Study Title:

Retuning the Nervous System in Youth with Chronic Pain

Investigators:

Robert C. Coghill, Ph.D.

Flavia Di Pietro, PT, Ph.D.

Kenneth R. Goldschneider, M.D.

Sara E. Williams, Ph.D.

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1 SPECIFIC AIMS

Pain in both youth and adults is a complex, subjective and personal experience, and remains poorly understood. One particularly perplexing dimension of some forms of pain is the tendency of pain to spread outside of an affected body site to adjacent location, and then to unaffected body sites. Such widespread pain may reflect an altered spatial tuning of somatosensory processing, such that lateral inhibition is diminished, thereby allowing pain to spread. To date, no therapies exist which are designed specifically to diminish or even reverse the spatial spread of pain. However, training in two-point discrimination holds the potential to retune spatial aspects of somatosensory processing and may represent a novel therapy for widespread pain. Thus, the present investigation will test the following aims:

Aim 1. Do youth with chronic pain have disrupted spatial tuning of somatosensory processing? Deficits in two point tactile discrimination have long been noted in adults with chronic pain, but such deficits remain poorly documented in pediatric chronic pain patients. In order to determine if such deficits exist, youth with both chronic pain and healthy youth will undergo assessment of two point discrimination thresholds.

Aim 2. Does two-point discrimination training result in diminished pain and disability in youth with somatic pain? After initial characterization of tactile discrimination thresholds, youth with chronic pain will participate in multiple sessions of either two-point discrimination training or a single-point spatially-directed attentional control condition. Training will involve up to 9 additional sessions. Efficacy of training will be assessed by 1) reductions in the spatial extent of pain, 2) reductions in pain intensity and unpleasantness, and 3) reductions in pain-related disability.

2 SIGNIFICANCE AND INNOVATION

2.1 Scientific Premise

Highly disabling persistent pain is a frequent complaint in children, with prevalence estimated at approximately five percent in Western societies (Huguet and Miro, 2008; Hechler et al., 2014). Pain prevalence rates increase with age (King et al., 2011) and as such, chronic pain in adolescence represents a significant economic problem in the USA (Groenewald et al., 2014). Adolescence is a critical period for development physically, psychologically and socially, and pain severely interferes with such an important phase of life (O'Sullivan et al., 2012). Adequate management of pain in adolescents should clearly be a goal in itself, but the evidence suggests that management of pain in young people may also help prevent pain in adults (Hestbaek et al., 2006).

From a mechanistic standpoint, fundamental questions about pain remain unanswered, and this has meant the treatment needs of pain sufferers have largely been unmet. To date the intensity of pain has been a focus of investigation and

treatment, but pain intensity is only one dimension of the pain experience. Research into the spatial dimension of pain has been grossly neglected in comparison; we still do not fully understand how the nervous system processes and spatially tunes incoming sensory information from the body. This avenue of inquiry is critical, given that one of the most common and intriguing symptoms of chronic pain is the spread of pain well beyond the site of the original injury. Our knowledge of sensory function in adolescents is particularly lacking.

Several lines of evidence point towards abnormal processing of sensory information in adult patients with chronic pain disorders. For example, when it comes to a painful body part, sufferers are typically unable to perceive the sensation of two individual stimuli on the skin when those two points are located close together in space (termed two-point discrimination) (Flor et al., 2001; Lotze and Moseley, 2007; Wand et al., 2010). This poor tactile acuity indicates abnormality in the nervous system's normal spatial tuning, or surround inhibition, of sensory information; in patients it appears that each sensory stimulus is not activating a distinct population of neurons as it would in a healthy pain-free person (Defrin et al., 2008),(Gardner et al., 2000). Poor tactile acuity has been correlated with pain intensity (Flor et al., 2006; Lotze and Moseley, 2007) and with the spread of pain (Maihofner et al., 2003, 2004). Not only do patients with CRPS have impaired 2-point discrimination in their affected extremities compared with their unaffected extremities, but they also have diminished ability to learn 2-point discrimination in comparison with control subjects (Maihofner et al, 2007). All this suggests a global impairment in spatial tuning within and in comparison to external controls.

