RESEARCH PROTOCOL

Cognitive Recovery After Electroconvulsive Therapy and General Anesthesia

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1. STUDY SYNOPSIS

Study Title	**Cognitive Recovery After Electroconvulsive Therapy and General Anesthesia**
Objectives	1. Characterize the order and consistency in which cognitive function recovers following treatments of electroconvulsive therapy (ECT) and ketamine general anesthesia 2. Characterize the electroencephalography (EEG) changes during recovery from ECT and ketamine anesthesia
Study Period	**Planned enrollment duration:** 3 years **Planned study duration:** 3 weeks
Study Design	Single academic center, prospective, longitudinal, observational Randomized, crossover, repeated measures
Number of Patients	**Target enrollment:** 15-20 patients
Inclusion and Exclusion Criteria	**<u>Inclusion Criteria:</u>** Treatment resistant unipolar or bipolar depression requiring outpatient ECT, planned right unilateral ECT stimulation, English speaking, 18 years of age and older, able to provide written informed consent. **<u>Exclusion Criteria:</u>** Known brain lesion or neurological illness that causes cognitive impairment,

	schizophrenia, schizoaffective disorder, blindness or deafness or motor impediments that may impair performance for cognitive testing battery, inadequate ECT seizure duration with etomidate
Measurements	(1) Cognitive function (COGNITION battery) (2) Multichannel EEG (3) 3D-CAM (3D-Confusion Assessment Method) (4) Mood Self-Assessment Manikin (SAM) (5) PROMIS-CAT (Computer Adaptive Testing) for depression (6) Scale of Suicidal Ideation (7) ECT Seizure duration (8) ECT electrical dose (9) Subjective assessment of whether ECT was performed (10) Quick Inventory of Depressive Symptomatology, Self-Report (16-Item), QIDS-SR1 (11) Structural MRI
Outcomes	(1) Cognitive recovery (2) Delta, theta, alpha, and beta EEG band power, functional connectivity, entropy, and phase lag measurements measures (3) Delirium (4) Mood (5) Depression (6) Suicidal ideation (7) Assessment of blinding quality (8) Satisfaction with ECT following involvement in study.

2. STUDY PROTOCOL

2.1 Background, Significance, and Preliminary Data

2.1.1 Seizures – Unique States for Probing the Return Consciousness and Cognition

The return of consciousness following reversible states of unresponsiveness is relevant to neuroscience and clinical practice. Neural mechanisms underlying these processes appear to be distinct from those perturbed during loss of consciousness, with implications for anesthetic practice(Kelz, Sun et al. 2008) and sleep/wake disorders(Trotti 2016). While states incurred by general anesthesia(Boveroux, Vanhaudenhuyse et al. 2010, Palanca 2015, Ranft, Golkowski et al. 2016) and sleep(Massimini, Ferrarelli et al. 2007, Landsness, Crupi et al. 2009) have suggested neural substrates necessary for sustaining consciousness(Koch, Massimini et al. 2016), the recovery from these depressed states of neural activity remains poorly characterized. Comparatively less is known regarding the recovery from states of highly synchronized neural activity incurred through generalized seizures(Yu and Blumenfeld 2009, Englot, Yang et al. 2010). Characterizing the recovery of neural activity and cognitive function following these states may provide a system to complement states of brain suppression given that: 1) action potential synchronization is a fundamental mode of information processing in the cerebral cortex distinct from the decrements in neuronal firing rates and 2) seizures arise from changes in the excitatory and inhibitory synaptic balance in different brain regions.

The relationships of underlying electroencephalographic (EEG) activity and the recovery from generalized seizures remain unclear is currently limited and challenging to investigate(So and Blume 2010). Generalized seizures are characterized by the loss of consciousness coincident with ictal EEG spike-and-wave complexes, polyspike-and-wave complexes, and spikes(Hrachovy and Frost 2006). External phenotypes, ranging from convulsions to immobile staring, likely depend on the precise disruption in sub-cortical arousal systems, cortical-subcortical interactions, or neocortical connectivity(Yu and Blumenfeld 2009, Englot, Yang et al. 2010, Blumenfeld 2012). Inter-individual heterogeneity among clinical seizures may arise from diverse structural or metabolic derangements. Moreover, seizures are typically sporadic, unpredictable in occurrence, and may vary in intensity and character, making them difficult to study systematically. Following the disappearance of epileptiform EEG signatures, the postictal period begins and culminates in a return of

consciousness and cognitive function. There is little standardization of postictal clinical and behavior testing to facilitate objective comparison to EEG changes during the postictal period. Critical barriers to generating inferences from reproducible seizures may be addressed in the context of electroconvulsive therapy (ECT)(Fink 1979), where seizures are electrically induced under safe controlled conditions.

2.1.2 EEG Activity and Cognitive Dysfunction Following ECT

The potential of EEG to inform clinicians on the future efficacy and side effects of ECT has not been fully realized. EEG is commonly monitored during ECT, a proven treatment for depression, bipolar illness, and psychosis(Lisanby 2007). Following the delivery of the ECT stimulus charge, epileptiform activity in the bilateral fronto-mastoid EEG can complement the assessment of peripheral tonic-clonic muscle activity(Fink and Johnson 1982). Clinically relevant EEG measures beyond the length of seizure duration(Mayur 2006) have unclear clinical utility(Dinwiddie, Glick et al. 2012). Optimally, EEG markers would be available for predicting and refining ECT administration to balance efficacy and side effects that accrue over the course of therapy. Such advances in the field have not occurred since prior work establishing a relationship between cognitive performance and ECT stimulation parameters(Weiner, Rogers et al. 1986, Abrams 2002). This void may be due to the paucity of studies that have characterized EEG across widely distributed brain regions using either 10-20 montages(Brumback and Staton 1982, Luber, Nobler et al. 2000, Nobler, Luber et al. 2000, Zoldi, Krystal et al. 2000) or high-density EEG. The spatial resolution offered by high-density EEG is likely needed to associate cognitive an affective perturbations to specific EEG patterns. High-density scalp EEG has shown superiority over standard 10-20 montage recordings in guiding surgical treatment for epileptic seizures (Brodbeck, Spinelli et al. 2011). Extension of this paradigm to the ECT setting may yield clinically relevant EEG markers for tailoring treatment at an individual patient level.

During the ictal period, seeming stereotyped evolution EEG patterns develop and resolve(Weiner 1982), with proposed phases of activity(Brumback and Staton 1982). Brief periods of EEG suppression or rhythmic bilateral 14-22 Hz oscillations may first emerge(Brumback and Staton 1982). Induction of bilateral poly-spike activity occurs, often with greater power on the side of the stimulation electrode in unilateral ECT(Brumback and Staton 1982, Gerst, Enderie et al. 1982). Spike/spike-and-wave complexes then occur, followed by termination within three minutes(Brumback and Staton 1982, Weiner 1982). This ictal activity may

be followed by postictal generalized EEG suppression, a marker associated with ECT therapeutic efficacy(Krystal and Weiner 1999, Mayur 2006, Azuma, Fujita et al. 2007) and with potential implications for understanding sudden unexpected death in epilepsy(Ryvlin, Nashef et al. 2013, Bauer, Thijs et al. 2017). Delta waves (<4 Hz)(Weiner 1982) emerge that are gradually replaced by theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) rhythms(Weiner 1982). The dynamics of these EEG changes may aid in our understanding of seizures in general and help to reveal the efficacy/side effects of ECT in the postictal period following future large-scale investigations.

The continued resolution of postictal EEG changes may also correlate with the cognitive impairments incurred immediately after individual sessions and progress over the course of ECT treatments. Perturbations in processed EEG measures persist even when individuals appear to be awake in the postictal period (Thimmaiah, Thirthalli et al. 2012, Soehle, Kayser et al. 2014). Patients with greater suppression in processed EEG measures following ECT are more likely to experience prolonged memory impairment(Koitabashi, Oyaizu et al. 2009). Specific EEG markers that can be linked to both underlying neurobiology and cognitive function have not been developed for the acute period after ECT. Beyond individual sessions, persistent slow theta and delta oscillations have been observed in the EEG(Volavka, Feldstein et al. 1972) and may resolve only weeks following the last session(Kolbeinsson and Petursson 1988, Sackeim, Luber et al. 1996). These markers that remain weeks after ECT sessions may be linked to either therapeutic efficacy(Sackeim, Luber et al. 1996) or the extent of disorientation and retrograde amnesia(Sackeim, Luber et al. 2000). Definitive relationships remain speculative.

