Title: Brain Mechanisms of Attention and Pain in Youth with Functional Abdominal Pain Disorders

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1. Abstract: The goal of the current project is to enhance understanding of the neural mechanisms associated with the pain experience in youth with functional abdominal pain disorders (FAPD), which is the most common and debilitating presentation of FAPD. This study will examine the neural mechanisms associated with pain induction and diminished attentional regulation during pain in FAPD. Findings from pilot studies indicate that increased anxiety in FAPD is associated with higher pain-related impairment, and that anxiety may adversely impact response to a cognitive behavioral intervention for pain. While pain outcomes improve when anxiety is also addressed in treatment for FAPD, a sizable portion fail to respond to currently available interventions. Further, the PI found that induced pain in FAPD is associated with changes in regional brain activity and functional connectivity between brain regions that are implicated in chronic pain. It is crucial to better understand the neural mechanisms which may place youth with FAPD at risk for poorer outcomes in order to ultimately develop more effective treatments. In this study, neural mechanisms of response to a pain symptom provocation task in youth with FAPD will be compared to healthy controls. The impact of anxiety levels will also be explored. This study will also examine neural mechanisms associated with disrupted attentional regulation during pain induction in youth with FAPD.

2. Purpose of Study: The *objectives* of this study are to identify neural mechanisms of increased pain in pediatric FAPD and examine mechanisms of disrupted attention in the presence of induced pain. *The overarching goal* is to determine whether youth with FAPD process pain differently than healthy youth and to identify the brain areas involved.

2.A. *Specific Aims:*
Aim 1. Identify neural mechanisms during pain induction using the water load symptom provocation task (WL-SPT) in youth with FAPD vs HC. **H1a**. Brain regions associated with attentional, affective, and visceral afferent processing will show greater activations after the WL-SPT in youth with FAPD vs HC. **H1b**. AMY-PFC functional connectivity will be enhanced following WL-SPT in the FAPD group vs HC. **H1c**. Increased brain activity and functional connectivity will correspond to higher pain in FAPD.
Aim 2. Examine how diminished attention regulation impacts the WL-SPT response in FAPD. Regional brain activations after the WL-SPT (*H2a*) and functional connectivity between AMY-PFC (**H2b**) will be enhanced during a cognitive task, which will be related to higher pain ratings and response time (**H2c**).

3. Background
Functional abdominal pain disorders (FAPD) are a set of common pediatric chronic pain conditions associated with significant disability and substantial medical costs. FAPD is characterized by abdominal pain or discomfort which occurs at least for 2 months or longer in the absence of an identifiable organic cause (1). FAPD is present in 14% of youth in primary care (2), and accounts for nearly 50% of GI visits (3, 4). FAPD is associated with increased functional disability (5, 6), anxiety (7-9), and depression (10) that may persist (11, 12). Early and effective intervention is critical for preventing long-term problems; however, many (~40%) fail to respond to currently available evidence-based treatments such as cognitive behavioral therapy (CBT) (13).

Clinical anxiety is highly prevalent in FAPD and is predictive of poor outcomes. A large portion of youth with FAPD meet criteria for anxiety disorders (8, 10, 14). Anxiety exacerbates the severity of FAPD, predicts persistent pain and disability, and corresponds to poorer treatment outcomes (15-20). The PI (see *Preliminary Findings*) found that anxiety attenuates response to CBT for pain in youth with chronic pain, including FAPD (21). Although anxiety plays a key role in predicting poor FAPD outcomes, a mechanistic understanding how youth with FAPD may be cognitively impacted by their pain (22) is required to refine and modify improve upon current treatments.

