Official Title: Neuroimaging Biomarkers of Symptom Severity, Adverse Life Events and Prognosis in Motor Functional Neurological Disorders

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Detailed Protocol

I. Background and Significance

a. Historical Background:

Functional Neurological Disorder (FND) (a.k.a. conversion disorder) is a neurobehavioral condition at the interface of neurology and psychiatry. Neurologists see approximately 30% of outpatients for medically unexplained symptoms(1), and approximately 18% of those patients are diagnosed with functional neurologic syndromes(2). Despite this exposure, neurologists lack a neurobiological framework through which to understand FND(3) and have limited treatments available to offer patients.

Patients with motor-FND demonstrate an identifiable phenotype and are of particular clinical-translational research interest. This cohort includes psychogenic nonepileptic seizures (PNES), functional movement disorders (FMD), and functional weakness among other conditions. PNES are a common mimic of uncontrolled epilepsy(4), and are diagnosed in 25-50% of tertiary epilepsy center referrals(5). The prevalence of PNES is estimated to be 33 per 100,000 people, with an incidence of 3 per 100,000 individuals/year(6-8). Furthermore, PNES disproportionately account for a large economic burden from frequent doctor visits and reliance on social assistance programs(9). While much effort is directed diagnostically towards excluding epileptic seizures through video electroencephalography (vEEG), the current approach provides no affirmative neurobiological characterization. To similarly contextualize the impact of FMD, approximately 20% of movement disorder clinic patients have a FMD(10), and this condition impairs quality of life to similar degrees as Parkinson's disease(11). Overall, there is a critical lack of FND neurocircuit biomarkers, which would help guide prognosis and treatment development.

The purpose of this research is to investigate FND neurocircuit abnormalities compared to healthy subjects using functional and structural neuroimaging techniques. Particular subtypes of interest include patients with PNES, FMD, and functional weakness. Functional magnetic resonance imaging(fMRI) detects blood-oxygen-level-dependent(BOLD) signal which serves as a proxy for neural activity(12), and non-task, BOLD resting-state functional connectivity(rs-FC) methods can be used to study neural networks(13). Concurrent structural abnormalities can be examined through semi-automated structural quantitative analyses including cortical thickness(14) and voxel-based morphometry(VBM)(15) analyses.

b. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research:

Neuroimaging studies in FND have mainly investigated psychogenic unilateral motor and somatosensory disturbances(see Perez et al 2012)(3). The dorsolateral prefrontal, perigenual ACC, right posterior parietal cortex, and striatal-thalamic regions have been implicated in motor intention(16, 17), attention(18, 19), motor intention awareness, and self-agency(20) deficits. Affective disturbances have been minimally studied in FND(21, 22), yet characterization of frontolimbic abnormalities in other neuropsychiatric populations(23-26) has led to the identification of predictors of treatment response(27-30) and targets for therapeutic neuromodulation(31).

Limited neuroimaging studies have probed neurocircuit disturbances in PNES and FMD. rs-FC in 11 PNES patients compared to healthy subjects identified increased connectivity between emotional processing, executive control, and motor planning networks(32). A study of 20 PNES patients (with poorly characterized neuropsychiatric profiles) compared to healthy subjects identified aberrant OFC and amygdala structural connectivity using diffusion tensor imaging(33). A VBM study demonstrated decreased ACC, supplementary motor area(SMA) and cerebellar gray matter in 20 PNES patients compared to healthy subjects(34). In FMD-related neuroimaging studies, 16 hyperkinetic FMD patients with anxiety and depression exhibited increased amygdalar activation to positively valenced faces and increased amygdalar-SMA functional connectivity(22). In a within-subject study of 8 patients with

positional psychogenic tremors, the right temporoparietal junction was hypoactive during unexplained movements, and this region exhibited reduced functional connectivity with bilateral ventral ACC, medial prefrontal, sensory/motor, and right superior parietal cortices.

