PROTOCOL TITLE: Project 1 Aim 2, Adaptations of the brain in chronic pain with opioid exposure

PRINCIPAL INVESTIGATOR:
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STUDY SUMMARY:

Sample Size	80 Subjects
Funding Source	NIDA
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☒ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes ☐ No

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Participants (45 CFR Part 46), and the NIH Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:
Signed:_____Date: _____

Name: A. Vania Apkarian

TABLE OF CONTENTS

List of Abbreviations

ABC	The Addictions Behavior Checklist
ACS	Attentional Control Scale
AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ASL	Arterial Spin Labeling
AST	Aspartate Transaminase
BP	Blood Pressure
BDI	Beck Depression Inventory
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBP	Chronic Back Pain
CBP + O	Chronic Back Pain with opioid use
CBP - O	Chronic Back Pain without opioid use
CDC	Centers for Disease Control and Prevention
CFR	Code Of Federal Regulations
COWS	Clinical Opiate Withdrawal Scale
COMM	Current Opioid Misuse Measure
CPAQ	Chronic Pain Acceptance Questionnaire
CRF	Case Report Form
DA	Dopamine
DHHS	Department Of Health And Human Services
DMI	Drug Misuse Instrument
DMP	Prescription Monitoring Program
DTI	Diffusion Tensor Imaging
eACS	Emotional Attentional Control Scale
eCRF	Electronic Case Report Form
EDW	Enterprise Data Warehouse
ERQ	Emotional Regulation Questionnaire
FDA	Food And Drug Administration
FFMQ	Five Facets of Mindfullness Questionnaire
fMRI	Functional Magnetic Resonance Imaging
GI	Gastrointestinal
GMV	Grey Matter Volume
g/dL	Gram Per Deciliter
H or HIPP	Hippocampus
HCP	Human Connectome Project
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IND	Investigational New Drug Application
IP	Investigational Product

IRB	Institutional Review Board
ISM	Independent Safety Monitor
kg	killogram
LAQ	Loss Aversion Questionnaire
LOT-R	Life Orientation Test Revised
LSD	Least Significant Difference
MAIA	Multidimensional Assessment of Interoceptive Awareness
MEE	Morphine Estimate Equivalence
mg	Milligram
mL	Milliliter
MPQ	McGill Pain Questionnaire
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
ms	millisecond
N	Number (Typically Refers To Participants)
NAc	Nucleus Accumbens
NEOFFI	NEO Five Factor Inventory
NIDA	National Institute on Drug Abuse
NIH	National Institutes Of Health
NM	Northwestern Medicine
NMFF	Northwestern Medical Faculty Foundation
NMH	Northwestern Memorial Hospital
NODDI	Neurite Orientation Dispersion and Density Imaging
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NU	Northwestern University
NUCATS	Northwestern University Clinical and Translational Sciences Institute
OA	Offset analgesia
ODI	Oswestry Disability Index
OUD	Opioid Use Disorder
PANAS	Positive And Negative Affect Schedule
PASS	Pain Anxiety Symptoms Scale
PCS	Pain Catastrophizing Scale
PDQ	painDETECT Questionnaire
PET	Positron Emission Tomography
PFc	Prefrontal Cortex
pg	Picogram
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcome
PSQ	Pain Sensitivity Questionnaire

rsfMRI	Resting State Functional Magnetic Resonance Imaging
SAE	Serious Adverse Event/Serious Adverse Experience
SBP	Subacute Back Pain
SBPp	Subacute Back Pain-Persisting Phenotype
SBPr	Subacute Back Pain- Recovering Phenotype
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SNI	Spared-Nerve-Injury
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SOWS	Subjective Opiate Withdrawal Scale
SSRI	Selective Serotonin Reuptake Inhibitor
Unit/L	Unit Per Liter
UDT	Urine Drug Test
US	United States
VTA	Ventral Tegmental Area
WOCBP	Women Of Childbearing Potential

PROTOCOL SUMMARY

Title:

Project 1, Adaptations of the brain in chronic pain with opioid exposure

Summary:

In this project, we will study brain reorganization and behavioral responses in chronic pain with opioid exposure in CBP

Objectives:

Aim 1 of this study is being carried out under IRB approved STU00207384.

Aim 2a: In a double-blind, randomized, placebo-controlled crossover clinical trial, we track brain functional changes in individuals with i) CBP+O, and individuals with ii) CBP+OUD following a brief drug delay and re-exposure manipulation; re-exposure could be placebo, the participant's own opioid dose, or a dopaminergic treatment (50% of groups I & ii in Aim 1a, n=40/group).

Aim 2b: Track changes in motor, cognitive and emotional abilities and related brain properties, with brief opioid delay and re-exposure (all participants of aim 2a)

Aim 2c: To assess the dopamine dependence of OA induced by thermal stimuli in participants with chronic pain

Population: Sample size: 80

Gender: Male and Female

Age: 18 years and older

Demographic group: No racial/ethnic restrictions

General health state: generally good health

Phase: 2

Number of Sites: 2

Northwestern University, Chicago, IL 60611
Shirley Ryan Ability Lab. Chicago, IL 60611

Study Duration: 50 months

Participant Participation Duration: Up to 8 weeks

Estimated Time to Complete Enrollment: 48 months

1. KEY ROLES AND CONTACT INFORMATION

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2. OBJECTIVES:

Aim 1 is included in an already approved study under STU00207384.

Specific Aim 2:

Primary Outcomes

2.a. DA+NSAIDs and opioids provide superior pain relief compared to placebo in patients with CBP. The effect of the treatment on pain will be measured using a numeric rating scale (NRS) before and after treatment.
Hypothesis: Distinct changes will be seen in pain relief in subgroups treated with Carbidopa/Levodopa +Naproxen, opioid, and placebo.

Secondary Outcomes

2.b. DA+NSAIDs are non-inferior in pain relief compared to opioids in patients with CBP.

- The effect of the treatment on pain will be measured using a numeric rating scale (NRS) before and after treatment.

Hypothesis: Distinct changes will be seen in pain relief in subgroups treated with DA+NSAIDs, opioid, and placebo.
2.c. DA+NSAIDs and opioids provide superior withdrawal relief compared to placebo.
The effect of the treatment on withdrawal will be measured using the Pain and Craving Index (PCI) and Subjective Opiate Withdrawal Scale (SOWS) before and after treatment
Hypothesis: Distinct changes will be seen in withdrawal relief in subgroups treated with DA+NSAIDs, opioid and placebo.
2.d. DA+NSAIDs are non-inferior in withdrawal relief compared to opioids in patients with CBP.

- The effect of the treatment on withdrawal will be measured using the Pain and Craving Index (PCI) and Subjective Opiate Withdrawal Scale (SOWS) before and after treatment

Hypothesis: Distinct changes will be seen in withdrawal relief in subgroups treated with DA+NSAIDs, opioid and placebo.
2.e. Use a moderated mediation analysis to investigate how brain properties (functional and structural connectivity, brain morphology) affects pain and withdrawal before and after treatments.

- We will probe whether different neurocircuitry – descending pain modulation (i.e., periaqueductal grey) and the cortico-mesolimbic system (i.e., nucleus accumbens, medial prefrontal cortex, hippocampus, insula, anterior cingulate, somatosensory cortex) – are impacted differently by each treatment modality, further elucidating the neuromechanisms of pain analgesia and opioid withdrawal.

Hypotheses:
1) Human brain activity and functional network properties perturbed with psychological opioid withdrawal can be parceled to specific responses, identified with re-exposure to placebo, opioid, and DA+NSAID.
2) The relationship of re-exposure responses to analgesia/hyperalgesia and to OUD will identify respective brain areas and networks, revealing separation/overlap between pain and OUD reward-related circuits.
3) DA+NSAID may be a viable alternative for opioid use in a subgroup of CBP exploratory outcomes:

Exploratory outcomes

2.f. Evaluate the same outcomes between subjects with different chronic pain conditions.
2.g. Compare treatment effects on withdrawal symptoms between opiate dependent subjects with and without chronic pain.

3. BACKGROUND:

The overall premise of this project, and of our Center, is that opioid analgesia and opioid addiction have important interactions with the brain pathways involved in chronic pain, and that these interactions, in time, exacerbate opioid use disorder and diminish opioid analgesic efficacy**.** Opioids are the most efficient analgesics and the only source of immediate relief from severe pain, including post-operative pain and palliative care (mainly for cancer patients). However, opioid abuse is a major health care problem. The most recent CDC report [2] states that, from 1999 to 2014, more than 165,000 people died in the US from overdoses of prescription opioids. At least half of all US opioid overdose deaths involve a prescription opioid [3], and as many as 1 in 4 people who receive long-term prescription opioids for non-cancer pain struggle with addiction. Indeed, in 2014 alone, more than 14,000 people died from overdoses of prescription opioids.Because chronic pain is commonly treated with opioids and 116 million people in the US have chronic pain, opioid abuse is intimately linked with the management of chronicpain.

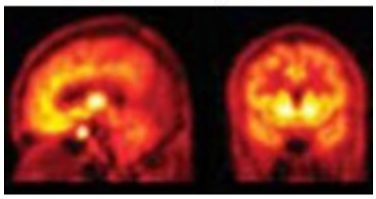


Fig. 1. Distribution of opioid receptor in the human brain, Opioid binding potential using radiolabeled carfentanil There is high binding in mesolimbic regions [1].

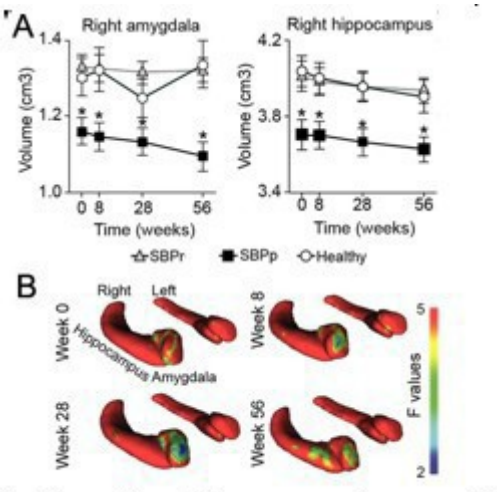


Fig. 2. Amygdala and hippocampus volumes are risk factors for chronic pain. (A) Repeated measure

The brain circuitry that is functionally reorganized in chronicpain overlaps extensively with the circuitry involved in affective evaluation, motivation and drug addiction -- including opioid addiction[4-15](**fig. 1).** What we don't know is how opioids affect the brain reorganization resulting from chronic pain, or how this reorganization affects the abuse potential of opioids and the resulting clinical response. There are several line of evidence suggesting that there is an interaction. First, in contrast to acute pain, the evidence that opioids potently reduce chronic non-cancer pain is not convincing [16-18]. In fact, recent studies suggest that opioids are not superior to non-steroidal anti0inflammatories in managing chronic pain[19-23]. Nevertheless, opioids continue to be used to manage chronic pain, since there seems to be someconsensus amongst clinicians that the long-term management of pain withopioids can be beneficial, or at least safe with appropriate patient selectionand dose titration[24-26], despite current CDC recommendations contradictingthis view [27]. But the basic science regarding the interaction betweenmechanisms of chronic pain and of long-term opioid use remains essentially unexplored. In a testimonial to Congress, the director of NIDA states: "*Little is yet known about the risk for addiction among those being treated for chronic pain or about how basic pain mechanisms interact withprescription opioids to influence addiction potential.*"

Chronic pain itself affects humans at epidemic proportions – more than the total affected by heart disease, cancer, and diabetes combined. Chronic pain also costs the US over half a trillion dollars each year in medical treatment and lost productivity [28]. A World Health Organization report indicates that chronic pain is the top source of disability in the US, and the 6th largest disability source worldwide [29]. Epidemiological studies show that 1 in 5 individuals suffers from chronic pain[30-36]. Most often, chronic pain persists for a lifetime. Despite a considerable research effort, there is no generally effective therapy for chronic pain.

