RESEARCH PROTOCOL

Postoperative Delirium: Brain Vulnerability and Recovery

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1. STUDY SYNOPSIS

Study Title	Postoperative Delirium: Brain Vulnerability and Recovery
Objectives	1. Characterize whether **EEG** slowing or **DMN functional connectivity (FC)** distinguishes epochs during delirium from those following resolution of symptoms. 2. Assess whether **DMN FC after recovery from delirium** is weaker than DMN FC in those who did not experience delirium. 3. Investigate the relationship between **preoperative DMN FC** and **postoperative delirium**.
Study Period	**Planned enrollment duration:**1-2 years **Planned study duration: 4-**5 days per subject: (**Preoperative testing**) ~2 hours within one month before surgery; (**Postoperative session 1-3**) ~1 hour between post-operative days 1-8; (Postoperative **session 4**) ~2 hours during the period between disconnection of chest tubes and within 1 month after hospital discharge.
Study Design	Single academic center, prospective, observational, longitudinal, case-control trial
Number of Patients	**Target enrollment:** 66 (evaluable) participants recruited from the Barnes-Jewish Hospital (BJH) Center for Preoperative Assessment and Planning (CPAP), BJH Center for Advanced Medicine (CAM), Cardiothoracic Intensive Care Unit (CT-ICU), or step-down floors. **Delirium Case Arm:** 33 patients diagnosed with postoperative delirium after surgery **Postoperative Control Arm:** 33 control patients without postoperative delirium after surgery
Inclusion and Exclusion Criteria	**Common Inclusion Criteria:** Age ≥ 60, surgery requiring cardiopulmonary bypass (CPB) for coronary artery bypass grafting, aortic repair/replacement, septal myectomy, and/or heart valve repair/replacement, English speaking **Common Exclusion Criteria:** Implanted pacemaker, automatic internal cardiac defibrillator, or other implant for which non-contrast magnetic resonance imaging (MRI) is contraindicated; concomitant cerebrovascular procedure or requirement of deep hypothermic circulatory arrest; inability to lay flat or still for MRI; legal blindness or severe deafness; seizure history, known focal brain lesion larger than 3 cm **Delirium Case Arm:** Delirious as diagnosed by the Confusion Assessment Method (CAM)/ Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) at some point during postoperative day 1-5. **Postoperative Control Arm:** Not delirious as diagnosed by the CAM/CAM-ICU on postoperative day 1-5.
Measurements	**Primary:** (1) **EEG before surgery, during delirium, and after recovery:** Delta (0.5-4 Hz), theta (4-8 Hz), and alpha (8-13 Hz) EEG power from 1 minute of continuous artifact-free data acquired during 30 minutes of eyes open wakefulness and 15 minutes of eyes closed wakefulness within one month before surgery and after surgery between POD 1-8. (2) **FC Diffuse Optical Tomography (fcDOT) before surgery, during delirium, and after recovery:** FC between anterior and posterior DMN regions assessed from a total of 30 minutes of fcDOT data with eyes open wakefulness, a total of 15 minutes of eyes closed wakefulness, and 3 minutes while listening to an audio recording within one month before surgery and after surgery between POD 1-8. (3) **Non-contrast fcMRI of patients before and after surgery in both individuals who do and do not develop delirium:** FC between anterior and posterior DMN regions assessed from 20 minutes of resting-state fcMRI acquired with eyes open wakefulness within one month before surgery and after surgery during the period between disconnection of chest tubes and within 1 month after hospital discharge. **Secondary:** (1) **fcDOT and EEG from patient controls** (2) **Patient Demographics**, including age and years of education, surgical and anesthetic exposure
Outcomes	(1) **Delirium incidence** as assessed by the CAM/CAM-ICU. (2) **Delirium severity** subscores as assessed by the CAM-S. (3) **Delirium duration** as the number of days with CAM+ listed in patient records. (4) **Pain level** using the BPS/BPS-NI and VAS Pain scores.

2. STUDY PROTOCOL

2.1 Background, Significance, and Preliminary Data

2.1.1 Postoperative Delirium

Postoperative delirium is a potentially life-threatening under-diagnosed disorder that costs the US billions of dollars annually[1]. An incidence of up to 50% follows both non-cardiac[2] and cardiac[3] procedures. Post-cardiac surgery delirium prolongs hospitalization[4], and is associated with greater risks of persistent functional decline [5-7] and mortality[4, 8]. Diagnosis and treatment are urgent to reduce self-injurious behavior and interference of rehabilitation but significant barriers exist. By definition, delirium manifests acutely with fluctuations of inattention and disordered cognition[9], so timing of assessment may preclude detection. Without direct verbal interrogation, clinicians can misdiagnose[10-12] the predominant hypoactive subtype[13], that manifests as disorganized thought and disengagement without agitation[14]. Lastly, manifestation peaks 1-2 days postoperatively[13, 15] but may vary in onset and reoccurrence. Neither pre- nor post-operative assays exist to predict incidence of this perioperative complication.

2.1.2 Encephalographic Markers of Postoperative Delirium

Electroencephalographic (EEG) changes have been noted during delirious episodes since 1944[16] but systematic longitudinal studies are lacking. Slowing in EEG[17], with patterns mirroring those observed during sleep and general anesthesia, are generally observed during hypoactive delirium, despite maintenance of arousal. Alpha and beta (12-20 Hz) rhythms are replaced by slower theta (4-8 Hz)[18-20] and delta (<4 Hz)[18, 19, 21]. A recent meta-analysis of postoperative delirium highlighted the lack of standard EEG markers used quantitatively by investigators[22]. Of the 14 investigations, some relied on reduction in relative alpha power[23-27], while others studied the increase in relative theta power[23, 24, 26-30] or increase in relative delta[20-22, 24, 26, 27, 29, 31]. A recent case-control study[31] revealed significant differences between delirious patients and their controls for these three metrics and for three others. These results were striking because significant differences between the two groups were observed across *all* electrode combinations studied (80 for eyes open and 210 for eyes closed). These widespread significant findings, high sensitivities (> 88%), and high specificities (>92%) require validation in longitudinal studies where patients serve as their own controls after delirium resolution. Controls to ensure that wakefulness has been maintained would aid in interpretation. Finally, such longitudinal studies would address whether aspects of EEG slowing (change in delta, theta, and/or alpha power) persist after recovery from acute manifestations of delirium. These aspects of validation would be needed to determine whether EEG may aid in routine surveillance for postoperative delirium.

2.1.3 Structural Neuroimaging of Delirium Vulnerability

Structural magnetic resonance imaging (MRI) has been investigated as a means identifying brain abnormalities posited to confer vulnerability for postoperative delirium[32]. Their existence has been suggested by preoperative risk factors of age[2], years of education, existing cognitive impairment[33], and even stroke without residual symptoms[34, 35]. Retrospective MRI of delirious patients implicated white matter disruption[36, 37], hyperintensities consistent with stroke [38], and total brain volume[39]. However, these markers demonstrated little prognostic value in recent prospective studies[32, 40]. As an alternative, characterizing the functional derangements within the brain prospectively may yield markers for vulnerability or insight into the etiology of delirium.

2.1.4 Functional Neuroimaging

In contrast to structural MRI, functional MRI has yielded insight into how distributed brain activity relates to cognition and behavior. This technique relies on relative changes in the blood-oxygen level dependent (BOLD) signal as a surrogate of altered blood flow reflecting underlying neural activity. Functional connectivity (FC) MRI

identifies brain regions with slow correlated fluctuations in the BOLD signals during passive wakefulness. These distributed brain regions with highly correlated signals recapitulate spatial patterns of BOLD activity observed during task paradigms. Functional connectivity (FC) describes the correlation strength between these components brain regions, which are collectively referred to as resting-state networks (RSNs).

