SUPRASPINAL PROCESSING OF SENSORY ASPECTS OF PAIN

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Version Number	Version Date	Summary of Revisions Made
1		
2	2/10/2023	- Revisions to inclusion/exclusion criteria for healthy controls, pilots and patient populations focusing on concise language. - Revision to data sharing language to allow for PHI data transfer to related studies with similar data goals to relieve testing burden on participants (pg 23) - Surveys added to capture more sleep behavior and additional pain domains.(Pg 16) - Payment structures revised to reflect participant effort more appropriately and add in structure for pilot participants and alter payment for pilots pg 33

1. PROJECT SUMMARY

Chronic pain affects approximately 20% of both adults and children in the US and is a source of substantial disability and health care costs. Chronic pain can be challenging to diagnose due to the presence of poorly understood symptoms. When diagnosed, current pharmacologic treatments for pain are remarkably ineffective, while effective non-pharmacologic treatments remain under-utilized. These shortcomings in the diagnosis and treatment of pain arise from tremendous gaps in our knowledge about the basic central nervous system systems that process nociceptive information and instantiate an experience of pain. These gaps are further amplified in the case of pediatric chronic pain due to a lack of basic/translational research. Our team of basic scientists and clinician scientists is uniquely positioned to perform human pediatric studies integrating functional neuroimaging with quantitative sensory testing and psychological assessments to delineate brain systems engaged during chronic pain. We will examine four distinct chronic pain syndromes: migraine, complex regional pain syndrome, functional abdominal pain, and musculoskeletal pain. We seek to 1) Identify shared and distinct brain systems engaged by different forms of pediatric chronic pain, 2) Determine if predictors of recovery differ across different chronic pain conditions, 3) Delineate brain systems associated with the spread of pain. To accomplish these aims, we will recruit 400 patients with chronic pain and 100 healthy participants (age range 10-17). We will follow all participants longitudinally for 1 year after initiation of treatment to assess the degree of recovery and spread of pain. This basic science investigation will provide a critical foundation of basic knowledge for future clinical trials of diagnostic markers for different forms of chronic pain and for the development of new treatments for chronic pain.

2. SPECIFIC AIMS

Chronic pain has a profound impact on children and adolescents. Millions of adolescents are affected by migraine, complex regional pain syndrome, musculoskeletal pain, and functional abdominal pain. In adolescents in the US, heath care costs associated with pain are estimated to be approximately $20 billion.(1) Youth with chronic pain have significant disability manifested by decreased school attendance, physical and social activities, and increased depression and anxiety.(2, 3) Current treatments for pediatric chronic pain are typically derived from adult care and are of limited efficacy,(4) leaving many children undertreated.(5) *Despite the high prevalence and poor outcomes, pediatric chronic pain remains understudied and poorly understood.*

Appropriate treatment for pediatric chronic pain is complicated by challenges with accurate diagnoses. Chronic pain presents in many forms with a plethora of symptoms and frequently is of unknown origin. Given the ambiguity of the symptoms of many chronic pain disorders, clinicians face many challenges in accurately providing the patient with an appropriate diagnosis and subsequent treatment.(6, 7) This diagnostic uncertainty is mirrored by the patient and is associated with increased pain intensity and significant disability.(8)

Delineation of brain systems engaged during chronic pain can provide insights critical for the better diagnosis and treatment of pain. For example, our data indicate that brain activation can be used to identify systems associated with successful therapy and can predict responsiveness to treatments prior to their initiation.(9) However, progress in this area is limited by the dearth of studies comparing brain systems across different chronic pain syndromes, a limitation arising from the treatment of different forms of chronic pain by different medical disciplines.

Our team is uniquely breaking down barriers between different disciplines and performing fMRI, quantitative sensory testing (QST), and psychological assessments of pediatric patients with diverse primary chronic pain conditions. Building on these ongoing studies, we will conduct a prospective basic science investigation to directly compare brain systems associated with different forms of chronic pain in a sample of youth (ages 10-17) with chronic pain (100 with migraine, 100 with complex regional pain syndrome, 100 with musculoskeletal pain, 100 with functional abdominal pain) and 100 age/sex-matched healthy control participants. Functional MRI (BOLD and ASL), QST, and psychological data will be obtained to address these aims:

Aim 1: Identify shared and distinct brain systems engaged by different forms of pediatric chronic pain. Parallel recruitment and investigation of patients before initiation of treatment (i.e. baseline) with these diverse conditions is critical for systematically identifying the brain systems engaged uniquely by each chronic pain condition as well as for determining common brain systems that may span multiple conditions. Accordingly, we will test the hypothesis that migraine, complex regional pain syndrome, functional abdominal pain, and musculoskeletal pain engage partially distinct brain systems. Identification of these systems will lead to a mechanistic foundation for better diagnoses of these complex conditions and will greatly add to our general understanding of pediatric chronic pain.

Aim 2: Determine if predictors of recovery differ across different chronic pain conditions. We will longitudinally examine youth with chronic pain for 1 year to assess recovery trajectories following multidisciplinary (psychological, physical, and pharmacological) treatment to determine if different (or similar) multivariate predictors (neuroimaging, QST, and psychological assessments) of recovery are required for different chronic pain syndromes. Different predictors would underscore the unique brain systems associated with each diagnosis, while similar predictors would point towards a more global brain system driving chronic pain. Development of trajectory predictors will have a significant impact on patient care as patients with markers for poor trajectories could be immediately directed to intensive inpatient rehabilitation instead of

having to unsuccessfully undergo months of outpatient therapy and suffer further entrenchment of their chronic pain.

Aim 3: Delineate brain systems associated with the spatial distribution and spread of pain. The spread of pain is a particular problem with pediatric chronic pain.(10) Importantly, the prevalence of widespread pain increases progressively with age (11) indicating an urgent need to develop effective treatments for children so that they do not transition to adults with intractable chronic widespread pain. Using a combination of innovative, spatially-directed QST and comprehensive pain mapping across the body, together with neuroimaging, we will identify brain systems that are associated with the spatial spread of pain. Longitudinal follow-up of patients will allow us to specifically examine patients who have increasing spread of pain to determine the brain systems that predict such adverse changes.

3. SIGNIFICANCE

Chronic pain in adults and in youth remains a tremendous problem and is associated with tremendous societal costs. More than 20% (50.0 million) adults in the US have chronic pain, with 8.0% (19.6 million) of the total population having high-impact chronic pain.(12) Women, older adults and economically disadvantaged individuals have higher rates of both chronic pain as well as severe chronic pain.(12) Youth are impacted by chronic pain at similar, surprisingly high rates, with estimates ranging from 15-33% having chronic pain, and more than 5% having severe chronic pain.(13, 14) In adults in the US, pain is associated with added health care costs of $261-300 billion(15), while in adolescents in the US, heath care costs associated with pain are estimated to be approximately $20 billion.(1) The costs of lost productivity are significant, with costs ranging more than $300 billion. Similar to adults, youth with chronic pain have significant disability manifested by decreased school attendance, physical and social activities, and increased depression and anxiety.(2, 3) *Despite high prevalence, pediatric chronic pain remains under-studied and poorly understood.*

A unique challenge of pediatric chronic pain is that it occurs within the developing brain. The brain continues to mature through adolescence and into early adulthood. In particular, the prefrontal cortex is one of the last brain structures to mature.(16) This region is critically important to the modulation of pain and is activated during multiple interventions for pain relief including expectations(17), meditation(18), cognitive behavioral therapy (CBT)(19), and placebo.(20) The presence of chronic pain during this critical phase of the development of pain modulatory structures may have dire implications for the patient, as pain exposure early in life can lead to long term increases in pain sensitivity. Consistent with this idea, *youth with chronic pain frequently transition to adults with chronic pain despite the availability of state-of-the-art treatments.(21)*

Appropriate treatment for chronic pain is complicated by challenges with accurate diagnoses. Chronic pain presents in many forms with a plethora of symptoms and frequently is of unknown origin. Given the ambiguity of the symptoms of many chronic pain disorders, clinicians face many challenges in accurately providing the patient with an appropriate diagnosis and subsequent treatment.(6, 7) This diagnostic uncertainty is mirrored by the patient and is associated with increased pain intensity and significant disability(8) and causes continued searches for what would be perceived as appropriate diagnoses.(22) *Development of an improved understanding of the neurophysiological systems supporting symptoms of different types of chronic pain is critical for development of better diagnoses for chronic pain.*

Spatial aspects of pain have long remained challenging to explain and can pose tremendous clinical problems. Spread of pain away from the initial locus can complicate diagnoses by obscuring the location of the underlying problem and by raising questions about the veracity of the patient's report. Moreover, pain can spread outside of dermatomal boundaries in a fashion not adequately explained by the underlying neuroanatomy.(10, 23) However, the spread of chronic pain and sensory disturbances occurs with great frequency. For example, the spread of pain during complex regional pain syndrome to multiple limbs occurs in a high proportion of patients.(23) Patients with pain that radiates exhibit contralateral radiation most frequently, but significant proportions exhibit ipsilateral radiation.(23) In addition, our Co-I Williams has determined that the spatial distribution of pain is associated with poor outcomes in pediatric patients following intensive therapy.(24) *Despite the frequency and importance of this sensory dimension of chronic pain, remarkably little research has addressed spatial mechanisms of pain.*

Pharmacologic therapies for chronic pain exhibit limited clinical efficacy. Despite the widespread use of pharmacologic therapies for chronic pain, they are effective for a remarkably

small number of patients. A recent meta-analysis of clinical trials of drugs for neuropathic pain reveals that the 7.2 patients need to be treated in order to produce either a 30 or a 50% reduction in neuropathic pain of one patient.(25) Our Co-I's Powers and Hershey have recently shown that the most commonly used preventative drugs for pediatric migraine (amitriptyline and topiramate) are no more effective than placebo.(26) Consistent with this finding, a recent review of pharmacologic treatments for pediatric chronic pain reveals that there is limited evidence supporting the efficacy of pharmacologic therapy.(27) Moreover, this limited efficacy of pharmacotherapy for chronic pain in both adults and children may, in part, result from the distribution of nociceptive processing across dozens of neurotransmitters and neuromodulators.(28) Thus, targeting a single neurotransmitter system is not sufficient to adequately disrupt nociceptive processing when a myriad of other neurotransmitter systems are sufficient to maintain a state of chronic pain. *Given this lack of efficacy of pharmacologic therapies, dramatically different systems-level approaches are needed to treat chronic pain.*

