Neuroimaging of Anesthetic Modulation of Human Consciousness
NCT #:03361605
Document date: 03/10/2020

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Specific Aims

Administering anesthetic drugs to suppress consciousness is an imperatively important step in major surgical operations. Yet the neurobiological mechanisms that underlie loss of consciousness under general anesthesia remain elusive. Despite advancements in understanding the molecular, synaptic, and cellular effects of anesthetics, the large-scale, systems-level modulation of neuronal processes that support conscious cognitive functions is incompletely understood. While profound decreases in global and regional brain metabolism, blood flow, and functional connectivity have been reported, these changes often fail to correlate with the loss and return of consciousness. To date, we have no "consciousness meter" or "gold standard" to objectively assess and monitor the level of consciousness under general anesthesia. Several studies suggest that residual cognitive functions may not completely vanish under general anesthesia; however, the level and complexity of *residual information processing* in the anesthetized brain remains unknown. Finally, the neurobiological mechanisms that govern anesthesia *induction and emergence* appear to be partially different, but the relevance of these differences to the modulation of the state of consciousness is unclear.

Our fundamental hypothesis has been that consciousness emerges from brain function as a network phenomenon, and that loss of consciousness during general anesthesia results from a *disruption of communication in networks* that support information integration. Our findings suggest that anesthetic unconsciousness correlates with a decrease of functional connectivity in the thalamocortical systems, particularly in the "*nonspecific" thalamocortical division*. Our recent data also suggest that anesthetics modulate additional *intrinsic networks* involved in information integration in specialized cognitive subsystems.

During the last decade, we have been developing novel blood-oxygen level-dependent (BOLD) functional MRI (fMRI) and resting-state functional connectivity MRI (R-fcMRI) methods with high spatial and temporal resolution to test specific hypotheses about the anesthetic modulation of cognitive functioning, network organization, and information integration in the human brain. Accordingly, our general plan of work includes both *task-dependent* and *task-free (resting state*) imaging of brain networks. We focus on determining the brain's ability for integrative functioning under wakefulness and graded levels of suppressed consciousness achieved with *propofol*. Our specific Aims are:

Specific Aim 1. *To determine the order and neural correlates of the loss of cognitive and motor functions of the brain in time and space during deepening of anesthesia up to a complete loss of consciousness.* ***Hypotheses*****: 1) Anesthetics suppress consciousness by diminishing integrative functional networks of the brain in a graded, top-down manner, suppressing the most complex systems first and the simplest systems last. 2) These changes can be characterized by assessing the anesthetics' effect on the behavioral response and neural activity to a series of tasks that depend on different levels of information integration.** Specifically, we focus on anesthetic modulation of sensory reaction, attention, semantic processing, motor execution, and the associated state of awareness, up to a total unconsciousness.

Specific Aim 2. *To determine the resting-state anesthetic modulation of functional connectivity, integration, and reconfiguration of brain networks at four conditions: wakeful baseline, mild sedation, deep sedation, and recovery.* Our hypotheses are: **(1) anesthetic-induced loss of consciousness correlates with specific changes of functional connectivity and network integration in thalamocortical and frontoparietal networks, (2) some intrinsic networks, particularly the attention, executive control, and salience networks, are significantly**

affected by anesthetics, while others, such as the default mode network (DMN) and sensory networks, are not, and (3) significant modular network reconfiguration occurs in response to anesthetic intervention, reflecting the changes in resource distribution and integrative processing.

Specific Aim 3. *To determine the different neural mechanisms of recovery of consciousness from anesthesia as opposed to loss of consciousness during deepening anesthesia.* This aim seeks a deeper understanding of how the brain responds to anesthetic modulation in network interaction and self-reorganization as a function of its prior state. Based on the "neural inertia" theory and our preliminary findings, we hypothesize that **(1) anesthetic-modulated loss and return of consciousness are mediated in part by different neural processes that show a prior state dependency, as reflected by various brain network interaction measures** (e.g., connectivity, mutual information, etc.), and **(2) the restoration of consciousness from anesthesia requires additional neural resources over those for maintaining consciousness at wakeful baseline, reflecting a reconfiguration capability of the healthy brain as a self-organizing system for resource management and functional resilience.**

Number of Subjects, Recruitment and Informed Consent. Statistical power analysis (see below) requires a group of 30 subjects for each of the proposed Specific Aims. As such, a total of 30 subjects (ages between 18-40 years old) will be required to complete the study. Healthy participants will be recruited by listing on UMClinicalStudies.org and by postings at area colleges and community groups in Ann Arbor. Interested volunteers will call the phone number of a designated recruiter for an initial phone screening. The initial phone screening will consist of questionnaires related to medical history, demographic information, handedness, inclusion and exclusion criteria and procedure standard MRI screening questionnaire. If interested, the participant will complete the questionnaires, which will be reviewed by the study team. The health status will be confirmed by the attending anesthesiologist before the study on site. Once eligibility is confirmed by the study team, the one-time research study session will be scheduled.