Insights into FND neurocircuit abnormalities may also be hypothesized from the psychological profile and the neural substrates of its co-incident neuropsychiatric conditions. FND typically occurs in young women with a history of interpersonal trauma and a psychological profile notable for heightened impulsivity, anxiety, dissociation, and somatization(3, 35-38). The limited studies comparing PNES and FMD patients have identified similar reported somatization, depression, anxiety, and chronic pain in both groups(39, 40), suggesting these conditions may potentially represent a phenotypic spectrum for a single disorder. Frequent co-incident conditions include depression, post-traumatic stress disorder(PTSD)(41), borderline personality disorder(BPD), and dissociative-somatoform disorders. The amygdala, critical for emotional learning(42), demonstrates increased activity in PTSD and BPD(24, 43). The OFC, dysfunctional in mood and impulse control disorders(44), is implicated in emotion and value-based decision making(45, 46), constraint, behavioral flexibility and choice maintenance(47). Medial/lateral OFC functional distinctions based on monkey and human post-mortem anatomical connectivity studies suggest the medial OFC may subserve behavioral responses in the context of viscerosomatic functions, while the lateral OFC may mediate sensory-based evaluations(48). Rs-FC and symptom-specific correlation analyses would aid the *in vivo* parcellation of OFC structure-function relationships.

An examination of the FND psychologic profile, particularly in PNES subjects, reveals many symptom similarities with the expected phenotype of limbic, paralimbic and attentional circuit dysfunction outlined above. PNES subjects exhibit a propensity for impulsive behavior as examined by the Barrett Impulsivity Scale (49). Dissociative tendencies are well documented in this group using the Dissociative Experience Scale (50). Alexithymia has also been described in PNES subjects using the Toronto Alexithymia Scale (51). Somatization phenotypes are also described (50, 52). Scores on the Beck Depression Inventory and Spielbeiger State and Trait Anxiety Inventory reveal increased depression and anxiety in PNES subjects (36, 53). In response to stressful situations, PNES subjects are more likely to employ escape avoidance rather than problem solving coping strategies as categorized by the Ways of Coping-Revised Version(54). Examination of attachment style in PNES populations suggests a tendency for fearful attachment as demonstrated by the Relationships Scales Questionnaire(55). Furthermore, while the interaction of personality, stress related coping style and resilience have yet to be fully elucidated in PNES, hypotheses translatable to FND implicate a role for fronto-limbic network involvement; we hope to explore the neurobiology of this interaction further by using the NEO Five Factor Inventory, the Connor-Davidson Resilience Scale(56) and the Ways of Coping-Revised Version questionnaire(57).

c. Rationale behind the proposed research and potential benefits to patients and/or society:

As noted above, research into the neurobiology of FND is in its early stages. Improved biological understanding of this disorder at the interface of Neurology and Psychiatry would reduce stigma associated with this condition, and potentially identify neuroimaging biomarkers of prognosis and treatment response as has been done for other neuropsychiatric disorders including PTSD(27, 30). Understanding the neurobiological basis of FND may aid disease prevention, risk factor identification, and promote the development of more successful and cost effective therapeutic interventions. Indeed, there is evidence to suggest that the earlier FND is identified and treated, the greater the likelihood of curing the illness(58) and avoidance of subsequent disability. Furthermore, the development and recognition of a neuropsychiatric model of this definable condition will also offer translational clinical and research opportunities to the larger problem of psychosomatic disease.

Examining the neurobiology of FND will also facilitate a better understanding of the larger problem of psychosomatic illness that burdens our healthcare system. Psychosomatic illness is associated with those patients who most frequently attend medical clinics(59). The medical and human costs of repeated and unrevealing evaluations are astronomical, including the direct cost of diagnostic

evaluations in clinics, emergency rooms and intensive care units, often involving repeated MRIs studies, extensive EEG monitoring, epileptic drug (AED) prescriptions (60), and other inappropriate treatments (61). Missed work and the emotional toll on concerned family members constitute additional expenses that are difficult to quantify but potentially avoidable with improved diagnosis and treatment.

