BMJ Open

# Protocol for the Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) study: a prospective observational study of delirium in elderly cardiac surgical patients

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**To cite:** Smith SK, Nguyen T, Labonte AK, *et al*. Protocol for the Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) study: a prospective observational study of delirium in elderly cardiac surgical patients. *BMJ Open* 2020;**10**:e044295. doi:10.1136/bmjopen-2020-044295

► Prepublication history and supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-044295).

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Received 31 August 2020
Revised 30 September 2020
Accepted 05 October 2020



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## ABSTRACT

**Introduction** Delirium is a potentially preventable disorder characterised by acute disturbances in attention and cognition with fluctuating severity. Postoperative delirium is associated with prolonged intensive care unit and hospital stay, cognitive decline and mortality. The development of biomarkers for tracking delirium could potentially aid in the early detection, mitigation and assessment of response to interventions. Because sleep disruption has been posited as a contributor to the development of this syndrome, expression of abnormal electroencephalography (EEG) patterns during sleep and wakefulness may be informative. Here we hypothesise that abnormal EEG patterns of sleep and wakefulness may serve as predictive and diagnostic markers for postoperative delirium. Such abnormal EEG patterns would mechanistically link disrupted thalamocortical connectivity to this important clinical syndrome.

**Methods and analysis** P-DROWS-E (Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography) is a 220-patient prospective observational study. Patient eligibility criteria include those who are English-speaking, age 60 years or older and undergoing elective cardiac surgery requiring cardiopulmonary bypass. EEG acquisition will occur 1–2 nights preoperatively, intraoperatively, and up to 7 days postoperatively. Concurrent with EEG recordings, two times per day postoperative Confusion Assessment Method (CAM) evaluations will quantify the presence and severity of delirium. EEG slow wave activity, sleep spindle density and peak frequency of the posterior dominant rhythm will be quantified. Linear mixed-effects models will be used to evaluate the relationships between delirium severity/duration and EEG measures as a function of time.

**Ethics and dissemination** P-DROWS-E is approved by the ethics board at Washington University in St. Louis. Recruitment began in October 2018. Dissemination plans include presentations at scientific conferences, scientific publications and mass media.

**Trial registration number** NCT03291626.

## Strengths and limitations of this study

- ► The Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography study is a prospective observational study conducted in a perioperative patient population burdened with a high incidence of postoperative delirium.
- ► Longitudinal delirium assessments in tandem with electroencephalography (EEG) across diverse states of arousal will provide important insight into patient trajectories throughout the perioperative period.
- ► Coupling serial delirium assessments with structured chart review may improve sensitivity for detecting delirium despite its transient and fluctuating nature.
- ► Wireless wearable EEG recording devices outfitted with dry electrodes allow for data acquisition with minimal interference in patient care; however, sensitivity to motion artefact and patient tolerance may challenge data acquisition and interpretation.
- ► Prolonged postoperative sedation in the intensive care unit may complicate the interpretation of delirium assessments and EEG.

## INTRODUCTION

### Postoperative delirium: a significant clinical problem

Delirium is a potentially preventable disorder with substantial negative impact on perioperative outcomes. Postoperative delirium

is associated with prolonged hospitalisation, persistent functional decline and mortality.[1–6] Moreover, this postoperative problem is part of a larger problem that costs the USA up to $152 billion annually.[7] After major cardiac and non-cardiac surgery, the incidence of delirium in elderly patients is estimated to exceed 25%.[8 9] However, the condition may be underdiagnosed. First, assessment timing and frequency may compromise detection because delirium exhibits a fluctuating course of inattention and disordered cognition. Manifestation peaks within the first two postoperative days, but variance in onset and recurrence impairs detection across individuals.[10 11] Second, without use of sensitive screening instruments, clinicians may underdiagnose the more common hypoactive delirium subtype that arises subtly as disorganised thinking and disengagement.[11–15] Finally, subsyndromal delirium may also be difficult to detect as patients may show signs without fulfilling all diagnostic criteria.[16–18] These cases are clinically impactful and have been targeted for palliative intervention due to associated poor outcomes.[17–22] Despite this, no quantitative biomarkers exist that predict delirium onset, trajectory or severity. Identifying such prognostic markers may help develop preventative or abortive therapies and may elucidate underlying neural mechanisms.

## Perioperative sleep disruption: a potential contributor to delirium

Sleep addresses critical homoeostatic needs for restoring physiological processes such that deficiencies result in cognitive decrements and immune and endocrine system impairments.[23–25] Acute sleep deprivation is linked to increases in oxidative stress, increased blood brain barrier permeability and reduced clearance of extracellular metabolites—all putative mechanisms underlying postoperative delirium.[26] Furthermore, chronic sleep disorders are prevalent in neurodegenerative disorders including Alzheimer's disease (AD) and may increase delirium susceptibility.[6 27 28] Advanced age is also associated with sleep disorder prevalence,[29] which may increase delirium susceptibility in older adults. In the perioperative arena, preliminary actigraphy studies suggest an association between abnormal sleep–wake cycle patterns and postoperative delirium.[30–32] These studies have not been followed by large-scale investigations of brain activity to examine the relationship between sleep structure and delirium outcomes. This is important because sleep may be a modifiable contributor to postoperative delirium.

Polysomnography (PSG), the gold-standard for studying sleep, requires patients to be tethered to amplifiers and acquisition computers. This hindrance to patient comfort and postoperative rehabilitation has limited perioperative studies of sleep. PSG relies on electroencephalographic (EEG) waveforms to detect wakefulness and classify sleep into distinct stages of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.[33] These stages, interspersed in cycles throughout sleep, are defined by well-known EEG waveforms and corresponding physiological processes (figure 1A). For instance, sleep spindles can occur in stage N2 sleep, which comprises approximately 50% of total sleep time. The presence of EEG slow waves defines stage N3 sleep, which is associated with restorative physiological benefits across multiple organ systems.[34–36] These EEG waveforms facilitate segmentation into sleep stages and have characteristics in the frequency domain (figure 1B).