2.1.5 The Default Mode Network

The Default Mode Network (DMN)[42] is an archetypal RSN[43] widely distributed across the cerebral cortex (**Figure 1**). The DMN contains regions that are most active during quiet resting[42] and are negatively correlated with those of other RSNs implicated in attention[44] and salience detection[45]. It plays a putative role in self-referential cognition and episodic memory[46]. Reduction of FC within the DMN occurs during slow-wave sleep[47, 48], coma[49], and anesthetic-induced unconsciousness[41, 50], and correlates with severity of Alzheimer's dementia[51, 52]. Moreover, alterations in DMN FC precede clinical dementia symptoms[53-55]. These observations are consistent with our hypothesis that latent DMN FC abnormalities in ostensibly normal patients reflect susceptibility to perioperative delirium. Our fcMRI study of healthy volunteers rendered unresponsive with sevoflurane demonstrated weakening of FC within the DMN (**Figure 2**)[41], suggesting that DMN FC is likely weakened during general anesthesia. Whether inflammation and surgical factors implicated in delirium pathogenesis converge on a vulnerable DMN remains unknown. Reduced DMN FC, as a marker of delirium, is supported by the weakening of DMN MRI FC between anterior and posterior regions during delirium compared to control patients (**Figure 3**)[56]. While suggestive, the role DMN FC as a MRI marker of delirium pathogenesis has not been established.

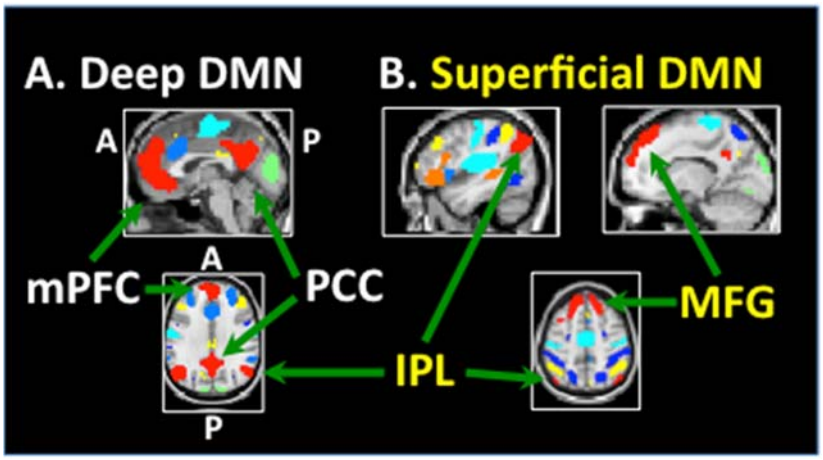

Figure 1. Superficial and deep regions of the Default Mode Network (DMN). Transverse and sagittal atlas sections with superimposed resting-state networks (RSNs) are shown. The DMN (red) contains deep regions (mPFC and PCC) and superficial cortical regions (MFG and IPL). Temporal regions are not shown. Other RSNs are shown in different colors. Adapted from Palanca et al., 2015[41].

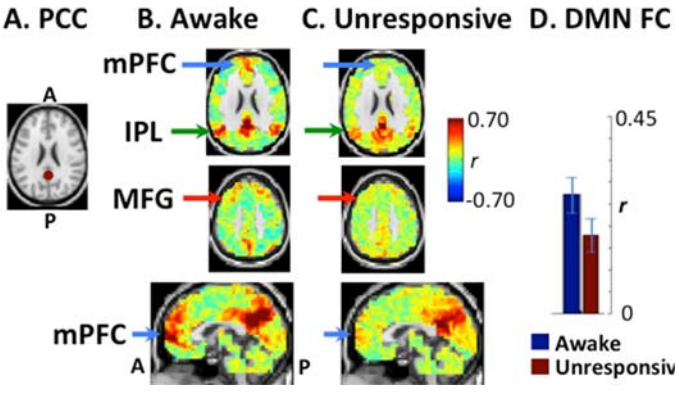

Figure 2. Reduction of DMN FC during sevoflurane sedation. A. PCC region. **B.** Transverse and sagittal sections showing PPC FC to the medial prefrontal cortex (mPFC) and superficial regions of the inferior parietal lobule (IPL) or middle frontal gyrus (MFG). **C.** During unresponsiveness induced by 1.2% sevoflurane, FC between the PCC and both anterior DMN components (mPFC and MFG) and posterior DMN (IPL) is weakened. Average **D.** FC among DMN regions is significantly reduced ($p < 0.05$, unpaired t-test). A: Anterior. P. Posterior. Adapted from Palanca et al., 2015[41].

2.1.6 Functional Neuroimaging of Delirium Episodes

Considering logistics and safety, only a single study[56] has investigated resting-state fcMRI in patients with delirium. **These data are not from our group but are reproduced as preliminary data to support the potential role of the DMN in delirium pathogenesis.** Reduction in MRI FC between anterior and posterior

DMN regions during delirium is shown in **Figure 3**. The precuneus region (**Figure 3A**) used in this analysis is a deep posterior DMN region adjacent to the PCC. Regions with significant connectivity to the precuneus are plotted in transverse and sagittal section color t-maps as in (**Figure 2B**). DMN connectivity is recapitulated in t-maps of control patients (**Figure 3B**) with areas of high significantly high positive correlations (yellow and red) to DMN components, including the medial prefrontal cortex (mPFC, arrow). In contrast, significant mPFC-precuneus FC is spatially limited in patients during delirium (**Figure 3C**, arrowhead).

Comparison maps from 13/20 patients following recovery from delirium **(Figure 3D**) demonstrates minimal significant precuneus-mPFC connectivity. Censoring of motion artifact, now recognized by the neuroimaging community as a source of spurious differences in FC[57], also was not performed. **Since fcMRI was not performed prospectively before delirium, it is unclear whether fcMRIDMN connectivity in those who previously experienced delirium was similar to controls (Figure 3B).**

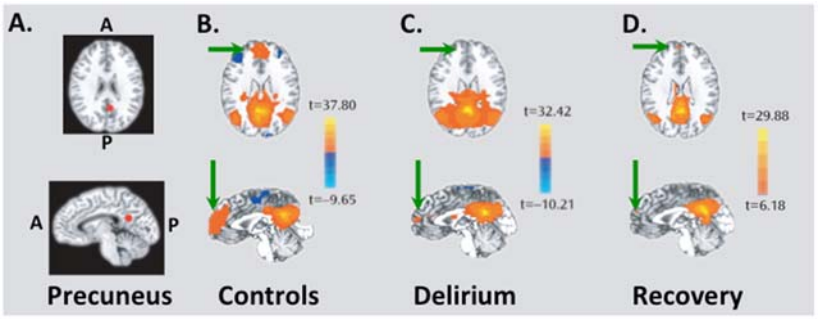

Figure 3. Weakening of fMRI functional connectivity between anterior and posterior DMN regions. Adapted from Choi et al., 2012[56].A. Precuneus region used for FC analysis. **B.** FC t-maps from controls show significant DMN FC in the medial prefrontal cortex (mPFC, green arrow, N=22). **C.** Significant FC between the precuneus and the mPFC is substantially limited during delirium (N=20). **D.** Reduction in DMN FC is not restored after recovery from delirium (N=13). A: Anterior. P: Posterior.

