Central Nervous System Amplification in Lumbar Failed Back Surgery Syndrome

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Protocol Date: 25AUG2020

NCT Number: NCY03444168

University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

Version date: August 25, 2020

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

Spine pain is the most common reason for which patients visit their doctor. Between 12-15% of the U.S. population seek care each year with associated costs exceeding $200 billion.[1-3] Although the majority of pain patients can be managed with conservative therapy, there are millions of individuals who each year undergo surgery for an existing and refractory chronic pain condition, including surgeries such as lumbar spine surgery or joint arthroplasty.[4-9] One of the most challenging sequelae for these patients is the failure to derive pain relief despite the surgical intervention. Lumbar failed back surgery syndrome (FBSS) is one of the most under-studied post-surgical pain syndromes and embraces a constellation of conditions describing recurrent or persistent low back pain, with or without leg pain, following one or more lumbar spine surgeries.[10]

Research has shown that there may be common phenotypic and genotypic characteristics at the individual level that contribute to poor analgesic outcomes after surgical procedures performed for the relief of pain.[11-14] Individuals who fail to get meaningful relief of pain after surgery have been shown to share commonalities in how their central nervous systems (CNS) process and modulate nociceptive stimuli - known as *CNS pain amplification or centralized pain* - that can predispose them towards developing chronic pain after surgery. To date, there exists not even a single study investigating for the presence of CNS pain amplification in FBSS patients. **Our overall hypothesis** is that although peripheral nociceptive input is important in the initiation and maintenance of pain and symptom expression, patients who do not have a favorable analgesic outcome after lumbar spine surgery (FBSS) likely possess evidence of increased CNS pain amplification that contributes to the persistent expression of pain and co-morbid symptoms**.** *The proposed novel initial studies are <u>foundational</u> and the necessary first steps to proving the presence of CNS pain amplification in this population*, *which will be the key driving force for a new avenue of research into this condition*. The **short-term goals** of this study proposal are to use multiple rigorous research methods to establish that patients who fail to derive pain relief from lumbar spine surgery (FBSS) will exhibit phenotypic and physiologic evidence of CNS amplification and centralized pain. The proposed research will generate the preliminary data to provide the premise for an **R01 application** to advance **our long-term goal** of designing and performing large-scale studies that will move us towards mechanisms-based "personalized analgesia" treatment strategies and risk stratification for lumbar spine surgery patients in an effort to reduce or prevent FBSS.

<u>Aim 1</u>: To demonstrate that common patient characteristics consistent with a centralized pain phenotype are associated with a patient's failure to derive benefit from lumbar spine surgery. In order to accomplish this aim, and to prepare for an independent career in academic pain research, the candidate will acquire formal training in patient-reported outcomes measurement, so as

to accurately "phenotype" lumbar spine surgery patients for relevant trait and state constructs associated with centralized pain. *Hypothesis 1a: Pre-operative patient characteristics associated with a centralized pain phenotype will be associated with and potentially predict a patient's failure to derive benefit from surgery intended to treat chronic pain. Hypothesis 1b: Patients who fail to obtain pain relief from lumbar spine surgery in a longitudinal cohort will appear phenotypically similar to a cross-sectional cohort of established-FBSS patients and those who do obtain pain relief from lumbar spine surgery will appear phenotypically similar (except for back pain) to healthy controls.*

Aim 2: **To confirm that altered pain processing mechanisms consistent with centralized pain are seen in patients who have failed to respond to lumbar spine surgery.** In order to accomplish this aim, the candidate will learn how to perform and analyze the results of quantitative sensory testing (QST) (detecting pain thresholds, testing the integrity of descending analgesic pathways, and temporal summation). *Hypothesis 2a: Pre-operative altered pain processing mechanisms consistent with centralized pain will be associated with and potentially predict a patient's failure to derive benefit from surgery intended to treat chronic pain. Hypothesis 2b: Patients who fail to obtain pain relief from lumbar spine surgery in a longitudinal cohort will have augmented QST changes similar to a cross-sectional cohort of established-FBSS patients and those who do obtain pain relief from lumbar spine surgery will have QST changes similar to healthy controls.*

Aim 3 (Exploratory): **To investigate whether structural, functional, and chemical brain imaging provides evidence of the neurobiological signature for centralized pain in patients who fail to derive benefit from lumbar spine surgery.** To accomplish this aim, a small subset of lumbar spine surgery patients, healthy controls, and established-FBSS patients will undergo structural, functional, and spectroscopy MRI brain imaging, as recent research has shown alterations in all three imaging paradigms can identify stereotypical features of centralized pain. *Exploratory Hypothesis 3: Lumbar spine surgery patients with increased pre-operative levels of centralized pain (measured by the 2011 Fibromyalgia Survey Criteria score) will exhibit increased neuroimaging findings (stronger neuroimaging presence of CNS pain amplification, altered brain structure, and abnormal levels of CNS neurotransmitters) compared to those with lower levels of centralized pain.*

B. Background and Significance

Research has shown that there may be common phenotypic and genotypic characteristics at the individual level that contribute to poor analgesic outcomes after surgical procedures performed for the relief of pain.[11-14] Individuals who fail to get meaningful relief of pain after surgery have been shown to share commonalities in how their central nervous systems (CNS) process and modulate nociceptive stimuli - known as *CNS pain amplification or centralized pain* - that can predispose them towards developing chronic pain after surgery. To date, there exists not even a single study investigating for the presence of CNS pain amplification in FBSS patients. **Our overall hypothesis** is that although peripheral nociceptive input is important in the initiation and maintenance of pain and symptom expression, patients who do not have a favorable analgesic outcome after lumbar spine surgery (FBSS) likely possess evidence of increased CNS pain amplification that contributes to the persistent expression of pain and co-morbid symptoms**.** *The proposed novel initial studies are foundational and the necessary first steps to proving the presence of CNS pain amplification in this population*, *which will be the key driving force for a new avenue of research into this condition*. The **short-term goals** of this K23 proposal are to use multiple rigorous research methods to establish that patients who fail to derive pain relief from lumbar spine surgery (FBSS) will exhibit phenotypic and physiologic evidence of CNS amplification and centralized pain. The proposed research will generate the preliminary data to provide the premise for an **R01 application** to advance **our long-term goal** of designing and performing

large-scale studies that will move us towards mechanisms-based "personalized analgesia" treatment strategies and risk stratification for lumbar spine surgery patients in an effort to reduce or prevent FBSS.

The number of spine surgeries performed in the United States has steadily increased in the past several decades.[15,16] Between 1990 and 2000, there was a 220% increase in the number of spinal fusion surgeries[16] and in 2002, there were more than 1 million spinal procedures performed in the United States.[17-19] In 2004 alone, spinal fusion surgery alone generated costs exceeding $16 billion in hospital charges.[20] Despite the staggering numbers of patients having spine surgery, the incidence of patients that will fail to achieve adequate pain relief after lumbar spinal surgery (failed back surgery syndrome (FBSS)) is commonly quoted in the range of 10%-40%.[10,21-23] Treatment guidelines are scant for FBSS, in large part due to the complexity and heterogeneity of the entity, with a vast array of differing underlying etiologies.[24] A practical understanding of the etiology of FBSS can be categorized into preoperative, intraoperative, and postoperative factors. Intraoperative surgical factors include poor technique, wrong-level surgery, and inability to achieve the proposed aim of the surgery. Post-operative factors for FBSS include: progressive disease (e.g., new disc herniation or spondylolisthesis), epidural fibrosis, and surgical complications including nerve injury, hematoma, or infection. Although anatomic factors may play a role in failure to derive analgesic benefit after lumbar spine surgery, psychosocial risk factors have been found to be much more powerful in predicting low back pain disability than structural abnormalities.[25] Psychological factors that have been shown to correlate with poor analgesic outcomes (FBSS) after spine surgery include significant levels of anxiety and depression, poor coping, and somatization.[26-29] Social factors that have been associated with FBSS include the presence of a personal injury claim or worker's compensation claim.[26,30-33] *While some of these studies used a prospective design and adequate sample sizes, many of them were retrospective in nature - making temporal relationships difficult to infer, and there was great variety in the selection of patient-reported outcomes and questionnaires to draw their associations.*