Neural mechanisms of FAPD are poorly understood. Despite efforts to identify aspects of the brain-gut axis responsible for the development and maintenance of FAPD, results are inconsistent (23). Neuroimaging studies focusing on the IBS subgroup suggest common areas of activation in response to pain include regions associated with *visceral afferent processing*, such as the thalamus, insula (INS), anterior midcingulate cortex (aMCC) (24) and the primary and secondary sensory cortices (S1 & S2) (25). Brain regions associated with *affective processes* and *emotional arousal*, including the amygdala (AMY) and the pregenual anterior cingulate cortex (pgACC), are activated by pain induction (rectal distention) in patients with IBS, but not in healthy controls (24). In a recent study of pediatric IBS, structural abnormalities were found in regions implicated in *attention regulation* (e.g., prefrontal cortex (PFC), posterior cingulate (PCC), INS, and S1 (26)). Further, functional abnormalities were found between the PFC-PCC; however, pain induction was not performed. Unfortunately, the broader FAPD group (3, 4) has not yet been explored in neuroimaging research. While anxiety impacts the severity of FAPD (9, 20, 27, 28), the rates of anxiety during pain induction has not been consistently studied in fMRI research.

Diminished attention regulation may contribute to amplified pain levels in youth with FAPD. Pain has a unique attention demanding quality, and pain and attention can influence one another (29). *Diminished attention regulation* (i.e., increased attention to pain) may characterize children with chronic pain and persistent disability. Increased attention towards pain increases pain perception (30). A review (23) suggests multiple pain processing regions (i.e., ACC, SI,

INS), can be modulated by areas associated with attention (e.g., PFC) in FAPD (31-37). Further, poorer performance on a challenging cognitive task in the presence of pain is considered characteristic of chronic pain conditions (38) such as FAPD. This *pain-attentive* group has 1) more gray matter in pain/salience regions (anterior INS, aMCC, supplementary motor area, orbitofrontal cortex, thalamus, caudate), and 2) greater functional connectivity in sensorimotor and salience resting-state networks (38), which may account for increased impairment.

Anxiety-facilitated disruptions in attention regulation may categorize youth with FAPD at greatest risk for poorer outcomes, *though associated neural mechanisms have not yet been studied***.** Clearly, anxiety has adverse effects on attention and cognitive performance (39), and attention to pain may be due to appraisal of pain as a source of threat (40, 41). Brain regions associated with anxiety and attention may amplify bottom-up nociceptive input and create an intrusive pain experience. Targeting both *attention and anxiety* may disrupt the pain experience. Indeed, research suggests children who focus on their abdominal pain report higher levels of pain and anxiety (42, 43). However, these studies relied on subjective reports, which are biased. Interestingly, brain imaging studies based on healthy adults (44-47) identified a pain network within the brain which may capture areas associated with attention *and* anxiety (23). Understanding the effects of diminished attention regulation on FAPD in youth with varying levels of anxiety may lead to novel treatments (29) by identifying new targets to enhance existing by identifying new targets to enhance existing approaches. Since FAPD pain can vary, *functional connectivity analysis* (BOLD) may shed insights into patterns of brain regions activated during *transient* pain (29, 48-50) whereas ASL provides understanding of brain activation during *stable* pain.

Current treatments are ineffective. Pharmacologic treatments (i.e., antispasmodic agents, low dose anti-depressants) have limited support (51). Although CBT is helpful for some (52), *~40% fail to respond* (13). Moreover, youth with chronic pain and high levels of anxiety have a limited response to CBT (21). It is plausible that CBT fails in many patients with FAPD because the attentional demands from the pain interferes with the ability to learn and benefit from CBT strategies to cope with pain (53), such as relaxation and changing negative thoughts. Therefore, targeting the disrupted attentional processes in treatment through mindfulness meditation or attention bias modification training may enhance the effects of other CBT components. Therefore, targeting the disrupted attentional processes in treatment training may enhance the effects of CBT. It is important to examine disrupted attention regulation and other neuromechanistic factors impacting pain (54, 55) to ultimately develop and test interventions to enhance outcomes (PI's future research).