2.1.7 Bedside Functional Neuroimaging

Recent work by members of our team (Culver, Eggebrecht) have allowed the generation of high density diffuse optical tomography systems for assaying task-evoked and resting-state functional connectivity. The imaging system relies on fiberoptic cables implanted in a wearable cap. The fibers are arranged in a grid such that sources and detectors are interspersed along the scalp to allow measurements of near-infrared light (750 nm and 850 nm) in a manner similar to cerebral oximetry. Preprocessing of multiple overlapping measurements of light intensity include source modeling, spectroscopy, and atlas reconstruction to generate oxy- and deoxyhemoglobin maps as a surrogate of neural activity. fcDOT has been recently validated against fcMRI[58, 59], with superficial regions of the DMN accessible by fcDOT[58] (**Figure 4A-B**). A portable clinical system has also been developed[60]. Using this system, fcDOT is currently in use for bedside imaging of RSNs during natural sleep with simultaneous EEG lasting several hours (Palanca, Eggebrecht, Culver, **Figure 4C-E**). Sleep staging and censoring of motion artifact is performed prior to FC analysis. Maps plotting FC to a left frontal region demonstrate bilateral connectivity during rapid eye movement sleep (REM) that is reduced during slow wave sleep (SWS). As EEG during delirium demonstrates slower frequencies in a similar manner as SWS and other sleep stages, these data lend feasibility toward imaging fluctuations in FC that mirror established electrophysiologic correlates and symptomatology. As shown in **Figure 4G**, the cart and fibers of the portable fcDOT system are not expected to impact clinical care, even in the intensive care unit.

2.1.8 Existing Infrastructure for Tracking Delirium

We are involved in the ENGAGES Trial to assess an association between postoperative delirium and intraoperative EEG suppression (NCT02241655, NIH 1UH2AG050312-01, 4UH3AG050312-02, PI, Avidan). The ENGAGES study has enrolled at least 3 cardiac surgical patients per week. Over its first 19 weeks, the incidence rates of delirium are 26% for CABG, 30% for valve, and 71% for combined CABG/valve procedures. Cardiothoracic intensive care unit nurses routinely assess for delirium at least once per shift, with routine notation in medical records.

2.2 Objectives

The ***rationale*** underlying our research agenda is that electrophysiologic and neuroimaging during manifestation and recovery from postoperative delirium may provide markers for future translation into preoperative risk stratification and diagnosis. Our goal is to substantiate commonly used EEG markers of postoperative delirium (Aim 1), utilize bedside optical imaging techniques to investigate DMN connectivity during delirium (Aim 2), assess for functional neuroimaging markers that distinguish patients based on delirium incidence and severity (Aim 3), and investigate the relationship between preoperative DMN FC and postoperative delirium (Aim 4) .

Specific Aim 1: Establish that EEG slowing during postoperative delirium reverses after recovery.

Hypotheses: Relative delta and theta power in frontoparietal EEG are greater during delirium than after resolution. Relative alpha power in frontoparietal EEG is lower during delirium that after recovery.

Specific Aim 2: Determine if DMN connectivity is weaker during delirium than after recovery

Hypothesis: Postoperative DMN FC, measured by fcDOT, is weaker during delirious epochs than after delirium resolution.

Specific Aim 3: Establish whether postoperative DMN FC distinguishes delirious patients from controls.

Hypothesis: Postoperative DMN FC, measured by fMRI and fcDOT, is weaker in those who developed postoperative delirium compared to those who did not experience delirium.

Specific Aim 4: Investigate the relationship between preoperative DMN FC and postoperative delirium.

Hypothesis: Preoperative DMN FC measures will be greater for those who do not experience delirium and will vary inversely with peak postoperative delirium severity.

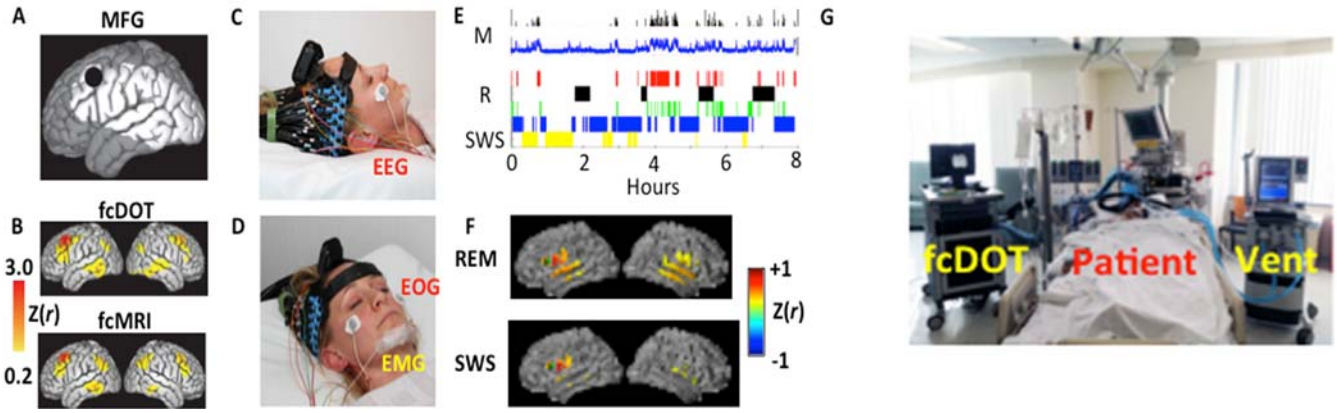

Figure 4. Feasibility of fcDOT imaging of superficial DMN in the perioperative environment. A. The dorsolateral medial frontal gyrus (MFG), an anterior superficial region of the DMN, is accessible to fcDOT. **B.** Comparison of FC maps fcDOT and fcMRI FC. fcDOT data were acquired from healthy volunteers using a stationary fcDOT system, reproduced from Eggebrecht et al., 2014[58]. **C, D.** Volunteer wearing a clinical system cap currently in use for long recordings (> 8 hours) during fcDOT sleep studies comparing rapid eye movement sleep (REM) and slow-wave sleep (SWS). Sleep staging is accomplished using EEG.

2.4 Design and Participants:

2.4.1 Study Design

This prospective observational study is geared toward longitudinal imaging and electrophysiology study of cardiac surgical patients at Barnes-Jewish Hospital. Patients who are recruited in the delirium arm will serve as their own controls in comparisons of EEG and fcDOT data (**Aims 1 and 2**) to study neural correlates of the delirious state. Secondary analysis are planned to compare these measures between patients who experienced delirium and control patients.

Case-control comparisons of both fMRI and fcDOT DMN FC between patients who did and did not experience delirium (**Aim 3**) will provide information on whether reduced DMN FC may be a correlate of vulnerability to

postoperative delirium, as well as whether preoperative DMN FC is associated with postoperative delirium **(Aim 4**).

2.4.2 Pre-Study Period: None

2.4.3 Subject Screening, Enrollment, and Consent Process:

Sixty-six patients who have had cardiac surgery will be recruited in the Center for Preoperative Assessment and Planning (CPAP), Center for Advanced Medicine (CAM), cardiothoracic intensive care unit (CT-ICU), or step-down floors of Barnes-Jewish Hospital (BJH) in St. Louis. Depending on equipment and research personnel availability, patients may be recruited before or after surgery.

Given that the incidence of postoperative delirium is not predictable for an individual and to spare the cost and resources associated with consenting all cardiac patients, a partial HIPAA waiver will be obtained to allow preliminary eligibility screening of patients based on electronic medical records. Research personnel will screen the surgery schedule for Barnes-Jewish Hospital for procedures fitting the inclusion criteria the following week. Surgeries that meet inclusion criteria will then be screened for all eligibility criteria prior to surgery and being approached. Information regarding eligible patients will be kept in a screening log that will be destroyed once recruitment is complete.

Depending on equipment availability, research personnel may approach eligible patients in CPAP, CAM, CT-ICU, or step-down floors before surgery for consent. Patients consented before surgery will undergo preoperative fMRI, fcDOT, and EEG within one month before surgery, as well as a baseline CAM assessment. If patients are approached preoperatively and there is not enough time for preoperative testing to take place (i.e. patient enrolled day before surgery), patients will complete a baseline CAM assessment before surgery and participate in postoperative testing. Patients not consented before surgery will be approached as early as postoperative day 1 following surgery. To screen for dementia at baseline, we will apply the AD8[61].

