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Examining Associations Between Sources of Stress and Experimental Pain Sensitivity in Pediatric Patients with Functional Abdominal Pain Disorders

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EXAMINING ASSOCIATIONS BETWEEN SOURCES OF STRESS AND EXPERIMENTAL PAIN SENSITIVITY IN PEDIATRIC PATIENTS WITH FUNCTIONAL ABDOMINAL PAIN DISORDERS

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ABSTRACT

Functional abdominal pain disorders (FAPDs) are one of the most common pain complaints among children and adolescents. Research demonstrates a relationship between multiple sources of stress and pain responses. However, research has not yet explored the role of stress in pain processing and sensitivity in youth with FAPDs. Thus, the present study aimed to examine associations between biopsychosocial sources of stress and experimental pain sensitivity in pediatric patients with FAPDs. Additionally, racial differences in clinical and experimental pain responses were explored. Analytical findings did not support hypotheses as the biological, social, and psychological sources of stress did not predict experimental pain sensitivity based on statistical significance. However, psychological stress, in isolation, did predict temporal summation of mechanical pain. One analysis also suggested higher average temporal summation of mechanical pain in non-Hispanic White subjects compared to non-Hispanic Black subjects. However, both of these findings should be interpreted with caution given the lack of power. Results from this study suggest that the chosen biopsychosocial sources of stress may not contribute to pain sensitivity in youth with FAPDs. Results may also be explained, in part, by the absence of critical variables or the effects of stress-induced analgesia.

Keywords: functional abdominal pain disorders; pediatric psychology; biopsychosocial model; stress; experimental pain sensitivity

DEDICATION

For my brother, the late William Sanders Evans, whose life and death inspired me to become a pediatric psychologist and whose memory reminds me daily of the preciousness of life and the sanctity of good health.

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TABLE OF CONTENTS

Page

LIST OF TABLES

Tables *Page*

LIST OF FIGURES

Figures *Page*

LIST OF ABBREVIATIONS

ACE	adverse childhood experiences
BMI	body mass index
CRP	c-reactive protein
FAP	functional abdominal pain
FAPD	functional abdominal pain disorders
FGID	functional gastrointestinal disorder
hrQOL	health-related quality of life
hsCRP	high sensitivity c-reactive protein
IBS	irritable bowel syndrome
NHB	non-Hispanic Black
NHW	non-Hispanic White
QOL	quality of life
QST	quantitative sensory testing
RAP	recurrent abdominal pain

Introduction

Functional Abdominal Pain Disorders

Functional abdominal pain disorders (FAPDs) are a subset of functional gastrointestinal disorders (FGIDs) that are characterized by recurrent episodes of abdominal pain that occur over a period of months and cause mild to severe impairment in daily functioning. Aside from recurrent abdominal pain, other FAPD symptoms can include diarrhea, constipation, nausea, bloating, and distention of the abdomen (Korterink et al., 2015b). FAPDs are a subset of functional gastrointestinal disorders (FGIDs). FAPDs are diagnosed using Rome IV criteria (Brusaferro et al., 2018). Four disorders fit into this category: functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, and FAP – not otherwise specified. To meet diagnostic criteria for a FAPD, symptoms must occur weekly for at least three months (Korterink et al., 2015b). FAPDs are common in youth in the United States, with prevalence rates as high as 19% (Chitkara et al., 2005). In up to 90% of FAPD cases, no organic cause can be identified. Thus, symptoms are referred to as "functional" (Spee et al., 2013) to indicate a problem in functioning rather than structure or biochemistry. Although the physiological cause of these various symptoms is largely unknown, the current consensus is that FAPD symptoms are a product of abnormalities in gastrointestinal motility and pain processing (Mayer et al., 2008).

