IDENTIFYING MARKERS OF TRAJECTORY IN PEDIATRIC COMPLEX REGIONAL PAIN SYNDROME

PROTOCOL

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Date: July 12, 2018

SYNOPSIS

Title	Identifying markers of trajectory of short-term and long-term recovery in pediatric complex regional pain syndrome (CRPS)
Study Objectives	Characterize neurological and psychosocial markers of trajectory of recovery in pediatric CRPS.
Significance	1. CRPS is a severe and complex chronic pain condition in children. 2. Many psychosocial factors impact its development and recovery. 3. CRPS has a strong central component, which is reflected by structural and functional changes in the brain. 4. The interaction between these cerebral changes and recovery has been seldom investigated to date. 5. Interactions between cerebral changes and psychosocial factors, which might affect recovery, are unknown.
Study Design	Basic science investigation of children with CRPS undergoing outpatient and inpatient treatments at CCHMC and of healthy children.
Primary Aim	To characterize markers that are predictive of trajectory of recovery in CRPS patients
Sample size	63 youth/parent dyads
Study Duration	Two years of data acquisition, unlimited analyses
Inclusion Criteria	*All Children:* – Age between 10 and 17 years old – Fluent in English

	Inpatients: – Diagnosis of CRPS – Former unsuccessful treatment for CRPS – Scheduled for or beginning the usual inpatient treatment for CRPS at the FIRST clinic at CCHMC. *Outpatients:* – Diagnosis of CRPS – Scheduled for or beginning the usual outpatient treatment for CRPS at the pain management clinic *Healthy children:* – No diagnosis of chronic pain. *Parents:* – Fluent in English – Child participating in the study
Exclusion criteria	*All child participants:* – Weight/size incompatible with MRI scanner – Identification of brain, neurologic, or severe psychiatric abnormalities beyond those normally associated with chronic pain. – Documented developmental delays or impairment – Any MRI contra-indication, including o Braces, stents, clips, pace-maker or other metal implants affecting the safety of the participants in the scanner and/or the quality of the images o pregnancy o claustrophobia

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1 Specific aims

Pediatric Complex Regional Pain Syndrome (CRPS) is a severe and complex type of pediatric chronic pain, which impacts majorly the children's and their families' lives (McClain & Suresh, 2011). CRPS is divided into Type I and Type II, which are differentiated by the absence (Type I) or presence of a discreet nerve injury (Type II) (Harden et al., 2010). CRPS is treated, in the first instance, with outpatient multidisciplinary interventions (Carter & Threlkeld, 2012; Dickson, 2017; Katholi, Daghstani, Banez, & Brady, 2014; Maihöfner, Seifert, & Markovic, 2010). However, several psychosocial factors, such as pain catastrophizing, depression, and/or familial environment, can affect pain symptoms and recovery (Bruehl & Chung, 2006; Cruz, O'Reilly, Slomine, & Salorio, 2011; Vervoort, Trost, & Van Ryckeghem, 2013). In such cases, more intensive interventions necessitating hospitalization are necessary to help the patients (Dickson, 2017). Defining which factors predict the trajectory of recovery could allow for better targeting of the treatment that a patient needs to successfully recover. In this study, the effect of psychosocial and sensory factors and possible brain markers predicting changes in pain symptoms before – after treatment will be investigated in children diagnosed with CRPS and currently undergoing the usual inpatient or outpatient treatment at CCHMC. In addition, brain changes before – after treatment will be analyzed, as well as potential psychosocial influences on these changes. To establish a baseline of changes associated with CRPS recovery, potential psychosocial and sensory markers, as well as brain activation and connectivity in CRPS patients will be compared to healthy children. To assess the psychosocial environment, parents of children enrolled in the study will complete a series of questionnaires.

For this purpose, we define the following specific aims to investigate in a main study:

1.1 Specific aim 1

Identify changes in psychosocial, psychophysical, sensory, and cerebral characteristics associated with CRPS.

Psychosocial, psychophysical, sensory, and cerebral measurements in children diagnosed with CRPS will be compared with such measurements in healthy children before or at the beginning of an inpatient or outpatient treatment at CCHMC.

We hypothesize that children diagnosed with CRPS will differ from healthy children in their responses to psychosocial, psychophysical, sensory, and cerebral measurements.

1.2 Specific aim 2

Develop predictors of short-term and long-term recovery from CRPS using psychosocial measures, sensory sensitivity, and brain function and structure.

Changes in symptoms of CRPS, such as pain and functional disabilities, will be investigated in relation to potential psychosocial, sensory, and brain markers. Variables obtained at baseline will be examined for significant relationship with recovery.

1.3 Specific aim 3

Investigate the evolution of changes in psychosocial, psychophysical, sensory, and cerebral measures, associated with CRPS.

Short-term and long-term changes in psychosocial, psychophysical, sensory and cerebral measures in children diagnosed with CRPS will be compared to changes in healthy children.
We hypothesize that differences in psychosocial, psychophysical, sensory and cerebral measures between children with CRPS and healthy children will be reduced immediately after treatment, as well as six-month post treatment.

2 Background information

2.1 Background

Pediatric chronic pain is an important health issue that affects up to 46% of children (McClain & Suresh, 2011). Although no clear statistics on its prevalence can be found, CRPS is a severe form of pediatric chronic pain, which is seen frequently in intensive pain treatment programs (Friedrichsdorf et al., 2016; McClain & Suresh, 2011). It has major consequences on the social and psychological well-being and development of the child, often affecting family life and school attendance (Dickson, 2017).

