Title: Effects of Chronic Pain, Dyspnea, and Physical Activity Promotion on Functional Connectivity of the Brain in COPD

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TABLE OF CONTENTS

1. Protocol Summary/Abstract

Objectives:	Persons with COPD have both chronic musculoskeletal pain and dyspnea that require accurate diagnosis and treatment, ultimately to optimize functional status. We will use advanced neuroimaging techniques to understand central mechanisms of chronic pain, dyspnea, and physical activity promotion in COPD. We will correlate subjective symptoms (chronic pain and dyspnea) with an objective central biomarker (resting state functional connectivity) and examine their changes in response to a non-pharmacological, non-addictive physical activity (PA) promotion in Veterans with COPD. Resting state functional connectivity magnetic resonance imaging (fcMRI) is used in brain mapping to evaluate interactions and communications between brain regions that occur in a resting state, before a sensory event or when an explicit task is not being performed. The resting pattern and strength of functional connectivity specifically within the "default mode" network (DMN) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus) have been examined in several studies of clinical disease states, as this network is reliably detected and well-characterized. The DMN is a critical network involved in many functions with high interconnectivity with other networks and could be a sensitive network that responds to symptom change. These resting communications are altered in older adults with chronic musculoskeletal pain. Chronic musculoskeletal pain has not been specifically studied with neuroimaging in COPD.
Research Design:	The study is a pilot observational study of 30 Veterans with COPD who will be recruited through a current VA Boston IRB approved study (#3199) of a web-based PA intervention (Every Step Counts ESC) or through VA Boston's clinical PR program. Participants will undergo a fcMRI of the brain at baseline and after one of these PA/exercise program for approximately 3 months. Scans will be performed in the Neuroimaging for Veterans Research Center (NeRVe) of VA Boston. **Aim 1:** Characterize and correlate the relationship between functional connectivity and chronic musculoskeletal pain and dyspnea in 30 persons with COPD (aiming for approximately 10 with both symptoms, 10 with chronic pain, and 10 with dyspnea). **Aim 2:** Explore changes in functional connectivity and changes in symptoms in 30 persons with COPD after PA promotion through use of the ESC intervention or conventional PR.

Methodology	**Aim 1:** Group average correlation maps will assess cross-sectional differences in functional connectivity between those with combined chronic musculoskeletal pain and dyspnea, compared to those with either symptom alone. Our analysis will involve modeling with group as the independent variable and baseline neuroimaging parameters as the dependent variable. **Aim 2:** After completion of the PA/exercise intervention, associations between longitudinal increases in PA measured as daily step counts and changes in mean regional connectivity will be assessed in each of the three groups and computed over the cortex using multiple linear regression with FreeSurfer's mri_glmfit and MATLAB (Mathworks; Natick, MA). Clinical characteristics associated with functional connectivity when analyzed individually in preliminary analyses will be included in the regression models.
Clinical Implications:	This proposal will provide insight into the biologically complex relationships between symptoms (chronic pain and dyspnea), behavior (PA), and biology at the central level (functional connectivity).

2. Background Information

Chronic musculoskeletal pain and dyspnea coexist and are highly prevalent in COPD.

Chronic obstructive pulmonary disease (COPD), a major cause of global morbidity, is the fourth leading cause of death in the United States.[1,2] COPD affects up to 11% of all VA healthcare patients.[3] Patients with COPD experience significant dyspnea despite optimization of medical therapy.[4,5] Breathlessness is an "all-consuming and life-changing" experience associated with profound fear.[5,6] In addition, pain significantly impacts health-related quality of life (HRQL) and functional ability, but remains poorly understood in COPD.[7-10] Patients with COPD report almost 2.5 times greater pain compared to healthy adults.[7] Over half of patients with COPD experience chronic pain--largely musculoskeletal pain.[8-10] Importantly, the *co-occurrence* of dyspnea and chronic back or arthritis pain exists in 50-67% of persons in a Medicare database.[11] Participants with dyspnea have a considerably higher prevalence of pain than those without, 64 vs. 18%, respectively.[11] In COPD, increased pain levels are associated with increased dyspnea.[7-10]

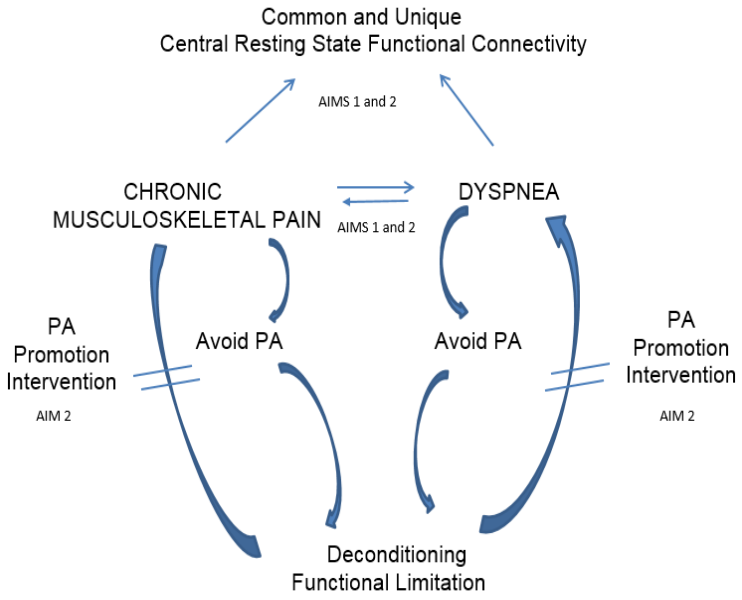
Effective treatment depends on accurately distinguishing between chronic pain and dyspnea.

Patients who suffer from both chronic musculoskeletal pain and dyspnea may have their perceptions of one symptom amplified or modulated by the other.[7-11] Clinically, it is often difficult to distinguish a patient's perception of chronic pain from dyspnea using self-report and questionnaires. Yet, it is critically important to distinguish them to make accurate diagnostic and treatment decisions. Patients who experience and report pain, heightened by worsening dyspnea, may be overtreated with narcotics which can lead to respiratory suppression or opioid dependence. Similarly, a patient's report of dyspnea,

amplified by worsening chronic pain, may lead to unnecessary testing for etiologies of dyspnea and undertreatment of pain. Novel diagnostic tools are needed to accurately and objectively distinguish between these symptoms in persons with COPD.