Previous research elucidates a biopsychosocial model of chronic pain in which the combination of ongoing biological, psychological, and social stressors impacts the

severity and chronicity of a child's pain experience (Riddell et al., 2013). Although this model is accepted as a standard conceptualization of pediatric pain, very little research has examined the impact of biopsychosocial sources of stress on the neurobiological correlates of pediatric FAPD. The current study will begin to address this gap by examining associations between biopsychosocial sources of stress and experimental pain responses in youth with FAPD.

Of importance, the current literature suggests a robust association between exposure and responses to stress and gastrointestinal symptoms (Gulewitsch et al., 2017; Nelson & Cunningham, 2020; Rakesh et al., 2005; Thomsen et al., 2002). Thus far, evidence suggests that stress interferes with the parasympathetic and sympathetic pathways implicated in the brain-gut axis and this produces gastrointestinal symptoms, including abdominal pain (Rakesh et al., 2005). However, limited research has examined this phenomenon in pediatric populations.

Ongoing investigation regarding the causes and contributors to FAPD symptomatology is desperately needed. FAPDs are some of the most difficult GI conditions to treat given that typical gut-directed treatments are not always effective. Additionally, identifying an effective combination of pain management strategies can involve several rounds of trial and error (Brusaferro et al., 2018; Drossman, 2008; Grover & Drossman, 2010). Many children endure thorough and costly medical investigations before being diagnosed with an FAPD (Korterink et al., 2015) and families report frustration with the FAPD diagnostic process and lack of effective treatments available (Nieto et al., 2020). Since traditional medical and pharmacological intervention has been largely unsuccessful in treating pediatric FAPD, current research efforts are now focused

on identifying potential psychosocial correlates associated with FAPDs, which may serve as effective treatment targets (Tarsitano et al., 2018; Yacob et al., 2021).

Biological Contributors to Functional Abdominal Pain Disorders

At this time, no universal biological causes of FAPDs in youth have been identified (Korterink et al., 2015a). However, mounting evidence suggests that neurobiological factors such as abnormal brain-gut interaction, abnormal immune activation, and visceral hypersensitivity contribute to symptoms, including pain, in children and adolescents with FAPDs (Korterink et al., 2015a; Simreń et al., 2013).

One body of literature demonstrates visceral hyperalgesia in children with FAPDs and other FGIDs. Visceral hyperalgesia refers to having a lower detection threshold for pain as well as a lower pain tolerance in response to noxious, pain-inducing stimuli (Cervero & Laird, 1999). Specifically, research demonstrates rectal sensitivity in children with FAPDs compared to healthy controls (Faure & Wieckowska, 2007; van Ginkel et al., 2001). One study using gastric and rectal barostat procedures found that children with recurrent abdominal pain (RAP) and IBS demonstrated significant hyperalgesia compared to healthy controls in both areas (di Lorenzo et al., 2001). Additionally, this study found higher rates of anxiety and depression in both FAPD groups which was associated with symptom severity but not visceral hyperalgesia scores (di Lorenzo et al., 2001). The exact physiological mechanisms underlying visceral hyperalgesia in youth with FAPDs are unknown at this time. However, research suggests that visceral hyperalgesia in FAPDs may be a result of hyper sensitization of spinal cord and enteric neurons in addition to the abnormal modulation of pain pathways (Faure & Wieckowska, 2007).

Additionally, abnormal immune activation, resulting from dysregulated gut microbiota, has also been suggested as a biological contributor to pain in FAPDs. The human GI tract is comprised of close to 500 different species of bacteria which make up the gut microbiome (Xu & Gordon, 2001). The GI microbiome is closely linked with one's immune system such that decreased levels of "good bacteria" in the gut can trigger an immune response. Repeated overactivation of one's immune system because of dysregulated gut microbiota can lead to downstream consequences including obesity, infection, and diarrhea (Ju et al., 2008; Maruvada et al., 2017; Sekirov & Finlay, 2009; Turnbaugh et al., 2006).