II. Specific Aims:

Primary Aim and Hypotheses
The primary goal of this study is to provide objective measures of neural circuit activity that can clarify the neurobiology of motor-related FND, using advanced MRI techniques. In addition, psychological variables are also assessed to determine differences between FND and healthy subjects as well as compare differences across FND subtypes.

Specific Aim 1: SA1) To examine resting-state functional connectivity patterns and correlations with measures of interest in patients with motor-related FND compared to healthy subjects.
Hypotheses: Compared to healthy subjects, PNES, FMD and functional weakness related FND subtypes will demonstrate diminished rs-FC between the orbitofrontal cortex(OFC), anterior cingulate cortex(ACC) and the amygdala. rs-FC will also be abnormal across emotional processing, attentional and motor control networks in patients with motor-related FND compared to healthy subjects.

Secondary Aims and Hypotheses:
SA2) To examine volumetric differences between motor-related FND (e.g. PNES, FMD, functional weakness) and healthy subjects.
Hypotheses: FND patients will demonstrate structural alterations in limbic-paralimbic, attentional and motor related brain regions.

SA3) To examine psychometric differences between FND and healthy subjects, as well as compare differences between PNES, FMD, and functional weakness patients.
Hypotheses: FND patients will demonstrate increase anxiety, depression, dissociation and decreased resilience to stress compared to healthy subjects. PNES patients compared to other patient groups will report more extensive dissociative and psychological trauma based symptoms.

III. Subject Selection

a. Inclusion/exclusion criteria:

Inclusion criteria: FND patients of several distinct subtypes will be recruited including: 120 PNES subjects diagnosed by vEEG and/or clinical criteria(62), 120 FMD subjects meeting established clinical diagnostic criteria(63, 64), 120 patients with functional weakness diagnosed by “positive” signs suggestive of functional weakness including but not limited to a positive Hoover’s sign, and 120 healthy subjects will be recruited. Of note, patients with PNES or FMD will be recruited to include individuals who are clinically suspected to have PNES or FMD. Additionally, 60 patients with other somatoform symptoms and 60 patients with depression (major depression, dysthymia or depression NOS) will be recruited as patient control groups. Individuals between the ages of 18 and 99 will be offered the potential for study participation.

Exclusion criteria: Any significant major neurological disorder resulting in specific MRI abnormalities (i.e. encephalomalacia, severe traumatic brain injury (TBI)), poorly controlled major medical illness with known central nervous system consequences, inability to read English, pregnancy, claustrophobia, or inability to satisfy MRI safety measures.

Subject Recruitment: FND, other somatoform symptoms and depression patients will be recruited by Dr. Perez and collaborators from neurology and psychiatry clinics at the Massachusetts General Hospital(MGH). Patients may also be recruited from inpatient services at the MGH. Healthy subjects will be recruited by advertisement.

Note: all study procedures except recruitment will occur at the MGH.

b. Source of subjects and recruitment methods:

Recruitment of FND, other somatoform symptoms, and/or depression subjects will occur through physician referral at outpatient Neurology and Psychiatry departments at the MGH. Flyers advertising the study may be posted in the neurology and psychiatry centers. A recruitment letter may be mailed to potential research subjects who are referred by their physicians for possible study participation. Referring physicians may also be offered the opportunity to email patients the referral letter via SEND SECURE partners email or through patient gateway. Patients who express interest in this research study may be approached in person in the outpatient clinics or inpatient wards. Note that Dr. Perez will directly oversee patient recruitment from MGH.

Control subjects and individuals with depression will be recruited by advertisement (including from online websites such as Craiglist.com, http://clinicaltrials.partners.org and email lists) and posted flyers around Boston.

All subjects who have agreed to learn more about this research study will be approached in person or contacted by telephone and/or mail with a subsequent confirmation of eligibility and desire to participate in our study prior to informed consent and scheduling.