CRPS affects the peripheral and central systems. Peripherally, pediatric CRPS affects predominantly the lower limbs unilaterally or bilaterally (Low, Ward, & Wines, 2007). In addition, CRPS is thought to have a strong central component (Jänig & Baron, 2002). Previous studies have highlighted changes in brain activation and connectivity in patients with CRPS compared to healthy children. Such changes have been highlighted in areas previously associated with pain, such as the insula, thalamus, somatosensory cortices, as well as in the fear and reward networks, including the amygdala and basal ganglia (Erpelding, Sava, et al., 2014a; Erpelding, Simons, et al., 2014b; Lebel et al., 2008; Linnman et al., 2013; Simons et al., 2016). It remains unclear if these changes vary as a function of the severity of the CRPS symptoms. It is also unknown whether some of these changes could predict the success of treatments or the spread or worsening of symptoms.

CRPS symptoms often require treatment. Although outpatient multidisciplinary treatment is recommended as first line intervention (Katholi et al., 2014), intensive inpatient treatments is sometimes needed to achieve sufficient improvement of CRPS symptoms (Katholi et al., 2014; Logan et al., 2012). Such treatments have been associated with significant reduction in pain and functional disabilities, as well as with changes in central mechanisms underlying CRPS (Erpelding, Simons, et al., 2014b; Logan et al., 2010; Williams, Collins, Pruitt, & Rose, 2015). Although several psychosocial factors have been associated with CRPS, relatively little is known about the influence of these factors on the success of a treatment.

Psychosocial factors, such as pain catastrophizing, depression, readiness to change, family environment, and parental response to child's pain are associated with children's experience of pain (Bruehl & Chung, 2006; Carter & Threlkeld, 2012; Palermo & Eccleston, 2009; Pielech et al., 2014; Simons, 2016), suggesting a potential association of such factors in the development and the resolution of CRPS symptoms. However, to our knowledge, no study so far has investigated the relation between these factors and the severity of CRPS symptoms, as well as their impact on the success of the treatments.

Finally, sensory perception has been suggested to be altered in patients with CRPS. Hypersensitivity to visual and auditory stimuli is sometimes described by clinicians treating CRPS patients. It is so far unclear if this hypersensitivity affects multiple sensory modalities or if hypersensitivity might impact on the efficacy of the treatment for CRPS.

Sensitivity to thermal and mechanical stimuli has been previously reported as altered in pediatric CRPS. Interestingly, these alterations vary among patients (Sethna, Meier, Zurakowski, & Berde, 2007). Mechanisms responsible for such variation are not known yet, nor is it know if such a mechanism could be associated with the severity of the CRPS symptoms. Furthermore, it is not known if treatment affects these abnormalities of sensory perception.

2.2 Prior studies

Two studies performed in CCHMC have established the efficiency of multidisciplinary treatments (Lynch-Jordan et al., 2014; Williams et al., 2015). In the first study, which was conducted in the outpatient pain management clinic, pain treatment included cognitive behavioral therapy and medical treatment. In the second study, which took place in the inpatient "Functional Independence Restoration Program" (FIRST), chronic pain patients received a multidisciplinary treatment, including occupational therapy, physical therapy, rehabilitation therapy, psychotherapy, and medical treatment. Results from these studies highlight a significant reduction in pain disabilities, as well as in pain intensities in patients diagnosed with chronic pain, supporting the validity of such treatments.

The project described in this protocol will extend this knowledge by investigating psychosocial, sensory and brain markers that might predict the efficiency of these treatments.

2.3 Rationale of the study

Pediatric CRPS is a severe form of chronic pain that often leads to disability and is difficult to treat. Relatively little is known about its underlying physiological mechanisms and psychosocial factors, which might influence success of treatments. This study will extend our knowledge in several ways:

1. Different techniques will be used to identify predictors of long-term recovery. These techniques include questionnaires, sensory tasks, as well as functional magnetic resonance imaging (fMRI), pseudo-continuous arterial spin labeling (pCASL), and diffusion tensor imaging (DTI) scans.
2. In addition to collecting psychosocial data in the children, psychological well-being of the parents and their response to their child's pain will be assessed. Although parental response to their child's pain has been shown as impacting chronic pain, its association with children's CRPS trajectory remains to be defined.
3. Few studies have investigated brain changes in CRPS children before and after treatment. It has not been studied so far whether some of these changes might be predictive of the long-term success of treatment, nor whether these changes differ as a function of the severity of CRPS symptoms.
4. Hypersensitivity to auditory and visual stimuli is sometimes reported anecdotally as an issue in children with CRPS by clinicians. This study will seek to better define if sensory modalities are hypersensitive in patients undergoing treatment for CRPS. In addition, cerebral representations of sensory sensitivity will be analyzed as potential brain markers predicting long-term response to treatment.

2.4 Rationale for the study outcomes

2.4.1 Ratings of pain intensity and unpleasantness

Ratings of pain intensity and unpleasantness will be used to assess reduction in spontaneous and experimental pain following outpatient or inpatient treatments. Visual analog scales (VAS) will be used for this purpose. VAS are commonly used tools to quickly assess different aspects of such sensations. Differences between pain intensity and unpleasantness will be explained to participants, following instructions described in Price et al. (Price, McGrath, Rafii, & Buckingham, 1983).

