of higher latency and greater variability in neuronal response to cathodal than anodal stimulation suggests that cathodal pulses may disrupt the regularity and simultaneity of firing necessary to bring a neuronal population into synchrony and subsequent seizure.

Our finding of lower threshold with the FEAST electrode configuration relative to conventional BL electrodes supports earlier findings (Amassian *et al*, 1989a, b, 1990; Cracco *et al*, 1989; Sackeim, 2004). The effect of electrode configuration on ECT seizure threshold was first shown with the increased efficiency of RUL placement that, like FEAST, places one electrode near the motor cortex (which has a lower seizure threshold than frontal cortex).

The increased ictal power in the posterior anode FEAST condition may reflect the fact that the posterior electrode was much larger than the anterior electrode and, thus, may have stimulated a larger population of neurons. The assumption that electrode size relates to the focality of the cortex affected by stimulation is supported by classic work with TES (Amassian *et al*, 1990; Cracco *et al*, 1989) and more recent work with tDCS (Nitsche *et al*, 2007). Likewise, the posterior anode FEAST condition had greater ictal power on the left hemisphere, which was the site of the large posterior anode placement. The reasons for the greater post-ictal suppression seen in the anterior anode FEAST condition are not known. It is possible that this could reflect more robust inhibitory action at the site of our anteriorly placed EEG recording leads resulting from an anteriorly triggered seizure, or it may have resulted from the simultaneous cathodal stimulation of the large posterior electrode providing a dampening effect. Further studies will be needed to clarify these mechanisms. Strong post-ictal suppression is of clinical interest, as it has been correlated with the clinical efficacy in ECT (Azuma *et al*, 2007; Gangadhar *et al*, 1999; Nobler *et al*, 1993; Suppes *et al*, 1996), although some studies have questioned the strength of such a correlation (Perera *et al*, 2004).

Limitations of this study include small sample size and lack of a reversed polarity condition in unidirectional BL stimulation. Because anatomical (Falk *et al*, 2003) and electropharmacological (Davidson *et al*, 1992) hemispheric asymmetries have been found in the monkey frontal cortex, the possibility of a hemispheric effect on seizure threshold even in the symmetrical BL condition cannot be ruled out. Although we found FEAST seizure threshold to be lower than BL ECT, we did not compare it with RUL ECT. Additionally, the observed differences were found at specific pulse amplitude, width and frequency, factors also known to influence threshold. Finally, we cannot know from the data presented here whether the 12.8% decrease in seizure threshold seen with unidirectional FEAST confers clinically significant benefits in terms of improved cognitive outcome, nor whether these seizures have antidepressant efficacy.

In continuing to pursue a balance between clinical efficacy and side effects, it is important to consider all stimulus parameters that might increase the efficiency of ECT. Our data suggest that current directionality, polarity, and electrode configuration are parameters that may increase stimulus efficiency and that warrant further investigation into their potential for translation into clinical application. Specifically, unidirectional stimulation with standard electrode placements could be readily implemented clinically. Our results suggest that the effects of unidirectional stimulation on efficacy and side effects should be explored in clinical trials.

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DISCLOSURES

Mr Spellman has no disclosures. Drs Peterchev and Lisanby are inventors on patent applications from Columbia University on technology not related to the topic presented here. Dr Peterchev has received grant support from Columbia University, NIH, DARPA and NYSTAR. Dr Lisanby has received research support from NIH, Stanley Medical Research Foundation, DARPA, NYSTAR, Magstim Company, Neuronetics, Cyberonics, AFAR, NARSAD, and ANS. She chairs a Data Safety and Monitoring Board for Northstar Neuroscience.

REFERENCES

Abrams A, Taylor MA (1973). Anterior bifrontal ECT: a clinical trial. *Br J Psychiatry* **122**: 587–590.

Amassian VE, Crocco RQ, Maccabee PJ (1989a). Focal stimulation of human cerebral cortex with the magnetic coil: a comparison with electrical stimulation. *Electroencephalogr Clin Neurophysiol* **74**: 401–416.

Amassian VE, Maccabee PJ, Crocco RQ (1989b). Focal stimulation of human peripheral nerve with the magnetic coil: a comparison with electrical stimulation. *Exp Neurol* **103**: 282–289.

Amassian VE, Quirk GJ, Stewart M (1990). A comparison of corticospinal activation by magnetic coil and electrical stimulation of monkey motor cortex. *Electroencephalogr Clin Neurophysiol* **77**: 390–401.