The extent of association of opioid treatment in CBP with drug abuse/addiction is unclear. Inconsistencies in addiction terminology hamper efforts to define and quantify opioid abuse arising as a direct result of opioid pain treatment (iatrogenic opioid addiction). Repeated administration of any opioid almost inevitably results in tolerance and physical dependence [37,38]. In contrast, addiction occurs only ina small percentage of patients exposed to opioids [37]. Only a few studies have examined the prevalence of OUD (signs and symptoms associated with drug abuse which may reflect addiction) among patients receiving opioids. In patients with CBP receiving opioid treatment, the prevalence of substance use

disorders ranges from 3% to 43%, with a lifetime prevalence as high as 54% [39-41], and the true prevalence most likely remains unknown.

The traditional view regarding mechanisms of chronic pain has emphasized the role of injury-induced enhanced nociceptive signaling (end organ-driven peripheral sensitization) and related spinal cord synaptic changes giving rise to spinal sensitization [42-45]. But it is clear that the brain has a major impact on chronic pain. Many lines of clinical observation demonstrate that the characteristics of the peripheral injury are not sufficient to explain the chronicity of the pain response. With the advent of human brain imaging technology, it became possible to peer inside the brain of patients. A series of studies, pioneered by the Apkarian lab, provided clear evidence that chronic pain is associated with abnormal brain anatomy and physiology [46-51]. These observations have now been replicated for many chronic pain conditions [52,53], and establish that the circuitry involved in chronic pain cannot be deduced from that responsible for acute pain. Since all prior brain imaging studies of chronic pain had been cross-sectional in nature, they were not able to distinguish between causes and consequences. To directly address this issue, we performed the first prospective observational brain imaging based study, following back pain patients for up to three years after an initial acute/sub-acute back pain episode. In subjects whose back pain persisted (i.e., who transitioned to chronic pain), a time-dependent re-organization of the brain anatomy and functional connectivity was observed [54]. The emergence of chronic pain was not dependent upon the initial intensity of back pain, or related brain activity. Rather, persistent and recovering pain groupings could be predicted within weeks of onset of back pain, based on anatomical and functional biomarkers of the brain circuitry. Various properties of this circuitry accurately (>80%) predicted subjects who would develop chronic pain. These included: 1) functional connectivity between mPFC and NAc [54], 2) white matter myelination and branching differences in fiber tracks underlying the mesolimbic system [55], 3) intrinsic and cortical connectivity of the hippocampus (H) [56], 4) volumes of H and amygdala (Amy) [57] (fig. 2), and 5) white matter and functional connectivity of the limbic circuitry linking the mPFC, NAc and Amy [57]. Altogether these observations showed that properties of the limbic brain determine individuals' risk for chronic pain. Many of these same biomarkers are commonly associated with addiction [54-59].

In summary, there is a huge disconnect between the magnitude of the opioid epidemic and the degree of scientific knowledge regarding the underlying mechanisms involving appropriate and inappropriate opioid use. The CBP patient population, the largest group of chronic pain patients worldwide, is perhaps the type of chronic pain most exposed to opioid use and its untoward consequences. Since our scientific knowledge of the underlying mechanisms of chronic pain is best known in CBP and in the rodent SNI pain model, we have a unique opportunity to study opioid exposure in these complementary conditions.

The central hypothesis to be tested, is that continued exposure to opioids exacerbates brain maladaptive plasticity that defines chronic pain, diminishing analgesic efficacy, and increasing the risk of opioid abuse. Therefore, we will examine brain reorganization relative to chronic pain with opioid exposure, in various CBP subgroups (CBP in patients properly managed with opioids [CBP+O], CBP in patients with mild/moderate opioid use disorder [CBP+OUD], CBP managed without opioids [CBP-O] and healthy controls (**Aim 1**); when such patients (CBP+O, CBP+OUD) undergo a brief drug delay and re-exposure with placebo, opioids, or DA+NSAID (**Aim 2**); In all subjects in **Aims 1 & 2** we will also track cognitive, emotional, and motor abilities, and their perturbations with drug delay and re-exposure, and relate them to brain adaptations.

3.1 Innovation

1. Overall: This project is the first systematic investigation of the mechanisms regarding the interaction between chronic pain and opioid exposure in humans. This gap in knowledge was pointed out back in 2009 by the American Pain Society Guideline on the topic [25].
2. Conceptually, our study is designed to challenge the traditional view, which distinguishes between mechanisms of opioid analgesia and opioid addiction in chronic pain. While we are the first to formulate this concept, it is based on solid scientific evidence.
3. Hypotheses proposed are all novel, and should be considered somewhat speculative. Thus, we also expect surprises.
4. From an experimental design viewpoint, our studies are novel because we study the impact of opioid exposure on the brain cross-sectionally, and evaluate within-subject brain properties when drug exposure is manipulated.
5. We have pioneered the concept of using multimodal brain imaging in pain research, an approach that

has led to uncovering the fundamental mechanisms that provide the background for this project. We extend these studies in this protocol utilizing state-of-the-art analysis methods, combined with assessing pain, opioid exposure and abilities, to provide a comprehensive study of properties of the condition, and integrate mechanisms across physiological domains.

6. We continue to develop novel measurement tools to study the brain in pain, including:
   a) Graph theoretical methods and global network measurements to assess brain properties (**figures 5-7**).
   b) Off-site large datasets used as unbiased ground-truth controls, compared to our own data (T1, DTI, rsfMRI: C1000 (Connectome1000), n = 1000 subjects, HCP (Human Connectome Project) data n = 900 subjects) (**figures 5, 6**).
   c) Use of multi-shell diffusion imaging to differentiate the microstructure of grey matter [70,71].
   d) Here we begin using state-of-the-art 3D pseudo-continuous arterial spin labelling (ASL), an MRI-based technique to measure cerebral perfusion, which provides the means to calculate absolute rates of human brain metabolism [72].
   e) We also have adapted a new data analysis blinding method to diminish data processing biases and enhance reproducibility (see [73]). Moreover, to ensure that obtained results are rigorous and generalizable, data are collected in two separate labs, on two separate, but identical brain scanners (NU & AbilityLab), and are used for discovery and validation. Although the data are collected independently, all brain imaging data analyses are done (blinded) using the same tools and software.

3.2 Rationale

The traditional view is that independent brain circuits mediate opioid analgesia and opioid reward/addiction [37]. Specifically, it is assumed that opioid analgesia is mediated through descending modulation of the spinal cord by PAG opioidergic neurons and by opioid interneurons in the spinal cord that regulate nociceptive signalling. In contrast, opioid reward/addiction is thought to be mediated by themesolimbic system, which controls hedonic, affective and motivational aspects of behaviour [16,37,74], see **fig. 1**. Our work shows that this presumed separation between analgesia and opioid addiction is not tenable in chronic pain. Besides our human studies, the results from the cellular examination of NAc physiology shows strong correspondences between opioid addiction and the transition to chronic pain. Chemogenetic modulation of dopamine D2 spiny neurons in the medial shell of NAc (d2SPNs in NAc shell) effectively and bi-directionally controlled tactile allodynia in SNI mice, showing that this NAc network causally influences analgesia. Complementing these results, it has recently been shown that morphine decreases d2SPN excitability [75]. Additionally, VTA DA neurons exhibit increased tonic inhibition with chronic administration of morphine thus reducing DA inputs to NAc [76]. Similarly, in SNI, the ongoing firing rate of VTA DA neurons are decreased and DA concentration within NAc is concomitantly decreased [65]. These results support our central hypothesis that chronic pain primes the limbic brain for opioid addiction. However, virtually nothing is known about how opioids, particularly repeatedly self-administered opioids,affect the re-organization of brain circuits in the chronic pain state, nor how this state changes the actionsof opioids in humans.

Neuroimaging of opioid dependence and addiction has been studied mainly for illicit opioids. Most human neuroimaging research has focused on the acute effects of opioids on experimentally-induced pain in healthy subjects [18,77-80]. Observations from such studies show that activations in mesolimbic regions are maximally suppressed at the lowest opioid dose, consistent with the high opioid receptor densities seen throughout the limbic brain (**fig. 1).** Clinical research on the neurobiological aspects of opioid dependence on brain systems has focused on illicit opioids [81-84]. Two human neuroimaging studies are relevant to our project. A cross-sectional study in 10 opioid dependent individuals (without pain, relative to 10 age-matched controls) showed bilateral volumetric loss in Amy, and decreases in functional connectivity in the anterior insula, NAc and Amy [85]. In a longitudinal MR study [86], 10 CBP patients were administered oral morphine daily for 1 month, and compared to those who used placebo. Significant volumetric differences were observed in Amy and this effect was persistent 5 months after cessation of treatment. Results from both studies are consistent with our main tenet that opioid exposure impacts mesolimbic anatomy and function, exaggerating maladaptive changes of chronic pain.

Overall, the science of the interaction between chronic pain and opioid exposure is minimally explored.

The current project is therefore designed to unravel the relationship between opioid analgesia and abuse potential from a mechanistic viewpoint.

Mechanisms to explain known risk factors for OUD remain unknown. We propose to define brain biomarkers to provide mechanistic support for OUD risk factors. Women comprise a majority of all chronic pain populations [87], receive more prescriptions for – and exhibit use of – higher doses of opioid analgesics [88]. Reports of higher rates of opioid misuse in women may result from: a) greater chronic pain prevalence, b) distinct hormone-dependent mechanisms mediating opioid analgesia and tolerance to chronic morphine [87,89], and c) higher rates of anxiety and depression, which positively correlate with opioid misuse [88]. Sex differences in opioid-induced analgesia in chronic pain remain controversial, given that most human and rodent studies are conducted in healthy individuals exposed to acute pain [90]. Therefore, we expect important differences both in behavioral outcomes and brain properties of female CBP, with opioid exposure. We will test the sex dependence of all of our primary outcomes.

Chronic pain patients with opioid use disorder exhibit high rates of psychiatric comorbidities, including anxiety and mood disorders [91]. CBP itself is commonly associated with various comorbidities [92]. In the past, we studied CBP at the exclusion of comorbidities; but here, we will include CBP patients with comorbidities. We expect that these will exacerbate opioid abuse liability, particularly since mood and pain comorbidities also impact on the limbic system. Moreover, we attempt to make the present study concordant with the common clinical population. Therefore, we will test the influence of comorbidities on brain adaptations.

The majority of people exposed to drugs of addiction are resilient, and only a minority are vulnerable to addiction [93]. The same is true for opioid use disorder [37,94], and for developing chronic pain. Therefore, we assume that subsets of our CBP patients will show signs of vulnerability. Therefore, identifying brain biomarkers associated with OUD resilience is a primary objective in humans (Aim 1).