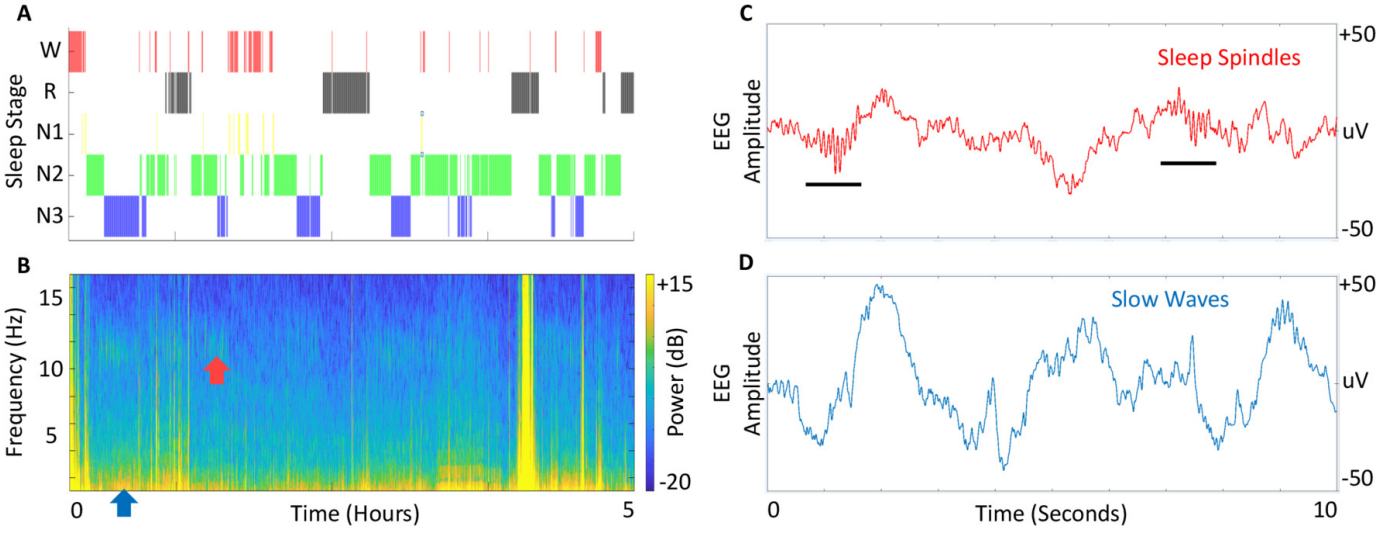


**Figure 1** Overnight electroencephalography (EEG). A hypnogram acquired with the EEG device reveals cycling of sleep stages over an evening with wakefulness (W), rapid eye movement sleep (R) and non-rapid eye movement sleep stages (N1, N2 and N3) (A). The corresponding spectrogram shows signal power in the frontal EEG decomposed by frequency as a function of time. Slow waves (blue arrow) carry low frequency power during N3 sleep, while sleep spindles (red arrow) have power in higher frequencies and occur primarily during N2 sleep (B). Sleep spindles (underlined) occurring at the point designated by the red arrow in panel B are reflected by ~13 Hz power (C). Slow waves occurring at the point designated by the blue arrow in (B) are reflected by 0.5–4 Hz power (D).

Despite technical limitations, small studies have demonstrated profound postoperative changes in sleep architecture with unknown clinical implications. N3 sleep suppression occurs on the day of anaesthesia in volunteer studies and persists on subsequent postoperative nights.[37 38] Fragmentation of sleep architecture and overexpression of N2 with reduction of N3 and REM sleep occur in the first postoperative night following both cardiac and non-cardiac surgery.[38–45] N3 and REM sleep return on the third or fourth postoperative nights.[32 38 43 46] However, the clinical impact of NREM sleep disruption remains unclear as EEG waveforms defining different sleep stages have not been related to postoperative delirium or other perioperative outcomes.

## EEG markers of sleep and wakefulness and thalamocortical disruption

Sleep stages, characterised by EEG waveform morphology, are normally regulated by circadian and sleep homoeostatic processes.[47 48] Preliminary studies in critically ill, ventilated patients with delirium have revealed abnormal EEG waveform characteristics corresponding to sleep–wake states. For instance, sleep spindles are absent during phenotypic sleep while slow waves are present during apparent wakefulness.[49 50] Taken together, these data suggest that investigating EEG during perioperative sleep and wakefulness may aid in correlative studies on the time course of delirium onset.

### Sleep spindles

Originally described by Loomis *et al*,[51] EEG sleep spindles reflect thalamocortical connectivity for sustaining sleep and consolidating memory.[52] These oscillations in N2 and N3 sleep (reviewed in Loomis *et al*[53]) originate from the thalamic reticular nucleus and propagate across the cortex with differential expression patterns in occipital and frontal EEG.[54 55] Sleep spindles possess a waxing and waning pattern of at least 0.5 s in duration (figure 1C). Within an individual, the dominant frequency of sleep spindles in the 9–16 Hz range is conserved.[56] Sleep spindle expression is under inverse homoeostatic control with a reduction in density following acute sleep deprivation.[57] Sleep spindle density, calculated as the number of spindles per unit time, varies over an evening of sleep.[58 59] This measure may be a useful marker of chronic sleep deprivation and cognitive dysfunction; decrements mirror the severity of cognitive episodic memory dysfunction in AD patients.[58 60] Furthermore, abnormal sleep spindle expression occurs in patients with severe dementia and schizophrenia and is predictive of dementia in patients with Parkinson's disease years after measurement.[61–64] Analogues of sleep spindles are observed during sedation and general anaesthesia with an unknown impact on subsequent homoeostatic regulation and expression.[65–67] Overall, perioperative sleep spindle expression has not been characterised or related to perioperative outcomes.

