PET Imaging of Chronic Pain Syndromes

Principal Investigator: Andrew Newberg, MD,
Director of Research, Marcus Institute of Integrative Health, Brind/Marcus Centers

Co-Investigators:

Daniel Monti, M.D. Director, Marcus Institute of Integrative Health, Brind/Marcus Centers

1.0 INTRODUCTION

1.1 Introduction

Pain is a process that is mediated by the nervous system through changes that occur both peripherally and centrally.[1,2] Specialized nerve endings (nociceptors) located predominately in the covering of tissues, elicit action potentials primarily in C and A-delta fibers, whose cell bodies reside in the dorsal root ganglion. These action potentials transmit information about actual or potential tissue damage to the spinal cord to synapse with secondary neurons and a complex feedback network that modulates the response. The axons of the secondary neurons ascend in the spinothalamic tract to the thalamus, with substantial input to the reticular activating system. From the thalamus, projections go to the sensory cortex, but also to multiple other sites in the brain. Central nervous system (CNS) changes associated with pain have been difficult to measure until the development of functional neuroimaging techniques such as positron emission tomography (PET).[3]

The pain induced CNS changes and the response to pain therapies have been studied with these modalities.[4,5] We have previously observed asymmetry in the thalamus associated with chronic pain that is altered during acupuncture therapy.[6] Other areas where changes are seen in pain patients include the frontal lobes and the insular cortex. Imaging studies of therapeutic techniques for chronic pain in animals and humans have been quite limited. One FDG PET scan study of 12 subjects with neck pain showed that chiropractic therapy resulted in increased glucose metabolism in the inferior prefrontal cortex, anterior cingulate cortex, and middle temporal gyrus, while there was decreased glucose metabolism in the cerebellar vermis and visual association cortex.[7] However, there were no controls in this study and hence the results are difficult to interpret.

Patients with chronic pain frequently visit a chiropractor for non-pharmacological management of their symptoms. Chiropractic can help patients avoid problematic pain medications such as opioids. The proposed study is based on our growing understanding of chronic pain and our ability to use functional brain imaging to study in vivo neurophysiologic processes. In this study, we propose to use FDG PET to measure changes in cerebral glucose metabolism in patients with chronic pain. We also plan to scan patients already planning to utilize standard chiropractic care before and after that care. FDG PET has the additional advantage of allowing imaging of the entire body in order to detect areas of inflammation that might be associated with chronic pain conditions. FDG is a radioactive tracer utilized to measure the metabolic rates of normal and abnormal tissues. Many investigators have noted the affinity of FDG for active inflammatory and infectious disorders, such as sarcoidosis, pancreatitis, pneumonia, asthma, colitis, sinusitis, myositis, vasculitis, and thyroiditis.[8,9,10,11]

This study will be the first to utilize FDG PET-MRI imaging of both the brain and body in order to assess CNS changes and peripheral body changes related to chronic pain and its potential management.

1.2 Utilizing PET-MRI Imaging in Chronic Pain Patients

A key component of our program is to evaluate the physiological correlates of chronic pain in both the brain and body. Neuroimaging of awake humans has contributed substantially to our understanding of different aspects of pain perception. A number of cortical and subcortical brain structures have been found that are involved in the processing of pain sensations in addition to the thalamus and primary sensory cortex. In particular, increased activity has been reported in the anterior cingulate gyrus, insular cortex, premotor cortex, and periaqueductal gray area in painful conditions.[12,13] The anterior cingulate gyrus, inferior frontal cortex, and thalami

may be associated with the gating function of the pain threshold[14] and the encoding of pain unpleasantness.[15] The thalamus, sensory cortex, hypothalamus, and brain stem nuclei have been described as part of the process of sensory integration.[16,17] The basal ganglia, nucleus accumbens, and the limbic system may play a role in sensory-discrimination as well as affective and cognitive aspects of pain.[18,19] The hypothalamus and peri-aqueductal grey areas are known to be involved in the descending regulation of the pain process,[20] in part through the release of endogenous opioids, which can produce prolonged analgesia. A consistent finding in chronic or persistent pain is the decreased activity in the contralateral regions usually involved in the perception of pain, including the thalamus.

In addition to the neurophysiological changes associated with chronic pain, the origin of the pain in the body is frequently associated with increased metabolic activity related to chronic injury, inflammation, or various excitatory states (i.e. muscle fasciculation). Thus, it is important to image the body, particularly the regions involved with pain, in order to determine the metabolic activity patterns associated with that pain. In addition, if pain is relieved, it will be important to determine if the pain relief is associated with central or peripheral mechanisms of action.

