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Investigating the impact of electroconvulsive therapy on brain networks and sleep: an observational study protocol

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ABSTRACT

Introduction Electroconvulsive therapy (ECT) is a highly effective treatment for refractory depression, but it may also cause cognitive side effects. Despite decades of use, the mechanisms by which ECT exerts both its antidepressant and cognitive effects are still poorly understood, with the latter substantially limiting referral and adherence to therapy. ECT induces changes in correlated neural activity—functional connectivity—across various brain networks, which may underlie both its clinical efficacy and associated cognitive side effects. Electroencephalography (EEG) could address these knowledge gaps by identifying biomarkers that predict therapeutic outcomes or cognitive side effects. Such developments could ultimately improve patient selection and adherence. Such markers likely span large-scale functional brain networks or temporal dynamics of brain activity during sleep. We hypothesise that enhancement in slow wave sleep mediates the relationship between antidepressant effects and changes in functional connectivity throughout the course of ECT.

Methods and analysis Disruptions of Brain Networks and Sleep by Electroconvulsive Therapy (DNS-ECT) is an ongoing observational study investigating the impact of ECT on large-scale brain functional networks and their relationships to sleep slow waves, an EEG marker linked to synaptic plasticity. The novelty of this study stems from our focus on the assessment of EEG markers during sleep, wakefulness and ECT-induced seizures over the course of therapy. Graph-based network analyses of high-density EEG signals allow characterisation of functional networks locally in specific subnetworks and globally over large-scale functional networks. Longitudinal assessments of EEG alongside clinical and cognitive outcomes provide a unique opportunity to improve our understanding of the circuit mechanisms underlying the development of cognitive impairments and antidepressant effects incurred during ECT.

Ethics and dissemination Recruitment for this 5-year study started in March 2023. Dissemination plans include presentations at scientific conferences and peer-reviewed publications. This study has been registered with ClinicalTrials.gov registry under identifier.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Wireless wearable devices will address previous barriers to the longitudinal study of sleep microstructure in patients undergoing a course of electroconvulsive therapy (ECT).
⇒ High-density electroencephalography will allow capturing of the temporal dynamics of brain activity during wakefulness, and ECT-induced seizures.
⇒ Graph-based analysis will allow characterisation of segregation and integration of information in brain networks over the course of ECT.
⇒ A web-based cognitive battery using the Oxford Cognitive Testing Portal will be administered to assess a variety of cognitive domains, with a focus on working and episodic memory.
⇒ The study is observational in nature and lacks a control group, which may limit the ability to draw causal conclusions.

Trial registration number NCT05905705.

INTRODUCTION

Electroconvulsive therapy (ECT): highly effective but poorly understood

Depression is one of the world's most destructive illnesses and a significant cause of death due to elevated rates of medical comorbidities and suicide.[1–3] With a lifetime prevalence of 21%, this disorder accounts for more disability than any other illness.[1 3–5]

Across a variety of indications, approximately 1.4 million individuals receive ECT globally each year.[6] ECT is an effective treatment for refractory depression in patient who have not responded to multiple interventions. It is also recommended intervention for individuals with persistent suicidal ideation or significant weight loss due to severe depression. ECT is usually administered two to three times a week and continued until remission is

achieved or the clinical response reaches a plateau. Up to 70% of patients respond to a course of ECT.[7–9] Despite its efficacy, ECT is often limited by significant concerns about cognitive side effects, shared by patients,[10] providers[11] and the public.[12] A better understanding of ECT's effect on brain function could help optimise treatment protocols to mitigate cognitive side effects, thereby enhancing acceptance among patients and providers.[13 14]

ECT-associated cognitive side effects include both short- and longer-term cognitive impairments. Short-term memory impact is common and relatively well documented, while the effect on longer-term memory is believed to be less frequent but remains less studied.[15 16] Nonetheless, these side effects can be highly distressing for patients, often influencing the decision to continue treatment based on the trade-off between benefits and cognitive side effects. While ECT requires the induction of generalised seizures by applying an electrical current through the scalp, postictal agitation and confusion can emerge in 7–36% of patients.[17 18] Cognitive side effects, particularly memory loss, remain a concern for patients undergoing ECT[10 19] and contribute to its associated stigma,[20] with estimated incidence rates ranging from 5% to 55%.[21 22] The mechanisms by which ECT alters cognition are poorly understood. There is no cellular evidence of brain damage following ECT.[13 23] Instead, several neuroimaging studies posited that changes in neural functional connectivity across various brain networks induced by ECT are closely linked to both its effectiveness in alleviating depressive symptoms[24] and impairments in cognitive performance.[25] Changes in the functional connectivity within the hippocampus, as well as salience and default mode networks, have been associated with cognitive side effects of ECT.[26–30] Overall neuroimaging research findings have contributed to advance mechanistic understanding of ECT; however, the specific roles of various brain regions in its cognitive side effects remain unclear.[13] Moreover, MRI-based approaches are suboptimal due to their high cost, limited accessibility in clinical practice and challenges in capturing dynamic brain activity during ECT in real time. These issues highlight the need for a reliable and accessible biomarker that can predict both treatment response and the risk of cognitive side effects, paving the way for more individualised and safer therapeutic approaches.

Electroencephalography (EEG) is a useful and accessible tool for identifying clinical biomarkers and uncovering underlying circuit mechanisms involved in ECT efficacy and side effects. During routine ECT treatment, one to two EEG signals are used to monitor the initiation, expression and termination of seizures,[31] but are insufficient for a detailed characterisation of brain networks during ictal and postictal periods.[32 33] These ictal and postictal EEG signatures may serve as possible biomarkers of clinical response or underlying mechanisms of action.[34 35] Ictal central-positive complexes (CPCs) are generalised high-amplitude ictal waveforms with maximum positive voltage over the vertex that are consistently present during ictal periods across participants, stimulus charge, time and anaesthetic agent.[36] In addition, low voltage (<10 mcV) postictal encephalographic electrical suppression (PGES)[33 37 38] has often been shown to predict antidepressant response.[39] While these EEG markers are not being used in clinical practice, advanced analyses of ictal and postictal signatures hold significant potential.