2.4.2 Pain disabilities

Pain disabilities will be assessed before and after treatment using the Functional Disability Inventory (FDI) (Walker & Greene, 1991). This questionnaire is frequently used in research and in the clinic to evaluate disabilities associated with pain. Disabilities are known to be an important factor in chronic pain, having important consequences on the social, emotional, and physical well-being of chronic pain patients.

2.4.3 Brain activation and connectivity

Changes in brain function associated with CRPS has been previously highlighted in the literature. In this study, brain activation at rest and during a sensory task, in which participants will evaluate the intensity and unpleasantness of visual, auditory, and tactile stimuli, will be analyzed to define, first, the effect of the severity of CRPS symptoms and, second, the effect of treatment. In addition, functional connectivity at rest and structural connectivity will be measured.

Taken together, these outcome measures will allow us to have an accurate representation of the effect of treatments.

3 Study design

3.1 Overview

This is a basic science investigation of potential psychosocial, sensory, and brain markers predicting trajectory of short-term and long-term recovery in pediatric CRPS following both inpatient and outpatient treatment.

The usual inpatient treatment lasts on average three weeks and includes physical, occupational, and recreational therapy, as well as psychotherapy, while patients keep their regular pharmacological treatment. The usual outpatient treatment lasts on average several months and includes physical therapy and psychotherapy, in addition to pharmacotherapy. For both inpatients and outpatients, the primary anti-neuropathic pharmacotherapy typically includes gabapentin, pregabalin, or amitriptyline, or, less frequently, duloxetine. It is important to note

that this study is not designed to investigate the efficacy of treatment per se, instead it aims to predict trajectory during the course of treatment as usual. This study is primarily mechanistic and does not include any intervention or modification of treatments. Therefore, patients, who are scheduled for regular inpatient or outpatient treatment of CRPS, are free to refuse to enroll without any consequences for the scheduled treatment.

The investigated markers will be assessed in patients undergoing inpatient or outpatient treatments. To define potentially relevant markers, measurements in patients will be compared to the same measurements in healthy children. For this purpose, participants will undergo a testing session just before the beginning of their treatment or as close as possible from the beginning of their treatment.

To establish the influence of potential markers on short-term recovery, patients will undergo an additional session upon completion of their treatment. To investigate the effect of the previously defined markers on long-term recovery, patients will complete a third session at six months after treatment. For comparison purposes, healthy control children will undergo sessions following the same schedule as the patients. To assess the association between symptoms of CRPS in children and social environment, at least one parent of each enrolled child will be asked to complete three sessions following the same schedule as their child.

Each testing session will include self-reported questionnaires for the children and their parents and a brain imaging session for the children. Each session will last approximately three hours for the children and 1.5 hour for the parents. Additional sessions might be scheduled in case of equipment failure.

To avoid distraction or psychosocial influences, participants to these studies will be alone with the experimenter during the sessions, with the exception of the consenting/assenting part of the study and the completion of the medical history and MRI screening forms. Similarly, parents will be left alone in a room while completing questionnaires. In addition, participants and their parents will be asked to shut down their cellphones and other electronic devices during the sessions to further avoid distraction.

3.2 Study sessions

The study described in this protocol will include up to three sessions. Each session will include the same testing components. Only the timing of the sessions differs (Figure 1). The timing of the sessions will be scheduled following the normal duration of the inpatient or outpatient treatment. No intervention will be scheduled during the regular inpatient or outpatient treatment at the FIRST clinic or at the Pain Management Center. In addition, no alteration of the usual inpatient or outpatient treatment associated with this study will occur.

Figure 1. **Timeline of sessions**

3.2.1 First session

The first session will take place right before or as early as possible during the inpatient or outpatient treatment of children diagnosed with CRPS.

Demographic information and medical history of the children and their parents will be reviewed with participants and their parents. A urine sample may be collected from female participants to test for pregnancy if they are post-menarchal. A urine sample will also 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. In addition, participants and their parents will complete questionnaires assessing their psychological wellbeing, responses to pain, and influence of their social environment. Current pain sensations will be assessed in patients with CRPS by recording ratings of pain intensity and unpleasantness on VAS. To assess the extent of their pain, participants will report affected body parts on a picture of themselves and fill in the Pain and Symptom Assessment Questionnaire.

Participants will then undergo a brain MRI scan, during which fMRI, DTI, pCASL, and/or anatomical images will be collected to assess brain changes underlying CRPS. While in the

scanner, scans will be performed during rest and during tasks, including quantitative sensory testing and a multisensory visuo-audio-motor task.

3.2.2 Second and third testing sessions

Patients will complete two additional sessions following the one described above. The second session will take place upon completion of the treatment. The third session will be scheduled six months after treatment completion.

For comparison purposes, healthy children will undergo the second and third sessions as well. Timing of these sessions will be as closely matched as possible to the timing of the patients' sessions.

These sessions will include the same components as the first sessions. Participants and their parents will complete questionnaires. Urine tests will be repeated. Finally, brain imaging scans will be repeated. In addition, patients with CRPS will be asked to provide information on their current pain sensations and disabilities. For participants who are unable or unwilling to attend an in-person session, questionnaires and pain ratings will be administered remotely.