Pain is processed in a highly distributed fashion. I have recently developed a new overarching conceptual framework for understanding pain that provides the foundation for our future studies.(29) This framework, termed the Distributed Nociceptive System (DNS), integrates two neglected concepts - population coding(30) and distributed processing.(31-33) The DNS provides an integrated conceptual structure for understanding nociceptive mechanisms across the spinal cord and the brain. The central tenet of this framework is that the extraction and utilization of nociceptive information is a process that can be accomplished separately and largely independently by populations of neurons across multiple sites within the central nervous system. As such, processing of nociceptive information can occur in a highly distributed fashion, yielding a system that is very resistant to disruption. The DNS provides a bridge between the basic neuroscience and clinical worlds by providing a mechanistic framework for developing an understanding of the perplexing symptoms of chronic pain. For example, altered receptive field tuning may result in enhanced recruitment of nociceptive neurons and spread of pain. Thus, examining systems supporting spatial tuning may provide important insights into how pain can spread and how this spread can be reversed. Moreover, the widely distributed

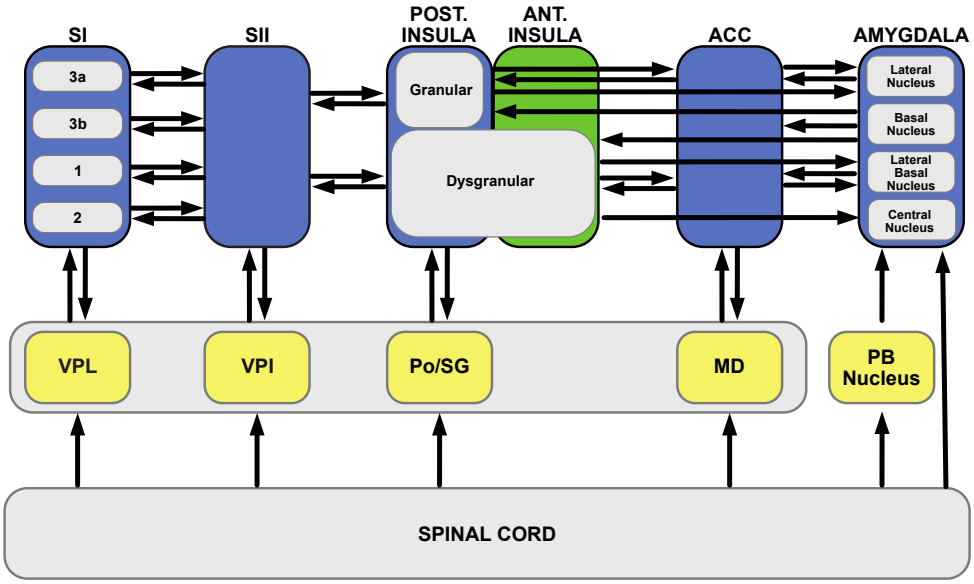

Figure 1 Anatomic substrates supporting the distributed processing of nociceptive information. Note the extensive interconnectivity of the amygdala with the anterior cingulate cortex and insular cortex.

brain systems that are involved in the construction of the pain experience may require distributed regulation to instantiate either positive or negative changes. Brain regions such as the amygdala have extensive connectivity with regions known to be involved in nociceptive processing and are ideally situated to regulate their activity (Fig. 1). Accordingly, our preliminary studies have focused heavily on the functional connectivity of the amygdala and its role in different forms of chronic pain. *Our team of basic scientists and clinician-scientists is uniquely positioned to perform human studies that are firmly grounded in this mechanistic framework.*

4. STUDY DESIGN

Overview of experimental design and study flow: We will collect QST, fMRI, and psychological data from up to 500 youth, including 400 with chronic pain and 100 healthy controls in order to 1) Identify shared and distinct brain systems engaged by different forms of pediatric chronic pain, 2) Determine if predictors of recovery differ across different chronic pain conditions, 3) Delineate brain systems associated with the spatial distribution and spread of pain. Pediatric chronic pain patients will be assessed (QST, fMRI, psychological assessment), ideally at initiation of treatment, (baseline) and will be followed longitudinally for a period of 1 year to track the trajectory of their recovery following multidisciplinary (pharmacological, psychological, physical) treatment, and the spatial distribution of their pain, as well as the emergence of new chronic pain conditions. Healthy youth will undergo the same assessments at analogous time points. Both traditional massive univariate as well as multimodal deep *Ensemble* learning methods will incorporate all modalities of assessment to classify chronic pain and to predict trajectory.

Participants: A total of up to 500 participants (age 10-17 at the time of enrollment) will be recruited for combined QST, fMRI, and psychological assessments, with approximately 100 having complex regional pain syndrome (CRPS), 100 with migraine, 100 with musculoskeletal (MSK) pain, and 100 with functional abdominal pain, and 100 age and sex matched healthy controls. We anticipate that the sex distribution will be approximately 70% female, 30% male, with approximately 5% of participants having a gender identity as non-binary. These participants will be MRI compatible (i.e., no claustrophobia, no metal/electronics that could increase risk and/or diminish image quality) and will meet inclusion criteria delineated in detail below. We are actively performing studies on all of these different patient populations (and healthy controls), and based on our current recruitment rates, we can readily meet these recruitment objectives.

Pilot participants: An additional 20 participants (age 10-65) may be recruited to optimize selected study procedures. These participants would have no contraindications for the procedures that they experience.

Participant Timeline: Individuals with chronic pain will undergo (QST, MRI, psychological) assessments at baseline, ideally prior to initiation of multidisciplinary treatment. They will be followed with quarterly remote assessments and as well as with an in-person study visit (QST, psychological assessments) after one year to track the trajectory of their pain and to characterize emergence of spatial spread of their pain.

5. PARTICIPANT SELECTION, RECRUITMENT, AND RETENTION PLAN

Version 2

5.1 Eligibility Criteria

A total of 500 participants (+20 pilot participants) will be enrolled in this project, with all children undergoing MRI scans quantitative sensory testing. Patients evaluated at Cincinnati Children's Hospital will be eligible for the study. Patients may have more than one chronic pain condition. All individuals regardless of gender, race, ethnicity and socioeconomic class will be considered potential study participants.

Healthy Volunteers

Inclusion Criteria:

1. Male, Female, or Non-binary, age 10-17 years.
2. Good general health, no history/active chronic pain
3. English speaking, able to complete interviews and questionnaires in English
4. Parent or guardian (as applicable) and participant willing to comply with protocol, complete study assessments, and provide written informed consent.
5. Access to the internet either by laptop, tablet, or phone (for REDCap Surveys)

Exclusion Criteria:

1. Pregnant females
2. Morbid obesity or weight/size incompatible with MRI scanner
3. History/active chronic pain
4. Psychiatric medications
5. Diagnosis of epilepsy, other neurological diseases, or medical condition (e.g. diabetes, cancer)
6. MRI contraindications
7. Orthodontic braces or other metallic implants which obscure or interfere with the MRI.
8. Claustrophobia
9. Skin conditions or past skin damage on the arms or legs in or near sites of sensory testing
10. Medications that may alter pain sensitivity or brain activity

Patients

Inclusion Criteria:

1. Patients will need a diagnosis of a chronic pain derived congruent with ICD-11 criteria [*MG30.0; chronic primary pain - pain in 1 or more anatomic regions that persists for > 3 months, is associated with significant distress or functional disability and cannot be better explained by another chronic pain condition (e.g., arthritis, lupus).(34)*] related to headache (migraine, daily headache), abdominal (FAPD), localized MSK (single limb/joint, low back or chest pain), diffuse MSK (widespread MSK pain), or CRPS
2. If on medications, they need to be on stable doses of prescribed pain and/or psychiatric medications for 4 weeks before the baseline study visit.

3. Male or female, age 10 -17 (inclusive)
4. English speaking, able to complete interviews and questionnaires in English

Exclusion Criteria:

1. Weight/size incompatible with MRI scanner
2. Orthodontic braces, metallic or electronic implants, or other metal objects in the body which obscure or interfere with the MRI, or pose a risk from heating, movement, or malfunction in the MRI environment
3. Claustrophobia
4. Youth who are pregnant
5. Any comorbid rheumatic disease, diagnosis of epilepsy, other neurological diseases, or medical condition (e.g. diabetes, cancer, IBD)
6. Present psychiatric disease as defined by DSM IV (e.g. psychosis, bipolar disorder, major depression, generalized anxiety disorder), alcohol or drug dependence, or documented developmental delays or impairments (e.g., autism, cerebral palsy, ADHD, or mental retardation) that, in the opinion of the investigator, would interfere with adherence to study requirements or safe participation in the study
7. Skin conditions or past skin damage on the arms or legs in or near sites of sensory testing
8. Outside the age range (9 years old or younger; 18 years or older) at the time of consent

Pilot Volunteers

Inclusion Criteria:

6. Male, Female, or Non-binary, age 10-65 years.
7. Good general health, no history/active chronic pain
8. English speaking, able to complete interviews and questionnaires in English
9. Parent or guardian (as applicable) and participant willing to comply with protocol, complete study assessments, and provide written informed consent.
10. Access to the internet either by laptop, tablet, or phone (for REDCap Surveys)

Exclusion Criteria:

11. Pregnant females
12. Morbid obesity or weight/size incompatible with MRI scanner
13. History/active chronic pain
14. Psychiatric medications
15. Diagnosis of epilepsy, other neurological diseases, or medical condition (e.g. diabetes, cancer)
16. MRI contraindications
17. Orthodontic braces or other metallic implants which obscure or interfere with the MRI.
18. Claustrophobia

19. Skin conditions or past skin damage on the arms or legs in or near sites of sensory testing
20. Medications that may alter pain sensitivity or brain activity

5.2 Recruitment

Healthy Volunteers

Healthy volunteers will be recruited through on-line advertisements, social media, paper advertisements, word of mouth, and e-mail.