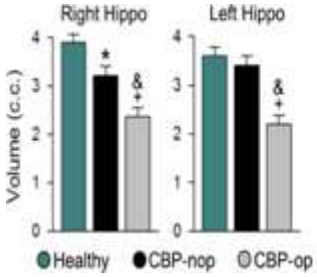


Fig. 4. Opiate use is associated with decreased Hipp volume in CBP. Mean±sem. for regional volumes for healthy, CBP-nop and CBP-op. CBP-op showed decreased Hipp volume compared to healthy and CBP-nop. (+ $p<0.05$ CBP-op vs. Healthy; & $p<0.05$ CBP-op vs. CBP-nop; * $p<0.05$ CBP- nop vs. Healthy).

Aim 2 attempts to untangle pain and opioid dependence circuits. There are no studies that we know of, regarding brain imaging of brief opioid withdrawal and re-exposure in chronic pain. The general addiction literature amply demonstrates that originally neutral stimuli regularly associated with drug intake become conditioned stimuli and evoke drug craving by stimulating an appetitive response [95]. Conditioned drug cues also activate counter adaptive homeostatic mechanisms that induce conditioned withdrawal if subsequent drug consumption does not occur; drugs are then craved to abolish withdrawal symptoms and negative mood states. Stimulation of an appetitive response involves activation of the DAergic reward system and its opioidergic inputs [96], while activation of conditioned withdrawal includes a glutamatergic/GABAergic imbalance with increased excitatory and decreased inhibitory transmission [97]. How these circuits become distorted with chronic pain managed with repeated opioid exposure, occasionally leading to the OUD state,is the question we address by mildly perturbing the system with a transient, open-labeled withdrawal followed by a blinded re-exposure in Aim 2. Given that pain relief is intrinsically rewarding, chronic pain places the organism in a complex state where the euphoric and pain-relieving rewarding values of opioidsare presented together repeatedly, within a state that is primed for addiction due to limbic maladaptations as a result of the chronic pain itself. Thus, these interactions are complex, and they are time- and dose- dependent as well.

In Aim 2, we re-expose participants (CBP+O and CBP+OUD) to DA+NSAID in order to assess behavioral responses and test brain responses. We expect that in some subjects, DA+NSAID will replicate brain opioid effects. This will provide evidence for the utility of replacing opioids with this non-

addictive therapy for chronic pain. Our approach follows from data we have generated and the fact that transmission within DAergic mesolimbic circuitry is consistently affected by all drugs of abuse. Further, human brain imaging studies of drug dependence provide similar consistent evidence [98] We have done so, initiating a clinical trial to test whether this treatment (twice a day for 3 months) would diminish transition to chronic pain in subjects with early back pain. The study remains blinded. More than 50 participants have completed the study. We observe minimal adverse side effects and no signs of addiction. Administering DA+NSAID in CBP is thus safe. Importantly, it should mimic opioid control of CBP, as the NSAID should provide an analgesic effect while DA will be activating DAergic circuits that opioids would also induce. This combination treatment is thus potentially a non-addictive alternative to managing chronic pain with opioids.

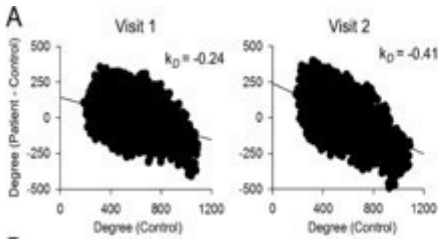


Fig. 5. Degree rank order shift with opioid withdrawal. Scatter plots depict the individual patient k_D compared to off-site healthy control group before (Visit 1) and 24 hours (Visit 2) after skipping opioid meds.

Offset analgesia (OA) is a pain psychophysical phenomenon best described as “disproportionately large decreases in pain ratings evoked by small decreases in [nociceptive] stimulus intensity”[127]. While many healthy individuals experience a complete analgesic response, OA is blunted in those with chronic pain. On average, chronic pain patients have a 30% lower OA response than healthy controls, and it is the only known psychophysical pain assessment that is markedly impaired in pain patients[128]. There is reason to believe such findings are mediated by the limbic circuitry—the same circuity that areinvolved in addiction[129]. Data from our group demonstrate that, upon removal of a nociceptive stimulus,nucleus accumbens is activated in healthy controls (reward of pain relief), but deactivated in chronic pain patients (punishment)[130]. Moreover, brain activity in the limbic circuitry is distinct between healthy individuals and patients with chronic pain[131]. These findings are reflected by a body of work suggestingchronic pain is maintained by altered limbic pathways[132]. If limbic pathways are responsible for OA, then OA may noninvasively probe the circuity at the epicenter of chronic pain and drug abuse. By pharmacologically perturbating dopamine levels, we can assess the dopamine dependence of OA. Therefore, we will incorporate a brief OA protocol into our existing study to assess the dopamine- dependence of OA in chronic patients on opiates. If OA is dopamine dependent, we expect L-dopa to amplify OA, while placebo and opiates will not have any effect. Such a finding will advance our knowledge of OA and the limbic circuity in general, pointing to a new mechanism of analgesia and a way to noninvasively prone the pain and addiction circuitry.

3.3 Preliminary results supporting proposed hypotheses.

1) Long-term opioid exposure in CBP is associated with smaller limbic volumes. We compared Hipp volumes in matched CBPgroups, one managed exclusively with opioids and one not, and healthy matched controls. The volumes of right and left Hipp were calculated for each subject. Group comparisons were performed using an ANCOVA with volume as the dependent factor, the group as categorical factor, and age and gender as covariates of no interest. Since the number ofsubjects was small, pairwise post-hoc comparisons wereperformed using a Fisher- LSD test. We observed significant group differences (right Hipp: $F_{2, 13}$ = 18.1, p = 0.0001, and left Hipp: $F_{2, 13}$ = 17.2, p = 0.0002). As in our previous report[57], both CBP groups exhibited smaller Hipp volumes compared to health subjects. More

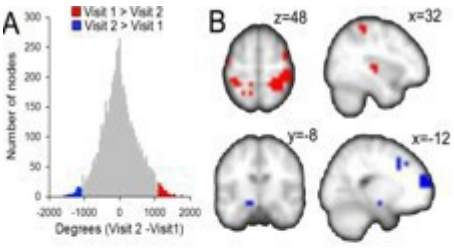


Fig. 6. Localized connectivity changes with opioid withdrawal. (A) Distribution of nodal degree difference (visit 2- visit 1). Red and blue represent the top 1% of nodes that showed increased and decreased connectivity following drug withdrawal resoectively. (B) The spatial localization of the top 1% nodes.

importantly, we observed that CBP patients on opioids showed an additional reduction in Hipp volumes compared to CBP not on opioids (**fig. 4**). These results suggest opioid use in CBP impacts limbic structures, reinforcing our primary hypothesis.

2) The brain connectome in chronic pain. We recently addressed the reverse question: is there a brain signature for the state of chronic pain that can be generalized across types of chronic pain? We used rsfMRI employing graph theoretical techniques to calculate nodal degree maps in individual subjects [100].

The approach tests the general concept that chronic pain may be characterized as an abnormal brain network state. Brain graphs were derived from 5,828 regional cortical and subcortical nodes, with edges (16,979,878 total possible) drawn between nodes to represent their functional correlation in CBP patients (n=25) and age- and gender-matched healthy controls (n = 75) [100]. We used a unitary measure which assesses whole-brain degree rank order disruption (k_D), defined as the gradient fitted to the mean difference in nodal degree between any given subject in relation to the mean nodal degree in a control population. CBP, but not our healthy group, showed significant degree rank order disruption (unpaired t-test = - 14.84, $p < 0.00001$); and individual k_D scores strongly correlated with intensity ofback pain. We observed a similar relationship for other chronic pain conditions and in rodent models of chronic pain (SNI).

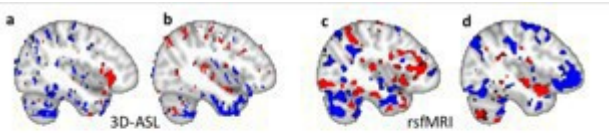
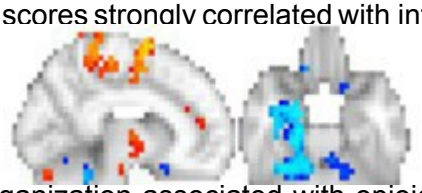


Fig. 8. Changes in blood flow (a,b) and VTA fuctional connectivity in a CBP+O, between withdrawal and re-exposure for placebo (a, c)and opioid (b, d). Red = increases; blue = decreases; for CBF change >150ml/10g/min; for rsfMRI change >4 in Fisher's z.



3) Distortion of brain connectome in a CBP with a 24-hr opioid withdrawal. We examined global and local functional reorganization associated with opioid withdrawal (24 hours) in one patient who was on opioid therapy for years. Opioid withdrawal was associated with an increase in the magnitude of spontaneous pain from 7 out of 10 to 9 out of 10. We observed rank order disruption similar to that observed in CBP patients (**Fig. 5**). To investigate local nodal degree changes following opioid withdrawal, we identified the top 1% of voxels showing either increased or decreased functional connectivity between the 2 scans (**Fig. 6A**).

Opioid withdrawal increased nodal degree in bilateral primary and secondary sensory regions and ACC, and decreased nodal degree in frontal regions and Amy (**Fig. 6B**). We acknowledge that these results are not placebo controlled, and may also be due to changes in pain.

Given the results 2) and 3) we will use k_D scores in all rsfMRI data (human and rat) to assess the global impact of opioid exposure on the brain in chronic pain.

4) Long-term opioid exposure distorts VTA functional connectivity. This relationship was evaluated in 21 chronic pain subjects managed with opioids vs. 21 matched chronic pain managed without opioids. These results are not corrected for physiological confounds (not available) and thus are only suggestive (**fig. 7**).

5) Brief opioid withdrawal and re=exposure distorts brain metabolism and VTA connectivity. In two CBP+O participants, we implemented parts of the paradigm for aim 2. **Fig. 8** shows ASL and rsfMRI changes in one subject.

6) Opiate preference and opiate analgesia show injury type and time dependence (**fig. 2** in Overall). Our preliminary MCPP experiments in SNI/sham mice, 5 days and 30 days after injury (n=8/group), showed morphine place preference acquisition and post MCPP tactile allodynia were dependent on the groups by time interaction, with acquisition being stronger in SNI at 30 days, and allodynia stronger at 5days.

7) Brain metabolism differences between SNI and sham rats, with a single dose of morphine (**fig. 9**). Our preliminary PET FDG results show overall decrease in brain metabolism in SNI & sham rats 1-hour after 5mg/kg morphine, as well as localized between group differences.

4. STUDY ENDPOINTS

Specific outcomes for Aim 2a: We have piloted this protocol in 2 CBP+O patients, and adjusted the paradigm accordingly. Preliminary results are very encouraging as we observed robust changes in metabolic activity and in VTA functional connectivity between opioid delay and re-exposure (**fig. 8**). An issue we have encountered is that opioid re-exposure may induce somnolence. Thus, scans might require a minimal task to test for wakefulness, for example, implementing a visual fixation point which slowly changes in color during scanning. Participants will then be instructed that at the end of each scan, we will interrogate them as to the properties of the point. We have also tested the monitoring of heart rate and breathing, which will be collected regularly and used as confound covariates. Given rodent evidence that DA involvement in opiate reward is enhanced with dependence [113], brain responses to DA+NSAID should be related to OUD. This design requires subjects spending 3 full days with us, but has not been a problem in the 2 participants studied thus far, although other candidate subjects were wary about the extent of time needed. Given the limited number to be enrolled (80 over 5 years), we are confident this trial goal is readily achievable.