To aid subject identification, the medical records of patients admitted to the inpatient neurology service and those scheduled for the post-diagnosis outpatient epilepsy/neuropsychiatry/behavioral neurology clinic will be reviewed to enable investigators to approach clinicians about potential appropriate research referrals.

IV. Subject Enrollment

a. Methods of Enrollment:

During the initial communication, the researcher will describe the nature of the study to the patient (i.e. psychologic assessment, focused chart review, MRI based brain imaging, follow-up questionnaire assessments) and verify eligibility based on our inclusion and exclusion criteria (see attached phone script). If appropriate, the researcher will then schedule a date and time for subject to present in person to provide informed consent and begin study participation.

Control subjects once identified by our recruitment methods will likewise be contact by phone to describe the nature of the study (i.e. psychologic assessment, MRI based brain imaging) and verify eligibility based on our inclusion and exclusion criteria (see attached phone script) prior to scheduling a date and time for participant to present in person to provide consent and begin study participation.

All subjects will visit MGH on up to five instances based on subject participation preference for the following activities:

Depending on researcher availability, subjects may also be given the opportunity to complete structured clinical interviews either at the end of session 2 or via telephone if completion as part of session one is not possible. Healthy control subjects may be given the option of completing REDCAP based questionnaire via an emailed link or to complete all questionnaires on the same day as the brain scan. FND subjects participating in follow-up sessions may be given the option of completing REDCAP-based questionnaires via an emailed link. This option will only be offered to subjects who are deemed by a study doctor to pose minimal risk of mental health symptoms requiring immediate evaluation or monitoring. This specific data capture method is being used to enable the capture of follow-up data in patients whom have improved to the point that they are no longer being followed longitudinally in clinic or for those individuals whom for other reasons (i.e. geography) are not being followed longitudinally clinically but are interested in participating in longitudinal aspects of the research study. Whenever possible, follow-up visits will take place in-person.

1. Informed consent to explain the study and for access to relevant medical records, and permission to contact for future possible follow-up studies.
2. Completion of structured clinical interviews and self-report psychological questionnaires
3. Brief day of scanner psychological assessments and MRI based brain scanning.
4. Follow-up clinical and psychological questionnaires at approximately 6 months, 12 months, and 24 months (FND Subjects Only).

Subjects may participate in this study for a maximum of 8-9 hours for the initial assessment (1-3). If subjects, elect to participate in the follow-up questionnaires, an additional approximately 2 hours of participation is expected for each session**.** Subjects participating as healthy volunteers will complete an abbreviated set of self-report questionnaires (2), and may participate in this study for a maximum of 6 hours for the initial assessment (1-3).

b. Method for obtaining informed consent:
Written informed consent will be obtained from the patient or normal subject prior to his/her participation. Consent will be obtained by designated laboratory members with prior explicit training in consent administration. The consent form will be discussed in detail with the subject; the form will be reviewed item by item to ensure an understanding of the purposes and potential risks of the study, including its investigational nature. Subjects will be allowed to read and review the consent in full at their leisure before agreeing to participate. Only patients capable of giving informed consent will be studied.
As noted, participants will complete most psychologic assessments on a separate day from MRI scanning (see detailed list below).

Subjects will be reimbursed 50 dollars for their participation in our detailed psychologic assessment and 50 dollars for participation in our neuroimaging study with brief additional psychologic assessment. Subjects will also be reimbursed an additional 25 dollars for participation in each follow-up assessment. Subjects will also be reimbursed for parking via a parking voucher at both the MGH main campus and the Charlestown sites.

c. Treatment assignment and randomization:
This segment is not applicable to our study because no treatment is offered.

V. Study Procedures
a. Study visits and parameters to be measured:
Participants will visit MGH up to five times. During the initial visit, informed consent will be obtained. Participants will also provide consent for a focused review of their medical records pertaining to the diagnosis of FND (i.e. admission and progress notes, EEG reports, neuroimaging reports, neuropsychological assessments and consult or service notes from Psychiatry, Neurology, Psychology and Social Work). We will also ask consent to review hospital records on current and prior medication use and for permission to contact them in the event of future follow-up research studies. Subjects may decline future follow-up contact. Following consent, all eligible participants will either be administered a clinical interview and a battery of self-report measures or participate in the resonance imaging paradigm with associated brief psychologic and cognitive assessments. The order of study participation will be determined by scanner availability and/or participant and investigator preference.