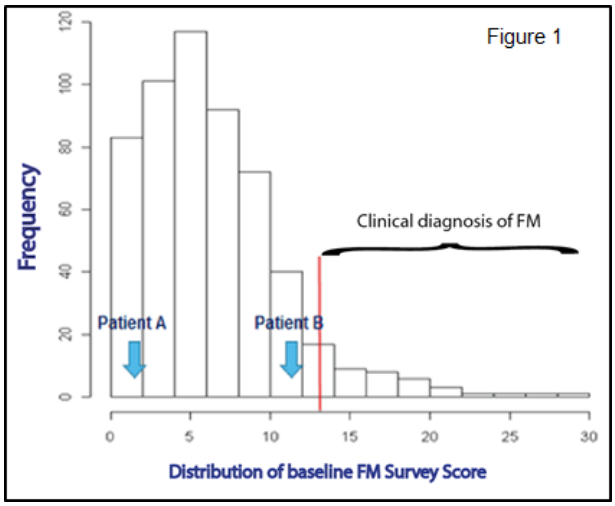
There is a growing appreciation of the importance of augmented central nervous system (CNS) pain processing and centralized pain in many chronic pain states.[34,35] ***The term "centralized pain" has been used to describe any CNS dysfunction or pathology that may be contributing to the development or maintenance of chronic pain***.[35-37] The pain experienced by individuals with centralized pain is typically multifocal (with a high current and lifetime history of pain in many bodily regions), rated as more severe, and characterized by neuropathic pain descriptors. Beyond pain, co-existing somatic symptoms including memory difficulties, fatigue, and sleep disturbances as well as cognitive/affective symptoms (e.g., catastrophizing, anxiety, depression) are frequently observed.[36,38,39] Another hallmark of the centralized pain phenotype is the frequent presence of hyperalgesia and/or reduced or absent endogenous analgesia.[40-42] Data from quantitative sensory testing (QST) studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population. Most, but not all, individuals with centralized pain fall on the right side of this curve and have QST findings consistent with notable hypersensitivity (hyperalgesia and allodynia).[36,43-49] Some of the chronic pain conditions where QST evidence of widespread hypersensitivity is consistently seen include fibromyalgia (FM), irritable bowel syndrome, tension headache, low back pain, temporomandibular joint disorder, interstitial cystitis, and vulvodynia.[50-60]

The prominent role of central factors in chronic pain is substantiated by the fact that there is no chronic pain condition in which the extent of tissue damage or inflammation alone (e.g., as evaluated by an X-ray or MRI) accurately predicts the presence or severity of pain.[61-65] Many people have "normal" radiographs or MRIs yet report unbearable pain, while others have significant radiographic or MRI findings yet report no pain. It has been theorized that this discrepancy exists because individuals with chronic pain display variable degrees of CNS pain amplification and the current 2011 Fibromyalgia

(FM) Survey[66] is hypothesized to be a surrogate measure of the degree of centralized pain. Wolfe coined the term "fibromyalgia-ness" (FMness) to describe the phenomenon that where an individual lies on this FM continuum markedly influences how much pain they will experience in response to peripheral nociceptive damage or an inflammatory process.[67] Recent well-powered, prospective studies (described in detail below) have shown that increasing FMness strongly predicts poor analgesic outcomes *and* decreased responsiveness to opioids after surgery meant to improve pain.[11,12,14]

Although there are no definitive laboratory tests or single biomarker of pain centralization, multiple constructs can be used to infer its presence. *Neuroimaging has been shown to corroborate QST findings of diffuse hyperalgesia and altered endogenous pain modulation in centralized pain states*.[35,54,68-70] Recent neuroimaging studies provide additional insight into the underlying CNS changes in centralized pain, and demonstrate notable structural, chemical, and functional changes in pain-related brain areas. Structural alterations in gray matter are seen in pain processing regions such as the thalamus, insula, cingulate, and somatosensory cortices.[71] Neurochemical changes include increased levels of excitatory neurotransmitters (e.g., glutamate) and decreased levels of inhibitory neurotransmitters (e.g., γ-aminobutyric acid (GABA)).[72] Finally, increased resting brain network connectivity to pro-nociceptive brain areas and reduced connectivity to anti-nociceptive brain areas are also commonly present.[73-76] *Together, these QST and neuroimaging findings are believed to represent the neurobiologic signature for centralized pain*.

Surgical procedures and peripherally-directed interventions are postulated to be less effective for individuals with centralized pain as they may fail to address the underlying CNS amplification.[77-80] The specific associations of centralized pain with poor post-operative analgesic outcomes have been reported by mentors on this application, Drs. Clauw and Brummett. In 2015, Brummett et al reported that a higher 2011 FM Survey Criteria score (a robust index of centralized pain) independently predicted less improvement of pain after knee and hip arthroplasty and for every one-point increase in FM survey criteria score, there was a 17.8% increase in the odds of failure to meet a 50% improvement in pain.[12] Figure 1 depicts the distribution of FM scores in this cohort and also shows two hypothetical patients with osteoarthritis. Although neither patient would meet criteria for being termed "FM-positive" (the red line indicates the cut point for the categorical diagnosis of FM), *Patient B (FM score = 11) would need an adjusted 80mg greater oral morphine equivalents during the post-operative hospital stay and would be 5 times less likely to have a meaningful improvement following knee arthroplasty when compared to Patient A (FM score = 2).* **This magnitude of differential outcome is extremely meaningful clinically and whether or not this same relationship exists between FMness and FBSS has never been investigated.** Furthermore, by using robust and validated standardized research paradigms, similar findings have been replicated in other post-surgical populations – including hysterectomy and shoulder surgery.[13,14]



Preliminary Data: In an IRB approved pilot study, Dr. Nicol administered the 2011 FM Survey to a total of 98 patients at the KUMC Marc A. Asher, MD Comprehensive Spine Center presenting with a chief complaint of chronic low back pain. Enrollment of this sample size only took 2 months, highlighting the large volume of chronic pain patients available for screening and possible enrollment into the proposed studies. In this cohort, 36% of patients (n=35) had a history of persistent pain after lumbar spine surgery (FBSS). The mean FM score for the FBSS group was 13.7 and the proportion of

FBSS patients who met criteria for being FM-positive was 60% (n=21). These findings are similar to published data by Drs. Brummett and Clauw where 42% of spine pain patients seen at the University of Michigan's pain clinic met criteria for being FM-positive.[81] Furthermore, the 2011 FM Survey Criteria score has been shown to be predictive of poor outcomes at values well below the threshold used to diagnose FM.[11-14] Thus, although a majority of this small KUMC sample did not meet criteria for FM-positive and the mean FM score was below the threshold for FM-positive, this likely suggests the presence of "central pain amplification" and justifies the proposed studies on a larger-scale and in a longitudinal fashion. ***These aforementioned studies provide the premise of the research described in this application, which seeks to utilize robust and replicable research paradigms to perform novel and foundational investigations on the influence of CNS pain amplification and the centralized pain phenotype in the failure to derive analgesic benefit from lumbar spine surgery.***

C. Rationale

As previously discussed, FBSS is a woefully understudied post-surgical pain syndrome. Although a handful of researchers have implicated certain psychological and surgical risk factors with FBSS, there are ***no*** studies that have investigated the presence of phenotypic and physiologic characteristics associated with CNS pain amplification/centralized pain in this specific chronic post-surgical population. *The proposed study will perform the necessary novel and foundational investigations to determine whether phenotypic, physiologic, and brain neuroimaging characteristics known to be present in centralized pain states and indicative of CNS pain amplification are associated with failure to derive analgesic benefit from lumbar spine surgery.* **Demonstrating that a centralized pain phenotype is associated with FBSS would represent a novel and meaningful advance in the understanding of the condition.** Furthermore, it could lead to the ability to predict patients at high risk for FBSS, thereby allowing for further research on mechanisms-based pre-operative or peri-operative interventions, better informed consent for the risk of FBSS for elective procedures, and cost-effective and efficient clinical trials targeting prevention. Currently, the treatment of FBSS and other post-surgical pain syndromes can be frustrating for patients and physicians alike, rarely resulting in full resolution of the pain syndrome. An improved understanding of the patient characteristics associated with high-risk patients will be a key step towards prevention and/or peri-operative treatment strategies to fully optimize the likelihood of a positive outcome.

