Protocol Title: Using fMRI to understand response to an integrative treatment for pain and anxiety in pediatric functional abdominal pain disorders (FAPD)

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1. Abstract:

Functional abdominal pain disorders (FAPD) are the most common chronic pain conditions of childhood and are associated with significant functional disability and comorbid anxiety that adversely impacts outcomes. In this study, a psychological intervention, Aim to Decrease Anxiety and Pain Treatment (ADAPT), was developed and will integrate mindfulness meditation with cognitive behavioral therapy approaches for managing pain and anxiety to improve patient outcomes. Preliminary testing has shown that ADAPT successfully reduces pain and anxiety over time. In this study, brain mechanisms implicated in the modulation of pain and response to a psychological intervention for pediatric FAPD will be investigated. Participants with FAPD and comorbid anxiety will be randomized to either ADAPT or a waitlist control (each condition will last for 6 weeks). A post assessment will be conducted approximately 6 weeks after group assignment. Participants will undergo an fMRI to explore changes in functional connectivity during visceral pain induction (via the water load symptom provocation task; WL-SPT) after ADAPT intervention as compared to waitlist control. Those randomized to waitlist control will be eligible to receive ADAPT after their participation in the post assessment visits. In Aim 1, functional

connectivity patterns associated with a subjective response to pain inductions in youth with FAPD who receive ADAPT will be compared to the waitlist control. Conventional blood oxygenation level dependent (BOLD) fMRI will be used to assess functional connectivity to capture moment-to-moment fluctuations in activity. In Aim 2, changes in regional brain activation for those receiving ADAPT will be compared to those in the waitlist condition. The novel arterial spin label (ASL) MRI technique will be used to gain inferences into regional brain activity since these activations represent a relatively steady-state. In line with the NCCIH funding priorities, this study seeks to increase understanding of the mechanisms through which mind and body approaches impact clinical outcomes in chronic pain and anxiety. Results will advance the field by providing crucial information needed for the refinement and testing of a tailored mind body intervention for FAPD and comorbid anxiety.

2. Purpose of Study:
Complex FAPD with co-occurring anxiety are highly prevalent in children, can be very disabling, and are not responsive to currently available treatments. This research aims to better understand the neural mechanisms involved in a promising nonpharmacological treatment for FAPD to ultimately guide the development of more targeted treatment approaches for afflicted youth.

2.A. *Specific Aims:*
Aim 1. lAMY-PFC functional connectivity will be reduced post ADAPT vs. waitlist.
Aim 2. Brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will be more diminished after ADAPT vs. waitlist.
Exploratory Aim. Changes in functional connectivity and brain activations following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

3. Background:
Functional abdominal pain disorders (FAPD) are the most common chronic pain conditions of childhood and are associated with significant functional disability. FAPD impacts >10% of youth in community samples (1, 2) and accounts for up to 50% of gastroenterology (GI) visits (3, 4). FAPD is associated with significant functional impairment (5-7), including psychological problems, such as anxiety and depression (8, 9). Youth with FAPD are more prone to social and academic difficulties (7), including school refusal/absences, poor academic performance, and social problems (10). Impairment and disability are likely to persist, with 25%-45% affected after 5 years (11, 12). Increased healthcare utilization and medical costs are substantial and include invasive and unnecessary medical procedures (13), such as blood work-up (92%), endoscopic studies (51%), and abdominal x-rays (39%). Such work-ups are common, costly ($6,104 per patient), and are associated with medical complications. Although the total cost of pediatric FAPD is unknown, the cost in adults is estimated to be $20 billion a year (14). Given that a substantial proportion of youth continue to experience symptoms over time and may even develop other chronic pain conditions (15), the total cost of pediatric FAPD is likely substantial. Early and effective intervention may play a key role in preventing long-term problems.
Anxiety is highly prevalent and predicts poor outcomes. A large proportion of youth with FAPD meet criteria for a concurrent anxiety disorder (8, 9, 16). Anxiety disorders are characterized by extreme distress and worry and may be generalized or result from specific triggers, such as separation from attachment figures or social situations (17). In youth with FAPD presenting to GI clinics, anxiety disorders are estimated to affect 42% to 85% (18-20). Further, prior research (18, 21, 22) has found that *clinically significant anxiety* is common and predicts increased functional impairment (20, 23). Clearly, youth with FAPD *and* clinical anxiety are the most common and most clinically complicated manifestation of FAPD.
Conventional treatments are ineffective for many youth with FAPD. Pharmacologic treatments (i.e., antispasmodic agents, low-dose psychotropics) for FAPD have limited evidence and efficacy (24). Cognitive behavioral therapy (CBT) for pain is a conventional non-pharmacologic treatment that uses

cognitive strategies (e.g., reducing catastrophic thinking about pain) and behavioral approaches (e.g., activity pacing, behavioral activation) to improve functioning and reduce pain symptoms in youth with chronic pain such as FAPD (25, 26). However, a substantial proportion (~40%) fail to respond (27) and the presence of elevated anxiety can attenuate response to pain-focused CBT (28). Including specific treatment components to manage clinical anxiety (29, 30) is the next logical step for these patients. Mindfulness may amplify the efficacy of conventional treatments. Mindfulness includes attending to experiences in the present moment and using a nonjudgmental attitude, and is effective for managing pain (31, 32) and anxiety (33, 34). Pain reduction following mindfulness in healthy adults has been shown to be related to changes in activation of the S1, INS, ACC, and PFC brain regions (35). Moreover, improvements in anxiety following mindfulness are characterized by enhanced PFC connectivity with the AMY during resting state (36) and changes in the ACC, PFC, and INS in healthy adults (37).
Given this research evidence, Aim to Decrease Pain and Anxiety Treatment (ADAPT) was developed. ADAPT is a cognitive behavioral approach to manage pain and anxiety for youth with FAPD and comorbid anxiety.(38). For the current study, ADAPT is enhanced with mindfulness meditation. Thus, ADAPT focuses on decreasing attention to pain and anxiety using conventional strategies (CBT), as well as training in mindfulness meditation techniques, such as mindful breathing, developing a mindful awareness of bodily sensations, recognizing the impact of stress on functioning.. ADAPT utilizes a blend of in-person sessions and web-based, self-paced modules. Preliminary results indicate that ADAPT has a positive impact on disability and anxiety. However, there is a lack of evidence regarding mechanisms of action for this promising treatment.