Specific outcomes for Aim 2b: Our pilot results show specific changes in abilities, depending on the type ofre-exposure. Brain activity and connectivity changes that would reflect shifts in ability remain to be identified. These results complement the data collected in **aim 1b**, and together they have the potential to clarify thespecific influence of both chronic pain and opioid exposure on human abilities.

5. STUDY INTERVENTION(S)/ INVESTIGATIONAL AGENT(S):

5.1 Carbidopa/levodopa, SINEMET®

1) Name: Carbidopa/levodopa, SINEMET®

2) Composition: Carbidopa/levodopa is a white, crystalline compound, slightly soluble in water.

3) Storage and Handling: Carbidopa/levodopa will be maintained in a controlled environment between 15ºC-300ºC. It will be stored in a secure location by the NMH investigational pharmacy. . Carbidopa/levodopa has a 6-month shelf-life.

4) Dose: 25mg carbidopa/ 100mg levodopa

5) Administration: Carbidopa/ levodopa will be administered once per patient. Carbidopa/levodopa will beadministered alongside naproxen.

6) Masking: The Carbidopa/Levodopa tablets supplied by the manufacturer will be overencapsulated at Northwestern Memorial Hospital Pharmacy by putting the supplied tablet inside of another capsule and fillingthe remaining space with excipient. The excipient for the capsules will be Lactose NF. A 00 hard, gelatin, opaque capsule will be used.

7) Acquisition: Carbidopa/levodopa will be sourced via Northwestern Memorial Hospital (NMH) Pharmacy.

5.2 Naproxen

1) Name: Naproxen

2) Composition: Naproxen is an odorless, white to off-white crystalline substance, practically insoluble inwater at high pH.

3) Storage and Handling: Naproxen will be maintained in a controlled environment between 15ºC-30ºC. Itwill be stored in a secure location by the NMH investigational pharmacy. The expiration date of the naproxen will vary based on when it is acquired and will be documented and monitored closely.

4) Dose: 500mg

5) Administration: Naproxen will be administered once per patient. Naproxen will be

administered alongside carbidopa/levodopa.

6) Masking: The naproxen supplied by the manufacturer will be overencapsulated at NMH Pharmacy by putting the supplied tablet inside of another capsule and filling the remaining space with excipient. The excipientfor the capsules will be Lactose NF. A 00 hard, gelatin, opaque capsule will be used. This will differ in color from the capsule used for the carbidopa/levodopa.

7) Acquisition: Naproxen will be sourced via NMH Pharmacy.

5.3 Placebo

A matching capsule containing lactose will be prepared by NMH pharmacy. The appearance and properties of these capsules will be identical to those containing the active treatment and all labeling will be identical other than participant identifier. Placebo capsules of both colors will be prepared as all participants will receive 2 capsules at each treatment episode.

5.4 Opioid

All participants will be on a short-acting opioid medication. They will be instructed to not take their regular morning opioid dose. Using the online Prescription Monitoring Program (PMP), the clinical investigator will confirm participant's opioid medication and order a single dose of the medication from NMH investigational pharmacy. The pharmacy will fill and over encapsulate the prescribed medication in a 00 hard, gelatin, opaque capsule which will be identical to the other non-naproxen treatment options.

Protocol will be updated on changes based on drug availability and investigational pharmacy, as appropriate.

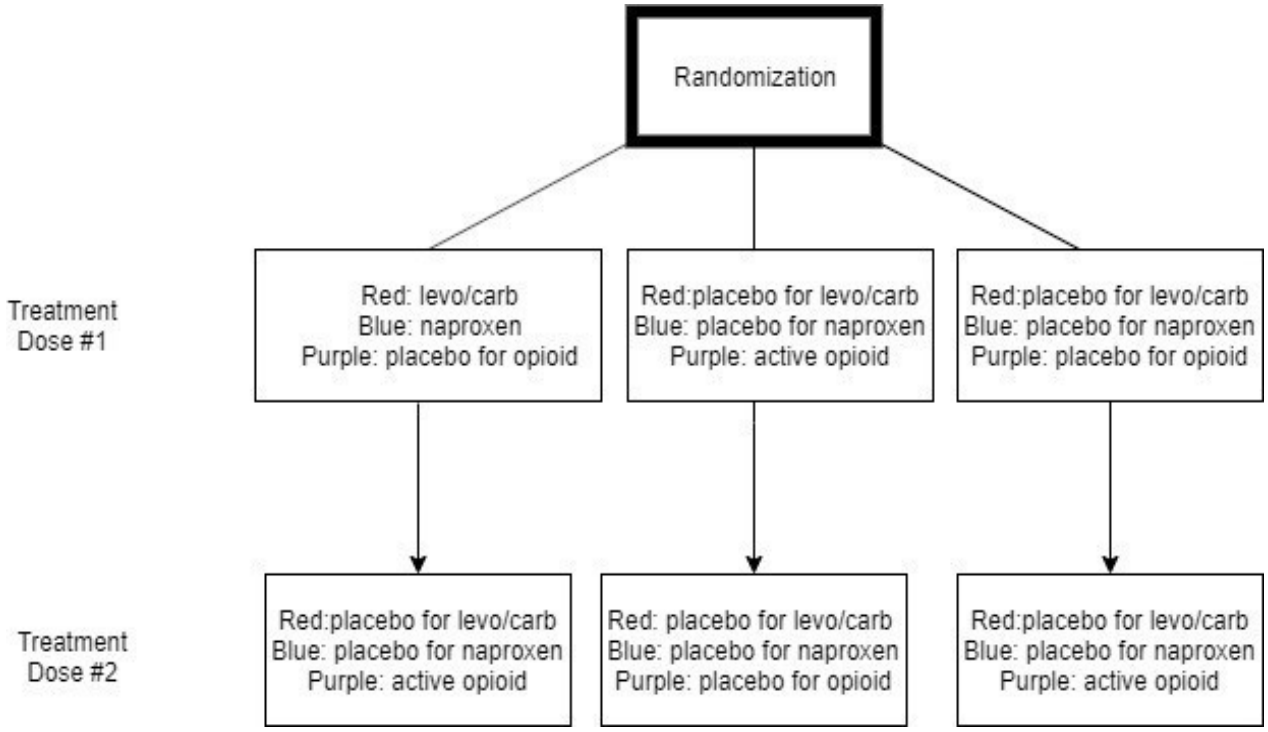
5.5 Masking

After confirming the participant's opioid medication using the PMP, the clinical investigator will order a single dose of the participant's medication from NMH investigational pharmacy. The pharmacy will fill and over encapsulate the prescription accordingly. The pharmacy will have the allocation tables for the study. Eachnew participant will receive the next study ID number and receive the appropriate sequence of drug from the pharmacy. Participants will receive a different treatment option for their initial treatment period at each of the 3imaging visits.

Each treatment period will consist of three capsules: a red, blue and purple capsule. The red capsule will always either be l-dopa/c-dopa or placebo for l-dopa/c-dopa. The blue capsule will always either be naproxen or placebo for naproxen. The purple capsule will always either be active opioid or placebo for opioid.

In the event that a participant is taking multiple opioids, an additional placebo pill will be prepared per additional opioid dose taken to maintain the blind.

Depending on the allocation table, "treatment period 1" will be one of the following three sequences:(1) l-dopa/c-dopa, naproxen, and placebo for opioid (2) placebo for l-dopa/c-dopa, placebo for naproxen and active opioid or (3) placebo for l-dopa/c-dopa, placebo for naproxen, and placebo for opioid; "treatment period 2" will be one of the following three sequences: (1) placebo l-dopa/c-dopa, placebo for naproxen, and active opioid (2) placebo for l-dopa/c-dopa, placebo for naproxen, and placebo for opioid or (3) placebo for l-dopa/c-dopa, placebo for naproxen and active opioid; respective to "treatment period 1." This is demonstrated below:



The pharmacy will have two containers, one labeled “treatment period #1” and the other labeled “treatment period #2.” They will place the determined appropriate treatment in each container, respectively, and give thecontainers back to the blinded staff who will administer the treatments accordingly.

Individuals who are allergic or cannot tolerate naproxen or l-dopa may still be enrolled but will have only 2 imaging visits, receiving either opioid or placebo at each visit based on their treatment allocation. All other procedures will be identical.

6. PROCEDURES INVOLVED:

Potential eligible subjects will be identified from existing clinical practices at NU and AbilityLab, and will be contacted by phone, and if eligible and willing, invited to participate.

6.2 Procedures for Aim 2:

6.1 Procedures for Aim 1

Procedures for Aim 1 are carried out under IRB approved STU00207384.

6.2 Procedures for Aim 2

For new participants and those who participated in Aim 1 more than three months prior to starting Aim 2, therewill be an additional screening visit. These participants will have four visits in total (Screening, Visit 1, Visit 2, and Visit 3). At the screening visit, participants will first be consented and if they meet inclusion/exclusion criteria will continue on to the remaining procedures of the visit. The screening visit will also require participants to complete questionnaires (in REDCap) regarding their general health, pain, function, mood and personality.

For those participants that are transitioning from Aim 1 to Aim 2 within 3 months of having completed Aim 1, participants will first be consented and if they meet inclusion/exclusion criteria, participants will continue on to the remaining procedures of the visits.

All participants will be asked to not take their morning opioid dose. All participants will at one of their 3 imaging visits receive each of three possible interventions (placebo + placebo, (their) opioid+ placebo, orDA+NSAID).

The procedures done at each visit are presented in detail below. To summarize, participants complete a series of surveys and procedures enumerated below while being monitored hourly for changes in both pain and behavioral changes consistent with waning opioid effects utilizing the Pain and Craving Index instrument and the Subjective Opiate Withdrawal Scale (SOWS). After the imaging they will be randomized and receive their first treatment period medication, provided by the pharmacy as detailed elsewhere. They will then complete a similar set of surveys and procedures as previously done and have a second brain scan. Following that scan, they will receive their second treatment period medication and be discharged. The same set of steps outlined above are done at each visit.

Between visits, all participants will use an eDiary to log their back pain intensity, mood, proper medication use, and other information that they may wish to report. Participants will be required to complete eDiary ratings between each imaging visit. eDiary entries are immediately transmitted from a smartphone device or computer through the Internet to a secure web site, downloaded daily to assess compliance, and stored in a second secure server. Our group has been using such an eDiary for about 2 years and this process has been very effective. If needed, participants can also complete their eDiary ratings on paper.