Migraine Patients

Cincinnati Children's Headache Center will be the primary source of recruitment of migraine patients. About 2,000 children and adolescents per year are evaluated there. Our group with Co-I Hershey has successfully enrolled 3 to 5 participants per month in imaging and sensory testing studies consistently.

Outpatient Chronic Pain Clinic

Patients with complex regional pain syndrome, musculoskeletal chronic pain conditions will be recruited from the Outpatient Chronic Pain Clinic. This clinic sees 300 patients per year and is a site of active recruitment for ongoing studies of complex regional pain syndrome and musculoskeletal pain in collaborations with Co-I Kenneth Goldschneider.

Functional Independence Restoration Program (FIRST)

Patients with complex regional pain syndrome, musculoskeletal pain, and multiple overlapping chronic pain conditions will also be recruited from the FIRST program. This inpatient program sees more than 50 patients per year and is the site of ongoing recruitment of CRPS patients and patients with widespread musculo-skeletal pain in collaborations with Co-I Sara Williams. Our recruitment rates have been extremely high (>90% for eligible patients) as research can be incorporated into patients' daily schedule and barriers related to travel are non-existent.

Gastroenterology Clinic

Patients with functional abdominal pain will be recruited from the Gastroenterology Clinic. This clinic sees more than 100 functional abdominal pain patients per year and is the site of active ongoing studies in collaboration with Co-I Neha Santucci.

Other Forms of Recruitment

Patients and their families may hear about the study through clinicaltrials.gov or approved advertisements. If they are not patients at CCHMC, CCHMC clinical personnel will evaluate their chart to ensure appropriate diagnoses and eligibility.

Recruitment and Retention Strategies Common to All Patients

Potential patients will be identified during an evaluation at one of clinics (mentioned above) at Cincinnati Children's Hospital. The physician/nurse practitioner/psychologist who examines the child or adolescent will explicitly state that they will continue to receive the same high quality of care from them should they choose not to participate. If the family is interested in participating, informed consent and assent will be obtained. The physician, nurse practitioner, research coordinator, and/or a study PI will provide a full description of the study and answer any questions that the family may have. Approved procedures and forms of the Institutional Review Board will be utilized. The purposes and the risks of the investigation and the procedures of the study will be explained. The families will be explicitly told that their medical care will not be

affected if they choose not to participate. No research screening or assessment procedure will occur until after written consent is obtained.

Identification of Eligibility

Patients and their caregivers who meet eligibility criteria will be informed of the study by their pain clinicians or study personnel at clinic appointments and could be provided a study brochure or flyer. Study brochures or flyers for all active clinical studies are typically posted on bulletin boards in the clinic, patient rooms, or waiting rooms.

Screening

For each patient referred to the study, the study team will determine if the patient meets inclusion criteria by performing a chart review and administering a screening survey. The screening survey may include the Functional Disability Inventory, PEDSMidas, Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) for pain ratings.

Retention Strategies

In an effort to retain each recruited patient, various methods could be employed such as 1) ride share service (as needed), 2) reminder calls, texts or emails, prior to each lab visit and follow-up clinical endpoint survey completion, 3) onsite childcare or a babysitting allowance for siblings, and 4) providing participants who reach the 1 year endpoint with a 3D print of their brain.

Pre-screening of Clinical Patients

Patient charts via EPIC may be reviewed by research staff for inclusion. Patient history, demographics, clinic notes and clinical pain records may be reviewed to determine whether a patient meets initial inclusion/exclusion criteria. The information from the chart reviews can be used to generate an electronic list of potential study patients. A recruitment letter/message and/or email may be sent to the parent or guardian regarding the study. In addition, the study staff may also reach out to the family. If interested, adolescents and their families may be approached before/following their clinical visit or another convenient time.

MyChart Recruitment Communication

The research team must confirm that the patient’s family is potentially interested in research prior to contact, either through a clinician’s verbal or electronic acknowledgment or through the patient’s EPIC profile. Additionally, previous involvement in research would be considered as grounds for potential interest in future research opportunities. If interested, and potentially eligible as per the previously detailed pre-screening strategies, communication can be sent in the form of a MyChart message, a communication feature in the EPIC healthcare tracking system.

Study personnel may wait in the various clinics and then approach patients in between provider visits to assess their interest in participating in research. The plan was to inform, consent and enroll participants in the study in-person. We also provide a virtual option. If the study personnel is made aware of a patient’s potential interest and eligibility in this study through EPIC, previous study involvement, or clinician communication, a coordinator would be able to reach out to the potential participant via MyChart. The ability to use MyChart as an additional method of communication will allow for more options of communication with the participant. This tends to be a preferred method of contact for families and is a more readily accessible communication channel as it's used to communicate with clinicians. Regardless of the method of initial contact (e.g. call, text, email, MyChart) study coordinator will primarily communicate with participant in the method they express is preferable.

From the patient's perspective: approaching/soon after a visit in clinic, they would receive a MyChart message from a CRC with a brief summary of the study. We would explain that they were contacted because they are potentially eligible. If they're interested in learning more and being screened, we will confirm contact info, and offer to discuss additional details over their preferred method of communication at their earliest convenience.

Waiver of Consent for Screening

Ensuring the study is a good fit for the participant is an important aspect of the recruitment process and study goals. To this end, we request a waiver of consent for approaching potential participants through utilizing screening surveys and/or pain rating scales as a preliminary screening method. If the participant meets initial eligibility criteria they will be invited to enroll in the study after appropriate material review. Additionally, staff will be collecting and storing contact information such as name, phone number, and email from either chart review or physician referral to aid in recruitment efforts. All unused (ineligible) contact information will be deleted at the end of recruitment, maintained only to ensure potentially ineligible families are not repeatedly approached.

5.3. Informed Consent

Process for Obtaining Consent: Informed consent will be obtained prior to conducting any study procedures—excluding waived pre-screening measures. A single informed consent form will be used.

The study investigator or coordinator typically provides a detailed explanation of the study to a prospective patient. The study coordinator will provide the potential participant and his/her guardian a copy of the informed consent form and assent form to review. The staff member will review the document with the family, describing any study procedures and potential risks and benefits associated with participating in the study. A HIPAA form will be incorporated into the Informed Consent Form. The HIPAA form describes participant and data confidentiality associated with the study. After allowing adequate time for review, the participant and parents will have the opportunity to ask questions and receive answers. When all questions have been answered, the consent and assent will be signed and a signed copy provided to the participant and parents. This will all be conducted before any study measures and interventions are undertaken.

A patient will be informed that he/she is not obligated to participate in the study. The informed consent process should ensure that there is no penalty for *not* participating in a research study and that treatment will not be compromised if patients do not participate or if they cease participation at any time. Adequate time will be allowed for the prospective participant to ask questions.

The patient, their legal representative, and the investigator or person obtaining the consent must sign the informed consent. A copy of the signed form must be provided to the participant. The informed consent form is to be retained in the participant source binder, along with the completed informed consent process note documenting the consenting process.

If the participant is between the ages of 10-17 parental consent will be obtained during the consent process. If the participant is ≥18 the participant will sign consent without the need of parental consent.

eConsenting: Consent may take place by several methods: in-person paper consent, in-person electronic consent (using REDCap for the eConsent, detailed below) or over the phone and/or secure video line (via REDCap for eConsent, detailed below). No matter the consenting

process, study procedures will not occur prior to a fully executed consent form. A copy of the consent form will either be given to the participant in paper form or emailed to them via REDCap depending on how the consent is completed. In all cases, the consent process will be documented on the informed consent process note.

Staff will make sure that the eConsent database is updated as soon as possible after a new version of the paper consent is approved. Staff will also make sure paper consents are used to consent eligible participants in the event that the eConsent database is not updated prior to eligible participants being available for consent approach by a member of the study staff. For the reasons described, the eConsent will not be submitted to the IRB for approval.

Integrating Consent Electronically: The IRB approved consent document will be uploaded into the database instrument. The IRB approved consent will be modified to an electronic format that includes all the same elements found on the paper document (i.e. IRB number, approval dates, version number, etc.). The elements of the consent requiring a signature has been added as a generated field. The instrument includes fields to capture full name, signature, and date and time of the signature for the consenter, and witness and conditional text that states that all signatures are associated with the Participant ID# registered in the database. When completed, REDCap will generate a footer that contains the long date and time the document was submitted and “Confidential” listed in the header as an added precaution to preserve the research participants' confidentiality. REDCap's 'Auto-Archiver + eConsent Framework' will be used. The 'Auto-Archiver + e-Consent Framework' survey option adds two things to the typical survey-taking process. 1) Before a participant completes the survey, an extra certification page is added to end of the survey that displays an in-line PDF copy of their survey responses in which they will be asked to confirm that all information in the document is correct. Once they confirm all is correct, the survey will then be marked as complete. The survey will not be considered complete until they fulfill the certification step. 2) Upon completion of the survey, a static copy of their responses in the form of a consent-specific PDF will be stored in the project's File Repository. The consent-specific PDF may have the values of the e-Consent Framework Options inserted at the bottom of each page in the PDF. These values (i.e., name, date of birth, etc.) are added to the PDF as extra documentation of the identity of the person who is consenting.

The HIPAA Consent is integrated into the consent form.

Signature Process: Participants—and legal guardians if the participant is underage—and witnesses/individual obtaining signature will type their first and last name into a text box, sign their name in the signature field with a stylus or finger and then click “Now” by the date field to automatically enter the date and time. A copy will be sent electronically to the participant.

eConsenting Process: Participant presenting to clinic will be given an electronic tablet with the preloaded IRB approved and HIPAA documents for the study. Participants will be given time to read through the consent form(s) and then the study coordinator (or designee) will review the consent, and any study handouts with the participant. Once the consenting process has been completed and all questions have been answered, the study and HIPPA consents will be signed and dated by the participant and witness and submitted via the REDCap database. Participants be sent an electronic copy of the ICF documents through their provided email and will receive documents. Signed and submitted documents will be available as a PDF in REDCap's File Repository. A PDF of the eConsent document will be sent to CCHMC HIM per requirements.