Furthermore, some research suggests that gut microbiomes are affected by more than biology alone. Research using animal models suggests that exposure to physical and psychological stress early in life is associated with disrupted gut microbiota (Galley et al., 2014). Additionally, current research suggests an association between abnormalities in gut microbiota and pain responses. The current understanding in the literature is that disrupted gut microbiota initiates an overactivated immune response which produces a cascading effect and activates nociceptive pathways. This can disrupt one's pain modulation in the central nervous system (Simreń et al., 2013). However, more research is needed to confirm this current hypothesis and determine whether these associations generalize to pediatric pain populations.

Some research suggests that abnormalities in gastrointestinal motility may partially explain why children with FAPDs experience pain. Studies using noninvasive ultrasonography have demonstrated impaired antral motility and delayed gastric emptying in children with IBS, functional dyspepsia, RAP, and FAP (Devanarayana et

al., 2012; Devanarayana et al., 2013a; Devanarayana et al., 2013b). Similar to research on the gut microbiome and FAPDs, studies using animal and human models show that exposure to stress is associated with significantly delayed gastric emptying rates (Devanarayana et al., 2013a; Jiang & Travagli, 2020; Ochi et al., 2008). In particular, one study found that children with IBS that have been exposed to stressful events early in life exhibit significantly delayed gastric emptying compared to those without stress exposure (Devanarayana et al., 2013a). In FAPDs, and functional dyspepsia specifically, delayed gastric emptying is associated with increased symptom severity, including increased abdominal pain (Devanarayana et al., 2012; Devanarayana et al., 2013b).

Further, exposure to repeated or chronic stress over time can have other significant physiological consequences known as allostatic load (Calcaterra et al., 2019; Guidi et al., 2021; Nelson et al., 2021). Some more advanced calculations of allostatic load can include additional neurobiological markers such as cortisol, dehydroepiandrosterone (DHEA), and norepinephrine and pro-inflammatory cytokines including interleukin-6 (IL-6) and C-reactive protein (CRP) (Calcaterra et al., 2019; Duong et al., 2017; Guidi et al., 2021). Specifically, exposure to stress during important development stages in childhood and adolescence can have lasting negative impacts on physical health outcomes including higher risk for cardiovascular disease, diabetes, musculoskeletal disorders, and mood disorders (Guidi et al., 2021).

The adult pain literature demonstrates a replicable association between allostatic load and pain severity (Sibille et al., 2017; Slade et al., 2012). However, less is understood about the associations between allostatic load and pain outcomes in pediatric populations. One study found that children with chronic health conditions exhibit higher

allostatic load compared to healthy counterparts (Ersig et al., 2021). Another study in this area found that children with chronic pain have elevated allostatic load compared to healthy peers (Nelson et al., 2021). However, little to no research is available examining the relationships between allostatic load and GI-related pain. Therefore, the current study will aim to address this gap in the literature.

Furthermore, previous research shows significant disparities in allostatic load between Non-Hispanic White (NHW) vs. Non-Hispanic Black (NHB) adults (Chyu & Upchurch, 2011; Duru et al., 2012; Tomfohr et al., 2016). This disparity remains even when accounting for individual factors such as SES and health behaviors (Duru et al., 2012). Moreover, some research suggests that the disparity in allostatic load between NHW and NHB individuals may be partially explained by differences in sleep quality because of higher rates of experienced anger due to discriminatory experiences endured by NHB persons (Tomfohr et al., 2016). Research demonstrates that NHB youth living in impoverished neighborhoods experience significant increases in allostatic load over time which can be detrimental to their health (Brody et al., 2014). Although emerging research suggests an association between neighborhood SES and experimental pain outcomes in youth with FAP (Morris et al., 2022), no research has examined the relationship between allostatic load and pain in diverse youth with FAPDs. Examining this relationship could further our understanding of the biological contributors to FAPD symptoms and potentially provide evidence for biomarkers of FAPD pathology in youth.