6.3 Details of Aim 2 Visit Activities and Procedures

Activities at Screening Visit (~2-3 hours)(if applicable):

- Informed Consent.
- Demographics.
- General medical history and medications.
- W-9
- Questionnaires in REDCap (all or only a subset to be determined):
    - NRS
    - BDI
    - SF-12 Health Survey
    - SFMPQ
    - ODI
    - MAIA
    - Promis57 Survey
    - PDQ
    - CPAQ
    - PASS
    - PSQ
    - ERQ
    - ACS
    - eACS
    - FFMQ
    - NEOFFI
    - LOT
    - LAQ
    - PANAS
    - PCS

- COMM
- Height and weight
- Seated vital signs (temperature, blood pressure, respiration, pulse) measured.
- Urine toxicology screen.
- Physical Exam (if needed)
- Urine pregnancy test for all women of child bearing potential.
- Blood collection.(Comprehensive Chemistry Panel, CBC w/ diff)
- MRI safety questionnaire.
- Set up eDiary

Participants will complete the following procedures at the first imaging visit:

The below will only be done at the first visit or if otherwise deemed necessary:

- Read, discuss, and sign this consent form.
- W-9

Participants will complete these procedures at each of the imaging visits (~8-9 hours):

- Asked to not take their morning opioid medication before coming for this visit
- Answer the following Pain and Craving Index questions (completed once before each imaging visit and a subset collected once per hour during each imaging visit)
  - "Over the past 24 hours, how strong was your urge to take more opioid medication than prescribed?"
  - "Over the past 1 hour, how much did your mood or anxiety level affect any urge to take more opioid medication?"
  - "Over the past 1 hour, how often have you found yourself thinking about your next opioid dose?"
  - Over the past 1 hour, how much have you craved the medication?"
  - "Over the past 1 hour, what has been your average pain level?"
  - "What is your pain rating now?"
- Asked to rate their current mood (once before each imaging visit, as well as once per hour during each imaging visit)
- Asked to complete SOWS questionnaire to monitor symptoms of opiate withdrawal (hourly) Answer questionnaires in REDCap regarding their pain, mood, thoughts and feelings (some or all of the following): PainDetect
  COWS
  SFMPQ
  NRS
  PANAS
  PCS
  SOWS
- Collect blood and urine sample
- Psychophysics thermal stimuli
- Receive treatment dose 1
- Answer questions on pain and craving (completed once per hour)
- Answer questionnaires in REDCap regarding their pain, mood, thoughts and feelings (some or all of the following):
  COWS
  SFMPQ
  NRS
  PANAS
  PCS
  SOWS

- MRI scan
- Collect blood sample
- Psychophysics thermal stimuli
- Receive treatment dose 2
- Discharge

Below is a reiteration of these activities. Please note that questionnaires and blood draw can happen before or after the MRI brain scan.

Individuals who are allergic or cannot tolerate naproxen or l-dopa may still be enrolled but will have only 2 imaging visits, receiving either opioid or placebo at each visit based on their treatment allocation. All other procedures will be identical.

6.4 Brain Imaging Procedures

Brain data collection and analysis procedures and software are all in place. All brain scans will be done on Trio Prisma 3T multichannel scanners (NU or AbilityLab), using HCP matched parameters [120]. Our data collection rate for this proposal is thus highly feasible, especially since half the data will come from Baliki's lab.

- T1-MRI, DTI-MRI, resting state fMRI and ASL will be performed as described (Baliki M, 2012) (Mansour A, 2013) at all imaging visits, with pulse and respiration rates obtainedduring thescans.
- All brain imaging is done on two 3.0 T Siemens Trio whole-body MRI scanner with echo- planar imaging (EPI) capability and using a 64 channels head-coil. Both scanners are dedicated for research and shared between 15 NIH funded research groups. The university has guaranteed us access to these magnets for the next 5 years. The magnets are managed by Radiology Department and are fully staffed and equipped. They are core human imaging facilities of NU. Their signal-to- noise ratio is excellent and they have produced very nice results over the last 5 years of operation, and >100 publications.
- We will acquire four different types of brain images:
  - Anatomical T1-MRI (high resolution anatomical magnetic resonance imaging): voxel size = 1 ×1

  × 1 mm, repetition time = 2.3 s, echo time = 2.4 ms, flip angle = 9°, in-plane matrix resolution =256 ×256; 176 slices, field of view = 256 mm.
- Resting state fMRI (functional MRI): multi-slice T2*-weighted echo-planar images with repetition time = 555 ms, echo time = 22 ms, flip angle = 47°, number of volumes = 1110, slicethickness = 2 mm, voxel resolution = 2 x 2 x 2 (mm). The slices are covering the whole brain from the cerebellum to the vertex.
- DTI-MRI (diffusion tensor imaging): diffusion weighted images are acquired along 30 and 64 isotropic directions using b values of 700 and 2000 s × mm-2, respectively. Field of view=1044 x 1044, repetition time = 3.5 s, echo time = 92 ms, flig angle = 90. .
- ASL (arterial spin labeling): The ASL sequence applies a pseudo-continuous label scheme to temporarily label or change the magnetic properties of the flowing blood spins. A "label" image with altered blood signal is acquired with a 3-dimensional readout method that facilitates removal of background tissue signal using appropriate radiofrequency pulses. A "control" image where the magnetic properties of blood spins are not altered is also acquired. Subtraction of thelabel image from the control image further removes non-perfusion related signal and generates a perfusion map that can be converted to physiological units (mL/100 g tissue/minute) based on published quantification models. Six alternating pairs of control and label images are acquired for signal averaging, which reduces noise.
- Brain imaging data analysis is done on free-share software including FSL, SPM, FreeSurfer, Caret, MRIcron as well as ad-hoc routines written in Matlab, C++, Pearl, Awk. The university maintains a user contract for Matlab and other software that we use routinely. We have a dedicated server for brain imaging data analysis. This is a 23 TByte data management system and with large number

of processors, which runs on Linux. This server is our main brain imaging data storage and processing system. It is accessible through Internet, and all data processing is performed on it, mainly by remote access.

6.5 Laboratory Procedures/ Evaluations

Baseline laboratory values will be collected for determination of inclusion/exclusion criteria and to assess safety and also will be entered into the study database. Repeat laboratory testing will only be done if there is a clinical basis for further testing. Blood and urine samples will be collected at the first study visit. Blood samples will be collected at each visit. Urine pregnancy tests will be processed before any imaging visits. Blood samples will be processed through Pathology Laboratory at NMH, 251 E. Huron St., Chicago, IL 60611. All results will be faxed to the study doctor for review before participants begin study medications.

Samples will not be frozen nor stored for long-term or future use.

Screening laboratory evaluations will include complete blood count and differential, urine screen for pregnancy and illicit drug use, and a chemistry panel (16 tests that assess liver and kidney function and electrolyte balance.)

6.6 Surveys and Questionnaires

Questionnaire tools that we plan on using include health assessment, pain and mood related characteristics, personality traits, and opioid use and abuse related tools. They are all validated measures and show fairly high sensitivity and specificity. Health is assessed only at the first visit. Pain related measures, Opioid use and disuse measures, and personality questionnaires will be collected throughout the study but not necessary at all visits.

Personal Health History (PHH): This general questionnaire will assess demographic information (sex, age, marital/relationship status, race/ethnicity, socioeconomic data and education), pain history (descriptions, diagnostic testing history, and treatment history), general health history (other medical/surgical history, concurrent medications, health behaviors, a general symptom checklist, and health-care utilization), and work history. The entire questionnaire will be completed at the baseline visit. Participants will be asked about any changes to concurrent medications at subsequent visits. History and physical examination will be done to confirm diagnosis, inclusion and exclusion criteria and assess overall safety.

Numerical Rating Scale (NRS): is an 11-point numerical rating scale used to measure pain intensity.

McGill Pain Questionnaire - Short Form (MPQ): is a pain measure, which permits separation of sensory and affective components of pain, as well as a total score.

PainDETECT: A 12-item self-report instrument that assesses neuropathic pain properties.

Positive and Negative Affect Schedule (PANAS): is a 20-item self-report instrument that measures positive and negative mood states.

Pain Catastrophizing Scale (PCS): The PCS is a 13-item instrument. It asks participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain.

Subjective Opioid Withdrawal Scale (SOWS): Contains 16 symptoms which the subject rates in intensity.

Clinical Opiate Withdrawal Scale (COWS): This is an 11 item scale administered by the staff. It assesses objective signs of withdrawal symptoms.

Current Opioid Misuse Measure (COMM): This is a 17-item self-report measure of risk for aberrant medication related behavior among persons with chronic pain who are prescribed opioids for pain.

State Prescription Monitoring Program (DMP): This information is collected from the clinic where a given patient was recruited from. Illinois Prescription Monitoring Program (PMP). The PMP is an electronic tool that collects information on controlled substance prescriptions, schedules II, III, IV and V. This data is reported on adaily basis by retail pharmacies dispensing in Illinois. Prescribers and Dispensers of controlled substances areallowed to obtain a user ID and password to query their current or prospective patients.

Illinois Prescription Monitoring Program (PMP).
The PMP is an electronic tool that collects information on controlled substance prescriptions, schedules II,III, IV and V.

Psychophysics thermal stimuli:
The participant will sit and a thermode (T06, QST Lab, Strasbourg, France) will be placed on the forearm. The thermode can deliver heat and cold stimuli. In this study, we will only use heat stimuli. We will deliver a series ofstimuli until we determine what the participant rates the pain as an 80/100; this will serve as the maximum stimulus used for that individual over the course of the experiment. No participant, at any point, will receive a stimulus that exceeds this submaximal threshold, and the stimuli used will not be extreme enough to cause tissuedamage (i.e., all stimuli will be between 30°C and 50°C for short durations, inclusive of the extremes; this represents the stimulator's limits). Finally, the participant can withdraw/stop the stimulus at any time during the experiment.

Experimental stimuli will be defined relative to experimentally obtained participant-specific pain thresholds or device capabilities (e.g., the device is limited to temperatures ≤ 50°C), using whichever is less extreme. We will deliver 10-minute stimulus trains, each containing 3-4 stimuli with 45 sec—2 minutes between each stimulus. There will be 10 minutes rest between each stimulus train. There will be a total of 2 stimulus trains before study treatment is administered and 2 stimulus trains after study treatment is administered. The participant will be asked to rate their pain using an electronic visual analog scale (eVAS). These stimuli will not exceed 80% of a person's maximum—the participant will not be exposed to this 8/10 pain for more than 1-minute at a time, totaling about 30% of each 10-minute stimulus train. Note, most participants will not be exposed to an 8/0; i.e., most ratings will be lower since our calibration protocol produces conservative estimates. Each stimulus train will last approximately 10 minutes. The entire duration of the experiment should not take longer than 1.5 hours.

Chronic Pain Acceptance Questionnaire (CPAQ): A 20-item questionnaire measuring the effort participants put into either actively controlling their pain or passively accepting their pain.

Emotional Regulation Questionnaire (ERQ): A 10-item questionnaire measuring two kinds of strategiespeople use to control their positive and negative emotions.

Attentional Control Scale (ACS): A 20-item questionnaire assessing the voluntary control of attention during a variety of situations.

Emotional Attentional Control Scale (eACS): An 18-item questionnaire assessing the voluntary control ofattention during emotionally demanding situations, which could include pain.

Five Facets of Mindfulness Questionnaire (FFMQ): A 39-item questionnaire measuring the five main components of mindfulness—observing, describing, acting with awareness, non-judging of inner experience, andnon-reactivity to inner experience—as a skill set.

NEO Five Factor Inventory (NEO-FFI): A 60-item questionnaire measuring participants' scores on thepersonality dimensions of extraversion, agreeableness, conscientiousness, neuroticism, and openness.

Life Orientation Test-Revised (LOT-R): A 10-item questionnaire measuring dispositional optimism.