4. Duration: Six months will be allotted to develop the cognitive task and complete preliminary data collection. We anticipate actively enrolling study participants for the remaining 1.5 years. Physicians will identify potentially eligible youth and introduce the study, and study staff will then assess eligibility during an initial *screening* after the medical visit.

fMRI visit: Participants will complete one study visit (~2 hours) where they will report on baseline symptoms (~15 minutes). The research staff member will complete the following items with the child (~15 minutes): measures of pain intensity/unpleasantness/anxiety (via the Visual Analog Scale), information on child abdominal pain symptoms (child and caregiver). Next, participants will participate in an fMRI scan (~100 minutes). This will include pain intensity and unpleasantness ratings/state anxiety, a cognitive task, and a symptom provocation task to induce abdominal discomfort during an fMRI scan. The total time required to complete the study visit is approximately 2 hours. Participants will enter the MRI (total scan time ~1 hour and 40 minutes) and perform a cognitive task to enhance attention to pain. Following study completion, we estimate 6 months for data analysis.

5. Potential Benefits: There are no direct benefits expected. For the fMRI portion of the study, any structural brain abnormalities identified will be examined by a radiologist and the information will be provided to the child's primary care physician in addition to informing the primary caregiver of the participant in the unlikely event of the detection of an abnormality. However, the scans will be of limited diagnostic value, and should not be considered a benefit.

6. Potential Risks, Discomforts, and Inconveniences:
a) **Emotional Distress.** Self-report measures about symptoms and psychological functioning typically does not result in distress; however, staff will check in periodically to assess distress.

b) **Time Commitment and Fatigue.** The neuroimaging study visit will require approximately a two hour time commitment which may cause slight discomfort or inconvenience. In addition, participants will be removed from the scanner half-way through the data collection process (after ~45 minutes) to complete the water loading task (WL-SPT) prior to resuming the fMRI data collection. Research staff will regularly check in to assess patient comfort and fatigue.

c) **Confidentiality.** There is a small risk data may be viewed by those outside the study team.

d) **fMRI related Risks**. fMRI does not pose any known risk to the participants. There are no known risks from exposure to the magnetic fields and radio waves used in the fMRI data collection procedure. However, it is not assured that harmful effects will not be recognized in the future. A known risk is that strong magnetic fields attract iron or steel metal objects, thus posing a safety risk. In addition, although we will screen participants for claustrophobia, it is possible that participants may feel uncomfortable or confined once inside the imaging machine. Any participant who experiences discomfort or exhibits distress will be monitored visually and via microphone to ensure they are tolerating the procedure. As the scanner is very loud, participants' hearing will be protected with noise-reducing headphones specifically designed for use in the fMRI scanner. Finally, as participants are lying in a supine position, they may feel sleepy/bored.

e) **The water loading symptom provocation task** (WL-SPT) is a non-invasive and validated procedure for induction of gastroenterological discomfort in youth with FAPD. We have successfully pilot tested the feasibility of this task in 17 youth with FAPD undergoing neuroimaging with no adverse events. Moreover, the WL-SPT procedure was previously validated by Walker and colleagues (2006). Children are, by design, likely to experience abdominal discomfort during the procedure, which produces symptoms similar to but less intense than those naturally experienced by children with FAPD. As noted by the authors of the validation study, "This level of discomfort was acceptable to children and their parents" (Walker et al., 2006, p. 710). It will be explained to families in the consent/assent process that participation is completely voluntary and that they may drop out of the study at any time, for any reason, which will in no way compromise the child's medical care.

There is a small risk of vomiting if children consume water beyond the point of feeling completely full. During the water load period, children will be asked to rate their fullness at 5-minute intervals – to make sure they do not push themselves to consume water beyond the point of perceived fullness. One child (out of 230) in Walker's original study vomited following water ingestion. "In subsequent administrations of the water load, children were cautioned that vomiting was a possibility if they continued to consume water beyond the point of feeling completely full." (Walker et al., 2006; p. 707). We will caution children similarly in our study.

Another potential concern could be for the rare occurrence of water toxicity. To eliminate this risk, a daily fluid maintenance formal will be used based on their weight to determine the maximum fluid value for each child. The amount of water will be capped at that

value (up to 1.5 L). Further, allowing a specific time frame (up to 15 minutes) creates conditions which make water toxicity impossible. Study staff will be on hand to check in on participants and ensure the participant stops drinking water after a complete sensation of fullness is attained. A GI study physician (Dr. Farrell or Denson) will be on call in the event of any questions/concerns. In addition, participants will be instructed that they are free to terminate the task at any time.