Preoperative: For patients consented before surgery, full written informed consent will be obtained directly from the patient. Consent many take place in CPAP, CAM, CT-ICU or step-down floors of BJH**. The participant's previous medical record will be reviewed to ensure they meet all inclusion & exclusion criteria.**

Research personnel may contact possible patients identified by the CPAP or surgery schedule by phone prior to their CPAP appointment. Since many patients will have their CPAP appointment the day before surgery, calling patients to confirm interest will allow enough time to schedule the preoperative MRI scan, which typically takes a minimum of 24 hours. Research personnel will discuss the study using a phone script and, if the patient is interested in the study, will go over the inclusion and exclusion criteria with the patient to ensure eligibility. Research personnel will then meet the patient at Barnes-Jewish Hospital on the day of their CPAP appointment or on a day at the convenience of the patient for written informed consent. Due to the availability of the scanner and the patient, preoperative testing procedures may take place on a different day than the CPAP appointment. Written informed consent will be obtained prior to any study procedures.

Postoperative: For patients consented after surgery, mental status of the patient will be assessed by the study team or by monitoring electronic medical records for signs of altered mental status. Consent will take place in the CT-ICU or step-down floors at Barnes-Jewish Hospital. **Delirious:** Given that the patient will be unlikely to provide full informed consent, and to respect the vulnerability of the study population, a legal authorized representative will be approached for informed written or verbal consent. Lack of dissent/tacit assent will be obtained from the patient prior to any study procedures. The patient will not be enrolled if he or she refuses to participate at this time. **Control:** Consent will be obtained directly from the patient.

For each study participant, modifications including session termination will be pursued on any signs of physical or emotional distress. For patients who experience postoperative delirium, full written informed consent will be obtained after delirium resolution for study participation at subsequent time points if delirium resolution occurs before hospital discharge. Patients may withdraw from the study at any time.

2.4.4 Inclusion/Exclusion Criteria

Table 1 lists the inclusion and exclusion criteria common to both patient study arms.

Inclusion Criteria	Exclusion Criteria
Age ≥ 60	Implanted pacemaker
Surgery requiring cardiopulmonary bypass for Coronary artery bypass grafting (CABG), aortic repair/replacement, septal myectomy, and/or heart valve repair/replacement	Automatic internal cardiac defibrillator Other implant for which MRI is contraindicated Concomitant cerebrovascular procedure or requirement of deep hypothermic circulatory arrest
English Speaking	Inability to lay flat or still for MRI Legal blindness or severe deafness Seizure history Known focal brain lesion larger than 3 cm

Table 1: Common Inclusion and Exclusion Criteria for Study Enrollment

Delirium Case Arm: Delirious as diagnosed by the Confusion Assessment Method (CAM)/Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) at some point during postoperative day 1-5. The presence of hypoactive delirium will be confirmed after consent has been obtained and prior to measurements.

Postoperative Control Arm: Not delirious as diagnosed by the CAM on postoperative day 1-5.

2.4.5 Study Involvement

Preoperative Testing: Approximately 2 hours. This will occur within one month before surgery and will take approximately 2 hours total. A baseline CAM assessment will be completed at this time. Research personnel will also assess for pain using the Behavioral Pain Scale for Non-Intubated Patients (BPS-NI). Patients will then be asked to sit upright and still for 30 minutes while watching television or moving toes or fingers to maintain wakefulness. EEG and fcDOT data will be acquired. An additional 15 minutes of data will be acquired while patients keep their eyes closed. To maintain wakefulness, patients will be asked to keep moving toes or fingers. Patients will also listen to an auditory recording for 3 minutes while EEG and fcDOT data is acquired for source localization. Patients will then be asked to remain awake and still in an MRI scanner for 1 hour to allow fMRI data to be acquired. The MRI may not be performed on the same day as preoperative EEG and DOT due to the availability of the scanner. Pulse oximetry may be used during data acquisition, with supplemental oxygen, if needed.

Postoperative Sessions 1-3: Approximately 1 hour each. These sessions will occur between postoperative days 1-8. A CAM assessment will be completed to determine delirium outcome prior to other procedures. If patients are intubated at the time of assessments, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[62] will be used. If the patient is sedated (RASS level -4 or -5), delirium will not be assessed. Patients may also be assessed using the CAM-ICU if the patient's current condition cannot tolerate the long-form of the CAM. Research personnel will also assess for pain using the Behavioral Pain Scale (BPS)/Behavioral Pain Scale for Non-Intubated Patients (BPS-NI), depending on the status of the patient, and the Visual Analog Scale (VAS) pain scores**.** Patients will then be asked to sit upright and still for three 10 minute periods while watching television or moving toes or fingers to maintain wakefulness. EEG and fcDOT data will be acquired. An additional 15 minutes of data will be acquired while patients keep their eyes closed. To maintain wakefulness, patients will be asked to keep moving their toes or fingers. Patients will also listen to an auditory recording for 3 minutes while EEG and fcDOT data is acquired. These data will maximize interpretability by allowing localization of auditory cortex. Pulse oximetry may be used during data acquisition, with supplemental oxygen, if needed.

Session 4-5: Approximately 2 hours. This will occur during the period between disconnection of chest tubes and within 1 month after hospital discharge. A CAM assessment will be completed to determine delirium outcome prior to other procedures. Patients may also be assessed using the CAM-ICU if the patient's current condition cannot tolerate the long-form of the CAM. Research personnel will assess for pain using the Behavioral Pain Scale (BPS)/Behavioral Pain Scale Non-intubated (BPS-NI), depending on the status of the patient, and the Visual Analog Scale (VAS) pain scores**.** Patients will be asked to sit upright and still for 30 minutes while watching television or moving toes or fingers to maintain wakefulness. EEG and fcDOT data will be acquired. An additional 15 minutes of data will be acquired while patients keep their eyes closed. To maintain wakefulness, patients will be asked to keep moving toes or fingers. Patients will also listen to an auditory recording for 3 minutes while EEG and fcDOT data is acquired for source localization.

Patients will then be asked to remain awake and still in an MRI scanner for 1 hour to allow fMRI data to be acquired. Due to the availability of the scanner, patients may undergo the MRI scan on a different day as the session 4 fcDOT and EEG recording session. A CAM assessment will be completed on the day of the scan to assess delirium. Pulse oximetry may be used during data acquisition, with the administration of supplemental oxygen, if needed.

Subjects may be contacted after session 4 to ask about their health status.

Chart Review: We will continually monitor the participant's electronic medical record (EMR) during their enrollment to ensure you remain eligible for study procedures and to help coordinate timing of study procedures. In addition, we will collect information pertaining to the participant's surgery, recovery progress, and indicators of delirium. We will continue to access the participant's EMR after discharge from the hospital.

2.4.6 Intervention: None

2.4.7 Observations and Measurements

2.4.7.1 Electroencephalography Acquisition and Processing (Aims 1).

Skin of patients will be prepped in the following manner. An alcohol swab will be used to degrease the sites. Gentle debridement of dead skin cells will be performed using a sponge and ELPREP (Biopac) prior to placement of electrodes. If detected, high impedance (> 50 kOhm) electrodes will be replaced to maximize signal quality and minimize electrical artifact.

EEG will be recorded using Biopac MP150, wireless Bionomadix transmitters, and AcqKnowledge 4.2 (Biopac Systems, Inc. Goleta, CA). Data will be acquired at 200 Hz. These will be visualized assessed online for EEG motifs associated with light non-rapid eye movement sleep (K-complexes and sleep spindles). During acquisition, patients will be awakened if these are noted. As these motifs have not been described in awake delirious patients, epochs with these periods will be excluded during analysis.