The neurobiological underpinnings of visceral pain in FAPD are poorly understood (64) although anxiety is likely to play a crucial role in understanding psychological treatment response for pain (65). Research suggests pain is experienced through the pain connectome (39), a whole-brain-wide network that integrates cognitive, affective, and sensorimotor aspects. Recent reviews of prior neuroimaging studies in IBS, the most common subtype of FAPD, suggest that 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) (40), and the primary and secondary sensory cortices (S1 & S2) (41). Interestingly, brain regions associated with emotional arousal, including the pregenual anterior cingulate cortex (pgACC) and amygdala (AMY), are also activated by pain induction in FAPD, but not in healthy controls (40). In adolescents with FAPD (IBS), structural abnormalities were observed in the INS and S1, in addition to structural and functional abnormalities in the prefrontal cortex (PFC), and posterior cingulate (PCC) (42). Although brain regions associated with anxiety may play an important role in the expression of pain (i.e., FAPD), there is limited hypothesis-driven research examining the role of anxiety (42). Anxiety alone is associated with AMY hyperactivations and PFC hypoactivations (43-45).
Neural mechanisms may offer insights on response to a tailored intervention for youth with FAPD. There have only been two research studies examining neural mechanisms of treatment response to non-pharmacologic interventions for FAPD (in adults with IBS). However, these studies use an invasive and potentially risky pain induction technique (rectal distention), though less invasive methods (such as water loading) to induce visceral pain are available (46).The first found that improvements in pain using cognitive therapy were associated with reduced rectal distention-induced activations in the AMY and the pgACC (47). However, functional connectivity analysis was not undertaken. The second (48) compared hypnotherapy for pain to an educational control and found that the brain response to rectal distension after treatment was similar to that observed in HCs, suggesting that the treatment had a normalizing effect on the central processing abnormality of visceral pain signals in IBS. Hypnosis responders demonstrated a BOLD attenuation in posterior INS while education responders had a BOLD attenuation in prefrontal cortex. Moreover, in a pediatric pain sample, a positive response to an intensive integrated treatment for complex regional pain syndrome was related to a reduced hyperconnectivity between the lAMY and regions including the PFC (49); but research specific to pediatric FAPD is needed. Dr. Cunningham's pilot study has shown lAMY-PFC changes in functional connectivity following a symptom provocation task. Further, Dr. Coghill has shown that CBT for pediatric pain (migraine) alters interactions between

affective regions (AMY) and structions involved in cognitively driven pain modulation (PFC). Thus, the AMY might represent an important mechanism linking anxiety to sensory processing mechanisms.

These findings suggest that complex neuromechanistic processes account for response to psychological interventions. However, there is no research to our knowledge that distills the mechanism of the effect in a psychological intervention for youth with FAPD and comorbid anxiety. It is plausible that a psychological intervention tailored to anxiety and pain symptoms in FAPD would impact neuromechanisms that link cognitive and visceral afferent processing with emotional arousal (i.e., lAMY-PFC connectivity). Determining such information is critical for identifying brain mechanisms of effective treatments. For example, if lAMY-PFC connectivity is altered following ADAPT, this evidence would offer further support for the importance of targeting anxiety and pain in youth with FAPD.

4. Duration:

It is anticipated that we will be actively enrolling participants for 3.5 years. Participants will be recruited from GI clinic and enrolled in the study during that visit (immediately). Thus, *study eligibility is determined prior to randomization*. They will then come in for the baseline assessment, which will occur approximately one week after enrollment (though up to six weeks after enrollment will be allowed to account for MRI scanner availability). Following that visit, they will then be randomized to either the ADAPT group or a waitlist control group (each six weeks in duration) and will be informed of group assignment within a week of their baseline assessment, and will begin ADAPT/waitlist approximately one week after group assignment (with up to three weeks allowed to begin ADAPT). Upon completion of ADAPT or waitlist control, participant outcomes will be reassessed at the post assessment visits (approximately six weeks after ADAPT/waitlist). After completing the post assessment visit, participants in the waitlist control group will be given the opportunity to complete ADAPT. Participants randomized to ADAPT will be actively involved in the study for a ~10 week period. Those who are randomized to the waitlist control and then opt to receive ADAPT afterwards will be involved for ~16 weeks. After study completion, three additional months will be allotted for data analysis.

5. Potential Benefits:

5.A. Research Participants: Although we cannot guarantee a direct benefit to participants and families, on our prior research suggests that ADAPT leads to improvements in pain, pain-related disability, and anxiety symptoms. We do not yet know how/if the intervention will yield a neuromechanistic effect.

5.B. Other Potential Benefits: If successful, this line of research has the potential to reveal mechanisms by which treatment is effective for youth with FAPD and comorbid anxiety. If clinically indicated (e.g., based on psychological problems identified by screening), participants will be provided with referrals to the Division of Behavioral Medicine and Clinical Psychology for treatment. Thus, potential benefits (detection of problem and referral for appropriate care) may outweigh the risks (emotional distress, time commitment) to participants.