All participants will give written informed consent according to institutional guidelines prior to any testing. The Principal Investigators or their designee will obtain consent using a written consent form approved by the Institutional Review Boards of the University of Michigan Medical School (IRBMED). It will contain detailed information regarding the purpose, risks and benefits of participating. Copies of the signed consent form will be given to the subjects; the original consent will remain with the study team. Subjects will be compensated for their involvement.

Inclusion and exclusion criteria. Volunteers are screened using a medical history and demographics questionnaire.

Inclusion Criteria: The subject population will consist of healthy study subjects with ASA-1 status. The participants' health status will be assessed by the attending anesthesiologist prior to inclusion in the study. The participants will be right-handed adults between the ages of 18 and 40 with a body mass index (BMI) less than 30. Participants will have the experience of playing tennis (or other racquet sport) at least 30 times in their lifetime. All subjects will be English speakers.

Exclusion Criteria: Participants will be excluded if they have any medical contraindication to MRI scanning; are unable to undergo MRI scanning because of possible pregnancy, extreme obesity, metallic substances in the body, claustrophobia, anxiety, or cardiopulmonary disease; or have an intracranial structural abnormality on T1-weighted MRI scans. Potential subjects will be excluded if they have a history of allergic reaction to eggs, neurological, cardiovascular, or pulmonary illness; significant head injury with loss of consciousness; learning disability or other

developmental disorder; sleep apnea or any severe snoring history; gastroesophageal reflux disease (GERD) or heartburn; or sensory/motor loss sufficient to interfere with performance of the study. Participants with tattoos in the head or neck region will be excluded from study; other tattoos are subject to determination by investigators based on their assessment regarding participant safety. To eliminate aspiration risk subjects will also be excluded if they have had recent food or liquid intake (within 8 hours). Subjects will be excluded if they have a history of drug use, have a positive drug screen, are unwilling to abstain from alcohol for 24 hours prior to dosing, or have a current history nicotine use. Women will be required to take a pregnancy test prior to participation to ensure a negative result.

Procedures

Imaging. Noninvasive functional magnetic resonance imaging will be performed in the Philips 3T (MR2) Research MRI at the University of Michigan Health System, University Hospital, Department of Radiology.

1) SPGR high-resolution images. Acquire T1 weighted spoiled gradient recalled echo (SPGR) images for high spatial resolution of anatomical images. The SPGR images can be employed for tissue segmentation and volumetric analysis using FreeSurfer, and image registration for functional neural network. The localized T1-weighted axial and sagittal plane slices will be acquired to provide structural information and to define the number of slices and location. Three-D high-spatial resolution anatomical images (T1-weighted SPGR sequence) will be acquired with parameters: 124 axial slices with 1.0 mm thickness, TR = 24 ms, TE = 5 ms, flip angle = 45^{o}, image matrix 256 ´ 256, and one excitation-per-phase encoding step for 7 min.