This study will also make use of FDG PET-MRI which has the additional advantage of allowing imaging of the entire body, and particularly the pain regions, in order to detect areas of inflammation that might be associated with chronic pain conditions. FDG is a radioactive tracer utilized to measure the metabolic rates of normal and abnormal tissues. This radiopharmaceutical is transported across the cell membrane by the same transporters that carry glucose. Deoxyglucose is phosphorylated by hexokinase to deoxyglucose-6-phosphate. However, in contrast to glucose-6-phosphate, which is eventually metabolized to carbon dioxide and water, deoxyglucose-6-phosphate is not a substrate for glucose-6-phosphate dehydrogenase. Therefore, deoxyglucose-6-phosphate and its derivatives are essentially trapped in most tissues long enough to allow imaging with modern PET instruments. Thus, FDG uptake reflects the glucose utilization of a given tissue and many investigators have noted the affinity of FDG for active inflammatory and infectious disorders such as myositis, inflammatory bowel disease, or vasculitis.[21,22,23,24]

Our group has obtained FDG PET data in patients with a variety of inflammatory disorders. We have the ability to quantify the metabolic activity in pain related regions using the Region of Interest Visualization, Evaluation, and Image Registration (ROVER) image analysis software. In general, our studies have found an excellent correlation between regional disease assessment and metabolic uptake on the PET scan (correlation coefficient of ~0.65, $p < 0.001$). Thus, this technique can provide important metabolic information in patients with chronic pain and enable an evaluation of both body and brain physiology associated with the pain.

2.0 OBJECTIVES

AIM #1: To use PET-MR to define abnormal brain and body activity in patients with chronic pain syndromes. We hypothesize that in subjects with chronic pain, there will be a pattern of activity in the pain pathways such as the thalamus and insular cortex and there will be increased activity in sites of inflammation and pain in the body.

AIM #2: To use PET-MR to demonstrate changes in the brain and body activity in response to patients who are already undergoing standard chiropractic care and evaluate changes in those who respond and those who do not respond.

3.0 STUDY PLAN

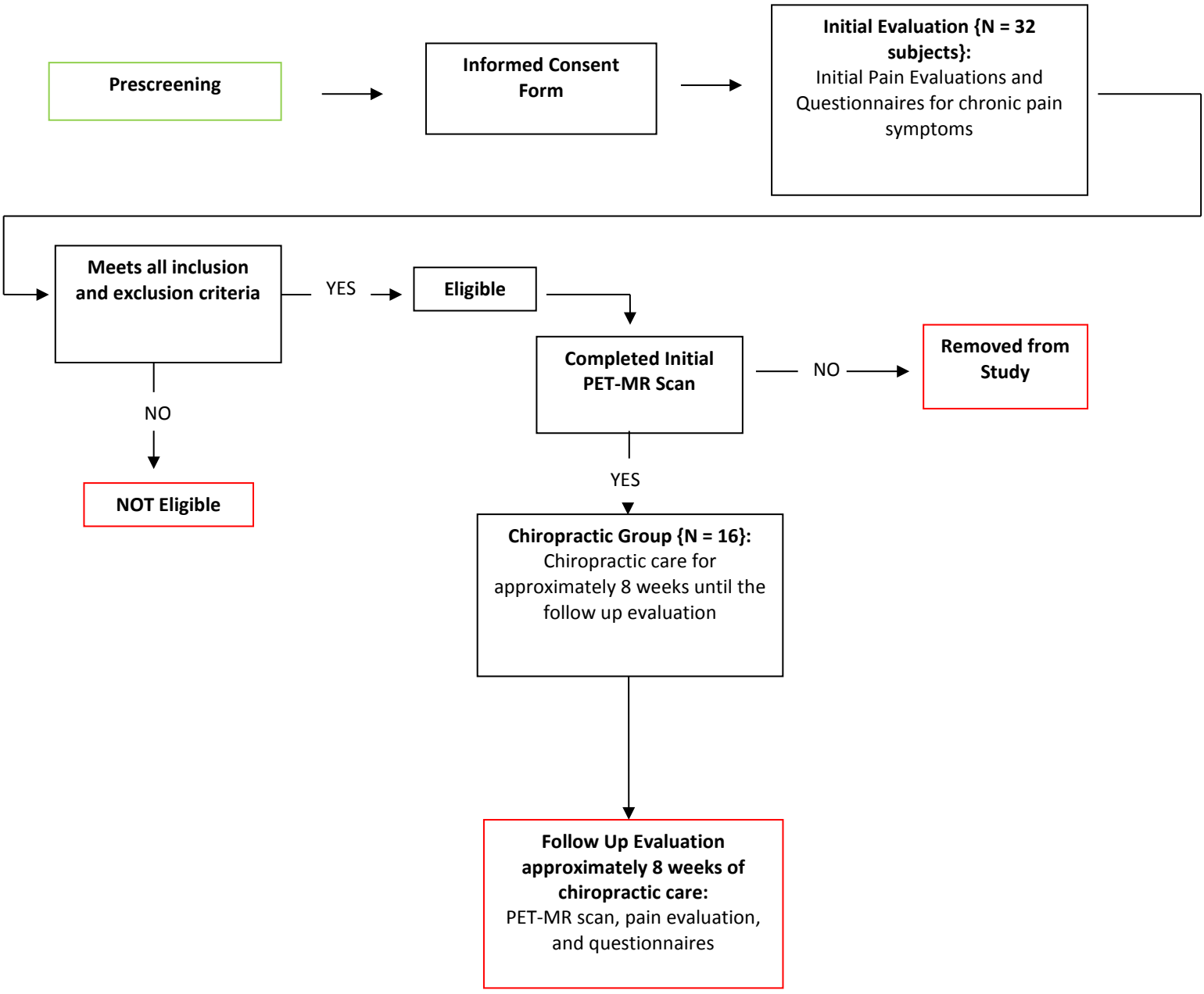
3.1 Subject Recruitment for chronic pain treatments

