Psychosocial, Behavioral, and Radiologic Changes following Neurologic Events or Interventions: A Prospective, Non-Interventional, Observational Study

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2. Background

2.1 Functional Neurologic Imaging following Interventions or Underlying Disease

Functional magnetic resonance imaging (fMRI) and diffusion tensor tractography (DTI) have rapidly expanded since its emergence two decades ago. fMRI is well established as the single most powerful method for detecting changes in neural activity *in vivo*, albeit indirectly by detection of changes in blood oxygenation level dependent (BOLD) signals that reflect hemodynamic changes subsequent to neural activity. A conventional fMRI experiment involves the comparison of two or more brain states followed by statistical tests to identify which brain regions were involved in a particular task. The identification of patterns of highly correlated low-frequency MRI signals in the resting brain provides a powerful approach to delineate and describe neural circuits, and an unprecedented ability to assess the manner in which distributed regions work together to achieve specific functions. Since the first reports of temporal correlations in BOLD baseline signals, several distinct cortical long-range networks have been identified and characterized in the resting state, including a default mode network. Moreover, observations of altered resting state connectivity in several disorders and as a function of behavior or cognitive skills suggest these correlations reflect an important level of brain organization and may play a fundamental role in the execution and maintenance of various brain functions. DTI is also an exceedingly important imaging modality that has elucidated the neural connectivity inherent between various cortical and subcortical structures. DTI is routinely used and has enhanced our understanding of functional connections between various parts of the brain. Prior to interventions, DTI is commonly obtained, so that interventionists can avoid critical circuitry. There is suggestion that both fMRI and DTI imaging is influenced by organic or interventional variables, however this is understudied. The neuroscientists and clinicians would greatly value information that would expand our working knowledge of the basic neural substrates and functional neural changes that occur in patients organically or after interventions. A non-invasive, non-interventional, observational study is needed to show the changes that happen to patients organically or in standard of care settings. A greater working understanding of the neural connectivity and changes that happen in the brain is of great future benefit to patients, science, and society as well as future therapeutic development such as post-stroke care, rehabilitation, post-traumatic brain injury, or post-treatment care in the brain that has previously been influenced by intervention or disease.

3. Protocol

3.1. Purpose

A number of studies from the literature suggest important behavioral, psychosocial, or radiologic changes occur following significant neurologic events or interventions such as stroke, neurosurgery, medications, radiation, systemic therapy, or injury (ref. 1-10). The purpose of this study is to describe these changes with advanced neurologic imaging and targeted neurologic and neuropsychiatric assessments. This is a non-interventional observational study of minimal risk to participants as there is no medical intervention. The results of this study will be used to inform patients, scientists, and society in the development of future treatments.

3.1.1 Study Objective

Primary objective: Describe changes in radiologic, behavioral, psychosocial domains after neurologic events or interventions.

3.2. Protocol

3.2.1 Synopsis

Study Title: Psychosocial, Behavioral, and Radiologic Changes following Neurologic Events or Interventions: A Prospective Non-Interventional Observational Study

Study Design: Prospective non-interventional observational study

Number of Participants: We will aim to enroll 50 patients in this observational study to describe broad changes in neurologic circuitry and function.

Study Population: VUMC adult patients with neurologic disease or patients with neurologic interventions such as neurosurgical procedures or radiation therapy

Study duration: We estimate that this study will accrue 50 patients over 5 years.

Visit Schedule: Participants will be asked to attend zero or more assessment intervals for this observational study by study investigators at the convenience of the subjects.

3.2.2 Study Design

This is a prospective, observational study involving non-invasive assessments of neurologic function. There are no medical, therapeutic or invasive components to this study. These include survey-based assessments, behavioral assessments, and imaging procedures.

3.2.3 Participant Selection

The study population will be current patients at Vanderbilt University Medical Center identified by the investigators.

Men and women of any ethnicity, race or socioeconomic status who meet inclusion criteria will be offered enrollment into the study. Patient will be greater than 18 years of age and meet

inclusion and exclusion criteria. Patients eligible for this study will include patients with neurologic events, including but not limited to stroke, depression, infections, psychiatric disease. Intervention is not part of this study, however, patients receiving neurologic interventions, such as neurosurgical procedures or radiation therapy, would be eligible.