3.2.3 Testing sessions for parents

At least one parent or legal guardian of all the children included in this study will be asked to enroll as well. During each of their child's session, parents will be asked to complete questionnaires in a different room. Response to these questionnaires will be used to assess the association between CRPS symptoms and recovery and the social environment of the patients.

3.2.4 Schedule of the measurements

3.2.4.1 Schedule of the measurements

Measurements	Sessions		
	1	2	3
Consent/assent	x		
Pregnancy test	x	x	x
Health assessment	x		x
Questionnaires	x	x	x
MRI	x	x	x

3.2.4.2 Schedule of the questionnaires

Children				Parents			
Questionnaires	**Sessions**			**Questionnaires**	**Sessions**		
	1	**2**	**3**		**1**	**2**	**3**
Functional Disability Inventory (FDI)	x	x	x	Pain Stages of Change Questionnaire (PSOCQ-P)	x	x	x
Pain Catastrophizing Scale for Children (PCS-C)	x	x	x	Pain Catastrophizing scale for Parents (PCS-P)	x	x	x
Fear of pain questionnaire for children (FOPQ)	x	x	x	Parents fear of pain questionnaire (PFOPQ)	x	x	x
Pain Stages of Change Questionnaire (PSOCQ-A)	x	x	x	PROMIS	x	x	x
PROMIS	x	x	x	Screen for child anxiety-related emotional disorders (SCARED) - parent version	x	x	x
Screen for child anxiety-related emotional disorders (SCARED) - child version	x	x	x	Adults response to Children symptoms questionnaire	x	x	x
Child and Adolescent Mindfulness Measure (CAMM)	x	x	x	Freiburg Mindfulness Inventory (FMI)	x	x	x
Insomnia Severity Index (ISI)	x	x	x	Parental Stress Scale	x	x	x
Morningness-Eveningness Scale for Children (MESC)	x	x	x	Sleep Hygiene Inventory for Pediatrics (SHIP)	x	x	x

3.3 Procedure to avoid/minimize bias

While in the scanner, participants will perform sensory tasks to evaluate their psychophysical and cerebral responses associated with sensory perception of visual, auditory, thermal, and mechanical stimuli. All participants performing these tasks will receive the same stimuli. To minimize any potential order effect, the order of the stimuli will be counterbalanced between participants.

3.4 Experimental procedures and measures

3.4.1 Consent/assent procedure

Before any experimental measure is collected, participants and their parents will be asked to consent to their participation in these studies. Participants and their parents or legal guardians will be given ample time to read the consent/assent forms. After reviewing these forms with them and answering any questions, the experimenter will quiz participants and their parents to ensure the understanding of key aspects of this study. In addition, the experimenter will thoroughly explain to the participants that they may refuse to enroll in the study without consequences for their treatment. As a consequence, the scheduled treatment for CRPS will not be affected by the patients' refusal to participate in the study. Participants may also refuse to complete any of the tasks included in the study. Participation will be re-evaluated upon refusal to complete a task.

Once a good comprehension of this study has been confirmed and if participants still agree to enroll in the study, participants will sign an assent form, while parents will sign two consent forms. The first consent form will allow the participation of their child to the study; the second consent form will confirm their participation in the parent portion of the study. The experimenter will then sign these forms. A copy of the signed forms will be provided to the participants and their parents.

This procedure will be documented and added to the participants' folder.

3.4.2 Screening

Once consent has been obtained, the experimenter will confirm the eligibility of the participants for the study. The experimenter will review health and demographic information, including

height and weight, with the participants and their parents or legal guardians. An MRI screening form will be filled to ensure the safety of the participants in the MRI scanner.

3.4.3 Behavioral and clinical measures

Participants to the study might be asked to complete the following behavioral and clinical measures.

3.4.3.1 Clinical measures

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.

Evaluation of the extent of CRPS symptoms

Body mapping:

Patients might be asked to indicate body parts that are affected by pain on a picture of himself/herself.

Pain and Symptom Assessment Questionnaire (PSAQ):

This questionnaire, which was originally developed for the evaluation of fibromyalgia symptoms (Ting et al., 2016), includes two subscales. The first subscale assesses the widespread of the symptoms, while the second subscale assesses the severity of the symptoms.

Functional disability inventory (FDI)

This self-reported scale investigates disabilities associated with pain which might impact on everyday functioning of children (Walker & Greene, 1991). It includes 15 questions assessing the children's capacity to perform everyday tasks, such as doing chores, walking, or eating regular meals. Participants evaluate their capacity to perform these tasks on Likert-type scale, ranging from "No Trouble" to "Impossible".

3.4.3.2 Questionnaires assessing psychosocial characteristics in the participants

Pain Catastrophizing Scale for Children (PCS-C)

Catastrophizing about pain has been suggested as a critical determinant in pain responses and adaptation to pain conditions. This scale is an adaptation from the original PCS, allowing the use of this scale in children enrolled in fourth grade and above (Pielech et al., 2014). It includes eleven items assessing psychological responses to pain. Children report their agreement with each item on a 5-point Likert-type scale ranging from “not at all true” to “very true”.