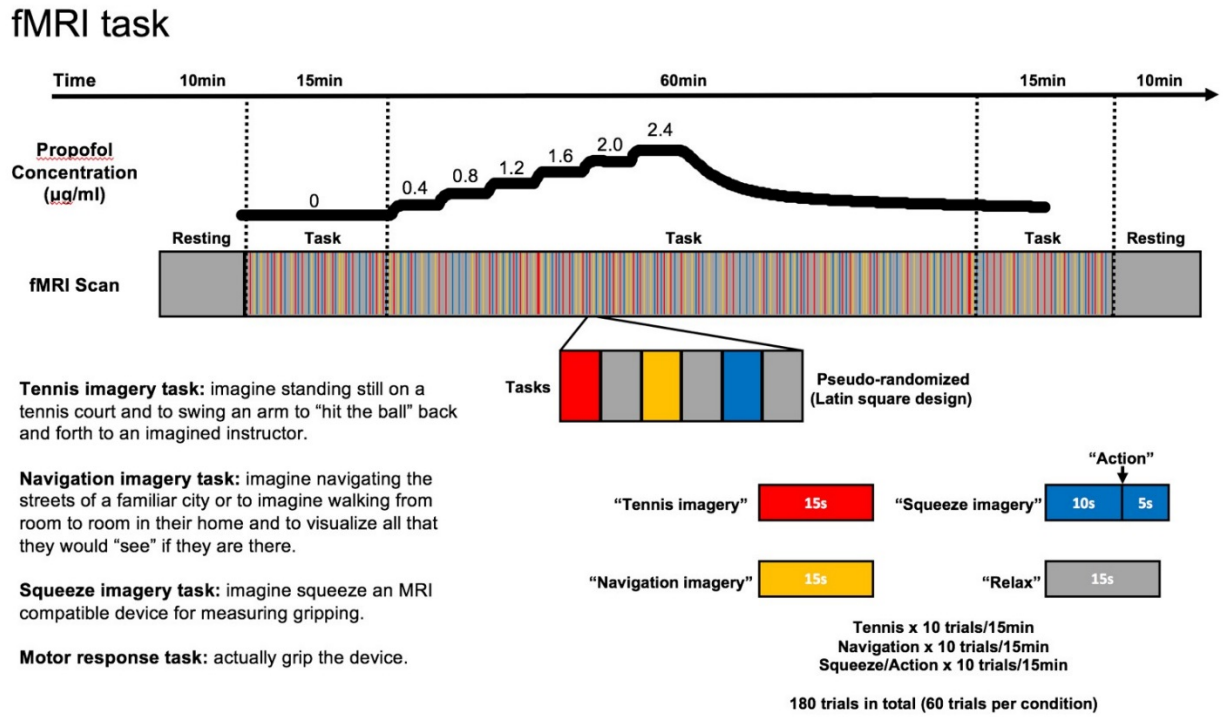
2) fMRI images. A gradient-echo EPI pulse sequence will be employed to acquire functional images over the whole brain. Imaging parameters will be first optimized by comparing the data quality among three different sampling rates in TR of 2 sec, TR of 1 sec or TR of 800 ms (based on multiband fMRI acquisition). The TE will be adjusted according to the TR setting to yield optimized signal to noise ratio (e.g. 25 ms). FOV of 22 cm, in-plane resolution with 64 ´ 64 matrix, bandwidth of 125 kHz, slice thickness of 6 mm, sagittal image orientation. There will be 120 min of data (continuous scanning) including the 15 dummy scans to avoid T1 effects. The number of slices per TR will be 21 image slices obtained with voxel resolution of 6 ´ 3.4375 ´ 3.4375 mm^3. Note, the residue respiratory signal will be filtered by low-pass filter. The cardiac aliasing and variation of respiratory signal will be minimized with RETROICOR. In addition, we have recently added real-time on-site fMRI acquisition, so we can identify subject movement during experiments and immediately determine if scan repetition is necessary in order to increase the rate of successful scans. There will be a 5-10 minute break in between the first resting-state (10 min), the first task-state (15 min), sedation period (60 min) with task, the second task-state (15 min), and the second resting-state (10 min).

3) Quality control (FBURN). Apply FBURN imaging protocols for control imaging quality, including acquiring field map. All these imaging protocols and data acquisition will be completed within a singular two-hour scanning session for each subject.

Anesthesia. Sedation will be achieved by target-controlled IV infusion of propofol. The IV line will be placed after application of a local anesthetic. Propofol will be administered by intravenous infusion. All anesthesia equipment, supplies, and drugs will be provided by anesthesiologists from the University of Michigan Health System.

We will manually control the infusion of propofol to achieve target effect-site concentrations of 0, 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4 μg/ml in a stepwise fashion. A maximum target concentration between 1.2 and 2.4 ug/ml will be chosen at the anesthesiologists' discretion for each participant. The intermediate target concentrations will be maintained for 5 minutes. Depending on the highest target concentration chosen, the last level could be held for 5-30 minutes before

the infusion is terminated and the propofol concentration is allowed to gradually decrease. The figure below illustrates the case of propofol dosing to the highest level. Participants will be instructed to perform cognitive and motor tasks as described below.