An important randomized trial in adults with phantom limb pain trained patients' tactile acuity with repeated stimulation over the stump. The training led to improved pain levels, together with increased tactile acuity and reversal of the associated abnormal brain activation patterns (Flor et al., 2001). Regarding chronic limb pain, Moseley and colleagues found that repetitive stimulation of the skin improved pain levels and patients' tactile acuity in the affected area (Moseley et al., 2008). Importantly, the stimulation program involved instructions on attending to and evaluating the nature of the stimulation – that is, a discrimination task. Tactile stimulation alone did not have the same effects.

Our translational work with spatial aspects of pain provides a mechanistic rationale for extending and refining the work of Moseley. First, using lasers to deliver noxious heat in two different patterns - two simultaneous points (4-8 cm separation distance, 5 mm diameter) or a contiguous line (4-8 cm long, 5 mm width), we sought to identify a psychophysical correlate of lateral inhibition (Quevedo et al., 2017). Despite the considerably larger surface area being stimulated with the line, participants perceived the two point stimuli as more intense. This suggests that, in healthy individuals, there is a lateral inhibition that was recruited by the line stimuli, but not by the two point stimuli (Quevedo et al., 2017).

This lateral inhibition may be modified by attention. Using contact heat stimuli, we routinely demonstrate spatial summation of pain (i.e., enhanced pain response) when two stimuli are delivered at 10 cm separation distances. This occurs when

participants are instructed to make one overall rating of pain. However, when subjects are given a different attentional directive - i.e. to rate pain from each probe separately - spatial summation of pain is abolished and some inhibition is generated (Quevedo and Coghill, 2007). We have hypothesized that to accomplish this task, lateral inhibition at some level of the neuraxis is increased by the attentional directive. This, in turn, minimizes spatial interactions among populations of neurons responding to each stimulus, and abolishes spatial summation. Moreover, this increased lateral inhibition may sufficiently reduce the total population response to account for inhibition unmasked at distal stimulation sites (Quevedo and Coghill, 2007).

Despite this growing body of research in adults, demonstration of these processes in children and adolescents is lagging behind. What if we were able to demonstrate deficits in and restore spatial tuning of the sensory nervous system in adolescents with widespread pain? This project aims to meet this objective, using a targeted and innovative treatment paradigm.

2.2 Innovation and Importance of this Study

To date, there are no therapies targeted specifically at minimizing and reducing the spatial spread of pain. As such, if this study is successful, an important new therapy for pain may emerge.

2.3 Supporting Data-Previous Evidence

The proposed investigation is highly novel and builds on our prior spatial studies described above. To date, no investigations have used two point discrimination training to demonstrate deficits in children and adolescents with chronic pain as have been found in adults or as a potential treatment for widespread pain.

3 STUDY DESIGN

Prior to commencing this investigation we will optimize the tactile discrimination threshold testing (i.e. as per baseline visit, below), and the training conditions, in up to ten participants (patients and/or healthy controls). This will serve as a pilot to refine operational aspects of study procedures before we commence the main investigation proposed herein. Following this, youth with either chronic pain (ages 10-17, n=40) or healthy youth (ages 10-17, n=20) will undergo assessments of two-point and single-point discrimination thresholds in an initial session (Aim 1). After this initial session, youth with chronic pain will participate in up to 9 additional sessions of attentional training (Aim 2). These chronic pain patients will be randomized to either two-point discrimination training (n=20) or a single-point spatially-directed attentional control condition (n=20). Participants will not be informed of which intervention they will receive (single-blind study). Psychological questionnaires will be completed in the first and last sessions in order to determine how these variables relate to tactile discrimination and response to training.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Chronic Pain Patients:

Somatically located chronic pain including amplified musculoskeletal pain syndrome, complex regional pain syndrome, low back pain, fibromyalgia, other forms of chronic, widespread pain.

Male or female, 10-17 years (inclusive**)**

High fluency in written and oral English language

Control Participants:

Youth in good general health

Male or female, 10-17 years (inclusive**)**

High fluency in written and oral English language

4.2 Exclusion Criteria

Present significant mental health disorder as defined by DSM V (e.g. psychosis, bipolar disorder, major depression), alcohol or drug dependence, or documented developmental delays or impairments (e.g., autism, cerebral palsy, or mental retardation) of a magnitude that would interfere with adherence to study requirements or safe participation in the study

Primary complaint of migraine or visceral (abdominal) pain, with minimal somatic pain.