Disruption of sleep structure over the course of ECT

Sleep is a complex physiological process necessary for the entire organism and its functioning during wakefulness.[40] Poor quality sleep has long been associated with depression,[41] as sleep disturbance is present in up to 90% of those undergoing treatment for depression.[42] Characteristic sleep changes such as an increase in sleep onset latency, wakefulness during sleep and a decrease in total sleep time and sleep efficiency are associated with depressive symptoms.[43]

Sleep architecture is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) stages N1–N3. Sleep slow waves are large-amplitude, spontaneous low-frequency EEG oscillations, with predominance during NREM stage N3/slow wave sleep (figure 1A). The EEG power of these slow oscilations in the 0.5–4 Hz frequency band is often calculated as the sleep slow wave activity (SWA). SWA provides an important measure of homeostatic regulation of synaptic plasticity[44–46] and it is linked to physiologic recovery, declarative memory consolidation and processes regulating cortical plasticity.[47–49] Besides, slow wave oscillations provide a putative basis for information processing and transfer within thalamocortical circuits, and overactivation of these oscillations has been posited to facilitate dysfunctional negative biased thoughts.[50] Deficits of slow wave sleep are associated with worsened mood in healthy adults without depression.[51 52] Consistent with these findings is an observation of lower SWA individuals with depression compared with those without depression.[53] Hence, changes in SWA could serve as a valuable biomarker in depressed individuals undergoing ECT. SWA could enable tracking the extent of cortical reorganisation over the course of ECT, offering insight into the treatment's impact on synaptic plasticity, clinical improvement and cognitive side effects.

Sleep and wakefulness are regulated by homeostatic processes in humans and animals.[44 53–55] EEG data recorded during wakefulness can facilitate the identification of additional biological markers of sleep propensity.[44 53 55] Specifically, EEG theta activity during wakefulness is associated with sleep SWA in healthy individuals.[44 53] Absence of this association was observed in dysregulated sleep-wake homeostasis in individuals with depression.[53] Theta activity in the frontal cortex has also been associated with cognitive control demands[56] and has shown to be decreased in depressed individuals.[57–59] Increased theta activity in the frontal cortex has been correlated with the efficacy of ECT,[60] suggesting that this could be a factor in depressive symptom improvement. The impact of ECT on sleep-wake dysregulation in individuals with depression

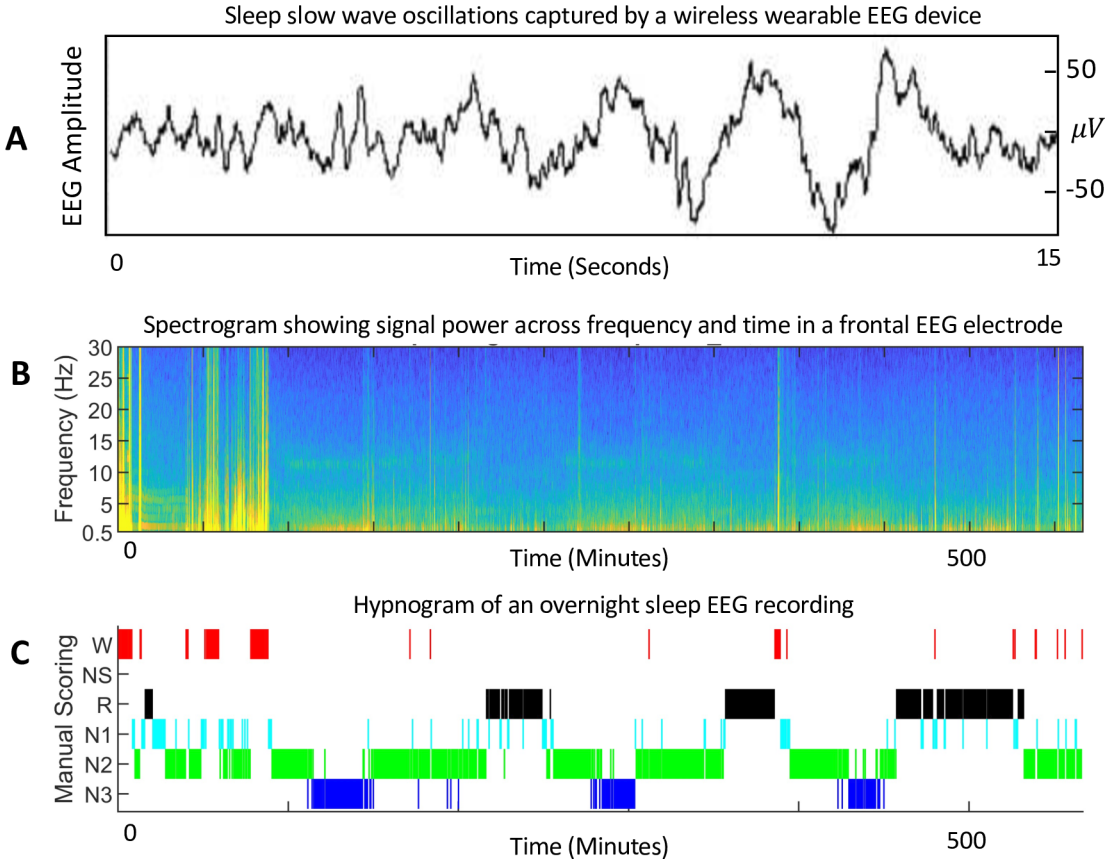

Figure 1 Unattended at-home sleep studies in patients undergoing electroconvulsive therapy. (**A**) Slow waves captured by a wearable consumer-grade headband continuously records electroencephalography (EEG) during overnight sleep without on-site staff. The frontal EEG channels are sufficient to allow quantitation of sleep slow wave activity. (**B**) The spectrogram of the frontal EEG data displaying frequency contents over time. Slow waves have EEG power in the 0.5–4 Hz during N3. (C) A hypnogram demonstrating different sleep stages. W, wakefulness; NS, non-scorable; R, REM; N1–N3, NREM stages 1–3.

has not yet been studied over the course of therapy or in the context of information transfer within functional brain networks. This study provides a unique opportunity to investigate the relationship between sleep and wakefulness EEG markers, offering a deeper understanding of how ECT may influence sleep-wake regulation and its disruption in individuals with depression.