Remote eConsenting Process: The remote econsent process will follow the same process outlined above with two minor differences. 1) Communication with participant will be not be in-person. 2) Witness/Individual obtaining consent will enter their first and last name, signature, and time of signature in a separate instrument outside of the main consent form. This might lead

to a signature time difference between witness and participant (plus parent, if applicable). This separate instrument will additionally capture the REDCap/CCHMC username of the individual obtaining consent.

5.4 Withdrawal

Participant withdrawal from the study

This is not a treatment study and participants are free to withdraw at any time without consequences. The reason for withdrawal will be documented for all participants withdrawn from the study.

Investigator-initiated withdrawal criteria

Given that this is not a treatment study, there are several circumstances where the investigator may terminate the involvement of a participant.

1. Participants are unable to adequately communicate and understand the consent form and instructions given to them.
2. Participants decline further participation in the study.
3. Participants are unable to keep the appointments.
4. Participants fail to comply with experimental protocol or instructions.
5. Identification of brain, neurologic, or severe psychiatric abnormalities beyond those normally associated with chronic pain.
6. Experimenter assesses that withdrawal from the study is in the participant's best interest.
7. Patients fail to adequately comply with or complete sufficient portions of their treatment.
8. Healthy control participants are using opioid or other analgesic drugs or patients are using non-prescribed drugs (positive drug test).

5.5 Re-Consenting Patients Turning 18

Participants may turn 18 after enrolling due to the longitudinal nature of the study. Participants that turn 18 during their involvement of the study will be invited to reconsent as legal adults. If the participant does not reconsent, the participant will be discontinued from remaining study procedures.

5.6 Option for Future Re-Contact of Participants

The dual principal investigators would like to maintain the option for future re-contact of study participants after completion by the participant or termination of the study. The purpose for re-contact would be to invite participation in the conduct of related or ancillary studies with a sub-population of study participants. An optional consent for re-contact will be included in the study informed consent and assent documents.

6. STUDY PROCEDURES

6.1 Timeline of Procedures

Participants will be examined at in person baseline session(s), will complete quarterly remote surveys, and will return for a 1 year follow-up in person session. Parent(s)/Guardian(s) may also be asked to complete surveys.

Baseline Session(s): Participants will undergo symptom assessment, psychosocial characterization, quantitative sensory testing, and MRI. Questionnaires may be completed remotely while quantitative sensory testing and MRI will be in-person. QST and MRI assessments may be on separate days to minimize participant burden.

Quarterly Remote Surveys: Participants will undergo symptom assessment and psychosocial characterization at approximately 3, 6, and 9 months after their baseline visit.

1 Year Follow-up: Participants will undergo symptom assessment, psychosocial characterization, quantitative sensory testing. Questionnaires may be completed remotely while quantitative sensory testing will be in-person.

6.2 Symptom Assessment

Ratings of pain: Patients will be instructed to provide ratings of pain intensity and unpleasantness at the beginning of each session and during quantitative sensory testing. To help them differentiate between pain intensity and unpleasantness, standardized instructions as described in Price (Price et al., 1983) will be used. Ratings of the spatial extent of pain may also be acquired.

Demographic and Health History: Parents will be asked to provide information related to their child's demographic (e.g., *age, biological sex, gender, date of birth; ethnicity/race*), known medical or psychiatric diagnoses, and current medications and therapies. This information will determine final study eligibility. We will also collect information about the (a) parents' pain history, (b) the child's sleep history, and (c) the child's current residential address (city, state, zip code, and county). The address will be used for geospatial coding neighborhood measures (e.g., deprivation index(35-37), poverty(38, 39), proximity to greenspace(40, 41)) related to socioeconomic status (SES). After processing the address data for different geomarkers (e.g., deprivation index, greenspace), all HIPAA identifiers will be removed. As part of the health history, parents (or guardian) will be asked to complete a health care use assessment reflecting medical and other treatments for pain.

Puberty status *(Pubertal Development Scale, PDS)* and additional questions (i.e., medications) about their menstrual cycle (biological females) will be assessed.

Body map(42)*:* Patients will be asked to indicate body parts that are affected by pain.

CCHMC Headache Questionnaire(43-45)*:* Will be used to characterize the experience of migraines and headaches (e.g., frequency, intensity, quality, and location) based on ICHD3 criteria.

Pediatric Migraine Disability Assessment (PedMIDAS)(46)*:* Will be used to assess migraine related disability.

CRPS diagnostic questionnaire: Will be used to assess the extent of CRPS symptoms according to the IASP diagnostic criteria. In addition, participants will be asked to describe any potential injury that was associated with the beginning of the symptoms.

Rome IV Diagnostic Questionnaire for the Pediatric Functional GI Disorders (47)*:* Will be used to assess FAPDs, including irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine, and functional abdominal pain - not otherwise specified (FAP-NOS).

Abdominal Pain Index (API) (48)*:* Will be used to characterize frequency, duration, intensity, and other aspects of abdominal pain.

Pain Severity Assessment Tool (PSAT)(49)*:* Will be used to characterize the presence of multiple sites of pain (based on several MSK sites) and the presence and severity of somatic symptoms. Subscales are generated for "Widespread Pain Index" (WPI) and "Symptom Severity" (SS), which are used to dichotomize the presence or absence of widespread MSK pain. Also, the subscales can be combined for a Total Symptom Severity Score.

Pediatric Pain Screening Tool (PPST): Will also be used to (1) discriminate between pain-free and chronic pain cases and (2) determine low- vs. high- (i.e., overlapping pain) risk groups.

Additional screeners (e.g., temporomandibular disorders - 3Q/TMD(50)) may also be used.

6.3 Psychosocial Characteristics

Revised Adolescent Sleep and Wake Scale (rASWS, (51)): 10 item plus sleep duration items. ASWS will be used to assess participant's sleep quality.

Child Fear of Pain Questionnaire (FoPQ-Child, (52)): FoPQ will be uses to assess participant's behaviors towards pain.

Functional Disability Index (FDI,(53)): FDI will be used to assess a participant's level of function with pain.

Pain Catastrophizing Scale (PCS-C, (54, 55)): PCS-C will be used to assess participant's behavior towards pain.

Pain Stages of Change Questionnaire – Adolescent Short Form (PSOCQ13-A, (56, 57)*):* This survey will be used to assess how a participant copes with their pain.

PROMIS Measures(58):

Pediatric Anxiety: Will be used to assess anxiety.

Pediatric Depressive Symptoms: Will be used to assess depressive symptoms.

Pediatric Fatigue: Will be used to assess fatigue.

Pediatric Cognitive Function 7a: Will be used to assess cognitive functioning.

Pubertal Development Scale (PDS): The pubertal development scales PDS will determine a non-invasive account of pubertal development.

Pain Frequency, Severity, & Duration Scale (PFSD,(59)): Will be used to collect clinical pain history.

Children's Somatic Symptoms Inventory (CSSI, (60)*):* Will capture levels of somatic complaints and sensory pain qualities.

PROMIS Pain Quality – Sensory(61): Will capture levels of somatic complaints and sensory pain qualities.

PROMIS Pain Interference(62): Will capture pain-related disability over the past week.

Tampa Scale of Kinesiophobia-11 (TSK-11, (63-65)) – Will capture fear of movement.

Pediatric Daytime Sleepiness Scale (PDSS, (66-68)) – Will assess daytime sleepiness

Pre-Sleep Arousal Scale (PSAS, (69)) – Will assess pre-sleep arousal related to cognitive (e.g., racing thoughts, worry, and anxiety at bedtime) and somatic (e.g., tense muscles, cold extremities, or pounding heart before falling asleep) factors

Morningness/Eveningness Questionnaire (MEQ, (70)) – Will capture circadian phase preference (e.g., "chronotype") related to morningness vs. eveningness

Adolescent Sleep Hygiene Scale (ASHS, (71)) – Will assess typical sleep habits

Adolescent Insomnia Questionnaire (AIQ, (72)) – Will capture behaviors and experiences related to insomnia

Life Orientation Test (YLOT, (73)) – Will assess dispositional optimism (e.g., positive expectations of the future).

10-Item Positive and Negative Affect Schedule for Children (PANAS-C-SF) - Will be used to assess positive affect (i.e., joyful, cheerful, happy, lively, proud) in addition to negative affect (i.e., miserable, mad, afraid, scared, sad) over the past few weeks

Connor-Davidson Resilience Scale 10-item (CD-RISC-10, (74-76)*)* - Measures one's ability to cope with stress and adversity.

Child PTSD Symptom Scale(77) (CPSS-V, (77)*) -* Participants are asked to identify the most distressing or traumatic event that bothers them and assess post-traumatic stress symptoms over the past month.

PROMIS Ped Family Relationships 8a, v1.0) – Will ask about relationships.

PROMIS Ped Peer Relationships 8a, v2.0 - Will ask about relationships.