4.3 Participant Withdrawal Criteria

Participant (or legal guardian) declines further study participation.

Participant fails to comply with experimental protocol or instructions of study staff.

Identification of brain, neurologic, or severe psychiatric abnormalities that may confound procedures.

In the investigator's judgment, it is in the participant's best interest.

5 STUDY INTERVENTIONS

5.1 Two Point Discrimination Training: Two-point discrimination threshold (TPD) training may be performed 1) at spatial locations remote from pain, 2) at spatial locations adjacent to the region of pain, and/or 3) at spatial locations in the site of pain, if the participant will tolerate it. TPD is defined as the smallest distance between two points at which someone can recognize two points, and not one, touching their skin. As such this is a test of one's ability to identify separate stimulation of two discrete areas, and relies heavily on lateral inhibition. Highly

precise mechanical calipers will be gently placed onto the skin and the distance between the prongs will be increased/decreased. After repeated decreases and increases in the distance between the prongs, the TPD will be deemed as the distance at which participants consistently report two points instead of one (Moseley et al., 2008,)(Wand et al., 2010). One-point stimuli will be interleaved to serve as a control condition. Participants will be informed immediately of correct and incorrect responses as part of the discrimination training.

5.2 Control Stimulation: Participants will undergo a single-point discrimination training at the same sites as described above. We will employ a discrimination paradigm similar to that described by Moseley et al. (2008). Probes of different sizes will be used for this portion - a small diameter probe (~1-5 mm) and a large diameter probe (~6-50mm). The probes will be gently placed in contact with the participants' skin, and the participant will be instructed to respond if they were contacted with the small or large probe. Participants will be informed immediately of correct and incorrect responses as part of the discrimination training.

6 STUDY PROCEDURES AND MEASURES

6.1 Study Recruitment/Enrollment Procedures

The primary methodology for identifying and recruiting chronic pain patients for this study will be through identification of potential participants from the inpatient and outpatient chronic pain clinics at Cincinnati Children's Hospital Medical Center, as well as community advertisements. Over the course of this project, we will enroll up to 50 patients.

Healthy control participants will be identified via word-of-mouth recruitment as well as advertisements throughout the community. We will enroll up to 30 healthy control participants.

Methods and processes for identifying patients will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

To support our recruitment and retention, progress will be evaluated weekly and existing challenges and potential solutions will be discussed with the study team to ensure we meet our projected timeline.

6.2 Consent/Assent Procedure

Participants and parents/guardians will be given ample time to read the consent document. To ensure comprehension, the experimenter will ask a brief series of questions to ensure that both participants and/or parents/guardians understand key aspects of the study. Once comprehension has been demonstrated the participant and parents/guardian will sign the consent form. The experimenter will then sign the consent form. A copy of the signed consent form will be provided to participants. This procedure will be documented on a form which will be placed in the participants' folder.

6.3 Participant Characterization

Medical History: A medical history will be completed to capture pain diagnosis, medication usage, and concurrent conditions. This will be augmented and crossreferenced with information from the participant's medical record.

Body Morphometry: Height, weight, and hip and waist circumference will be obtained.

Menstrual Cycle: Position in the menstrual cycle will be noted by onset of last menstrual period in women who are not on oral contraceptives. For women on oral contraceptives, the phase of the cycle will be determined by the contraceptive pill packet.

6.4 Pain Assessment

Psychophysical Assessment of Pain Magnitude: Pain intensity and pain unpleasantness will be assessed by mechanical and computerized visual analogue scales (VAS) (Price et al., 1994). These scales have been repeatedly demonstrated to 1) provide reliably separate assessment of intensity and unpleasantness, 2) to be internally consistent, and 3) to approximate ratio scale measurement accuracy (Price, 1999). Participants will be instructed in their use via a radio analogy (Price et al., 1989). These scales have been used extensively by the PI in ongoing studies in youth. We may also provide auditory stimuli via calibrated headphones (up to 95 dB for 10s) to provide a cross-modality training procedure to reinforce the concepts of intensity and unpleasantness.

Pain and Symptom Assessment Questionnaire: This questionnaire documents pain location and additional pain related symptoms.

Assessment of Pain Location: Pain location will be characterized by having the participant draw regions of pain on a paper or electronic body map or photo of themselves.