Loss Aversion Questionnaire (LAQ): A 20-item questionnaire measuring how sensitive participants are to a wide variety of potential "losses" in their lives.

Pain and Craving Index: A 6-item questionnaire used to measure pain and craving intensity.

Other information regarding procedures:

Definition of CBP+O vs CBP+OUD vs CBP-O. Dr. Wasan, a co-investigator developed the DMI, which is an accepted method for determining adherence/nonadherence (use disorder) to opioid therapy tested in multipleclinical trials[115,116] . The DMI triangulates three domains: patient self-report using the Current Opioid Misuse Measure (COMM), provider assessment of use disorder using the Addiction Behaviors Checklist (ABC) and the state Prescription Monitoring Program (DMP), and UDT results to determine adherence to opioids. The DMI is positive if use disorder is found on any domain. The DMI has been able to distinguish between a mild to moderate OUD and severe OUD .The Subjective Opiate Withdrawal Scale(SOWS) will be used to describe psychological and physical withdrawal symptoms. These domains will determine whether a participant presents with use disorder.

Morphine estimate equivalence (MEE) will be calculated for total use, blood levels, and specific dose ingested at scan time. There is clear evidence of inter-individual variability of opiate efficacy (PK-PD) in different clinical responses among patients[118]. Still, MEE allows us to estimate the dose of morphine, based on the dose of opioid use, route of administration, and conversion ratio. There are multiple calculators available, we will use[119].

eDiary. Documenting pain and drug craving in the natural setting of everyday life reduces the bias of patients attempting to "please the caregiver" and better characterizes these parameters. We have tested such atool in 120 CBP patients and observed very high compliance. We will adapt this app, using validated queries[103].

7. DATA AND SPECIMEN BANKING

We foresee that the brain imaging data and related PROs may be used in future studies, either by us or whenwe make this data available on OpenPain for use by other researchers (Apkarian, 2014). In all such cases all data will be fully anonymized prior to their availability for future use by investigators outside of Apkarian's lab.

Stored blood specimens used to collect MEE will be kept within frozen lab storage up until 5 years after end of study. Specimens will be destroyed after 5 years.

8. SHARING RESULTS WITH PARTICIPANTS

Copies of lab results may be provided to subjects who request these.

9. STUDY TIMELINE

For Aim 2, we expect to initiate recruitment in October, 2019 and complete enrollment by June, 2022. This willrequire our enrolling approximately 1-2 participants/month in each of the CBP+O & CBP+ OUD groups.

10. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria for all patients:

1. History of chronic localized pain for a minimum of 6 months daily (prior to screening), meeting theQuebec Task Force Classification System symptom categories I-III;
2. Male or female, age equal or greater than 18 years, with no racial/ethnic restrictions;
3. Must be able to read and speak English and be willing to read and understand instructions aswell as questionnaires
4. Must be in generally stable health;
5. Must sign an informed consent document after a complete explanation of the study documenting that they understand the purpose of the study, procedures to be undertaken,possible benefits and potential risks, and are willing to participate;

6. Must be willing to complete daily smartphone/computer eDiary ratings;
7. Must be on regular opioid therapy for at least 3 months prior to randomization, which will beup to the clinical investigator's decision
8. Must be on a short acting opioid therapy (anticipated duration of action < 6 hours)
    - As defined by Massachusetts Health and Human Services, short-acting opioids includebut are not limited to the following medications:
        - Acetaminophen/codeine
        - Codeine
        - Fentanyl tablets
        - Hydrocodone/acetaminophen
        - Hydrocodone/ibuprofen
        - Hydromorphone
        - Morphine
        - Oxycodone/acetaminophen
        - Tramadol
    - This will also be left up to the discretion of the clinical PI

Exclusion Criteria for all patients:

1. Chronic localized pain associated with any systemic signs or symptoms, e.g., fever, chills;
2. Any clinically significant comorbid chronic pain or neurological conditions including CRPS,Alzheimer's disease and other dementia-related conditions;
3. Use of therapeutic doses of antidepressant medications at unstable doses (i.e., tricyclic depressants, SSRIs, SNRIs; low doses used for sleep may be allowed);
4. Any clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal,neurologic, malignant, metabolic, psychiatric, or other condition that, in the judgement of the Investigator, would pose a safety risk, or cause subject to be unsuitable for participation and/or unable to complete the study procedures.
5. Uncontrolled hypertension;
6. Clinically significant renal insufficiency;(correlated creatinine clearance < 40mL/min or serumcreatinine ≥2)
7. Subject unable or unwilling to follow requirements and instructions;;
8. Evidence of poor prior treatment compliance;;
9. Intra-axial implants (e.g. spinal cord stimulators or pumps);
10. Contraindications for undergoing MRI, i.e : metallic implants, brain or skullabnormalities, tattoos on large body parts, and claustrophobia;
11. Pregnancy, or inability to use an effective form of contraception in women of child-bearing age;
12. An established diagnosis of diabetes (type 1 or type 2)
13. Lactose intolerance
14. Use of a patch or long acting opioid therapy (e.g. anticipated duration of action > 6 hours)

11. RECRUITMENT METHODS

Aim 2:

We plan to recruit 80 individuals (40 CBP+O & 40 CBP+OUD). Those participants from Aim 1 that are taking short-acting opioid therapy will be given the option to participate in Aim 2. We expect to complete 50% recruitment for Aim 1 by year 2.5. All recruitment is anticipated to be finalized by the middle of year 4.

We anticipate screening over 500 individuals (to enroll 250 participants) with chronic back pain over 4 years, all drawn from the Chicago metropolitan area. There are no racial, ethnic or gender restrictions and no upper age limit. It is anticipated that the study population will generally reflect that of Chicago. Our experience from previous chronic back pain studies provides us reassurance that we will be able to identify this number of individuals required to be screened and that we will achieve a diverse participant cohort.

Participants will be drawn from two major pools of individuals: those being seen within the Northwestern

Medicine (NM) healthcare system and those being seen the Shirley Ryan Ability Lab, with approximately 50% of participants coming from each source. If additional recruitment is necessary, we will utilize our recruitment database and local recruitment efforts such as print ads and social media to reach out to the local community.

NM maintains an electronic data warehouse (EDW) that contains and makes accessible for researchers the electronic medical records of all individuals who are seen by clinicians within the system and who provide consent. Access is obtained through requests based on specific ICD-10 codes and providers. We have used this system since its inception several years ago with great success, allowing us to identify and contact a large number of people with well-defined illnesses, including back pain. We have supplemented this approach by direct involvement with specific practitioners who deal with large numbers of chronic back pain patients, primarily with the departments of orthopedic surgery, neurosurgery and anesthesiology. We have on-going relationships with specific clinicians and research coordinators within these groups to assist in the identification and recruitment of specific populations. The combination of the EDW referrals and the direct physician referrals assures a high number of potential candidates with well-defined backgrounds and illnesses for studies. We have utilized both these approaches in our past as well as on-going studies in patients with CBP and are confident that these referral sources will continue to be productive.

Media Advertising: Advertising in the media (newspaper and radio) has proven to be extremely effective in identifying people with low back pain in our previous longitudinal study. Expertise in media placement as well as use of experienced phone personnel is a core competency within our research group. A recruitment plan specific for this study will be developed and implemented by the recruitment division staff, working in close conjunction with the investigators and other study personnel. This methodology in the past has yielded 20-30% of participants for trials of this sort.

Online Advertising: Advertising using online resources (including but not limited to social media, e.g., Facebook and Twitter, www.craigslist.com, online newspaper classifieds, and websites for people who work with or have low back pain or related conditions has been a fruitful approach to identifying individuals with CBP for our previous and on-going CBP research. As with traditional media advertising, we are able to control when and how often we place these advertisements to make maximum use of our staff's time. This approach has generated 20-30% of participants for trials of this sort in the past, and this percentage is growing with traditional media advertising decreasing over time.

Community Advertising: Given the high reliance on public transportation in the Chicago area, advertising in bus, train, and rail stations/facilities reaches a large number of citizens from broad socioeconomic backgrounds. Ridership reports indicate the Chicago Transit Authority ridership exceeds 2 million bus, train, and rail rides each day. Even short-term advertising in these venues has repeatedly resulted in large numbers of calls that continue to come in over long periods of time. In addition, coffee shops and libraries are opportunities to tap into diverse communities. As with the above approaches, this methodology will be expected to yield approximately 1-20% of the participants for this trial.

We anticipate a population that will roughly approximate the Chicago area with regard to ethnicity and race (approximately 25% Hispanic; 30% African-American, 40% non-Hispanic White, 5% Asian).

Materials that will be used, will be added as a separate modification and will receive IRB approval prior to implementation.

All recruitment materials will be submitted as a modification to the IRB, and approved prior to being implemented.

12. COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Aim 2: Subjects will be paid $75.00 for visits 1 and 2 and will be paid $150.00 for study visit 3. Subjects will be paid via PNC card, cash or check for Visits 1 through 3. For any subjects that are required to complete a screening visit prior to the study visits, they will be compensated $25 in cash. For any subjects that require transportation, it will be provided. And for any subject that requires a parking voucher, $5.00 will be

deducted from the total payment for the visit to cover the cost of the voucher.

Payment will be prorated based on visit completion. If a participant does not complete a study visit in its entirety,they will receive only $10.In addition, participants will receive $0.25 per value eDiary entry recorded throughout the study as instructed.

Lunch may be provided to subjects. In the event it is a $20.00 limit will be instituted.

13. WITHDRAWAL OF PARTICIPANTS

Subjects may be withdrawn from the research study if:

- They fail to follow instructions
- The Investigator decides it would not be in the subject's best interest to finish the study
- The Investigator, NIH or FDA decides to end the study for either medical or administrativereasons

There are no procedures for subjects who decide to withdrawal from the research.

14. RISKS TO PARTICIPANTS

14.1 Risks from Procedures

MRI scans

The MR environment is hazardous and only people properly trained regarding safety procedures are allowed to use the facility. There is risk of claustrophobia and anxiety involved with the fMRI scanning procedure; subjects will be queried about any concerns they may have prior to testing. Subjects must consent to tolerate being in the scanner, which involves the potentially uncomfortable experience of lying in a relatively confined space with minimal head and body movements for up to 60 minutes at a time. In this time period, their back pain may become worse. Personnel continuously query the subject in the scanner as to their level of pain and will discontinue the scan and relieve the subject from the discomfort at any time requested. Our routine procedure is to give subjects multiple breaks from scanning, which minimizes fatigue and decreases anxiety, resulting in high-quality data. It is possible that the anatomical scans may uncover a brain abnormality of which the participant was not aware. In such cases, the participant is removed from the study and given appropriate medical advice by Dr. Schnitzer. The likelihood of this happening is low (<1%). Over the last 5 years of doing brain scans in various chronic pain patient populations, the main limiting factor has been claustrophobia. Although we query subjects onthis routinely, participants often are surprised at how anxious they feel in the scanner and simply cannot tolerate it. Otherwise, chronic pain patients are usually enthusiastic in participating in these trials.

Psychophysics thermal stimuli

Physically, the thermal stimuli applied may cause some temporary pain or discomfort. However, there is minimal risk that the stimuli will lead to actual tissue damage (e.g. burn or broken skin). Inthe event there is injury, we will provide first aid as necessary.