Inclusion Criteria

- Age ≥ 18 years old and willing and able to sign a written informed consent.
- Eligible for Brain MRI
- History of neurologic event or intervention OR future planned neurologic intervention

Exclusion Criteria

- Contraindications to MRI of the brain
- Patient declining participation in study
- Pregnancy

3.2.4 Study Procedures

3.2.4.1 Screening procedures

Potential subjects will be identified by the investigators at Vanderbilt University Medical Center. They will be approached by the principal investigator (PI), a co-investigator (co-I), and/or appropriately trained research personnel in a private setting. Those participants who express interest in taking part in the research study will be asked to sign a written informed consent that has been approved by the Vanderbilt University IRB. Subjects will have the study explained to them and will be given the opportunity to read and review the consent documents and have any questions addressed. Subjects will be given a copy of the signed informed consent document.

Once informed consent is obtained, final eligibility for enrollment into the study will be determined based on the inclusion/exclusion criteria. We will review the patient's medical history. Patient registration will be managed by research coordinator to be determined. The following documents must be completed before enrollment in the study can be considered complete: (1) IRB-approved informed consent. (2) Patients will be assigned a study ID number at the time of registration. (3) Patient Screening using inclusion/exclusion criteria checklist on case report form-enrollment form, (4) No study procedure will take place prior to obtaining written informed consent.

3.2.4.2 Assessments

During the study, subjects may be asked by investigators to complete one or more of the following standardized surveys for behavioral assessment during various study sessions:

i. Y-BOCS Survey
ii. RAND 36-item Quality of Life survey
iii. Mini Mental Status Exam
iv. MOCA Cognitive Exam

v. QUEST
vi. PDQ 39
vii. PHQ2 Depression Screening
viii. PHQ9 Depression Inventory
ix. Beck's Depression Inventory
x. PROMIS Pain Intensity Short Form 3A
xi. McGill Pain Scale
xii. Visual Analog pain scale
xiii. Barrow Neurologic Institute Scale
xiv. Hopkins Verbal Learning Test
xv. Dimensional Obsessive-Compulsive Scale
xvi. Mood Disorder Questionnaire
xvii. FTM (Tremor Scale)
xviii. YGTSS (Tourette/Tic scale)

Radiologic tests may include one or more of the following procedures:

i. Brain MRI 1.5 or 3 Tesla
ii. fMRI 1.5 or 3 Tesla
iii. Diffuse tensor MR imaging with fiber tractography 1.5 or 3 Tesla

During the study, medical history, including but not limited to past medical history, past surgical history, medications, social history, family history, immunizations, and allergies may be recorded from the medical record.

Behavioral tests may include one or more of the following procedures:

1. Upper extremity testing:
    a. Both hands with digital hand grip dynamometer.
    b. Three times
    c. There are no known risks associated with this test.
2. Perdue Peg Board testing:
    a. This is a test to see how quickly and accurately subject can work with your hands
    b. Test is performed by each hand and both hands.
    c. Each test session takes about one minute.
    d. There are no known risks associated with this test.
3. Hand tactile detection and discrimination test:
    a. This test is used to determine the vibration detection and spatial and temporal discrimination ability of both hands.
    b. A fully automatic Case IV Computer Aided Sensory Evaluator system and two manually administered devices are used.
    c. There are no known risks associated with this test.
4. Temperature and pain threshold testing:
    a. These tests are used to determine the detection thresholds of temperature and pain of both hands.
    b. A fully automatic Case IV Computer Aided Sensory Evaluator or an Medoc computer system are used. These computer systems have their own risk management system which will automatically shut down if potential harmful temperature, pressure or duration is reached. The temperature, pressure, and duration limits are built-in functions of the two

automatic computer systems and based on a large number of studies performed with these FDA approved systems. A second layer of protection comes from the subject's own control of the stimulus delivery. Subjects can press a button to stop the session at any time.

c. A hand-hold sharp probe is used to test the sharp threshold.