6.5 Psychological Assessment/Questionnaires

Variation in psychological states can contribute substantially to the construction of the experience of pain, and may importantly influence attentional processes related to pain. Thus, participants will undergo extensive psychological characterization with a particular focus on variables known to influence pain. Many scales will be useful for enabling comparisons of these patients with chronic pain patients in other studies, and are part of our standard testing battery.

Anxiety: The PROMIS Anxiety pediatric scales will be used to assess anxiety. The SCARED anxiety scale will be used to further characterize anxiety.

Mood and Affect: The PROMIS Depression pediatric scales will be used to assess depression. The Positive and Negative Affect Schedule - Expanded will be used to characterize mood and affect.

Mindfulness: The Freiburg Mindfulness Inventory will be used to assess mindfulness.

Impulsivity: The Barratt Impulsiveness Scale will be used to assess impulsivity.

Handedness: The Edinburgh Handedness Inventory will be used to assess the degree of handedness and will be critical in the interpretation of differences in the lateralization of nociceptive processing.

Sleep: Sleep deprivation may substantially alter pain sensitivity. The Epworth Sleepiness Scale will be used to quantify the level of daytime sleepiness, while the Pittsburgh Sleep Quality Index will be used to assess sleep quality.

Pain Interference, Disability, and Catastrophizing: The PROMIS Pain Interference Scale (pediatric version) will be used to assess how much pain interferes with daily living. Pediatric versions of the pain catastrophizing scale will be used to assess pain-related catastrophizing, while the Functional Disability Index will be used to characterize disability.

Social Status and Discrimination: Insurance, income, education level, and experience of discrimination will be used to quantify socio-economic variables.

7 Study Visits

The duration of two-point discrimination needed to improve pain remains completely unknown. To optimize retention, we may truncate the number of visits, depending on subject availability, with procedures in Visit 10 being performed at the final visit. Healthy control participants will only participate in the baseline visit.

7.1 Baseline + Intervention - Visit 1 (up to 3 hours)

Completion of informed consent/assent prior to initiation of study procedures

Obtain information for payment, provide ClinCard

Randomize to intervention

Review medical history

Document all concomitant medications including prescribed, over the counter, and nutraceutical supplements

Administer questionnaires

Assess pain intensity, unpleasantness, qualitative aspects of pain

Assess spatial extent of pain (body map or patient's own photo)

Demonstration of two-point/single-point discrimination procedure

Assess two-point/single-point discrimination

Initiate intervention (TPD training or Control)

Assess pain intensity, unpleasantness

Assess spatial extent of pain

7.2 Intervention - Visits 2-9 (1 hour)

Determine any changes in medications or concurrent conditions

Assess pain intensity, unpleasantness, qualitative aspects of pain

Assess spatial extent of pain

Continue intervention (TPD training or Control)

Assess pain intensity, unpleasantness, qualitative aspects of pain

Assess spatial extent of pain

7.3. Intervention+Completion - Visit 10 (up to 3 hours)

Assess pain intensity, unpleasantness, qualitative aspects of pain

Assess spatial extent of pain

Final intervention (TPD training or Control)

Assess two-point/single-point discrimination

Assess pain intensity, unpleasantness, qualitative aspects of pain

Assess spatial extent of pain

Administer psychological questionnaires

Note that some of the procedures above may be omitted for the purpose of streamlining the study visits, or if procedures are deemed to be incongruent with the participants' ongoing clinical treatments. Omitting these procedures would reduce participant burden and would have no impact on safety.

8. SAFETY ASSESSMENTS AND MONITORING

This study involves no increase over minimal risk, so a Data Safety Monitoring Board will not be created for this study. Any adverse events related to the study procedures will be reported to Cincinnati Children's Hospital Medical Center's Institutional Review Board.

9. STATISTICS

9.1 Statistical Analysis Plan

Aim 1:

A mixed model analysis of variance will be utilized to determine differences between groups (chronic pain patients vs. healthy controls - between factor) and body site (within factor), and group X body site interactions.

Aim 2:

To maximize the utility of data collected, a mixed model analysis of variance will be utilized to determine differences between groups (between factor), differences over time (within factor), and time X group interactions.