Subjects may be pre-screened by telephone using a standardized script and screening form. Verbal consent and HIPAA Authorization to obtain the prescreening information will be obtained from subjects prior to the prescreening interview. If subjects are prescreened in person, a signed consent and HIPAA Authorization to obtain prescreening information will be obtained. Information collected during pre-screening will be incorporated into the research records as source documentation for subjects included in the study. If subjects are not eligible to participate in the study they will be asked if the information provided in during prescreening maybe retained for consideration in other studies. Prescreening information will be retained for an indefinite period on an official screening form that will be kept in a secure locked area that will only be used by persons involved with research with this research Study.

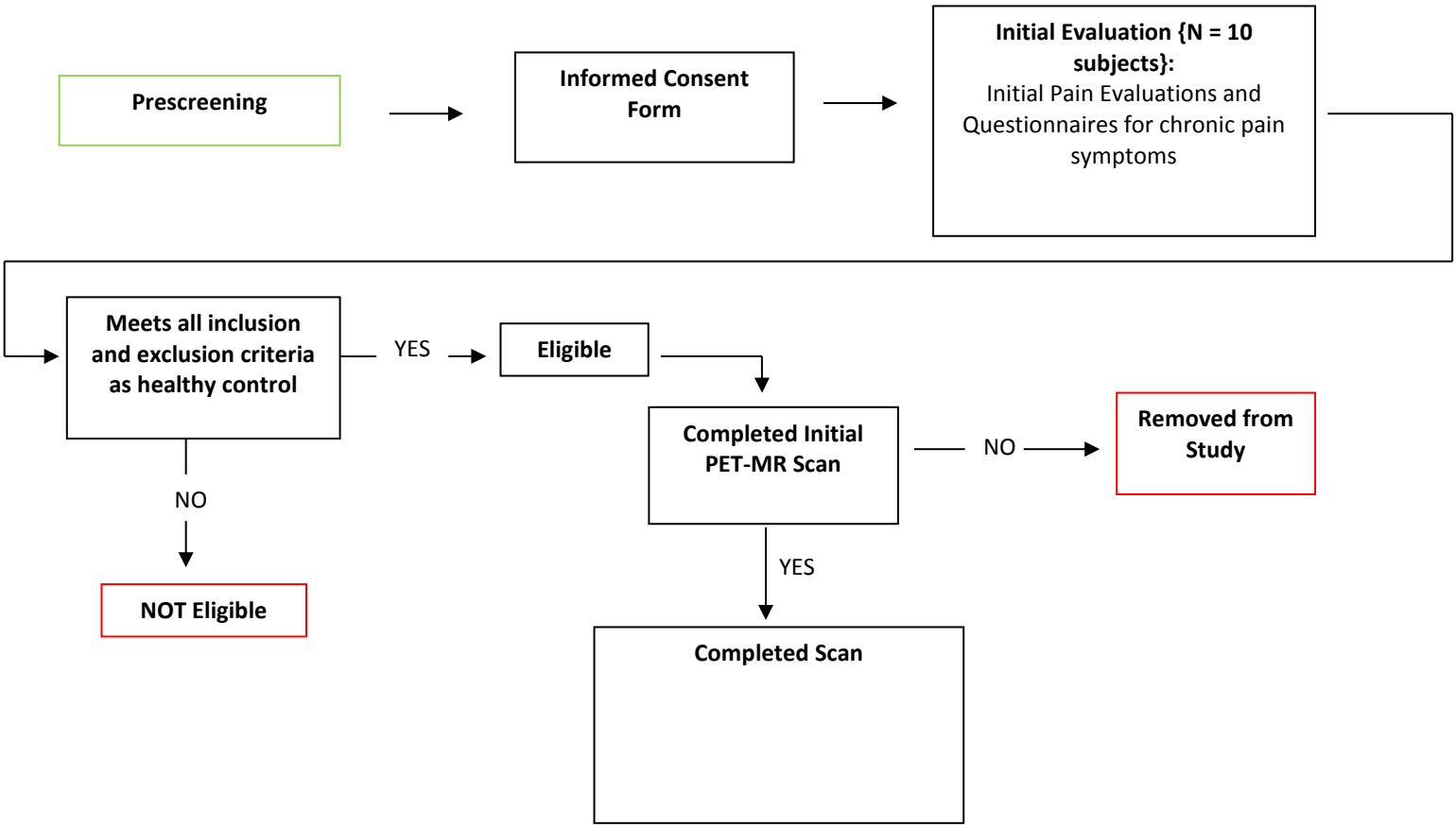
The object of this study is to demonstrate the changes in glucose metabolism in the brain and body in patients already planning on receiving standard clinical chiropractic care. The research study is only for the clinical evaluations and PET-MR imaging. Thirty-two patients with chronic pain will be recruited over two years and evaluated with FDG PET imaging before and after receiving chiropractic care. The chiropractic care is not part of the study protocol as patients will be enrolled only if they are already planning to receive chiropractic care for their chronic pain. The study is designed to use the PET-MR to evaluate their pain in a longitudinal manner. In addition, patients will complete several clinical questionnaires including the Brief Pain Inventory, the Numeric Rating Scale for Pain Intensity for specific locations (a 0-10 rating scale that has been used in many clinical trials), the Profile of Mood Scale (POMS), and the PROMIS for quality of life assessment. All patients will have an initial FDG PET-MRI scan of both their brain and body to assess for the metabolic correlates of pain within the brain and also evidence of inflammatory regions in the spine and body. Patients will then go to their chiropractor as planned for their standard clinical care. Patients will have 2 FDG PET scans, one initially and one after approximately 8 weeks. We also will plan to evaluate patients who experience a delay in getting the chiropractic program (e.g. due to scheduling problems). These subjects will receive 2 scans but without intervening chiropractic therapy. Scans may be performed at the Marcus Institute of Integrative Health PET-MRI scanner using standard head coils or a 32 channel research head coil (Ceresensa: London, ON) which is medically equivalent to currently available head coils, but designed specifically for the PET-MRI scanner. This head coil poses no additional risk to the patients. At the conclusion of the study, a thorough evaluation will be performed on understanding which tests revealed clinically important abnormalities and how such findings predicted outcome and response to the treatment algorithm.