Psychosocial Contributors to Functional Abdominal Pain Disorders in Youth

An established body of literature suggests a clear connection between psychological functioning and pain severity and functional disability in youth with

chronic pain (Kashikar-Zuck et al., 2016; Lewandowski Holley et al., 2013). More recent research in pediatric FAPD demonstrates psychological and social factors as correlates of symptom severity and functioning. For example, research suggests that psychosocial factors such as low socioeconomic status, living in a single parent household, early exposure to psychological stress as well as internalizing problems like anxiety and depression may contribute to FAP in youth (Chitkara et al., 2005; Korterink et al., 2015a)

Research demonstrates a strong association between anxiety and chronic pain in youth (Campo et al., 2004; Mahrer et al., 2012). One study examining a clinical sample of children with recurrent abdominal pain (RAP) found that 79% of participants met diagnostic criteria for an anxiety disorder and that anxiety symptoms preceded RAP symptoms in most children (Campo et al., 2004). The exact cause(s) of this association between abdominal pain and anxiety in children remains unknown. Current theories suggest a potential diathesis model in which anxiety and chronic abdominal pain share certain features or are products of the same pathophysiological process (Campo et al., 2004). However, further investigation is needed to answer this question. Another theory suggests that the association between anxiety and functional abdominal pain in children may be explained by a temperamental sensitivity to stimuli perceived as threatening. In this theory, abdominal pain is understood as a somatic manifestation of a larger neurobiological process (Campo et al., 2004).

Current findings in the adult literature suggest a bidirectional relationship between anxiety and pain such that the onset of pain precludes symptoms of anxiety which may, in turn, disrupt pain pathways leading to further pain catastrophizing and anxiety (Beesdo et al., 2009). Some research suggests that anxiety sensitivity may explain the relationship

between anxiety and pain in chronic pain populations. Martin and colleagues (2007) studied a sample of children with chronic pain and found that anxiety sensitivity predicted a child's fear of pain which, in turn, was associated with pain-related disability (Martin et al., 2007). Additional studies involving pediatric chronic pain populations have demonstrated an association between anxiety sensitivity and other functional outcomes including psychological well-being and social functioning (Tsao et al., 2007)

Additionally, research in children with RAP suggests an association between depressive symptoms and abdominal pain. Specifically, one study found that 43% of sampled children with RAP met diagnostic criteria for a depressive disorder (Campo et al., 2004). Similarly, the cause(s) underlying the association between depressive symptoms and abdominal pain is not well understood. Research in both children and adults with FAPD suggests that this correlation may be explained by differences in pain reporting and perceived pain efficacy as opposed to differences in pain sensitivity or pain experience (Anderson et al., 2008; Dorn et al., 2007). Additionally, one study with children with chronic abdominal pain found an association between non-GI symptom rates and clinically significant depressive symptoms, suggesting that the relationship between abdominal pain and depressive symptoms may be psychosomatic (Little et al., 2007). Additional studies support this notion and provide evidence that the connection between depressive symptoms and abdominal pain may be explained by the mediating roles of pain catastrophizing and/or somatization (Hollier et al., 2019).

Additionally, research suggests that adverse childhood experiences (ACEs) may be implicated in the pathophysiology of FAPD. ACEs include experiences of abuse, neglect, and exposure to domestic violence, substance abuse, mental illness, or separation

from parents due to divorce, death, or incarceration (Felitti et al., 1998). Some research suggests that there exists a higher prevalence of ACEs in children and adolescents with chronic pain complaints compared to healthy counterparts (Groenewald et al., 2020; Nelson et al., 2017; Stensland et al., 2013). Early FAPD research suggests that adults with FAPDs are more likely to have experienced abuse as a child or adult; including more severe events like sexual assault and life-threatening physical abuse, compared to healthy counterparts or adults with organic gastrointestinal conditions (Drossman et al., 1990; Talley et al., 1994). Furthermore, research shows that the effect of ACEs on FAPD symptoms is stronger in females compared to males (Drossman et al., 1990). The current adult literature continues to support a significant association between early adverse life events and the development of IBS in adulthood (Bradford et al., 2012). However, additional research is needed to understand how ACEs may contribute to neurobiological differences in pain processing that may account for functional abdominal pain symptoms during and after childhood.