6.3.1 Timeline of Survey Administration (Table1)

Timing (Approximate)	Data Collection Procedure	Survey Completion Timing**				
		Base (T_1)	3m (T_2)	6m (T_3)	9m (T_4)	12m (T_5)
Primary (In-person Preferred, Remote for QHU)	Pubertal Development Scale (PDS)	⭘	✞	✞	✞	✞
	Menstrual Cycle (MC)	⭘	⭘	⭘	⭘	⭘
	Functional Disability Inventory (FDI)	⭘	⭘	⭘	⭘	⭘
	PROMIS Ped Anxiety	⭘	⭘	⭘	⭘	⭘
	PROMIS Ped Depression	⭘	⭘	⭘	⭘	⭘
	PROMIS Ped Fatigue	⭘	⭘	⭘	⭘	⭘
	PROMIS Ped Cognitive Function	⭘	⭘	⭘	⭘	⭘
	CHOIR Body Map	⭘	⭘	⭘	⭘	⭘
	Pain Symptom Assessment Tool (PSAT)	⭘	⭘	⭘	⭘	⭘
	CCHMC Headache Questionnaire	⭘	⭘	⭘	⭘	⭘
	Pediatric Migraine Disability Assessment (PedMidas)	⭘	⭘	⭘	⭘	⭘
	ROME IV	⭘	⭘	⭘	⭘	⭘
	Abdominal Pain Index (API)	⭘	⭘	⭘	⭘	⭘
	3Q/TMD	⭘	⭘	⭘	⭘	⭘
	Pediatric Pain Screening Tool (PPST)	⭘	⭘	⭘	⭘	⭘
	Pain Frequency, Severity, & Duration Scale (PFSD)	⭘	⭘	⭘	⭘	⭘
	PROMIS Pain Quality - Sensory	⭘	⭘	⭘	⭘	⭘
	PROMIS Pain Interference	⭘	⭘	⭘	⭘	⭘
	Pain Catastrophizing Scale – Child (PCS-C - Child)	⭘	⭘	⭘	⭘	⭘
	Tampa Scale of Kinesiophobia-11 (TSK-11)	⭘	⭘	⭘	⭘	⭘
	Revised Adolescent Sleep Wake Scale (rASWS)	⭘	⭘	⭘	⭘	⭘
	Pediatric Daytime Sleepiness Scale (PDSS)	⭘	⭘	⭘	⭘	⭘
	Pre-Sleep Arousal Scale (PSAS)	⭘	⭘	⭘	⭘	⭘
	Adolescent Insomnia Questionnaire (AIQ)	⭘	⭘	⭘	⭘	⭘
Supplemental (Remote Preferred)	Children's Somatic Symptoms Inventory (CSSI)	⭘	✞	✞	✞	⭘
	Fear of Pain Questionnaire (FOPQ – Child)	⭘	✞	✞	✞	⭘
	Pain Stages of Change Questionnaire (PSOCQ)	⭘	✞	✞	✞	⭘
	Child PTSD Symptom Scale for DSM-5	⭘	✞	✞	✞	⭘
	Positive & Negative Affect (PANAS)	⭘	✞	✞	✞	⭘
	Youth Life Orientation Test (YLOT)	⭘	✞	✞	✞	⭘
	Connor-Davidson Resilience Scale (CDRS-10)	⭘	✞	✞	✞	⭘
	Adolescent Sleep Hygiene Scale (ASHS)	⭘	✞	✞	✞	⭘
	Chronotype Questionnaire (MEQ)	⭘	✞	✞	✞	⭘
	PROMIS Ped Family Relationships	⭘	✞	✞	✞	⭘
	PROMIS Ped Peer Relationships	⭘	✞	✞	✞	⭘

** **Anticipated Survey Completion**: Surveys or procedures conducted (⭘) and not conducted (✞) at Screening (T0), Baseline Visits (T1) and Quarterly Visits at 3-, 6-, 9, and 12-months (T2-T5)

6.3.2 Parent Surveys (Table 2)

Timing (Approximate)	Data Collection Procedure	Research Domain*	Survey Completion Timing** Base (T_1)	3m (T_2)	6m (T_3)	9m (T_4)	12m (T_5)
Pre-Visit (Remote)	Participant demographics	1	⭘	⭘	⭘	⭘	⭘
	Health history form (Participant & Parent)	1	⭘	✞	✞	✞	✞
	Health history form (Participant) - QHU	1	✞	⭘	⭘	⭘	⭘
	Health care cost diary (Participant)	1	⭘	✞	✞	✞	✞
	Health care cost diary (Participant) - QHU	1	✞	⭘	⭘	⭘	⭘
	Fear of Pain Questionnaire (FOPQ – Parent)	5	⭘	✞	✞	✞	⭘
	Pain Catastrophizing Scale – Child (PCS-C, Parent)	5	⭘	✞	✞	✞	⭘

QHU, Quarterly health update

**** Anticipated Survey Completion**: Surveys or procedures conducted (⭘) and not conducted (✞) at Screening (T0), Baseline Visits (T1) and Quarterly Visits at 3-, 6-, 9, and 12-months (T2-T5)

6.4 Thermal Imaging

To better describe participants' symptoms, temperature of their affected and unaffected body regions will be measured using an infrared camera. Changes in temperature in the affected limb is part of the diagnostic criteria for CRPS. Thermal imaging will provide valuable information on the symptoms exhibited by the participants, without any risk.

6.5 Quantitative Sensory Testing

Participants will first undergo psychophysical training in which they receive a standard set of heat and cold stimuli (up to 33 stimuli of 5 sec plateau duration) ranging from 0-49°C. This procedure provides participants with experience using the rating scales, facilitates generalizability of results, and provides a measure of pain sensitivity that is independent from that obtained during the fMRI portions of the study. Such training sessions also maximize reproducibility of pain ratings (78). After completion of training, participants will undergo the following battery of sensory tests for the remainder of the psychophysical session.

Threshold Assessments:

Thermal thresholds: Innocuous warm, innocuous cool, cold pain, and heat pain thresholds (up to 6 presentations/modality) will be assessed using the method of limits.

Tactile Thresholds: Von Frey filaments with increasing thickness will be applied perpendicular to the participant's skin with a very light pressure. The applied pressure will be enough to slightly buckle the filament. To avoid visual clueing, participants will keep their eyes closed for the whole duration of this task. Each filament will be applied up to 5 times at a given body site and threshold will be defined when participants are able to identify the touch in 80% of the trials.

Pressure Pain Threshold (PPTh): PPTh will be assessed with a hand-held algometer (Algomed, Medoc) across up to three repetitions of stimuli applied perpendicularly on testing site. Participants will be instructed to press a button and/or say "pain" at the first sensation of pain (PPTh).

Spatial Tasks:

Conditioned Pain Modulation: Conditioned pain modulation (also known as diffuse noxious inhibitory control) will be activated by immersion of the hand in 0-10°C water and evaluated by examining the reduction in pain intensity ratings to a pressure pain threshold and noxious heat

stimulus (up to 49°C) applied to the trapezius and ventral forearm (respectively), as we have done recently (79).

Spatial Summation of Pain: Spatial summation of pain will be assessed by placing two thermal stimuli (up to 49°C) on participants' legs or other body regions, typically at a 10cm separation distance. Participants will be instructed to rate overall pain with one rating. Control stimuli (up to 49°C+35°C, and up to 49°C alone) will allow the assessment of spatial summation.

Attentional Inhibition of Pain: During the spatial summation paradigm, participants will provide ratings during two attentional conditions: 1) Participants will be cued to rate overall pain with one rating. 2) Participants will be cued to divide their attention between both stimuli and instructed to rate pain from each stimulus separately. Control stimuli (up to 49°C+35°C, and up to 49°C alone) will allow the assessment of spatial summation and attentional inhibition of pain.

Graphesthesia: A graphesthesia task in which numbers between 0 and 9 will be drawn in a pseudo-randomized order on the participant's skin using a rounded tip stylus-like device with very light pressure. The pressure will be enough to allow for a sensation of the stylus moving across the testing area. To avoid visual clueing, participants will keep their eyes closed for the whole duration of this task.

Two-point discrimination: One or two innocuous tactile stimuli will be delivered at various distances and the participant will report whether they perceive one or two points.

Temporal Tasks

Offset Analgesia: Offset analgesia will be assessed using the three temperature method (up to 49°C 5s, 50°C 5s, 49°C 20s) using continuous ratings of pain intensity, as we have done previously (80).

Temporal Summation (TS): A standardized pinprick stimulator, up to 256 mN will be used for the assessment of TS. VAS ratings of single pinprick stimulation will be compared with a series of 10 repeated pinprick stimuli of the same force over the same area. The mean ratings of series divided by the mean pain ratings of single stimuli was calculated as the WUR. We may also collect two additional ratings (e.g., 15 and 30 seconds after the 10 stimuli) of any remaining pain (e.g., after-sensations).

6.6 Brain Imaging

Total scanning time: Together with inter-scan intervals and time needed for positioning participants in the scanner, the proposed sequences (below) can be obtained in a 1-1.5 hour duration MRI scanning session. This duration has been used in the vast majority of our imaging studies since 1992 and we have found that participants can tolerate this duration with minimal difficulty. Participants are queried for possible discomfort at the end of every series. Participants can generally remain still during the 5-12 minutes acquisition series and can shift/reposition arms and legs between series if needed.

Structural scan: A high-resolution T1-weighted sequence will be used for visualization of brain anatomy and for spatial normalization of functional imaging data. This sequence will last approximately 5 minutes. These data can be used for volumetric brain mapping of cortical and subcortical structures. T2 sequences and diffusion tensor imaging sequences may also be acquired to further characterize aspects of brain anatomy.

Resting-state functional connectivity: Resting-state functional brain images will be acquired using conventional or multiband BOLD sequences. These sequences consist of rapidly-acquired series of brain images covering the whole brain. Each resting-state series acquisition will last up to 12

minutes. These images will be used to investigate functional connectivity between brain areas at rest.

Cerebral Blood Flow (CBF): CBF will be measured in a fully quantitative fashion with arterial spin labeled (ASL) imaging (Luh et al., 1999). This technique, which is regularly used in our laboratory, allows investigation of steady-state brain activity, but has also been successfully used to study task related activity.

Task-related activity: Functional brain images will be acquired using a BOLD sequence to similar to the one used for assessment of functional connectivity. ASL sequences may also be used for selected tasks. While these images are acquired, participants will undergo several sensory tasks.

Multisensory task: The multisensory task will include visual (reversing/flashing checkerboard), auditory (tones) and sensorimotor (finger opposition) stimuli. Participants will be asked to focus on these stimuli while brain images are acquired.