5. Lower extremity Testing:
    a. Timed up and Go test (TUG)
    b. This is a simple rising from a chair, walking three meters, turning around, and walking back to the chair and sitting down test. This test is used to assess a person's mobility and requires the static and dynamic balance.
    c. There is a potential for the subject to fall during this test. If the subject and/or KSP administering the test suspect the possibility for a fall, the procedure will be terminated.
6. Myomotion Inertial Motion Testing:
    a. While performing the TUG test, the Myomotion Inertial Motion Testing System (with 7 sensors, Noraxon, Phoenix, AZ) will be used to quantify kinetics of the movement, including gait data (cadence, step length, single limb stance time) and 3 dimensional data of the hips, knees, and ankles.
    b. All data collected will be compared to established normative values for age and sex of each subject.
    c. There are no known risks associated with this procedure.

The study investigators will determine the type and frequency of assessments for each patient based on their medical history.

3.2.4.5 Study Participant Termination/Withdrawal

Participant Termination

- In the judgment of the investigator, further participation in the study would not be in the best interest of the patient
- Substantial non-compliance by the patient with the requirements of the study
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The patient is lost to follow-up
- Development of an intercurrent illness or situation which would, in the judgement of the investigator, affect assessments of clinical status and study endpoints to a significant degree

Participant Withdrawal

- Patient decision to withdraw from the study at any time. Patients will still receive standard medical care

Screen Failure

- Patients who sign an informed consent that are withdrawn or terminated and have already undergone screening procedures will be considered screening failures. A record of these patients will be maintained.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation.

3.2.5 Data Analysis

Sample size:
For this pilot observational imaging and patient-reported outcomes study, we will enroll 50 patients. This is based on predicted ability to accrue and follow. Future studies will be informed by the data of this pilot study.

Radiologic:

Each measurement will be performed in a minimum of five subjects to assess its variability. Standard measures of image quality (e.g., image signal-to-noise ratio, image and functional contrast-to-noise ratio, and magnitude of artifacts) will be used to judge optimal experimental parameters for all sequences.

Single-subject analyses of functional connectivity will calculate the linear correlation coefficient (r) between a seed region and all other regions. These correlation values will be converted to z-scores using the Fisher r-to-z transformation $z = \tanh^{-1}(r)(dof–3)^{1/2}$ where dof is the estimated degrees of freedom for each voxel after correction for first-order autocorrelation. A statistical threshold of $|z| > 3.29$ (a two-sided 99.9% confidence interval) will be used to protect against type I errors. A minimum cluster threshold of nine contiguous interpolated voxels will also be used to further protect against spurious correlations.

For group-level analyses of functional connectivity, a two-tailed Wilcoxon signed rank test with $p < 0.01$ will be used to identify distributions of z-scores (calculated for each subject as described above) that are significantly different from zero.

Analysis plan for questionnaires:
Continuous variables (e.g. patient age) will be summarized overall and by group using the 25^{th}, 50^{th} (median), and 75^{th} percentiles or the mean and standard deviation depending on whether data can be assumed to follow a normal (Gaussian) distribution. Categorical data will be summarized in frequency tables and percents overall and by group. State of the art graphical analysis including trellis plots of bivariate scatterplots, BliP plots, and plots for the assessment of modeling assumptions (i.e., QQ plots to assess normality) will be constructed.

Subscale and overall summary scores (SI) are sums of the scores across subscales and over all questions. We hope to achieve >95% complete data and we will impute missing observations of subscales if at least 80% of the data for a given time period are observed. We will evaluate internal consistency/reliability within subscales using Crohnbach's alpha and interclass correlations (ICC). We will use a mixed models analysis of variance to estimate longitudinal effects on continuous outcomes measured in this study. For categorical (e.g., yes/no and ordinal) models, we will use the generalized linear model employing a binomial or multinomial link function to estimate effects on the odds scale or proportional odds scale as appropriate. These latter models will employ the Huber-White sandwich estimator for variance estimation. These modeling approaches properly account for the intra-patient correlation among repeated measures.