### Slow wave activity

Sleep slow waves are characteristic of N3 sleep and may be useful for tracking cognitive function.[68] They are putative markers of synaptic pruning, memory consolidation and have been related to the clearance of beta-amyloid and other metabolites.[69–72] Sleep slow waves are defined through high amplitude, low frequency oscillations on EEG (figure 1D). In order to correlate cognitive function with low frequency oscillation amplitude, sleep slow wave activity (SWA) is calculated as the total EEG power of contributory low frequencies (eg, 1–4 Hz) per minute.[73 74] Regional sleep SWA positively correlates with learning and subsequent visuomotor task performance[75] that may be impaired by auditory interventions.[76] Exogenous enhancement of SWA potentiates memory and task performance.[77] In contrast, selective acute SWA deprivation induces a rebound in magnitude on the next day based on the preceding deficit.[78–80] Furthermore, reduced SWA is associated with beta amyloid deposition, tau pathology,[81] atrophy in prefrontal cortical regions and impaired memory.[71 82]

In adults, slow waves observed during wakefulness[83–86] are usually associated with underlying structural or functional pathology.[87] Moreover, diffuse slow waves may represent disrupted thalamocortical connectivity.[88] Previous work has identified slow waves during apparent wakefulness in patients with postoperative delirium.[89–91] Furthermore, low EEG frequency predominance has been reported as a non-specific marker of hepatic encephalopathy,[92–95] sepsis-associated encephalopathy[96–99] and postoperative delirium.[89 90 100–109] Slow waves are associated with altered thalamocortical connectivity during general anaesthesia.[110] Whether overexpression of slow waves during wakefulness precedes postoperative delirium remains unknown.

### Posterior dominant rhythm

The posterior dominant rhythm (PDR) is a robust marker of thalamocortical connectivity, integrity and cognitive function during relaxed wakefulness with eyes closed.[33 111 112] The PDR consists of oscillations evoked by eyelid closure that have greatest amplitude in occipital EEG derivations.[112 113] For the vast majority of adults, the dominant frequency of the PDR lies within the 8–13 Hz (alpha) frequency band (figure 2). Lower PDR frequencies observed in AD patients are associated with thalamic deficiencies of norepinephrine.[114 115] Similarly, low PDR frequencies during apparent wakefulness have shown promise as a marker of early and advanced cognitive impairment of AD.[116–120] The severity of slowing appears to correlate with the degree of cognitive impairment[121–125] but has not been evaluated longitudinally in the perioperative period.

## Hypotheses and aims

We hypothesise that delirium is a disorder of both sleep and wakefulness resulting from abnormal thalamocortical connectivity. Furthermore, we hypothesise that