3.1.1 Subject Recruitment for healthy controls

Up to 10 healthy controls will be recruited for a single PET-MR scan using the same imaging protocol as for the patients with chronic pain. The scan data will be necessary to better compare the results from the chronic pain patients to a normal database. **3.1.2 Flow Chart**


Prescreening
Informed Consent Form
Initial Evaluation {N = 32 subjects}:
Initial Pain Evaluations and Questionnaires for chronic pain symptoms
Meets all inclusion and exclusion criteria
YES
Eligible
NO
NOT Eligible
Completed Initial PET-MR Scan
NO
Removed from Study
YES
Chiropractic Group {N = 16}:
Chiropractic care for approximately 8 weeks until the follow up evaluation
Follow Up Evaluation approximately 8 weeks of chiropractic care:
PET-MR scan, pain evaluation, and questionnaires

3.1.3 Flow chart for healthy controls



3.1.4 Inclusion criteria for chronic pain patients

1. Age greater than 18 years old.
2. Have chronic pain symptoms for >3 months;
3. Have moderate pain (>3/10) in 2 or more areas for more than 5 out of 7 days
4. Is planning on undergoing chiropractic care for the clinical management of the chronic pain.
5. May be on pain medications provided that they are on a stable dose for at least 1 month
6. Patients have no other pre-existing and active significant medical, neurological, or psychological disorders.
7. Minor, stable health problems that should have no substantial effect on cerebral blood flow will be allowed (i.e. controlled hypertension, medication controlled diabetes).
8. Patients will be allowed to be taking medications or supplements at the initial intake, but they must be on a stable dose regimen for at least 1 month.

Able to give informed consent and willing to complete the study.

3.1.5 Inclusion criteria for healthy controls

1. No significant current active medical conditions.
2. Stable medical conditions as determined by the PI are allowed.
3. No brain or body abnormalities that would affect the acquisition or analysis of the scan.

3.1.6 Exclusion criteria for chronic pain patients and healthy controls

1. Previous brain surgery.
2. Pregnant or breast feeding
3. Enrollment in active clinical trial/ experimental therapy within the prior 30 days.
4. Subject is unable or unwilling to lie still in the scanner (i.e. due to claustrophobia or weight)
5. Subject has metal in their body or other reason that they cannot undergo magnetic resonance imaging.