The cause(s) of the association between ACEs and FAPD symptoms in humans is not well understood. However, animal models provide some guidance regarding the potential neurobiological underpinnings of this disease process. Studies with rat models show that perinatal stressors (e.g., maternal separation) are associated with the development of several symptoms that mimic those associated with FAPDs, including visceral hypersensitivity, increased defecation, mucosal dysfunction in the intestines, increased hypothalamic-pituitary-adrenal axis responses, and anxious behavior (Coutinho et al., 2002; Gareau et al., 2006, 2007; Ladd et al., 1996). One study examined the relationship between childhood adversity and experimental pain sensitivity and found that

healthy individuals with higher childhood adversity also had increased temporal summation of second pain sensitization and slower decay of subsequent aftersensations. These findings suggested that childhood adversity may contribute to increased central sensitization which, in turn, may contribute to greater pain intensity and hypersensitivity (You & Meagher, 2016). Other human subjects research in pediatric chronic pain suggests that the association between ACEs and chronic pain may be explained by a heightened vulnerability to anxiety and mood disorders (Sachs-Ericsson et al., 2017). Overall, more research is needed to better understand the relationships between ACEs and pain experience in youth.

A substantial body of research has demonstrated several social determinants of pediatric pain, including pediatric abdominal pain. Research suggests that there is an association between family living situation and FAPD such that children living in single parent households tend to be at risk for recurrent abdominal pain symptoms (Bode et al., 2003; Korterink et al., 2015a). Furthermore, differences in family functioning have been associated with a range of pediatric chronic health conditions, including pediatric chronic pain. Specifically, research demonstrates that increased attention from parents and reinforcement of the "sick role" may perpetuate higher symptom reporting in children with chronic pain (Feldman et al., 2010; Peterson & Palermo, 2004; Walker et al., 2006). One study found that good family functioning (e.g., effective communication, social and emotional support, etc) was protective against pediatric abdominal pain incidence (Feldman et al., 2010). However, more research is needed to better understand how social factors, such as family functioning, impact the development of neurobiological pain processes in youth with FAPDs. Specifically, research using quantitative sensory testing

and longitudinal models may help us better understand the degree to which social sources of stress may impact pain processing (i.e., central sensitization) and contribute to greater pain chronicity and severity in this population.

Furthermore, research suggests that peer relationships are significantly affected by chronic pain. Although most of this research has been conducted with adults, emerging research suggests that children and adolescents with chronic pain report deficient peer relationships (Forgeron et al., 2010; Kashikar-Zuck et al., 2007). Research suggests that peer relationships can serve as both a protective factor and source of stress for children living with chronic pain (Carter et al., 2002; Forgeron et al., 2013). In particular, adolescents with chronic pain describe feeling "different" from their friends due to their chronic pain, leading to social isolation (Forgeron et al., 2013). Some research suggests that children with chronic pain may try to disguise their pain (e.g., avoid facial expressions and other pain behaviors) to better fit in among their peers (Carter et al., 2002). While extant literature documents the relationship between social functioning, including peer relationships and subjective pain experience, very little is understood about how social functioning may be related to pain processing, including pain sensitivity and facilitation (Morris et al., 2016, 2022).

Although previous research suggests that females are disproportionately affected by FAPDs, research does not suggest differences in prevalence rates between White and Black youth with FAPDs (Lewis et al., 2016). Research does suggest that racial minority groups are chronically exposed to social and economic disadvantage, which is associated with disparities in physical health outcomes (Bauman et al., 2006; Williams, 2018). Considering well demonstrated race-based differences in clinical and experimental pain

outcomes in other populations, it is important to examine this in a diverse pediatric sample with FAPD (Morris et al., 2015a, 2015b; Rahavard et al., 2017). Furthermore, this could partially explain potential racial disparities in clinical pain severity among youth with FAPDs, but more investigation is needed.