Questionnaire Risks

Although the majority of participants will find the questionnaires to be harmless, mundane, or possibly interesting, there is always a possibility that some of the questions may be sensitive in natureand may make them uncomfortable (particularly those asking about mood or personality). In the past,we have added an option into our REDCap database that allows participants to skip questions they don't feel comfortable answering, so they will never be forced to answer something they do not want to. We have found that most people still answer all questions fully despite having this optional button and that most participants have no missing data. Therefore, we will continue to use this option in theproposed study.

Dr. Griffith, a licensed clinical psychologist, will be available to consult about any concerns that patients have about their mental health, including referrals to appropriate providers. All participants willbe given a list of referral sources in case they wish to seek mental healthcare, and participants will be invited to contact the research team with questions about getting connected with appropriate healthcare.

Additionally, the clinical research managers are trained in suicide prevention techniques should any immediate need arise during a study visit or follow-up.

Phlebotomy risk

The possibility exists for pain, ecchymosis and rarely localized infection as a consequence of phlebotomy. These will be minimized by careful aseptic technique and involvement of experienced phlebotomists.

Delay of opioids risk

While patients will only delay their opioid medication briefly, there is potential risk in doing so. To ensure thatpatient safety is being upheld, the clinical co-investigator will be on call to respond to any patient needs. Thismay also lead to a brief worsening of back pain.

14.2 Risks from Medications
Carbidopa/Levodopa

Carbidopa/Levodopa is a therapy that combines the dopamine agonists Levodopa and Carbidopa. The combination aims at increasing the levels of dopamine in the brain while preventing any similar increase in the rest of the body, hence minimizing side effects. The list of adverse events noted below derives from the package insert for Carbidopa/Levodopa and was a consequence of AEs reported in clinical trials of individuals with Parkinson's disease who have depleted brain dopamine levels. The most common side effects (prevalence ≥ 1.5%) of Carbidopa/Levodopa are shown below and information from the package insert which lists all reported side effects, regardless of prevalence, follows (Sinemet CR, 2011).

Adverse Experience	**Carbidopa/Levodop a (n = 524)**
Dyskinesia	12.2%
Nausea	5.7%
Hallucinations	3.2%
Confusion	2.3%
Dizziness	2.3%
Urinary Tract	2.3%

Infection	
Headache	1.9%
Vomiting	1.9%
Constipation	1.5%

As noted, the most common adverse reactions reported with Carbidopa/Levodopa have included dyskinesias,

such as choreiform, dystonic and other involuntary movements, and nausea.

The following other adverse reactions have been reported with Carbidopa/Levodopa:

- Body as a Whole: chest pain, asthenia.
- Cardiovascular: cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.
- Gastrointestinal: dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.
- Hematologic: agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.
- Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).
- Musculoskeletal: back pain, shoulder pain, muscle cramps.
- Nervous System/Psychiatric: psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome, bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with Carbidopa/Levodopa has not been established.
- Respiratory: dyspnea, upper respiratory infection.
- Skin: rash, increased sweating, alopecia, dark sweat.
- Urogenital: urinary tract infection, urinary frequency, dark urine.
- Laboratory Tests: decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with Levodopa alone and with various Carbidopa/Levodopa formulations, are:

- *Body as a Whole*: abdominal pain and distress, fatigue
- *Cardiovascular*: myocardial infarction.
- *Gastrointestinal*: gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.
- *Metabolic*: edema, weight gain, weight loss.
- *Musculoskeletal*: leg pain.
- *Nervous System/Psychiatric*: ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

- *Respiratory*: pharyngeal pain, cough.
- *Skin*: malignant melanoma, flushing.
- *Special Senses*: oculogyric crises, diplopia, blurred vision, dilated pupils.
- *Urogenital*: urinary retention, urinary incontinence, priapism.
- *Miscellaneous*: bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.
- *Laboratory Tests*: decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

Naproxen

A dose of Naproxen 500mg will be administered alongside the carbidopa/levodopa administration once per patient. Participants with uncontrolled hypertension, history of recent myocardial infarction, peptic ulcer disease, renal disease or history of allergies to NSAID medication will be excluded.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short- term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg Naproxen compared to those taking 750 mg Naproxen.
In controlled clinical trials with about 80 pediatric patients and in well-monitored, open- label studies with about 400 pediatric patients with juvenile arthritis treated with Naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking Naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1 to 10% of patients are:

- *Gastrointestinal (GI) Experiences*, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis
- *Central Nervous System*: headache*, dizziness*, drowsiness*, lightheadedness, vertigo *Dermatologic*: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura *Special Senses*: tinnitus*, visual disturbances, hearing disturbances
- *Cardiovascular*: edema*, palpitations
- *General*: dyspnea*, thirst
- *Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1 to 10% of patients.

- *Gastrointestinal (GI) Experiences*, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking Naproxen during clinical trials and through post-marketing reports. Those adverse reactions observed through post-marketing reports are italicized.

- *Body as a Whole*: anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)
- *Cardiovascular*: congestive heart failure, vasculitis
- *Gastrointestinal*: gastrointestinal bleeding and/or perforation, hematemesis, jaundice, pancreatitis, vomiting, colitis, abnormal liver function tests, nonpeptic gastrointestinal ulceration, ulcerative stomatitis
- *Hemic and Lymphatic*: eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia
- *Metabolic and Nutritional*: hyperglycemia, hypoglycemia
- *Nervous System*: inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction
- *Respiratory*: eosinophilic pneumonitis
- *Dermatologic*: alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.
- *Special Senses*: hearing impairment
- *Urogenital*: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

- *Body as a Whole*: fever, infection, sepsis, anaphylactic reactions, appetite changes, death
- *Cardiovascular*: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction
- *Gastrointestinal*: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, hepatitis, eructation, liver failure
- *Hemic and Lymphatic*: rectal bleeding, lymphadenopathy, pancytopenia
- *Metabolic and Nutritional*: weight changes
- *Nervous System*: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations
- *Respiratory*: asthma, respiratory depression, pneumonia

- *Dermatologic*: exfoliative dermatisis
- *Special Senses*: blurred vision, conjunctivitis *Urogenital*: cystitis, dysuria, oliguria/polyuria, proteinuria

14.3 Emergency care

If participants need emergency medical care, they will be instructed to go to the closest emergency room and inform the healthcare provider that they are enrolled in this study. If the need is not emergent, they will be asked to come to the clinic to be seen by Dr. Schnitzer. Participants will be responsible for the cost of any emergency or non-emergency medical care that may arise during or as a consequence of their involvement in this study.

14.4 Protections against RiskGeneral
The primary protection will be the enrollment only of eligible subjects, i.e., subjects meeting all inclusion and exclusion criteria. Individuals having clearly identified causes of chronic localized pain will be carefully excluded. In addition, individuals who cannot tolerate the confinement of an MRI scannerand those who may not be able to be scanned because of implanted metal devices will be excluded. Following treatment administration, safety monitoring for non-serious and serious adverse events is planned at each study visit until the completion of the trial. All adverse events will be collected and reviewed by the clinical lead investigator and principal investigator on a monthly basis. A chronological log of all SAE's will be maintained and reviewed by the PI every month, as well. Privacy and confidentiality will be maintained by the use of allocation numbers throughout the study, with the master study list (excluding randomization codes) being maintained by the PI with availability limited to those study personnel who have a documented need for this information.

In addition to the PI's responsibility for oversight, study oversight will be under the direction of an Independent Safety Monitor (ISM), who has expertise in clinical trials. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regardingadverse events and other safety issues. Careful monitoring of safety will be undertaken by the study team with regular oversight by the clinical investigator and the principal investigator.

Aim2:
Statistical analysis of the data collected will be led by co-investigator Dr. James Griffith.

15. POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct benefit to subjects.

Taking part in this study may help scientists to better understand more about pain and addictive behavior. It will also help scientists to determine if opioid analgesia and opioid addiction have important interactions with the brain pathways involved in chronic pain and if in time, exacerbate opioid use disorder and diminish opioid analgesic efficacy.

16. DATA MANAGEMENT AND CONFIDENTIALITY

All analyses will be done blinded.

16.1 Statistical Considerations and Power Analysis:

Our primary comparison is between categories of opioid exposure in CBP. In addition, we will have brain- based measures, collected once in Aim 1, and three times in Aim 2. In the discovery phase, we will perform whole-brain contrasts (with proper correction for multiple comparisons) where we will have 25-40 subjects per group (Aim 1). Power considerations for Aim 2 will be finalized after initiation of Aim

1; however, with 30 subjectsper group but with 6 observations per subject contrasted to each other; a within-subject repeat contrasted acrossgroups will result in more power than in Aim 1. This provides power >80% for detecting effects sizes of 0.75 or greater, assuming alpha = 0.01 (two-tailed). Our published whole-brain contrasts have been based on average n = 25 subjects per group. Comparison between groupings for behavioral outcomes should also be able to detect effect sizes of 1.0 with n=25 per group, with power approximately 80% assuming alpha = 0.01 (two-tailed). We will recruit a diverse population with comorbidities and likely high variability, and we plan on an aggressive brain-motion correction given recent reports of its large effect on network properties [121], and also because there are concerns that fMRI statistics have been inflated in the past [122] (note: we will strictly use permutation testing to ensure statistics are precise). Only a minimal set of results will be tested for replication in the validation data.

Biomarkers for resilience are brain parameters that differentiate CBP+OUD and CBP+O, and do not change between opioid withdrawal and re-exposure. For model building, our power analyses indicate that our sample sizewill be adequate, even after accounting for missing data. If we approach the analyses by classifying people into resilient/vulnerable (~50% expected in each group), statistical power would be adequate; assuming overall N = 80, an odds ratio of 2.0 as the effect size for a target predictor (which would be clinically significant) with an overlap ofother predictors of R^2 = .09 (a medium-sized relationship with other predictors), and a two-tailed Type I error rate of .05, power would exceed 85%. These power analyses are based on a binary classification of the dependent variable, but we are also familiar with methods that treat the dependent variable as continuous (e.g., mixed modeling, latent growth curve modeling [123]), techniques that increase statistical power. For model validation, algorithms derived will be applied to new cases. For all analyses, cases with and without missing data will be compared, and multiple imputation strategies will be explored.

16.2 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of thedata reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate CRFs, and source documentation. The records will be stored offsite at REEBIE storage for 7 years past study completion. After the 7 years, data is destroyed.

16.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. UPs and AEs must be reviewed by the investigator ordesignee.

16.4 Data Capture Methods

We plan to use REDCap (*http://www.project-redcap.org/*) as our data management tool. Participant-entered data will be collected directly into the REDCap. If needed, the REDCap entered data can be printed for paper records. PROs, will not contain any PHI and will be directly entered into REDCap.
Clinical (e.g., medical history and physical examination, pain evaluations) and functional (e.g., brain phenotype) entered into REDCap. There will be a source document used to confirm a participant's passing or failing inclusion/exclusion criteria. Other data collected by study staff pertainingto the study visit will be entered into REDCap. Results of labs and any other documents that are received will be stored on paper and electronically in REDCap. Consent forms containing the subject'ssignature and date will be stored on paper and electronically uploaded to REDCap as well.