Subjects unable to participate in the MRI portion of the study for any reason, may still be offered the opportunity to participate in the clinical interview, self-report questionnaire and review of medical records portion of the study.

During the neuroimaging portions, data will be collected during the resting state. Structural measures will also be acquired.

Depending on subject and investigator availability, healthy control subjects only may be given the opportunity to complete secure web-based questionnaires through an emailed link. In addition, structured

clinical interviews and the full battery of questionnaires may be performed at the end of session 2 or offered via telephone depending on researcher availability.

FND subjects will be offered the opportunity to participate in follow-up questionnaire based assessments at approximately 6 months, 12 months, and 24 months from initial follow-up. For FND subjects completing follow-up clinical and psychological questionnaires, the opportunity to complete some questionnaires over a secure, web-based emailed link (REDCAP) may be provided. This option will only be offered to subjects who are deemed by a study doctor to pose minimal risk of mental health symptoms requiring immediate evaluation or monitoring. Whenever possible, follow-up visits will take place in-person. Remote participation will allow for investigators to capture valuable data from subjects whose health has improved to the point that they are otherwise lost to clinical follow-up.

Subjects will complete consent forms and psychologic assessments at available clinical research space within the MGH (including the Martinos Center and available MGH outpatient clinic offices). Brain scanning will occur at designated MRI scanners within the MGH Martinos Center in Charletown.

b. Drugs to be used:
No drugs will be administered.

c. Devices to be used:
Images are acquired with a 3 Tesla MRI scanner.

d. Procedures/surgical interventions, etc:
No procedures or surgical interventions will be performed.

e. Data to be collected and when the data is to be collected:
Following informed consent, eligible participants will be administered the Structured Clinical Interview for DSM-IV Disorders (SCID I & II), the Edinburgh Handedness Inventory(65), the Montreal Cognitive Assessment (omitted for healthy volunteers), and the Wide Range Achievement Test – 3 (WRAT – 3) (omitted for healthy volunteers).

Participants will also complete the following self-report measures:
Participant Questionnaire (omitted for healthy volunteers)
Medical Functional Syndromes Questionnaire (omitted for healthy volunteers)
Race-Ethnicity Form
Childhood Trauma Questionnaire(66)
Barratt Impulsivity Scale (omitted for healthy volunteers)
Spielbeiger Trait Anxiety Inventory
Toronto Alexithymia Scale(67)
Connor-Davidson Resilience Scale(56)
Ways of Coping Scale-Revised Version (omitted for healthy volunteers)
NEO Five Factor Inventory
Patient Health Questionnaire(68)
Relationships Scales Questionnaire (omitted for healthy volunteers)
Educational Background Assessment
Beck Depression Inventory(69)
Dissociative Experience Scale(70)
Somatoform Dissociation Questionnaire-20
Pain Catastrophizing Scale (omitted for healthy volunteers)
SF-36v1 Healthy Survey
Social Network Inventory (omitted for healthy volunteers)
Difficulties in Emotion Regulation Scale (omitted for healthy volunteers)
The Brief Illness Perception Questionnaire (for all subjects)
The Multidimensional Assessment of Interoceptive Awareness (for all subjects)

Multidimensional Health Locus of Control Version C (for all subjects)

Note, subjects may be offered either the Clinician Administered PTSD Scale (CAPS) or the self report PTSD Checklist (PCL). The Life Events Checklist will be included as part of either the CAPS or the PCL. The CAPS will not be offered to healthy volunteers.
The PCL and Life Events Checklist will be offered to healthy volunteers.