Spatial tuning task: The brain mechanisms regulating spatial tuning may be further delineated using our divided attention paradigm.(81) Two noxious thermal stimuli (≤48°C, 10s) will be delivered to participants' legs at a 10cm separation distance. Participants will provide ratings during two attentional conditions: 1) Participants will be cued to rate overall pain with one rating. 2) Participants will be cued to divide their attention between both stimuli and instructed to rate pain from each stimulus separately. Control stimuli (≤48°C+35°C, and ≤48°C alone) will allow the assessment of spatial summation and attentional inhibition of pain.

Graphesthesia Task: Spatial processing disruptions may be further probed with the graphesthesia task. Numbers will be traced onto the legs of the participant and the participant will indicate which number was traced.

6.7 Opting-out and Omission of Experimental Procedures

All experimental procedures are observational only and do not involve provision of any treatment. Accordingly, participants will be allowed to opt out of any experimental procedure without prejudice. Similarly, time constraints or technical issues may result in omission of certain experimental procedures. Partial data sets will still have great utility given the lack of knowledge of pediatric pain. Opted-out and omitted experimental procedures will be documented with a note to file, and as they are anticipated, will not be considered a deviation.

6.8 Pregnancy

Adolescents who are pregnant or nursing may not participate. A urine pregnancy test may be conducted to confirm a lack of pregnancy if the participant is sexually active and not using appropriate birth control. Underage participants who test positive for pregnancy will have their parent/caregiver notified. Participants who become pregnant after the baseline session may remain enrolled.

6.9. Drug/Substance Use

A urine sample will be collected from all participants to assess the usage of non-prescribed drugs/substances. Healthy participants with positive tests for opioids or other analgesics will be excluded. Patients using non-prescribed substances may also be excluded. Underage participants who test positive for drugs/substances will have their parent/caregiver notified.

7. DATA ANALYTIC PLAN

Behavioral data: Mplus(82) will be used to conduct all behavioral analyses to: 1) handle missing data via either maximum likelihood estimation or multiple imputation, with both allowing auxiliary

correlate variable inclusion(83, 84); an attrition analysis will be performed using SAS PROC MI to identify possible non-random attrition dependent variable values (MNAR). If dropout is systematic, Selection and Pattern Mixture Models, and their newer mixture versions, (85, 86) will be used to appropriately address MNAR attrition(83), 2) utilize several default parameter estimation algorithms (e.g., MLR, MLF, WLSMV) robust to Type-1 errors arising from non-normal response data, and 3) to allow additional options (e.g., start values, Cholesky decomposition) in the unlikely event of parameter estimation non-convergence.

Neuroimaging Data: The FSL (FMRIB's Software Library, Oxford, UK) software package will be used for the vast majority of image processing operations and statistical analyses. FSL analyses will be augmented by AFNI and/or CONN(87) and python scripts.

Spatial processing and transformation: T1-weighted images will be brain extracted and then non-linearly warped into standard anatomic space (MNI152). EPI images will be motion-corrected, unwarped, and registered to the high resolution T1 structural image and then nonlinearly warped to standard space. To facilitate intersubject comparisons and to reduce the number of statistically independent comparisons, BOLD images will be smoothed with a 5 mm FWHM filter.

Processing of pCASL images into CBF images: A single fully quantified CBF volume (ml/100g/min.) will be calculated from each 4D series of PCASL images(88) following motion correction, tag-control subtraction, and assessment of T1 signal. CBF images will be transformed to standard space as described above.

Statistical analysis of ASL data: CBF data from each individual will be motion corrected, and ratio normalized to minimize the impact of fluctuations in global signal. A first level fixed effects analysis will be executed within FEAT to identify within subject effects. A second level random effects analysis will be executed within FEAT to identify between group effects. Clusters of activation will be identified using a threshold of $Z>3.1$ and their statistical significance will be estimated according to Gaussian random field theory.(89)

BOLD / Connectivity analyses: The aCompCor approach will first be used to reduce variability due to physiological and scanner noise(90) using a processing pipeline integrating modules from FSL and AFNI. Denoised data will then be imported into FEAT. Time courses of activity will be extracted from seed regions. These seed regions will be objectively defined on the basis of each participant's anatomy. Next, first level, fixed-effects analyses will be run for each BOLD series to identify voxels that have time courses that are significantly correlated with that of the seed or of the task. Second level analyses will examine effects across imaging series, but within subjects. Finally, third level random effects analyses will identify differences in functional connectivity according to groups. Clusters of activation will be identified using a threshold of $Z>3.1$ and their statistical significance will be estimated according to Gaussian random field theory.(89) Age and sex will be added as covariates.

Conjunction analyses: Conjunction analyses will be performed on both CBF and BOLD data in order to determine if activation (or connectivity) overlaps between chronic pain groups.(91) This analysis tests the null hypothesis of no overlap, and as such, is an optimal method to test for similar patterns (but not magnitudes) of activation or connectivity. Statistical significance of overlapping clusters will be determined according to Gaussian Random Field theory.(89)

Structural analyses: T1-weighted structural data will be analyzed with FSL-VBM as we have done previously.(92) A regression analysis will be performed using a general linear model to examine the relationship between treatment type and grey matter differences across the whole brain. Age and sex will be added as covariates. Permutation-based nonparametric testing (10,000 permutations) will be used to evaluate this relationship in a voxel-wise fashion.

Threshold-free cluster enhancement will be utilized to define significant clusters. A familywise error corrected P value of P < .05 will be applied to correct for multiple comparisons and to identify clusters exhibiting a significant relationship between grey matter density and treatment type.

Multi-task deep Ensemble learning model: We will design the novel multi-task deep *Ensemble* learning model to be a two-level ensemble model (Fig. 7), combining the predictive power of both state-of-the-art deep learning and traditional machine learning. We will 1) first build a diverse model library. The diversity plays a key role, and it is a necessary and sufficient condition in building a powerful stacking ensemble model.(93-95) Each input data type (*i.e.*, features extracted from fMRI, QST, and psychological assessments) will be used to create a series of unique machine learning models. We will build a model library that will consist of a diverse set of multiple traditional models, including SVM,(96) Artificial Neural Networks (ANN),(97) random forest (RF),(98) LR,(99) Ridge(100) and least absolute shrinkage and selection operator (LASSO).(101) Multiple models will be trained with different hyperparameter settings and training datasets. 2) We will then integrate the multiple machine learning classifiers from the model library using our multi-channel deep neural network (DNN) as a fusion model.(102, 103) The number of channels is designed based on the number of models in model library. Each input channel will contain several neural network blocks. The multiple input channels will be eventually fused into one output channel through a fusion block. Each block will consist of a fully connected layer, a batch normalization layer, and a dropout regularization layer. Followed by the fusion block, a softmax output layer will be used to predict chronic pain conditions (i.e., migraine, complex regional pain syndrome, musculoskeletal pain, functional abdominal pain, as well as heathy controls) and pain trajectory. We will perform nested k-fold cross-validation (i.e., training, validation, and testing dataset split method) to evaluate our model with multiple metrics, including multi-class accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). We will perform data augmentation on training data to prevent model overfitting using our prior method.(104) Hyperparameters of the model will be optimized based on validation data before testing on unseen test datasets. For feature ranking, we will apply a connection weights method(105) to identify the most discriminative features for each chronic pain condition or trajectory of recovery. The deep *Ensemble* learning model will be implemented using Python, scikit-learn, and Tensorflow package. Prior chronic pain studies(106) demonstrated that a robust deep learning model can be obtained using ~200 samples. Thus, we expect that the sample size (500 subjects) in this work, combined with the data augmentation strategy, is sufficient for our deep learning model. During the data collection period, we will develop/optimize analysis pipelines with existing patient and control data.

Power analysis and missing data: Power calculations were performed for ***neuroimaging data*** to ensure that we have an adequate sample size 1) to detect brain activity changes in hypothesis-directed analyses and 2) to identify relevant brain mechanisms through deep Ensemble learning techniques. Power calculations for neuroimaging data are challenging since such calculations depend crucially on effect size as well as properties of the imaging data and statistical approach used to deal with the multiple comparisons of >20,000 voxels. We used the NeuroPower tool(107) to calculate statistical power and sample sizes based on our preliminary BOLD in youth with migraine. Based on between group comparisons of functional connectivity data between migraine patients and controls (preliminary data C.2.2), 36 participants (18 participants/group) would be required for 80% power in between group comparisons. However, contrasts between patient groups would likely need greater numbers due to potentially more subtle differences. Consistent with this expectation, power calculations examining differences in functional connectivity of the amygdala between migraine and functional abdominal pain (preliminary data C.2.4) revealed that approximately 108 participants (54 participants/group) would be required to reliably detect differences between two chronic pain conditions. Both

power calculations were performed using z-transformed statistical images of the whole brain, a cluster-forming threshold of $z>3.1$ and $p<0.05$, isotropic smoothness of 5mm, and voxel sizes of 2x2x2mm, and a Gaussian Random Field theory-based approach for multiple comparisons. For these complex data, statistical power is defined as an 80% probability of correctly detecting an active peak for all peaks above the cluster-forming threshold. Power calculations for the deep Ensemble learning techniques are nearly impossible to develop given the nature of the analyses, however, analogous machine learning approaches with pain data required 109 participants to develop a marker for a single group.(108) Accordingly, we estimate that 100 participants/group would provide adequate power for both hypothesis-directed analyses and machine learning analyses.

Plan for Robust and Unbiased Results: Our group has a history of producing highly reproducible imaging and psychophysical studies. Our original psychophysical finding of offset analgesia(109) has been replicated in more than 22 papers by laboratories across the world. Our original finding of anterior insular activation during pain(32) has been replicated by hundreds of brain imaging studies.(110-113) Our imaging studies have been highly reproducible, in part, because we always use whole-brain searches rather than region of interest (ROI) analyses, consistent corrections for multiple comparisons using conservative cluster-forming thresholds, and random effects statistical models to increase generalizability and to diminish outlier effects. This highly-powered data set will be analyzed with a conservative, statistically rigorous approach designed to maximize reproducibility.(114) Towards this end, all analyses will be performed across the entire brain and both positive and negative relationships will be assessed and reported.(115, 116) These analyses will be controlled for multiple comparisons by cluster-based methods, such that family-wise error rates will be held to a $p<0.05$. Region of interest approaches will be avoided in order to minimize errors due to confirmation bias and “double-dipping.”(115, 116) Analyses will be conducted by individuals blinded to group assignment in order to further minimize biases.