Unique patterns of resting state functional connectivity may be a novel marker for symptoms.

Unique brain activity networks and specific structural changes in the brain are traditionally associated with chronic pain stimuli.[12] It has also been shown that resting state functional connectivity, between the anterior insular cortex and brainstem periaqueductal gray, determines pain perception in healthy humans.[13] Resting state functional connectivity magnetic resonance imaging (fcMRI) is used in brain mapping to evaluate interactions and communications between brain regions that occur in a resting state, before a sensory event or when an explicit task is not being performed.[14,15] The resting pattern and strength of functional connectivity specifically within the "default mode" network (DMN) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus) have been examined in several studies of clinical disease states, as this network is reliably detected and well-characterized.[16] The DMN is an anatomically defined brain system that is one of the most studied networks during resting state and one of the most easily visualized networks. It is a critical network involved in many functions with high interconnectivity with other networks and could be a sensitive network that responds to symptom change.[16] These resting communications are altered in older adults with chronic musculoskeletal pain who show greater functional connectivity between the posterior cingulate and left insula, superior temporal gyrus, and cerebellum.[17] Chronic musculoskeletal pain has not been specifically studied with neuroimaging in COPD.



Physical activity (PA) can interrupt the cycle of chronic musculoskeletal pain and dyspnea that leads to deconditioning and functional limitation in COPD.

Currently, the central mechanisms of dyspnea in COPD are unknown. "Dyspnea is not a carbon copy of pain."[18] Neuroimaging of dyspnea is in its infancy; most studies to date focus on acute dyspnea elicited in healthy volunteers. Only two studies have examined dyspnea in patients with COPD, and characterized its association with resting state functional connectivity in the anterior insular cortex, anterior cingulate cortex, prefrontal cortex, and posterior insular cortex.[19,20] Even less is known about brain activity or functional connectivity in persons with COPD who experience ***both*** chronic pain and dyspnea.[21] No study has examined the relationships between chronic musculoskeletal pain and dyspnea, and resting state functional connectivity. Unique patterns and varying strength of functional connectivity may be novel biomarkers to assess underlying mechanisms of symptom perception and understand the unique contributions of chronic musculoskeletal pain and dyspnea to a COPD patient's symptom complex,

for accurate diagnosis and clinical management. Based on our preliminary work using questionnaires and the published literature, we propose a Conceptual Model (Figure 1) in which COPD patients with both chronic musculoskeletal pain and dyspnea have common and unique resting state functional connectivity.

Physical activity is non-pharmacological therapy for chronic musculoskeletal pain and dyspnea.

It is also important to understand chronic musculoskeletal pain and dyspnea in COPD because they are common barriers to engaging in physical activity (PA)[8,22] and exercise.[23-25] The clinical course of COPD is characterized by a downward spiral of dyspnea, physical inactivity, and deconditioning.[4,5] Chronic pain similarly leads to a negative cycle of physical inactivity and functional limitation. Symptoms worsen with even minimal movement, ultimately resulting in significant physical disability (Figure 1). Nevertheless, exercise and PA are effective non-pharmacological therapies for management of chronic pain and dyspnea.[7,22,24-30] Conventional Pulmonary Rehabilitation (PR) is the standard of care to promote exercise and is the most effective therapy for dyspnea in stable COPD.[24] There is also a need to include pain interventions in PR.[9,10] However, PR is inaccessible and underutilized.[26] Thus, we developed Every Step Counts (ESC), a technology-mediated intervention accessed via the internet, to promote PA in COPD.[31-34] Based on the Theory of Self-Regulation,[35,36] ESC couples a dynamic website with pedometer use to directly monitor step counts. The website provides individualized step-count goals, iterative feedback, education on disease self-management, motivation, and online social support .[33,34,37-40] In two randomized studies in Veterans with COPD, we demonstrated ESC's safety, feasibility, and efficacy to increase PA and improve HRQL over 3-4 months.[38,40] We have shown that ESC can improve dyspnea as assessed with questionnaires. Using the same web-based platform, Krein et al. showed that PA promotion decreases chronic back pain-related disability in the general Veteran population.[41] No study has examined structured PA/exercise as treatment for both chronic musculoskeletal pain and dyspnea in COPD. Novel tools are needed to assess the impact of PA promotion on pain and dyspnea, highly prevalent symptoms in Veterans with COPD.

Symptom response to exercise may be associated with unique functional connectivity patterns.

The biological mechanisms underlying the benefits of PA are only beginning to be elucidated. Neuroimaging studies focused on pain have shown distinct patterns in prefrontal cortex activity associated with pain improvement after cognitive and meditative therapies.[42] One small study showed that decreases in dyspnea after PR are associated with brain activity changes in the insula, anterior cingulate cortex and prefrontal cortex.[20] Little is known about changes in resting state functional connectivity patterns associated with changes in chronic musculoskeletal pain and dyspnea as a result of PA and exercise interventions in COPD. We propose a Conceptual Model in which PA can break the cycle of functional limitation in COPD that results from chronic musculoskeletal pain and dyspnea, and reduction in these symptoms may map to unique functional connectivity patterns in the brain (Figure 1). No studies have examined changes in chronic musculoskeletal pain and dyspnea in response to PA and exercise, and their associated effects on functional connectivity, in persons with COPD. We propose to address this gap in knowledge and examine these central mechanisms using resting state functional connectivity magnetic resonance imaging (fcMRI) in a well-characterized cohort of Veterans with COPD who have used the ESC web-based PA intervention or conventional PR.

Neuroimaging in elderly patients with COPD is feasible. There are a limited number of neuroimaging papers currently available on PubMed that examine resting state functional connectivity[19, 44,45], brain

activity[20], or the default mode network (DMN)[43] in persons with COPD. Yu et al. identified the insula as a seed region associated with dyspnea in 15 patients with COPD, compared to 15 controls.[19] Wang et al. showed abnormal intrinsic brain activities in the posterior cingulate cortex, precuncus, and brainstem in 19 patients with COPD.[44,45] Herigstad et al. showed that PR is associated with altered neural responses related to learned breathlessness in 31 patients with COPD, average age 68 ± 9 years.[20] Finally, Hu et al. showed that cognitive impairments correlate with changes in the DMN in 29 persons with mild COPD, 30 with moderate COPD, and 24 with severe COPD.[43] These results highlight the dearth of data about central mechanisms of chronic musculoskeletal pain and dyspnea in COPD. Nevertheless, the published results provide guidance for our current proposal (i.e. sample size, insula as possible seed region) and demonstrate feasibility for imaging and interpreting fcMRI results from the COPD population. In addition, Dr. Salat (Co-Investigator) has extensive experience studying functional connectivity and the DMN in Veterans (Figure 2), and interpreting neuroimaging data from elderly adults.[46-48] The Lifespan Human Connectome Project in Aging, recruiting 1200+ healthy adults aged 36-100+, will provide context for interpretation of our fcMRI data in the proposed COPD cohort with an estimated mean age of 72 ± 8.[40,47] Normative data are also available from the VA Boston Translational Research Center for Traumatic Brian Injury and Stress Disorders (TRACTS) which images Veterans with demographics and comorbidities similar to our COPD cohort.[49]