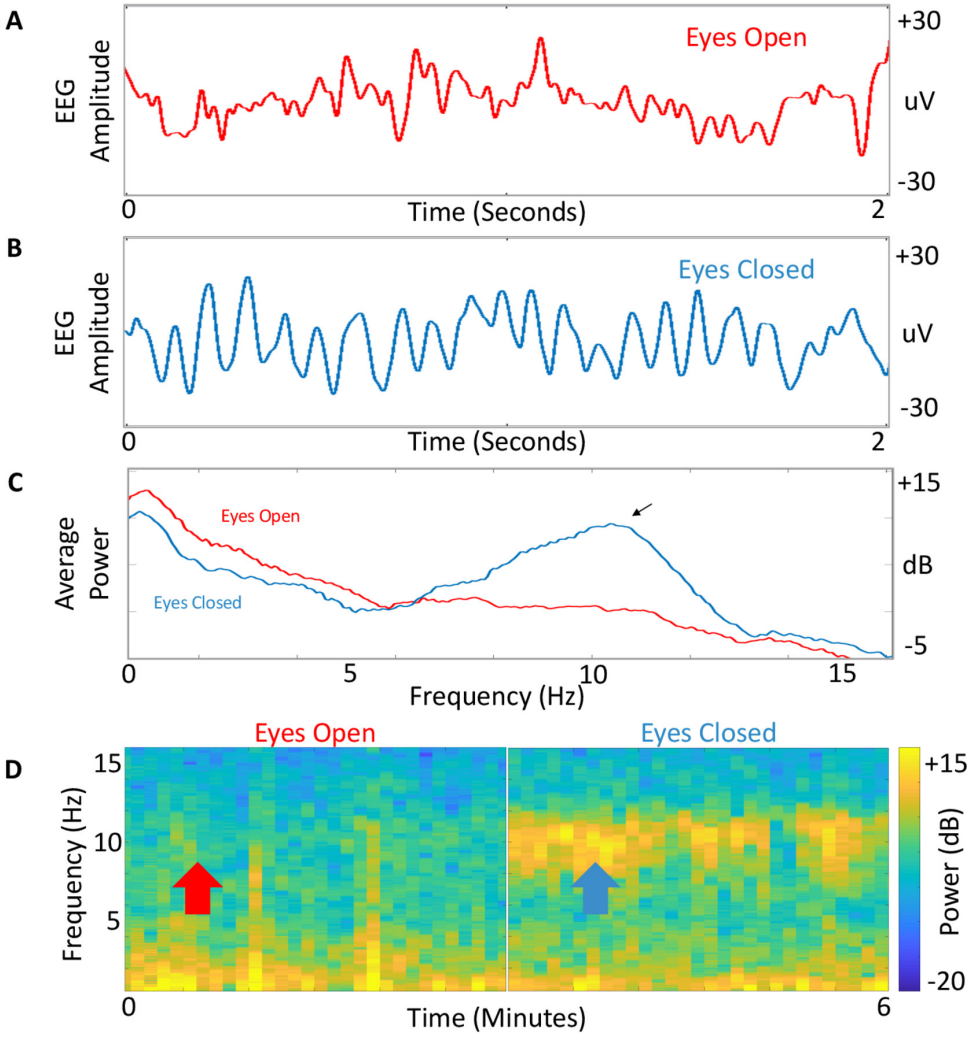


**Figure 2** The posterior dominant rhythm (PDR) during eyes closed wakefulness using the electroencephalography (EEG) recording device. Alpha oscillations are not easily discernable during eyes open wakefulness (A). During eyes closed wakefulness, the PDR in cognitively intact adults is comprised oscillations in the alpha (8–13 Hz) frequency band (B). This activity is apparent in the decomposition of these two signals into power at corresponding frequencies by spectral analysis. The PDR emerges during eyes closed wakefulness with signal power at ~10 Hz (blue) compared with signal power during eyes open (red) (C). A power spectrogram demonstrates quantifiable fluctuations in the ~10 Hz power during epochs of eyes open vs eyes closed wakefulness (red vs blue arrow) (D).

EEG alterations can predict delirium onset and severity. Our specific aims include the following: (1) evaluate whether preoperative EEG measures of sleep and wakefulness predict postoperative delirium and its severity; and (2) assess whether postoperative abnormalities in EEG measures of sleep and wakefulness correlate with delirium onset, severity and clinical course. For our first aim, we hypothesise that the EEG power of preoperative sleep slow waves, sleep spindle density and PDR frequency will correlate negatively with the peak severity of postoperative delirium. Our second aim, focused on postoperative findings, addresses three hypotheses: (1) delirium onset and peak severity will correlate with an increase in SWA and diminished PDR frequency during wakefulness; (2) delirium onset and peak severity will correlate with the reduction in postoperative sleep spindle density relative to preoperative measurements; (3) delirium recovery will coincide with a reversion of the dominant PDR frequencies toward preoperative values.

## METHODS

### Research design overview

Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) is a prospective longitudinal cohort observational investigation. The Human Research Protection Office at Washington University School of Medicine approved the study in 2017. P-DROWS-E was registered prior to enrolment and conforms to the Standard Protocol Items: Recommendations for Interventional Trials checklist (see online supplemental file 1).

## Study participants

We will enrol 220 patients undergoing elective cardiac surgery at Barnes-Jewish Hospital, St. Louis, Missouri. Inclusion criteria are (1) English-speaking, (2) age 60 years or older and (3) undergoing elective major cardiac surgery requiring cardiopulmonary bypass (eg, coronary artery bypass grafting, aortic repair/replacement, septal myectomy, Maze procedure and/or heart valve repair/replacement). Exclusion criteria are (1) undergoing surgery requiring deep hypothermic circulatory arrest, (2) pre-existing delirium, defined by a positive preoperative confusion assessment method (CAM) evaluation and (3) inability to participate sufficiently in delirium screening due to deafness, blindness or poor English fluency. We minimised exclusion criteria to maximise generalisability of findings to the general cardiac surgical population. Participants will be compensated for their efforts: $50 for each preoperative EEG recording and $25 for each intraoperative and postoperative EEG recording, up to $300.

## Recruitment

Recruitment and enrolment of eligible patients will occur following screening of the cardiac surgery schedule at Barnes-Jewish Hospital, the Center for Preoperative Assessment and Planning clinic schedule, and inpatient census lists from cardiology and cardiothoracic wards by study coordinators.

## Data collection

### Preoperative screening and assessment tools

Baseline sleep–wake function will be evaluated through questionnaires including daytime sleepiness with the Epworth Sleepiness Scale,[126] overall sleep–wake function with the Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Related Impairment/Sleep Disturbance Scale,[127] sleep quality with the Pittsburgh Sleep Quality Index[128] and obstructive sleep apnoea risk estimation with the Snoring, Tiredness, Observed apnea, high blood-Pressure, BMI, Age, Neck circumference, and male Gender (STOP-BANG) questionnaire.[129]

Baseline depression, cognition and prior education are prognostic factors for postoperative delirium. Therefore, patients will complete the Geriatric Depression Scale short form[130] and the Montreal Cognitive Assessment, which screen for cognitive impairment.[131] In addition, the AD-8,[132] a rapid screen that has been validated against AD biomarkers, will be used.[133] The number of years of education will also be recorded. Finally, the CAM[134] and serial pain assessments will be performed.

### Confusion assessment method

The CAM is used to diagnose delirium based on five key domains: (1) acute onset, (2) fluctuating course, (3) inattention, (4) disorganised thinking and (5) altered level of consciousness.[134] It is a validated tool for delirium diagnosis with a sensitivity of 94% and specificity of 89% against full neuropsychiatric evaluation.[135] CAM administration takes 10–20 min at our institution and consists of a formal patient interview comprised questions that identify delirium symptoms and test cognition.

CAM assessments will be performed by researchers who have undergone an established rigorous training process.[136 137] All assessments will be independently reviewed by a separate, trained research team member for internal scoring consistency and completeness. Ambiguous assessments will be reviewed by the research team and PI weekly with concomitant adjudication of each domain and the overall delirium determination. The patient's family and nurse are also questioned about the patient's postoperative mental status as needed. Patients whose medical condition prohibits the use of the CAM will be assessed using the CAM for the intensive care unit (CAM-ICU) instrument.[138 139] Both the CAM-ICU and the CAM have been shown have good agreement with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for delirium.[140–142]

### Pain assessments

A limited number of studies suggest an association between acute postoperative pain and delirium.[143–145] Therefore, serial pain evaluations will be completed using the Behavioral Pain Scale (BPS)/BPS Non-Intubated and the Visual Analog Scale.[146] Evaluations will be performed after each CAM assessment.