8. DATA MANAGEMENT

An Electronic Data Capture (EDC) system that is designed to support reliable and secure entry of non-imaging data will be used for the study. Paper forms might be used for recording of pain ratings and may be used as backups for questionnaires in the event of computer malfunction during data acquisition.

Data Entry: Data can be entered directly via a fully validated and 21 CFR Part 11 compliant, secure application and stored centrally. Data will be entered by subject study identification number; names will not be linked with participant data in the database.

Data Validation and Monitoring: Real-time validations will be integrated into the data entry system. Inconsistent or questionable values can be flagged during entry, and reports can be automatically generated to the data entry client. These reports provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values.

Data Security and Integrity: All data changes are written to an audit trail. The audit trail identifies the data item by table, column and key field. The entry includes the user, date and time, as well as the old value and new value. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection.

The following levels of security are employed to ensure privacy and integrity of the study data:

1. Access to the study data and protocol requires use of assigned user names and passwords.
2. Individual roles and access levels are assigned by the study data manager.
3. Passwords are changed regularly.
4. Web-based entry uses secure socket layer data encryption.

9. DATA SHARING AND FUTURE USE

Data That Will Be Shared: Data sharing represents a critical dimension of the proposed research and is a requirement for publication in many journals and is required by NIH. The data will be quite complex with psychological, psychophysical, demographic information collected outside of the scanner, and multiple modalities of MRI information collected during scanning. Accordingly, this rich dataset can be utilized for many secondary analyses. All modalities of data will be shared, with raw data included. We will share identified data with other related studies at CCHMC for which participants have given consent that ask them to do the same procedures in order to decrease participant burden in scientifically appropriate situations.

Formatting of Data to Facilitate Sharing: As data is acquired, it will be named and placed into directory structures according to the BIDS standard (Brain Imaging Database Structure: http://bids.neuroimaging.io/). This standard accommodates all types of neuroimaging data to be acquired in the present proposal, and also allows for the inclusion of non-neuroimaging data such as psychological, psychophysical, and demographic information. Importantly, when data is in this format, it can be readily shared within OpenFMRI and other data warehouses.

Prior to sharing, all data will be de-identified in a HIPPA-compliant fashion. Data sets will be carefully reviewed to make sure that information such as age and sex cannot be used to gather additional information that could potentially identify individual subjects. For example, only year of birth, rather than date of birth, will be made available. All categorical demographic variables will be collapsed into categories large enough so that combinations of demographic categories for age, sex, area of residence, etc., will have 10 or more individuals in each cell. Neuroimaging data may be "de-faced" to further protect the privacy of participants. This data set will be accompanied by a data dictionary describing the content of each data set.

Deposition into Open Databases for Distribution: Upon completion of the study (including primary and secondary analyses), the principal investigators will generate public use data sets for distribution. There are several potential data warehouses for distribution of this dataset: OpenfMRI, an NSF-funded project led by Russ Poldrack, OPEN PAIN, a NIH-funded project led by Vania Apkarian, COINS, led by Vince Calhoun, the Pain and Interoception Imaging Network (PAIN), led by Emeran Mayer. The final choice for deposition will be driven by the efficiency/accessibility of the database at the time of study completion. All of these databases support non-neuroimaging data (i.e. psychological questionnaire, pain ratings, migraine frequency, demographics, etc.) as well as neuroimaging data.

Accessibility of the Data: Once deposited into an open database, data will be open to the greater scientific community according to the terms of the individual database. Data will then be fully available for secondary analyses, data mining, and to facilitate discovery by combining our data with that of other centers for large-scale analyses. We anticipate making the study data publicly available following the publication of the primary papers describing the results from the proposed specific, individual study (with a goal time line of within 12 months of the final data lock).

10. RISKS TO THE SUBJECTS

10.1 Human Subjects Involvement, Characteristics, and Design.

Children will be recruited to undergo quantitative sensory testing and MRI scans in order to gain insights into central nervous system mechanisms supporting pain.

10.2 Study Procedures, Materials, and Potential Risks.

At initial screening, participants will complete questionnaires to ensure eligibility. At study visits, subjects (and their parent/primary caregiver, when appropriate) will provide information on demographics and complete standardized, psychometrically validated questionnaires and tests. Quantitative sensory testing will be conducted during the baseline and the followup visits. Magnetic resonance imaging of the brain will also be obtained during the baseline visit. At each study visit, a review of adverse events will be conducted.

10.3 Potential Risks.

The risks associated with confidentiality are minimal because all data will be coded by subject number. Any potential risk associated with participation in this study related to potential side effects of the experimental task (i.e. sensory stimulation) and procedures (functional imaging and quantitative sensory testing) will be closely monitored in this study.

Magnetic Resonance Imaging.

While MRI involves the use of powerful magnetic fields and radiowaves, scanning does not expose subjects to any physical risks. There are no adverse effects identified to date from undergoing functional imaging studies with MRI. Potential risks from MRI are addressed in the guidelines for the operation of clinical MR systems by the FDA in 2014 .

MRI Incompatible Objects in/on the Participant: MRI incompatible objects in/on the body have the potential to move, heat, and/or malfunction. Participants with MRI incompatible objects within or on their body will be excluded from the study. Participants will be carefully screened before entry into the experiment and before entry into the scanner environment to minimize this risk.

Main Static Magnetic Field: The 3.0 Tesla static magnetic field strength of the MRI scanners to be used in this study is below the 8.0 Tesla limit recommended by the FDA guidelines for human research. The FDA has concluded that magnetic field below 8.0 Tesla does not by itself impose a risk to human participants.

Specific Absorption Rate: The FDA guidelines for the specific radiofrequency absorption rate (SAR) are set by limiting the patient's core temperature rise to less than 1 degree Celsius. In the absence of core temperature monitoring equipment, the recommended FDA limits for the head are 3.2 W/kg, on average. The MRI scanner system limits the SAR to 3.2 W/kg. In the event that this value is exceeded, the transmitter power supply is turned off automatically within 3 to 5 seconds. These measures ensure that the MRI scanner is well within the current FDA regulations on SAR.

Gradient Speed: The FDA suggested rate of change of magnetic field (dB/dt) is based only on avoiding discomfort to the participant. Peripheral nerve stimulation and other symptoms do not usually occur until dB/dt >20T/sec, and all sequences will be designed to avoid generation of such symptoms.

Acoustic Noise: The FDA deems risks from scanner noise significant when the peak unweighted sound pressure level exceeds 140 dB or when the A-weighted root mean square (rms) sound

pressure level is greater than 99 dBA with hearing protection in place. Hearing protection will be accomplished with our MRI compatible A/V system headphones. These specially designed headphones provide up to 30 dB of sound isolation from the MRI scanner, and will ensure that scanner noise levels do not pose any risk to hearing.

Claustrophobia within the MRI Scanner: Healthy participants will be queried for claustrophobia and excluded. On occasion, a participant may be unaware of their claustrophobia until they are in the scanner. Since this is a basic research investigation, participants unable to tolerate the scan will simply be removed from the scanner. In addition, participants will be given a "panic" button to hold during the scans. In the event that a participant becomes uncomfortable, he or she can press the panic button to notify the operator of the need for immediate attention. Intercom contact will be opened immediately, and the participant can be removed from the scanner if needed. In addition, participants will be monitored visually and via microphone during the whole procedure to ensure that they are tolerating it.

Experimental Pain.

The experimental pain procedures are widely used and safe procedures. We have specifically adapted them to be well-tolerated by children. While generally safe, the experimental pain procedures confer some limited risks. One risk common to all procedures is that the subject will experience pain or discomfort. Specific risks of each procedure are discussed below.

Thermal pain. There is limited risk associated with the delivery of thermal pain. However, this task may produce transient reddening of the stimulated site.

Cold Immersion. There is limited risk associated with the cold immersion procedure.

Pressure Pain. There is limited risk associated with the pressure pain procedure. However, this task may produce minor bruising or other transient trauma at the stimulation site in some subjects.

Innocuous Sensory Stimulation

Side effects or adverse events associated with the experimental tasks involving innocuous sensory stimulation are expected to be relatively minor. However, chronic pain patients may find normally innocuous tactile, visual, and auditory stimuli as painful or unpleasant.

Psychological Questionnaires

Completion of psychosocial measures, aka questionnaires, may feel intrusive and uncomfortable to some persons. This might induce some mild psychological distress. If participants experience such feeling, they will be instructed to inform the experimenter.

11. ADEQUACY OF PROTECTION AGAINST RISKS.

11.1 Informed Consent and Assent

Potential subjects will be identified during an evaluation at Cincinnati Children's Hospital. In the case of patients, the physician/nurse practitioner/psychologist who examines the child or adolescent will explicitly state that they will continue to receive the same high quality of care from them should they choose not to participate. If the participant/family is interested in participating, informed consent from the adults and assent from the child will be both obtained. For both patients and healthy volunteers, the physician/nurse practitioner, research nurse/coordinator, and/or a study PI will provide a full description of the study and answer any questions that the family/participant may have. Approved procedures and forms of the Institutional Review Board will be utilized. The purposes and the risks of the investigation and

the procedures of the study will be explained. The families/participants will be explicitly told that their medical care will not be affected if they choose not to participate.

11.2 Protection Against Risk

Baseline evaluations will be conducted and exclusion criteria applied to ensure that subjects who are enrolled are not at known risk (e.g., metal orthodontia and fMRI). Open-ended questions about possible adverse health experiences will be employed in this study to prospectively assess potential risks among participants.

Magnetic Resonance Imaging. The primary risk of MRI involves: 1) scanning in the presence of magnetic implants (or material) attached to the subject, and 2) claustrophobia. To minimize these risks, subjects will be screened prior to the imaging procedure. In addition, subjects will be informed that they can discontinue the procedure at any time should they become uncomfortable. Subjects will be monitored visually and via microphone to ensure that they are tolerating the procedure. As the scanner is very loud, subjects' hearing will be protected with noise-reducing headphones specifically designed for use in the MRI scanner.