7. Risk/Benefit Analysis: 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.

8. Data and Safety Monitoring Plan: This project involves functional imaging with a symptom provocation task. We recognize the need to provide a plan to ensure scientific integrity and safeguard the well-being of participants. Adverse events will be carefully monitored and documented. During the study visit, adverse events (whether or not they are thought to be study-related) will be monitored and documented in several ways. The PI and the study team will maintain an individual log to record increases in pain (beyond what is expected from the WLSPT) or mood-related problems during the study. In the event of a suspected adverse event, the PI will consult with study team members including study physicians and Dr. Kashikar-Zuck, a licensed clinical psychologist. The PI will also report any significant study-related or unanticipated adverse events to the Institutional Review Board. Given that this study is using evidence-based protocols, it is felt that monitoring at the level of the PI, her research team, with oversight from the IRB and study sponsor is sufficient.

8.A. Safety Events: We anticipate no adverse safety events (e.g. extreme pain). Vomiting, while unlikely, is an expected safety event. 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. 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. No sedation will be used during the MRI.

8.B. Data Management: All data will be identified with ID numbers exclusively and kept in locked files in a space in Dr. Cunningham's research laboratory that is designated specifically for the purposes of this project. All deidentified data (with the exception of fMRI data that will be stored on a separate, secure server) will be entered into a Redcap database on a network devoted solely to the research activities of BMCP. Electronic data stored on CCHMC's network is backed up nightly. The server is maintained and all backups are conducted by the Division of Information Services. Access to data and participant identities will be limited to Dr. Cunningham and key study personnel (e.g., mentoring team, research coordinator, fellow). The fMRI data will also be stored on a secure server, backed up nightly, which will only be accessible to study staff.

9. Methods:

9.A. Study Design: Youth with FAPD and healthy controls will be recruited (see recruitment sections and participant inclusion/exclusion criteria below)

Pilot testing phase: To determine initial feasibility, up to 5 HC and 5 youth with FAPD who otherwise would not meet the broader fMRI safety criteria (e.g., agoraphobia, braces) will be recruited. For these participants, the cognitive task with and without WL-SPT will be conducted outside of the scanner. Measures of pain intensity, pain unpleasantness, and state anxiety will be obtained throughout. We will compare differences in RT in youth with and without FAPD after the WL-SPT. The total time of this visit is expected to be 1.5 hours.

Active study phase: At the neuroimaging visit, all children will receive an fMRI scan, where they will complete some preliminary scans and then a cognitive task, and then be removed

from the scanner to complete a water loading symptom provocation task (WL-SPT), a non-invasive validated procedure in pediatric FAPD populations to induce abdominal sensations similar to those experienced during an FAPD episode (see Walker et al., 2006). After the WL-SPT task, they will resume the fMRI scan and will complete additional scans including the cognitive task they completed earlier to assess for diminished attentional regulation. Measures of pain intensity, pain unpleasantness, and state anxiety will be obtained throughout. The duration of the brain imaging visit is two hours, with the majority of that time spent in the scanner.

9.B. Participants: A total of 10 youth with be recruited to pilot test the procedures outside of the scanner (up to 5 HC and up to 5 with FAPD). Then, for the active part of the study, a total of 50 participants will be recruited (25 with FAPD and 25 HC). Children with FAPD will be recruited based on the presence of an FAPD diagnosis (see inclusion/exclusion criteria below). Healthy controls (HC) will not have an FAPD diagnosis.

Inclusion Criteria:

a. Children (boys and girls) between 11-16 years of age and their parent/primary caregiver.
b. Meets criteria for one of two study groups:
    - FAPD: based on physician diagnosis of FAPD confirmed by a validated Rome IV measure.
    - HC: based on a rule out of an FAPD diagnosis (using the Rome IV measure).