The return of cognitive function following individual ECT sessions has not been fully characterized. Recent analyses have shed light on the incidence and persistence of cognitive side effects related to this procedure(Semkovska and McLoughlin 2010). Presumably, perturbations in attention, memory, and cognition during the postictal period have bearing on short- and long-term deficits in functionality as patients become rehabilitated into the community. Approximately 5-12% of patients experience postictal agitation and disorientation after ECT(Kranaster, Janke et al. 2012, Tzabazis, Schmitt et al. 2013) that may last 1-2 hours after ECT. Postictal agitation does not occur reproducibly in the same patients following subsequent treatments(Fink 1993). Disorientation during the early postictal recovery from ECT appears to decrease with number of sessions(Calev, Cohen et al. 1991). Interictal confusion accumulates prior to successive ECT

sessions(Calev, Cohen et al. 1991). Cognitive side effects may persist for 90 minutes following seizure termination(Perera, Luber et al. 2004). Cumulative treatments of ECT may be associated with anterograde(Sobin, Sackeim et al. 1995) and retrograde amnesia(Nobler and Sackeim 2008), primarily following the entire course of an ECT regimen (Semkovska and McLoughlin 2010). The extent to which these forms of cognitive dysfunction contribute to missed work and caregiver burden are not known. Given that each session of ECT requires the administration of general anesthesia during seizure induction, systematic study requires accounting for these potent neuromodulatory agents.

2.1.3 Control for Anesthetic Exposure

Elucidating cognitive recovery following seizures in the context of ECT requires a control to account for the effects of general anesthesia. This is because modern ECT is conducted under general anesthesia and pharmacologic neuromuscular paralysis. Anesthetics with mechanisms invoking γ-aminobutyric acid (GABA) A-type receptor agonism (e.g. etomidate) or NMDA-receptor antagonism (ketamine) are commonly used. Ketamine has received greater attention recently since subanesthetic doses of ketamine have shown efficacy in treating refractory depression(Mathew, Shah et al. 2012, Mathews and Zarate 2013, Murrough, Iosifescu et al. 2013, Murrough, Perez et al. 2013). Relative to other anesthetics in use for ECT, ketamine may provide faster recovery from cognitive impairment on the day of treatment(McDaniel, Sahota et al. 2006, MacPherson and Loo 2008) or additive benefits on ECT efficacy(MacPherson and Loo 2008). Thus, ketamine may be useful in a sham ECT condition to control for anesthetic

2.2 Hypotheses and Aims

We hypothesize that the reconstitution of cognitive function will markedly vary in rate and order, depending on the presence of seizures induced by electrical brain stimulation. Our specific aims include: (1) assess whether the time to return of responsiveness will be prolonged with ketamine + ECT compared with ketamine + sham ECT; (2) ascertain whether the time of restoration to baseline function in each cognitive domain will take longer after ketamine + ECT than after ketamine + sham ECT; (3) determine if postictal delirium is associated with delayed restoration of baseline function in all cognitive domains; and (4) determine whether the sequence of

reconstitution of cognitive domains is similar to that occurring after an isoflurane general anesthetic; we also anticipate these cognitive disturbances

2.3 Design and Participants:

2.3.1 Study Design

We propose over three years to randomize fifteen to twenty patients with refractory depression to one of three treatments in two consecutive weeks of an ECT treatment cycle. Each patient will complete seven study visits. The first visit will be conducted during the dose-charge titration ECT treatment. Following the titration visit, there will be six separate experimental treatments per patient in two blocks of three, with a random sequence in each block (Figure 1). During these six visits, patients will be randomized to receive one of three treatments, all of which are likely to have efficacy in treating refractory depression: 1) ketamine alone, 2) ketamine plus ECT, or 3) standard of care anesthetic plus ECT.

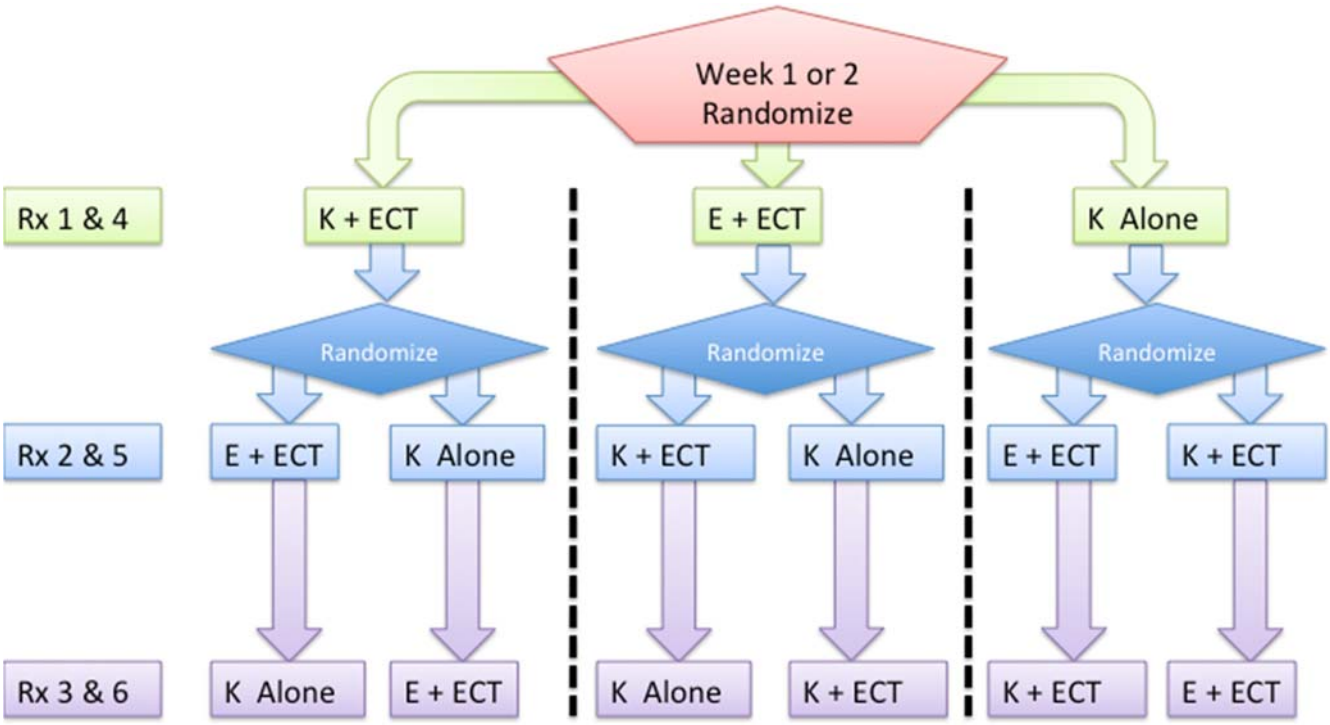


Figure 1: Block randomized, repeated measures, crossover experimental design for reconstitution of consciousness and cognition following electroconvulsive therapy (ECT) and general anesthesia. K, ketamine; E, etomidate, Rx, treatment.

2.3.2 Pre-Study Period: None

2.3.3 Subject Screening, Enrollment, and Consent Process:

Screening and informed consent will occur at Barnes-Jewish Hospital, following ECT referral by staff psychiatrists.

2.3.4 Inclusion/Exclusion Criteria

Inclusion criteria: Referral for ECT via right unilateral stimulation for treatment-resistant non-psychotic unipolar or bipolar depression, English-speaking, at least 18 years old, able to provide written informed consent.