II. Research Plan and Design

A. Study Objectives:

Spine pain is the most common reason for which patients visit their doctor. Between 12-15% of the U.S. population seek care each year with associated costs exceeding $200 billion.[1-3] Although the majority of pain patients can be managed with conservative therapy, there are millions of individuals who each year undergo surgery for an existing and refractory chronic pain condition, including surgeries such as lumbar spine surgery or joint arthroplasty.[4-9] One of the most challenging sequelae for these patients is the failure to derive pain relief despite the surgical intervention. Lumbar failed back surgery syndrome (FBSS) is one of the most under-studied post-surgical pain syndromes and embraces a constellation of conditions describing recurrent or persistent low back pain, with or without leg pain, following one or more lumbar spine surgeries.[10] Research has shown that there may be common phenotypic and genotypic characteristics at the individual level that contribute to poor analgesic outcomes after surgical procedures performed for the relief of pain.[11-14] Individuals who fail to get meaningful relief of pain after surgery have been shown to share commonalities in how their central nervous systems (CNS) process and modulate nociceptive stimuli - known as *CNS pain amplification or*

centralized pain - that can predispose them towards developing chronic pain after surgery. To date, there exists not even a single study investigating for the presence of CNS pain amplification in FBSS patients. Our overall hypothesis is that although peripheral nociceptive input is important in the initiation and maintenance of pain and symptom expression, patients who do not have a favorable analgesic outcome after lumbar spine surgery (FBSS) likely possess evidence of increased CNS pain amplification that contributes to the persistent expression of pain and co-morbid symptoms. *The proposed novel initial studies are foundational and the necessary first steps to proving the presence of CNS pain amplification in this population*, *which will be the key driving force for a new avenue of research into this condition*. The short-term goals of this study are to use multiple rigorous research methods to establish that patients who fail to derive pain relief from lumbar spine surgery (FBSS) will exhibit phenotypic and physiologic evidence of CNS amplification and centralized pain. The proposed research will generate the preliminary data to provide the premise for an R01 application to advance our long-term goal of designing and performing large-scale studies that will move us towards mechanisms-based "personalized analgesia" treatment strategies and risk stratification for lumbar spine surgery patients in an effort to reduce or prevent FBSS.

Aim 1: To demonstrate that common patient characteristics consistent with a centralized pain phenotype are associated with a patient's failure to derive benefit from lumbar spine surgery. In order to accomplish this aim, and to prepare for an independent career in academic pain research, the candidate will acquire formal training in patient-reported outcomes measurement, so as to accurately "phenotype" lumbar spine surgery patients for relevant trait and state constructs associated with centralized pain.

Aim 2: To confirm that altered pain processing mechanisms consistent with centralized pain are seen in patients who have failed to respond to lumbar spine surgery. In order to accomplish this aim, the candidate will learn how to perform and analyze the results of quantitative sensory testing (QST) (detecting pain thresholds, testing the integrity of descending analgesic pathways, and temporal summation).

Aim 3 (Exploratory): To investigate whether structural, functional, and chemical brain imaging provides evidence of the neurobiological signature for centralized pain in patients who fail to derive benefit from lumbar spine surgery. To accomplish this aim, a small subset of lumbar spine surgery patients, healthy controls, and established-FBSS patients will undergo structural, functional, and spectroscopy MRI brain imaging, as recent research has shown alterations in all three imaging paradigms can identify stereotypical features of centralized pain.

B. Study Type and Design:

Pain perception is a complex process composed of both physical and psychosocial components. Physicians from different training backgrounds often approach and view pain in varying ways. One of the major strengths of this proposal is the *diversity in the backgrounds of the research and mentor team, including anesthesiology/pain management, internal medicine and rheumatology, brain imaging, and neurosurgery*. Drs. Clauw and Brummett along with and other researchers at the University of Michigan are internationally recognized for their leadership in the development and refinement of research methods designed to "phenotype" individuals with chronic pain.[53,60,82-116] Their highly rigorous and reproducible methods were originally developed and applied in the context of gaining a better

understanding of FM, but they have also used them to help identify CNS pain amplification in other chronic pain conditions.[36,53,54,57,97,100,101,104,105,108,112,113,117-130]

Overall Study Design. For Aims 1 and 2, a prospective, observational study will recruit 100 men and women with chronic low back pain (+/- leg pain) who are scheduled to undergo lumbar spine surgery the University of Kansas Medical Center (KUMC). 50 will participate in phenotypic characterization and 50 will participant in phenotypic characterization and quantitative sensory testing (QST) procedures. After screening, informed consent, and enrollment into the study, all subjects will undergo an evaluation which includes a comprehensive battery of questionnaires for patient phenotyping that will assess symptoms including pain, physical function, depression, anxiety, and catastrophizing symptoms. QST parameters will only be performed on half of the cohort of lumbar spine surgery patients. Patient phenotyping and QST procedures will take place in one visit pre-operatively. At two weeks, one month, three months, & six months post-surgery, we will administer one questionnaire to determine analgesic response to surgery. This will establish longitudinally-designated post-surgical analgesic outcome groups (see Statistical Analysis section for definitions). Instead of just a three month time point that is often used in analgesic trials, a six month time point was chosen to give adequate time for recovery and response to surgery. Phenotyping and QST will also be done in a cross-sectional manner on 50 age and sex-matched healthy controls and 50 age and sex-matched patients with an established diagnosis of FBSS (established-FBSS) to compare to the longitudinally-designated post-surgical analgesic outcome groups. For Aim 3, 30 men and women with chronic low back pain (+/- leg pain) who are scheduled to have lumbar spine surgery at KUMC will undergo pre-operative functional, structural, and chemical neuroimaging studies. 15 age and sex-matched healthy controls and 15 age and sex-matched established-FBSS patients will also undergo the same neuroimaging studies to compare to the longitudinally-designated post-surgical analgesic outcome groups. Patients for Aim 3 will be recruited from both the prospective and cross-sectional cohorts enrolled for Aims 1 and 2. The goal of the studies in Aim 3 are to investigate whether pre-operative functional, structural, and chemical neuroimaging findings known to be associated with centralized pain and indicative of CNS amplification are associated with the centralized pain phenotype and possibly predictive of failure to achieve pain relief after lumbar spine surgery. We acknowledge that these studies are exploratory and may be underpowered but feel that they will at a minimum provide critical preliminary data for future studies.

C. Sample size, statistical methods, and power calculation

Aim 1 Analyses: To demonstrate that common patient characteristics consistent with a centralized pain phenotype are associated with a patient's failure to derive benefit from lumbar spine surgery. ***Analysis 1a****:* Analgesic outcomes (AOC) for patients in the prospective cohort will be defined as "AOC-success" or "AOC-failure" for the purposes of further analyses. AOC-success is defined as those who demonstrate a 50% reduction in pain scores from baseline to 6 months, which would be a response more commensurate with the invasiveness of the intervention of spine surgery than a minimal clinically important difference score (MCID). FMness as measured by the 2011 FM Survey Criteria score[66] is the primary measure of interest and will be split by median score (and defined as FM-high and FM-low). Differences in surgical failure proportions (determined by pain score change as described above at 6-months) between the FM-high (n=50) and FM-low (n=50) groups will be tested using a two-sided chi-squared statistic at α=.05. In addition to FMness, differences between AOC-success and AOC-failure groups for each of the constructs contained under the subheading "Comprehensive Phenotyping Battery" will be examined using appropriate parametric or non-parametric analyses. Furthermore, we wish to explore how multiple patient characteristics vary across these cohorts. A stepwise logistic regression model will then be fit to evaluate multivariate relationships. The analyses conducted in this aim will provide the candidate an opportunity to learn multivariate data analysis with advanced regression modeling as well as more familiarity with patient reported outcome measures. ***Analysis 1b****:*

Phenotypic differences between the AOC-failure group and the established-FBSS group will be examined using appropriate parametric or non-parametric tests to see if the longitudinally designated AOC-failure cohort is phenotypically similar in nature to the cross-sectional established-FBSS patients. We hypothesize that AOC-failure patients will appear similar to established-FBSS patients. The same comparisons will be explored for the longitudinally designated AOC-success group compared to the cross-sectional healthy controls group.

Aim 2 Analyses: To confirm that altered pain processing mechanisms consistent with centralized pain are seen in patients who have failed to respond to lumbar spine surgery. Pain thresholds, cuff algometry, CPM, and temporal summation scores will be treated as continuous measures and normality will be assessed prior to analysis. The same analyses as those conducted for Aim 1 will be used for this aim.