3.2.6 Adverse Events

3.2.6.1 Definitions

Adverse event is defined as any undesirable experience that appears or worsens during the clinical study
A ***related adverse event*** is an event in which there is a reasonable possibility that study related procedures caused or contributed to the event.
A ***serious adverse event*** is defined as an adverse event whereby the patient outcome meets any of the following criteria:
a. Results in death as a result of the study procedures
b. Is life-threatening (defined as an event in which the participant was at substantial risk of death at the time of the adverse event)
c. Requires inpatient hospitalization due to study procedures
d. Prolongs an existing hospitalization due to study procedures
e. Results in new persistent or new significant disability (substantial disruption of a person's ability to conduct normal life functions)

A "Report of Unanticipated Problem Involving Risk to Participants or Others" is submitted to the IRB as soon as possible, but no later than 7 calendar days after the Investigator first learns of the event or problem. This form contains the Investigator's assessment of causality (related or not related to the study) and a description of the actual event. The form also contains an evaluation of whether the event meets the following criteria:

a. An event that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized;
b. Unanticipated (i.e., the event was not foreseeable); and
c. Related (i.e., likely to have been caused by the research procedures) and Any associated materials such as medical record notations or reports with the name and medical record number of the individual redacted (removed).

As far as reasonably possible, data recorded about each adverse event will include the following:

1. the severity grade according the CTCAE v5.0
2. its relationship to the study therapy (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event

All adverse events should be treated appropriately. Such treatment may include starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention

<u>AE Term Selection</u>

To facilitate proper analysis of any observed adverse events within the study, consistent and medically accurate standards of AE term selection will be applied. Whenever possible, an AE term will be the formal diagnosis or disease term experienced by the patient per the CTCAE v5.0. If the final diagnosis remains differential or is pending, then the presenting signs,

symptoms and/or abnormal laboratory results will be captured as AEs until a diagnostic term can be applied.

3.2.6.2 Protocol Deviations

Protocol deviations are defined as any incidents involving non-adherence to the protocol and may result from actions of the participant, investigator, or staff. Protocol deviations will be recorded and will be reported to the reviewing IRB per IRB policy. Protocol deviations intended to protect the life or physical well-being of a participant in an emergency situation and any incidence of failure to obtain informed consent will be reported to the reviewing IRB as soon as possible but no later than 5 working days after the emergency occurred.

3.2.6.3 Investigator Responsibilities

Investigators are responsible for conducting the study in accordance with applicable FDA regulations for protecting the rights, safety, and welfare of subjects under the investigator's care, and for obtaining informed consent from each research participant prior to any study-related procedures.

Abnormal findings discovered as a result of the study procedures will be communicated to the treating physician by the investigators. The treating physician will be advised at that time regarding communication of the abnormal findings to the patient.

3.3 References

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8. Pranckeviciene et al. Depression screening in patients with brain tumors: a review. *CNS Oncology*. 2015;4(2):71-78.
9. Murray B et al. Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury. *JAMA Psychiatry*. 2019;76(3):249-258.
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4.RISKS

Potential Risks to Subjects (Uncommon)
The risks of MRI include:

1. Ferromagnetic objects brought into the room will be pulled toward the magnet.
2. Implanted metal or medical devices may experience abnormal torques or fail to function properly.
3. There is a risk of tissue heating due to power deposition of radiofrequency magnetic waves.
4. There is a risk of peripheral nerve stimulation if gradients are switched too rapidly.
5. The subjects may experience a claustrophobic reaction.
6. There are loud banging noises with MR imaging that may be uncomfortable.
7. The subjects may experience dizziness or nausea if very quick head movements are made within the scanner.

During a BOLD hypercapnia scan, which is currently a clinical scan offered to patients at Vanderbilt University Medical Center, 5% CO2 is delivered via a facemask for brief periods of time. While there have been no adverse events from this protocol since its implementation at Vanderbilt, the risks of a controlled hypercapnia stimulus include:

1. Slight discomfort while the mask is on, or in some cases a slight sensation of shortness of breath.

The behavioral testing procedures involve non-invasive measurements of the test subject and present minimal to no risk of adverse effects. However, though not anticipated, the testing may make some subjects agitated and will be immediately terminated if necessary by the study team member and/or at the request of the subject.