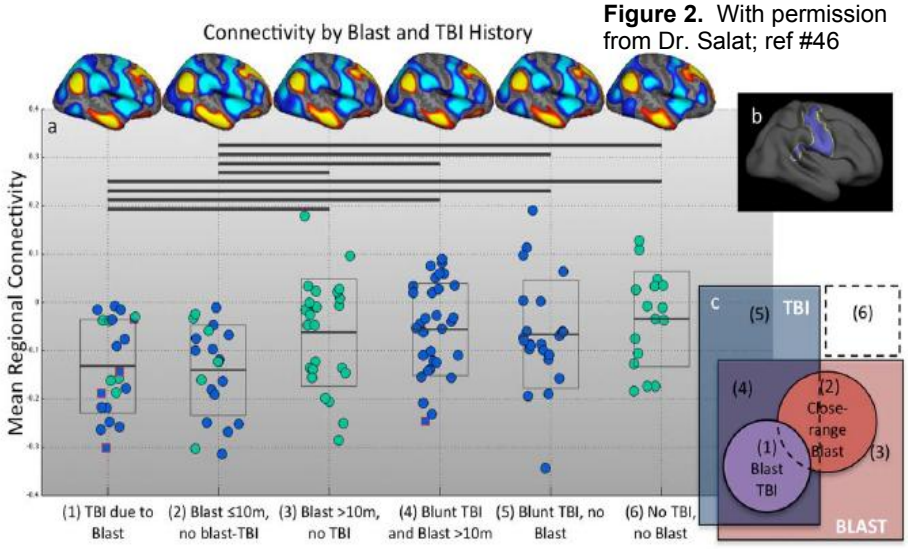


Figure 2. With permission from Dr. Salat; ref #46

3. Rationale and Purpose

Statement of the Problem

COPD is the nation's fourth leading cause of death and affects up to 11% of all VA healthcare patients. Patients with COPD experience significant dyspnea despite optimization of medical therapy. In addition, over half of patients with COPD experience chronic pain--largely musculoskeletal pain. Clinically, in patients who suffer from both chronic pain and dyspnea, it is difficult to distinguish a patient's perception of one symptom modulated by the other. Novel objective diagnostic tools are needed to complement patient self-report and accurately distinguish symptoms in patients who have both chronic pain and dyspnea to optimize clinical management. It is also important to study chronic pain and dyspnea in COPD because they are common barriers to engaging in physical activity (PA) and exercise. The clinical course of COPD is characterized by a downward spiral of dyspnea and chronic pain, physical inactivity, and significant functional limitation. Although chronic pain and dyspnea can be barriers, PA and exercise are powerful, but underused, non-addictive therapies for management of

these symptoms in COPD. Conventional Pulmonary Rehabilitation (PR) delivers exercise in a supervised setting and is an intervention that can improve pain. Because a large percentage of patients with COPD cannot access conventional PR, we developed Every Step Counts (ESC), a technology-mediated intervention based on the Theory of Self-Regulation, to promote PA in COPD. We have demonstrated ESC's safety, feasibility, and efficacy to increase PA and improve health-related quality of life in Veterans with COPD. In two separate studies using questionnaires, ESC has been shown to improve dyspnea in COPD and relieve chronic back pain in Veterans. An important next step is to understand the mechanisms of benefit of conventional PR and PA interventions, like ESC, in the many COPD patients with both chronic musculoskeletal pain and dyspnea to optimize treatment of these symptoms. Currently, the central mechanisms of chronic pain and dyspnea, and how they change in response to PA promotion in COPD are largely unknown. It has been shown that pre-stimulus resting state functional connectivity determines pain perception in healthy humans. Resting state fcMRI evaluates interactions between brain regions before a sensory event or when an explicit task is not being performed. These communications are altered in older adults with chronic musculoskeletal pain. Functional connectivity among regions specifically within the "default mode" network (DMN) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus) have been examined in clinical disease states, as this network is reliably detected and well-characterized. Functional connectivity may be a novel biomarker of chronic pain and dyspnea.

Hypotheses or Key Question

Persons with COPD have both chronic musculoskeletal pain and dyspnea that require accurate diagnosis and treatment, ultimately to optimize functional status. We propose to use advanced neuroimaging techniques to understand central mechanisms of chronic pain, dyspnea, and physical activity promotion in COPD. Our novel proposal to correlate subjective symptoms (chronic pain and dyspnea) with an objective central biomarker (resting state functional connectivity) and examine their changes in response to a non-pharmacological, non-addictive physical activity promotion (ESC or conventional PR) will personalize the care of Veterans with COPD.

We hypothesize that, in COPD, there will be unique differences in the mean regional connectivity in the DMN between those with both chronic musculoskeletal pain and dyspnea versus those with either symptom alone, and that, after a PA promotion intervention (either web-based ESC or conventional PR), functional connectivity will have specific changes associated with changes in chronic pain and dyspnea.

4. Objectives

Aim 1: Characterize and correlate the relationship between functional connectivity and chronic musculoskeletal pain and dyspnea in 30 persons with COPD (aiming for approximately 10 with both symptoms, 10 with chronic pain, and 10 with dyspnea).

Aim 2: Explore changes in functional connectivity and changes in symptoms in 30 persons with COPD after PA promotion through use of the ESC intervention or conventional Pulmonary Rehabilitation.

This proposal will provide insight into the biologically complex relationships between symptoms (chronic pain and dyspnea), behavior (PA), and biology at the central level (functional connectivity).