Sleep changes induced by seizures may give valuable information to the underlying mechanisms of ECT, but these changes remain poorly characterised. Prior studies comparing REM sleep measures before and after a completed course of ECT have shown mainly a reduction in total REM duration, decreased REM latency and increased REM density.[61–63] In comparison, generalised seizures in individuals with epilepsy are associated with an increase in N2 sleep[64 65] and a decrease in slow wave sleep.[66] Changes in slow wave sleep over the course of ECT remain an area of interest for further investigation. The Disruptions of Brain Networks and Sleep by Electroconvulsive Therapy (DNS-ECT) study builds upon our recent work,[67] aiming to address a gap in the field regarding how functional networks during wakefulness and ECT-induced seizures are influenced by changes in sleep throughout treatment. Insights from this investigation could enhance our understanding of the neural circuit mechanisms involved in the development of cognitive impairments and the antidepressant effects associated with ECT.

Graph-based analysis to characterise segregation and integration of information in brain networks over the course of ECT

High-density EEG captures the temporal dynamics of distributed brain activity during ECT-induced seizures and enables characterisation of large-scale functional networks during different arousal states (figure 2A, B).[68] Using this approach, coherence can be computed as a measure of communication efficiency between neural populations (figure 2C).[69] During different states of arousal, the rich dimensionality of the data can provide critical information about large-scale functional brain networks in different frequency bands. ECT alters neural connectivity within large-scale functional networks,[70 71] including frontotemporal subnetworks.[72] Quantification of the network alterations could lend insight into mechanisms for both ECT's antidepressant effects and cognitive side effects.

Graph-based network analyses model the brain as a complex set of connected nodes, allowing quantification of segregation and integration across large-scale brain