Fear Of Pain Questionnaire for Children (FOPQ-C)

Fear of pain is an important contributor to disabilities in chronic pain patients, as it can influence the development of avoidance behavior for activities that may induce or increase pain sensations. This 24-item scale focuses primarily on physiological and behavioral responses to pain (Simons, Sieberg, Carpino, Logan, & Berde, 2011). Children reported their agreement with each statement of the scale on a 5-point Likert-type scale, ranging from “strongly disagree” to “strongly agree”.

Pain Stages of Change Questionnaire for Adolescents (PSOCQ-A)

Readiness to change has been suggested as a critical factor for the success of a therapy. PSOCQ-A is a 30-item scale(Guite, Logan, Simons, Blood, & Kerns, 2011). It measures the readiness of adolescents to self-manage their pain using a 5-point Likert-type scale, ranging from “strongly disagree” to “strongly agree”. It includes three subscales: precontemplation, contemplation, action – maintenance. The highest score on these subscales can be used to characterize the stage the adolescent is in.

Because this scale was developed for adolescents enrolled in 6th grade and above, i.e. 12 years old and older, it might not be used in all the participants included in this study. Decision to give this scale to participants will be done on an individual basis.

PROMIS measures

These measures will be used to assess anxiety, depression and pain interference in participants (Irwin et al., 2010; Varni et al., 2010). Each scale includes 24 items. Participants indicate how often they encounter each situation on a 5-point Likert-type scale, ranging from "never" to "almost always".

Screen for Child Anxiety-Related Emotional Disorders (SCARED) – child version

This questionnaire is widely used to characterize clinically significant symptoms of anxiety in youth (Birmaher et al., 1999; 1997). The child version of this scale will be used to further characterize manifestations of anxiety in our participants. It has been validated for children as young as 8 years old. This scale includes 41 items, which accuracy is estimated by the participants on a 3-point Liker-type scale, ranging from "not true" to "often true".

Child and Adolescent Mindfulness Measure (CAMM)

This 10-item self-reported questionnaire assesses mindfulness in children of school age and adolescents (Greco, Baer, & Smith, 2011). This scale will be used to measure mindfulness in the child participants enrolled in this study, in order to define the impact of mindfulness on CRPS.

Insomnia Severity Index (ISI)

This 7-item scale assesses insomnia (Bastien, Vallières, & Morin, 2001), a common issue in chronic pain conditions. Although the scale was first developed in adults, it has been successfully used in 10 to 18 year old children (Kanstrup, Holmström, Ringström, & Wicksell, 2014). Each item is evaluated on a 5-point Likert-type scale.

Morningness-Eveningness Scale for Children (MESC)

This scale assesses sleep pattern of children and adolescents (Koscec, Radosevic-Vidacek, & Bakotic, 2013) and can be used as young as in 11 year old children (Carskadon, Vieira, & Acebo, 1993). It includes 14 items. Participants select the pattern that matches best their habits.

3.4.3.3 Questionnaires assessing psychosocial factors in the parents or legal guardians of the participants

Parents of children enrolled in this study will be asked to complete the following behavioral measures.

Pain Stages of Change Questionnaire for Parents (PSOCQ-P) (in patients only)

Similarly to the PSOCQ-A, this scale focuses on readiness of the parents to adapt a self-managed approach to their child's pain (Guite et al., 2011). It includes 30 items, which are split into four subscales: precontemplation, contemplation, action, and management. The highest score in these subscales indicate the stage the parents are in.

Pain Catastrophizing Scale for Parents (PCS-P)

This 13-item scale is used to assess catastrophizing thoughts of parents towards their child's pain (Goubert, Eccleston, Vervoort, Jordan, & Crombez, 2006; Pielech et al., 2014). Parents report the extent to which they experience the described thought or feeling on a 5-point Likert-type scale, ranging from "not at all" to "extremely".

Parents Fear Of Pain Questionnaire (PFOPQ)

This 21-item scale focuses on fears and avoidance behaviors of parents in response to their child's pain (Simons, Smith, Kaczynski, & Basch, 2015). Parents report how much they agree with each item on a 5-point Likert-type scale, ranging from "strongly disagree" to "strongly agree".

PROMIS

These measures are similar to the ones used in participants to this study and will be used to assess depression and anxiety in their parents (Pilkonis et al., 2013).

Screen for Child Anxiety-Related Emotional Disorders (SCARED) – parent version

This questionnaire is used to characterize symptoms of anxiety in children by their parents (Birmaher et al., 1997; 1999). This scale will be used to further characterize manifestations of

anxiety in our participants. It includes 41 items, which accuracy is estimated by the parents on a 3-point Liker-type scale, ranging from “not true” to “often true”.

Adult responses to children’s symptoms questionnaire

This scale assesses three types of response of parents to their child’s pain: minimization, protection, and distract/monitor (Van Slyke & Walker, 2006). Parents report on a 5-point Likert-type scale (range: “never” to “always”) how regularly they display the described behavior.

Freiburg Mindfulness Inventory (FMI)

This 14-item questionnaire is widely used to measure mindfulness in adults with and without prior meditation experience. This scale will be used to assess mindfulness in the parents of children enrolled in this study and its impact on the child’s CRPS symptoms and recovery. Parents will report how frequently they experience the described behavior on a 4-point Likert-type scale (range: “rarely” to “almost always”).

The Parental Stress Scale

This scale assesses stress levels associated with parenting (Berry & Jones, 1995). It includes 18 statements. Parents evaluate on 5-point Likert type scale their agreement with each statement. Higher scores indicate a higher level of stress associated with parenting.