For the fMRI scan, any structural brain abnormalities identified will be examined by a radiologist and participants/caregivers will be informed in the unlikely event of the detection of an abnormality. However, the scans employed will be of limited diagnostic value, and should not be considered a benefit.

6. Potential Risks, Discomforts, and Inconveniences:

1) **Emotional Distress.** Given the risk of elevated anxiety and mood problems in individuals with FAPD, some responses on these measures may reveal anxiety, depressive affect, and/or suicidal thoughts. Youth may also find some questions embarrassing or uncomfortable to talk about. To help reduce potential discomfort, the research protocol includes standardized measures. Suicidal ideation may be directly queried during the depressive symptom screener. Participants' responses will be monitored to assess any safety issues such as suicidal ideation. Although ADAPT online modules do not specifically elicit

responses that may reveal depression/suicidal ideation, such symptoms (anxiety and mood) may arise during ADAPT. A safety assessment will occur via telephone if indicated. ADAPT is an evidence-based intervention and has not been found to be associated with any adverse effects. All participants will continue to receive their medical care as usual during the study.

In the event that a participant reveals severe depressive symptoms or suicidal ideation, the following steps will be taken (1) Dr. Kashikar-Zuck, the co-investigator (licensed clinical psychologist), or another covering psychologist will be immediately notified and will address these concerns (2) A professional and confidential risk assessment, including detailed information about suicidal ideation, intent and/or plans, access to means to hurt themselves, major stresses, availability of social supports, access to treatment, and plans for safety will be discussed in detail with the participant and their parent. The assessment will be conducted by the interventionist (an advanced graduate student with a Master's degree in psychology or postdoctoral fellow) , in close consultation with Drs. Zuck, and (4) A referral to the ER and/or a referral to the Psychiatry Division or an outpatient Psychology clinic, as appropriate, will be made. If the family refuses to follow through on the aforementioned recommendations, we will contact the appropriate authorities as warranted to ensure the safety of our participants. All actions will be documented.

Of note, all participants will be carefully screened for depressive symptoms and suicidal ideation using a validated measure *prior to* engaging in the fMRI portion of the study. Those who have high levels of depression and/or active suicidal ideation (T score $\geq$ 80) will be referred for mental health care and will not be eligible for the study.

During assessment and/or treatment procedures, participants may reveal experiences of abuse to the assessor or study therapist. In the event that the project staff becomes aware of suspected or actual abuse or neglect, Dr. Zuck will be notified. A report will be immediately filed with the appropriate state agency when necessary. The informed consent/assent procedures specify that confidentiality will be breached if research staff learn that a minor is the victim or suspected victim of abuse or neglect.

2) **Time Commitment and Fatigue.** The assessment visits will require approximately a 2 hour time commitment (clinical measures/fMRI visit),which may cause slight discomfort. Assessors will be trained to assess fatigue, and will give participants a 5-10 minute break if needed. For ADAPT sessions, there should be minimal discomfort due to the shorter length of these sessions (60 minutes or less).

Participants will be informed of their right to refuse to participate in any part of the data collection and will be given the phone numbers of the Principal Investigator as well as the Institutional Review Board of CCHMC in the event that they desire further information or would like to issue a formal complaint.

3) **Confidentiality.** There is a minimal risk that the data collected for each participant may be viewed by individuals outside the research team. 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. 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. Zuck's lab space 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 the pediatric pain research laboratory will be identified and used exclusively for the purposes of this study.

4) **fMRI related Risks**. fMRI has been approved for routine research and clinical applications and does not pose any known risk to participants. There are no known risks from exposure to the magnetic fields and radio waves used during fMRI data collection. 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. Prior to participation in the fMRI scans, participants will be given questionnaires to determine if they if they are eligible to complete the fMRI procedure. If they have metal objects in their bodies, they will

be excluded from participating in the study. In addition, any removable metal (e.g., glasses, watch, clothes with zippers) on the day of imaging will be removed before the participant enters the fMRI rooms.

In addition, 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. In addition, an alarm system is used to monitor the temperature and air. 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, the child may at times feel sleepy or bored. If participants express a desire to leave the machine, either temporarily or permanently at any point, they will be removed immediately.

5) **The water loading task** is a non-invasive and validated procedure for induction of abdominal discomfort in youth with FAPD. The procedure was validated by Walker and colleagues (2006). Children are, by design, likely to experience abdominal discomfort during the task. The procedure produces symptoms similar to but less intense than those naturally experienced by children with FAPD. As noted by the authors, "This level of discomfort was acceptable to children and their parents" (Walker et al., 2006, p. 710). It will be explained to families that participation is completely voluntary and that they may drop out of the study at any time, for any reason, and that this will not affect 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. "During debriefing, the child reported that he had pushed himself to drink water beyond the point of feeling full. 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 unlikely concern is exceptionally 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 to make water toxicity impossible.

Study staff will be on hand to c ensure the participant stops drinking water after a complete sensation of fullness. Drs. Farrell and Denson (GI physicians) 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. Overall, the study does not significantly increase the participants' risk of harm beyond those risks that are inherent in ordinary daily living. All study procedures can be terminated immediately. In addition, all participants will be able to receive an evidence-based intervention (ADAPT). Preliminary data suggests this intervention has a positive impact on symptoms associated with FAPD and comorbid anxiety. Information obtained from this study will be valuable for refining behavioral interventions for the treatment of youth with chronic pain and comorbid anxiety.

8. Data and Safety Monitoring:

8.A. Monitoring Adverse Events: Adverse events and unanticipated problems will be carefully monitored and documented at each study visit. During all phases of the study (i.e., assessment and treatment), adverse events and unanticipated problems (whether or not they are thought to be study-related) will be monitored and documented in several ways.