Aim 3 Analyses: To investigate whether structural, functional, and chemical brain imaging provides evidence of the neurobiological signature for centralized pain in patients who fail to derive benefit from lumbar spine surgery. AFNI, BrainVoyager, LCModel, FSL, MatLab, SPM, and Freesurfer will be used for functional MRI, structural MRI, and spectroscopy MR analyses based on the analytical methods previously described by Dr. Clauw and his research colleagues.[54,58,74,76,122,131-141] ***Analysis 3a****:* Pre-operative neuroimaging data for lumbar spine surgery patients will be split based on median baseline 2011 FM Survey Criteria score into two groups (FM-high and FM-low). Neuroimaging findings between these two groups will be compared and we hypothesize that lumbar spine surgery patients with higher preoperative 2011 FM Survey Criteria scores will have (1) *more hyperalgesia and decreased pain inhibition on QST and functional magnetic resonance imaging (fMRI), (2) characteristic functional connectivity changes on fMRI (e.g., decreased functional connectivity to descending anti-nociceptive analgesic brain networks and increased connectivity to pro-nociceptive regions), (3) increased CNS levels of glutamate in pro-nociceptive regions on proton spectroscopy, and (4) increases in S1/M1 gray matter volume.* ***Analysis 3b***: We will perform whole brain analyses as per analysis 3a for all modalities with no *a priori* hypotheses to investigate the relationships between baseline imaging findings and post-surgical analgesic outcome status (AOC-success and AOC-failure) at six months.

Sample size for Study Procedures in Aims 1 and 2: We anticipate screening approximately 60 pre-operative lumbar spine surgery patients per year for possible enrollment into the study. Assuming a 50-60% recruitment rate, we estimate approximately 30-35 lumbar spine surgery patients enrolled per year during Years 1-4 of the award. This leads to an estimated total sample size of 100 lumbar spine surgery patients. We will also aim to recruit and enroll equal distributions of established-FBSS patients (n=50) and healthy controls (n=50). For the assumed effect size (population of 0.10 vs 0.50) and sample sizes (50 and 50 based on 2011 FM Survey Criteria score median split) and α=.05 (two-sided) the power is 0.99. Several different assumptions were also explored. For example, if the assumed effect size is (population of 0.15 vs 0.45) or (population of 0.17 vs 0.43), then the respective power calculations are 92% and 82%, both which are adequate for significance purposes (e.g., >80%). The larger sample size will also be important for exploring multivariate models and potential subgroup analyses. The inclusion of healthy controls and established-FBSS patients will ensure adequate matching of gender and age to the patient cohorts for analyses.

Sample size for Study Procedures in Aim 3: We aim to recruit 30 lumbar spine surgery patients, 15 healthy controls, and 15 established-FBSS patients out of the total cohort to participate in the

neuroimaging study procedures. As this study is powered for the primary hypothesis in Aim 1, issues of power are of less concern for these investigatory neuroimaging studies.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

Participants will be recruited directly by the Candidate and by referral from specialist physicians at the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center. The KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center boasts numerous faculty in various specialties such as Neurology, Anesthesiology/Pain Medicine, and Physical Medicine & Rehabilitation who can refer patients for screening into the proposed study. The Frontiers Registry and the Pioneers Community Research Recruitment services through the Frontiers: The Heartland Institute for Clinical and Translational Research will also be used to foster the recruitment of participants from the community. Both males and females will be included, and because of the potential for sex differences in pain processing, we will take care to ensure that our overall participation rate will contain relatively equal numbers of males and females in each cohort. Children under the age of 18 will be excluded from participating in this study. The rationale for this exclusion is primarily based on the fact that children in this age group rarely suffer from chronic low back pain requiring surgery or lumbar failed back surgery syndrome. In the rare cases where these surgical procedures are performed on children, the pathology is likely to be different than in adults (typically related to congenital scoliosis or other congenital spinal condition). Also, many of the measures proposed for this study are not validated in children under 18. We also will exclude individuals between the ages of 18-21 as the psychosocial circumstances of individuals under 22 are quite different from those 22 and above (i.e., educational, financial) and thus could affect study findings. Given that our study cohorts will only include patients age 22 years and older, we will not recruit any children (less than 18 years and adults between 18-21years) as healthy controls or established-FBSS patients. No ethnic or racial groups are excluded from this protocol, nor will it involve populations that are susceptible to coercion; all subjects should be able to provide their own consent.

1. Inclusion and Exclusion Criteria for All Participants

Eligibility Criteria (All Self-Reported)

Inclusion (ALL)	**Exclusion (ALL)**
• Able to Read and Speak English • Between 22-70 years old • Stable dose (or not on) of adjunctive pain medications for at least 2 weeks prior to QST • Able to provide informed consent	• Diagnosis of a medical condition that isn't minor or stable • Current litigation regarding a medical illness • Drug or alcohol abuse • Severe physical impairment • Co-morbid medical conditions that may impair physical functional status • Psychiatric condition that may impair functional status (active psychosis or suicidal ideation) • Pregnant or nursing • Liver failure, cirrhosis, hepatitis • Severe cardiovascular disease
Inclusion (ALL) QST • Right-Handed • Willingness to refrain from alcohol and nicotine on the day of QST • Willingness to refrain from pain meds 12 hours prior to QST	**Exclusion (ALL) QST** • Current or recent (6 months) use of artificial fingernails or nail enhancements • Neuropathy or loss of feeling in upper or lower extremities

• Willingness to refrain from strenuous exercise that would cause muscle or joint soreness 48 hours prior to QST	
Inclusion (Healthy) In addition to (ALL) above: n/a	**Exclusion (Healthy)** In addition to (ALL) above: • Diagnosis of a chronic pain syndrome (mild is fine; but less than 3/10 pain score on any body region) • Score >3 on FM 2011 survey
Inclusion (FBSS) In addition to (ALL) above: • Has chronic low back pain (+/- leg pain) for > 6 months after a lumbar spine surgery • Low back pain severity greater than or equal to 4/10	**Exclusion (FBSS)** In addition to (ALL) above: • Involved in litigation for low back pain or previous low back surgery
Inclusion (LSS) In addition to (ALL) above: • Low back pain severity greater than or equal to 4/10 • Willingness to participate in longitudinal follow-up questionnaires post-op	**Exclusion (LSS)** In addition to (ALL) above: • Involved in litigation for low back pain or previous low back surgery • History of a previous back surgery • LSS is due to spinal cancer-related diagnoses • LSS is urgent or emergent

Eligibility (MRI): In addition to eligibility within each group

Inclusion: • Able to lie still in an MRI scan for up to 2 hours • Normal vision acuity or corrected vision • No contradictions to MRI screening form	**Exclusion:** • Severe Claustrophobia • BMI > 40 or unable to lie comfortably in the MRI • Implantable Device (Cardiac pacemaker/defibrillator), Gastric Pacemaker, Neurostimulation Device, Bladder Stimulator, Cochlear Implant) • Heart Heart Valve Replacement • Hearing Aid, Lyric Device • Hydrocephalus/Spinal Shunt • Aneurysm/Vascular Clips • Stents, Filters, or Coils • Seizure History • Bullet, BB, or Foreign Body • Eyelid Spring/Wire • History of Metal in Eyes • Medication/Insulin Pump • Prosthetic Device • Body Piercings (permanent) • Medication Skin Patch

	• Dentures/Partials • Kidney Disease • Kidney/Liver Transplant • Liver Cirrhosis / Cancer • Permanent Eyeliner • Vascular IV Access ○ FEMALE PATIENTS: • I.U.D. Device

Medical conditions that are not minor or stable examples: uncontrolled hypertension/diabetes

Severe physical impairment examples: Blindness, deafness, paraplegia

Co-morbid medical conditions example: autoimmune disorders, history of non-skin malignancy

Severe cardiovascular disease: history of a heart attack, severe coronary artery disease, unstable angina, congestive heart failure, severe valvular abnormalities

Psychiatric conditions: Stable anxiety and depression are NOT considered exclusions

2. **Withdrawal/Termination criteria:** If during the study, the patient develops or shows any of the exclusion criteria for their cohort, they will be withdrawn by the investigator. They may voluntarily withdraw at any time.
3. Patients may participate in another research study while enrolled in this study.

E. Specific methods and techniques used throughout the study
Study Procedures:

Comprehensive Patient Phenotyping: This battery of questionnaires is intended to understand key aspects of pain, mood, and function as quickly and efficiently as possible. The focus of these measures are on obtaining an accurate assessment of pain, while also asking about physical function, anxiety, depression, and other associated somatic disturbances. Dr. Clauw and other CPFRC researchers have been instrumental in developing this protocol of questionnaires. On average, the battery of questionnaires used for phenotyping take anywhere from 10 minutes to 60 minutes to complete depending on study visit.