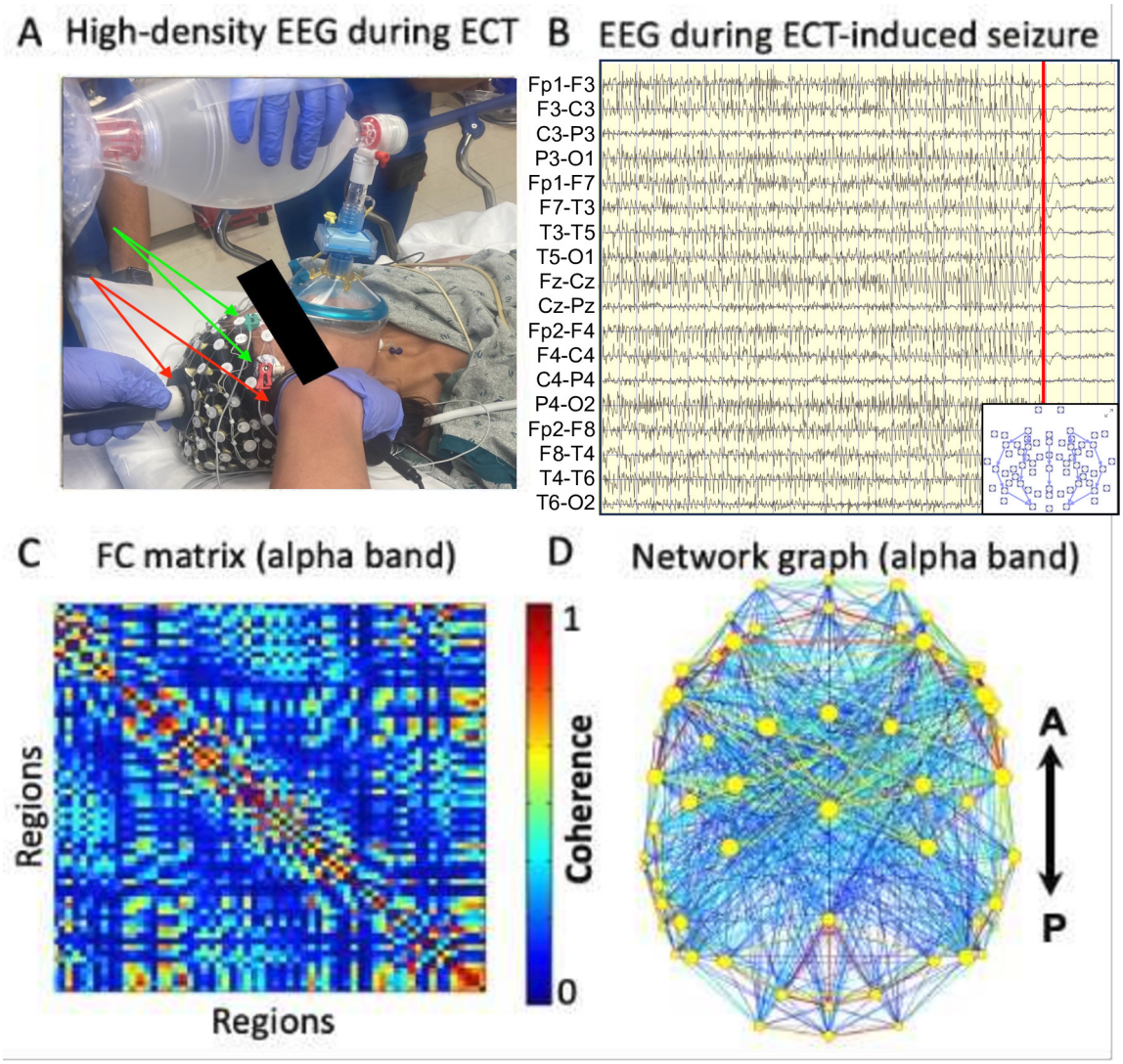

Figure 2 Functional network measures extracted from high-density electroencephalography (EEG) data. (**A**) 64-channel EEG net to record before and immediately following stimulus delivery by paddles (yellow asterisks) during session of right unilateral electroconvulsive therapy (ECT).[18] (**B**) High-density EEG data during ECT-induced seizure based on double banana montage.[19] The red vertical line represents seizure termination in this 30 s EEG data visualisation with an amplitude scale of 20 µV/mm, a high-frequency filter 70 Hz and a low-frequency filter 1 Hz. The sensor layout of the visualised EEG montage is shown in the inset plot at the bottom right. C, central; F, frontal; O, occipital; P, parietal; T, temporal. (**C**) Functional connectivity (FC) matrix using an alpha band (8–13 Hz) coherence measure derived from high-density EEG data from an ECT-induced seizure. (**D**) Network graph associated with FC matrix in panel (**C**). The size of each node represents the strength of that node computed by summing up its weights. A, anterior; P, posterior.

networks (figure 2D). Local efficiency (Elocal) quantifies information segregation and characterises within-network communication, while global efficiency (Eglobal) measures the efficiency of information integration transfer among all network node pairings.[73] Elocal and Eglobal imbalances in specific frequency bands provide insight into neuropsychiatric pathology. For example, Elocal is reduced in awake individuals with depression,[74] and Eglobal has been shown to be a critical measure for general cognitive impairment,[75–77] and in dementia.[78] These measures provide powerful tools to characterise the abnormalities in the organisation of brain networks in different pathological conditions (eg, schizophrenia and Alzheimer's disease). Such characterisation could be instrumental in identifying biomarkers related to ECT's effects on brain network efficiency, providing valuable insights into its therapeutic mechanisms and impact on cognition.

Objectives and specific aims

The study's primary aim is to develop biomarkers that can predict development of cognitive impairments and antidepressant effects caused by ECT (table 1). The study will leverage longitudinal assessments of clinical and cognitive outcomes alongside EEG measurements to accomplish three aims listed as follows:

Aim 1: Assess relationships between sleep SWA and awake Elocal over the course of ECT. Our hypothesis is

Table 1 Primary, secondary and tertiary outcomes of the Disruptions of Brain Networks and Sleep by Electroconvulsive Therapy study

Endpoints	Outcomes	Measures
Primary	Sleep microstructure	Sleep slow wave activity during N3, and as a secondary analysis during N2 and N3
	Depression severity	16-Item Quick Inventory of Depressive Symptomatology-Self Report
	Graph-based network measures of high-density EEG data	Theta Elocal during eyes-closed wakefulness Alpha Eglobal during ECT-induced seizures
	Cognitive performance assessments (conducted using OCTAL)	Oxford Memory Test Object-in-Scene Memory Task
Secondary	Depression severity	Montgomery-Asberg Depression Rating Scale
	Cognitive ability	Montreal Cognitive Assessments ElectroConvulsive therapy Cognitive Assessment
Tertiary	Suicidality	Columbia-Suicide Severity Rating Scale
	Circadian rhythms	Morningness-Eveningness Questionnaire
	Motivation	Apathy Motivation Index
	Sleep quality	Insomnia Severity Index Pittsburg Sleep Quality Index
	Cognitive performance assessments (conducted using OCTAL)	Digit Symbol Substitution Test Trail-Making Task Reaction Time Testing Verbal Learning Memory

N2, non-REM stage 2; N3, non-REM stage 3; OCTAL, Oxford Cognitive Testing Portal; REM, rapid eye movement.

that ECT will augment sleep SWA and promote theta band Elocal in frontotemporal subnetworks during wakefulness. We expect changes in sleep SWA to predict changes in awake Elocal over the course of therapy.

Aim 2: Quantify relationships between depression severity and awake Elocal over the course of ECT. We hypothesise that theta band Elocal in frontotemporal subnetworks during wakefulness will predict decrease in depression severity throughout ECT course.

Exploratory Aim 3: Characterise relationships between memory and alpha band Eglobal measured during ECT-induced seizures over the course of ECT. We expect changes alpha band Eglobal during seizures will predict changes in memory performance measures.

METHODS AND ANALYSIS

Study design

DNS-ECT is a single-centre, prospective, longitudinal, observational study (ClinicalTrials.gov: NCT05905705). The study overview and timeline are illustrated in figure 3A, B. ECT is administered using a dose-titration paradigm. The treating psychiatrist will use seizure threshold and treatment response among other factors to determine stimulus placement, charge and number of treatments in the course. High-density EEG data will be recorded before each ECT session during a period of wakefulness and then during treatment from stimulus onset until return of consciousness. Because sleep measures on nights following ECT could be affected by general anaesthesia, sleep data will primarily be acquired on nights prior to ECT sessions with an at-home wireless EEG device. Cognitive data will be collected using the Oxford Cognitive Testing Portal (OCTAL, available at https://octalportal.com; figure 4A, B) at a consistent time every week to ensure adequate data collection and quality. This manuscript is based on the most recent approved protocol (version dated 13 December 2024).

Study participants

Inclusion and exclusion criteria

The inclusion criteria in this study include inpatients and outpatients aged 21–65 years who are newly refered to receive ECT for major depressive disorder or bipolar depression. Exclusion criteria for this study are a diagnosis of schizophrenia, schizoaffective disorders and inability to tolerate at-home sleep EEG device for sleep recordings.