Exclusion criteria: Known brain lesion or neurological illness that causes cognitive impairment, schizophrenia, schizoaffective disorder, blindness or deafness that may impair performance for cognitive testing battery, inadequate seizure duration with etomidate, defined at our institution as bilateral spike-and-wave complexes present for less than 10 seconds.

2.3.5 Study Involvement

The randomized, crossover design of the study is powerful, as it will allow several within-patient comparisons, which will provide optimal efficiency to address the hypotheses. Specifically, the design will allow us to distinguish between the effect of ketamine anesthesia alone versus the combined effect of ketamine plus ECT. Recovery of consciousness after etomidate is generally rapid. Therefore, the etomidate plus ECT arm should yield additional insights into the contribution of seizures in the form of ECT to impaired consciousness and cognition and provides an additional comparator condition to the ketamine + ECT arm. Intra-patient repetition of each of the three exposures over two weeks will help to establish the reproducible effect of each exposure on the outcomes of interest.

2.3.6 Randomization and Blinding

A trained team member will use a computer-generated randomization algorithm among 18 potential combinations of initial cognitive task and order of study interventions. Random assignments will account for investigator-physician availability for ketamine + sham ECT sessions. The patient will be blind to the order of treatment condition. Study and clinician teams will be aware of the treatment arm at each session and maintain blinding by maintaining consistency of routine checks and monitoring before and after anesthetic induction. Thus, for all treatments sessions, patients will not be able to view the syringe during anesthetic induction. Furthermore, stimulation electrode and conducting gel will be placed on the scalp following loss and prior to return of consciousness. Post-anesthetic evaluation by anesthesiology, psychiatry, and nursing staff will be consistent across sessions.

To maximize study rigor and reproducibility, investigators evaluating study measurements for data quality and development of analytical tools will be blinded to details of the treatment intervention, whenever possible(Nuzzo 2015).

2.3.7 Interventions

Each patient will be included for seven sessions. As with all non-study patients, the first sessions consists of a dose-charge titration that is used to determine the current required to induce the seizure. At Barnes-Jewish Hospital, etomidate is commonly used to induce general anesthesia for this session. During four of the next six sessions, the patients will receive care that is currently within the standard of care for refractory depression, namely general anesthesia (standard of care or ketamine) plus ECT. In addition, during two sessions, patients will receive only general anesthesia with ketamine, which has now been shown to have efficacy in treating refractory depression. Apart from these treatments, patients will be monitored with full montage electroencephalography and will complete tests of cognition, mood and depression before and for approximately two hours following the general anesthesia (with or without ECT).

2.3.8 Observations and Measurements

Dose-Charge Titration Visit (Visit 1)

During the titration visit, the study team will assess baseline cognitive function and EEG prior to ECT, tolerability of cognitive testing and EEG recording. Patients will have baseline assessments, including a

cognitive battery (COGNITION), continuous electroencephalography, 5 minutes of resting state EEG with eyes open and 5 minutes for eyes closed, depression testing (PROMIS-CAT) and mood assessment (Self-Assessment Manikin), suicidal ideation (Scale of Suicidal Ideation)(Beck, Kovacs et al. 1979), and the 3D Confusion Assessment Method (3D-CAM) before the ECT therapy session .ECT charge will be delivered via a Thymatron System IV (Somatics, LLC, Venice, FL, USA). Per ECT laboratory procedures, stimulation parameters include current 0.9 amperes, pulse width of 0.3 milliseconds, with escalating dosage: (5% total charge: 24.9 millicoulombs, 10 Hz stimulation, 4.6 second duration; 10% total charge: 50.8 millicoulombs, 20 Hz stimulation, 4.65 second duration, 15% total charge: 75.6 millicoulombs, 20 Hz stimulation, 6.98 second duration). Subsequent planned ECT treatment is based on six-fold increase in charge delivery. Thus, individuals without suitable seizure duration at projected 100% charge will be withdrawn from the study.

Experimental Treatment Visits (Visit 2-7)

Baseline assessments will be performed at each session immediately prior to ECT and will include a cognitive battery (COGNITION), electroencephalography, depression testing (PROMIS-CAT) and mood assessment (Self-Assessment Manikin), suicidal ideation (Scale of Suicidal Ideation)(Beck, Kovacs et al. 1979), and the 3D Confusion Assessment Method (3D-CAM). Details regarding these assessments are provided as an appendix at the end of the protocol.

During four of these six sessions, the patients will receive care that is currently within standard practice for ECT: general anesthesia (standard of care or ketamine), muscle paralysis (succinylcholine), and electrical stimulation. For the remaining two sessions, patients will undergo a ketamine general anesthetic without muscle paralysis or ECT stimulation.

High-density EEG, bilateral fronto-mastoid clinical EEG, and full American Society of Anesthesiologists (ASA) monitoring will commence prior to the induction of general anesthesia. Prior to induction, audible squeeze toys will be placed in each hand of the patient, who will be instructed to follow serial commands to either “Squeeze your left hand twice” or “Squeeze your right hand twice.” Every 30 seconds, one of these commands will be played at random, to monitor loss and return of consciousness. Patients will be pre-oxygenated by mask and

anesthesia will be induced with ketamine, approximately 2 mg/kg, or standard of care. Following bolus of the induction agent, loss of responsiveness and eyelash reflex will be confirmed. Loss of consciousness will be recorded as the first time when a subject fails to correctly respond to the command. Care adherent to the ASA guidelines will be performed regardless of treatment session. For sessions with ECT, pre-stimulation hyperventilation and assisted ventilation will also be performed. Central seizure duration will be assessed from bilateral fronto-mastoid EEG by the psychiatry team. Peripheral seizure duration will be determined through monitoring of tonic-clonic activity(Fink and Johnson 1982). During the sessions that subjects receive ECT, other drugs will also be administered according to current practice and as clinically indicated. The return of eye opening will be assessed every 30 seconds and defined for the initial time at which the patient opens his eyes to verbal command. The ability to extend the thumb to verbal command ("thumbs up") will be assayed every 30 seconds. Return of responsiveness to auditory command will be defined as the first time at which the patient has squeeze his correct hand the number of times instructed via auditory commands. At this time, defined as t = 0 minutes, the subject will begin a series of cognitive and behavioral assessments, which are repeated every 30 minutes up to two hours after return of responsiveness. Patients will be permitted to take brief breaks to use the restroom and eat or drink, as necessary. At the conclusion of each treatment session, depression testing (PROMIS-CAT) and mood assessment (Self-Assessment Manikin) will be performed to assess for early improvements in mood. To assess blinding quality, the patient will be asked their impression of whether they received ECT that day. They will be discharged according to standard post-anesthesia care unit discharge criteria upon completing the last neurocognitive test battery. A study site coordinator will contact each subject within 24 hours of the study day to assess and document any adverse events.

EEG and Video Acquisition

EEG will be collected during the dose-charge titration session and during all treatment sessions to assess pre-ECT and pre-anesthetic baseline EEG recordings. An appropriately fitted 64-channel EEG Geodesics Sensor Net (Electrical Geodesics, Inc. Eugene, OR, USA) will be affixed to the scalp. Elefix electrode paste (Nihon Kohden America, Inc., Irvine, CA, USA) will be injected to maintain conductivity to the silver/silver-chloride electrodes. Electrode impedances on each channel will be optimized to be less than 100 kOhms/channel, per manufacturer's suggestions. Data (DC to 2000 Hz bandwidth 500 Hz sampling rate) will be acquired with a Net Amps 400 amplifier and Net Station version 5.0 and above (Electrical Geodesics, Inc.

Eugene, OR, USA) via a Late 2012 Mac Pro Workstation (Apple Cupertino, CA, USA). Whenever possible, video synchronized to EEG will be acquired using an Axis P3364LV network camera (Axis Communications, Lund, Sweden).

2.4.7.1 Outcomes (Further details on instruments are provided in appendices)

Primary and Secondary Outcomes

Primary outcomes include: the temporal recovery profiles for cognitive task performance, as measured using the Cognition assessment battery (Basner, Savitt et al. 2015); times for the return of responsiveness to auditory command; and the presence of delirium, evaluated through the 3-Minute Diagnostic Assessment for CAM-defined delirium (3D-CAM)(Marcantonio, Ngo et al. 2014).