- *Demographics*: Sex, age, race/ethnicity, marital status, education level, family history of pain, and body mass index (BMI) will be assessed in the context of standardized case report forms. Sex is an important biologic variable to investigate as centralized pain is more common in females, and is probably largely responsible for the fact that nearly any chronic pain condition is 1.5 – 2 times more common in women than in men.[142]
- *Fibromyalgia-ness (FMness)*: FMness is a measure of pain and co-morbid symptom extensiveness and severity. It is calculated by combining the scores from the Widespread Pain Index with the Symptom Severity Scale from the 2011 FM Survey[66] to derive a continuous metric purportedly indicative of the degree of CNS pain amplification present in a given individual.[67]
- *Early Life Trauma History.* Trauma history will be assessed using The Childhood Traumatic Events Scale (CTES).[143] This scale assesses not only for physical and sexual abuse but also other

forms of early trauma such as a prolonged childhood illness, neglect, or death of a parent. Early life trauma is hypothesized to be associated with the top-down variant of centralization.

- *Clinical Pain:* Pain severity (worst, least, average, and current)due to pain will be assessed using the *Brief Pain Inventory (BPI)*. The *BPI* is validated for chronic, non-malignant forms of pain, and asks patients to rate their current pain intensity, as well as their worst, least and average pain in the 7 days (0-10 NRS) and has been recommended by IMMPACT as a measure of choice for the assessment of pain in clinical research.[144-146]
- *Neuropathic Pain Descriptors:* The *PainDETECT* is a 9-item measure of sensory descriptors and spatial and temporal characteristics that has demonstrated utility in identifying central neuropathic pain.[147]
- *History of Co-occurring Somatic Symptoms.* The Complex Medical Symptoms Inventory (CMSI) is a 41-item symptom checklist of past year and lifetime symptoms associated with FSS.[110,148-151] This measure provides a standardized method of counting symptoms as well as counting FSS given the published diagnostic criteria for a variety of FSS are included within the instrument. This measure is currently the instrument of choice for assessing the newly designated grouping of chronic overlapping pain conditions (COPC's) by the NIH Pain Consortium. In addition to facilitating counting number of FSS, it also contains items related to hypersensitivity to light, sound, odors, tenderness and chemicals.
- *Psychiatric History, Status, and Affective Style: We will use the PROMIS Depression (8-item) and PROMIS Anxiety (8-items) short forms to assess emotional status.[152] Affect style will be assessed using the Positive and Negative Affect Schedule (PANAS-SF) short form.[153] The PANAS-SF is a 20-item measure of both positive and negative affect and can be scored to include a metric of affect balance (e.g., greater negativity over positivity).*The well-validated *Hospital Anxiety and Depression Scale (HADS)* will be used to assess symptoms of both depression and anxiety.[154]
- *Physical Function/Disability specific to Low Back Pain:* The Oswestry Disability Questionnaire (ODI) consists of 10 items that query pain intensity and areas of disability (e.g. personal care, walking, sitting).[155,156]
- *Cognitive Dysfunction, Stress, and Catastrophizing:* Two traits associated with worse pain and the progression of chronic pain will be assessed using the 10-item Perceived Stress Scale (PSS)[157] and the 6-item catastrophizing scale from the Coping Strategies Questionnaire(CSQ-CAT).[158] Based upon IRT and PROMIS item banks for cognition, the Multidimensional Inventory of Subjective Cognitive Impairment (MISCI)[159] was developed. The MISCI is a brief 10-item inventory that will assess five domains of cognitive problems: mental clarity, memory, language, executive functioning, and attention/concentration. Similarly, emotional resilience will be evaluated with the Conner-Davidson Resilience Short-Form (10-item).[160]
- *Functional status, sleep, fatigue, and social functioning*: To avoid patient burden with the multiple domains, this study will take advantage of the static short forms developed by the NIH roadmap initiative PROMIS. The following PROMIS short-forms will be used in this study: PROMIS-Fatigue Battery (6-items), PROMIS-Sleep Related Impairment (8-items), PROMIS Emotional Support (4-item), PROMIS Social Participation (4-item), PROMIS physical functioning short form (8-items), and PROMIS Pain Interference (www.NIHPROMIS.org).[152] They will also complete a one-item measure of Life Satisfaction, as well as the SOAPP screener for potential opioid abuse[161].
- *Patient Global Impression of Change (PGIC)*: A single question asks patients "After my treatment, my pain is:" with a 7-point scale ranging from -3 (very much worse) to 0 (no different) to +3 (very much improved). [162] This measure will be a secondary determinant of

analgesic response to surgery and will only be administered at 3 months and 6 months postoperatively.

Follow Up. With the exception of the diagnostic and early life traumatic events measures, most or all measures will be repeated at 2-weeks, 1 month, 3 months and 6 months (for the prospective cohort of patients undergoing lumbar spine surgery). Healthy controls and established-FBSS patients will only perform the full phenotyping battery of questionnaires once. In addition, we will assess the PGIC as is recommended by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) group at 3 and 6 months and will not be given to the healthy control or established-FBSS groups.[163,164] Additionally, LSS patients will be sent a new survey for 10 days prior to surgery, 14 days after surgery, and 10 days 6 months after surgery, we will administer a pain "diary" that will consist of 1-4 questions asking about the participant's daily pain.

Quantitative Sensory Testing (QST): Pain testing for a variety of parameters will be performed using various pain testing devices as described below. QST requires significant training of personnel, manuals of operations and procedures, scripting, and other techniques to get good reproducible results. Participants will be familiarized with the procedures and equipment before testing. Half of the patients (n=50) patients undergoing lumbar spine surgery will complete this testing pre-operatively. Healthy controls and patients with established FBSS will only perform this testing once. Patients who participate in Aim 3 studies will also have a portion of the QST listed below as part of their MRI experimental protocol (see below).

- *Generalized Pressure Pain Sensitivity.* Pressure pain threshold (PPT) at the mid-trapezius (an unaffected site in all cohorts) will serve as the primary measure of generalized pain sensitivity in all participants (*trap-PPT*). Increased pain sensitivity at remote or unaffected body areas is stronly suggestive of central pain mechanisms and occurs in many chronic pain conditions. Here, PPT will be measured bilaterally using a digital algometer with a 1-cm^2 rubber probe (Somedic, Hörby, Sweden). Pressure will be manually increased at a rate of 30-50 kPA/s (1000 kPa max). Participants will press a response button to indicate their first sensation of pain. Pressure intensity at the time of button press is recorded as the PPT. Measurements will be conducted 3x/side (20-s intervals) with means used for analysis. Pressure-evoked pain at the thumbnail will serve as a secondary measure of generalized pain sensitivity, using the Multimodal Automated Sensory Testing (MAST) System, a computerized QST device developed at the University of Michigan, and currently being employed in several clinical trials, including the NIH MAPP network.

  My mentors have extensive experience using thumbnail pressure as an evoked pain stimulus. The MAST system will deliver an ascending series of 5-s duration stimuli at 25-s intervals, beginning at 0.50 kg/cm^2 and increasing in 0.50 kg/cm^2 intervals up to tolerance or a maximum of 10 kg/cm^2. Pain intensity will be rated after each stimulus on a 0 (no pain) – 100 (extreme pain) numerical rating scale (NRS). Pressure pain threshold and tolerance will be determined from this procedure, as well as the PAIN50, the pressure intensity that provokes a response halfway between threshold and tolerance.
- *Localized Pressure Pain Sensitivity.* Localized or regional pain sensitivity, measured as a PPT (see above for method), will be determined for the lumbar spine in all cohorts as an indicator of peripheral sensitization. The lumbar spine will be stimulated over the bilateral lumbar spine areas at approximately L4-5.
- *Cuff Algometry.* Large volume, deep muscle sensitivity[165,166] will be assessed by pressure cuff using a MRI-compatible rapid cuff inflator (Hokanson, Bellevue, WA).[167-169] Participants will

first receive an ascending series of cuff pressures, starting at 20 mmHg and increasing in 20 mmHg steps (10-s pressures, 20-s intervals) to tolerance or a maximum of 400 mmHg. Each pressure will be rated after deflation on a 0-100 NRS. These pain ratings will be used to interpolate a series of 8 tolerable cuff pressures that will delivered in randomized order and rated individually. Stimulus response curves will be constructed for each participant and used for analysis, along with several derived variables: *cuff-PPT, cuff-Pain50, and cuff-TOL*. In addition, tonic pain induced by continuous cuff pressure will be assessed (*tonic-Cuff)*. Each participant's individually calibrated Pain40 pressure (i.e., pressure that evokes a 40/100 pain rating) will be applied for 6-min to one gastrocnemius muscle. Pain intensity and unpleasantness ratings will be obtained every 60-s. The same P40 pressure will be applied for 6 minutes in the MRI scanner.