Experimental Pain Procedure. Stimuli that have been used extensively by our laboratory and others' laboratories do not produce tissue damage, burns, or frostbite. Temperatures in this range are frequently encountered in daily life (*snow, ice water bath, handwashing, dishwashing, etc.*) and have been determined to not represent more than a minimal risk in other protocols at Cincinnati Children's Hospital. While they produce pain, risk to the subject is minimal, because: (1) the pain is transient in nature, and generally subsides immediately after the procedure; (2) subjects are instructed that they may stop any procedure at any time with no adverse consequences; and (3) the level of pain experienced by subjects is below their tolerance level. Also, risks will be minimized by adhering to the exclusion criteria, and full discretion by the PI to exclude subjects for whom they feel there is excessive risk for participation. Specific considerations will be used for the following assessments:

Thermal Pain: Combinations of stimulus temperatures, areas, and durations will never be sufficient to produce tissue damage. For example, the temperature range that we routinely use with a 16x16mm probe would extend from 35°C-49°C. All thermal stimuli will be delivered by devices that automatically shutdown in the event of malfunctions leading to temperatures sufficient to produce burns. Furthermore, all participants will be conscious and will be free to terminate the stimulus at any time. To facilitate escape from stimulation, probes will never be strapped to the participant. Instead, probes will be either manually applied by the study staff, held in place by a spring-loaded device, or applied by having the participants passively rest their limb in contact with the probe. Thus, the participants will only have to move their body part away from the probe in order to escape the stimulus.

Cold Immersion: While the cold water is perceived as unpleasant, there is minimal risk associated with this procedure. Subjects will immerse their foot to the ankle or hand up their wrist. Subjects will continue until the end of that trial or until they report intolerable pain. Subjects are told to remove their foot or hand anytime if it becomes intolerable. The maximum immersion time for any trial will be 90s with a minimum temperature of 0°C for the foot and hand.

Pressure Pain: Pressure will be delivered by a hand-held algometer (spring-controlled device delivering calibrated pressure via a flat 10mm diameter rubber tip) at an approximate rate of 30pka/sec until reaching the first sensation of pain. Subjects will continue until the end of that trial or until they report intolerable pain. Subjects are told to say 'stop' anytime it becomes intolerable. The risks of bruising and lingering pain will be diminished by applying brief stimuli well below the subject's tolerance level.

Innocuous Sensory Stimulation: The innocuous sensory stimuli are not delivered at an intensity with potential to damage the skin or elicit significant discomfort in healthy participants. However, chronic pain patients may perceive these stimuli as painful and/or unpleasant. As in the case of the noxious sensory stimuli, all participants will be able to stop the procedure at any time.

Psychological Questionnaires: If participants experience psychological discomfort during completion of psychological questionnaires, they will be able to skip any/all items of the questionnaires.

11.3 Adverse Event Reporting.

All participants will be monitored for safety during the study. Adverse Events will be reported from Visit 1 until the final endpoint. Beginning at Visit 1, each visit will include a review of any adverse events solicited by use of standard open ended question. AEs include new events not present prior to initiation of study procedures or events that were present prior to study procedures but have increased in severity. AEs will be recorded and monitored using an AE case report form that will record AEs by body system, preferred term, severity and relationship to the study, actions that were taken, and current status of the participant. Study staff will notify the PI immediately of any serious adverse events or any adverse events that are suspected to be related to the study.

11.4 Incidental Findings

The imaging protocol used in this study includes only the minimum MR scanning needed to execute the tasks and paradigms for the research project. Board-certified radiologists at CCHMC have determined that the limited anatomical images generated are not adequate to diagnose or to rule out pathology. No report will be generated or supplied to the participant/parents/legal guardians of the participants. However, all scans performed for this project will be reviewed for gross abnormalities by a board-certified or board-eligible radiologist through the PACS system. Although no diagnosis will be made, in the event that abnormal findings are identified, the PI will be informed and will assume responsibility for notifying the parents/legal guardians of the participants.

We will collect contact information for the physician of each participant on the first visit. In the case that abnormal findings are identified, the participant's physician will be contacted by the PI, or a designee of the PI and the findings reported. A report generated by the radiologist will be made available to the physician if requested.

There is a small chance that psychological assessments and other procedures may reveal that participants are at high risk for clinically significant psychological/psychiatric issues. If clinically significant findings are detected, participant/parents will be notified and referred for psychological/psychiatric evaluation. In the event that research personnel become aware of suicidal ideation on the part of any study participant, the following steps will be taken: (1) immediate referral to a licensed clinical psychologist associated with the study, (2) professional and confidential assessment of suicide risk and resources available, (3) immediate notification of parent or legal guardian (if applicable), and (4) referral for appropriate services. It is important to note that data entry and evaluation of psychological questionnaires may be completed days or weeks after patient visits, but that these procedures will still be followed upon identification of suicidal ideation.

For clinically significant findings of neuroimaging, the participants/parents/legal guardians of the participants may choose to obtain appropriate clinical care or seek a second opinion. This might change the participant's insurability and employability as it relates to the clinical finding only. Seeking care may place the participant at risk for unforeseen medical costs, particularly

for conditions that are benign. However, the presumption is that detection of a potentially clinically significant finding will prove to be beneficial.

11.5 Confidentiality

Investigators will take all reasonable measures to protect the confidentiality of participants and their families, including the following:

Attribution of an ID number to each participant: Each participant is assigned a Participant Identification Number (PID). All interview and research data are stripped of identifiers and labeled with the study number. The enrollment log with participant identifiers will be maintained in a secured, locked location available only to the study staff. The participant's name and any other identifying information will not appear in any presentation or publication resulting from these studies. In addition, findings from these studies will be reported in an aggregate manner. Disclosure of the participants' answers outside the research could not reasonably be thought to place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Securing Files: All participant records, including consent forms, will be maintained in a filing cabinet in the locked office of the PI or designees, and will be accessible only to the principal investigator and designees. Computer data files (without subject identifiers) will be stored on computer servers with secure passwords or encrypted electronic storage devices.

Deposition of Data into a Repository: Information from all testing, including MRI data, will be placed into a central data repository that can be accessed by other researchers. Data and samples will be de-identified before submission to any central repository.

12. DATA SAFETY AND MONITORING PLAN

We recognize the need for careful safety, performance, and data monitoring plans to ensure the well-being of the children and adults in this study as well as the scientific integrity of the project. Under the guidance of the study statistician, the research team will generate data and assist the PI in preparing regular safety, performance and data monitoring reports.

Safety Monitoring: Since this study involves no increase over minimal risk, we are proposing that the PI will provide regular oversight of patient safety. At each quarterly monitoring interval, the PI will review adverse events for significance and relationship to the study as well as reasons for losses for follow up. Safety data reports, which will include overall summaries and summaries by experimental group will be reviewed in a blinded fashion to ensure confidentiality of subjects. Suspected serious adverse events will be directly and immediately reported to the PI and physicians overseeing this study (Kenneth Goldschneider, Andrew Hershey, Neha Santucci). If a serious adverse event is reported, the PI may review the data in an unblinded manner. Any adverse events related to the study procedures will be reported to Cincinnati Children's Hospital Medical Center's Institutional Review Board.

Performance Monitoring: The PI in conjunction with members of the study team will meet regularly to evaluate the progress of the study, including accrual and retention, performance, protocol adherence, and other factors that can affect study outcome.

Data Monitoring: The study biostatistician or other study team members will provide routine data monitoring reports including assessments of data quality, data completeness, and timeliness of data entry. These metrics will be used by the study team to evaluate the progress of the study.

Stopping Rules: If an unanticipated serious adverse event occurs as a direct result of participation in the study occurs, subject accrual will discontinue until the Institutional Review

Board (IRB) has reviewed the information and the subject has received adequate care. Subject recruitment will commence again only after the IRB has given the principal investigator the permission to continue. If during the course of the study new information becomes available about the safety of any procedure, the PI will review the evidence to make a decision about discontinuing the study.

13. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO RESEARCH PARTICIPANTS AND OTHERS.

There is expected to be no direct benefit to the participants of the proposed research as it is designed to examine basic mechanisms of pain. However, the knowledge gained will be crucial for developing a better understanding of pain mechanisms and can provide a foundation for the development of new diagnoses and treatments for pain. The risks associated with this study are no more than minimal.

14. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED.

The knowledge gained in this study has the potential to provide translational evidence about pain mechanisms in children. As such, it can provide a foundation for the development of new diagnostic and treatment procedures. The risks associated with this study are no more than minimal, and thus, are reasonable in relation to the importance of the knowledge that may result.

15. COST OF PARTICIPATION

There are no costs associated with study participation.

16. REIMBURSEMENT FOR STUDIES

Participants will typically receive up to $410 as payment for their participation. Pilot participants will typically receive up to $150 as payment for their participation. Funds will be placed on the ClinCard after completion of every session. If sessions are repeated due to technical failure or other factors (i.e. MRI scanner ceases to function), participants will receive additional compensation in line with the regular payment schedule.

Participants will receive payment according to the following schedule:

Baseline visit: Sub-total: $225

This amount includes a payment of $50 for the completion of the questionnaires, $75 for quantitative sensory testing, and $100 for the MRI scan.

Online sessions: Sub-total: $60

During each of the three online sessions, children will receive $20 for the completion of the questionnaires.

One-year follow-up: Sub-total: $125

This amount includes a payment of $50 for the completion of the questionnaires, $75 for quantitative sensory testing

In addition, at the completion of the 1 year follow-up session, participants will receive a 3-D print of their brain using their baseline MRI scan. If a baseline scan is not available, children will have the option to choose from two other proportional 3-D print objects.

Pilot participants will receive payment according to the following schedule:

Baseline visit: $150

This amount includes a payment of $25 for the completion of the questionnaires, $50 for the quantitative sensory testing, and $75 for the MRI scan.

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