We will recruit approximately 50% of HCs with and without clinical levels of anxiety (e.g,. SCARED cut-off score greater than or equal to 25) to match the anxiety levels anticipated in the FAPD group.

c. Sufficient English language ability necessary to complete study measures and protocol

Exclusion Criteria

a. Children with significant medical condition(s) with an identifiable organic cause including those that may account for abdominal pain symptoms (e.g., Inflammatory Bowel Diseases such as Ulcerative Colitis and Crohn's Disease). Rationale: Children with a significant medical condition may impact the study results. Further, youth with organic conditions that include abdominal pain may not meet criteria for FAPD even if they present with similar symptoms.
b. Children with a documented developmental delay, autism spectrum disorder, a previously diagnosed thought disorder (i.e., psychosis), or bipolar disorder will be excluded. Rationale: These comorbidities may confound the study aims by impacting the dependent measures.
c. Significant visual, hearing, or speech impairment. Rationale: Children will be excluded if they are not able to see the testing stimuli, hear the test examiner, or respond verbally to the test examiner, even with the help of corrective or assistive devices (e.g., glasses, hearing aids).
d. Organic brain injury. Rationale: Children must not have a history of epilepsy, a head trauma associated with a loss of consciousness, or any other organic disorder since these conditions could possibly affect brain function and cognition and interfere with study results.
e. *Other exclusionary criteria specific to the fMRI component of the study:
    a. Participants with an implant such as a cochlear implant device, a pacemaker or neurostimulator containing electrical circuitry or generating magnetic signals will be excluded. Participants must also not have any significant ferrous material in their body that could pose the potential for harm in the fMRI environment or

cause signal suppression of key regions (i.e. orthodontia). Rationale: Implant devices can malfunction and/or be damaged. Strong magnetic fields in the fMRI environment can cause some metallic objects to move and/or heat, and therefore pose a safety risk. All children will be screened prior to participation using a standardized questionnaire in the fMRI component of the study to ensure that the fMRI magnetic fields will not pose any risk to their safety.

b. Female participants who report current/suspected pregnancy will be excluded. Rationale: There is minimal yet potential fetal risk due to electromagnetic radiation from the MRI. Female participants who self-report that they may be pregnant will be excluded from the study.
c. Participants with evidence of claustrophobia will be excluded. Rationale: Such participants may experience extreme distress when entering the fMRI scanner. Claustrophobia will be assessed using a validated module of the Anxiety Disorders Interview Schedule as part of the initial screening process. Youth will be excluded from participating if they report excessive fear of enclosures.

*Note that these exclusionary criteria do not apply to those recruited for the study's pilot portion.

9.C. Procedure:

9.C.1. Recruitment and Screening: Eligible participants with FAPD will be identified for the study from new or existing participants seen at the outpatient pediatric GI clinics. We request a waiver of HIPPA authorization for preparatory research to identify potential participants based on inclusion/exclusion criteria. We are also requesting a waiver of documentation of consent for the screening process. Participants will be assured that their usual medical care will not be affected based upon whether or not they choose to participate. HCs will be enrolled using a multi-pronged recruitment approach potentially including flyers placed in the community and around CCHMC, a CCHMC database of healthy individuals willing to participate in research, and online advertisements (e.g., CCHMC email blasts). HC who express interest will be contacted by research staff via telephone. Research staff will describe the study, answer questions, and complete a brief (IRB approved) phone screening with the caregiver and child to assess for FAPD, anxiety, and MRI eligibility. If potentially eligible, HC will be invited to complete a neuroimaging visit where they will be formally consented by research staff and complete the formal study measures.

For both youth with FAPD and those that are HC, written consent from the primary caregiver and written assent from the child will be obtained. All participants will be notified that screening is necessary and study entry is not guaranteed at this point. If the child is not eligible and the family is interested in the child receiving mental health services, contact information for the psychology service at CCHMC will be provided. Following informed consent and child assent, the following screening measures will be completed with the child by a member of the research staff: a measure of FAPD symptoms/diagnosis, clinical anxiety, and questions regarding fMRI eligibility. This process takes ~10 minutes. Study staff will complete the ROME IV FAPD diagnostic checklist with the participant's gastroenterology provider to ensure that the child meets FAPD criteria. Some patients will have already completed the SCARED at their medical visit as a part of clinical practice. For those patients, SCARED data will be obtained through EPIC. The participants and families will answer questions to ensure the child can safely enter the scanner and undergo fMRI and study procedures. Screening may take place after the clinic visit. If youth are determined to be eligible, they will be invited to participate in an fMRI visit.