Antal A, Kinces TZ, Nitsche MA, Bartfai O, Demmer I, Sommer M *et al* (2002). Pulse configuration-dependent effects of repetitive transcranial magnetic stimulation on visual perception. *Neuroreport* **13**: 2229–2233.

APA (2001). *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, and Privileging: a Task Force Report of the American Psychiatric Association*. American Psychiatric Association: Washington, D.C.

Arai N, Okabe S (2005). Comparison between short train, monophasic and biphasic repetitive transcranial magnetic

stimulation (rTMS) of the human motor cortex. *Clin Neurophysiol* **116**: 605–613.
Asanuma H, Arnold A, Zarzecki P (1976). Further study on the excitation of pyramidal tract cells by intracortical microstimulation. *Exp Brain Res* **26**: 443–461.
Azuma H, Fujita A, Sato K, Arahata K, Otsuki K, Hori M *et al* (2007). Postictal suppression correlates with therapeutic efficacy for depression in bilateral sine and pulse wave electroconvulsive therapy. *Psychiatry Clin Neurosci* **61**: 168–173.
Berman RM, Sackeim HA, Truesdale MD, Luber B, Schroeder C, Lisanby SH (2005). Focal electrically administered seizure therapy (FEAST): Nonhuman primate studies of a novel form of focal brain stimulation. JECT. **21**: 57.
Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB (1989). Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroencephalogr Clin Neurophysiol* **74**: 417–424.
Cronholm B, Ottoson JO (1963a). Ultrabrief stimulus technique in electroconvulsive therapy: II. Comparative studies of therapeutic effects and memory disturbance in treatment of endogenous depression with the Either ES electroshock apparatus and Siemens Konvulsator IIIin EST by unilateral stimulation of the non-dominant hemisphere. *J Nerv Ment Dis* **137**: 268–276.
Cronholm B, Ottoson JO (1963b). Ultrabrief stimulus technique in electroconvulsive therapy: influence on retrograde amnesia of treatments with either the ES electroshock apparatus, Siemens Konvulsator III and of lidocaine-modified treatment. *J Nerv Ment Dis* **137**: 117–123.
Davidson R, Kalin NH, Shelton SE (1992). Lateralized effects of diazepam on frontal brain electrical asymmetries in rhesus monkeys. *Biol Psychiatry* **32**: 438–451.
Diggle P, Heagerty P, Liang KY, Keger SL (2002). *Analysis of Longitudinal Data*, 2nd edn. Oxford University Press: Oxford.
Epstein J, Wender L (1956). Alternating current vs unidirectional current for electroconvulsive therapy-comparative studies. *Confin Neurol* **16**: 137–146.
Falk D, Hildebolt C, Cheverud J, Vannier M, Helmkamp RC, Konigsberg L (2003). Cortical asymmetries in frontal lobes of rhesus monkeys (Macaca mulatta). *Brain Res* **512**: 40–45.
Friedman E (1942). Unidirectional electrostimulated convulsive therapy. *Am J Psychiatry* **99**: 218–223.
Friedman E, Wilcox PH (1942). Electrostimulated convulsive doses in intact humans by means of unidirectional currents. *J Nerv Ment Dis* **96**: 56–63.
Gangadhar BN, Subbakrishna DK, Janakiramaiah N, Motreja S, Narayana Dutt D, Paramehwara G (1999). Post-seizure EEG fractal dimension of first ECT predicts antidepressant response at two weeks. *J Affect Disord* **52**: 235–238.
Gavan JA, Swindler DR (1996). Growth rates and phylogeny in primates. *Am J Phys Anthropol* **24**: 181–190.
Hyrman V, Palmer LH, Cernik J, Jetelina J (1985). ECT: the search for the perfect stimulus. *Biol Psychiatry* **20**: 634–645.
Impastato DJ, Berg S (1956). Convulsive therapy with amplitude modulated unidirectional currents (Reiter). *Am J Psychiatry* **112**: 932–934.
Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN (2003). Effects of transcranial direct current stimulation over human motor cortex on corticospinal and transcallosal excitability. *Exp Brain Res* **156**: 439–443.
Libet B, Alberts WW, Wright Jr EW, DeLattre LD, Levin G, Feinstein B (1964). Production of threshold levels of conscious sensation by electrical stimulation of human somatosensory cortex. *J Neurophysiol* **27**: 546–578.
Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA (2003a). Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology* **28**: 1852–1865.
Lisanby SH, Moscrip T, Morales O, Luber B, Schroeder C, Sackeim HA (2003b). Neurophysiological characterization of magnetic seizure therapy (MST) in non-human primates. *Suppl Clin Neurophysiol* **56**: 81–99.
Littell R, Milliken G, Stroup W, Wolfinger R (1996). *SAS System for Mixed Models*. SAS Institute: Cary, North Carolina.
Marsden CD, Merton PA, Morton HB (1982). Direct stimulation of corticospinal pathways through the intact scalp in human subjects. In: Desmedt J (ed). *Motor Control Mechanisms in Health and Disease*. Raven Press: New York, NY. pp 387–392.
Moscrip T, Terrace HS, Sackeim HA, Lisanby SH (2004). A primate model of anterograde and retrograde amnesia produced by convulsive treatment. *J ECT* **20**: 26–36.
Moscrip T, Terrace HS, Sackeim HA, Lisanby SH (2006). Randomized controlled trial of the cognitive side-effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS). *Int J Neuropsychopharmacol* **9**: 1–11.
Nitsche MA, Doemkes S, Karakose T, Antal A, Liebetanz D, Lang N *et al* (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* **97**: 3109–3117.
Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke K, Frommann K *et al* (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur J Neurosci* **19**: 2720–2726.
Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS *et al* (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* **568**(Pt 1): 291–303.
Nobler MS, Sackeim HA, Solomou M, Luber B, Devanand DP, Prudic J (1993). EEG manifestation during ECT: effects of electrode placement and stimulus intensity. *Biol Psychiatry* **34**: 321–330.
Nowak LG, Bullier J (1998). Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. *Exp Brain Res* **118**: 477–488.
Perera TD, Luber B, Nobler MS, Prudic J, Anderson C, Sackeim HA (2004). Seizure expression during electroconvulsive therapy: relationships with clinical outcome and cognitive side effects. *Neuropsychopharmacology* **29**: 813–825.
Peterchev A, Berman R, Luber B, Schroeder CE, Truesdale MD, Kaplan DM *et al* (2007). Relationship between electric field and ictal power induced by electroconvulsive shock (ECS) and magnetic seizure therapy (MST) in nonhuman primates. *American College of Neuropsychopharmacology 2007 Annual Meeting*.
Rothwell JC, Thompson PD, Day BL, Dick JPR, Kachi T, Cowan JMA *et al* (1987). Motor cortex stimulation in intact man. General characteristics of EMG responses in different muscles. *Brain* **110**: 1173–1190.
Sackeim HA (2004). Convulsant and anticonvulsant properties of electroconvulsive therapy: toward a focal form of brain stimulation. *Clin Neurosci Res* **4**: 39–57.
Sackeim HA, Decina P, Portnoy S, Neely P, Matitz S (1987). Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry* **22**: 249–268.
Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ *et al* (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New Engl J Med* **328**: 839–846.
Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S *et al* (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* **57**: 425–434.
Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N *et al* (2008). Effects of pulse width and electrode

placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulat* **1**: 71–83.

Shorter E, Healy D (2007). *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness*. Rutgers University Press: New Brunswick, NJ.

Spellman T, McClintock SM, Terrace H, Luber B, Husain MM, Lisanby SH (2008). Differential effects of high-dose magnetic seizure therapy and electroconvulsive shock on cognitive function. *Biol Psychiatry* **63**: 1163–1170.

Squire LR (1977). ECT and memory loss. *Am J Psychiatry* **134**: 997–1001.

Squire LR, Zouzounis JA (1986). ECT and memory: brief pulse versus sine wave. *Am J Psychiatry* **143**: 596–601.

Squire SR, Slater PC (1978). Bilateral and unilateral ECT: effects on verbal and nonverbal memory. *Am J Psychiatry* **135**: 1316–1320.

Suppes T, Webb A, Carmody T, Gordon E, Guttierez-Esteinou R, Hudson JI *et al* (1996). Is postictal electrical silence a predictor of response to ECT? *J Affect Disord* **41**: 55–58.

Taylor JL, Loo CK (2007). Stimulus waveform influences the efficacy of repetitive transcranial magnetic stimulation. *J Affect Disord* **97**: 271–276.

Tigges J, Gordon T, McClure H, Hall E, Peters A (1988). Survival rate and life span of rhesus monkeys at the Yerkes Regional Primate Research Center. *Am J Primatol* **15**: 263–273.

Tings T, Lang N, Frithjof T, Paulus W, Sommer M (2005). Orientation-specific fast rTMS maximizes corticospinal inhibition and facilitation. *Exp Brain Res* **164**: 323–333.

Varghese FT, Singh BS (1985). Electroconvulsive therapy in 1985—a review. *Med J Aust* **143**: 192–196.

Weiner RD (1980). ECT and seizure threshold: effects of stimulus wave form and electrode placement. *Biol Psychiatry* **15**: 225–241.