Sleep Hygiene Inventory for Pediatrics (SHIP)

In this questionnaire, parents evaluate the sleep habits of their children (Rabner, Kaczynski, Simons, & Lebel, 2017). 15 sleep behaviors are presented and parents indicate how frequently their children display each described behavior.

3.4.4 Quantitative sensory testing

3.4.4.1 Stimuli

The MEDOC TSA-II and/or Pathway stimulators will be used to deliver the majority of thermal stimuli. These devices are compatible with use in the MRI scanner and can deliver relatively

complex stimuli via computer control. All targeted stimulus temperatures will be less than or equal to 50°C, and participants will be free to escape the stimulator at any time by removing their arm or leg from the probe. Participants will be instructed to try their best to maintain contact with the stimulus. However, at various points in the study (i.e. switching stimuli or rating method), it will be reiterated that participants are free to escape from the stimulus if it becomes intolerable.

Probes with a 16x16 mm and a 30x30 mm surface areas will be used to deliver suprathreshold heat stimuli. These stimulus areas allow a relatively wide range of noxious stimuli to be delivered (up to 49°C for 30 sec, 50°C for 5 sec) without either tissue damage or significant participant withdrawals/drop-outs. It is important to note that we have used these devices for more than 16 years and have extensive experience in delivering combinations of stimulus intensity, areas, and duration to various body regions in a manner that does not produce burns. We have used this combination of stimulus temperatures in numerous Wake Forest School of Medicine IRB approved studies (BG-99-006, 582 participants completed; BG04-318, 32 participants completed, IRB00000392, 19 participants completed; IRB00001643 16 participants completed. IRB00002720, 23 participants completed; IRB00006971, 19 participants completed; IRB00016912, 102 participants completed).

Noxious cold will generally be delivered with probes up to 30x30 mm or water baths to ensure adequate spatial summation to produce sensations of robust cold pain. Participants will be free to pull out of the water bath at any time. We reiterate that no stimulus will produce tissue damage.

3.4.4.2 Sensory testing, psychophysical and physiological assessment

Psychophysical assessment of pain: Pain intensity and pain unpleasantness associated with the stimuli will be assessed by mechanical and computerized VAS (Price et al., 1994), as described above.

Participants will undergo the following battery of quantitative sensory testing on the affected limb and on a non-affected limb. Note that testing will prioritize threshold measurements. To

minimize exacerbation of ongoing pain, suprathreshold stimulation paradigm will be carefully tailored.

Tactile Thresholds: Von Frey filaments from 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 five times and threshold will be defined when participants are able to identify the touch in 80% of the trials.

Vibration Thresholds: Stimuli of decreasing vibration amplitude will be applied with a Rydel-Seiffer tuning fork until participants no longer perceive the vibration stimuli. Stimuli will be applied perpendicularly to participants' skin. This test will be repeated three times. Results of these tests will be averaged and considered the vibration threshold of the participants.

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.

Suprathreshold responses: Responses to noxious heat (43-49°C) and noxious cold stimuli (0-10°C) with plateau durations of up to 20s will be assessed with VAS ratings of pain intensity and pain unpleasantness. These stimuli may be delivered either singly or in trains.

Pain tolerance: Pain tolerance will be assessed by having participants immerse one hand in a cold (0-10°C) water bath, as we have done previously (Starr, Houle, & Coghill, 2010). Tolerance will be defined by the time of hand withdrawal. VAS ratings of cold pain intensity may be obtained periodically, and both pain intensity and pain unpleasantness will be recorded upon hand withdrawal. Limb immersion in the cold-water bath will be terminated after 120 s if participants do not withdraw their hand before then.

Endogenous Pain Control Mechanisms: Endogenous pain modulatory capacities contribute substantially to inter-individual differences in pain sensitivity. 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 (Yelle, Rogers, & Coghill, 2008). Conditioned pain modulation (also known as diffuse noxious inhibitory control) will be activated by immersion of the foot in 0-10°C water and evaluated by examining the reduction in pain intensity ratings to a

noxious heat stimulus (up to 49°C) applied to the ventral forearm, as we have done recently (Nahman-Averbuch et al., 2012).

Autonomic Activity: Blood pressure, heart rate, and respiratory rate may be assessed during rest and during noxious stimulation during various phases of the study.

3.4.5 Brain imaging

3.4.5.1 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 hours 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. In case of an unexpected delay in the testing schedule scans will be run based on their importance to complete the study's aims. Their priority order is as follow: structural scan, resting-state Blood Oxygenation Level Dependent (BOLD), BOLD with sensory task, resting-state pCASL, and Diffusion tensor images (DTI).

3.4.5.2 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 might also be used for volumetric brain mapping of cortical and subcortical structures.

3.4.5.3 Resting-state functional connectivity

Resting-state functional brain images may be acquired using conventional or multiband BOLD sequences. These sequences consist in rapidly-acquired series of brain images covering the whole brain. Each resting-state series acquisition will last up to 12 minutes. These images might be used to investigate functional activation and connectivity between brain areas at rest.

3.4.5.4 Brain activity associated with sensory perception

Functional brain images will be acquired using a similar sequence to the one used for assessment of functional connectivity. While these images are acquired, participants will undergo several sensory tasks.