Secondary outcome measures based on the EEG will include definitions of the seizures by standard techniques using both expert reader interpretation and quantitative techniques (Haider, Esteller et al. 2016). Central seizure duration will be visually determined by clinician evaluation of the frontal-mastoid bipolar EEG ictal complexes. Additional measures will be calculated from windowed analyses of the high-density EEG: power spectral measures of the interval between anesthetic induction to delivery of ECT stimulus charge; the seizure envelope for 1-12 Hz EEG power; peak-to-peak amplitude, calculated from the difference in maximum and minimum voltages within 300 millisecond time; periodicity of epileptiform discharges; inter-hemispheric symmetry of seizure discharges; intra- and inter-hemispheric coherence. When possible, these measures and power spectral estimates will be derived different phase of the ictal waveforms(Gerst, Enderie et al. 1982). The following postictal EEG measures will be assessed: duration of postictal EEG suppression; power spectral parameters flanking the return of responsiveness to verbal command; power spectral parameters from eyes open and closed epochs, including assessments of the posterior dominant rhythm. Spatiotemporal analyses will also focus on the propagation of EEG signatures during the ictal and early postictal period.

2.4.7.2 Data Collection

Outcomes, such as delirium assessments, will be entered into the Washington University School of Medicine Research Electronic Data Capture (REDCap) application. The baseline medications will be collected from the electronic medical record. The anesthetic and recovery record will be retrieved from the hospital's perioperative electronic medical record (Metavision by *i*MD*soft*®, Needham, MA). The cognitive assessments will be

completed using the COGNITION cognitive battery designed at the University of Pennsylvania(Basner, Savitt et al. 2015). The computer-based depression questionnaire will be completed through assessmentcenter.net developed by Northwestern University's Department of Medical Social Sciences. As standard care for tracking depression symptoms during an ECT course, treating psychiatry teams will administer the Quick Inventory of Depressive Symptomatology, Self-Report (16-Item), QIDS-SR16(Rush, Trivedi et al. 2003). To fully assess each patient's treatment response to ECT, the research team will use the electronic, as well as paper, medical records to access and record the following information for each treatment from the patients' entire ECT treatment course at Barnes-Jewish Hospital: QIDS scores, reason for treatment (diagnosis), the method of ECT (right-unilateral, bilateral, or bifrontal), treatment number, date of treatment, any medications including doses, charge/treatment parameters, central and peripheral seizure duration, any adverse events from the sessions, and any clinical notes regarding treatment efficacy or recovery from each procedure.

2.4.7.3 Optional Magnetic Resonance Imaging

In addition to the above procedures listed, patients will be given the option to undergo non-contrast magnetic resonance imaging (MRI). The MRI data will better allow interpretation of the EEG signals in relation to structural brain anatomy. The MRI scan will take place following completion of the patient's ECT treatment course at Barnes-Jewish Hospital. Structural MRI will be performed at the 10th floor West Pavilion Center for Clinical Imaging Research (CCIR). The MRI scan will use clinical sequences and will be read by board-certified neuroradiologist. The reading and images with be placed in the electronic medical record. Significant incidental findings will be disclosed to the patient and his/her physician. The patient will decide s(he) on disclose of Incidental findings of unclear clinical significance. Patients will be compensated $50 for their time. There will be no charge to the patient for the MRI scan. If patients are unable to arrange transportation to/from Barnes-Jewish Hospital for pre-treatment testing, the study team will provide patients with such transportation through cab vouchers.

2.5. Analytical and Statistical Methods

This is an exploratory study that seeks to track and characterize the reconstitution of consciousness and cognition following ECT coupled with general anesthesia. We hypothesize that the pattern (sequence and time

course) of reconstitution of consciousness and cognition following ECT with general anesthesia is different from general anesthesia alone. In particular, we propose that the cognitive and electroencephalographic features following ECT will be similar to those seen during postoperative delirium, which is a disorder of consciousness and cognition.

2.5.1 Statistical Analysis

We will employ mixed-effects models to quantify trajectories of cognitive recovery over time while addressing inter-subject variance and missing data. Linear models with appropriate transformations will be used preferentially over non-linear models. Time and treatment intervention group will be included as fixed effects while random effects will account for repeated measures provided by each participant. Day of treatment relative to the dose-charge titration session will allow consideration of cumulative effects of treatment order that may remain biased despite randomization. To address differences in ECT-stimulation responsiveness, regression approaches will account for dose charge, central seizure duration, and age. Models will assess for the effects of treatment on the timing for the return of responsiveness to verbal command and the presence of delirium. Separate mixed-effects models will be generated to assess task performance in a group of young healthy volunteers during the recovery from isoflurane general anesthesia (Maier, McKinstry-Wu et al. 2017).

2.5.2 Primary Analyses:

Recovery of Responsiveness: Given that the induction of generalized seizures by electrical stimulation may compound the recovery from general anesthesia, we expect that interval from loss to return of responsiveness following ketamine + ECT will be longer compared to the period for ketamine + sham ECT. We will determine the median and 95% confidence intervals for this measure in relation to the treatment intervention.

Recovery of Cognition: Given that postictal suppression may be prolonged with ketamine than with etomidate(Hoyer, Kranaster et al. 2014), we hypothesize that the time needed for the return of cognition to baseline on individual sessions will be greatest for ketamine + ECT, followed by etomidate + ECT, and ketamine + sham ECT. Separate mixed-effects models will be generated based on reaction time and accuracy. We will determine the time of convergence for 95% confidence intervals for the marginal responses related to

the three treatment groups. To determine the timing for the recovery to baseline, we will determine the time when the same 95% confidence intervals include 0.

Postictal Delirium and Cognitive Recovery: We expect the incidence of delirium (3D-CAM) to be associated with delayed restoration of baseline function in all cognitive domains. The magnitude and significance of this relationship will be determined from the mixed effects models for each cognitive test.

Comparison of Cognitive Recovery After ECT and Isoflurane General Anesthesia: We hypothesize that the time for recovery to baseline will be quicker for treatments involving ECT compared to that for the recovery from isoflurane general anesthesia. Convergence for 95% confidence intervals will be compared between treatment groups.

2.5.3 Secondary Analyses

Recovery of Cognition: Principal measures of performance are based on preliminary data(Basner, Savitt et al. 2015) of the Cognition test battery. Additional measures include: PVT response speed, DSST throughput, PVT lapses, VOLT duration and accuracy, AM duration and accuracy, and DSST errors. Cognition performance measures associated with lower effect sizes will also be assessed. These include AM accuracy, VOLT accuracy, F2B reaction time, MPT accuracy, MPT duration, and F2B accuracy. Overall, we expect F2B, VOLT, and AMT to recover the slowest due to taxing of short-term memory after ketamine + ECT compared to ketamine + sham ECT.

Recovery in the Spontaneous EEG: We will evaluate mixed-effects models to test the hypotheses that the predominance of frontal delta or theta power during passive eyes opening or occipital alpha power during eyes closed predict cognitive performance (Cognition scores) or delirium (3D-CAM scores). We will also compare these EEG spectral measures across treatment sessions to evaluate the impact of anesthetic and ECT.

Relationship of ECT Seizure Duration to Return of Responsiveness to Verbal Command: We expect that the length of ECT-induced seizures will correlate with the intervals from the loss of responsiveness to the return of responsiveness.

Mood and Depression Severity: We expect improvement in these clinical outcomes to be greatest with ketamine + ECT, followed by etomidate + ECT, and then ketamine + sham ECT.

Treatment Satisfaction: We expect satisfaction to be greatest for ketamine + ECT, followed by ketamine + sham ECT, and then by etomidate + ECT.