9.C.2. Assessments: Qualifying participants and their respective caregivers will be scheduled to complete an in-person neuroimaging visit. Next, participants will enter the MRI and perform a

cognitive task to enhance attention to pain. *Performance is measured by reaction time*. This task was previously used in brain imaging studies of healthy adults to understand the effects of pain induction, and captures a "pain-attentive" group (i.e., reaction times >100 ms) (38) thought to categorize chronic pain conditions such as FAPD. This task involves judgements on groups of digits to indicate 1) the most frequently listed digit ignoring the value, and 2) the largest digit ignoring the frequency. Similar tasks were used in a pain study of healthy adults (50), and with healthy children (without pain) with evidence of brain activations in expected areas (56).

Imaging protocol. Brain images will be acquired via a 2015 model Philips 3T Ingenia MRI system using a 32-channel head coil. Pain intensity/unpleasantness and state anxiety ratings will be acquired after each sequence. Imaging will occur using block design, and will include sequences obtained at rest, and in the presence/absence of the cognitive task (with and without water loading). The pilot testing phase will allow for refinement of a neuroimaging protocol for the active study.

9.C.3. Payment: Families will receive payment for this study in the form of a reloadable debit card (ClinCard). A handout will be given to families that will explain how to use the card. Because families are being paid for their participation, CCHMC is required by the Internal Revenue Service (IRS) to collect and use the participant's social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that they are pain. Families will need to complete a Federal W-9 form for this income tax reporting. This form requires the participant's Social Security number. This form will be given to the CCHMC business office. It will not be kept as part of the participant's study chart. Subjects will receive a $25 incentive for their screening visit. Participants recruited to participate in the pilot testing phase (no MRI) will be compensated $50. We will reimburse families and participants who are recruited as part of the active research project for the visit that includes the MRI an additional $100.

9.D. Measures: *Standardized, psychometrically validated* instruments used in prior pediatric pain studies will be used. These measures will be administered using the REDCap data capture platform.

Screening:

FAPD questionnaire (57) . Measure to confirm diagnosis of FAPD based on Rome IV diagnostic criteria.

Screen for Child Anxiety Related Disorders (SCARED) (58, 59). A 41-item measure of anxiety over the past 3 months for children ages ≥8 (60). Scores ≥25 = clinical anxiety cut-off. The SCARED was validated in pediatric pain (61), and >50% of children with FAPD experience clinical anxiety, which is related to higher pain/disability (9). If this measure is not obtained clinically, it will be administered as part of the research protocol.

MRI Safety and Screening. Research staff to determine if patient can safely complete fMRI protocol.

Numeric Rating Scale (NRS) (62) for pain. Average, highest, and lowest pain levels in the past week will also be assessed.

Functional Disability Inventory (FDI) (63). 15-item measure of physical/daily function in last few days. This measure has been validated in pediatric chronic pain (64) and used in pediatric FAPD samples (9,24).

Note. **For patients with FAPD, some measures (SCARED, FDI, NRS) may be available as part of the participants clinical screening. If so, they will be obtained from the EMR.**

Measures administered during fMRI visit:

Pain History. Family socio-demographic factors (e.g., age, parent employment), and child pain information (e.g., duration, location, medication) will be obtained (available as covariates).
Pain Intensity/Unpleasantness via the Visual Analog Scale (VAS) (65, 66). Scale with the words "no pain intensity/unpleasantness" and "worst pain intensity/unpleasantness", validated for children ≥8 years. Large effects after the WL-SPT have been observed (67).
State Anxiety (VAS) (68). 0-10 self-report of how anxious the child is feeling in the moment.
Fullness Rating Scale (67). Youth will be asked to indicate how full they felt after water ingestion by selecting from images representing different levels of fullness, from empty to full.
Pain Catastrophizing Scale for Children (69). A valid measure of maladaptive beliefs about pain and feelings experienced when in pain.