### EEG apparatus

Perioperative EEG will be used to assess markers of wakefulness, sleep and delirium. To address the technical limitations of PSG, we will employ a consumer-grade wearable wireless EEG device (Dreem, Rhythm, New York, New York, USA) requiring minimal clinical intervention and maintenance (figure 3A).[147 148] It yields continuous multichannel EEG data through dry electrodes, heart rate through infrared detectors and head movement through accelerometers. In addition to frontal forehead sensors (F7, F8 and Fpz), occipital EEG signals are acquired using posterior sensors (O1 and O2). Adequate signal quality will be assessed by research staff.

### Preoperative EEG acquisition

To maximise patient compliance and signal quality, research staff will demonstrate wireless EEG device usage. Patient head circumference will be measured, and the device will be adjusted for proper fit. To obtain baseline PDR, patients will be asked to remain still and relaxed for 4 min with eyes open followed by a 4 min period of eyes closed (figure 3B). Patients will demonstrate comprehension by donning the device and initiating a recording themselves.

Patients will be requested to wear the device for up to two nights before surgery to allow for EEG sleep structure assessment. For inpatients, research staff may assist with device application. For outpatients, the device, charger, alcohol wipes, an educational video and an instruction sheet will be provided. Research staff will also be available

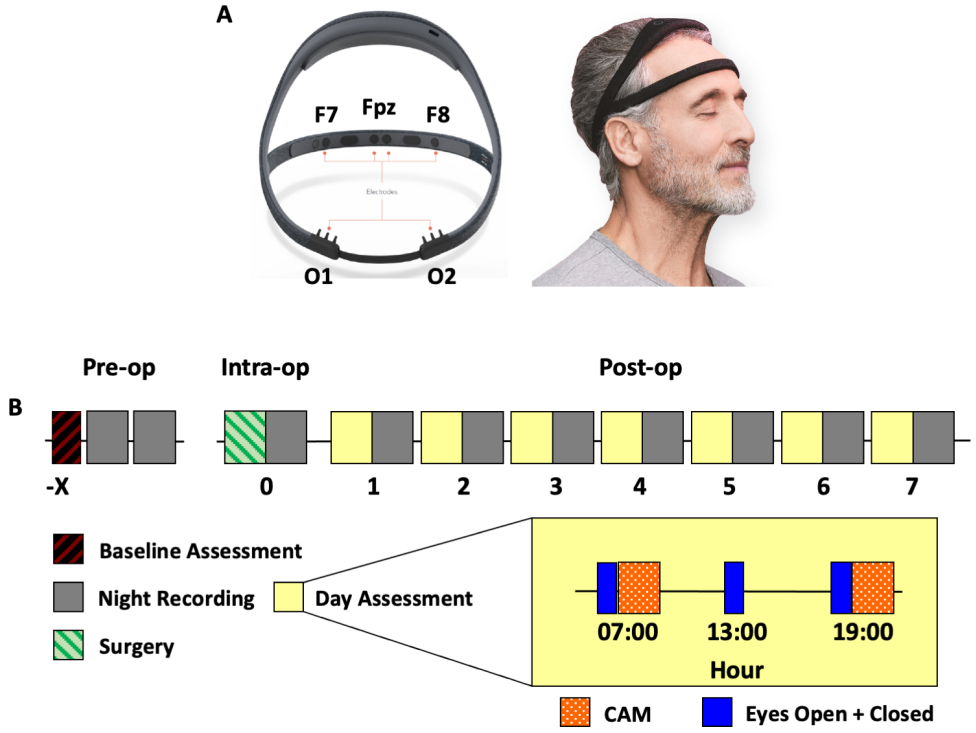


**Figure 3** Overview of electroencephalography (EEG) device and patient participation workflow. Perioperative EEG will be obtained via the Dreem device, a consumer-grade wireless wearable EEG device that records from five sensors, pulse oximetry and accelerometry (A). Longitudinal assessments of EEG and delirium symptomatology will occur preoperatively, intraoperatively and postoperatively. Following consent in the Center for Preoperative Assessment and Planning/inpatient unit, a baseline confusion assessment method (CAM) and EEG are acquired. Postoperative daytime assessments occur within a 2-hour window surrounding 07:00, 13:00 and 19:00 until postoperative day 7, patient withdrawal or hospital discharge (B). The human in this figure is a model and not a patient. Permission was granted for non-commercial use of this image by Dreem.

by phone to address questions. Patients will be contacted by phone to ensure compliance, satisfaction and data quality.

### Day of surgery EEG acquisition

If necessary, additional preoperative awake EEG data will be obtained. The Dreem will then be used throughout anaesthetic induction, maintenance and emergence (figure 3B). Research staff will optimise EEG acquisition through device adjustments, as needed.

### Postoperative EEG acquisition, delirium assessments and pain scores

Semi-continuous EEG recordings will be acquired up to postoperative day (POD) 7, patient withdrawal or hospital discharge (figure 3B). To enhance data collection, participants will be asked to wear the device within 2 hours of 07:00, 13:00 and 19:00 for 4 min each during eyes open and eyes closed periods. The 07:00 and 19:00 recording sessions will coincide with acquisition of CAM and pain scores. CAM-ICU will be used for intubated patients.[149] EEG but not CAM data will be obtained for unresponsive patients (Richmond Agitation-Sedation Scale (RASS)[150] level −4 or −5). Participants will wear the device overnight to provide data on nocturnal sleep structure.