Study recruitment and retention

Potential participants will be identified after referral for ECT at a tertiary academic centre Barnes-Jewish Hospital in St. Louis. 50 participants will be recruited in the study. Participants will be consented to study prior to initiating treatments on a voluntary basis and they may withdraw at any time. The research team may also withdraw participants for significant non-compliance with study procedures. Patients are compensated up to $600 based on the number of study procedures completed. Once enrolled, study participants will be assigned a study ID to protect

A

DNS-ECT Study Goals: (a) Assess relationships between sleep SWA and awake theta Elocal in the frontotemporal subnetwork (b) Quantify relationships between depression severity and awake Elocal (c) Assess relationship between memory and alpha band Eglobal measured during ECT-induced seizures over the course of ECT.	
Rationale: Biomarkers found during sleep, treatment, and in the patient's cognitive abilities early on in treatment may predict patient outcomes and shape individualized treatment plans.	
Inclusion Criteria: a) Unipolar or bipolar depression b) 21 to 65 years old c) Starting treatment for ECT	Exclusion Criteria: a) Schizophrenia b) Schizoaffective disorders c) Inability to tolerate at-home EEG device

B

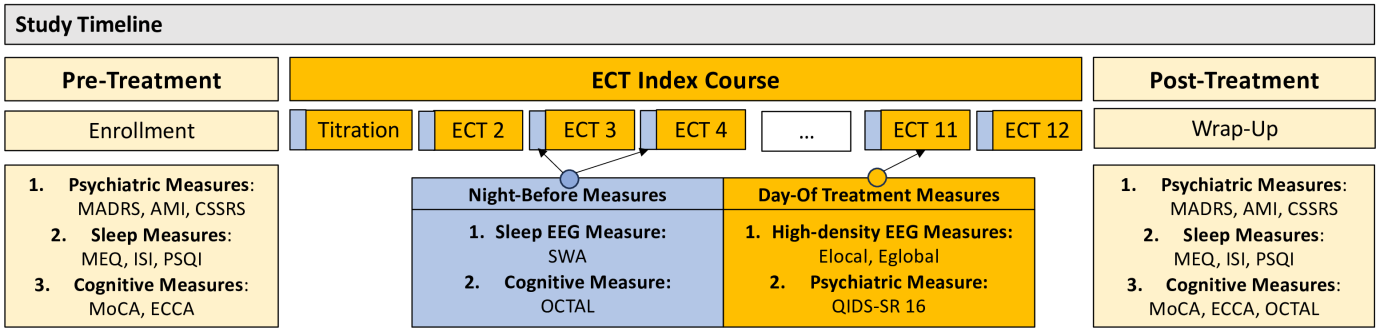

Figure 3 Study overview and timeline. (**A**) Overview of study goals, rational, inclusion and exclusion criteria. (**B**) Study timeline showing study measures collected across timepoints. AMI, Apathy Motivation Index; CSSRS, Columbia-Suicide Severity Rating Scale; ECCA, Electroconvulsive Cognitive Assessment; Eglobal, global efficiency; Elocal, local efficiency; ISI, Insomnia Severity Index; MADRS, Montgomery–Åsberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; MoCA, Montreal Cognitive Assessment; OCTAL, Oxford Cognitive Testing Portal; PSQI, Pittsburgh Sleep Quality Index; QIDS-SR 16, 16-Item Quick Inventory of Depressive Symptomatology-Self Report.

the confidentiality of personal health information. The study protocol has been approved by the Institutional Review Board (IRB) at Washington University (IRB Number: 202204161). Participant recruitment began in March 2023 and will conclude by July 2027.

ECT procedure

ECT will be conducted at a dedicated ECT suite at Barnes-Jewish Hospital using the following standard-of-care clinical protocols. Three stimulation approaches are offered, including right unilateral (RUL, right temple and vertex), bilateral (BL, right and left temple) and bifrontal (BF, bilateral forehead directly 5 cm above the eye's outer canthus). Patients typically begin with RUL ECT but depending on clinical needs they can be switched to BL ECT if response is insufficient as determind by the clinical ECT team. BF ECT is typically used to decrease cognitive side effects associated with bilateral treatments. Treatments will typically occur three times a week but can also be reduced to twice a week to reduce cognitive side effects.

Before an ECT treatment, a high-density EEG electrode cap will be placed on the head to acquire wakefulness resting-state EEG data. Participants will then be transported to a preprocedural area in the ECT suite, where they get prepared and wait until being taken to the procedure room for general anaesthesia. Anaesthetic agent will be chosen by the treating anaesthesiologist, with input from the treating psychiatrist; protocol typically uses etomidate 0.2 mg/kg, methohexital 1 mg/kg or ketamine 1.5 mg/kg. Standard American Society of Anesthesiologists safety monitoring is used according to standard clinical care.

The ECT current will be administered using the Thymatron System IV according to standard clinical practice. Initial treatment charge will be determined by a standard method of first establishing a seizure threshold for that electrode placement. Individuals who are starting with RUL ECT titration will receive 5% charge (0.3 ms pulse width, 40 Hz frequency). The charge will be increased incrementally until a seizure is observed according to motor signs or EEG recordings. For the subsequent RUL ECT session, the charge will be set at six times the titration level. Bilateral ECT titration begins at 10% charge (1.0 ms pulse width and 30 Hz frequency); once seizure threshold is determined, bilateral treatments occur at double the titration charge. With each electrode placement (RUL, BL or BF), treatment charge may also be increased to 100% if antidepressant response is insufficient. Individuals will recover in a post-procedure space when determined by the treating anaesthesiologist to have regained consciousness and are stable to leave the procedure room. They will continue to be monitored until they are stable for discharge to their home or going back to to the inpatient ward.