3.4.5.4.1 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.

3.4.5.4.2 Quantitative sensory testing

Participants will undergo a short quantitative sensory testing in the scanner, including thermal and mechanical stimuli. As previously, measurements will be carefully tailored to minimize exacerbation of ongoing pain.

3.4.5.5 Cerebral Blood Flow (CBF)

This technique, which is regularly used in our laboratory, allows investigating relationships between brain activity and other variables. CBF may be measured in a fully quantitative fashion with pCASL imaging (Luh et al., 1999).

3.4.5.6 Structural connectivity

Diffusion tensor images (DTI) may be acquired for white matter tractography. These analyses on structural connectivity might provide important information on potential changes in the brain structures associated with CRPS symptoms.

4 Participants

Participants to this study may be part of one of the following groups: children diagnosed with CRPS undergoing inpatient treatment at the FIRST clinic (CCHMC), children diagnosed with CRPS underdoing outpatient treatment at the pain management clinic (CCHMC or comparable outpatient programs), or healthy children. Our groups will be matched as well as possible for BMI, sex, and age.

4.1 Inclusion criteria

For all child participants

1. 10-17 years old
2. fluent in English

For inpatient participants

1. Diagnosis of CRPS
2. Previous unsuccessful attempt(s) of treatment
3. Scheduled for or beginning an intensive therapy at the FIRST clinic following the clinic's regular treatment plan

For outpatient participants

1. Diagnosis of CRPS
2. Scheduled for or beginning an outpatient treatment for CRPS at the Pain Management Center following the center's regular treatment plan

For healthy controls

1. No chronic pain diagnosis

For parents

1. Fluent in English
2. Child enrolled in the study

4.2 Exclusion criteria for child participants

1. Any MRI contra-indication
2. Pregnancy
3. Weight/size incompatible with the scanner
4. Significant psychiatric or neurological disease, non-associated with CRPS, and potentially interfering with assessment of brain structure and function
5. Developmental delays or impairment

4.3 Participant withdrawal criteria

For all child participants

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 (positive drug test).

For parent participants

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 fails to comply with experimental protocol or instructions.
5. Their child declines further participation in the study.
6. Experimenter assesses that withdrawal from the study is in the participant's best interest

4.4 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.

4.5 Recruitment / Enrollment Procedures

Participants will be recruited via word-of-mouth, internet, email, printed and/or broadcast CCHMC-approved advertisements in the community as well as contact from the volunteer database of the Clinical Trials Office. Recruitment will be continuous through the course of the study. If necessary to obtain adequate minority representation, under-represented racial groups might be targeted specifically for recruitment. Potential participants will undergo telephone screening to ensure that they meet the inclusion/exclusion criteria. If potential participants choose not to enroll or fail to meet inclusion criteria, all PHI will be destroyed.

Potential participants from the outpatient and inpatient clinics will be approached during the planning of their treatment at CCHMC by their clinical provider. If the patients express interest for the study, experimenters will contact them to confirm interest and assess eligibility.

4.6 Safety assessment and monitoring

This study involves no increase over minimal risk. Therefore, no data safety monitoring board will be created.

Any adverse event will be documented and reported to the Institution Review Board as soon as they are known. In addition, annual report of adverse events will be submitted in the annual review of the protocol.

5 Statistics

5.1 Statistical plan

5.1.1 Analyses of neuroimaging data

All structural and functional image data will be primarily processed by the FSL software package (FMRIB Software Library, Oxford, UK). Such processing will generally include motion correction, co-registration of structural and functional data, transformation of structural data to standard space, temporal and spatial filtering, image segmentation, and tractography. Other packages such as CONN, SPM, AFNI, FreeSurfer, and others may be used to augment image processing. Functional and structural data will be statistically analyzed using both parametric and non-parametric approaches, independent component analyses, in addition to multivariate pattern analysis. In general, fixed effects statistical models will be used for within-participants components of analyses, while random effects models will be used for between participant's components. These statistical analyses will generally be executed within FSL or similar software packages developed or adapted for analyses of functional and structural data.

5.1.2 Analyses of behavioral and psychophysical data

Questionnaires data will be scored and used to characterize patients-control differences and serve as potential covariates in current and future analyses.

The effect of behavioral factors on the trajectory of our outcome measures, i.e. changes in pain ratings, in functional disabilities over time, and brain function and structure, might be assessed by multilevel regressions and mixed ANOVAs. Post-hoc analyses will be performed when appropriate.

5.2 Number of participants to be enrolled

A total of 63 participants, i.e. 21 participants per group, will be enrolled in this study. Power calculations were performed for both imaging data and behavioral data to ensure an adequate sample size to detect changes in brain activity and interpret them in the context of behavioral effects.

Neuroimaging

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. As no data is accessible so far in youth with CRPS, we used the NeuroPower tool to calculate statistical power and sample sizes based on our preliminary ASL data in youth with migraine, which study had a similar design to the one described here. Within-subject power calculations of ASL activation differences indicate that 19 participants per group would be required for 80% power with this imaging modality for treatment related changes in activity within group. All comparisons were calculated 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 (8mm for ASL), 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.