9.E. Data Analysis: For the fMRI data, image processing and data analysis will be accomplished using FSL (70). Each subject's functional images will be registered to their structural data using a six-parameter linear 3-D transformation and then nonlinearly warped to standard space (MNI152) (71-73). The aCompCor approach will be used to preprocess BOLD data for functional connectivity and psychophysiological interaction analyses (74). This process minimizes the impact of global signal changes as well as signal changes induced by movement and other sources of noise. Analyses of data will be accomplished via mixed effects ANOVAs. Pain-related activation will be identified in images by comparing pre vs. post water loading data within subjects. These findings will then be contrasted across FAPD and HC groups. Multiple regression analyses will be used to examine if the changes in brain regions are related to the pain intensity/unpleasantness/anxiety. Next, changes in pain-related brain activation and functional connectivity *during* the cognitive task following the WL-SPT will be examined. There will also be a wealth of data available for exploratory analysis. Such analyses may include examining resting state FAPD data vs. HC data and exploring groups by anxiety level.

9.F. Sample Size: Analyses were powered to address pain intensity/unpleasantness differences measured during the pilot WL-SPT study (67). A Monte Carlo simulation was performed to obtain a power estimate for the analyses under the following assumptions: 1) equivalent sample sizes for the two groups, 2) covariates (age, gender, ethnicity, SES, baseline pain) will explain ($R2 = 0.35$) 35% of the variance, and 3) an effect size difference between FAPD and HC of $d = 0.73$ is observed. Monte Carlo simulation results showed power >0.80 to detect a $d = 0.55$ difference if 20 per group (total $N = 40$) are available for analysis after proper handling of missing data. Additional power calculations using http://neuropowertools.org/neuropower/neuropowerinput were conducted based on neuroimaging data available from Dr. Coghill (mentor). *For between group changes*, data comparing youth with chronic pain (migraine) to healthy controls was utilized. Based on these data showing moderate to large effect size differences, a total of 35 subjects are required for power of .8 and $p < 0.05$. Thus, a total sample size of at least 40 (which assumes 20% of data will be lost due to motion and other artifacts) ensures adequate power to observe at least moderate effects. Furthermore, 10-15 per group is sufficient to detect differences in child (75, 76) and adult (77) fMRI studies.

10. Security: To minimize risk to confidentiality, every effort will be made to ensure that research data are kept confidential and stored so that data cannot be accessed by individuals who are not part of the research team. All project staff will be required to take the Collaborative Institutional Training Initiative (CITI) course on research responsible conduct. Research personnel will be informed of the study aims and procedures, with particular attention given to the importance of confidentiality. Unique identification numbers will be assigned to participants, and all data forms will be coded with this number rather than a name. A master list linking the identification number to participant names will be locked in a file cabinet in Dr. Cunningham's

office separate from the study data. Access to the master list will be limited to key study personnel. Upon study completion, all study materials and participants' personal information will be destroyed. Locked filing space within Dr. Cunningham's research laboratory will be identified and used exclusively for study purposes. CCHMC IRB approval will be obtained for this study prior to participant recruitment and data collection, and the IRB will be immediately informed of any adverse events that occur across the duration of the proposed study. In addition to the licensed clinical (Dr. Zuck) and medical (Drs. Farrell and Denson) providers, Dr. Cunningham herself is a licensed clinical psychologist and has a wealth of experience in conducting research involving vulnerable populations (e.g., children) and sensitive topics (e.g., anxiety).

11. Protection of Children: The sample will consist of children ages 11-16, and their parent, because the study is tailored for the age-group of children most affected by FAPD and representative of the patients seen in our clinics. The study team will obtain assent from child participants and consent from caregivers. The study will be explained in developmentally appropriate language. The PI, a licensed clinical psychologist, has considerable experience working with youth ages 11-16 through a wide array of research and clinical experiences with pediatric samples throughout her training, including the pilot studies for this current application. The study team has extensive clinical and research experience with this population as well. The PI will directly oversee the process of screening patients, running participants, and maintaining data. Thus, the PI will be able to assure protection from risk, confidentiality, and assessment of psychological functioning.

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