Using a bandpass filter (0.5-35 Hz), slow drift, EMG, and electrical artifact will be reduced in the EEG recordings. Power spectral analysis will be performed on the first 1 minute of artifact-free data. Total power (TP) will be computed between 0.5 and 30 Hz. Relative Delta Power will be calculated as power between 0.5-4 Hz / TP. Relative Theta Power will be calculated as power between 4-8 Hz / TP. Relative Alpha Power will be calculated as the power between 8-12 Hz / TP. These measures will be calculated for each patient during eyes open and eyes closed epochs, and during both delirium and after resolution.

2.4.7.2 fcDOT processing, and FC analysis (Aims 2).

High-density fcDOT will be performed using a clinical CW imaging system (near-infrared wavelengths of 750 nm and 850 nm, 48 sources and 34 detectors) paired with optical fibers embedded in a wearable imaging cap. This

cap (Figure 4C-D) will provide coverage over DMN components that are anterior (dorsolateral middle frontal gyrus, MFG) and posterior (inferior parietal lobule, IPL). Patients will be instructed to keep their eyes open and to stay awake for three 10-minute runs. Pre-processing will continue as previously described[58]. Briefly, source-detector measurements will undergo log-mean transformation prior to filtering, reconstruction, spectroscopy, and transformation to MNI atlas space. Superficial signal regression and a motion censoring metric similar to DVARS will be used to reduce physiologic and motion artifacts. Bandpass filtering (0.009-0.8 Hz), Pearson correlations will be Fisher z-transformed prior to averaging to maximize normality. The median DMN FC taken across all DMN region pairs will serve as our summary metric for DMN integrity at an individual level.

2.4.7.3 MRI Acquisition, Image Processing, and FC (Aim 3)

Structural and functional MRI will be performed at either the Center for Clinical Imaging and Research (CCIR), located on the 10thfloor of Barnes Jewish Hospital, or the 5th floor Mallinckrodt Institute of Radiology (MIR). The two scanners are the same model and will be equipped with the identical MR sequences. The same MR sequence will be used for each scan. Preoperative testing: The patient will undergo an MRI scan at BJH within one month of surgery, either at the CCIR or in the MRI suite of 5th floor of MIR. A study physician will be present during the scanning of inpatients to improve safety and monitoring. A CAM assessment will be completed on the same day as the scan. Pulse oximetry may be used during data acquisition, with the administration of supplemental oxygen, if needed. Session 4: The patient will undergo an MRI scan during the period between disconnection of chest tubes and within 1 month after hospital discharge at BJH, either at the CCIR or in the MRI suite of the 5th floor of MIR. A study physician will attend inpatient scans to improve safety and monitoring. A CAM assessment will be completed on the same day as the scan. Pulse oximetry may be used during data acquisition, with the administration of supplemental oxygen, if needed.

Image acquisition, preprocessing, and FC analysis will be performed as recently described[41] with minor modifications. Participants will be instructed to remain still and awake with eyes open during scans. Data will be uploaded into CNDA, which is a database used exclusively by Washington University in St. Louis to manage, share, and analyze imaging data. This database will be used to store acquired images, perform various analyses, and share data amongst collaborators. Only de-identified data will be stored in the database. Preprocessing includes motion correction, resampling in Talairach atlas space (3 x 3 x 3 mm cubic voxels), and intensity normalization to a whole-brain mode value of 1000[63]. We will employ motion censoring using the DVARS measure [57, 64] set at 04% root-mean-square frame-to-frame BOLD signal change[65], a critical step in reducing FC changes related to motion artifact. Additional noise reduction will be done via regression of CSF, white matter, and whole brain global signal. For FC analysis 9 x 9 x 9 mm cubes with at least 50% gray matter will be used. ROIs will have been assigned to 1 of 7 RSNs[66] with over 95% probability. Pearson correlations will be Fisher z-transformed prior to averaging to maximize normality. The median DMN FC taken across all DMN region pairs will serve as our summary metric for DMN integrity at an individual level.

2.4.7.4 Outcomes

Delirium Diagnosis: Assessments will occur during preoperative testing (if applicable) and at the beginning of sessions 1-4. If the patient undergoes the session 4 MRI scan on a different day from the fourth EEG and DOT recording session, a CAM assessment will be completed prior to the patient entering the scanner. We will use the Confusion Assessment Method (CAM, long form)[67] to assign the presence or absence of delirium. The CAM is a validated tool for delirium diagnosis, with a sensitivity of 94% and specificity of 89%[68]. Administration of the CAM takes 10-20 minutes at our institution. If patients are also enrolled in The ENGAGES study (HRPO# 201407128), CAM assessment and CAM chart review data will be retrospectively and prospectively obtained from their research records to determine delirium diagnosis, severity, and duration, including both preoperative and postoperative assessments.

Delirium Severity: Delirium severity will be quantified using the CAM-S, a validated weighting of CAM subscores[69]. We will apply the long form of the CAM-S as it has a finer scale from 0 to 19.

Delirium Duration: # days of CAM+ will be determined by CAM outcome and from examination of the patient's electronic medical record through delirium chart review.

Pain level: Assessed using the Behavioral Pain Scale for the Non-Intubated Patient (BPS-NI) and the Visual Analog Scale (VAS) Pain Scores. If patients are also enrolled in The ENGAGES study (HRPO# 201407128), pain assessment data will be retrospectively and prospectively obtained from their research records, including both preoperative and postoperative assessments.

2.5. Analytical and Statistical Methods

2.5.1 Aim 1: Establish that EEG slowing during postoperative delirium reverses after recovery.

Hypotheses: Relative delta power and theta power in frontoparietal EEG are greater during delirium than after resolution. Relative alpha power in frontoparietal EEG is lower during delirium that after recovery.

Analysis: Wilcoxon sign-rank tests will be used to assess differences in delta, theta, and alpha power, for both eyes open and eyes closed conditions. Bootstrapping will be used to assess statistical significance and confidence intervals.

Expected Findings: Median delta and theta power during delirium will be greater during delirium than after resolution. Median alpha power will be greater during delirious episodes than after recovery.

Interpretations and Future Directions: These EEG changes are similar to those observed during non-rapid eye movement sleep and general anesthesia but have also been reported during delirious epochs. Resolution in longitudinal studies would support the hypothesis that arousal is maintained during delirium but that the dynamics of cerebral cortex mirrors that of sleep states. Future studies would be geared toward using these EEG signatures to assist in the detection/diagnosis of delirium in the ICU and to determine whether these different patterns reflect delirium severity or subtypes with syndrome components.

Problems/Alternative Approaches: Eye closed recordings will address blink/movement artifacts that are present in eyes open recordings. Despite our efforts, patients may still find difficulty in remaining awake, particularly during eyes closed recordings. **Sleep.** EEG will be assessed for signs that the patient is sleeping rather than awake and delirious.

2.5.2 Aim 2: Determine if DMN connectivity is weaker during delirium than after recovery

Hypotheses: Postoperative DMN FC, measured by fcDOT, correlates with delirium severity and is weaker during delirious epochs than after delirium resolution.

Analysis 1: A Wilcoxon sign-rank test will assess for differences in median DMN FC between periods corresponding with the presence or absence of delirium.

Expected Finding: Median DMN FC during delirium will be lower than during neurologically intact periods.

Analysis 2: Regression analysis will determine the correlation of median DMN FC and CAM-S.

Expected Findings: Among patients imaged during postoperative delirium, median DMN FC will vary inversely with symptom severity.