3.2 Registration Guidelines and Recruitment

Study subjects initially will be recruited by referral from the Jefferson University Practices physicians, the Marcus Institute of Integrative Health, and self-referrals. Subjects will be recruited only if they are already planning on receiving standard clinical chiropractic care for their pain. If any recruitment materials are developed, they will not be distributed without IRB approval.

The subject population is derived from the greater Philadelphia area, which represents a racially and economically diverse population. We will make efforts for this protocol to be widely accessible, including offering the procedures protocol without charge to the subject.

3.3 Treatment Plan:

3.3.1 Informed consent will be obtained from all subjects before protocol specific activities are carried out. Every patient enrolled in the study will undergo 2 FDG-PET scans (an initial and follow up scan). All imaging studies will be performed at Marcus Center on the Siemens mMR PET-MR scanner. This instrument provides high quality images with concomitant MRI imaging for anatomic co-registration and is considered the most advanced in the discipline. As standard practice for any FDG PET scan, the patient will fast overnight or for a duration of 4 hours and will be given an intravenous dose of 5mCi FDG soon after he/she arrives at the Center. 30 minutes after the administration of FDG, images of the brain will be performed. When the brain scan is completed (approximately 20 minutes), the patient will then immediately undergo PET imaging of the rest of the body.

3.4 Criteria for Removal from / Cessation of Protocol

3.4.1 Measuring Endpoints: Endpoints will be measured approximately 2 months after the initial scan and evaluation. Any serious adverse events also will result in immediate discontinuation of the subject from the study.

3.4.2 Subject Withdrawal: The subject may withdraw from the study at any time for any reason.

3.4.3 Missing Appointments: Discontinuing the chiropractic care will lead to exclusion from the study. All reasons for discontinuation of procedure will be documented in study flow sheets.

3.5 Adverse Events

The OHRP defines an adverse event as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research." Adverse events can additionally be classified as an unanticipated problem, meaning it was not expected to occur during the course of the research. If an unexpected adverse event were to occur, it then needs to be determined whether or not it is due to the research being conducted. If the event is a result of the research procedures, most likely the event is directly connected to the subject's participation in the research. It is also vital to determine whether an adverse event is serious. The OHRP defines a serious adverse event as one that a) results in death, b) is life-threatening, c) results in patient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability/incapacity, e) results in congenital anomaly, or f) jeopardizes the subject's health to the point where they may need medical or surgical intervention. If the adverse event is unexpected, related to the research, and serious (where it is causing harm to subjects), then it is also classified as an unanticipated problem and must be reported to the Thomas Jefferson University Hospital IRB. All adverse events will be reported in accordance with Jefferson IRB Adverse Events Report. The IRB shall be notified in a written safety report if any serious and unexpected adverse

experience associated with the use of the oral or intravenous nutritional supplements occurs.

3.6 Data Collection and Submission Schedule

3.6.1 Data Submission: Data must be submitted according to the protocol requirements for all subjects registered, whether or not assigned treatment is administered.

3.6.2 Master files, such as case report forms and progress reports, are prepared, and updated, by the study coordinator. Case report forms will include eligibility checklist, demographic data, baseline history and physical laboratory results, adverse events, and off-study document. These will be completed by the study coordinator under the supervision of the principal investigator.

3.7 Measurement of Effect of the Nutritional Supplements

3.7.1 Clinical Response

Subjects will be evaluated initially and then at 2 months. The primary pain outcome will be used to assess responders versus non-responders. We will use a >50% reduction in pain perception for the area with the greatest pain based on a 0-10 numeric rating scale (NRS) which is a standard measure used in the pain treatment literature.[25,26,27, 28] Pain also will be measured using the Brief Pain Inventory short form which captures two broad pain domains: 1) the sensory intensity of pain, and 2) the degree to which pain interferes with different areas of life.[29] In addition, all subjects will be administered the Speilberger State Trait Anxiety Inventory (STAI) at the time of study. The STAI contains a total of 40 questions, half of which relate to the way subjects are feeling at the moment and half of which ask them to describe how they usually feel. The Profile of Moods Scale (POMS) will be administered. The Beck Depression Inventory is a standard 21item questionnaire probing cognitive and somatic symptoms of depression. We will also use the PROMIS scale to evaluate quality of life.

3.7.2 PET Imaging Procedure

(a) Subject Preparation - An indwelling catheter needle will be inserted into an antecubital vein. FDG will be administered through the indwelling line as per standard protocol.