1) During screening, assessments, and for those completing the ADAPT intervention, the interventionist will maintain an individual log to record any increases in pain or mood-related problems during the study. These logs will be reviewed by a study mentor (Kashikar-Zuck) each week.

2) In addition, the study team will have quarterly meetings to monitor the progress of the study, the integrity of the treatment, discuss the need for any protocol refinements, and conduct regular safety monitoring checks of adverse events and unanticipated problems. Severe depressive symptoms or active suicidal ideation will be recorded as an adverse event.

3) Any adverse events/unanticipated problems reported during the study including during the assessment (e.g., measures and fMRI/water loading) or during ADAPT sessions will be immediately brought to the attention of the study team. The team will also report any significant study-related or unanticipated adverse events to the Institutional Review Board and to the study sponsor based upon institutional and sponsor guidelines. In addition, there are three Independent Monitoring Committee (IMC) members with expertise in pediatric neuroimaging, pediatric behavioral trials, and biostatistics who will assess the safety and study-related concerns. Any reportable events that occur (which includes the occurrence of any safety issues related to the scanning procedures or to a breakdown of confidentiality) will be reported to the IRB immediately. Participation will be discontinued at any time at participant or parent request. A study team member will provide referrals, as appropriate, for treatment needs resulting from any adverse events or unanticipated problems. The IRB requires yearly renewal of study protocols, which provides additional monitoring of participant safety. The study team will review study data to ensure safety compliance and proper reporting to the IRB.

Safety Reporting: Case report forms for AEs and SAEs have been developed. An AE documentation form will be completed by a clinician at the second ADAPT session and during the post assessment. For those randomized to waitlist control who are completing ADAPT after the post assessment, they will complete this information during session 2 and 6 of ADAPT. The form documents whether or not an adverse event has occurred and throughout the trial if any AEs/SAEs are spontaneously reported by participants. AEs include new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity. AEs will be reported by body system and rated by level of severity (mild, moderate, severe, life-threatening). The primary study team will meet regularly to monitor the progress of the study and safety of participants in blinded fashion. Reportable events will also be recorded in a separate study database.

8.B. Serious Adverse Events (SAEs): For any adverse event meeting the definition of "severe" or "life threatening," study staff will notify the study mentor (Kashikar-Zuck) and complete a "Serious Adverse Event" reporting form within 1 working day. Any severe or life threatening adverse event report will be sent to the IMC and the IRB will be notified.

8.C. Data Management: All *data* will be identified with ID numbers exclusively and kept in locked files in a space in the pediatric pain research laboratory that is designated specifically for the purposes of this project. All de-identified data (with the exception of fMRI data) will be saved into Redcap, a password-protected database. Data output will be stored on a network devoted solely to the research activities of BMCP. In order to assure the accuracy of data entry, data will be verified by double-entry. 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. The fMRI data will also be stored on a secure server, backed up nightly, and will only be accessible to study staff.

9. Methods:

9.A. Study Design: Participants with FAPD (see below) will be recruited during gastroenterology clinic visits. Potentially appropriate participants will be approached by a study staff member. They will be described the study in detail and will have the opportunity to ask questions and voice concerns. If the patient/family is agreeable, informed consent/assent will be obtained and participants will be screened for study eligibility. Qualifying patients will then be scheduled to complete the baseline assessment visit

(clinical measures/WL-SPT with fMRI). After this visit, participants will be randomized to either the ADAPT treatment group or a waitlist control (each condition will last for 6 weeks). The post assessment will be similar in format to the baseline assessment. Those randomized to waitlist will be eligible to receive ADAPT after the post assessment.

9.B. Participants: We plan to approach approximately 124 participants, ages 11-16 years. Of those, we expect 75% will agree to participate (n=93) based on our pilot fMRI study. Of those, we expect approximately 65% will qualify. Thus, we anticipate recruiting n=60 to complete a baseline assessment. Based on our previously RCT, we expect 85% of those recruited in clinic will complete the baseline assessment (n = 50) and the majority will be retained in the study (90%, n=45). Based on our fMRI pilot study, we expect to lose approximately 10% of participant data to movement artifacts yielding n=40 with usable data. The minimum number of total completed participants allowed will be 34 and the maximum will be 50.

We will recruit males and females to participate in this study. While FAPD is more common in females, we have found that we are easily able to recruit males as well. Based on our prior research projects, we expect that we will recruit a sample of youth with FAPD that is 65% female and 35% male. The PI will check in with the mentorship team quarterly regarding enrollment and gender breakdown in a blinded fashion. If the gender breakdown is skewed, the PI will problem solve with study mentors to ensure the sample is representative of the population.

Inclusion Criteria

a. Children (boys and girls) between 11 and 16 years of age and their parent/primary caregiver.
b. Meets criteria for FAPD based on physician diagnosis of FAPD and ROME IV FAPD criteria
c. Meets criteria for presence of clinically significant anxiety (based on the Screen for Child Anxiety Related Disorders [SCARED] cut-off score ≥25).
d. Meets criteria for presence of greater than minimal disability (based on Functional Disability Inventory [FDI] cut off ≥8)
e. Meets criteria for greater than minimal pain (based on Pain Intensity Visual Analog Scale [VAS] cut off ≥3)
f. 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 include abdominal pain symptoms (e.g., Inflammatory Bowel Diseases).
b. Children with a documented developmental delays, autism spectrum disorder, a previously diagnosed thought disorder (i.e., psychosis), or bipolar disorder.
c. Significant visual, hearing, or speech impairment.
d. Organic brain injury.
e. Participants who are currently in psychological therapy for pain or anxiety.
f. Participants with severe depressive symptoms (T score ≥80) or active suicidal ideation reported on the CDI.
g. 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. Participants with 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).
b. Female participants who report current/suspected pregnancy.
c. Participants with evidence of claustrophobia.