Functional connectivity is a novel assessment to potentially address the clinical challenge of distinguishing between chronic musculoskeletal pain and dyspnea at baseline and in response to PA and exercise interventions. It may be particularly informative in the subgroup of debilitated patients with COPD who have a high burden of both symptoms. The proposed project focuses on a significant health problem and uses innovative and advanced approaches. This proposal has high potential to significantly impact the rehabilitative care of a vulnerable elderly population of Veterans with chronic disease.

5. Relevance to Veteran's Health

Understanding the relationships between chronic musculoskeletal pain and dyspnea using advanced neuroimaging tools could personalize the clinical management of complex COPD patients. Understanding the central mechanisms may target the use of novel drugs for relevant neurotransmitter systems.[50] Our proposed work to correlate subjective symptoms (chronic musculoskeletal pain and dyspnea) with an objective central biomarker (functional connectivity) and examine the impact of a non-pharmacological, non-addictive PA intervention on symptoms is aligned with VHA and RR&D research priorities. There are strong implications for translation into clinical practice to advance the rehabilitative care of Veterans by potentially (1) accurately assessing baseline and relative changes in chronic musculoskeletal pain and dyspnea in response to exercise rehabilitation, and (2) informing the design of PA interventions to improve treatment of these symptoms. Our work will establish feasibility of using neuroimaging as a biomarker.

6. Study Design

Conceptual model. Figure 1 illustrates our hypotheses that, in COPD, there will be unique differences in the mean regional connectivity in the DMN between those with both chronic musculoskeletal pain and dyspnea versus those with either symptom alone (Aim 1), and that, after a PA promotion intervention (either web-based ESC or conventional PR), functional connectivity will have specific changes associated with changes in chronic pain and dyspnea (Aim 2).

Table 1.	***2020 to 2021***			***2021 to 2022***		
Study Timeline	*Jul-Oct*	*Nov-Feb*	*Mar-Jun*	*Jul-Oct*	*Nov-Feb*	*Mar-Jun*
Participant Enrollment						
Cleaning Data Neuroimages						
Data Analysis						
Dissemination of Results						

Overview (Table 1). This neuroimaging pilot will enroll from either (1) participants who have enrolled in an active study examining the efficacy of a web-based intervention (ESC) to promote PA Veterans with COPD and who are assigned to the PA intervention group (RR&D Merit I01 RX002855; 2019-2023, VA Boston IRB #3199) or (2) patients who will enroll in conventional Pulmonary Rehabilitation (PR) as part of usual clinical care at VA Boston.

We will perform fcMRIs in a convenience sample of 30 males with COPD: aiming for approximately 10 participants with chronic musculoskeletal pain and dyspnea, 10 with pain alone, and 10 with dyspnea alone. The 30 participants will be enrolled over 16 months. A total of 60 neuroimaging scans (30 participants at 2 time points each, pre and post PA/exercise) will be performed. This neuroimaging study will not affect the conduct or validity of the #3199 study or conventional PR. All staff collecting and analyzing outcomes

data and the fcMRI data for the neuroimaging SPiRE will be blinded to assessment results, including responses on questionnaires that assess pain and dyspnea.

Pedometer and internet-mediated physical activity intervention (ESC). As part of IRB #3199 and covered under the #3199 IRB approval, participants assigned to the ESC intervention are asked to wear a Fitbit pedometer every day, except while asleep or showering/bathing, during the 3-month study period. Subjects are instructed to upload daily their date and time-stamped step-count data to the study website. The first step-count goal is calculated from the baseline step counts. Each Sunday thereafter, the study computer runs the goal calculation algorithm and provides each participant with his tailored daily step-count goal for the week.[38,40] Subjects have access to a personalized web page where they can view graphical displays of step counts and walking progress. They are encouraged to read the motivational and educational messages and participate in the online community. Daily step counts are assessed with the Fitbit pedometer at baseline and 3 months. If a participant agrees to participate in this neuroimaging study, he will have a fcMRI of the brain performed at baseline and at 3 months. We will schedule the fcMRI at a time that considers both scanning availability and the least amount of burden on the participant.

For participants who are enrolled in #3199 and agree to this neuroimaging study, the only new testing in is the fcMRI. All other assessments (including chronic musculoskeletal pain, dyspnea, and daily step counts) will be collected as part of #3199 for which participants are giving written consent to place their data into a data repository (VA IRB#2999). We may also use other information obtained as part of the subject's participation in #3199 including name, address, date of birth, and information such as SSN, pulmonary function tests, laboratory test results, X-ray images/readings, exercise tests, hospitalization records from other institutions, emergency contact information, PR evaluations, medical history, allergies, imaging studies and reports, procedure reports, or mental health treatment.

Conventional Pulmonary Rehabilitation.
As part of usual medical care and covered under the clinical PR program, participants engage in a supervised exercise program. The PI Dr. Marilyn Moy is the Medical Director of the VA Boston Pulmonary Rehabilitation Program. This is a clinical program comprised of a multidisciplinary team of specialists providing rehabilitative care to individuals with a variety of pulmonary diseases. The team includes physicians specializing in pulmonary care, a physician assistant, a respiratory therapist and a kinesiotherapist. The comprehensive evaluation, educational, and exercise components are offered on an outpatient basis approximately two hours twice weekly for 9 weeks for a total of 18 exercise sessions. PR is considered standard of care for patients with COPD and symptoms that affect their functioning.[24] It is the main clinical exercise program for Veterans with pulmonary disease at the VA Boston Healthcare System. Patients are referred by their healthcare providers. If a participant agrees to participate in this neuroimaging study, he will have a fcMRI of the brain performed before and after the PR program. We will schedule the fcMRI at a time that considers both scanning availability and the least amount of burden on the participant. For participants who will enroll in conventional PR and agree to this neuroimaging study, we will perform the fcMRI along with, PA assessment and questionnaires assessing pain, shortness of breath, and exercise. After completing the exercise program in conventional PR after 9 weeks, resting state fcMRI, questionnaires assessing chronic musculoskeletal pain and dyspnea, and PA monitoring will be repeated. We will complete a fcMRi in participants who have completed at least 9 of the 18 PR exercise

sessions. For participants who enroll from conventional PR, we will obtain 6 minute walk test and step count information from PR entry and exit clinical evaluations.

7. Study Subject Selection

a. Subject Inclusion Criteria

We will recruit only Veterans. The proposed MRI neuroimaging pilot study will enroll only men given the known sex differences in brain structure, neuroplasticity, and functional connectivity.