Interpretations and Future Directions: A lower median DMN FC during delirium than during lucid periods would suggest that DMN FC can be used to screen out patients with delirium. A strong correlation between delirium severity and DMN FC would support the potential of this marker for longitudinal tracking of delirium development and recovery. Future studies would be aimed at imaging prior to delirium symptom manifestation to assess for predictability during this latent phase where intervention may reduce subsequent incidence or severity.

Problems/Alternative Approaches: The clinical cap **(Figure 4C-D)** is expected to cover both frontal and parietal brain regions to the same extent as the stationary fcDOT system **(Figure 4A-B).** We will make adjustments as needed to cap coverage and light modeling needed. With structural MRI, we can also generate subject-specific light models top optimize fcDOT sensitivity.

2.5.3 Aim 3: Establish whether postoperative DMN FC distinguishes delirious patients from controls.

Hypothesis: Postoperative DMN FC, measured by fMRI and fcDOT, is weaker in those who developed postoperative delirium compared to those who did not experience delirium.

Analysis 1: A Mann-Whitney U-test will assess for differences in median DMN FC between those who did and did not experience delirium. Bootstrapping will be used to assess statistical significance and confidence intervals.

Expected Finding: Median DMN FC will be weaker for those did not experience postoperative delirium.

Interpretations and Future Directions: A lower median DMN FC for patients who developed delirium would reflect an underlying vulnerability against delirium. Subsequent prospective studies could correlate preoperative DMN FC, and postoperative delirium risk. Further studies would also be needed to generate a reference range to address the possibility that high DMN FC is associated with protection against delirium. The strength of the correlation will be informative for whether fcMRI or fcDOT is more sensitive. **Motion artifact.** If excessive during fcMRI or fcDOT acquisition, scanning length will be extended. We will also consider increasing head padding within the MR scanner coil. We will use frame censoring of motion artifact as in our prior study[41]. **Sleep.** Fluctuations in arousal can potentially confound fcMRI during wakefulness[70], so patients will be asked to remain still with eyes closed.

2.5.4 Aim 4: Investigate the relationship between preoperative DMN FC and postoperative delirium.

Hypothesis: Preoperative DMN FC measures will be greater for those who do not experience delirium and will vary inversely with peak postoperative delirium severity.

Analysis 1: A Mann-Whitney U-test will assess for differences in median DMN FC between those who did and did not experience delirium.

Expected Finding: Median preoperative DMN FC will be greater in those who do not experience delirium.

Analysis 2: Regression analysis will determine the correlation of peak delirium severity score and preoperative DMN FC.

Expected Finding: Preoperative DMN FC will vary inversely with peak delirium severity.

Interpretations and Future Directions: A lower median DMN FC for patients who developed delirium would reflect an underlying vulnerability against delirium and potentially pre-clinical Alzheimer's dementia.
Subsequent studies could correlate plaque burden, DMN FC, and postoperative delirium risk. Further studies would also be needed to generate a reference range to address the possibility that high DMN FC is associated with protection against delirium. The strength of the correlation will be informative for whether fcMRI or fcDOT is more sensitive.

Problems/Alternative Approaches: **Recruitment.** We expect to enroll approximately 1 patient per week. Poor recruitment may require additional data acquisition into Year 2 or expansion of recruitment to patients scheduled for concomitant procedures or percutaneous aortic valve replacement. **Nuisance covariates.** Despite the smaller sample size, we will consider a MANOVA to account for age and years of education. We will incorporate postoperative day in the model if variance is high for postoperative intubation length. Magnitudes of beta value would then be assessed for relative contributions to predicting delirium. **Motion artifact**. If excessive during fcMRI or fcDOT acquisition, scanning length will be extended. We will also consider increasing head padding within the MR scanner coil. We will use frame censoring of motion artifact in our prior study[41]. **Sleep.** Fluctuations in arousal can potentially confound fcMRI during wakefulness[70]We will record shorter (5-minute) epochs if patients are unable to remain awake for 10-minute scans.

2.5.5 Sub-studies

EEG and fcDOT from patient controls will be used for case-control studies or for improving the technology of fcDOT. Some evidence suggests that blinks and eye movements may be useful for the detection of delirium[71]. Once larger samples sizes are obtained, age, years of education, surgical and anesthetic exposure,

cardiopulmonary bypass duration, and aortic cross clamp time will be used in future studies as nuisance covariates.

2.6 Sample Size

Sample Size Justification: The study has been powered to compare differences in DMN FC between patients who did and did not experience delirium. While universal agreement in sample size is lacking, FC studies employing 15 minutes of scanner time and 15 or more individuals produce reliable fcMRI maps[72]. We anticipate the ability to observe large effects (effect size 0.8, beta 0.2, power 0.8) based on conventions for statistical power analysis in the behavioral sciences.[73]

2.7 Management of Intercurrent Events

2.7.1 Cross-over

There will be no planned cross-over of participants in this study. Patients who develop delirium over the course of the study will be assigned to the delirium arm.

2.7.2 Adverse Experiences

The investigator will closely monitor subjects for evidence of adverse events in this minimal risk study.
All adverse events will be reported to the IRB and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study, and any treatment required.

2.7.3 Premature Discontinuation

Patients will be withdrawn if discontinuation is in the best interest of the patient or if the patient requests withdrawal from the study for any reason.

2.7.4 Potential Risks

Interruption of clinical care: Timing of studies could potentially interfere with nursing, therapy, or medical assessments.

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

Discomfort related to DOT: No adverse effects have been reported with diffuse optical tomography, although it is possible that effects not yet reported may occur. The LED light used to make the measurements has very low power (less than 4 mW/mm2 at 800 nm) and below the ANSI limit for long-term exposure to infrared light. As the power is substantially less that that used in pulse oximetry, a standard anesthetic monitoring device uses the similar technology, even the risk of burns is very remote. The procedure does not cause stress or discomfort. Though unlikely to occur, the imaging cap may press or scrape uncomfortably against the scalp, producing a light skin reaction.

Non-contrast MRI: Claustrophobia, anxiety, discomfort from headphones used to shield out noise, hearing loss due to hammering noise. Additionally, patients with tattoos could experience irritation, swelling, heating, or instances of primary or secondary burns in the area of the tattoo. 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. There have been no adverse events noted for 3T MRI studies of patients with coronary stents, sternal wires, cardiac valves, or even retained temporary pacemaker wires[74].

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. Depending on logistical constraints, preoperative testing and session 4 may be split up to maximize convenience for our patient and alignment with MRI scanner availability. For example, DOT and EEG for session 4 may be acquired while the patient remains in the hospital whereas fMRI may be performed as an outpatient due to scheduling conflicts. A study physician will be present during the scanning of inpatients to address the risks associated with an MRI scan in a remote location. Additionally, if the participant is still in the hospital, the scan will be scheduled to occur after chest tubes have been removed and the patient is close to hospital discharge.

EEG: 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.

DOT: Placement and removal of cap adjustment will be undertaken to minimize any discomfort for the patient.

MRI Safety: The patient will be thoroughly screened for MRI-incompatible implants. Scans may be performed prior to surgery (Preoperative testing) and/or postoperatively, after removal of any temporal pacemaker wires and removal of chest tubes. Cardiac stents and valves will be checked to confirm compatibility. The MRI scan will occur at least 3 days after surgery to ensure that granulation tissue has formed around any sternal wires and minimize any risk of dislodgement. Scans performed on inpatients or after recent discharge (Session 4) will occur within the hospital (5^{th} floor MIR or CCIR on 10^{th} floor of BJH). A study physician will be present for inpatient scans.

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.

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 the study session by trained research personnel.

Participant Satisfaction: Physical and psychological risks to subjects will be minimized by obtaining feedback from participants. Patients studied during delirious episodes will be approached for full informed consent following recovery from their altered mental status if delirium resolution occurs before hospital discharge.