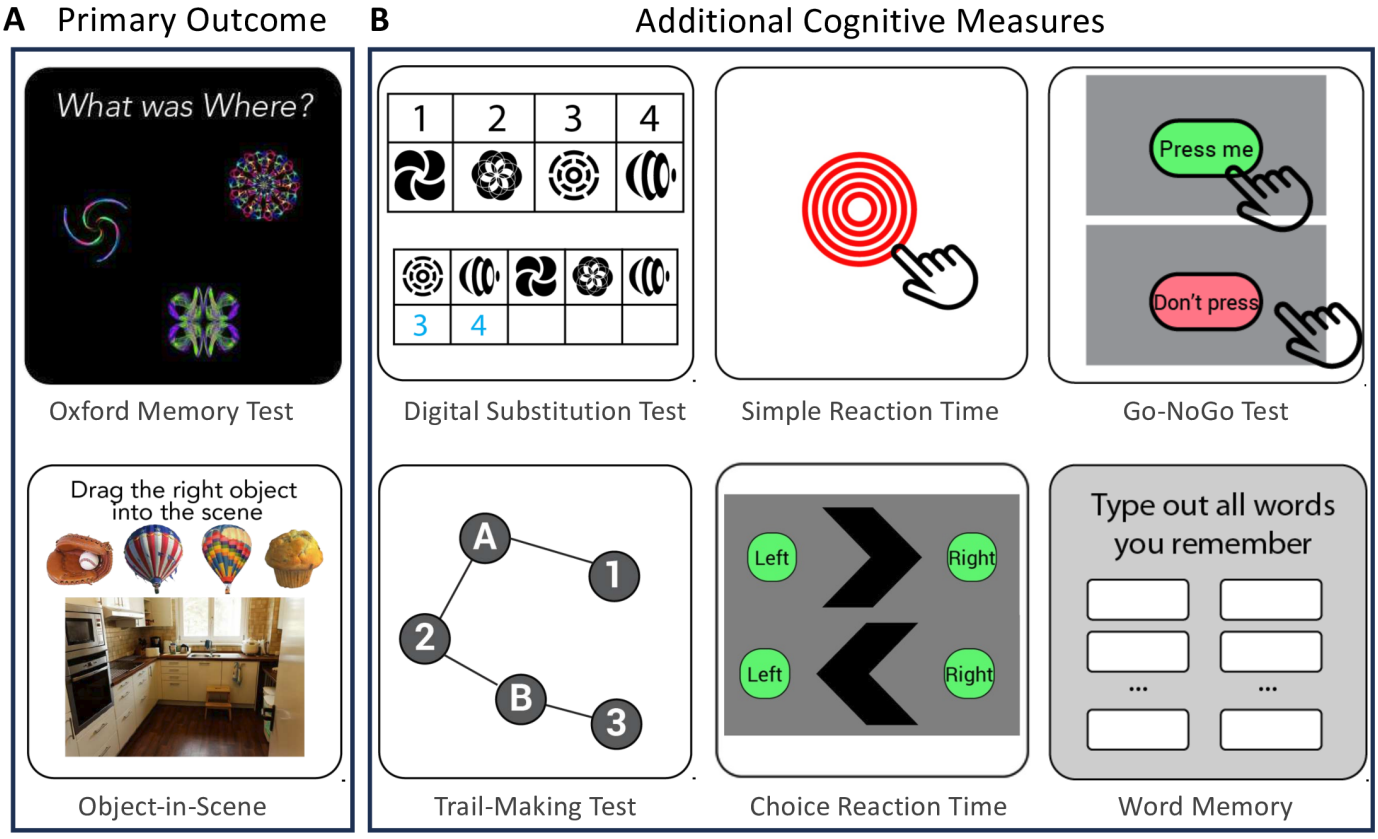

Figure 4 Cognitive assessment using Oxford Cognitive Testing Portal (OCTAL). (**A**) The Oxford memory test (OMT) and object-in-scene (OIS) test are assessments of working and episodic memory and the primary memory outcomes used in this study. (**B**) Additional cognitive assessments gathered as part of the OCTAL include the digital substitution test (DSST), trail-making task (TMT), simple reaction time (SRT), choice reaction time (CRT), Go-NoGo task (GNT), and word list free memory task (WFRM). These measures be used as teritiary outcome for secondary analyses. Cognitive tasks from OCTAL are available at https://octalportal.com/.

Data collection

Overnight sleep EEG recording using wireless wearable devices

Home sleep testing will be used to minimise intrusiveness and maximise data collection. We will employ advanced wireless wearable devices to acquire sleep recordings[79–81] of multilead frontal EEG data. These devices adequately detect sleep slow waves with a single night sufficient for establishing baseline sleep macrostructure.[79] Scoring of these data to multiple cycles of REM and NREM sleep stages N1–N3 is standardised through microstructural elements with different frequency profiles over time (figure 1B, C).

High-density EEG recording

64-channel sponge-based HydroCel Geodesic Sensor Nets (GSN) caps (Magstim, Eden Prairie, Minnesota, USA) will be used to acquire high-density EEG data. These caps will be modified to allow appropriate placement of ECT stimulation electrodes, while allowing acquisition and characterisation of high-density EEG data during ECT-induced ictal and postictal periods.[33 36 37 67 82 83] Modified electrodes (GSN E1, E4, and E54) will be flagged as bad channels in the preprocessing pipeline to be excluded from analysis. A saline solution using Potassium Chloride (KCL) will be applied to the EEG caps in order to keep electrode impedances less than 100 kΩ per EEG sensor. We will acquire video using a network camera (Axis P3364LV, Axis Communications, Lund, Sweden) that will be synchronised to EEG recordings to evaluate compliance and movement. Immediately prior to ECT sessions, 10 min of resting wakefulness EEG with both eyes open and eyes closed will be acquired. In the ECT procedure room, EEG data will be recorded continuously from ECT stimulation until they regain consciousness.

Psychiatric and mood assessments

The 16-Item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) will be used to rate depression symptom severity. QIDS-SR16 questionnaire assesses nine categories of depressive symptoms including sleep quality, depressed affect, weight and eating changes, concentration, self-image, suicidal ideation, anhedonia, energy level and psychomotor agitation.[84] The Montgomery-Asberg Depression Rating Scale (MADRS), a clinician administered clinical assessment tool for severity of depression symptoms,[85 86] will be collected on a weekly basis. A trained staff member will conduct the interview, score the assessment and address any care-related issues that arise to ensure participant safety. Apathy Motivation Index (AMI) test (a self-report

for patients and an objective report for caregivers) will be administered at the baseline and again within a week after the last study visit.[87] An optional questionnaire for assessing suicidality using Columbia-Suicide Severity Rating Scale (CSSRS)[88] will be completed at the baseline and within a week after the last study visit.