All participants will be offered a laboratory designed Patient Questionnaire assessing specific symptoms and clinical characteristics related to FND symptoms including: age of symptom onset, years spent having symptoms, current symptom frequency, duration of typical symptom, duration of longest event, number of hospitalizations or emergency room visits for FND symptoms, presence of symptom triggers, presence of multiple FND symptoms, relationship status, employment status, and medications used currently or within the past 6 months. Participants will also be offered a laboratory designed Medical Functional Syndromes Questionnaire that captures information about medical functional syndromes that may not have been captured by the Participant Questionnaire.

On the day of scan they will be asked to complete the following self-report measures:
Spielbeiger State Anxiety Inventory (Spielberger et al., 1970)
Screening for Somatoform Symptoms-Conversion Subscale(71)
Screening for Additional Somatoform Symptoms
Event Log (FND subjects with PNES and/or paroxysmal functional movement disorder subtypes only)

The Screening for Additional Somatoform Symptoms questionnaire is a laboratory designed extension of the Screening for Somatoform Symptoms-Conversion Subscale (71) questionnaire, and is meant to capture additional somatoform symptoms not otherwise captured.

The 6 month, 12 month, and 24 month follow-up assessments will include the following self-report measures:
Follow-up Participant Questionnaire
Spielbeiger State Anxiety Inventory
Spielbeiger Trait Anxiety Inventory
Toronto Alexithymia Scale
Connor-Davidson Resilience Scale
Ways of Coping Scale-Revised Version
Patient Health Questionnaire
Beck Depression Inventory
Dissociative Experience Scale
Somatoform Dissociation Questionnaire-20
SF-36v1 Healthy Survey
Screening for Somatoform Symptoms-Conversion Subscale
Screening for Additional Somatoform Symptoms
Event Log (for FND subjects with PNES and/or those with other paroxysmal functional motor symptoms)

Please note, either paper and pencil or REDCAP administered versions of the psychometrics will be used for all psychometric data collection. The opportunity will also be made available for healthy control subjects only to potentially complete REDCAP based psychometrics via an secure emailed link. Note, patients with depression will not participate in the follow-up portions of this study at 6, 12 and 24 months.

Also, subjects who have completed the above psychometrics for related studies by collaborators in close temporal proximity to our study may potentially not complete redundant psychometric but rather may have their data taken from those closely related studies. Questionnaires that were not completed during the baseline visit may be offered at follow-up.

Image Acquisition:

Functional imaging: BOLD contrast imaging, which reflects changes in venous deoxyhemoglobin associated with neuronal activity, will be used.

Rest Task Procedure:

The rest tasks will be acquired over 1-4 scanning sessions each up to 10 minutes while individuals are at rest.

Structural imaging: A high-resolution T1 weighted anatomical image will be acquired. In addition, diffusion tensor imaging acquisition sequences will also be acquired.

VI. Biostatistical Analysis

a. Specific data variables being collected for the study:

The self-report psychometrics collect data on variables such as impulsivity, depression dissociation, psychological trauma, resilience, personality, somatization, attachment, pain catastrophizing, reading ability, handedness and participant specific FND characteristics. Clinician administered psychometrics provide evidence for co-morbid psychiatric conditions while our focused chart review will help collect subject specific FND characteristics, risk factor qualification, review of prior diagnostic evaluations, and review of prior and current treatment strategies. Blood Oxygenation Level-Dependent contrast is measured during functional imaging to reflect changes in venous deoxyhemoglobin associated with neuronal activity. Volumetric quantification will be obtained from SPGR images and white matter tracts will be delineated using diffusion tensor imaging.

b. Study Endpoints

Study endpoint is recruitment of enough participants to comply with our power analysis (30 for each subject group).

c. Statistical Methods

Regions of Interest:

Functional Connectivity Analyses:

Functional connectivity analyses will be performed using region of interest (seed-based) and whole brain data driven approaches(72-74). Correlational analyses will also be performed to assess associations between connectivity patterns and psychometric measures of interest.