- *Conditioned Pain Modulation (CPM).* CPM is a measure of the integrity of descending analgesic pathways. Deficiencies in CPM have been identified in a wide variety of chronic pain states including fibromyalgia.[170-175] CPM assessment requires a painful "conditioning stimulus" to induce descending anti-nociception and alter pain perception, and a painful "test stimulus" to evaluate the anti-nociceptive response to the conditioning stimulus. CPM will be evaluated using two MAST pressure actuators positioned on opposite thumbnails. The test stimulus will be applied for 30-s to the dominant thumbnail at the PAIN50 pressure intensity and rated at 10-, 20-, and 30-s on a NRS. The conditioning stimulus will be applied for 60-s to the non-dominant thumbnail at the PAIN50 pressure intensity. Parallel to the last 30-s of CPM conditioning, the same test stimulus will be reapplied to the dominant thumbnail for 30-s and the patients will be again asked to rate the intensity of the test stimulus three times. *CPM magnitude* will be calculated as the difference (post-pre) in the mean of the three pain ratings given to the test stimulus prior to the conditioning stimuli and the three pain ratings of the test stimulus given during the conditioning stimuli. A reduction in test stimulus rating by conditioning stimulation implies functional (inhibitory) CPM, and the degree of reduction expresses the efficiency of CPM.
- *Temporal Summation (TS).* TS is the perceived increase in pain intensity to repeated stimulation at a constant stimulus intensity and is believed to reflect central sensitization. A 256 mN pinprick stimulus (MRC Systems, Heidelberg, Germany) will be applied once to the forearm or hand, followed by a train of 10 identical stimuli (1 Hz). Alternately, a 512 mN probe will be used for individuals that do not perceive the 256 mN probe to be at least faintly painful, defined as a rating ≥ 5/100 NRS units. Following the single stimulus and the train of 10 stimuli, patients will report the pain intensity of the pinprick sensation using a 0-100 NRS. This procedure will be repeated 3x. The mean pain rating of the three stimulus trains will be divided by the mean pain rating of the single stimuli to calculate a wind-up ratio (*WUR*); a WUR >1 indicates temporal summation.[176]

Magnetic Resonance Imaging: In addition to QST, patients enrolled in Aim 3 studies will also undergo four different neuroimaging procedures (all in one visit) to identify brain regions and associated neurotransmitters operative in pain processing and modulation: 1) *Functional connectivity MRI* (fcMRI) will be performed at rest, 2) *Proton magnetic resonance spectroscopy (^{1}H-MRS)* of the insula (anterior and posterior) as well as the anterior cingulate cortex (ACC) assessing combined glutamate and glutamine (Glx), 3) *Evoked pain fMRI* will be used with evoked thumb nail pressure pain to avoid affected body sites as well as tonic cuff pressure (at Pain 40), and 4) *Voxel based morphometry to assess gray matter volume in the primary somatosensory cortex (S1) and motor (M1) cortex.* The specific neuroimaging methods have

been employed heavily by Dr. Clauw's research group and are described in detail in their published research.[54,58,74,76,122,131-141] We will utilize these exact imaging protocols and adapt them for use in the Siemens Skyla 3T scanner at the KUMC Hoglund Brain Imaging Center. These different procedures investigate varying aspects of the brain's involvement in pain processing and modulation that will complement the QST methods by further providing a comprehensive picture of the neurobiological presence of pain centralization. Comprehensive training and familiarization procedures will be completed prior to MRI to reduce anxiety. Participants will be instructed that the neuroimaging can be stopped at any time if a procedure becomes unbearable. As for QST, all procedures have been evaluated for safety and are well tolerated by chronic pain patients and controls. Neuroimaging will require approximately 2 hours to complete.

All study procedures are solely for research purposes and none are part of usual standard therapy. No study procedures will be billable to insurance companies.

Timeline: **See last page.**

1. **Risk/benefit assessment:**

Physical risks:

Risks Associated with QST: QST may cause minor but temporary physical discomfort. Study personnel will be trained by the investigators to be sensitive to participant discomfort and concerns. Participants will be instructed that they can stop any QST procedure anytime that the pain or unpleasantness of the task becomes unbearable. There have been no significant adverse events associated with any of these procedures in the experience of its use at the Chronic Pain and Fatigue Research Center at the University of Michigan. Specifically, MAST testing may cause some temporary physical discomfort on the thumbnail. The MAST System incorporates a series of redundant mechanical, electrical, and software safety features to prevent patient injury in the event of user error or device failure, including a safety pin that the subject can turn to immediately remove the pressure actuator from his or her thumb. The test is terminated at or before 10 kg/cm^2 of pressure which is a commonly used maximum pressure level in human sensory testing and does not result in physical injury. Participants will always have personal control over the stimulus and can stop it at any time or express instructions to stop the stimuli. They can also withdraw their thumb from the device. The rapid cuff inflator is commonly used in QST studies and will not cause tissue injury at the maximum forces applied in this study (400 mmHg). However, these instruments may cause minor physical discomfort in the areas of testing that is expected to resolve within minutes of test completion.

Risks associated with MRI. Prior to inclusion in the study, the presence of potential MR risks, such as pacemakers, surgical clips or metallic surgical devices will be excluded by medical and surgical history using a standard review form. There may be some slight discomfort from noise produced by the MRI machine; individuals will be provided with foam earplugs. The primary risks known to occur from MRI are due to the magnet's ability to pull metal objects toward it. This pull can cause metal objects in the body (e.g. surgical clips or staples) to move and cause bleeding or disruption of surrounding tissue. Metal objects carried or worn by a person (e.g. jewelry, hair clips, tools) can be pulled toward the magnet and, if free to fly through the air, could strike an individual. The MRI can cause pacemakers or stimulators implanted in the body

to malfunction. There is also a risk that metallic objects in or on the body may be heated by the radio frequency waves, possibly causing burns. Also, claustrophobia may be problematic, and individuals will be screened for this problem. Women of childbearing potential will be screened for pregnancy with a urine pregnancy test immediately before they go into the scanner. Finally, there exists a potential to cause peripheral nerve stimulation. Peripheral nerve stimulation is a light touching sensation on the skin surface, lasting only a few seconds. It may cause mild discomfort, but it is not harmful. The MRI machine is operated within FDA guidelines so the potential for inducing peripheral nerve stimulation is low. The MRI procedure is painless and not uncomfortable, although it does require the subject to lie still with the head and part of the body confined in a tunnel-like device. Evoked pain (QST) will be conducted during portions of the scanning and will have the same risks as those discussed in the "Physical Risks" section above. Other than those described above, there are no known biological risks due to exposure to the magnetic fields such as those that will be utilized in this study.

Methods to reduce risks associated with QST (as conducted before and during MR/PET imaging) will include the following: a) the proposed settings and methods are widely used and have been shown to be safe in extensive use worldwide; b) participants are told that they are free to stop any testing procedure at any time; c) research personnel receive extensive training and follow detailed standardized operating procedures that ensure safely, d) the maximum pressures applied are set to be below levels that would cause tissue injury; e) the MAST and IPC-1000 automated pressure stimulators include redundant software, electrical, and mechanical safety features to ensure that the amount of pressure applied does not cause tissue damage, including a button that the patient or researcher can push to immediately release the device from his/her thumb; f) testing is automatically stopped if participants report maximal pain (e.g., 100 on 0 to 100 scale). During the performance of the MR, the volunteers will be monitored at all times by research personnel associated with the project (research assistant, radiology technologists) or the investigators themselves. Participants will be asked to complete and sign a safety screening form used by the KUMC Hoglund Brain Imaging Center and will be instructed to bring or wear clothing without metal fasteners, and remove jewelry and any other metal objects from their body. All people (including staff) who enter the exam room that contains the magnet are hand screened for magnetic material before entering. Participants will wear foam earplugs or headphones to reduce the loud noises made by the scanner. Participants will be able to communicate with the examiner throughout the scan. If needed, the participant can be removed immediately from the bore of the magnet. The MRI machine is operated within FDA guidelines so the potential for inducing peripheral nerve stimulation is low. Women of childbearing potential will be required to take a urine pregnancy prior to MRI testing. If refused, the participant will be excluded from any further aspects of the study. In addition, all the volunteers will have direct access to the phone numbers and pagers of the study coordinator and the responsible clinicians (Dr. Nicol), as well as a 24-hour contact number (emergency room services). These phone numbers are provided in the consent forms. One copy of the signed consent form is provided to the subjects. They will be encouraged to contact the investigators if they notice any unusual symptoms or untoward side effects.

Psychological risks: There is a possible risk of discomfort associated with being asked personal questions about the participant's health history. Patients may refuse to answer any question on the questionnaires or surveys that may be uncomfortable. There is the possibility that psychiatric disorders could be incidentally detected using measures such as the PROMIS Depression or Anxiety tools.