Sleep assessments

Pittsburgh Sleep Quality Index (PSQI)[89] will be used to evaluate subjective quality of sleep at the baseline and within a week after the last study visit. Insomnia Severity Index (ISI)[90] will be used to assess the severity of sleep problems completed at the baseline and within a week after the last study visit. The Morningness-Eveningness Questionnaire (MEQ)[91] will be used to assess the circadian peak of an individual's alertness and energy completed at enrolment and within a week after the last study visit. A daily sleep diary throughout the study period will be maintained by study participants to allow confirmation of bedtimes.

Cognitive assessments

The Montreal Cognitive Assessment (MoCA)[92] will be administered at the enrolment visit and again within a week after the last study visit to screen for global changes in cognition after course of the study. Additionally, the ElectroConvulsive therapy Cognitive Assessment (ECCA)[93] will be administered to patients to monitor cognitive side effects associated with ECT. Caregivers will complete informant sheets included within the ECCA to provide additional insight into cognitive changes. Both the patient and caregiver assessments will be conducted at three time points: prior to the first, before the sixth session and following the final ECT session.

For a more granular tracking of cognitive trajectories, a cognitive battery using OCTAL (https://octalportal.com, figure 4A, B) will be administered to assess a variety of cognitive domains, with a focus on working and episodic memory. Participants will take the test up to twice prior to their treatment start date, once a week during treatment course and once within a week after their last study visit. Outpatients are requested to use a desktop computer or laptop to complete the cognition battery at home. For inpatients, a laptop is provided, and the battery is administered in a designated study room within the inpatient unit. The cognition battery is compatible with Google Chrome, Firefox and Safari browsers. To maximise consistency in alertness and ability, participants will be encouraged to standardise time of testing. Working and episodic memory domains will be assessed using Oxford Memory Test (OMT) and Object-in-Scene Memory Task (OIS), respectively.[94]

In the OMT (figure 4A), participants are shown and asked to remember either one or three fractal patterns presented for 3 s before proceeding in three testing phases. After a 4 s delay, one of these fractal patterns will be shown alongside a foil pattern. Participants must recall the correct pattern and move it to its original location. In an acclimatisation phase, participants undergo six initial trials, three with three items and three with one item. Finally, participants are then asked to start the main test consisting of 40 total trials, 20 trials of one item and 20 trials of three items. Location on the screen, trail order and fractal patterns are all randomised to reduce recognisability, requiring approximately 196 fractal pattern options.[94] This task allows us to quantify eight different cognitive metrics including the following: (1) identification accuracy: proportion of correct identification; (2) identification time: reaction time for target identification; (3) location error: distance between target and response; (4) localisation time: reaction time to place object; (5) target detection: rate of detecting correct object and placing at target location; (6) miss-binding: rate of placing target at a non-target location; (7) imprecision: special precision of the response; (8) guessing: rate of random placement of target.

In the OIS (figure 4A), participants are initially prompted with the picture of a general scene (such as kitchen, meadow, mountain range) then shown a picture of an ordinary object (including baseball, muffin, toy). They are then shown the picture with the object superimposed and are asked to click on the object. Upon clicking, the object will disappear, and the participant will have a group of 20 objects to choose from to pick the right object and move it back to its precise location. After going through five different object-scene scenarios, the patient is then only shown the scenes and are asked to place the original object in each scene. Tests contain 20 total trials distributed randomly in four groups of five in order to quantify the participant's recall and spatial localisation accuracy along with short- and long-term memory retention.[94] Each object contained in the group has a similar counterpart designed to stop the participant from associating the object's name with each individual scene.[94] Three cognitive measures will be computed from OIS including the following: (1) object identification accuracy: proportion of trials in which participants correctly identified the original object with a chance level of 5%; (2) location error: the distance in centimetre from the original target item location to the centre of participant's response location; (3) semantic identification accuracy: proportion of objects correctly recalled as belonging to the same semantic category as the target with a chancel level of 10%.

The OCTAL cognition battery contains additional tasks to assesses executive function, visual attention, cognitive flexibility and psychomotor speed (figure 4B). These tasks include the Wordlist Free Recall Memory Task (WFRMT), Digit Symbol Substitution Test (DSST), Trial-Making Task (TMT), Simple Reaction Time (SRT), Choice Reaction Time (CRT) and the Go-NoGo task (GNT). Additional information about these tasks can be found in the online supplemental materials.

Data analysis

Manual sleep scoring

Sleep EEG recordings will be imported and preprocessed using EEGLAB and custom MATLAB (MathWorks, Natick, Massachusetts, USA) scripts.[95] EEG signals will be 0.5–50 Hz bandpass filtered and resampled to 250 Hz. Preprocessed EEG signals will be exported in European Data Format (EDF) for subsequent sleep scoring using specialised sleep software. Our sleep technologists are certified by American Academy of Sleep Medicine (AASM) and have scored greater than 90% agreement on assessments through the AASM interscorer reliability programme. They will stage sleep in 30 s epochs using Philips Respironics Sleepware G3 Software and modified AASM scoring rules developed for use on single frontal EEG channel recordings.[80 96]

Sleep SWA analysis

Sleep EEG data will undergo 0.1–50 Hz bandpass filtering using EEGLAB.[95] A band-stop filter between 0.1 and 0.6 Hz will remove the respiratory artefact. Spectral analyses will be performed in 5 s non-overlapping time windows using the Chronux toolbox[97] with a time-bandwidth product of three and five tapers. We will exclude 5 s windows with a maximum absolute EEG value of larger than 250 µV. Sleep SWA will be computed as the average of 0.5–4 Hz EEG power per minute during N3 sleep. As a secondary analysis, we will calculate SWA during N2 and N3 combined.