## Structured chart review for delirium

Coupling structured chart review with CAM/CAM-ICU increases sensitivity in detection of delirium without loss of specificity.[151 152] Therefore, formal structured chart reviews will be performed by independent trained clinical researchers who are blinded to EEG and CAM data. Reviews will occur daily until POD 7. The chart review methodology (table 1) will use patient information from the electronic medical record including mental status, progress notes, medication usage (including psychotropic, sedative and pain medications) and relevant clinical details (eg, length of stay, ICU behavioural interventions, extubation and/or re-intubation procedures, etc).[151 152] Structured chart review training will be adapted from previously published methods,[152] and only CAM trained staff will be eligible. In cases where chart review delirium outcome is uncertain, a consensus review will occur. In cases where chart review is discordant with both CAM assessments on a given day, a formally trained attending clinician blinded to all other metrics will determine the final outcome.

## Analyses

### EEG preprocessing and analysis

EEGLAB,[153] an open-source analytical suite for MATLAB (Mathworks, Natick, Massachusetts, USA), will be used

**Table 1** Chart abstraction for delirium during hospitalisation

| | |
|---|---|
| Was delirium diagnosed by a clinical provider?<br>(*Review diagnosis code summary in electronic medical record for any diagnoses related to delirium*.) | ► Yes<br>► No<br>► Uncertain |
| Was there any evidence in the chart of acute confusion (eg, delirium, mental status change, disorientation, hallucinations, agitation, etc)?<br>(*Review all handwritten and electronic notes, flowsheet data, and documented CAM-ICU results performed twice daily by nursing staff*.) | ► Yes<br>► No<br>► Uncertain |
| Was there any documentation of the use of delirium prevention strategies at any time during the hospitalisation before delirium occurred?<br>(*Review flowsheet data for nursing interventions such as reorienting patient to room, equipment, unfamiliar surroundings, person, situation, time and adjustment of lighting during day*.) | ► Yes<br>► No<br>► Uncertain |
| Was there any documentation of the use of a restraint or bed alarm/device recorded during the patient's stay?<br>(*Review flowsheet data for documentation of any restraint devices used*.) | ► Yes<br>► No<br>► Uncertain |
| Outcome<br>By chart review, delirium was | ► Present<br>► Absent<br>► Uncertain<br>► Cannot be determined |

Outcome is determined after a complete review of the medical record. Questions 1–4 are designed to help the reviewer identify evidence of delirium consistent with diagnostic criteria including an acute change or fluctuating course, inattention and disorganised thinking or altered level of consciousness.
CAM-ICU, confusion assessment method for the intensive care unit.

for down-sampling deidentfied EEG to 128 Hz after band-pass filtering (0.1–50 Hz first order Butterworth). Records will undergo visualisation and artefact removal using EEGLAB plugins and/or custom-coded MATLAB scripts. Multitaper methods will be used for power spectral analysis using the MATLAB Chronux toolbox.[154] Spectral estimates between 0.5 and 30 Hz will be based on 6 s non-overlapping time windows, time-bandwidth product of 3 and 5 tapers.

### Sleep technologist scoring

Records will undergo sleep staging with visualisation in Philips Respironics Sleepware G3 Software. They will be scored successively with a low frequency filter (LFF) of 1 Hz then 0.3 Hz and a high frequency filter of 30 Hz. The LFF of 1 Hz will attenuate artefacts related to sweat, respiration and movement. Rescoring with an LFF of 0.3 Hz will allow for best quantification of SWA and stage N3 sleep. Channels Fpz-F8, Fpz-F7 and F8-F7 will be used for visual scoring, while occipital derivations will be used secondarily. Additionally, accelerometer channels will be used to identify movement, respiratory patterns and arousals. Registered polysomnographic technologists will score the record in 30 s epochs using the modified American Association of Sleep Medicine (AASM) criteria (table 2).[33] Evaluators will be blinded to delirium clinical outcomes and automated scoring provided by the manufacturer.

### Quantitative measures of sleep spindle and slow waves

Sleep spindles will be scored manually by registered polysomnographic technologists using AASM guidelines and with the assistance of publicly available algorithms implemented in our laboratory.[63 155–162] Spindle density will be computed from the number of spindles per minute of N2 and N3 sleep. Dissipation in sleep spindle power (ie, total power across 11–16 Hz) will be assessed over the course of nocturnal sleep.

Custom-written MATLAB subroutines will compute the SWA as the total absolute spectral power in the 1–4 Hz frequency band, calculated in 1 min intervals during N2 and N3 sleep.[163] Custom-written MATLAB code will be used to detect individual slow waves and calculate their power.[164] For our second aim, predictor SWA measurements during phenotypic wakefulness will be computed from postoperative recordings where EEG slowing is noted despite persistent criteria for wakefulness (eg, eye movements, high frequency activity (>30 Hz) and motion artefact). Registered sleep technologists will review these expected discordant epochs.

### Quantitative measures of the PDR

Previously developed MATLAB scripts will be used to quantify PDR frequency from EEG recorded during eye closure. Registered sleep technologists will first screen the occipital EEG (Fpz-O1, Fpz-O2, O1-O2) recorded during eyes closed wakefulness (07:00, 13:00 and 19:00) to identify recording contamination by sleep. Band-pass filtering of the signals will then occur, and spectral estimates will be generated through the Chronux toolbox modules.[154] PDR frequency will be determined based on peak power.