The risk of breach of confidentiality includes:

1. Reputation or employment may be damaged.

We will employ the following protections to mitigate each of the above MRI risks:

1. The subject will be instructed not to bring metal objects into the magnet room.
2. The use of the MRI screening form will exclude potential subjects with implanted metal or medical devices.
3. The FDA has strict limits regarding power deposition. Safeguards built into scanner hardware and software prevent the operator from exceeding those limits.
4. The FDA has strict limits regarding gradient strengths and rise times. Safeguards built into scanner software prevent the operator from exceeding those limits.
5. Subjects will be warned of the potential for claustrophobic reactions and those with a prior history of such reactions will be excluded from the study. If a subject experiences an unexpected and severe claustrophobic reaction, the exam will be terminated.
6. The subjects will be provided with hearing protection.
7. Subjects will be advised not to make any quick head movements. The scanner bed automatically moves the subject at a rate sufficiently slow to avoid problems from peripheral nerve stimulation and nausea.

Regarding a BOLD hypercapnia scan:

1. Subjects will be informed of these sensations and if they feel uncomfortable will be told to notify the MRI technologists so the scan can be halted. Furthermore, hypercapnia scans will not be performed on subjects who have respiratory deficiencies. Therefore, we anticipate that the risks from Aim 2 are low for the population who will be enrolled.

Regarding subject confidentiality:

1. Careful data collection and storage procedures will be followed.

5. MONITORING PROCEDURES

The Principal Investigator is responsible for overseeing the safety and responsible conduct of the trial. The clinical data and adverse events will be reviewed by the Principal investigator in conjunction with the sub-investigators, research staff, and independent data safety monitor. The Principal investigator will be available for sub-investigators, nurses, and research staff to answer questions. If non-compliance by key study personnel is discovered, the principal investigator will be responsible for securing compliance and for providing review of the study protocol with the study personnel to ensure future adherence.

6. ADDITIONAL RECORDS AND REPORTS

Record Retention

The PI must retain all study records by the applicable regulations in a secure and safe facility. The institution must consult with the PI before disposal of any study records, and must notify the PI of any change in the location, disposition or custody of the study files. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The PI/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements. PI must be notified and will assist with retention should institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of PI to inform the institution as to when these documents no longer need to be retained.

If an Investigator moves, withdraws from an investigation, retires, requests to move records to another location or to assign these records to another party or (e.g. other Investigator) who will accept the responsibility, written notice of this transfer must be made to and agreed upon by each party.

Records will include all correspondence relevant to the investigation, IRB and FDA approved study documents, device accountability records, source and case report form documentation, to include signed consent documentation and any medical chart information relative to the research and device exposure by the participant.

Data Storage:
The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data called REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, REDCap's survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy. REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and IRB. REDCap has been disseminated for local use at more than 600 other academic/non-profit consortium partners in 54 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 63,000 projects and 82,000 users. More information about the consortium and system security can be found at
http://www.project-redcap.org/.

Data Privacy/Confidentiality Issues
The Principal investigator will collect data and enter it into password-protected computer in a locked office. Each patient will have a unique identifier number, with the key to the patient's medical record number kept in a locked cabinet in the office. Only research associates or those individuals directly involved with the study will have access to data. Information is for research purposes only and when used for publication purposes, all participants will have their names concealed. Access to identified patient information will be limited to the investigators listed within the IRB application. De-identified information with HIPAA identifiers removed will be available to other investigators following IRB approval. Confidentiality and security will be maintained for the database. The database is stored behind a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information system at Vanderbilt. This means that users must logon to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Only users approved through our institutional review board will be allowed access to patient identifiers. Other levels of authorization may exist for future approved users following IRB approval, e.g. access to de-identified data.
Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the Case

Report Form (CRF). The study data will be kept on site and in a securely locked room to protect patient confidentiality.

Study personnel (PI and co-investigators) and government regulatory agencies have access to all research records as required by law. Others (such as law enforcement agencies) may have access to records as defined by law.