2.5.4 EEG Preprocessing and Analysis

EEGLab will be used to assess for quality and the presence of motion and eye movement artifact(Delorme and Makeig 2004). Data will undergo pre-processing with band-pass filtering from 0.1-50 Hz with 1st order Butterworth filters. Frontal channels will be assessed for eye movement artifact. Reduction of severe eye movement artifacts will employ independent component analysis approaches in EEGLab. The following analysis time epochs will be evaluated for secondary outcomes related to EEG activity: pre-ECT and post-ECT periods with either eyes open or eyes closed, the interval between anesthetic induction to and ECT stimulation, the period between stimulus delivery and cessation of ictal waveforms/spike-and-wave complexes, postictal period of EEG suppression and slowing, and both 5-minute epochs flanking the return of responsiveness to verbal command.

Spectral analysis will be performed using the Chronux Toolbox(Mitra and Bokil 2008), including five tapers, time frequency bandwidth of 3, and 6-second non-overlapping time windows. Total power and peak amplitude will be computed within the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) bands. Coherence and phase lag will be computed using the Chronux toolbox. Global coherence(Cimenser, Purdon et al. 2011) and permutation entropy will be computed(Bandt and Pompe 2002). Quantitative measures will be derived from spectral and time-based analyses of the ictal EEG. These measures will evaluate seizure energy, periodicity, and symmetry, as well as propagation, and termination.

In parallel to power spectral analysis, we will track the time-varying connectivity between the measured brain regions. Data will be windowed into 5-10 second epochs within which several cross-channel connectivity metrics will be computed. These measures will include the Pearson correlation, directed entropy, and Shannon mutual information. Thus, windows will manifest different ‘networks’, each describing the association between channels (regions) according to its respective metric. These networks will be clustered into a set of distinct motifs, or microstates, by using a k-means algorithm with least-squares error criterion. Other methods to characterize the time-varying dynamics of the observed brain activity, including those based on network control theory, will also be considered.

Visualization and analyses of epileptiform EEG activity will be performed using Net Station and Persyst software (Persyst, Solana Beach, CA, USA), following interpolation of bad channels and re-referencing to the average signal. EEG dipole source localization, inter-hemispheric generalization, and phase-reversals will be assessed by epilepsy board-certified neurologists. Seizures will be staged according to the previously described three components of electrical seizures induced by ECT (phase I with initial 14-22 Hz rhythmic beta activity, phase II with arrhythmic polyspike activity, and phase III with rhythmic 2.5-3.5 Hz. spike/polyspike activity(Gerst, Enderie et al. 1982). Additionally, expanding on previous analyses of stationarity in epileptiform activity induced by ECT(Zoldi, Krystal et al. 2000), we will use high-density EEG to topographically map rhythmic sharp-wave discharges. To maintain rigor, evaluators will be blinded to the study intervention.

Structural MRI scans, including T1-weighted images will be used for source localization using Brainstorm software.

2.6. Sample Size

We based our targeted enrollment on safety consideration for a ketamine general anesthetic, expected differences in the recovery patterns of different domains assessed by the Cognition test battery, prior volunteer data with isoflurane emergence(Maier, McKinstry-Wu et al. 2017). Sample size calculations are based on 1-way pairwise of ANOVA (Analysis of Variance) comparisons of 4 means (t = 0, 30, 60, and 90 minutes). Expected effect sizes for differences in the modeled trajectories of cognitive function ranged from 20-40 minutes. Standard deviations were expected to range between 20 and 40 minutes. Using conservative assumptions, we calculated a sample size of 24 subjects (effect size, μ_A-μ_B, of 20 minutes; standard deviation, σ, of 20 minutes; two-sided alpha of 0.05; power of 80%). With liberal assumptions, we estimated a sample size of 12 participants (μ_A-μ_B of 40 minutes; σ of 20 minutes; two-sided alpha of 0.05; power of 99%). With this range of estimates and expected attrition of participants, we targeted for data collection from 15-20 participants.

2.7. Management of Intercurrent Events

2.7.1 Cross-over, repeated measures

The study design has a built in cross-over, repeated measures to allow patients to serve as their own control and to experience each of the treatments twice.

2.7.2 Adverse Experiences and Premature Discontinuation

The Washington University HRPO and the Data and Safety Monitoring Committee (DSMC) oversee the study's progression and adherence to protocol. Following each intervention, the principal investigators will affirm continued involvement or withdrawal based on patient tolerance and data quality. All adverse events will be reviewed by the DSMC and reported to HRPO, following the reporting policies and procedures, and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, known etiology, relationship to the study, and any treatment required. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to HRPO and appropriate parties. .

2.7.3 Potential Risks

Interruption of clinical care: While this is a theoretical risk, it is not envisaged that the conduct of this study will interfere with clinical care.

Discomfort related to EEG/EMG/EOG: Skin abrasions from scalp electrode placement or discomfort on removal of electrodes.

Non-contrast MRI: Claustrophobia, anxiety, discomfort from headphones used to shield out noise, or hearing loss due to hammering noise are all potential risks of undergoing non-contrast MRI. Patients with tattoos may experience irritation, swelling, heating, or instances of primary or secondary burns in the area of the tattoo. Additionally, patients with devices such as a pacemaker, bone hardware, or a device placed in their uterus may experience heating or movement of the device, device malfunction, or damage to the tissue that surrounds the device. These risks are unlikely to be common or severe.

Breach of Confidentiality: Another potential risk of participating in this study is that confidential information about the participant may be accidentally disclosed. We will use our best efforts to keep the information about participants secure, through de-identification of personal health information. We think the risk of accidental disclosure is very small.

2.8 Procedures to Minimize Potential Risks

Interruption of clinical care: The research team will be in open discussion with patients and nursing staff to ensure that there is no disruption in the patient's clinical care, comfort, and recovery.

EEG/EMG/EOG: Timing and manner of electrodes and adhesive removal will be based on patient's comfort and convenience. Discomfort will be minimized based on the use of sticker/adhesive/gel electrodes and not needle electrodes.

Confidentiality: This will be maintained by assigning each participant a number to be linked with data. Any protected health information of patient participants will be stored in a locked drawer within the locked office of the PI. Electronic protected health information will be stored on a password-protected server.

MRI Safety: The patient will be thoroughly screened for MRI-incompatible implants. Scans may be performed following completion of the patient's ECT treatment course at Barnes-Jewish Hospital. Scans will be performed within the hospital (10th floor CCIR).

Research Conduct: Studies are conducted at Washington University School of Medicine under the general supervision of a board-certified cardiac anesthesiologist who is familiar with postoperative surgical care. Patients will be monitored during emergence and recovery from anesthesia by the anesthetic and nursing staff in the ECT suite as per standard care. Additionally, research personnel trained in good clinical practices will be present during the acquisition of data. Monitoring and safety will be according to the current clinical standard. Patient confidentiality will be maintained through de-identification of personal health information. Identity and

linking information will be stored in a locked cabinet within the principal investigator's office, which is locked outside of business hours. Electronic data will be password-encrypted on secure servers.

Patient satisfaction will be monitored throughout the study. Ketamine may improve the efficacy of ECT and recovery of cognitive function following ECT. Patients may benefit from the additional EEG monitoring in the postictal period during which non-convulsive status epilepticus is rarely manifested. Patients will be withdrawn if discontinuation is in the best interest of the patient or if the patient requests withdrawal or removal of treatment blinding. In the event that a patient's condition significantly worsens and requires additional or different interventions from those allocated in the study, the patient will be released from the study and data collection will be discontinued. Participants are given a satisfaction survey to be returned by mail following the last study session(Sienaert, De Becker et al. 2005).

Participant Satisfaction: During the follow-up phone call for the last study session, participants will be asked about their satisfaction in the study(Sienaert, De Becker et al. 2005).

2.8.1 Adverse Event Reporting and Data and Safety Monitoring Plan

The investigators will monitor subjects for evidence of adverse events. All adverse events will be reported to the IRB following the IRB reporting policies and procedures and followed until satisfactory resolution.

3. HUMAN SUBJECTS RESEARCH

3.1 Protection of Human Subjects

The study will be conducted with strict adherence to Washington University Institutional Review Board protocol and consent form approval. An American Board of Anesthesiology board-certified and GCP-certified anesthesiologist with experience in conducting clinical studies will lead the study. Safety and privacy of study participants will be safeguarded.