Participants in this neuroimaging study will have agreed to participate in a PA/exercise promotion program, either: (1) the web-based ESC intervention as part of the Merit study IRB#3199, or (2) conventional PR as part of usual clinical care. Therefore, they would meet the inclusion criteria as stated in research study #3199 or would meet the clinical requirements for enrollment in clinical PR.

b. Subject Exclusion Criteria

For this neuroimaging pilot study, we will exclude Veterans with known brain lesions, claustrophobia, history of seizures, diagnosis of bipolar disorder, schizophrenia, psychotic disorder, or cognitive disorder like dementia. People who have any metal in their body including shrapnel, surgical medical clips, implants, pacemakers, or metal-based tattoos will be excluded.

In summary, participants will meet the inclusion and exclusion criteria of #3199 or they will meet the clinical indications for enrollment in conventional PR. In addition, *for the proposed neuroimaging study, exclusion criteria are:*

a) Female sex
b) Claustrophobia
c) History of seizures
d) Known brain lesion
e) Current diagnosis of bipolar disorder, schizophrenia, or psychotic disorder
f) Cognitive disorder such as dementia
g) Known metal in body including shrapnel, surgical medical clips, implants, pacemakers, or metal-based tattoos

c. Recruitment

We recruit from IRB #3199 participants assigned to the web-based ESC PA intervention. We also recruit from the VA Boston clinical PR Program.

(1) Those who enroll in #3199, have signed the #3199 ICF, and have been assigned to the ESC PA intervention group will be contacted by telephone by study staff already known to them. Eligible and interested participants will sign an ICF and HIPAA for the neuroimaging study.

(2) Recruitment of participants through conventional PR will be compatible with the established clinical workflow of the outpatient program based at VA Boston. During the PR intake assessments, candidates are evaluated by the PR staff at the Jamaica Plain campus to assess for safety and to formulate an individualized treatment program. Subjects typically start the PR program a median of 6-8 weeks after the clinical intake assessment, depending upon PR program

slot availability. The PR program consists of 18 sessions held twice weekly for 9 weeks; exercise classes are conducted at the Jamaica Plain VA under the clinical care of the core PR team based at VA Boston. At the final PR session, a clinical exit evaluation is performed at Jamaica Plain.

Dr. Moy and her study staff will review all incoming consults (see HIPAA waiver application) for eligibility based on COPD status. Once a potential subject has been identified, initial contact will be made through a letter which will be mailed to the subject's home address on file (Please see recruitment letter and reply postcard template). The letter will contain general information on the study, both in the body of the letter and in an enclosed brochure, as well as a postage-paid response postcard and telephone number to contact if the patient wishes to opt out of participation in the study. If the subject expresses interest, or if no opt-out response is received within 2 weeks, a member of the research team will contact the potential subject by telephone to assess interest and/or conduct a telephone screening for eligibility (Please see telephone screening script). We note that patients referred to VABoston's PR program but who choose to do a PR program outside of VABoston are eligible to participate in this neuroimaging study.

Recruitment will be conducted by research staff distinct from clinical staff. Enrollment in the neuroimaging study is voluntary and not a requirement of participating in #3199 or the clinical PR program. If a participant agrees to participate in this neuroimaging study, the main new assessment is the fcMRI of the brain.

Other methods of recruitment will be employed. We will post flyers in designated bulletin boards at VABoston. We will leave brochures with study information in the waiting areas of pulmonary and primary care clinics.

8. Data Collection/Study Measures

Data assessments will be conducted at VA Boston, JP campus, by trained research assistants. At the time of the fcMRI, all participants will complete assessments for pain (BPI and NRS) and shortness of breath (MMRC and UCSD SOB). These 4 questionnaires will take up to 15 minutes to complete.

Neuroimaging (All Participants). Participants will complete a fcMRI scan clearance form. Scans will be performed in the Neuroimaging for Veterans Research Center (NeRVe) of the VA Boston Healthcare System, and a clinical MRI technician will be present for all scans. Each scan will start with 5 minutes of familiarization with the equipment and will be completed at one visit that lasts 45-60 minutes. Physiologic monitoring will be synchronized with image acquisition. Chest expansion, oxygen saturation, and end-tidal CO_2 will be assessed. Neuroimaging data will be acquired on a 3-Tesla Siemens (Erlangen, Germany) TIM Trio scanner, using a 32-channel brain array.[46] Two multiecho MPRAGE (Magnetization Prepared Rapid Gradient Echo) T1-weighted anatomical scans (1 mm isotropic) will be acquired for surface reconstruction, functional connectivity seed placement, and inter-participant registration.[50,51] Resting state functional connectivity data will be acquired in two runs using high temporal and spatial resolution sequences recently developed for the Human Connectome Project Lifespan study.[47,48] The fcMRI is being performed for research purposes only. Participants will be paid $65 for participation in each fcMRI scan performed. They will be asked to disclose their personal identifying information (name, address, and social security number) to the VA Boston Fiscal Office in order to receive the cash payment.

The scans performed in this study are for specific research purposes and are not meant to find any medical abnormalities. The results from the research scan will not be routinely shared with the participant's clinical provider, except upon the participant's request. However, if the investigators or MRI technician notice any potential incidental finding, the scan will be reviewed by a clinical radiologist who will determine whether a clinical evaluation is warranted. If there is a finding that warrants a clinical follow-up, the PI Dr. Moy will discuss this with the participant. If any abnormality on the MRI is noted by the research staff, the participant will be notified to follow up with his usual provider.

Table 2. Study Measures at baseline and after PR
Demographics
Comorbidities and Medications
Daily Step Count
800-ft Walk Test
4-meter Gait Speed Test
Rapid Assessment of Physical Activity (intensity)
Physical Activity Recall Questionnaire
Barriers to Exercise
Exercise Adherence (Exercise Logs)
Exercise Self-Regulatory Efficacy
St. George Respiratory Questionnaire
Bristol COPD Knowledge Questionnaire
mMRC Dyspnea scale
Beck's Depression Inventory-II
Epworth Sleepiness Scale
MOS Social Support Survey
Brief Pain Inventory (short form) and Numerical Rating Scale for Pain
Healthcare Utilization
EQ-5D Health Utilities
Veterans Rand 36 Item Health Survey (VR-36)
CHAMPS Physical Activity Questionnaire