Tasks and testing. Participants will be asked to simply lay at rest in the scanner for the first 10 min and last 10 min scan. They will be asked to not move and to not fall asleep. Verbal instructions will be presented through earphones.

During the task period, participants will be asked to perform three imagery tasks (tennis, navigation and hand squeeze or finger tapping) plus a motor response task (actual hand squeeze or press a button). In the tennis imagery task, they will be instructed to imagine standing still on a tennis court and to swing an arm to "hit the ball" back and forth to an imagined instructor. In the navigation imagery task, participants will be instructed to imagine navigating the streets of a familiar city or to imagine walking from room to room in their home and to visualize all that they would "see" if they were there. In the squeeze imagery or finger tapping imagery task, participants will be instructed to imagine squeezing an MRI compatible device for measuring gripping (https://www.biopac.com/product/responsehand-force-for-mri/) or imagine tapping a button intensively and successively. In the motor response task (hand squeeze or press a button), participants will be instructed to actually grip the device or press a button. This motor response task always follows the squeeze (or tapping) imagery task. A pseudo-randomized (Latin square design) event-related design will be applied, in which the participants will be instructed to alternate between 15-second periods of mental imagery (except for a 5-second motor response period after squeeze or tapping imagery) and 15-second periods of rest. The whole scan will include 180 rest–imagery cycles or trials (60 trials per condition). The beginning of each trial will be cued with the spoken word "tennis imagery", "navigation imagery", "squeeze imagery (or tapping imagery)", or "action", and the rest periods will be cued with the word "relax". In addition, 10-minute resting-state fMRI scans will be applied at the beginning of the scan (wakefulness) and at the end of the task performance scan (recovery). A continuous scan will be performed. The complete scanning session will last for approximately 120 minutes.

To help prepare participants for the study tasks, they will be provided with a brief summary of the tasks the day before the study visit. This will help them be more prepared for the fMRI study tasks once they arrive. Additionally, we will have participants complete a short survey for both before and after the scan to receive some feedback.

All testing will be performed by the attending anesthesiologist. Spontaneous respiration, end-tidal CO_2, heart rate, and electrocardiogram will be continuously monitored. Noninvasive arterial pressure will be measured with magnetic resonance (MR)-compatible automatic monitor (BIOPAC). Oxygen will be available and used if needed. Post anesthesia care will consist of checking vital signs for 1 hour by the nursing staff. A wheelchair will be provided to assist the participant if needed. An anesthesiologist will be present during the entire duration of the study.

Primary outcome measure: Blood Oxygen Level Dependent (BOLD) Response to sensory stimuli during sedation (timeframe: baseline to 90 minutes).

Secondary outcome measure: Squeeze Pressure, defined as measurement of force of participants' hand squeezing on a rubber ball in response to instructions (timeframe: baseline to 90 minutes).

Data Analysis. Image analysis will be conducted using AFNI (http://afni.nimh.nih.gov/afni) and Matlab (The MathWorks, Natick, MA) software. Preprocessing includes despiking, detrending, and motion correction. Potential contaminating signals from the white matter (WM) and the cerebral spinal fluid (CSF) are extracted for each subject using the WM and CSF segments of the anatomical image. A general linear model fitting (3dDeconvolve in AFNI) is performed using regressors constructed from motion correction, WM, and CSF signals to minimize potential contaminations. As we did previously (1), the voxel-wise task-related hemodynamic responses during each run will be evaluated using the *area under the curve* of the estimated hemodynamic response functions (HRFs) for each voxel (2). Spatial smoothing of the response magnitude across voxels will be performed using a Gaussian kernel filter to compensate for intersubject variability. Lastly, in the group analysis, activation maps for each run are derived by applying voxel-wise one-sample t-tests followed by transformation to z-scores and correction for multiple comparisons (e.g., AlphaSim in AFNI).

Experimental contrasts and functional regions of interest (ROIs). The following activation maps will be computed for *each* anesthesia condition:

1. All stimuli vs. silent baseline: Identifies auditory sensory, attention, and action processing common to verbal instructions.
2. Tennis imagery vs. silent baseline: Identifies supplementary motor area.
3. Navigation imagery vs. silent baseline: Identifies parahippocampal gyrus.
4. Squeeze (or tapping) imagery vs. silent baseline: Identifies supplementary motor area.
5. Squeeze (or press a button) action vs. squeeze (or tapping) imagery: Identifies M1 and sensorimotor cortex.