Patient confidentiality will be maintained through de-identification of personal health information. Identity and linking information will be locked cabinet within the principal investigator's (PI) office, which is locked outside of business hours. Electronic data will be password encrypted on secure servers.

3.1.1 Indemnity

Washington University School of Medicine is responsible for any non-negligent damage incurred as a result of participating in the RCC II Trial. This indemnity is renewed on an annual basis. Washington University School of Medicine assures that it will continue renewal of the indemnity for the duration of the trial.

3.1.2 Ethics and Dissemination

The trial investigators will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and appropriate parties. The final trial dataset is the property of the investigative team and shall not be shared without permission from the principal investigator. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the RCC II trial in a peer-reviewed journal. Dissemination of results to study participants and their family members will be available upon request. Updates and results of the study will be available to the public at clinicaltrials.gov.

3.2 Sources of Materials

Patients will receive remuneration of $100 per session after the titration visit (Visit 2-7), or $600 for completion of the study. Patients who undergo an MRI scan will receive an additional $50 for their time. There will be no cost for involvement.

3.3 Recruitment and Informed Consent

Screening and enrollment of subjects will occur according to the protocol-defined inclusion and exclusion criteria.

3.4 Potential Benefits of the Proposed Research to the Participant and Others

This study will be the first to explore and elaborate how a seizure in the form of ECT (combined with an induction dose of intravenous anesthesia) impacts consciousness and cognition following termination of the seizure. The time course and sequence of reconstitution of consciousness and cognition will also be clarified. This investigation will yield novel insights into an excitatory impairment of consciousness, which has not previously been studied with a controlled, experimental design.

Candidates for ECT are refractory to multiple medical modalities. These patients may benefit from a greater understanding of the relationship between anesthetics and ECT on recovery of cognitive function and efficacy for depression treatment.

This study may benefit the patient directly. Ketamine may improve the efficacy of ECT and recovery of cognitive function following ECT. The patient may benefit from the additional EEG monitoring in the post-ictal period during which non-convulsive status epilepticus is rarely manifested.

3.5 Inclusion of Women

Efforts will be made to enroll patients regardless of gender.

3.6 Inclusion of Minorities

All studies in the Department of Anesthesiology encourage the participation of minorities in research.
Our minority recruiting typically matches the demographic composition of the Washington University patient population (30% white, 60% Black, 6 % Hispanic, 4% Asian).

3.7 Inclusion of Children

No children will be enrolled in this study.

Appendices:

1. Study Day (each experimental treatment day Visit 2-Visit 7)

Pre-Treatment:

An appropriately fitted 64-channel (n=15-20 subjects) EEG headcap (Electrical Geodesics, Inc. Eugene OR) will be affixed to the scalp. The actual placement of EEG electrodes might vary, depending on the requirements for ECT. Electrical impedances on each channel will be confirmed to be under 100kOhms/channel. Subjects will complete a baseline round of neurocognitive testing with ongoing EEG recordings, as well as 3D-CAM (3D-Confusion Assessment Method), Self-Assessment Manikin, PROMIS-CAT (Patient Reported Outcomes Measurement Information Systems - Computer Adaptive Testing) for depression, and the Scale of Suicidal Ideation (Table 1).

During Treatment:

Upon completion of the neurocognitive battery, the subjects will be pre-oxygenated by mask and anesthesia will be induced by either ketamine, 2 mg/kg or standard of care anesthetic, depending on group assignment. The induction agent will be slowly titrated until there is loss of responsiveness and eyelash reflex, which is current practice for ECT. During this time, an audio loop command will be issued every 30 seconds asking the subject to randomly squeeze their left or right hand. Loss of consciousness (LOC) will be recorded as the first time when a subject fails to respond to two consecutive commands. Antiemetic prophylaxis will be administered as clinically indicated. During the sessions that subjects receive ECT, other drugs will also be administered according to current practice and as clinically indicated. ECT will be conducted according to current standard practice. EEG will be acquired after the ECT charge has been delivered or continuously for non-ECT ketamine sessions. After the ECT has been concluded (or after the induction dose of ketamine has been administered), the patient will remain in the treatment room for subsequent testing and EEG recording.

Post-treatment:

Recovery of consciousness (ROC) will be defined as the first time at which subjects correctly responded to two consecutive audio loop commands. At this time, defined as t = 0 minutes, the subject will begin the neurocognitive battery of tests followed by a brief resting period. Neurocognitive testing will be repeated at t= 30, 60, and 90 minutes following emergence while the 3D-CAM will be completed at time 0 and every hour (Table 1) until the patient is scored negative for delirium. Each battery of neurocognitive testing will take

approximately 15-20 minutes to complete. During the rest period, EEG recording will occur with 5 minutes eyes open and 5 minutes eyes closed. At the 90 timepoint patients will not only complete the COGNITION cognitive test but also the 3D-CAM (if positive for delirium at t=60, PROMIS-CAT, Self-Assessment Manikin, and a questionnaire regarding patients' subjectivity of whether they received ECT. Subjects will be permitted to take a brief break to use the restroom and eat or drink, as necessary. Subjects will be discharged according to standard post-anesthesia care unit discharge criteria upon completing the last neurocognitive test battery. A study site coordinator will contact each subject within 24 hours of the study day to document any adverse events.

Table 1: Assessment at Each Experimental ECT Treatment (Visit 2-Visit 7):

Assessment	Baseline (Pre-ECT)	Time 0	Time 30	Time 60	Time 90
COGNITION Neurocognitive Testing	X	X	X	X	X
3D-CAM - Delirium (3D-Confusion Assessment Method)	X	X		X	X
PROMIS-CAT - (Computer Adaptive Testing for depression)	X				X
Mood Self-Assessment Manikin - mood	X				X
Scale of Suicidal Ideation	X				
Assessment for Blinding Quality					X

2. Description of Assessments:

Neurocognitive testing (COGNITION battery)

This battery for individualized neurocognitive assessment of fatigue has been tested in the context of sleep deprivation and is administered via a laptop. The effects of ECT and/or an induction dose of an intravenous general anesthetic (ketamine or etomidate) on all the tests below have not previously been well characterized.

During administration, the order will be pseudorandomized, with a full complement given at each testing block. Additionally, the first test for each block will be repeated at the end to address temporal order within the block.

Motor Praxis Test (MPT)

The motor praxis test (MPT) measures sensory motor speed and fluidity. Participants are presented with a square box that, once clicked with a track pad mouse, shrinks and moves to a different location on the computer screen. Participants must click the box each time it re-appears as rapidly as possible. It is expected that the accuracy for the MPT will be close to 100%. Therefore, the standard score for this test is determined solely based on the speed at which the subject is able to click each square. Previous studies have shown that sensorimotor function performance declines with sleep deprivation. The Motor Praxis task allows for multiple measures of sensorimotor function in less than 1 minute.

Psychomotor Vigilance Test (PVT)

The psychomotor vigilance test (PVT) measures sustained attention by recording reaction time to visual stimuli that are presented at random intervals. During the PVT, subjects are instructed to respond to a small red counter that appears at unpredictable intervals and reports time elapsed in milliseconds by clicking the space bar as soon as the counter appeared. This task is time limited as any response time greater than 500 milliseconds is recorded as a lapse or error of omission. The standard score for the PVT is based on response time and false starts. Originally, the PVT was designed for administration during 10-minute sessions. However, a shorter, modified PVT that remains sensitive to acute total sleep deprivation and chronic partial sleep deprivation was developed. Therefore, the PVT component of each neurocognitive battery in this study will be 3 minutes in duration. An advantage of using this task is that PVT is unaffected by learning and aptitude.

Digit Symbol Substitution Test (DSST)

During the digit symbol substitution test, subjects are presented with a key showing ten symbols and a number (0-10) that correspond with each. Symbols are presented on the center of the screen one at a time, and the subject must type the corresponding number as quickly as possible. This test measures complex scanning, visual tracking, attention, working memory, and visuomotor and visuospatial speed. The standard

score for this task is determined by accuracy and speed, with a severe scoring penalty based on response time. While learning effects can be observed in healthy individuals, individuals who chronically receive only 6 hours of sleep do not improve in this task over time while individuals who chronically sleep less than 6 hours display decline in performance over time. Similarly, acutely sleep deprived individuals display significantly decreased correct responses in this task.