Symptom and physical activity assessments (Enrolled through PR only). These will be assessed by either medical chart review or questionnaires (completed in person or mailed through USPS to the participants, who will return them to study staff using a pre-paid mailer) Table 2. Participants will be well-characterized at baseline with respect to demographics, medication use, comorbidities, lung function (all based on medical chart review), anxiety,[52] depression,[53] and sleep quality,[54] (based on self-administered questionnaires). We will review the participant's medical history and obtain information about cigarette use, supplemental oxygen use, and prior participation in PR. We will assess chronic musculoskeletal pain intensity and interference using the single-item Numeric Rating Scale (NRS)[55,56] and the Brief Pain Inventory (BPI) short form[57], respectively. The NRS asks participants to rate pain intensity over the past week on a numbered scale of 0 to 10.[55,56] The BPI asks about location of pain, severity of pain, impact of pain on daily function, pain medications, and amount of pain relief in the past 24 hours or the past week.[57] The BPI responds to both behavioral and pharmacological pain interventions and is validated in COPD.[57] The arithmetic mean of the four severity items of the BPI also measures pain severity; the arithmetic mean of the seven interference items measures pain interference.[57] Dyspnea will be assessed with the mMRC scale (responses 0-4 with 4 being the most dyspneic).[58] We will also use the UCSD Shortness of Breath Questionnaire for a detailed assessment of dyspnea.[59] The MCID has been determined to be ± 5 units.[60] To assess intensity of PA reported at baseline, we will administer the 9-item Rapid Assessment of Physical Activity (RAPA) which categorizes activity level as sedentary, underactive, and active.[62,63]

Exercise Adherence: We will measure exercise adherence by patient self-report. Subjects will be asked to complete daily exercise logs. The paper log is intentionally simple to minimize burden and potential influence to be part of the intervention. Subjects will circle a yes/no response to 2-3 questions about whether exercise was performed that day. Subjects will bring completed logs to their follow-up visits or will be given a prepaid return envelope to mail logs to study staff. Exercise adherence, calculated weekly or monthly, will be defined as > 70% of days with self-reported exercise. 70% is chosen since all participants are instructed to exercise most days (5 of the 7 days) each week.
Exercise Self-Regulatory Efficacy: The belief in one's ability to self-regulate and exercise regularly when faced with challenges is a key variable that influences engagement in exercise. The Exercise Self-Regulatory Efficacy Scale for persons with COPD measures exercise self-regulation, and incorporates items from Resnick's self-efficacy scale for older adults and McCauley's self-efficacy questionnaire for sedentary adults.[64] The 16-item questionnaire is reliable and valid in COPD.[64]
Health-Related Quality of Life: Respiratory-specific HRQL will be assessed with the St. George's Respiratory Questionnaire (SGRQ).[65] We will examine the composite Total Score (SGRQ-TS) as well as the subscales of Activity, Symptoms, and Impact. Lower SGRQ scores indicate better health status. The minimal clinically important difference (MCID) for the SGQR-TS is ± 4 units.[66] The SGRQ has been used extensively in COPD.
Dyspnea: Dyspnea will also be assessed using the Modified Medical Research Council scale (responses 0-4 with 4 being the most dyspneic).[58] We will also use the UCSD Shortness of Breath Questionnaire for a detailed assessment of dyspnea.[59] The MCID has been determined to be ± 5 units.[60]
Depression: Depression will be assessed with the Beck's Depression Inventory-II.[67] A score of 14 or higher represents a clinical diagnosis of depression. If responses meet the cut-off scores indicating a clinical diagnosis of depression or anxiety, with the patients' permission, we will inform their medical and mental health providers of the results for further evaluation and/or treatment.

Healthcare Utilization: Acute Exacerbation and Hospitalization History: Assessment of AEs and COPD-related hospitalizations is based on both self-report and medical chart review. During the study, all subjects will be instructed to call study staff with any changes in clinical status or medications. Most patients remember the occurrence of AEs because they are well-defined periods of worsening symptoms that require treatment with an antibiotic and/or prednisone.[69] At each research visit, study staff will assess changes in symptoms, changes in medications, prednisone and antibiotic use, visits to the emergency room, and hospitalizations. Participants will be asked to provide the dates and locations of all hospitalizations since the previous visit. Patient report will prompt study staff to request hospital discharge summaries, medication records, chest X-ray reports, CT scan reports, and any additional information. Patient reports will be verified with review of hospitalization and pharmacy records both in and outside VA facilities, whenever possible. An AE will be clearly defined as "a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days, requiring treatment with antibiotics or systemic steroids".[70] Occurrence of AEs within 14 days of each other will be considered a single AE.[71] This definition will also be used at the baseline visit for assessment of occurrence of AEs in the year prior to study entry.

We will also administer the following:
4-meter gait speed as a measure of overall frailty.

PA Recall Questionnaire,
Barriers to Exercise,
Bristol COPD Knowledge Questionnaire,
Epworth Sleepiness Scale,
MOS Social Support Survey,
EQ-5D Health Utilities
CHAMPS Physical Activity Questionnaire
Veterans SF-36

If a subject does not have time during the study visit to complete the study-related questionnaires, we will contact the subject by phone to finish the questionnaires by phone at a time after the visit or send the questionnaires home with the subject to be completed and sent back in a pre-paid mailer.

No 38 USC 7332 information (e.g., alcohol/drug abuse, HIV, sickle cell) be collected.
Participants can be removed from the study by the PI due to inappropriate or threatening behavior toward study staff.

All study data will remain at VA Boston, behind the firewall.

9. Planned Statistical Analyses

Analytic approach. For neuroimaging, all analyses will be performed with complementary advanced imaging procedures for brain network mapping, including seed-based and independent component analysis procedures, to assure the robustness of the findings. We will correlate neuroimaging data with clinical data. We will perform secondary analyses to examine the potential influence of PA and clinical characteristics that may contribute to the findings. Our main image analyses will use robust and careful seed-based DMN mapping procedures. Analyses will account for known contributors to the fcMRI signal including motion, respiration, and cardiac signals.[46-48] Neuroimaging data will be processed using a combination of FreeSurfer.20 AFNI.21 and FSL.22 based primarily on the FSFAST processing stream.[74,75] Surface models will be reconstructed from anatomical images using FreeSurfer.23.[76] Resting state fcMRI scans for each subject will be processed using a standard stream (motion correction, time shifting, concatenation of scans, motion regressed from time series, regression of the global mean and the average time courses from the white matter and the ventricles, band pass filtering between 0.01 and 0.1 Hz).[46] Time points, runs, and sessions with excessive motion will be excluded (0.5 mm/TR; 20 TRs/run; 30 TRs/session). Data will be sampled to and smoothed on the surface, and each brain will be warped to a surface-based template (fsaverage).[77] Seed regions will be derived from surface-based parcellations of the cortex providing more robust anatomical representation for each participant.[78] The vertex-wise partial correlation to the seed will allow further group-level analyses. We will focus on the DMN, but explore other networks including pain networks. We will also explore resting state functional connectivity associated with the anticipatory symptom scenarios.