The ADAPT treatment requires access to the internet to complete self-paced web module portion of the intervention. *All children with FAPD will be eligible for participation in the ADAPT portion of the study regardless of home access to the internet.* If a child does not have internet access at home, the family can choose to complete the web-sessions at a local setting (e.g., library, school) of the family's choosing.

Selection Criteria: Youth with FAPD, the presence of clinically significant anxiety, at least minimal functional disability, and reported pain in the past two weeks that is greater than or equal to 3/10 will be recruited from Cincinnati Children's Hospital Medical Center Gastroenterology Clinics.

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. Participants will be assured that their usual medical care will not be affected based upon whether or not they choose to participate 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.

FAPD participants will be introduced to the study in person by a medical staff member who will explain the study to the patient and the primary caregiver in greater detail. If interested, the patient and their family will complete consent/assent, the Screen for Child Anxiety and Related Disorders (SCARED), the Functional Disability Inventory (FDI), the Visual Analog Scale (VAS) for pain intensity, and the Children's Depression Inventory (CDI) before leaving their GI clinic appointment. Some patients will have already completed the SCARED, FDI, and VAS at their medical visit as a part of clinical practice. For those patients, 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. Additionally, study staff will complete the ROME IV FAPD diagnostic checklist with the participant's gastroenterology provider to ensure that the child meets FAPD criteria. These procedures will ensure that eligibility is determined prior to assessment or randomization. Participants who can complete the fMRI protocol procedures, evidence clinical anxiety, do not evidence severe depressive symptoms (T score ≥ 80) and meet FAPD criteria will be considered eligible for participation. If eligible, we will inquire whether females have achieved menarche. If yes, we will query the date of their last menstrual cycle, and inform them they we will schedule the neuroimaging on a date when they are not having pain due to menstruation.

9.C.2. Assessments: Qualifying participants and their respective caregivers will be scheduled to complete an in-person baseline assessment. Participants will complete additional study measures. Caregivers will complete several measures pertaining to their child's pain and child's worries in addition to a measure of their own psychological symptoms. Participants and caregivers will be given the option to either complete these measures during their baseline assessment visit or before this visit using their own electronic device (to reduce the length of the in-person visit). Participants will enter the MRI scanner, where scans of brain structure and cerebral blood flow will be performed while participants provide current pain ratings. Participants will then exit the scanner to undergo the WL-SPT, a validated non-invasive procedure for youth ages 8-16 to create visceral pain sensations (40). Participants will ingest water until they have achieved complete fullness eliciting discomfort (~5 minutes). Then, participants will re-enter the scanner and resume functional imaging.

- Imaging: *Pre-WL-SPT*. During imaging, the first 10 minutes will consist of positioning the participant and collecting structural images. BOLD and PCASL acquisitions will be obtained. *Post-WL-SPT*. Following the WL-SPT, BOLD AND PCASL acquisitions will also be obtained.

Participants will then be randomized within one week of their baseline assessment. Approximately one week after randomization, participants will complete either 6 weekly sessions of ADAPT or 6 weeks of waitlist. A post assessment (including fMRI) will be completed approximately one week after completion of treatment or waitlist. Participants will complete the same assessment measures and procedures as administered at the baseline assessment in addition to the measures that were administered at the screening.

Those randomized to the waitlist condition will be eligible to receive ADAPT after their post assessment. Waitlist control participants who choose to compete the ADAPT program after their post assessments will complete 3 brief measures (pain, anxiety, disability) via phone following their last ADAPT session.

9.C.3. Intervention: Participants will either begin ADAPT in the week following the treatment group assignment or after completing the post assessment (waitlist control). ADAPT is an individual therapy with caregiver involvement that consists of 2 in-person sessions (60 minutes) once per week for the first two weeks, followed by 4 weeks of self-paced web modules (45 minutes per week) in conjunction with interventionist phone support (15 minutes per week). The duration of ADAPT is 6 weeks and a total of 6 hours of intervention will be administered. Participants will be reminded via text message to complete their respective ADAPT web modules.

9.C.4. Protection of Protocol Integrity: ADAPT will be delivered by an advanced graduate student (with a Master's degree) or postdoctoral fellow in clinical psychology under the supervision of a licensed clinical psychologist (Kashikar-Zuck). Multiple interventionists will be utilized over the course of the study. In addition, there will be a back-up provider in the event of an absence of the primary provider. To ensure protocol integrity, staff training will include required human subjects training, GCP training, and study/intervention specific training. Study staff training will vary based on roles (i.e., interventionists will receive specific training on conducting the intervention from the PI and will be supervised by the study mentor). The PI or the study mentor (Kashikar-Zuck) will also oversee any study staff who are involved in screening.

9.C.5. Blinding: Blinding of study personnel will be employed when possible (Table 1). Of note, our study statistician (Dr. James Peugh) will only have access to subject IDs and Treatment A and Treatment B. He will generate monitoring reports for closed sessions based only on Treatment A and Treatment B. If there is an issue of serious concern (e.g., safety issues in one arm, differential attrition etc.) that requires complete unblinding, another statistician will run the unblinded reports. Dr. Peugh will also complete final analysis only by Treatment A versus B and the code will be revealed only after the data has been analyzed. Furthermore, the PI (Cunningham) will be blinded to group assignment. However, Dr. Zuck will not be blinded to group assignment ensure the safety of participants and the integrity of the study. It is critical for Dr. Zuck (a licensed clinical psychologist) to be aware of participants who are randomized to the ADAPT intervention in order to ensure treatment fidelity and patient safety (e.g., risk assessment for suicidal ideation, trauma/abuse, etc) during the course of the study. Of note, the study interventionist will be a Master's level clinician or post-doctoral fellow, and as such, and will require the supervision of a licensed clinical psychologist. The PI and study mentors will have no access to post-assessment data by group assignment until after the completion of the study.