Data and Safety Monitoring Plan
The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported to the IRB 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 enrolling human volunteers 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.

3.2 Sources of Materials

Patients will receive remuneration for time and effort ($450 possible per participant). Compensation for EEG recording will be $5 per each EEG recording, with a total of $25 possible. Compensation for DOT recording will consist of $45 per each DOT recording session, with a total of $225 possible. Participants will be given $100 for the completion of each MRI scan, for a total of $200 possible. Cab fare will be arranged and paid for ahead of any study-related outpatient visits by study staff to cover the cost of transportation for study procedures. If otherwise requested by the patient, parking vouchers will also be assigned to participants to cover the cost of parking for the duration of any required study-related visits. 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. Given that the incidence of postoperative delirium is not predictable for an individual and to spare the cost and resources associated with consenting all cardiac patients, a partial HIPAA waver will be obtained to allow preliminary eligibility screening of patients based on electronic medical records. Research personnel will screen the surgery schedule for Barnes-Jewish Hospital for procedures fitting the inclusion criteria the following week. Surgeries that meet inclusion criteria will then be screened for all eligibility criteria prior to surgery and being approached. Information regarding eligible patients will be kept in a screening log that will be destroyed once recruitment is complete.

Depending on equipment availability, research personnel may approach eligible patients in CPAP, CAM, or step-down floors before surgery for consent. Patients consented before surgery will undergo a preoperative fMRI, fcDOT, and EEG within one month before surgery. Patients not consented before surgery will be approached as early as postoperative day 1 following surgery and extubation. To screen for dementia at baseline, we will apply the AD8[61].

Preoperative: For patients consented before surgery, full written informed consent will be obtained directly from the patient. Consent many take place in CPAP, CAM, ICU, or step-down floors**.**

Postoperative: For patients consented after surgery, mental status of the patient will be assessed by the study team. Consent will take place in the CT-ICU or step-down floors at Barnes-Jewish Hospital. **Delirious:** Given that the patient will be unlikely to provide full informed consent, and to respect the vulnerability of the study population, a legal authorized representative will be approached for informed written or verbal consent. Lack of dissent/tacit assent will be obtained from the patient prior to any study procedures. The patient will not be enrolled if he or she refuses to participate at this time. **Control:** Consent will be obtained directly from the patient.

For each study participant, modifications including session termination will be pursued on any signs of physical or emotional distress. For patients who experience postoperative delirium, full written informed consent will be obtained after delirium resolution for study participation at subsequent time points if delirium resolution occurs before hospital discharge. Patients may withdraw from the study at any time.

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

The patient will have a structural and functional MRI that will be free of charge to them. MRI structural scans will be interpreted by board-certified neuroradiologists. Both the images and reports will be available to the patient within their Clinical Desktop record. While unlikely, the scan may aid in clinical decision making during hospitalization. These diagnostics are more likely to be useful for the patient as a baseline for comparison in the event that future neurological symptoms manifest and necessitate a future MRI scan.

The proposed work may assist in establishing DOT or EEG as a viable method for assisting in the diagnosis of postoperative delirium. MRI study of patients who previously developed postoperative delirium may elucidate an underlying structural or functional marker of vulnerability for this important under-diagnosed perioperative neurological complication.

Overall, this study is geared toward the development of markers that may assist in diagnosis, prevention, or mitigation of postoperative delirium.

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 obstetric patient population (30% white, 60% Black, 6 % Hispanic, 4% Asian).

3.7 Inclusion of Children

No children will be enrolled in this study.

4. REFERENCES

1. Franco, K., et al., *The cost of delirium in the surgical patient.* Psychosomatics, 2001. **42**(1): p. 68-73.
2. Dasgupta, M. and A.C. Dumbrell, *Preoperative risk assessment for delirium after noncardiac surgery: a systematic review.* J Am Geriatr Soc, 2006. **54**(10): p. 1578-89.
3. Brown, C.H., *Delirium in the cardiac surgical ICU.* Curr Opin Anaesthesiol, 2014. **27**(2): p. 117-22.
4. McKhann, G.M., et al., *Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction.* Arch Neurol, 2002. **59**(9): p. 1422-8.
5. MacLullich, A.M., et al., *Delirium and long-term cognitive impairment.* Int Rev Psychiatry, 2009. **21**(1): p. 30-42.
6. Jackson, J.C., et al., *The association between delirium and cognitive decline: a review of the empirical literature.* Neuropsychol Rev, 2004. **14**(2): p. 87-98.
7. Rudolph, J.L., et al., *Delirium: an independent predictor of functional decline after cardiac surgery.* J Am Geriatr Soc, 2010. **58**(4): p. 643-9.
8. Gottesman, R.F., et al., *Delirium after coronary artery bypass graft surgery and late mortality.* Ann Neurol, 2010. **67**(3): p. 338-44.
9. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2013, Washington, D.C.: American Psychiatric Association.
10. Nicholas, L.M. and B.A. Lindsey, *Delirium presenting with symptoms of depression.* Psychosomatics, 1995. **36**(5): p. 471-9.
11. Spiller, J.A. and J.C. Keen, *Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care.* Palliat Med, 2006. **20**(1): p. 17-23.
12. van Eijk, M.M., et al., *Comparison of delirium assessment tools in a mixed intensive care unit.* Crit Care Med, 2009. **37**(6): p. 1881-5.
13. Robinson, T.N., et al., *Postoperative delirium in the elderly: risk factors and outcomes.* Ann Surg, 2009. **249**(1): p. 173-8.
14. Lipowski, Z.J., *Delirium in the elderly patient.* N Engl J Med, 1989. **320**(9): p. 578-82.
15. Eide, L.S., et al., *Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement.* Am J Cardiol, 2015. **115**(6): p. 802-9.
16. Engel, G.L., Romano, J., *Delirium. 1. Electroencephalographic data.* Arch Neurol Psychiatry, 1944. **51**: p. 356-77.
17. Pro, J.D. and C.E. Wells, *The use of the electroencephalogram in the diagnosis of delirium.* Dis Nerv Syst, 1977. **38**(10): p. 804-8.
18. Reischies, F.M., et al., *Electrophysiological and neuropsychological analysis of a delirious state: the role of the anterior cingulate gyrus.* Psychiatry Res, 2005. **138**(2): p. 171-81.
19. Hanif, S., S. Sinha, and K.A. Siddiqui, *Electroencephalography findings in patients with acute post coronary artery bypass graft encephalopathy.* Neurosciences (Riyadh), 2014. **19**(4): p. 331-3.
20. Jacobson, S.A., A.F. Leuchter, and D.O. Walter, *Conventional and quantitative EEG in the diagnosis of delirium among the elderly.* J Neurol Neurosurg Psychiatry, 1993. **56**(2): p. 153-8.
21. Leuchter, A.F. and S.A. Jacobson, *Quantitative measurement of brain electrical activity in delirium.* Int Psychogeriatr, 1991. **3**(2): p. 231-47.
22. van der Kooi, A.W., et al., *What are the opportunities for EEG-based monitoring of delirium in the ICU?* J Neuropsychiatry Clin Neurosci, 2012. **24**(4): p. 472-7.
23. Plaschke, K., et al., *Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6.* Intensive Care Med, 2010. **36**(12): p. 2081-9.
24. Plaschke, K., et al., *EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit.* Anaesthesia, 2007. **62**(12): p. 1217-23.