Outcome variables of interest include 1) reductions in area of pain, 2) reductions in pain intensity and unpleasantness, 3) reductions in pain-related disability

Control variables include: 1) Improvements in tactile discrimination thresholds, 2) data from psychological questionnaires. These variables may be added as covariates to the overall model, or may be used to perform a manipulation check. JMP or R software will be used to perform analyses

9.2 Number of Participants to be Enrolled

This is the first investigation of an entirely novel question, and will be used to determine both effect size and variability. Thus, we will apply a heuristic approach based on prior experience obtained within-subjects variability in pain ratings in studies of spatial aspects in acute experimental pain in healthy adults (Quevedo and Coghill, 2007; Quevedo et al., 2017). With these studies, we have obtained reproducible results from 15 subjects in within subjects designs. Thus, we have selected N=20 per group to compensate for the reduced power of the between subjects design. Up to 10 additional participants will serve to optimize operational aspects of study procedures as potential pilot subjects.

9.3 Level of Significance

Statistical significance will be defined by $p<0.05$.

9.4 Participants to be Included in Analyses

All participants without excessive missing data (i.e. completion of <5 sessions) will be included in analyses.

10. 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 will be used for sensory testing data and may be used as backups for questionnaires in the event of computer malfunction during data acquisition.

10.1 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.

10.2 Data Validation and Monitoring

Real time validations can 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.

10.3 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.

Several levels of security are employed to ensure privacy and integrity of the study data, including the following: Study access requires use of assigned user names and passwords. Individual roles and access levels are assigned by the study data manager. Passwords are changed regularly. Web-based entry uses secure socket layer data encryption. Data with identifiers will not be stored on laptop computers.

11. ETHICS AND HUMAN PARTICIPANTS CONSIDERATIONS

11.1 Potential Risks and Minimization of Risk

Psychological Distress. There is a chance that participation in this study could cause psychological distress. The psychological questionnaires could make some participants uncomfortable.

Sensory Testing. The sensory stimuli will consist of innocuous tactile stimuli delivered for the two-point discrimination as well as the one point attentional control conditions. These stimuli are similar to those utilised during clinical practice and encountered during daily life, and pose minimal risk. Specifically, application of these stimuli to pain-free areas would never be expected to generate pain or cause tissue damage. In patients, testing in zones of chronic pain could possibly increase ongoing pain or could produce prolonged aftersensations. Testing in these zones is fully optional; if testing exacerbates pain, the participant can choose for the testing to be undertaken in a pain-free area, or testing can be immediately terminated if requested.

11.2 Reporting of Incidental Findings

We will collect contact information for the pain 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.

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

11.3 Confidentiality

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

Use of Participant ID Numbers: Each participant is assigned a participant identification number (SID). 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 this study.

Deposition of Data into a Repository: Information from all psychological and sensory testing may be placed into a central data repository. Data will be de-identified before submission to any central repository. Any photographs will be used only for mapping of pain in the current study, and not used for any other purpose. Only study personnel will be permitted to see the images.

11.4 Potential Benefits

The study may provide direct benefit to individual participants if our hypothesis is correct. The benefits are those to society as a whole in the improvement of knowledge of about spatial aspects of pain.

11.5 Risk/Benefit Ratio and Importance of Information to be Obtained

The risk/benefit ratio is favorable for this study and adverse events are not anticipated. The risk is minimal because all interventions can be terminated immediately. In addition, although an individual participant will not benefit from participation, the results of this study will make important contributions to the improvement of knowledge of the basic mechanisms of pain, the development of new diagnostic tests for pain, and ultimately in the improvement of treatment and prognosis of pain.

11.6 Special Considerations for Minors

Parents/guardians will not be permitted to remain in the room with their child during testing to avoid potential confounds. However, parents will be allowed to view the area where the study procedures will occur and will then be escorted to a separate area when the study procedures take place.

12. FUNDING

Acquisition and analysis of data obtained from children is supported by startup funds provided by the Department of Anesthesiology.

13. REIMBURSEMENT/PAYMENT FOR STUDIES

Participants or, in the case of children, the families will receive a pre-paid debit card immediately after they have provided consent. This card will be loaded with funds when the participant completes each visit (or withdraws from the study). Patients will receive $30 at the end of visit 1, and $20 at the end of visit 2-9, and $30 at the end of visit 10. Healthy controls will receive $40 at the end of the Baseline visit. This payment scheme is in line with other ongoing studies in youth by our group.

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