Table 1. Blinding of Study Personnel.

Stake holder	Intervention group assignment	Primary Mechanistic Outcome Measure	Clinical/ Functional Outcome Measure
Study subjects	Subjects will be aware if they are randomized	The subjects will participate in the collection of this data	Subjects will provide such data. As such, they will be aware of their

	to ADAPT versus waitlist.	but will not be involved in the interpretation of the data or the analysis of the results.	own responses on clinical/functional outcome measures.
Interventionists (graduate student or post-doctoral fellow)	The interventionist will know if participants are randomized to the intervention group.	The interventionist will not be involved in analyses.	The interventionist will not be involved in analyses.
Outcome Assessors (post-baccalaureate research coordinator)	Outcome assessors will be blinded as to group assignment.	The outcome assessor will be involved in the collection of such data, but will not be involved in the interpretation and analysis of results.	The study coordinator will serve as an outcome assessor. However, data will be collected directly from participants using online forms. In addition, the study coordinator will only access/manage post-assessment data that has been de-identified (with group assignment removed).
Data Analysts/Statistician	The biostatistician will be blinded to the group assignment.	The biostatistician will be blinded until the competition of this study	The biostatistician will generate reports and submit data as requested by NCCIH or the IMC for the duration of the study.
Principal Investigators	The PI will be blinded to intervention group assignment. Dr. Zuck (licensed clinical psychologist) will not be blinded to intervention group assignment and will oversee the interventionist and ensure treatment fidelity.	The PI and her mentorship team will be blinded to post-assessment data results until after the completion of the analysis. She will participant in processing/management of fMRI data without knowledge of group assignment.	The PI and her mentorship team will be blinded to post-assessment results by group assignment until after completion of the analyses.

9.C.6. Randomization: Randomization will be generated using PROC PLAN in SAS 9.3 by a biostatistician who is part of the University of Cincinnati's Center for Clinical and Translational Science and Training (CCTST). The CCTST biostatistician will not have access to the data. This data management support service will generate randomization and will assign a Treatment A/Treatment B designation. The randomization schedule and code sheet will be held confidentially by a senior Clinical Research Manager in Dr. Kashikar-Zuck's lab, and the study interventionist will contact the Clinical Research Manager to get assignment when a participant is enrolled in the study.

Gender and age will be used as blocking variables in randomization. Specifically, there will be four randomization tables for gender (male and female) by age (younger i.e., 11-13 years of age and older i.e., 14-16 years of age) combination:

- $11 \leq \text{Age} < 14$, Female

- 14 ≤ Age < 17, Female
- 11 ≤ Age < 14, Male
- 14 ≤ Age < 17, Male

Patients will be randomized to either ADAPT or WL. A separate randomization list will be produced for each of the four (4) blocks – Age x Sex. Per study protocol, a list of 10 treatment / control assignments will be produced per group. Within each group, a completely randomized design will be applied to allocate ADAPT or WL.

The test randomization and final randomization will require four seed numbers, one for each block size. The seed numbers below are for illustration only and will not be used.

- 11 ≤ Age < 14, Female: Seed = 111111
- 14 ≤ Age < 17, Female: Seed = 222222
- 11 ≤ Age < 14, Male: Seed = 333333
- 14 ≤ Age < 17, Male: Seed = 444444

The independent statistician will select seed numbers and will not share those final seed numbers with the project statistician nor other members of the project team. The randomization identification number (rand_id) will be comprised of 4 digits. The first digit will correspond to the blocks and the remaining 3 digits will be in sequential order, as listed below.

- Block 1: 11 ≤ Age < 14, Female. ID numbers 1001-1010
- Block 2: 14 ≤ Age < 17, Female. ID numbers 2011-2020
- Block 3: 11 ≤ Age < 14, Male. ID numbers 3021-3030
- Block 4: 14 ≤ Age < 17, Male. ID numbers 4031-4040

Given that other factors such as pubertal status and subjective pain levels could influence the outcome, these factors will be included in the analysis as control covariates. Each participant's exact age will be recorded at assessment allowing personnel to control for age as an additional covariate should the need become apparent during preliminary analyses.

9.C.7. 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. We will reimburse families and participants $100 for each assessment visit (up to $200 total).

9.D. Measures: Standardized, validated measures used in prior pediatric pain studies will be used (Table 2). These measures will be administered using the REDCap data capture platform. Home practice during ADAPT will also be measured (online module completion). Should a randomized participant prematurely discontinue participation in the study, study measures and endpoints will continue to be collected if possible. Any concomitant interventions (i.e., medical and psychological) experienced by the participants (either allowed or prohibited) will also be assessed for and recorded at baseline and post assessments. Participants will provide the reason and duration of concomitant interventions at the baseline and post assessment visits.

The protocol includes assessment of adverse events in the schedule of evaluations for the study. Adverse events will be assessed for at the second session of ADAPT and the post assessment.

Screening:

Screen for Child Anxiety Related Disorders, SCARED (50). Child reported anxiety in the past 3 months; ≥25 is clinical anxiety. This measure has been recommended for use by the American Academy of Pediatrics (51) and has been validated in pediatric chronic pain (50, 52, 53) and used in pediatric FAPD samples (20, 28).

Functional Disability Inventory (FDI) (55). 15-item measure of physical/daily function in last few days. This measure has been validated in pediatric chronic pain (56) and used in pediatric FAPD samples (20, 28).