Statistical analysis.
Aim 1: Group average correlation maps will assess cross-sectional differences in functional connectivity between those with combined chronic musculoskeletal pain and dyspnea, compared to those with either symptom alone. Our analysis will involve modeling with group as the independent variable and baseline neuroimaging parameters as the dependent variable. We will include any confounding variables in the models.

Aim 2: After completion of the PA/exercise intervention, associations between longitudinal increases in PA measured as daily step counts and changes in mean regional connectivity will be assessed in each of the three groups and computed over the cortex using multiple linear regression with FreeSurfer's mri_glmfit and MATLAB (Mathworks; Natick, MA).[46] Clinical characteristics associated with functional connectivity when analyzed individually in preliminary analyses will be included in the regression models. We note that although the exercise/PA from ESC and PR are of different intensities, we will be assessing daily step counts as a marker of PA which will be assessed and analyzed in the same way regardless of the exercise/PA program used.

Sample size/Power calculation. This is an exploratory proposal in a convenience sample of 30 Veterans with COPD. Findings from this study will inform the design and sample size of a future Merit Award application.

10. Ethical Issues

a. Risks to Subjects

Human Subjects Involvement and Characteristics:

Patients with a diagnosis of chronic obstructive pulmonary disease (COPD) who have been assigned to the ESC PA intervention group of the #3199 study or who have been enrolled in conventional PR at VA Boston will be eligible to participate in the proposed neuroimaging study.

Sources of Materials: Data will be collected from human subjects for research purposes. As part of the primary Merit #3199 or clinical Pulmonary Rehabilitation program, some or all of the following information will be collected at baseline and 3-months follow-up:

a) Demographic information and medical history
b) Step count data from the pedometer which all patients will wear for 10 days at baseline, and for 10 days at follow-up assessments.
c) Questionnaires to assess dyspnea, pain, health-related quality of life, depression, anxiety, and exercise self-efficacy.
d) 6-minute walk test distance to assess exercise capacity.

For the proposed neuroimaging study, additional sources of materials are:

a) fcMRI of brain

Potential Risks

Neuroimaging with MRI Scanning (All Participants): Minimal risks are associated with MRI scanning. Lying down in the MRI scanner may cause back discomfort or anxiety, particularly if the subject tends to be claustrophobic. There is a risk of falling getting on and off the scanner table. Extended periods of time in the MRI scanner can become uncomfortable. There is no risk of ionizing radiation exposure with MRI.

During the MRI procedure, participants will hear many different sounds. These sounds are sharp and repetitive and can cause anxiety in some subjects. While they may be annoying, these sounds are not harmful to one's hearing.

Potential risks to study participants enrolled through PR performing assessments include the following:

1. Subject discomfort with questionnaire items - It is possible that some questions on the questionnaires may make a subject feel uncomfortable. Subjects do not need to answer these questions.

Protection Against Risks

Neuroimaging (All Participants)

We will use all reasonable means to promote comfort including but-not limited to use of pillows and padding. Some people experience a "closed-in" feeling due to the relatively restricted space within the MRI machine. If a participant should experience such feelings, he can let the researchers know by squeezing the squeeze ball. He can do this at any time to stop the scan. We will minimize sharp sounds through the use of earplugs.

All safety precautions will be reviewed with the subject immediately prior to having the MRI. If there is any doubt as to whether the subject has metal in his body, he will be requested to have an X-ray to determine this. If the X-ray shows that there is metal in the participants, he will not be able to take part in the MRI study. If there is more than one part of the body in which metal is questionable, the participant will not be able to have an X-ray and will not be able to participate in the MRI study.

Study staff will provide pillows and close verbal communication to minimize anxiety and discomfort. The criteria for discontinuing a subject's participation in the neuroimaging protocol include the participant's request, any potential for harm, and any life-threatening or potentially disabling unintended event, including syncope, an injurious fall, new or worsened symptoms of musculoskeletal pain, shortness of breath, or chest pain, hemodynamic instability, mental status changes, dysrhythmia, angina, myocardial infarction, or anaphylaxis. These adverse events will be recorded and included in the database. Any subject who develops adverse events during the conduct of study protocols will be given immediate medical care and will be referred to his primary care physician for ongoing care.

Participant confidentiality and data security will be maintained at all times. Each participant will be given a unique study ID that will be used for all research purposes. Neuroimaging data will be stored behind the VA firewall at VA Boston. These data are backed up every night. The document linking the participant name to the study ID will be kept in a locked file separate from data collection files. Only the Principal Investigator or designee will have access to this file.

For those recruited through PR

We estimate the total time of testing to be approximately 1 hour per study visit (including the MRI). Staff performing the 6MWT will be trained in Basic Life Support. Emergency treatments including nebulizer therapy, an automated external defibrillator, and a code cart will be available. During the pulmonary function tests and 6MWTs, subjects can rest if short of breath and will be allowed to use supplemental oxygen if usually prescribed. Subjects will be instructed to bring their medications to the

visit and will be allowed to take their bronchodilators if needed after performing the walk tests. If oxygen saturation <85% is observed at the baseline 6MWT, subjects will be temporarily excluded and their primary provider contacted for further care. These subjects can be reassessed for eligibility at a later date when clinically stable. If hypoxemia occurs during a follow-up 6MWT, patients will be referred to their primary providers for assessment and suspended from the study until clinically stable. Hypoxemia and dyspnea predict balance impairment and falls in COPD; both are assessed right before the 6MWT is performed. Also, if the subject is unsteady on his feet during the short walk to assess device accuracy and is obviously a fall risk, the 6MWT will not be performed. Depression will be assessed with the Beck's Depression Inventory-II; a score of 14 or higher suggests a clinical diagnosis of depression. If responses meet the cut-off scores indicating possible depression or anxiety, with the patients' permission, we will inform their medical and mental health providers of the results for further evaluation and/or treatment. Additionally, the PI will be notified if participants report suicidal thoughts on question 9 of the Beck's, and the PI will evaluate the patient for need for referral to the ER for further evaluation and treatment. The clinical diagnosis of depression or anxiety will need to come from the participants' mental health or primary care providers, we are not diagnosing it in the research study.