Further, while this measure does not specifically query suicidal ideation, during the course of research such thoughts could be conveyed to research staff. Should psychiatric disorders and/or suicidal ideation be detected we will follow standard protocols for the triage and management of these participants that will have been approved by the KUMC IRB. This essentially requires that if we detect severe depression or suicidality either on questionnaires or verbal report, we have that person immediately evaluated by one of the available physicians (in this case Dr. Nicol or Arnold). Those individuals then make a clinical judgement regarding the appropriate clinical care.

Potential Benefits: There are no expected direct benefits to subjects participating in the aims of this study, other than monetary compensation for their time, and to help determine the mechanisms of pain centralization. This will be clearly stated in the informed consent where applicable. Future patients may however benefit from the research results, which may ultimately lead to improved ability to assess and treat future lumbar spine surgical and/or chronic low back pain patients. This research study has been designed to minimize the risks to participants. The risks in this study are reasonable in relation to the importance of knowledge gained as a result of this work.

Subjects will be informed that the medical significance of these studies is presently unknown, and the results will not influence their subsequent medical care. Risks to the volunteers are minimal, as outlined above. Experimental work using phenotyping, patient reported outcomes, quantitative sensory testing, and imaging is essential for the advancement of knowledge in the field. This research study seeks a better understanding of patients with lumbar failed back surgery syndrome and how they compare to patients with chronic low back pain (without a history of surgery) and healthy controls. Gaining a foundational understanding about the influence of CNS pain amplification in FBSS and whether these testing paradigms may be able to tease apart two possible subsets of centralized pain in FBSS: "top-down" vs "bottom-up" wherein the latter would represent a FBSS cohort that may be amenable to differing peripheral interventions compared to the former. Ultimately, the goal of the proposed research and future studies is to gain data and information that will allow for "personalized medicine and analgesia" for optimal and individualized treatment of chronic lumbar spine pain (including FBSS) and risk stratification with appropriate directed therapies for perioperative lumbar spine patients. The knowledge to be gained through these studies will also provide important objective information on the biochemistry and function of neurochemical systems in the human which is not obtainable by other means. These outcomes are central to the study of pain mechanisms and their response to treatment. Direct benefits to the subjects participating in the studies are not anticipated. Since risks to participants are of quite low order, we believe the gain of knowledge about the causes and consequences of persistent post-surgical pain (FBSS) outweigh these risks.

Location where study will be performed: Study procedures including questionnaires and QST will take place at the KUMC Hoglund Brain Imaging Center in Kansas City, Kansas. For LSS patients participating in surveys only, consent & questionnaires may be provided in the resource room of the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center prior to the pre-op appointments. Brain Imaging Studies will be done at the Hoglund Brain Imaging Center. A subset of LSS patients (survey only), Healthy Controls, and Failed Back Surgery Syndrome participants will perform their baseline surveys at home following a remote eConsent. Follow up questionnaires (LSS only) will be done via phone-call or via email depending on convenience for the patient.

G. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): PI, Study Coordinator, Research Assistant
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Study Coordinator, Research Assistant, PI
    b. Obtaining informed consent: PI, study coordinator, research assistant, or rotating research medical students
    c. Providing on-going information to the study sponsor and the IRB: PI
    d. Maintaining participant's research records: PI, Study Coordinator, Research Assistant
    e. Completing physical examination: N/A
    f. Taking vital signs, height, weight: N/A
    g. Drawing / collecting laboratory specimens: N/A
    h. Performing / conducting tests, procedures, interventions, questionnaires: PI, study coordinator, research assistant or rotating research medical students
    i. Completing study data forms: PI, study coordinator, or research assistant
    j. Managing study database: Study Coordinator & KUMC Department of Biostatistics

H. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB): Study team
    a. Data/events that will be reviewed: All study data, procedures, and any events
    b. Frequency of review: As needed
    c. Types of analyses to be performed: No interim analyses planned
    d. Safety-related triggers that would cause the PI to stop or alter the study: None expected.
2. Adverse events (AE) will be reported according to the FDA guidelines and reports will be sent to the University of Kansas (KUMC) IRB as required. The PIs will be notified when an AE occurs and will determine the attribution and relatedness of each AE. During the performance of the studies, the volunteers will be monitored at all times by research personnel associated with the project or the investigators themselves.

3. All the participants will have direct access to the phone numbers and pagers of the study coordinator and the responsible clinicians, as well as a 24-hour contact number (emergency room services). These numbers are additionally included in the consent form provided to the volunteers. They will be encouraged to contact the investigators if they notice any symptoms or untoward side effects. All adverse events are immediately communicated to the IRB.

III. Subject Participation

A. Recruitment:

1. Participants will be recruited from a variety of sources. We will use the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center's chronic pain clinics and surgical spine clinics. The Frontiers Registry and the Pioneers Community Research Recruitment Registry services through the Frontiers: The Heartland Institute for Clinical and Translational Research. Flyers will be placed around KUMC in addition to other KU affiliates (Turning Point, Indian Creek, etc.). Flyers and "advertisements" will be posted on KUMC departmental social media pages as well as Craig's List.

B. Screening Interview/questionnaire:

1. Potential participants will be screened by telephone to determine whether they are a candidate for the study and are interested in participating. These will be patients who are recruited using the information in the previous section. Participants will be asked prior to screening if they agree to participate in the pre-screening questionnaire. The study coordinator/research assistant will enter the potential participant's pre-screen data in to RedCap for the final approval of Dr. Nicol. If the participant is not eligible, their RedCap entry will be deleted.

IV. Informed consent process and timing of obtaining of consent

1 PI, study coordinator, research assistant and/or rotating research medical students will personally provide information about study procedures and obtain their written consent.
   A. A subset of study participants who are only participating in the survey portion of the study will utilize remote eConsent. Participants will be sent a RedCap survey link via email. The consent form will list study team member information for any questions that arise during the consent process. Participants will have the option to download a PDF version of their signed consent form.

2 The informed consent interview will be conducted by the study staff and will include a verbal and written explanation of the study, including the purpose, testing procedures, time commitment, inclusion/exclusion criteria, risks and benefits, alternative treatments, confidentiality, compensation, study personnel contacts, and required regulatory information. All individuals will be given the opportunity to ask questions. Once all questions and concerns are addressed to the participant's satisfaction, the participant will sign the consent form. Following informed consent, the study participant will be assigned an anonymous study identification number.
   A. Participants completing remote consent will have the option to go over the consent form with a member of the research team over the phone. If they choose the review the consent form alone, they will be provided the contact information of the study coordinator if any questions arise.

3 Andrea Nicol, MD will assess and determine candidacy for informed consent and this will only be allowed from the patient and not a proxy as this study requires patient participation for many testing procedures, we will only recruit those individuals with the capacity to provide consent themselves.

V. Alternatives to Participation: A statement of alternatives to participation in this research study, if any. N/A

VI. Costs to Subjects: No costs to the patient's insurance company will be incurred for any study procedures.

VII. How new information will be conveyed to the study subject and how it will be documented: If any new information regarding study or research procedures during the course of the study period, the PI (Andrea Nicol) will convey this information directly to the patient via telephone call and written letter mailed to the patient's listed home address.

VIII. Payment, including a prorated plan for payment: Individuals in the longitudinal lumbar spine surgery cohort who are only undergoing Comprehensive Phenotyping will be compensated $150 total for their participation ($50 for pre-operative questionnaires, $10 for 2-week follow up questionnaires, $15 for 1-month follow up questionnaires, $25 for 3-month follow up questionnaires, and $50 for 6-month follow up questionnaires). Lumbar spine surgery patients undergoing both Comprehensive Phenotyping and QST will be compensated $200 total for their participation ($100 for pre-operative questionnaires and QST, $10 for 2-week follow up questionnaires, $15 for 1-month follow up questionnaires, $25 for 3-month follow up questionnaires, and $50 for 6-month follow up questionnaires). Patients will receive compensation for each visit completed. The 50 individuals in each of the FBSS and Healthy Control cohorts that participate in the cross-sectional comprehensive phenotyping and QST procedures will be compensated $100 for their participation. The subset of FBSS and Healthy control patients who participate in remote eConsent and survey only, will receive $50 for their participation. Those patients in each cohort that go on to participate in the neuroimaging and QST procedures will be paid an additional $100 for their participation.

IX. Payment for a research-related injury: No injuries are expected, however, if there is a research-related injury, consultation with KUMC Risk Management and Research Institute will be obtained to ensure proper protocol for this.