Table 2 Modified American Association of Sleep Medicine scoring criteria for different sleep stages

| Stage | Criteria/description |
|---|---|
| W | **>50% epoch contains any of the following**<br>Posterior dominant rhythm: 8–13 Hz EEG oscillations over occipital region with eyes closed<br>Eye blinks: vertical eye movements of 0.5–2 Hz<br>Slow eye movements: conjugate, sinusoidal eye movements<br>Rapid eye movements: conjugate, irregular, sharply peaked eye movements |
| N1 | **Posterior dominant rhythm absent with any of the following**<br>Low amplitude mixed frequency EEG: 4–7 Hz activity<br>Vertex sharp waves: EEG sharp waves with duration <0.5 s<br>Slow eye movements: conjugate, sinusoidal or slow eye movements |
| N2 | **Either present during the first half of an epoch or last half of previous epoch**<br>K-complexes: EEG negative sharp wave and positive component with total duration >0.5 s and without arousal<br>Sleep spindles: crescendo-decrescendo EEG oscillatory pattern with frequency 11–16 Hz and duration of 0.5–3 s |
| N3 | **Presence over >20% of an epoch**<br>EEG slow waves: delta waves with a frequency 0.5–4 Hz and peak-to-peak amplitude >60 µV |
| R | **All of the following present**<br>Low amplitude mixed frequency EEG: 4–7 Hz EEG activity without K-complexes or sleep spindles<br>Sawtooth waves: EEG train of sharply contoured or triangular waves with frequency of 2–6 Hz<br>Rapid eye movements: conjugate, irregular, sharply peaked eye movements |
| NS | Epoch cannot be scored due to excessive artefact and/or inability to fulfil criteria for above stages |

EEG, electroencephalography.

### Processing of delirium outcomes

Daily delirium incidence will be coded as a binary variable defined by a positive CAM assessment and/or chart review. Delirium duration will be coded as a categorical variable defined by the total number of days with a positive delirium outcome, ranging from 0 to 7. Delirium subtype (hypoactive, hyperactive or mixed), based on the RASS and the CAM, will also be noted. Delirium severity will be quantified using the CAM-S and/or CAM-ICU 7. The CAM-S is a validated weighting of CAM sub-scores,[165] with a long-form version ranging from 0 to 19. The CAM-ICU-7[166] is a validated weighting of the CAM-ICU subscore ranging from 0 to 7. Raw severity scores will be normalised by the maximum score of the tool in order to yield scaled severity scores ranging from 0 to 1. The maximum scaled delirium severity score will be coded as a continuous variable in analytical models.

## Statistical analyses

Linear mixed effects models will be used to evaluate relationships between EEG measures and delirium severity and duration. For our first aim, principal independent variables will include preoperative measures of sleep spindle density, sleep SWA for stages N2 and N3, and PDR frequency. For our second aim, independent variables will include EEG changes relative to preoperative baseline for sleep spindle density, awake SWA and PDR frequency. Given that EEG measures may vary by age[167–169] and sex,[163 170] these factors will be included as relevant biological variables. Secondary analytical models will include relevant medications and comorbidities such as obstructive sleep apnea and depression as well as years of education. Additional covariates to account for intraoperative anaesthetic exposure will use intraoperative measures of SWA, sleep spindle density and burst suppression[171–173] derived from intraoperative EEG device recordings. As we expect that only 25% of our patients may develop postoperative delirium, we will consider zero-inflated models.

## Sample size calculations

Considering the heterogeneity of delirium phenotype and variable exposure to narcotics and other medications, we expect a large sample size to reduce the risk of completing an underpowered study. Based on preoperative recruitment of 220 patients, we expect 95% capture rate for preoperative and intraoperative recordings, and a 25% incidence of delirium based on results from the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study,[173] with the majority completing delirium assessments throughout the postoperative period. We expect at least 70% of these patients to provide usable postoperative EEG. We anticipate the ability to capture at least moderate effects (effect size 0.5, beta 0.2, power 0.8) based on conventions for statistical power analysis in the behavioural sciences.[174]

## Prespecified substudies

### Other physiological markers for predicting delirium outcomes

Additional physiological markers (accelerometry, blinks and heart rate measurements), and sleep EEG markers, including N1 vertex waves, N2 K-complexes and REM sawtooth waves will be evaluated against delirium outcomes.

### Device validation for elderly patients

This substudy will compare Dreem data and PSG in the geriatric population to complement early studies across a broad age.[148]

### Postoperative cognitive trajectories

This substudy uses a modified version of the Brief Test of Adult Cognition by Telephone to determine the rate of postoperative cognitive recovery and how delirium impacts cognitive recovery via interval assessments up to 6 months after surgery.[175 176] The battery will evaluate multiple cognitive domains including episodic memory, working memory, processing speed, attention and executive function. Associations between EEG measures and cognitive function will also be evaluated.

### Automated sleep staging

Staging provided by the manufacturer's automated algorithm will be compared with the manual sleep staging performed by registered PSG technologists.

### Relationship of sleep structure to clinical outcomes

Preoperative EEG/sleep measures, sleep surveys (Epworth Sleepiness Scale, STOP BANG) and Geriatric Depression Scale scores will be evaluated against secondary postoperative clinical outcomes, including 30-day mortality, ICU length of stay, depression, atrial fibrillation and acute and persistent pain scores.

### Comparisons of sleep and sleep-like EEG markers

Within-subject comparisons will be made between EEG markers spanning different states of arousal.

### Utility of intraoperative EEG markers

Intraoperative EEG measures, including burst suppression will be evaluated against postoperative outcomes.

## DISCUSSION

The P-DROWS-E study aims to enhance our understanding of perioperative delirium. We will use EEG recordings acquired across different states of arousal in tandem with serial perioperative delirium assessments to determine temporal associations between EEG markers and postoperative delirium outcomes. Our work is enhanced by integrating additional data including assessments of cognition and clinical variables (figure 4). As a result, we are well positioned to develop analytical models for predictive and diagnostic EEG markers of postoperative delirium.