Visual Analog Scale (VAS) (63) for pain. Average, highest, and lowest pain levels in the past week will also be assessed.

Rome IV FAPD Diagnosis Checklist (physician report). FAPD criteria based on the Rome IV. FAPD include irritable bowel syndrome (IBS), functional dyspepsia, and FAPD- not otherwise specified. To meet criteria for FAPD, a child must endorse continuous or episodic pain at least 4 times in a month that do not exclusively occur during a physiological event (e.g., eating, menses) for a periods of 2 months or longer that cannot be fully explained by another medical condition after appropriate evaluation. This questionnaire will allow us to group our sample into specific diagnostic subtypes of FAPD.

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

Children's Depression Inventory 2 (CDI) (54). A validated and reliable measure of depressive symptoms in the past 2 weeks.

Menstruation Query. Female participants will be asked if they have achieved menarche. If participants indicate that they have, we will query the date of their last menstrual cycle, and inform them they we will schedule the neuroimaging on a date when they are not having pain due to menstruation.

Assessment Clinical Interview and Rating Scales:

Participant measures:

Self-Efficacy Pain Scale- Child Version (57). A valid and reliable measure of child self-efficacy when in pain.

Affective Reactivity Index (ARI)- Self- Report (58). A valid 7-item measure of irritability in the last 7 days.

Pain Catastrophizing Scale for Children (59). A valid measure of maladaptive beliefs about pain and feelings experienced when in pain.

NIH Promis Pain Interference (60). A valid measure of functional impairment due to pediatric pain in the past 7 days.

Peterson Pubertal Developmental Scale (PDS) (61). A valid and reliable pubertal status assessed via clinician interview.

Edinburgh Handedness Inventory (62). A validated measure that assesses the dominance of a person's right or left hand in everyday activities. For the purposes of this study, one original item was removed (striking a match) given our pediatric sample.

Adverse Event Query Form. A form to be completed via clinician interview assessing for adverse events experienced by participants receiving the ADAPT treatment.

Caregiver measures:

Child Pain History & Sociodemographic Factors. Demographic factors, school absences, pain duration, location, and concomitant psychological treatments

Depression Anxiety Stress Scales (64). A validated and reliable measure of parent depression, anxiety, and tension/stress.

Visual Analog Scale (VAS) (63). Parent reported average pain experienced by their child over the past 2 weeks.

Parent Pain Catastrophizing Scale (PCS)(65). Validated measure of maladaptive beliefs about child pain.

Screen for Child Anxiety Related Disorders- Parent Report, SCARED (50). Parent-reported child anxiety symptoms over the past three months; ≥25 is clinical anxiety. This measure has been used in pediatric FAPD samples (20, 28).

Functional Disability Inventory (FDI)- Parent Report (55). 15-item measure of child physical/daily functioning in the past few days. This measure has been used in pediatric FAPD samples (20, 28).

Self-Efficacy Chronic Pain Scale- Parent Version (57). Parent reported child self-efficacy during pain. This measure has been validated.

Affective Reactivity Index (ARI)- Parent- Report (58). A valid and reliable 7-item measure of child irritability.

Concomitant Medication Form. Concomitant medication information (medication name, reason for taking, unit, frequency, route, etc.) will be obtained via chart review prior to the baseline visit. Study staff will confirm with caregivers that the information is correct and up to date at the baseline and post assessment visits. Any changes in medication from baseline to post assessment will be documented.

Measures administered during fMRI:

Pain Intensity and Unpleasantness Visual Analog Scales (VAS) (63, 66). Pain intensity is associated with nociceptive processing and is a common measure of treatment response (26). Pain unpleasantness is related to affective network activity (35), and is highly responsive to meditation (35).

State Anxiety (VAS) (67). 0-10 self-report of how anxious the child is feeling in the present moment.

Fullness Rating Scale (46). Youth will be asked to indicate how full they felt after water ingestion by selecting from images representing different levels of fullness, from empty (coded 0) to full (coded 4).

Table 2. Measures and Delivery Timeline (pain history/medication use also collected at baseline/post).

Measures	**Screening**	**Baseline Assessment**		**ADAPT Session 1**	**Post Assessment**		**Post WL/ ADAPT***
	Participant	*Participant*	*Parent*	*Participant*	*Participant*	*Parent*	*Participant*
fMRI/Water loading measures							
Current pain intensity/unpleasantness^		X			X		
State Anxiety (VAS) ^		X			X		
Fullness Rating Scale (during fMRI) ^		X			X		
Self-Report/Interview measures							
Screen for Anxiety and Related Disorders (SCARED)	X		X		X	X	X
FAPD screening measure^	X				X		
CDI	X				X		
Menstruation Query`	X						
Petersen Pubertal Development Scale (PDS)^		X			X		
Promis Pain Interference		X			X		
Edinburgh Handedness Inventory		X			X		
Pain VAS Scale	X	X	X		X	X	X
Functional Disability Inventory (FDI)	X	X	X		X	X	X
Pain Catastrophizing Scale		X	X		X	X	
Affective Reactivity Index (ARI)		X	X		X	X	
Self-Efficacy Chronic Pain Scale		X	X		X	X	
Depression Anxiety Stress Scales (DAAS)			X			X	
Demographic Information			X			X	
Child Pain History & Sociodemographic Factors			X			X	
Concomitant Medications			X			X	

Adverse Event Query Form				X	X		X

* For those in the waitlist condition who then complete ADAPT. Measures will be obtained via phone.
^ Clinician administered/facilitated
`Administered to female participants only