16.5 Types of Data

Our research staff will be collecting multiple types of data pertaining to the participants, such as those dealing with safety, imaging, and behavioral and medical participant domains. The safety of the participant will be initially assessed through obtaining a thorough history and assuring that participants meet all the criteria of the inclusion/exclusion checklist, which reviews comorbid illnesses. Safety datawill

continue to be collected at each contact with participants and recorded in the source documents.

There will not be a separate safety database. Imaging data will be collected during each of the scanning visits and will be collected based on well-documented protocols. Behavioral data will be provided through selected patient PROs that assess various aspects of pain and overall quality of life. Medical data will be collected primarily during physical examinations and from a baseline blood draw, inaddition to follow-up visits throughout the study. These measurements include BP, heart rate, chemistry panel, CBC, drug urine screening, and urine pregnancy screening.

Lab specimens will not be stored for future use. Specimens will be discarded after processing has been completed.

16.6 Confidentiality

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. All source documents pertaining to an individual participant is compiled into a participant folder. Each participant folder includes, but is not limited to, records on personal contact information, demographic information, physical exam, vital signs, personal health history, researcher comments from each visit, PROs, concomitant medication logs, study medication logs, indications of any AEs experienced, clinical laboratory results, and ICFs. PROs will be collected directly into REDCap (REDCap is the source document), but can be printed and maintained with the participant folder if need be. All folders are kept in a locked cabinet, located in a locked room away from all participant activity.
Only study coordinators have access to the locked room and cabinet. These paper charts are also kept separate from any hospital records acquired through NMH or the NMFF. Study staff will permit authorized representatives of NIH, the NU IRB and defined regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

All brain imaging data are maintained on a secure server, stored under lock at the NMH hospital server banks. Access to these data are password protected, and all brain scan data are anonymized and coded prior to being available on the server. Only NUCATS will maintain the lock for the specific subject-to-data correspondence, and this information is not anticipated to be used, except in some unusual emergency situation (such an event has not arisen in the past >15 years).

17. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OR PARTICIPANTS

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, as drafted by the US National Commission for the Protection of Human Participants of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

In order to monitor the progress of the study and to provide quality control, a number of reports will be regularly generated throughout the course of the study. The clinical investigator will have a weekly meeting with all study staff to review the status of the study and address issues that have arisen during the week. At this meeting, a recruitment and retention report will be presented and discussed. Dates of important summary reports (e.g., annual IND report, report to clinical committee, IRB annual renewal, etc.) will be highlighted. In general, a draft of any report to be circulated outside the study team will be prepared at least one week prior to the deadline for the report needing to be sent in order to provide adequate time for review and discussion. It is anticipated that there will be a data review regarding safety done semi-annually or more often as requested by the study oversight committee. Outcome data will not be reviewed until after database lock, though the integrity and completeness of data will beassessed on a semi-annually basis as part of quality assurance activities. The database will not be locked until all data fields have been checked and any remaining discrepancies dealt with. Once the database has been locked, no further changes will be made and the randomization code can be provided to the study statistician.

17.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies, as well as those who will enroll in future studiesusing similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study compound/drug, willbe monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study compound/drug for the changesobserved; or
- death.

The reporting of adverse events, serious adverse events and unanticipated problems will be done according to the guidelines of the Northwestern University IRB and the FDA*. As of August 20, 2007, Northwestern University IRB requires filing of internal or external adverse events reports, or safety reports only if they have been determined by the Principal Investigator to contain a report of unanticipated problems involving risks to subjects or others. NU considers unanticipated problems, in general, to include any adverse event, incident, experience, or outcome that meets all of the following criteria: (1) Unexpected (in terms of nature, severity, or frequency) given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol andinformed consent document; and (b) the characteristics of the subject population being studied. 1. Theknown or foreseeable risk of adverse events associated with the procedures involved in the research that are described in: a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document;
and b) other relevant sources of information, such as product labeling and package inserts; or 2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
(2) Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and (3) Suggests that the research placessubjects or others at a different or greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

NOTE: The following events are considered a serious adverse event and would place subjects at agreater risk of harm:

- *results in death;*
- *is life-threatening (places the subject at immediate risk of death from the event as it occurred);*
- *results in inpatient hospitalization or prolongation of existing hospitalization;*
- *results in a persistent or significant disability/incapacity;*
- *results in a congenital anomaly/birth defect; or*
- *based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).*

Unanticipated problems involving risks to subjects or others should be reported to the IRB within 10 working days (unanticipated deaths of subjects enrolled at NU or Affiliates need to be reported within24 hours).

All adverse events deemed to be serious, both unexpected and expected, will be reported to themedical monitor.

Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths related to participation in the study will be promptly reported by phone, by e-mail, or by facsimile to the FDA*.

The medical monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the FDA and NIDA. The medical monitor will comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on therelationship to participation in the study. The medical monitor will also indicate whether he/she concurswith the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reportsof events resulting in death will be promptly forwarded to the FDA and NIDA.

A summary table of adverse events collected will be submitted at least annually to the NorthwesternIRB and to NIDA.

17.2 Reporting of SAEs

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported tothe Independent Monitor, IRB, and NIDA in accordance with requirements.

- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor, IRB, NIDA, and other oversight organizations in accordance with their requirements.
- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NIDA Program Officer within 7 days.

17.3 Unblinding Procedures

Unblinding the study therapy may be necessary to ensure a subject's safety. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner(e.g., notification of IRB within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.). Otherwise, unblinding will not be done until each phase of the study is complete (thatis, when Aim 1 is finished running all enrolled participants, we can unblind the data).

17.4 Stopping Rules/Intervention Discontinuation

This study will be stopped prior to completion if there is difficulty in study recruitment or retention thatwill significantly impact the ability to evaluate the study endpoints; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that might warrant stopping the trial.

18. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Please see section below regarding privacy.

19. COMPENSATION FOR RESEARCH-RELATED INJURY

If a subject is injured as a result of this study (medications, or procedures), they should seek medical treatment through their primary care physician or treatment center of choice. They willbe instructed during the consent process to promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a badoutcome resulting from participation in this research study.

The coverage for such injury or illness is only available if the Northwestern University principal investigator and study sponsor, if applicable, have decided that the injury/illness is directly related tothe study drug, device, or procedures and is not the result of a pre-existing condition or the normal progression of the subject's disease, or because they have not followed the directions of the study doctor. If their insurance is billed, they may be required to pay deductibles and co-payments that apply. They should check with their insurance company about any such payments.

20. ECONOMIC BURDEN TO PARTICIPANTS

There will be no cost to subjects due to their participation in this study.

21. CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual agreeing to participate in thestudy and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject.
Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participantswill be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study.A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the participant folder.

22. PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

We are committed to respect participant privacy and to keep personal information confidential. When choosing to take part in this study, participants are giving us the permission to use their PHIthat includes health information in their medical records and information that can identify them. Forexample, PHI may include name, address, phone number or social security number. Health information that we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history including back pain history and family history of back pain
- Lab tests, or certain health information indicating or relating to a particular condition as well as information collected by cellphone apps and PROs
- Records about study medication or drugs
- Records about MRI scans
- Substance abuse information: current recreational drug use or history of alcohol or drugabuse

The following groups of people may give the researchers information about research participants: All current and previous health care providers, including but not limited to the NMFF, NMPG,

NMH. Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of NU and its clinical partners (or affiliates) will not contain subject's name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the PI's office]

- Authorized members of the NU workforce, who may need to see information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),
- Clinical affiliates, including but not limited the NMFF, NMH, and NMPG. Individuals' participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials and by other healthcare providers having access to this database.
- Other University research centers and University contractors who are also working on thestudy,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the FDA and theDHHS.

The informed consent document will include a HIPAA authorization as well.

The results of this study may also be used for teaching, publications, or presentation at scientific meetings. However, the individual's name and personal information will not be used.

23. NON-ENGLISH SPEAKING PARTICIPANTS

Subjects who are unable to read, and understand English will not be enrolled into this trial.

24. QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

This protocol requires identifying and recruiting approximately 185 individuals with chronic localized pain over an approximately 4 year period, with 160 of these individuals receiving opioid treatment (half with and half without OUD). We have had many years of experience dealing with the pain population, including both individuals being treated with non-opioid medications as well as those using opioids. As noted in the proposal, we have completed large, longitudinal studies in people with CBP and have screened over 500 individuals with CBP over the past 3 years and entered over 200 in various previous studies. Our staff is experienced in out-reach and screening, and we work closely with the NUCATS Institute which provides assistance in recruitment. Dr. Schnitzer has an excellent working relationship with the pain physicians both at Northwestern Medicine and at SRAL, being on the medical staff of both institutions. Both institutions have large pain clinics and medical management of CBP is an integral part of specialized programs at each of these medical centers. The pain specialists at each institution have been supportive and enthusiastic in support of all previous CBP studies and their assistance has been important for our success. In addition, both institutions have large electronic data warehouses which we have used to help facilitate identification of patients with specific diagnoses and concomitant treatment. Use of these resources, again in conjunction with the pain physicians, has been particularly helpful in recruitment. Identifying, screening and enrolling 20- 25 individuals with CBP treated with opioids (half with and half without OUD) at each institution per year will be readily accomplished. Additionally, recruitment will be facilitated by the relatively short duration of this study: 4 weeks for individuals completing only Aim 1 and an additional ~8weeks for individuals continuing on to Aim 2, and the proximity of the imaging and research centers to the clinics themselves.

In preparation for this proposal we have collected actual patient volumes and descriptors for the two major sources of participants. Dr. Calisoff's clinic sees around 100 patients on opioid meds per week, 50% of these are new cases, and 50% have CBP as their main chronic pain complaint. Dr. Rodes sees 30 patients per week on opioid meds, while the NU Pain Clinic overall sees 300 patients per week on opioid meds; again 50% of these suffer from CBP. Overall, both clinics estimate 50% of these patients to be female; 60% Caucasian and 20% Asian. We also have queried the NU EDW regarding patients seen with chronic pain and opioid med use over a 5-year period, using criteria for chronic pain and opioid drugs (ICD 9 = 338.2 AND medications: fentanyl, codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapendatol). The search identifies 5,512 patients; 3359 female and 2153 male; 2341 white and 1278 African American; with mean age of 50-60 years. In addition, to pilot Aim 2 procedures, we asked both NU and AbilityLab clinics for potential CBP+O patients. Within 2 weeks 30 candidates were identified, 6 of whom were willing to participate, and 2 actually performed parts of aim 2 procedures. Overall, we have a large population of patients ready to be recruited into the study.

Given our previous experience conducting several successful longitudinal and cross-sectional imaging studies in large samples of subacute and chronic back pain patients, as well as healthy controls, the recruitment goals outlined above are both feasible and readily achievable. Recruitment will begin immediately after all the regulatory, administrative and organizational matters have been completed (first quarter to second quarter of year 1) and is anticipated to continue through the middle of year 4 (approximately 4 years for enrollment). All participants will have concluded study visits by shortly after the middle of year 4.

Informed consent will be obtained by the project manager or research coordinator. Participants who have been screened previously by their physician will be referred to the study and seen in the research clinic. The research coordinator will discuss the study aims and objectives, the procedures that will need to be

followed, and the risks and potential benefits. A printed consent form will be provided to each subject prior to any procedures being carried out; this will be read by the potential subject and any and all questions answered by the coordinator and/or site investigator. A copy of the signed and witnessed consent will be given to the subject and the original will be placed in the subject's study record (both forms will be dated and time-stamped).

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