Until recently, technical limitations have impeded incisive probing of the relationships between sleep architecture and postoperative delirium. Our study uses a battery-operated, portable device that is specifically designed for continuous long-term EEG recordings with minimal need for direct assistance by staff. This approach should greatly enhance patient participation, tolerance and comfort while posing minimal interference to postoperative sleep and rehabilitation. The EEG

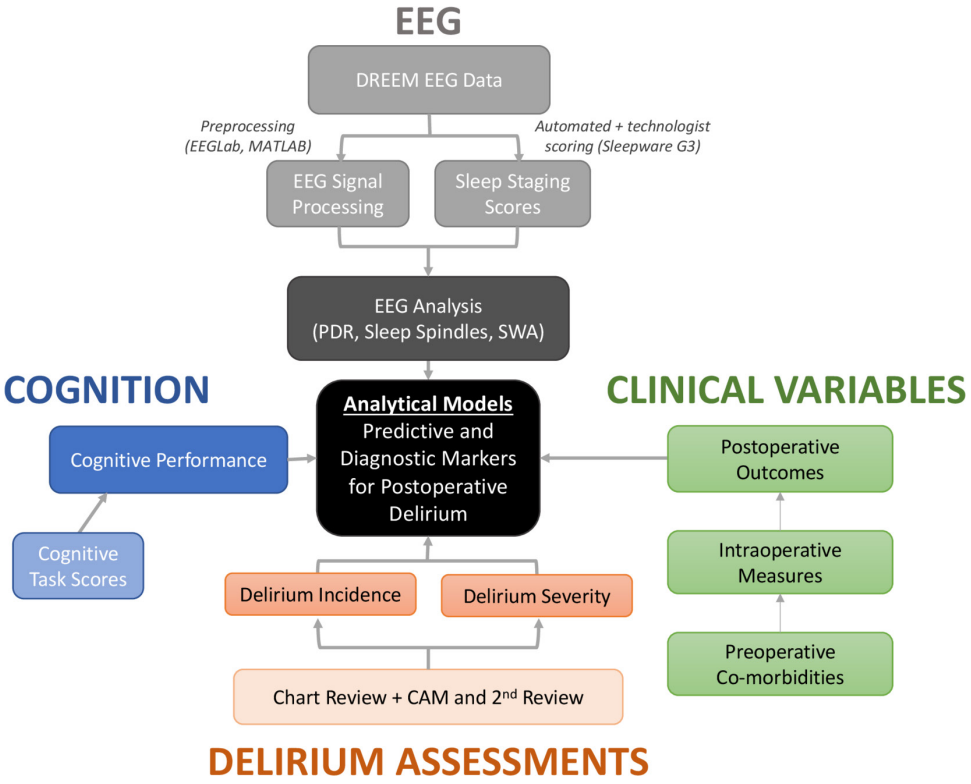


**Figure 4** Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography study overview. CAM, confusion assessment method; EEG, electroencephalography; PDR, posterior dominant rhythm; SWA, slow wave activity.

device, however, is not without limitations. Dry electrodes allow comfort and easy instrumentation, but they may be more prone to artefacts related to poor skin adherence. Thus, expertise and vigilance are required to differentiate EEG waveforms from artefact to fulfil the promise of this technological advance for large scale clinical sleep investigations. Another potential confounder for EEG interpretation and delirium outcomes includes the use of anaesthetics and opioids that may contribute poorly controlled sample variance in our study population. Nevertheless, P-DROWS-E will be an important early step in identifying prognostic associations between EEG and postoperative delirium.

### Application of findings and future directions

P-DROWS-E may yield EEG applications that are significant and far-reaching. The potential to better identify patients at risk for postoperative delirium and track their disorder quantitatively would advance perioperative and critical care medicine. The study also has important mechanistic implications for modulating sleep and wakefulness that have bearing on sedation and analgesic strategies in procedural medicine. Finally, the use of wireless wearable devices for monitoring brain activity is proof-of-principle for implementing neural telemetry in vulnerable populations in the future.

## ETHICS AND DISSEMINATION

The study design, study procedures and informed consent procedure were approved by the ethics board at Washington University, and the study will be carried out in compliance with the Declaration of Helsinki. All participants will provide informed consent (see online supplemental file 2).

Any protocol modifications, which may impact study procedures, administrative aspects or patient safety, will require a formal amendment to the protocol. Such amendments will be approved by the Institutional Review Board prior to implementation. The study will not have a data monitoring committee given that we do not anticipate severe adverse events and was not required for our study by the Institutional Review Board. To ensure the conduct of quality research, the Washington University School of Medicine IRB regularly conducts audits of research studies. Dissemination plans include presentations at scientific conferences, scientific publications and mass media.

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**Acknowledgements** The authors thank the additional members of the P-DROWS-E study group, including Jacob D Bolzenius, Emma R Huels, Amrita Aranake-Chrisinger, Jordan Oberhaus, Hersh Maniar, Daniel Park, Katie Dalton, Paul Galgani, Paul Krucylak and ShiNung Ching.

**Contributors** Authorship for this study was given to key personnel involved in study design, recruitment, data collection, data analysis. There are no publication restrictions and no professional writers were involved in the generation of the manuscript. BJAP, SKS, TN, AKL, MMK, OH, CSG, EW, BAF, DE, TJG, SJM, BPL, Y-ESJ, TSW and MSA are responsible for conceptualising study design. TN, AKL, MMK, OH, EW, CWC, AL, LBH, DE and TJG are responsible for recruitment, enrolment, data collection and/or editing the protocol. BJAP is responsible for drafting the protocol. All authors including BJAP, SKS, TN, AKL, MMK, OH, CSG, EW, CWC, AL, LBH, BAF, DE, TJG, SJM, BPL, Y-ESJ, TSW and MSA have critically revised the P-DROWS-E protocol manuscript and have approved the final version to be published. All authors agree to be accountable for the accuracy and integrity of all aspects of the P-DROWS-E study.

**Funding** The P-DROWSE study has been awarded funding by the National Institute on Aging (PI: Ben Palanca; award reference number: National Institutes of Health R01AG057901).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; peer reviewed for ethical and funding approval prior to submission.



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