9.E. Statistical Considerations: Our study aims are as follows and will be analyzed as described below:
Aim 1. Functional connectivity between the lAMY-PFC will be reduced post ADAPT compared to the waitlist.
Aim 2. Regional brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will be more diminished after ADAPT compared to the waitlist.
Exploratory Aim. Reductions in functional connectivity and brain connectivity following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

9.E.1. Analytic Approach for Aims: Subjects will first complete localizer sequences for targeting of other series. A B0 field map (B = magnetic field) will be used to correct for distortion due to susceptibility artifacts. A high resolution T1 weighted anatomical volume will be obtained to provide a detailed view of brain anatomy. Functional connectivity will be examined using the Blood Oxygenation Level Dependent (BOLD) effect. Brain activation during the WL-SPT will be assessed by arterial spin labeling (ASL). In order to examine relationships between resting brain activity and other variables, cerebral blood flow (CBF) will be measured in a quantitative fashion via ASL, which is the optimal for assessing steady-state conditions. Nine series will be obtained (5-10 mins each): Pre-WL-SPT: 1 MPRAGE; 2 resting ASLs; 2 resting BOLDs; post-WL-SPT: 2 ASLs; and 2 BOLDs.

9.E.2. Data Analysis: For fMRI analysis, image processing and data analysis will be accomplished by FSL software. Each subject's functional images will be registered to their structural data using a six-parameter linear 3D transformation and then nonlinearly warped to standard space (MNI152) (90-92). Analyses of both BOLD and ASL data will be accomplished via mixed effects ANOVAs. Data will be coded prior to analysis to conceal patient status to ensure blinding.

Clusters of activation will be identified using a threshold of $Z>3.1$ and statistical significance will be estimated according to Gaussian random field theory. Functional connectivity analysis will be conducted (Aim 1) to identify changes in functional connectivity between the AMY-PFC in ADAPT completers vs. those in the waitlist condition. A seed to whole brain analytic approach will be used to identify any/all differences observed. Pain-related brain activations are expected to diminish for those that complete ADAPT compared to the waitlist condition (Aim 2). For the exploratory aim, mechanisms associated with a positive treatment response (decreased pain intensity/ unpleasantness/ anxiety during WL-SPT) after ADAPT will be identified. Normalization of abnormal connectivity patterns are predicted to categorize changes in pain and anxiety. Specifically, decreases in brain activations and reductions in functional connectivity will be examined in relation to improvements in pain and anxiety post treatment using multiple regression.

Our intent-to-treat population will be defined as those subjects who complete a post-randomization assessment.

While all efforts will be made to minimize missing data through the use of electronic data capture and real-time adherence data collection, missing data is still inevitable in RCTs. Thus, we will employ several strategies to handle missing data with specific attention on how to handle missing not-at-random. Specifically, missing data will be handled via ML estimation with auxiliary correlate inclusion (e.g., Graham, 2003; Enders, 2010). Missing not at random will be addressed with mixture MNAR methods (e.g., Gottfredson, Bauer, & Baldwin, 2014; Muthen, et al., 2011; Sterba & Gottfredson, 2015).

9.F. Sample Size: We've used the following tool (http://neuropowertools.org/neuropower/neuropowerinput/) to conduct sample size calculations for the fMRI portion of the study. Power calculations were based on prior studies by the study mentor, Dr. Coghill, who collected functional connectivity data 1) pre and post psychological therapy for pediatric pain (migraine), and 2) comparing individuals with pediatric pain (migraine) to healthy controls. While these groups are not synonymous with those proposed in the current study (which aims to compare youth with FAPD who have received psychological therapy for pain and anxiety to those in a waitlist control condition), this preliminary data yields meaningful information by which we can estimate the power required for the proposed investigation. The power calculations and sample size requirements are detailed below:

For within group changes, we relied on the pre/post data following a psychological therapy for pediatric pain (migraine). Here we found that a total sample size of 34 would be required for power of .8 and $p < 0.05$. *For between group changes*, we utilized data comparing youth with chronic pain (migraine) to healthy controls. Based on these data, a total of 35 subjects are required for power of .8 and $p < 0.05$. We note moderate to large effects are observed for within and between group studies; thus, a total sample size of 40 ensures were are adequately powered to observe at least moderate effects.

10. Security: All study staff are trained and certified in human subjects' protections including protection of confidentiality. Confidentiality will be maintained through the use of subject identification numbers on all case report forms. All consent forms, contact information and identifying data will be stored in a secure location within the pediatric pain research lab. The subject codebook will be stored separately in a locked cabinet in the pediatric pain research laboratory. Before they begin the study, participants and parents will be informed about the importance of confidentiality and will agree that they will not share any personal or health information about other study participants outside of the focus group. Regarding the use of online measures and web modules, material development will be conducted in accordance with CCHMC policies. Hardware for this study will be provided and maintained by CCHMC Informatics, which maintains a secure Microsoft SQL Server cluster and web server for supporting projects that potentially contain protected health information (PHI) and are subsequently subject to compliance with federal and state regulations regarding data of this type. The data obtained from the web program will be stored in the Microsoft SQL Server, which will be backed up regularly.

11. Protection of children: The sample for the current proposal will consist entirely of children ages 11-16 because the study is tailored for the age-group of children most affected by FAPD and representative of the participants seen in our clinics. The PI will obtain assent from child participants and consent from caregivers regarding study participation. The study will be explained in developmentally appropriate language that would be understandable to a child. The PI and the study co-mentor, both licensed clinical psychologists, have considerable experience working with youth ages 11-16. The other co-investigators and research staff have extensive clinical and research experience with this population as well. With oversight from the PI or Dr. Zuck (post-randomization), the study staff will be screening participants, conducting the study, and maintaining data. The PI and/or Dr. Zuck will meet regularly with study staff to assure protection from risk, confidentiality, and assessment of psychological functioning.

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