Subjects do not have to answer any questions on questionnaires with which they are uncomfortable. Available 24/7 for emergencies, Dr. Moy, the PI, will contact participants by telephone if any reported adverse event suggests clinical deterioration warranting immediate medical attention.

Participant confidentiality and data security will be maintained at all times. Each participant will be given a unique study ID that will be used for all research purposes. Inadvertent disclosure of medical history information is guarded against by maintaining all completed questionnaires, collected by paper and pen, in a locked filing system. No data collection form will be linked to a participant's name. Study reports will be aggregated so that individual participants cannot be identified. All data will be stored in Access databases, identified only by study ID number, behind the firewalls at VA Boston. These data are backed up every night. The document linking the participant name to the study ID will be kept in a locked file separate from data collection files. Only the Principal Investigator or designee will have access to this file. Removal of access to research study data will be accomplished in a timely manner for study personnel when they are no longer part of the research team.

b. Potential Benefits

There are no direct benefits of the proposed neuroimaging study to the subjects and others. This multidisciplinary proposal will provide insight into the biologically complex relationships between symptoms (chronic musculoskeletal pain and dyspnea) and behavior (PA/exercise) using neuroimaging techniques. First, understanding how breathlessness and chronic musculoskeletal pain interact at the central level in individuals with COPD could lead to a personalized clinical decision-making process when choosing treatment options for a COPD patient suffering from both chronic pain and dyspnea. Understanding the relationships between chronic pain and dyspnea using neuroimaging tools could complement patient self-report to provide complete diagnostic information to personalize the clinical management of complex patients who suffer from both symptoms, ultimately to maximize functional recovery of Veterans with COPD. If we can identify an objective neuroimaging marker that distinguishes pain from dyspnea in COPD patients, this would reduce narcotic overtreatment and unnecessary testing for dyspnea. Functional connectivity is potentially a novel solution to address the clinical challenge of distinguishing between chronic pain and dyspnea. It may be particularly efficacious in the subgroup of

very debilitated patients with COPD who have a high burden of both symptoms. Understanding the central mechanisms may guide the use of drugs that target relevant neurotransmitter systems.

Second, understanding the impact that breathlessness and pain have on reducing PA/exercise would optimize health-related quality of life and maximize engagement in PA. In two separate studies using questionnaires, our web-based PA intervention improved dyspnea in COPD and relieved chronic back pain in Veterans. An important next step is to understand the mechanisms of benefit of PA interventions, like ESC, in the many COPD patients with both chronic musculoskeletal pain and dyspnea. Since not all persons with COPD benefit from conventional PR and PA interventions, neuroimaging may allow patient stratification to guide development of better PA interventions to personalize and optimize treatment of these symptoms. Thus, there are strong implications for translation into clinical practice to advance the rehabilitative care of Veterans by potentially (1) accurately assessing baseline and relative changes in chronic musculoskeletal pain and dyspnea in response to exercise rehabilitation, and (2) informing the design of better PA interventions to personalize and improve treatment of chronic musculoskeletal pain and dyspnea. Our proposed work will establish feasibility and acceptability, evaluate neuroimaging as a biomarker for chronic pain and dyspnea, and provide effect estimates for study design of a full Merit Award application. The VA ORD Strategic Plan includes research in COPD rehabilitation to optimize functional recovery.

c. Analysis of Risks in Relation to Benefits

The possible risks to subjects are reasonable in relation to anticipated benefits to subjects, and the anticipated importance of the knowledge that may reasonably be expected to result.

d. Stopping Rules

A participant may withdraw his participation at any time. There are no stopping rules in this observational cohort study.

11. <u>Safety Monitoring Plan</u>

All safety precautions will be reviewed with the subject immediately prior to having the MRI. If there is any doubt as to whether the subject has metal in his body, he will be requested to have an X-ray to determine this. Study staff will provide pillows and close verbal communication to minimize anxiety and discomfort. The criteria for discontinuing a subject's participation in the neuroimaging protocol include the participant's request, any potential for harm, and any life-threatening or potentially disabling unintended event, including syncope, an injurious fall, new or worsened symptoms of musculoskeletal pain, shortness of breath, or chest pain, hemodynamic instability, mental status changes, arrhythmia, angina, myocardial infarction, or anaphylaxis. These adverse events will be recorded and included in the database. Any subject who develops adverse events during the conduct of the study protocol will be given immediate medical care and will be referred to his primary care physician for ongoing care. Available 24/7 for emergencies, Dr. Moy, the PI, will evaluate participants if any self-reported adverse event suggests clinical deterioration warranting immediate medical attention.

Potential consequences of breach of confidentiality include loss of privacy, stigmatization, employability, insurability, as well as stress on interpersonal relationships. Participant confidentiality and data security will always be maintained. Each participant will be given a unique study ID that will be used for all research purposes. Inadvertent disclosure of medical history information is guarded against by maintaining all completed questionnaires, collected by paper and pencil, in a locked filing system. No data

collection form will be linked to a participant's name. Study reports will be aggregated so that individual participants cannot be identified. All data will be stored in Access databases, identified only by study ID number, behind the firewalls at VA Boston. Neuroimaging data will be similarly stored at VA Boston. These data are backed up every night. The document linking the participant name to the study ID will be kept in a locked file separate from data collection files. Only the PI or research designee will have access to this file.

All adverse events will be ascertained by research staff and reported to the PI. This will occur in real time as well as during monthly lab meetings. The PI will determine adverse events for severity, seriousness, relatedness, and expectedness. The PI will review aggregated adverse events at annual continuing review to determine whether there are trends that could affect subject safety. There is no blinding for this study. There is no Data and Safety Monitoring Board for this neuroimaging study.

12. Adverse Event/Unanticipated Problems Reporting Plans

All adverse events will be reported in writing to the IRB at continuing review. All serious adverse events and unanticipated problems will be reported in writing within 10 working days of the study staff being aware of the event/problem. The Principal Investigator at VABHS will report Unanticipated Problems, Adverse Events, and safety monitors' reports to the IRB in accordance with VHA Handbook 1058.01 and VABHS IRB SOP. Suspected information security and privacy breaches will be reported within one hour of the improper breach or disclosure to the Information Security and Privacy Officers and Research Administration.

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