25. Jacobson, S.A., et al., *Serial quantitative EEG among elderly subjects with delirium.* Biol Psychiatry, 1993. **34**(3): p. 135-40.
26. Katz, I.R., et al., *Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period.* Am J Geriatr Psychiatry, 2001. **9**(2): p. 148-59.
27. Thomas, C., et al., *Serum anticholinergic activity and cerebral cholinergic dysfunction: an EEG study in frail elderly with and without delirium.* BMC Neurosci, 2008. **9**: p. 86.
28. Thomas, C., et al., *Prolonged activation EEG differentiates dementia with and without delirium in frail elderly patients.* J Neurol Neurosurg Psychiatry, 2008. **79**(2): p. 119-25.
29. Koponen, H., et al., *EEG spectral analysis in delirium.* J Neurol Neurosurg Psychiatry, 1989. **52**(8): p. 980-5.
30. Katz, I.R., et al., *Bedside clinical and electrophysiological assessment: assessment of change in vulnerable patients.* Int Psychogeriatr, 1991. **3**(2): p. 289-300.
31. van der Kooi, A.W., et al., *Delirium detection using EEG: what and how to measure.* Chest, 2015. **147**(1): p. 94-101.
32. Saczynski, J.S., et al., *Cognitive and Brain Reserve and the Risk of Postoperative Delirium in Older Patients.* Lancet Psychiatry, 2014. **1**(6): p. 437-443.
33. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium.* N Engl J Med, 2012. **367**(1): p. 30-9.
34. Omiya, H., et al., *Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study.* Can J Anaesth, 2015.
35. Nah, H.W., et al., *New brain infarcts on magnetic resonance imaging after coronary artery bypass graft surgery: lesion patterns, mechanism, and predictors.* Ann Neurol, 2014. **76**(3): p. 347-55.
36. Shioiri, A., et al., *White matter abnormalities as a risk factor for postoperative delirium revealed by diffusion tensor imaging.* Am J Geriatr Psychiatry, 2010. **18**(8): p. 743-53.
37. Morandi, A., et al., *The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*.* Crit Care Med, 2012. **40**(7): p. 2182-9.
38. Morandi, A., et al., *Neuroimaging in delirious intensive care unit patients: a preliminary case series report.* Psychiatry (Edgmont), 2010. **7**(9): p. 28-33.
39. Gunther, M.L., et al., *The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study*.* Crit Care Med, 2012. **40**(7): p. 2022-32.
40. Cavallari, M., et al., *Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia.* Neurobiol Aging, 2015. **36**(6): p. 2122-9.
41. Palanca, B.J., et al., *Resting-state Functional Magnetic Resonance Imaging Correlates of Sevoflurane-induced Unconsciousness.* Anesthesiology, 2015.
42. Raichle, M.E., et al., *A default mode of brain function.* Proc Natl Acad Sci U S A, 2001. **98**(2): p. 676-82.
43. Greicius, M.D., et al., *Functional connectivity in the resting brain: a network analysis of the default mode hypothesis.* Proc Natl Acad Sci U S A, 2003. **100**(1): p. 253-8.
44. Fox, M.D., et al., *The human brain is intrinsically organized into dynamic, anticorrelated functional networks.* Proc Natl Acad Sci U S A, 2005. **102**(27): p. 9673-8.
45. Fox, M.D., et al., *Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems.* Proc Natl Acad Sci U S A, 2006. **103**(26): p. 10046-51.
46. Buckner, R.L., J.R. Andrews-Hanna, and D.L. Schacter, *The brain's default network: anatomy, function, and relevance to disease.* Ann N Y Acad Sci, 2008. **1124**: p. 1-38.
47. Horovitz, S.G., et al., *Decoupling of the brain's default mode network during deep sleep.* Proc Natl Acad Sci U S A, 2009. **106**(27): p. 11376-81.

48. Samann, P.G., et al., *Development of the brain's default mode network from wakefulness to slow wave sleep.* Cereb Cortex, 2011. **21**(9): p. 2082-93.
49. Vanhaudenhuyse, A., et al., *Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients.* Brain, 2010. **133**(Pt 1): p. 161-71.
50. Boveroux, P., et al., *Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness.* Anesthesiology, 2010. **113**(5): p. 1038-53.
51. Brier, M.R., et al., *Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression.* J Neurosci, 2012. **32**(26): p. 8890-9.
52. Rombouts, S.A., et al., *Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study.* Hum Brain Mapp, 2005. **26**(4): p. 231-9.
53. Hedden, T., et al., *Disruption of functional connectivity in clinically normal older adults harboring amyloid burden.* J Neurosci, 2009. **29**(40): p. 12686-94.
54. Sperling, R.A., et al., *Amyloid deposition is associated with impaired default network function in older persons without dementia.* Neuron, 2009. **63**(2): p. 178-88.
55. Sheline, Y.I., et al., *Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly.* Biol Psychiatry, 2010. **67**(6): p. 584-7.
56. Choi, S.H., et al., *Neural network functional connectivity during and after an episode of delirium.* Am J Psychiatry, 2012. **169**(5): p. 498-507.
57. Power, J.D., et al., *Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion.* Neuroimage, 2012. **59**(3): p. 2142-54.
58. Eggebrecht, A.T., et al., *Mapping distributed brain function and networks with diffuse optical tomography.* Nat Photonics, 2014. **8**(6): p. 448-454.
59. Ferradal, S.L., et al., *Atlas-based head modeling and spatial normalization for high-density diffuse optical tomography: in vivo validation against fMRI.* Neuroimage, 2014. **85 Pt 1**: p. 117-26.
60. Ferradal, S.L., et al., *Functional Imaging of the Developing Brain at the Bedside Using Diffuse Optical Tomography.* Cereb Cortex, 2015.
61. Galvin, J.E., et al., *The AD8: a brief informant interview to detect dementia.* Neurology, 2005. **65**(4): p. 559-64.
62. Ely, E., et al., *Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.* JAMA, 2004. **291**(14): p. 1753-1762.
63. Ojemann, J.G., et al., *Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts.* Neuroimage, 1997. **6**(3): p. 156-67.
64. Smyser, C.D., et al., *Longitudinal analysis of neural network development in preterm infants.* Cereb Cortex, 2010. **20**(12): p. 2852-62.
65. Power, J.D., et al., *Methods to detect, characterize, and remove motion artifact in resting state fMRI.* Neuroimage, 2014. **84**: p. 320-41.
66. Hacker, C.D., et al., *Resting state network estimation in individual subjects.* Neuroimage, 2013. **82**: p. 616-33.
67. Inouye, S.K., et al., *Clarifying confusion: the confusion assessment method. A new method for detection of delirium.* Ann Intern Med, 1990. **113**(12): p. 941-8.
68. Inouye, S.K., R.G. Westendorp, and J.S. Saczynski, *Delirium in elderly people.* Lancet, 2014. **383**(9920): p. 911-22.
69. Inouye, S.K., et al., *The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts.* Ann Intern Med, 2014. **160**(8): p. 526-33.
70. Tagliazucchi, E. and H. Laufs, *Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep.* Neuron, 2014. **82**(3): p. 695-708.
71. van der Kooi, A.W., et al., *Delirium detection based on monitoring of blinks and eye movements.* Am J Geriatr Psychiatry, 2014. **22**(12): p. 1575-82.

72. Liu, X., et al., *Neural origin of spontaneous hemodynamic fluctuations in rats under burst-suppression anesthesia condition.* Cereb Cortex, 2011. **21**(2): p. 374-84.
73. Cohen, J., *Statistical Power Analysis for the Behavioral Sciences*. 1988: Lawrence Erlbaum Associates.
74. Levine, G.N., et al., *Safety of magnetic resonance imaging in patients with cardiovascular devices: an American Heart Association scientific statement from the Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Council on Cardiovascular Radiology and Intervention: endorsed by the American College of Cardiology Foundation, the North American Society for Cardiac Imaging, and the Society for Cardiovascular Magnetic Resonance.* Circulation, 2007. **116**(24): p. 2878-91.