IV. Data Collection and Protection

A. Data Management and Security:

1. The PI, Study Coordinator, Research Assistant, and rotating medical students will have access to identified study data while the study is enrolling. After enrollment, only PI and study coordinator will have access to identified study data. Biostats and Co-PIs will only have access to de-identified data.
2. Subject data will be coded (assigned a unique anonymous study number), which will allow the researchers to link the data to other information you provide through questionnaires and study procedures. The code key linking the subject to their data will be maintained via RedCap The key will only be used to connect study information to the data. The code will never leave KUMC. A breach of confidentiality will be considered a serious adverse event and will be reported to the KUMC IRB within 5 days of occurrence and a remediation plan will be put in place immediately. Records will be retained for 3 years per university and federal (NIH) policy.
3. State whether human subjects will be identifiable directly or through coded information. Coded information.
4. If data will be coded, state who will maintain and have access to the key to the code. PI and Study Coordinator (Clinical Study Coordinator)
5. State how the data will be linked to the subjects during the study. Via Coding

6. Paper copies of study materials will be maintained in the KUMC Department of Anesthesiology Research division offices or PI office, which are locked room with access only to research division staff members. Electronic patient information will only be stored on RedCap, Qualtrics, KUMC p:drives, ClinCard and Velos, which will limit access to participant identifying information to only those with assigned appropriate permissions. . All data are stored in a HIPAA compliant manner. Neuroimaging data collected during the performance of the studies is coded by case number and temporarily stored in firewall-protected servers. After transfer of the data to the image-processing laboratory, it is stored in mirrored RAID arrays which are both firewall-protected *and* isolated from access outside the immediate local network. The RAID arrays are also used to store all other data from the volunteers, and are backed up in real time with a mirrored RAID. Even failure of the entire RAID does not result in the loss of data because the data resides in two identical systems. RAID array drives are also hot-swappable, and back-up drives are available in the event that individual drives may fail. None of the databases contain identifiers linkable to the volunteers.
7. This study will also use Qualtrics electronic data capture system. Survey distribution is through a personalized link specific to the patient that is sent to the patient's email address (security whitepaper for Qualtrics uploaded to eIRB application documents).
8. Discuss any use of mobile devices for data collection or storage. N/A
9. Discuss security measures if identifiable data are sent outside KUMC. N/A

B. Sample / Specimen Collection: N/A

C. Tissue Banking Considerations: N/A

D. Procedures to protect subject confidentiality: Several measures have been taken to reduce the risk of breach of confidentiality. These include training of study team members, electronic and physical security measures for data capture and storage, and collecting a minimum of identifiable information for each individual participant. The study team will take all possible steps to protect the privacy of subjects. This includes:

- Maintenance of protected health information (PHI) will include the assignment of a coded participant ID that will be used for accessing and merging of all records.
- Participant's data and specimens will be coded (assigned a unique study number) which will allow the researchers to link the data/specimens to other information that are provided through questionnaires and other study activities
- The code key linking the participant to their unique study number will be maintained via RedCap. The key will only be used to connect other study information to the data/specimens. This code will never leave the University of Kansas Medical Center.

A breach of confidentiality will be considered a serious adverse event. As such, it will be reported to the University of Kansas Medical Center IRB within 5 days of occurrence per University policies and procedures, and a remediation plan will be put in place immediately.

E. Quality Assurance / Monitoring

1. Describe steps to be taken to assure that the data collected are accurate, consistent, complete and reliable. (source data verification, audits or self – assessment) Self-assessment.
2. Describe whether there are plans to have ongoing third party monitoring. N/A

V. Data Analysis and Reporting

A. Statistical and Data Analysis: Refer to section 2.C.

B. Outcome: This research study seeks a better understanding of patients with lumbar failed back surgery syndrome and how they compare to patients with chronic low back pain (without a history of surgery) and healthy controls. Gaining a foundational understanding about the influence of CNS pain amplification in FBSS and whether these testing paradigms may be able to tease apart two possible subsets of centralized pain in FBSS: "top-down" vs "bottom-up" wherein the latter would represent a FBSS cohort that may be amenable to differing peripheral interventions compared to the former. Ultimately, the goal of the proposed research and future studies is to gain data and information that will allow for "personalized medicine and analgesia" for optimal and individualized treatment of chronic lumbar spine pain (including FBSS) and risk stratification with appropriate directed therapies for perioperative lumbar spine patients. The knowledge to be gained through these studies will also provide important objective information on the biochemistry and function of neurochemical systems in the human which is not obtainable by other means. These outcomes are central to the study of pain mechanisms and their response to treatment. There is no "success" or "failure" of this study as this is observational and seeking to generate data for further investigations. The end point of the study will be when all surgical patients have finished their 6 month follow up visit.

C. Study results to participants: At the conclusion of the study, when results are published in journals, study participants will be contacted to determine if they would like copies of the published results.

D. Publication Plan: At least one publication will result from the proposed research.

VI. Bibliography / References / Literature Cited: See below.

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APPENDIX I: VULNERABLE POPULATIONS

I. Cognitively or decisionally impaired individuals: **N/A**
II. Children: **N/A**
III. Pregnant women: N/A
IV. Prisoners: N/A
V. Students and/or Employees: N/A

STUDY SCHEDULE:

DOMAIN	INSTRUMENT	BASELINE	EMA1	SURG	14 days POST OP	2WFU	1MFU	3MFU	EMA2	6MFU
Pre-screen	Pre-screen form	A								
Consent	Informed Consent	A								
Eligibility	Eligibility form	A								
Enrollment	Enrollment	A								
Stop study	Stop study form									
Withdrawal	Consent withdrawal									
Demographics	Demographics	A								
	Family history	A								
Diagnostics	Complex Medical Symptom Inventory	A								
	SOAPP Opioid screen	A								
	2011 FM survey criteria	A					SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
Pain	Surgical Site Pain Severity(worst, ave)	SS, SS*, SS**				SS, SS*, SS**	SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
	Brief Pain Inventory Overall	A				SS, SS*, SS**	SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
	PainDetect at Surgical Site						SS, SS*, SS**			
	PainDetect	A						SS, SS*, SS**		SS, SS*, SS**
	10 day pain diary		SS, SS*, SS**						SS, SS*, SS**	
	14-day post-op diary(pain, Opioid, #)				SS, SS*, SS**					
	Concomitant Medications	A						SS, SS*, SS**		SS, SS*, SS**
	Opioid Follow up					SS, SS*, SS**	SS, SS*, SS**			

Allied Symptoms	PROMIS phys function 8	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS pain interference 8	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS sleep-related impairment 8	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS fatigue 16	A						SS, SS*, SS**		SS, SS*, SS**
	MISCI 10	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS depression 8	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS anxiety 8	A						SS, SS*, SS**		SS, SS*, SS**
	PANAS 20	A						SS, SS*, SS**		SS, SS*, SS**
DOMAIN	**INSTRUMENT**	**BASELINE**	**EMA1**	**SURG**	**14 days POST OP**	**2WFU**	**1MFU**	**3MFU**	**EMA2**	**6MFU**
	Perceived Stress Scale	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS depression 4 item and anxiety 4 item						SS, SS*, SS**			
	PROMIS physical function 4 item					SS, SS*, SS**	SS, SS*, SS**			
	Oswestry Disability Index	A				SS, SS*, SS**	SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
Social	PROMIS emotional support 4a	A						SS, SS*, SS**		SS, SS*, SS**
	PROMIS social participation 4a	A						SS, SS*, SS**		SS, SS*, SS**
Cognitive and situational factors	Life satisfaction Questionnaire	A					SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
	Coping strategies questionnaire -catastrophizing	A						SS, SS*, SS**		SS, SS*, SS**
	Childhood traumatic events scale	A								

	Patient Global Impression of Change						SS, SS*, SS**	SS, SS*, SS**		SS, SS*, SS**
	Conner Davidson Resilience	A						SS, SS*, SS**		SS, SS*, SS**
Imaging /QST Assessments	McGill Pain Questionnaire	SS**,FBSS*, HC*								
	fMRI screening form	SS**,FBSS*, HC*								
	fMRI imaging form	SS**,FBSS*, HC*								
	QST Record Sheets	SS*,SS,** FBSS*, HC*								

A All (SS, FBSS, HC)
SS Spine Surgery patients – Phenotyping only
SS* Spine Surgery patients – Phenotyping + QST
SS** Spine Surgery patients – Phenotyping + QST + imaging
FBSS Established FBSS patients
FBSS* Subset of FBSS getting imaging
HC Healthy Controls
HC* subset of HC getting imaging