(b) FDG PET Imaging Procedure – Subjects will receive a standard of care FDG PET scan initially. Subjects will be asked to arrive at the Marcus Institute of Integrative Health in the morning on the day of the study. A signed informed consent form will be documented after all questions have been answered. Women of childbearing potential must have had a negative pregnancy test within 48 hours before proceeding with the PET study. The intravenous catheter will be inserted and capped. FDG (4-8 mCi, ± 20%) will be injected intravenously. After injection of the FDG, the venous catheter will be removed, and then the subject will be asked to sit comfortably in a chair in a dimly lit room for approximately 30 minutes to allow for the uptake of the FDG. Subjects will receive an MRI to assist with anatomic delineation. In addition,

the MRI session will be utilized in order to obtain data assessing functional connectivity, tractography, and brain volumes.

(c) Image Acquisition and Processing – The FDG PET scan component will be obtained over approximately 30 minutes on the Siemens mMR PET-MRI scanner. This will allow for simultaneous acquisition of both the FDG PET data and MRI data (please note that the MRI acquisition is longer so some scanning will take place after the PET scan is completed while the patient continues to lie on the imaging table). The FDG PET scan will enable us to obtain quantitative regional metabolic values as determined by a commercially available software program called MIM neuro that quantifies uptake and compares the results to a normative database.

3.7.3 MRI Procedure

The imaging protocol will be performed simultaneously with the FDG PET scan and will include the following scans: On follow up days, only the functional MRI sequences will be run. The following scans may be obtained: (1) Localizer scan. (2) T1-weighted MPRAGE sequence. (3) DTI scan with 64-gradient diffusion-weighted (HARDI) sequence. (4) Resting state BOLD scan. (5) Perfusion ASL imaging for perfusion assessment. The MRI components will be performed at 2 months after the initial scan along with the PET scan. Total scan time including set-up will be approximately 1 hour.

3.8 Statistical Considerations

The initial analyses of the data will be descriptive in nature. Using means, standard deviations, median, and range, the clinical scores will be described for each time point. Graphical methods, such as plots of measurements over time, histograms, and boxplots are important tools for understanding the quality of the data, and assessing assumptions underlying statistical models (such as normality). Transformations will be applied as necessary to satisfy these assumptions. Plots of all of the measured variables over time will be important to assess longitudinal patterns of change.

FDG PET MRI data will be analyzed initially and then at 2 month follow up. For brain analysis, quantitation will be performed utilizing the MIMneuro software that provides activity values for a variety of brain regions compared to a normative database. These values will be obtained for both the pre and post treatment scans differentiated by responders and non-responders. Measures can then be compared between the pre and post treatment scans utilizing a linear mixed effects model and also correlated with changes in pain perception and other qualitative clinical measures.

For the purposes of this study, quantitative analysis of the body regions affected will be accomplished using the Region of Interest, Evaluation, and Image Registration (ROVER) program. This provides a Global Disease Activity score based on the activity level and overall volume of affected regions. The combination of the PET-MR system allows for this unique global quantitation of inflammation.

Testing of the specific aims will initially evaluate the FDG PET scan results in relation to the patient's chronic pain symptoms and also treatment response. In the brain, we will compare pre and post scan results using a linear mixed effects model to determine areas of metabolic activity (as determined by Standardized Uptake Values or SUVs) that have changed as the result

of the treatment and compared between responders and non-responders. In addition to the SUV analysis, Statistical Parametric Mapping will be utilized to further evaluate for any significant changes between the scans.

For the body analysis, we will start with a comparison of the locations of increased uptake in affected body regions (up to the 5 most prominent) and a comparison of mean SUV levels between the affected sites and the homologous site on the opposite side using an independent sample t-test initially and then a linear regression to evaluate the association between the severity of the symptoms and the SUV. As with the brain regions, we will also perform a comparison between SUVs in the affected body regions before and after treatment to determine the peripheral metabolic effects associated with pain management.

a. Functional Connectivity Analysis Using the Resting-state BOLD Imaging: In an effort to uniquely describe the communication between resting state networks without the influence of noise contaminants, a specialized analysis pipeline is required. This process starts with spatial preprocessing using SPM12 (Wellcome Group, UCL) in the Matlab environment (Mathworks, Inc.). Realignment and slice timing correction will be performed, ideally concurrently, to ensure proper voxel to voxel correspondence as well as adjusting for timing inconsistencies within single-shot EPI data. The data is next segmented to create gray matter, white matter, and cerebro-spinal fluid (CSF) maps to co-vary out confounding temporal effects. Warping to a standard template space (MNI) will be performed as well as spatial smoothing with a Gaussian kernel. Seed ROIs will be defined by the brain areas which are found to be activated and/or deactivated during task performance in the fMRI scans (BOLD, or ASL). Specifically, time series from the resting-state BOLD scan will be extracted from the activated/deactivated ROIs (such as PCC, vACC, MPFC, and MTLs) defined in the fMRI scans. Each such time series will then be used as a covariate of interest in a whole-brain, linear regression, statistical parametric analysis. In particular, we will be most interested in DMN which were found to involve brain regions that were deactivated during task performance.