Volumetric Analyses:

High-resolution T1-MRI images will be analyzed using semi-automated quantitative techniques such as voxel-based morphometry(15) and cortical thickness analyses(14, 75). Correlational analyses will also be performed to assess associations between volumetric patterns and psychometric measures of interest.

d. Power Analysis:

Based on neuroimaging studies in other neuropsychiatric populations(24, 76, 77), it is estimated that regions-of-interest will have a mean BOLD signal group difference of 0.7 with a standard deviation of 0.95. For a power of 0.8, approximately 60 total subjects would be needed. We are now adding plans for study replication which will include the need for 60 subjects in each additional study arm. Given that comparisons may include FND vs. Healthy subjects (30 in each group) as well as comparisons between PNES vs. Healthy Subjects, FMD vs. Healthy Subjects, and Functional Weakness Patients vs. Healthy Subjects a total of 30 subjects in each patient group and healthy subject group will be recruited.

VII. Risks and Discomforts

a. Complications of surgical and non-surgical procedures:

Risk of clinical exacerbation:

During psychologic assessment participants will be asked potentially sensitive and stressful information about themselves. Subjects will be made aware of this psychologic investigation both in the recruitment phase of the study and more explicitly during the consent process.

In the event that participants are found to have psychopathology requiring immediate psychiatric evaluation, such as that which entails potentially imminent risk of harm to self or others, they will be escorted to the Emergency Room for clinical evaluation and treatment. In cases where the presence of such psychopathology is unclear, the research physician will assess the participant/situation to determine whether immediate clinical psychiatric evaluation is required (in which case the participant would be escorted to the emergency room). If acute evaluation is not found to be necessary, but follow up monitoring and evaluation is advisable, this will be discussed with the participant, and the participant's primary care physician or physician primarily involved in care will be notified. To protect against forced disclosure of sensitive participant information, participants are asked to complete a certificate of confidentiality consent form.

For subjects who participate remotely for any follow-up session, a study doctor will be available to answer questions and address any concerns. The study doctor will selectively review questionnaire responses when the session is complete to determine whether these indicate mental health symptoms requiring immediate psychiatric evaluation. More specifically, item 9 of the Beck Depression Inventory will be reviewed to evaluate if a research subject has endorsed any suicidality. For a score of 1 or above, the study doctor will contact the subject by phone for an additional phone triage regarding any concern and if necessary will also notify the participant's physician.

Risk of uncovering structural brain pathology.
The pulse sequences used in these experiments are not those used for clinical diagnostic studies and are therefore not geared toward looking for structural pathology. If an abnormality is noted on the scans that are obtained, the patient and patient's physician will be notified.

Pregnant subjects:
Because risks of MRI to a fetus are possible and not fully understood, pregnant subjects will not be studied. If there is any question of pregnancy, the subject may be offered a urine pregnancy test prior to any scanning sessions. If there is any question that a pregnancy could exist but be at too early a stage for detection by this test, the woman would also be excluded from study.

b. Drug side effects and toxicities:
No drugs will be used in our study.

c. Device complications/malfunctions:
Magnetic Resonance Imaging (MRI) involves the use of a magnetic field produced by a 3.0 Tesla magnet and radiofrequency waves which are both transmitted and received, and are similar to those of an ordinary shortwave radio. Subjects with electromechanical devices (e.g. pacemakers), reactive surgical clips, or reactive metallic implants/fragments will be excluded from study due to routine MRI restrictions.
Claustrophobia. MRI scanning can be uncomfortable for claustrophobic subjects who can find it difficult to be inside of a large tunnel-like machine. Subjects with claustrophobia will be excluded from the study, decreasing the likelihood of this state occurring.

Collision Hazard. Because of the strong magnetic field associated with the scanner, one risk is that of a metallic object projecting toward the scanner and colliding with the subject. Although this can be potentially serious, it is extremely unlikely to occur since all subjects and personnel are carefully screened for metallic objects before entering the scanning room.

Noise. The MR scanner produces tapping sounds during operation, which may reach very loud levels. Since the subjects wear earplugs or headphones which decrease the level of noise, this is not considered to be serious.