The results of these contrasts obtained in the fully awake state will be thresholded (whole-brain corrected $p < 0.05$) to define ROIs representing each functional network. In some cases – particularly contrast #1 – the networks will be subdivided using anatomical information. For example, the activated areas for contrast #1 will be divided into a superior temporal auditory

ROI, a dorsal attention network (including intraparietal sulcus, frontal eye field, and anterior cingulate gyrus), and a sensorimotor action network (including primary sensorimotor and premotor cortex). These ROIs will then be overlaid on the activation maps for each anesthesia condition to measure the extent of activation (number of activated voxels) and magnitude of activation (mean beta coefficient) in each ROI across the levels of anesthesia.

For Aim 1, dynamic brain activation maps will be calculated as a function of anesthetics dose and behavioral responses. Similarly, for Aim 2 and 3, dynamic functional connectivity matrices will be calculated as a function of anesthetics dose and behavioral responses from the first 10min resting-state data, the residual data (after regressing out task component) of the 60 min task period, and the last 10 min resting-state data.

Power Analysis. For an fMRI study of cognitive function, Desmond and Glover (2002) reported that about 30 subjects are necessary to achieve 80% power for a 0.5% increase of activity (3). We also conducted power analysis based on nonspecific thalamocortical connectivity changes in deep sedation as compared with wakefulness (4, 5). We used Cohen's d (6) as a measure of the effect size (ES) of connectivity difference. The computation yields averaged ES=0.56, and for power=80% and alpha=0.05, N=22 human subjects will be needed. The obtained subject number is also very close to the suggested optimal group size for reliable statistics in functional MRI studies (7). Considering the potential failure rate estimated from our previous study (1), 30 human participants will be recruited for the study.

Potential Risks. There are no known risks associated with magnetic resonance imaging, as long as technical parameters remain within FDA guidelines. A licensed MR technologist is instructed in these guidelines and performs all machine manipulations. Complete histories, physical examinations and stringent medical guidelines exclude many potential subjects before they enter the study, thereby further minimizing risks. A crash cart is always present and regular safety drills are performed by the medical and experimental staff to prepare for any untoward effects.

<u>Risks related to MRI scanning:</u>

MRI Static Magnetic Fields: FDA guidelines for clinical product scanners limit the main magnetic field to 3 Tesla. Our studies will be performed on a standard, clinical 3 T Philips scanner. A substantial body of literature exits that supports the safety of field strengths up to 7 T. There are no known risks of exposure to 3 or 7 T fields for MR imaging.

Among the reported biological effects of exposure to strong static magnetic fields are the following: 1) Dizziness (with nausea) or stimulation of the sensory nerves in the soft palate has been reported as a result of the subject's head being moved while in the magnet. 2) Rapid eye movement has been reported (at 4 and 7 T) to cause magnetophosphene effects. First described in 1896, these flickering light sensations are similar to visual phenomena caused by direct electric current passage across the head or retina.

Radiofrequency (rf) Magnetic Fields: Radiofrequency energy burns are the result of high electric fluxes in the immediate vicinity of the patient. All MRI systems create some rf electric fields incidental to the production of the intended rf magnetic fields. The potential causes are malfunctions in the rf coil switching circuitry, improper use of the surface coils, design flaws in some clinical MRI system surface coils or cardiac gating patient connection leads. Nationally, 60 burn incidents have been reported to the FDA in the course of approximately 11 million exams. Our site has never experienced any difficulty in this regard.

Acoustic Noise: The sound generated by an MR system usually consists of a series of repetitive pulses. The relevant safety parameters required to characterize such a noise are the peak impulse sound pressure level (L_{peak}) and the time integral of the A-weighted sound pressure level (L_{eq}). In MR applications, the peak impulse sound pressure level is dependent upon the peak amplitude of the individual pulses, while the time integral of the A-weighted sound pressure level is dependent upon the continuous exposure to a series of such pulses. Acoustic noise is a result of the mechanical vibration produced by the gradient coils when the nominally large currents are applied to them to create time varying imaging gradient fields. The sound produced can be loud enough to produce temporary deafness (up to 95 dB). Foam earplugs will attenuate this noise by up to 30 dB. They are in routine use at the 3T systems, and have been proven effective.