b. DTI Analyses: The proposed acquisition scheme for diffusion imaging will enable for analysis of three distinct datasets. Rigid body motion correction will be performed using SPM to facilitate a more accurate tensor estimate. Quantitative DTI maps will be calculated for each slice, including three eigen value maps (λ 1, λ 2, λ 3), radial diffusivity ((λ 1 + λ 2)/2), mean diffusivity or apparent diffusion coefficient (ADC) ((λ1+ λ 2+ λ 3)/3) and fractional anisotropy. These indices will be calculated using the 30 directions at a b-value of 700s/mm2 through a non-linear least squares fit using dipy. Outlier rejection will also be used to eliminate spurious signal fluctuations to again ensure a more accurate tensor calculation. High angular resolution diffusion imaging (HARDI) data will be used for fiber tracking of the white matter structures associated with the DMN as well as resolving fiber crossings. Analysis will be performed in dipy using the first 4 spherical harmonic terms of the diffusion signal decomposition for calculation of the orientation distribution functions. Tractography will be used to delineate tracts of interest such as those connecting the frontal lobe and amygdala by normalizing subject data to MNI space and delineating seed regions. The same seeds will be used on every participant so as to eliminate any bias from repeated drawing of ROIs. Lastly, the two shell diffusion data will be used in calculating neurite orientation and dispersion (NODDI). Using a three compartment model will enable characterization of intracellular (space bounded by membranes of neurites),

extracellular (space around neurites), and CSF space. NODDI analysis will be conducted through the Camino toolbox.

c. Statistical Parametric Mapping (SPM) Method for the ASL fMRI data: We will perform a number of analyses on the fMRI data. Images will all be analyzed in SPM which will be used for both a voxel-wise analysis in order to assess changes in CBF throughout the brain, and also a region of interest (ROI) approach that will focus on the structures delineated in the specific aims. Thus, for each subject, fMRI images will be realigned to correct for head motion. A mean CBF map will be generated for each condition for each individual subject by averaging the CBF image series. These CBF images will be co-registered with corresponding high-resolution structural MRI, and then normalized into a canonical space (Montreal Neurological Institute standard brain) using SPM. Voxel-based analyses of the normalized CBF data will be carried out using the ANCOVA model provided in SPM. The voxel-based analysis will be performed to address the same specific aims as elaborated above regarding the ROI analysis. The CBF in each voxel at baseline will be compared between the responder and non-responder groups. In all the above analyses, global mean CBF will be included as a covariate along with age and gender.

3.8.4 Power Analysis: This is a pilot study to determine the effect size and the number of responders and non-responders. A preliminary power analysis based upon other related studies suggests a standard deviation of metabolic values in the brain of 20%. In order to compare the responder versus non-responder groups with regard to brain metabolism, for a power of .80 and an $p<0.05$, we would need approximately 16 subjects in each group to detect an effect size of 1.0. These calculations assume two-sided two-sample equal-variance t-test applied to the pre-to-post Tx changes. Thus, we are requesting 32 subjects for this pilot study.

4.0 RISKS

4.1 Potential Risks of FDG PET Scan: The FDG is a commercially available radioactive tracer that will be used according to its dose, route, and indication, but results in some exposure to ionizing radiation. The amount is acceptable for the research subjects who will directly benefit by receiving full clinical reads of these scans that their referring physician can utilize for determination of prognosis and treatment planning. Subjects will be required to lie still on the imaging table for 30-60 minutes, which can be uncomfortable.

4.2 Risks of venous cannulation: Venous cannulation is a routine clinical procedure that carries minimal risks when performed by trained personnel. It is possible that bruising could occur in some subjects. There is a theoretical risk of phlebitis or infection, which is very remote.

4.3 Magnetic Resonance Imaging: The MRI scanner requires a very strong magnetic field. MRI can be dangerous if a person has metal or metallic objects in their body. Subjects will be thoroughly screened to ensure that they have no metal in their body. Because of the magnetic field, metallic objects can move into the scanner and potentially injure the patient. All precautions are taken to ensure that no such metallic objects are in the scanning room that could result in an injury. The MRI requires the patient to lie still for approximately 1 hour, which can

be uncomfortable, or be claustrophobic. Due to the strength of the magnetic field of the MRI, there is a risk of being injured by receiving a burn on your skin.

5.0 REFERENCES

[1] Dotson RM. Clinical neurophysiology laboratory tests to assess the nociceptive system in humans. J Clin Neurophysiol 1997; 14(1): 32-45.

[2] Cervero F, Meyer RA, Campbell JN. A psychophysical study of secondary hyperalgesia: evidence for increased pain to input from nociceptors [see comments]. Pain 1994; 58(1): 21-8.