Fractal-2-Back (F2B)

The fractal-2-Back (N-back) test measures attention and working memory. Subjects are presented with images, one at a time, at a pre-set time interval and are asked to press the space bar when the current image is identical to the image that was presented two images prior. This task requires temporary storage and manipulation of information and performance is evaluated based on accuracy, since the images are presented at predetermined time intervals. Previous studies have shown both that the fractal-2-back is sensitive to sleep inertia and that healthy individuals exhibit reduced accuracy in this task following 24 hours of sleep deprivation.

Visual object learning test (VOLT)

The visual object learning test (VOLT) examines visual-spatial learning and memory. In this assessment, subjects are presented with a series of visual objects (shaded geometric shapes) consecutively at a pre-set time interval. Following this, the subject is presented with a single visual object and asked to identify if this objected was presented during the learning period. The standard score for the VOLT is determined primarily based on accuracy; however, a penalty may be applied based on mean response time. Verbal learning suffers as a result of sleep deprivation. The VOLT was designed to measure visual-spatial learning and memory analogously to verbal learning tests. Previous work reports that there is often a gender bias on measures of spatial learning, as men tend to perform better on spatial memory tests. However, the VOLT as developed by Glahn and colleagues reveals no differences between sexes.

Abstract Matching (AM)

Abstract matching (AM) examined abstraction and cognitive flexibility. During the abstract matching task, participants are presented with a single colored geometric shape as well as two sets of geometric shapes.

They then must choose the set that the object completes. Following each selection, the subject is told whether their selection was correct or not are able to use this feedback to determine the implicit rules that govern this task. The standard score for this task is determined by accuracy with a penalty based on mean response time. Cognitive flexibility or “divergent” thinking is significantly impaired by sleep deprivation. The AM task version used in this study was chosen because it can be completed in less than 4 minutes as compared to previous versions, which required 15-20 minutes for completion.

Delirium Assessment (3D-CAM)

The 3D-CAM is a delirium assessment tool based on the full Confusion Assessment Method (CAM) interview. The 3D-CAM takes approximately 3 minutes to complete. In order for a patient to be positive for delirium they must present 3 of the 4 features including acute onset, inattention, altered level of conscious and/or disorganized thinking.

3D-CAM Instrument

For Research : Version 3.0

Evaluator:

Date:

Patient:

Time:

COGNITIVE FUNCTION

Now I'd like to ask you some questions to check your memory. Don't worry if you don't know the answers.

[YOU MAY REPEAT EACH QUESTION ONCE]

(WRITE PATIENT'S ANSWERS TO ALL QUESTIONS AND CIRCLE NUMBER AS INDICATED)

ORIENTATION	CORRECT	ERROR	REF	DK/No Response
1. **What is the year**? _____	1	2	7	8
2. **What is the day of the week**? _____	1	2	7	8
3. **What type of place is this?** _____	1	2	7	8

*****If any of 3 items above are anything other than correct, feature 3 is present***

DIGIT SPAN

[SAY DIGITS AT RATE OF ONE PER SECOND]

Now I am going to read some numbers, but I want you to repeat them in backwards order from the way I read them to you. So for example if I said 6-4, you would say 4-6.

DIGITS BACKWARD		Response	Correct	Error	REF	DK/No Response
4.	**7 - 5- 1**	___ - ___ - ___	1	2	7	8
5.	**8 - 2 - 4 - 3**	___ - ___ - ___ - ___	1	2	7	8

6. DAYS OF WEEK BACKWARDS

Can you tell me the days of the week backwards? Say Saturday as your first day.

(May prompt with: "what is the day before Saturday? or if subject stops with Day X, say " what is the day before day X? …." This prompt may be used 2 times in total. If participant starts reciting days forward repeat overall instructions.

Day	Response	Correct	Error	REF	DK/No Response
Saturday	_____	1	2	7	8
Friday	_____	1	2	7	8
Thursday	_____	1	2	7	8
Wednesday	_____	1	2	7	8
Tuesday	_____	1	2	7	8
Monday	_____	1	2	7	8
Sunday	_____	1	2	7	8

Record response verbatim

Coding Instructions: If the subject leaves 1 day out, total recorded = 6, if 2 days are reversed, total recorded =5

7. MONTHS OF YEAR BACKWARDS

Can you tell me the months of the year backwards? Say December as your first month?

(*May prompt with: "what is the month before December? or if the subject stops with Month X, " say what is the month before Month X? …." This prompt may be used 2 times in total. If participant starts reciting months forward repeat overall instructions)*

Month	Response	Correct	Error	REF	DK/No Response
December	_____	1	2	7	8
November	_____	1	2	7	8
October	_____	1	2	7	8
September	_____	1	2	7	8
August	_____	1	2	7	8
July	_____	1	2	7	8
June	_____	1	2	7	8
May	_____	1	2	7	8
April	_____	1	2	7	8
March	_____	1	2	7	8
February	_____	1	2	7	8
January	_____	1	2	7	8

Record response verbatim.

Coding Instructions: If the subject leaves one month out, total recorded = 11, if the months are reversed, total recorded = 10

*****If any of items 4, 5, 6, or 7 above are anything other than correct, feature 2 is present***

PATIENT-REPORTED SYMPTOMS:
If the respondent answers yes to any of the following questions, probe him/her for more details and note responses. E.g. Frequency

If the respondent's answers are nonsensical, code as 8.

Now I am going to ask you some questions about how you have been thinking during the past day.

8. **Have you felt confused at any time during the past day?** *About basic info (i.e. orientation, reason for hospitalization) not details of medical condition/treatment.*

   1 - No 2 – Yes 7 - REF 8 – DK/Uncertain/NR 9 – NA

9. **During the past day did you think that you were not really here [in the hospital]?**

   1 - No 2 – Yes 7 - REF 8 – DK/Uncertain/NR 9 – NA

10. **During the past day, did you see things that were not really there?** (If patient is blind skip and code 9)

    1 - No 2 – Yes 7 - REF 8 -DK/Uncertain/NR 9 – NA

If any of items 8, 9, or 10 above are anything other than 'no', feature 1 is present

End of Patient Interview

Thank you so much for your time.

Proceed to area for completion of interview observation items and final coding.

OBSERVATIONS	FEATURE 4 IS PRESENT? 1 – No 2 - Yes
11A. Was the patient sleepy during the interview? (requires that they actually fall asleep, but is easy to arouse)	
11B. Was the patient stuporous or comatose during the interview? (Difficult to impossible to arouse.)	FEATURE 4 IS PRESENT? 1 – No 2 - Yes
12. Did the patient show hypervigilance such as excessively strong responses to ordinary objects/stimuli in the environment, being inappropriately startled, etc.?	FEATURE 4 IS PRESENT? 1 – No 2 - Yes
13. Was the patient's Flow of ideas unclear or illogical, for example saying something non-sensical, unrelated to the interview (tangential) or making contradictory statements	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
14. Conversation rambling, for example did he/she give inappropriately verbose and off target responses?	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
15. Was the patient's speech unusually limited or sparse? (e.g. yes/no answers) or unusually slow or halting?	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
16. Did the patient have trouble keeping track of what was being said during the interview, for example, fail to follow instructions or answer questions one at a time?	FEATURE 2 IS PRESENT? 1 – No 2 - Yes
17. Did the patient fail to attend to the interview due to being inappropriately distracted by environmental stimuli, for example, respond to questions asked of roommate?	FEATURE 2 IS PRESENT? 1 – No 2 - Yes
18. Did the patient's level of consciousness fluctuate during the interview, for example, start to respond appropriately and then drift off?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes
19. Did the patient's level of attention fluctuate during the interview, e.g., did the patient's focus on the interview or performance on the attention tasks (digit span, days & months backwards) vary significantly?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes
20. Did the patient's speech/thinking fluctuate during the interview, for example, patient spoke slowly for a while, then sped up?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes

CAM Summary – FEATURES 1-4

Coding for features 1 -4 (0)NO (1)YES	
_____	1. Acute Onset and Fluctuating Course - Code 'Yes' if any of the items 8, 9, 10, 18,19 and 20 are incorrect/present
_____	2. Inattention - Code 'Yes' if any of the items 4,5,6,7, 16 and 17 are incorrect/present
_____	3. Disorganized Thinking - Code 'Yes' if any of the items 1, 2, 3, 13, 14 and 15 are incorrect/present
_____	4. Altered Level of Consciousness - Code 'Yes' if any of the items 11 and 12 are present

COMPLETE ONLY IF FEATURE 1 IS NOT PRESENT AND FEATURE 2 AND EITHER FEATURE 3 OR 4 IS PRESENT

21. IF IT IS THE FIRST DAY OF HOSPITALIZATION OR NO PREVIOUS 3D-CAM RATINGS ARE AVAILABLE: **Consult the medical record or contact a family member, friend, or health care provider who knows the patient well to find out if the patient is experiencing an acute change. "Is the patient experiencing an acute change in their memory or thinking?"**	FEATURE 1 IS PRESENT? 1 – No 2 – Yes 9 – Skip
22. IF SECOND DAY OF HOSPITALIZATION OR LATER AND PREVIOUS 3D-CAM RATINGS ARE AVAILABLE: Review previous 3D-CAM assessments and determine if there has been an acute change in performance, based on ANY new "positive" items	FEATURE 1 IS PRESENT? 1 – No 2 – Yes 9 – Skip

The diagnosis of delirium by CAM requires the presence of features 1 AND 2 AND either 3 or 4.

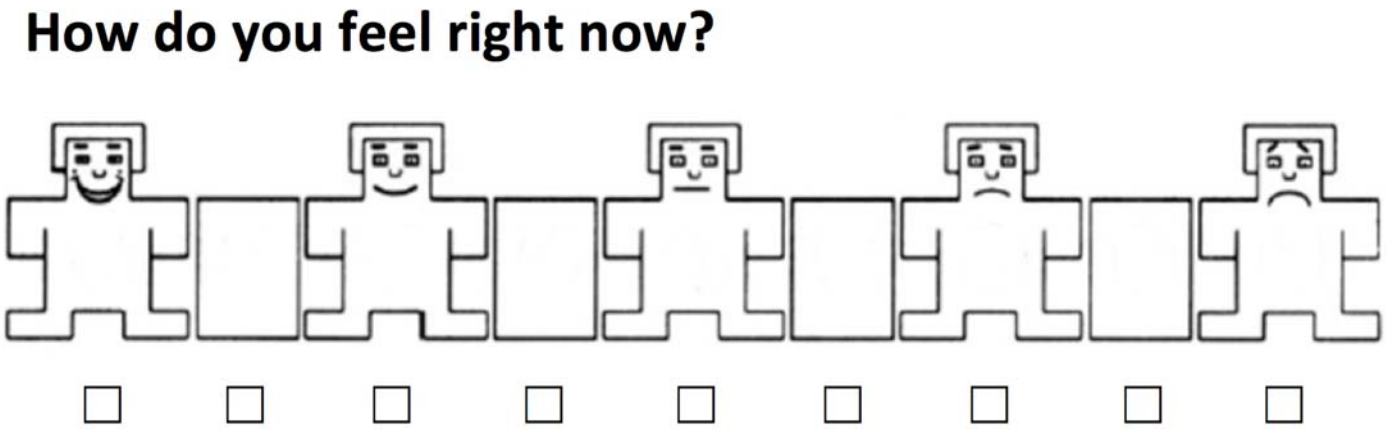
____ 5. Delirium present? (0) No (1) Yes

Depression (PROMIS-CAT)

The assessment of depressive symptoms using the PROMIS-CAT survey will be done separately from the routine clinical depression assessments that will be conducted by the psychiatrists who are caring for these patients. This is a computer-based questionnaire accessed through REDCap. As standard care for tracking depression symptoms during an ECT course, treating psychiatry teams will administer the Quick Inventory of Depressive Symptomatology, Self-Report (16-Item), QIDS-SR16(Rush, Trivedi et al. 2003).

Mood Assessment (Self-Assessment Manikin, SAM)

This assessment has been used to assess mood and mood changes with ECT. The SAM is a brief, reliable scale that are sensitive to the treatment effects of ECT and that are appropriate for patients with transient cognitive impairment(Bradley and Lang 1994).



We will use show the scale to the patient and read the following script:

"This scale asks how you are feeling right now. It ranges from a smile to a frown. This end of the scale (point) **means you feel completely happy, pleased, satisfied, contented, hopeful. The other end of the scale** (point) **means you feel completely unhappy, annoyed, unsatisfied, melancholic, despaired, bored. You can choose any of these points to describe how you feel right now. "**

The patient will then place a check mark in the box below the manikin row that most accurately depicts his/her mood.

Scale of Suicidal Ideation

This is a rating scale to assess the subjective desire to hurt oneself. We will use the first two questions only (http://www.psy-world.com/ssi_print.htm). These two questions have been used previously for assessing changes in suicidal ideation before and after a brief ketamine infusion for major depressive disorder(Ballard, Ionescu et al. 2014).

Item	Response	Points
1. Wish to live	moderate to strong	0
	weak	1
	none	2
2. Wish to die	none	0
	weak	1
	moderate to strong	2

Assessment of Blinding Quality

At the conclusion of study sessions 2-7, the patient will be asked, "Do you feel that you received ECT today? Was ECT painful?"

Assessment of Patient Satisfaction

1. Did you have any side effects or problems after receiving treatments? Please indicate after which treatment these side effects occurred (check all that apply).

	1st	2nd	3rd	4th	5th	6th	Yes, but not sure when
Nausea	☐	☐	☐	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐
Bruising or tenderness at IV site	☐	☐	☐	☐	☐	☐	☐
Fever	☐	☐	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐	☐	☐
Weakness	☐	☐	☐	☐	☐	☐	☐
Memory loss	☐	☐	☐	☐	☐	☐	☐
Agitation	☐	☐	☐	☐	☐	☐	☐
Hallucinations	☐	☐	☐	☐	☐	☐	☐
Jaw pain	☐	☐	☐	☐	☐	☐	☐
Nightmares	☐	☐	☐	☐	☐	☐	☐

Other:_____ ☐ ☐ ☐ ☐ ☐ ☐ ☐

The following items refer to your experience throughout the entire study. Please rate how well you agree with each statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
2. I was satisfied with my care.	☐	☐	☐	☐	☐
3. Overall, I felt comfortable throughout the study.	☐	☐	☐	☐	☐
4. I learned about consciousness and cognition by participating.	☐	☐	☐	☐	☐
5. I was well compensated for this study.	☐	☐	☐	☐	☐
6. I am satisfied with my interactions with the study team.	☐	☐	☐	☐	☐
7. I would participate in this study again.	☐	☐	☐	☐	☐
8. My condition improved after completing the treatments.	☐	☐	☐	☐	☐

9. What was the most physically uncomfortable or distressing part of the study?
    - ☐ Consent
    - ☐ Screening questionnaires (performed in the days or weeks before treatment)
    - ☐ EEG cap
    - ☐ Morning before treatment
    - ☐ Recovery from treatment
      If yes, please indicate which (check all that apply):
        - ☐ 1st
        - ☐ 2nd
        - ☐ 3rd
        - ☐ 4th
        - ☐ 5th
        - ☐ 6th
    - ☐ No period was particular uncomfortable or distressing
    - ☐ Other: _____

10. How physically uncomfortable or distressing was the experience selected in the previous question?
    - ☐ Extremely
    - ☐ A lot
    - ☐ A little
    - ☐ Not very
    - ☐ N/A

11. What did the study team do well?

    _____

    _____

12. Which aspects could the study team improve?

    _____

    _____

13. Additional comments:

    _____

    _____

    _____

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