Claustrophobia: While inside the magnet, subjects may experience an acute panic attack due to claustrophobia. Subjects are all prescreened for fear of tight places. Once inside the magnet, the subject will be given a squeeze ball to signal the MR operator if he or she is under acute distress.

Risks related to anesthesia:

Risks associated with intravenous catheter placement include brief, local discomfort and possible bruising, which can occur at the site of the IV line. There is also a possible (rare) chance of infection, but every precaution will be taken to reduce this risk by keeping the IV site clean and dry. Although rare, there is a risk of nerve damage at the arterial line insertion site.

Risks associated with propofol administration include: pain at the site of injection, possible allergic reaction to the drug, depression of respiration which may necessitate placement of an endotracheal tube to assist breathing, and mechanical ventilation, or a decrease in blood pressure which may necessitate giving a drug or IV fluids to bring the subject's blood pressure up. These effects disappear when propofol is discontinued.

Justification for the risks involved: The risks of the proposed procedure are minimal, and the importance to mankind of the potential knowledge gains is substantial, making the risk/benefit ratio very low. We combine the state-of-the-art brain imaging facility currently in place in the University of Michigan Health System with the experience of the imaging staff and clinic anesthesiologists in the Department of Anesthesiology. These experiments will provide a unique opportunity to understand the neurophysiological mechanisms of anesthesia modulation of human consciousness. Therefore, we will provide a unique opportunity to expand our knowledge of anesthesia-modulated human consciousness.

Procedures for minimizing risks. All research subjects will go through a screening process for inclusion and exclusion criteria performed by licensed physician. A licensed physician will be present at all MRI scanning sessions to monitor the subjects. When subjects express or exhibit anxiety regarding the scanner setting, they will be allowed to discuss these feelings. Attempts will be made to minimize the discomfort and anxiety. When in the scanner, subjects will be provided with a squeeze-ball alarm that will alert the scanner technician and the researcher that the subject desires to come out of the scanner. In such instances, the subject will immediately be removed from the scanner and appropriate measures will be taken to ensure his or her psychological health. Earplugs, demonstrated to reduce scanner noise to a non-damaging level, will be used to minimize hearing risks.

In addition, any other health problem that would be aggravated by an MRI scan will also be a cause for terminating the subject’s participation. In the event of serious cardiac-respiratory problems or other medical emergencies, the hospital code team will be activated. Other medical

problems will be treated by the monitoring physician. Any medical problems that arise after release, although unlikely, will be treated by a physician from the research team. All subjects will have to arrange transportation after the study, and agree to not drive, work, operate machinery, or make legal decisions for 24 hours after the study. Subjects will be informed of their right to withdraw from the study at any time.

A protocol has been established to handle unexpected medical emergencies arising in the scanner suite. This protocol deals with medical issues and the duties of each team member. This includes stopping the scanner, removing the patient and calling for outside medical assistance. All members of the research team participate in periodic emergency protocol drills in the scanner suite and a copy of the written protocol and protocol termination guidelines are present at all times. Subjects requiring intervention for any neurological or cardiovascular adverse event will be transferred to the Emergency Department for further evaluation and treatment as seen fit by the attending physician. More serious cardiac events such as ventricular tachycardia, ventricular fibrillation or any unstable rhythm will be immediately treated according to current Advanced Cardiovascular Life Support (ACLS) protocols. Research team physicians have immediate access to valium, diphenhydramine, epinephrine, lidocaine, and NTG for emergency use, in addition to a fully supplied and operational “crash cart” with EKG, defibrillator, suction, oxygen, and airway management equipment.

Confidentiality. Strict subject confidentiality will be maintained. Subjects will be assigned a code number following their first contact in the protocol. This number will be used throughout the experiment and will be the only identifier on behavioral and physiological archival data, and magnetic resonance (MR) scans. The identity of subjects will not be revealed at scientific meetings, in publications or other vehicles of public communication. Data will be pooled across subjects where appropriate. Only the PIs, Co-investigators, and the study coordinator will have access to the ID code, which will be stored in a locked file separate from the data.

Any behavioral data collected on the subjects will be coded by study ID numbers and entered directly into notebook computers used in the field. These computers are password protected and stored behind a locked door when not in use. Clinical and biographic data are entered into the database using the ID number only. Only select staff members have access to the actual paper copies. Medical information will be released by name only to health care providers, and then only with written permission from the subject.

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