[3] Jones AK. The contribution of functional imaging techniques to our understanding of rheumatic pain. Rheum Dis Clin North Am 1999; 25(1): 123-52.

[4] Adler LJ, Gyulai FE, Diehl DJ, Mintun MA, Winter PM, Firestone LL. Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. Anesth Analg 1997; 84(1): 120-126.

[5] Kupers RC, Gybels JM, Gjedde A. Positron emission tomography study of a chronic pain patient successfully treated with somatosensory thalamic stimulation. Pain 2000; 87(3): 295-302.

[6] Newberg AB, Hersh EV, Levin LM, et al. Double-blind, placebo-controlled, randomized pilot study of cerebral blood flow patterns employing SPECT imaging in dental postsurgical pain patients with and without pain relief. Clin Ther 2011; 33(12):1894-903.

[7] Ogura T, Tashiro M, Masud M, et al. Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain. Altern Ther Health Med 2011; 17(6):12-7.

[8] Tahara T, Ichiya Y, Kuwabara Y, et al., High [18]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study. J Comp Assist Tomogr 1989; 5:829-31.

[9] Shreve PD, Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. Euro J Nucl Med 1998; 25:259.

[10] Hara M, Goodman PC, and Leder RA, FDG-PET finding in early-phase Takayasu arteritis. J Comp Assist Tomogr 1999; 23:16-8.

[11] Derdelinckx I, Maes A, Bogaert J, et al., Positron emission tomography scan in the diagnosis and follow- up of aortitis of the thoracic aorta. Acta Cardiologica 2000; 55:193-5.

[12] Casey KL: Forebrain mechanisms of nociception and pain: analysis through imaging. Proceedings of the National Academy of Sciences of the United States of America 1999; 96(14): 7668-74

[13] Paulson PE, Minoshima S, Morrow TJ, Casey KL: Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 1998; 76: 223-229

[14] Tolle TR, Kaufmann T, Siessmeier T, et al.: Region-specific encoding of sensory and affective components of pain in the human brain: A positron emission tomography correlation analysis. Ann Neurol 1999; 45: 40-47

[15] Rainville P, Duncan GH, Price DD, et al.: Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997; 277: 968-971

[16] Craig AD, Bushnell MC, Zhang ET, Blomqvist A: A thalamic nucleus specific for pain and temperature sensation. Nature 1994; 372: 770-773

[17] Fuchs PN, Melzack R: Analgesia induced by morphine microinjection into the lateral hypothalamus of the rat. Exper Neurol 1995; 134(2): 277-280

[18] Devinsky O, Morrell MJ, Vogt BA: Contributions of anterior cingulate cortex to behaviour. Brain 1995; 118(Pt 1): 279-306

[19] Chudler EH, Dong WK: The role of basal ganglia in nociception and pain. Pain 1995; 60(1): 3-38

[20] Bodnar RJ: Neuropharmacological and neuroendocrine substrates of stress-induced analgesia. Annals of the New York Academy of Sciences 1986; 467: 345-60

[21] Tahara T, Ichiya Y, Kuwabara Y, et al., High [18]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study. J Comp Assist Tomogr 1989; 5:829-31.
[22] Shreve PD, Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. Euro J Nucl Med 1998; 25:259.
[23] Hara M, Goodman PC, and Leder RA, FDG-PET finding in early-phase Takayasu arteritis. J Comp Assist Tomogr 1999; 23:16-8.
[24] Derdelinckx I, Maes A, Bogaert J, et al., Positron emission tomography scan in the diagnosis and follow- up of aortitis of the thoracic aorta. Acta Cardiologica 2000; 55:193-5.
[25] Henschke N1, van Enst A, Froud R, Ostelo RW. Responder analyses in randomised controlled trials for chronic low back pain: an overview of currently used methods. Eur Spine J. 2014 Apr;23(4):772-8.
[26] Trudeau J1, Van Inwegen R, Eaton T, Bhat G, Paillard F, Ng D, Tan K, Katz NP. Assessment of pain and activity using an electronic pain diary and actigraphy device in a randomized, placebo-controlled crossover trial of celecoxib in osteoarthritis of the knee. Pain Pract. 2015 Mar;15(3):247-55.
[27] Licciardone JC1, Kearns CM, Minotti DE. Outcomes of osteopathic manual treatment for chronic low back pain according to baseline pain severity: results from the OSTEOPATHIC Trial. Man Ther. 2013 Dec;18(6):533-40.
[28] Kamper SJ, Maher CG, Herbert RD, Hancock MJ, Hush JM, Smeets RJ. How little pain and disability do patients with low back pain have to experience to feel that they have recovered [published online March 13, 2010]? Eur Spine J. 2010;19(9):1495-1501.
[29] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;19:129–138