Behavioral and psychophysical sample size estimation

We used G*Power to perform a power analysis for our behavioral data. This calculation resulted in an overall number of participants of 54, i.e. 18 participants per group, to achieve a small effect size f of 0.25 (Cohen, 1988) with a type I and II errors at 5%. An additional 15% has been added to that result to account for incomplete dataset due to participants' withdrawal and equipment failure. This number is consistent with that proposed for fMRI.

5.3 Level of significance

In general, whole brain statistical analyses will be performed with rigorous control of false positive rates using cluster-based methods (Worsley, Evans, Marrett, & Neelin, 1992). This substantially increases the reproducibility of findings relative to region-of-interest type approaches. Statistical significance will be defined by $p<0.05$.

5.4 Participants to be included in the analyses

All participants whose data passes quality assurance (i.e. no MRI artifacts, no excessive movement, no reconstruction errors) will be included in analyses. Many analyses will be executed on a condition-by-condition basis. Thus, every effort will be made to include participants who have partially complete datasets but have successfully completed scans for a given condition.

6 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.

6.1 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.

6.2 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.

6.3 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.
5. Data with identifiers will not be stored on laptop computers.

7 Ethics and human participants consideration

7.1 Potential Risks and Minimization of Risk

7.1.1 Potential risks associated with MRI Scanning

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[1].

- *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.

[1] http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm072686.htm

- *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.
- *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.

7.1.2 Potential risks associated with psychological discomfort

Completion of psychosocial measures, aka questionnaires, may feel intrusive and uncomfortable to some persons. This might induce some mild psychological distress. If participants or their parents experience such feeling, they will be instructed to inform the experimenter, as stipulated in the consent/assent forms. In addition, they will be advised to contact the PI of this study. If necessary, they will be referred to a clinical psychologist for follow-up.

7.1.3 Potential risks associated with the sensory tasks

The sensory tasks include auditory, visual, and sensorimotor stimuli. Some of these stimuli might feel unpleasant to the participants, especially for patients who might experience hypersensitivity to sensory stimuli. These stimuli will be defined to remain below damaging thresholds.

7.1.4 Potential risks associated with quantitative sensory testing

Participants with chronic pain may experience exacerbations of their pain by the stimuli used during quantitative sensory testing. Stimulation paradigms will prioritize threshold level stimuli, and suprathreshold stimuli will be carefully tailored to each individual patient to minimize exacerbation of pain.

Thermal stimulators and/or water baths will deliver noxious and non-noxious thermal stimuli for the quantitative sensory testing. Noxious thermal stimuli have been repeatedly demonstrated to produce reliable changes in brain activity that can be detected with fMRI. Individual stimuli will range from 0° to 50°C to encompass both heat and cold pain. Heat stimuli will typically be applied to the skin of the arms, legs, or other body regions in an intermittent manner with combinations of areas and durations that eliminate the possibility of tissue damage. Stimuli in this temperature range have been used extensively by our laboratory and a number of different laboratories around the world and 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.

As with any electrical device, there is a remote possibility that a stimulator malfunction could cause a burn. To minimize this risk, stimulators have fail-safe circuits to prevent excessive delivery of energy. Furthermore, all participants will be conscious, will not have any analgesic medications, 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.

7.2 Reporting of 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 research 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.

We will collect contact information about the primary care physician of each participant during the review of the medical history, which will be done in the first session. 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. If no primary care physician is identified by the participants, the PI will contact the physician associated to this study. A report generated by the radiologist will be made available to the physician if requested. The physician will be responsible for follow-up with the participants.

For clinically significant findings of neuroimaging, the participant 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.

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, adult participants or 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 Dr. Sara Williams, a licensed clinical psychologist, or to other licensed clinical psychologist, (2) professional and confidential assessment of suicide risk and resources available, (3) immediate notification of the adult participant, or 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.

7.3 Confidentiality

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

1. 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.

2. 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.

3. Deposition of Data into a Repository

   Information from all testing, including MRI data, may be placed into a central data repository. Data and samples will be de-identified before submission to any central repository.

7.4 Potential benefits

The study will not provide direct benefit to individual participants or families beyond the knowledge that the child's medical condition is being investigated to improve care. The benefits are those to society as a whole in the improvement of knowledge of factors influencing chronic pain conditions and the success of treatments. This knowledge will help improve these treatments.

7.5 Risk/benefit ratio and importance of the information to be obtained

The risk/benefit ratio is favorable for this study. There is no anticipation of adverse events. The risk encountered by the participants and their parents is minimal because all procedure can be terminated immediately.

There will be no direct benefit for the participants, but the results of this project are important for our understanding of underlying mechanisms of chronic pain and of response to treatment. Ultimately, this will help improve treatment, especially by improving the prognosis of the most adequate treatment for each patient.

8 Funding

Acquisition and analyses of data is funded by the Chapman family donation for research on CRPS and by startup funds provided by the Department of Anesthesiology.

9 Reimbursement for studies

This is a study on markers of trajectory in pediatric CRPS. Although measures will be taken before and after treatment, this study does not depend on treatment of CRPS. Therefore, treatment will not be covered by the researcher.

Children enrolled in this study will receive a payment up to $120 per session to compensate any inconvenience associated with their participation in this study. This amount includes a payment of $20 for the completion of the questionnaires, $50 for quantitative sensory testing, and $50 for the MRI scan. Similarly, parents will receive a payment of $20 per session for the completion of questionnaires. Payment will be proportional to the activities and sessions completed by the participants.

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