Neurostimulation. In some cases it is possible that the subject might experience neurostimulation effects, such as muscle twitches and tingling sensations, due to the rapid switching of magnetic field gradients used in these examinations. Stimulation of the muscles of the heart, causing an abnormal heart rhythm,

is much less likely to occur. The machine operates within guidelines established by the FDA which are considered to be safe.

Change in Body Temperature. A slight, but not serious, increase in body temperature may occur in the presence of radiofrequency waves.

RF Antenna Effects. If metal wires or electrodes are attached to a person being imaged, radiofrequency signals from the MR scanner may conceivably induce sufficient electrical currents in the wires to cause burns where the wires or electrodes contact the skin. If wires or electrodes are present, the scanner operator will inspect and arrange them to minimize the risk of induced currents.

d. Psychosocial (non-medical) risks:
The possibility of invasion of privacy is a risk in this study: Neurologic and psychiatric information will be obtained from the subject, referring physician and medical record. We feel that this is a minimal risk as every effort will be taken to ensure the confidentially of this information. Only individuals specifically designated for chart review with prior HIPPA training will be allowed access to patient records. All of the information will be collected, de-identified with a subject identification number and collected in a sensitive and respectful manner. A computer-based document and/or manual linking subject identification numbers with subject identity will be stored securely in the laboratory.

e. Radiation Risks:
No ionizing radiation will be used in this study.

VIII. Potential Benefits

a. Potential benefits to participating individuals:
Subjects will not receive any explicit or intended direct benefit from their participation. However, in our experience, patients have often reported that they found the studies interesting and meaningful. They expressed their sentiments with the knowledge that they would not receive any explicit or intended direct benefit from their participation.

b. Potential benefits to society:
The conditions and symptoms studied in this protocol impair quality of life and result in tremendous costs to society in terms of medical care and disability. As they are brain disorders, a neurobiological approach is the most effective means of learning more about them. The functional and structural neuroimaging techniques used in these studies are the only way to gain this information on an in vivo, systems level. The study represents a careful integration of, and bridge between, such clinical, neuropsychiatric, neuroscientific approaches and the basic behavioral neuroscientific approaches that can provide vital mechanistic information. Focusing upon the neurobiological and neuropsychological processes implicated in symptomatology is an important and direct way of increasing our understanding. Such an understanding provides a necessary foundation for the development of more targeted diagnostic, preventative, and therapeutic approaches to FND.

IX. Monitoring and Quality Assurance

a. Independent monitoring of source data/Safety Monitoring:
Because no clinical diagnosis will be made as part of this study, no interventions will be used, and procedures have been shown to be safe, an independent data safety monitoring board (DSMB) will not be established. The PI, co-investigators and study coordinator will continuously provide oversight to ensure that participants are not exposed to unnecessary or unreasonable risks and that they study is being conducted according to highest scientific and ethical standards.

b. Outcomes monitoring:
Diagnostic and behavioral forms are prepared by a researcher in subject-specific packets. Data are entered into an electronic database, checked against original instruments for inconsistencies, and corrected. Functional scans are analyzed daily to assure proper data acquisition and data quality.

All data will be analyzed and assessed by the PI, co-investigators, and members of the research lab to assure quality and accordance with the IRB-approved protocol.

c. Adverse event reporting guidelines:

Subjects will be able to ask any questions about the study to study investigators, who will be available at the request of the subject. Subjects have the option to withdraw from the study at any time, and this is explicitly stated in the consent form and will be emphasized at the time consent is obtained. Subjects may also be discontinued prematurely if they experience a clinically significant adverse event as determined by the clinical staff, if the subject requests to be withdrawn from the study, or if there are other conditions for which, in the investigator's opinion, it is in the subject's best interest to be withdrawn from the study.

All serious and/or unexpected adverse events will be reported to the IRB within 24 hours. All other adverse events will be reported in an annual continuing review report. This is not an interventional study, so the clinical care of these subjects will not be altered in any way.

X. References

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