High-density EEG data preprocessing

To prepare the high-density EEG data for analysis, several preprocessing steps will be applied. EEG signals will be bandpass filtered between 1 and 70 Hz to eliminate low-frequency drift and high-frequency artefacts. A 60 Hz notch filter will be applied to remove line noise. To reduce data size, signals will be downsampled from 500 Hz to 250 Hz. EEG channels exhibiting excessive noise will be identified and rejected through visual inspection and an automated algorithm. The automatic continuous channel rejection function in EEGLAB will be used to reject channels with amplitudes exceeding five SD above the mean of the probability distribution. Rejected channels will be subsequently interpolated using spherical spline interpolation from neighbouring electrodes. Following re-referencing to the average signal, EEG data then will be used to define network nodes at the sensor level.

Quantification of theta Elocal during eyes-closed wakefulness

Five minutes of visually assessed continuous high-density EEG data acquired during eyes-closed resting wakefulness will be selected for quantification of awake theta Elocal in the frontotemporal subnetwork. Functional connectivity between different nodes will be evaluated based on coherence measures, as a function of frequency using Chronux toolbox in MATLAB.[98] Results will then be averaged across theta frequency band (4–8 Hz) to generate connectivity matrices per 5 min recording. The Minimum Connected Component (MCC) technique will be used to binarised the connectivity matrix[99] without the need to specify a fixed threshold. Custom-written scripts, alongside Brain Connectivity Toolbox (BCT)[100] in MATLAB, will be used to quantify Elocal:[101]

$$E_{local} = \frac{1}{n}\sum_{i\in F}\frac{\sum_{j,h\in F, j\neq i} a_{ij}a_{ih}[d_{jh}(F_i)]^{-1}}{k_i(k_i-1)},\ k_i = \sum_{j\in F} a_{ij},$$

where F is the set of all nodes in frontotemporal subnetworks and n is the number of nodes. In addition, a_{ij}=1 if there exists a connection between nodes i and j, otherwise a_{ij}=0. $d_{jh}(F_i)$ is the shortest path length between nodes j and h that only contains neighbours of node i. Node degree, k_i, is the number of links connected to node i.

Quantification of alpha Eglobal during ECT-induced seizures

High-density EEG data of ECT-induced seizures alongside synced recorded video will be rated by neurologists to identify start and termination of phase III seizures (emergence of CPCs).[32] EEG data during phase III seizure periods will then be used to estimate functional connectivity within the alpha frequency band (8–13 Hz) in frontotemporal networks. Binarised connectivity matrix, processed as outlined in previous section, will be used to quantify Eglobal;[101]

$$E_{global} = \frac{1}{n}\sum_{i\in F}\frac{\sum_{j\in F, j\neq i} d_{ij}^{-1}}{n-1},$$

where d_{ij} is the shortest path length between nodes i and j.[100]

Statistical analysis

Linear mixed-effects models will be employed to account for missing data rather than data imputation or deletion. Models will be generated in MATLAB. To characterise the relationship between Elocal and SWA over the course of ECT for Aim 1, linear mixed-effects models will be constructed using SWA (independent variable), Elocal (dependent variable) and treatment number (covariate), accounting for age and sex (moderators). Similarly, to characterise the relationship between Elocal and treatment response in Aim 2, linear mixed-effects models will be constructed using Elocal (independent variable), QIDS score (dependent variable), and treatment number and SWA (covariates), with same moderators as in Aim 1. Finally, for Aim 3, separate mixed-effects models will be constructed for each memory task, including Eglobal (independent variable), individual score in each memory task (dependent variable), and treatment number and SWA (covariates), with the same moderators as in Aim 1.

Sample size calculations are based on published and preliminary data, following conventions for statistical power analysis in the behavioural sciences.[102] Previous studies have used 17–30 participants to detect changes in SWA.[53 103 104] Prior studies investigating changes in Elocal

and Eglobal after full course of ECT have used 22–23[72 105] participants. With an estimated partial η^2 value ranging from 0.05 to 0.1, sample sizes of 24–40 (power of 0.8, α of 0.05) are needed, based on a conservative assumption on the number of treatments (nine treatments) to account for missing a session or poor quality of EEG data. A sample size of 50 was chosen to account for missing data and/or attrition rate (~20%).

Endpoints

Table 1 presents the primary, secondary and tertiary outcomes of the study. Primary outcomes include longitudinal assessments of QIDS, SWA, Elocal during wakefulness and Eglobal during ECT-induced seizures. Secondary outcomes focus on psychiatric measures of mood using MADRS, and cognitive performance assessments with MoCA and ECCA. Tertiary outcomes include motivation assessed through AMI; sleep quality and rhythm evaluations using MEQ, ISI and PSQI; suicidality evaluations using CSSRS; and further cognitive function measures using DSST, TMT, SRT, CRT, GNT and WFRMT (detailed in the online supplemental materials).

Data management

Data will be stored in REDCap and local servers. Physical copies or paper data will be stored behind two locked doors.

Data management and sharing statement

The study team members will ensure that all paper documents are locked in a filing cabinet in a locked office. We will store all electronic documents on secure servers that are password protected and have various state-of-the-art firewall protections with frequent upgrades of these protections. Only members of the research team will have access to study documents, and the access will be controlled regularly by the PI. Data acquired in this study will be deidentified, analysed and stored for use in studies conducted in the future. Deidentified data may be shared with other researchers including those outside of the study. Permission to store and share data will be included in the informed consent.

ETHICS AND DISSEMINATION

The study design was informed by feedback from the National Institute of Mental Health and the Data and Safety Monitoring Board. The Washington University Human Research Protection Office (WU HRPO) approved study design, study procedures and informed consent process. Patients will be promptly informed on any protocol modifications that may alter study procedures or patient safety with any changes being formally amended and approved by the WU HRPO. All patients must undergo an informed consent with a member of the research team prior to administering any questionnaires or conducting any study procedures. This study will be conducted in accordance with the Declaration of Helsinki.

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