Consequences of Functional Abdominal Pain Disorders in Youth

Chronic FAP is associated with several negative psychosocial consequences in youth. Children with FAP, on average, have reduced health-related quality of life (hrQOL) compared to their healthy counterparts (Varni et al., 2015). In particular, children with FAPDs and other FGIDs experience decreased social functioning compared to children diagnosed with an organic gastrointestinal disorder (Varni et al., 2015). This reduced hrQOL is associated with higher rates of school absence for youth with FAPDs, increased work absence for their caregivers, and higher rates of healthcare utilization; particularly frequent pediatrician visits, emergency department visits for pain intervention, and prescriptions for analgesic and other pharmacological interventions (Hoekman et al., 2015; van Tilburg & Murphy, 2015; Varni et al., 2015).

Some research has demonstrated that youth with FGIDs have reduced quality of life (QOL) compared to youth diagnosed with organic gastrointestinal disorders (Varni et al., 2015; Youssef et al., 2006). Van Tilburg & Murphy (2014) refer to this as the "quality of life paradox." While one would expect QOL to be closely tied with symptom severity, research suggests that pediatric FGID patients often have less severe symptoms but poorer QOL compared to pediatric patients with organic gastrointestinal disorders. More research is needed to best understand why children with functional disorders have a lower QOL compared to children with organic disorders. However, some theorize that

this discrepancy exists because children with organic disorders feel they have greater control over treating their symptoms compared to children with functional disorders. Organic disorders are often associated with a defined treatment plan aimed at targeting the specific cause(s) of the child's symptoms. Children with functional disorders and their families often feel helpless due to difficulties identifying the cause of the child's symptoms and determining a clear treatment plan (van Tilburg & Murphy, 2015).

Pediatric FAPDs do not just affect the child but also their close family members and social systems. Compared to mothers of healthy children, mothers of children living with FAPDs are more likely to experience anxiety, depressive, and somatic disorders (Campo et al., 2007). Additionally, mothers of youth with FAPDs were more likely to have irritable bowel syndrome, chronic migraine, and other somatoform disorders compared to mothers of healthy children. These findings suggest that a heightened vulnerability to anxiety, depressive, and somatoform disorder symptoms may represent a mechanism for FAPD onset and maintenance in certain youth (Campo et al., 2007). Furthermore, it is possible that the negative physical and mental health consequences experienced by mothers of children with FAPDs represent biproducts of the difficulties of caring for a child with these conditions. More longitudinal and biological-focused research is needed to understand the direct impact of raising a child with FAPD on caregiver wellbeing.

Finally, many children with chronic pain conditions and their families face stigma due to the lack of medical explanation for the child's pain symptoms and related impairments (Wakefield et al., 2018, 2022). As a result of this stigma, many youth with chronic pain try to conceal their pain symptoms to avoid negative social consequences

(Wakefield et al., 2021). Little research has examined stigma and stigma concealment in youth with FAPDs. However, one study compared levels of enacted stigma using clinical vignettes of patients with irritable bowel disease, IBS, and adult-onset asthma. They found that individuals with IBS, an FAPD, experienced significantly higher rates of enacted stigma compared to individuals with inflammatory bowel disease or adult-onset asthma, disorders with known medical etiology (Taft et al., 2017). Furthermore, another study demonstrated that about 25% of adolescents with FAPDs report experiencing felt stigma and stigma concealment and that rates of both were higher in adolescents with IBS compared to individuals with other types of FAPD (Laird et al., 2020). Some research suggests that chronic concealment can contribute to negative physical and psychological health outcomes (Laird et al., 2020; Quinn et al., 2017). However, more research is needed to understand the impacts of felt stigma and stigma concealment on youth with FAPDs.

Quantitative Sensory Testing

Quantitative sensory testing (QST) represents a series of noninvasive sensory perception tasks that involve either mechanical, thermal, or other stimuli (Li et al., 2023). QST allows scientists to gather information about the possible neurobiological correlates of pain in various clinical pain populations. One commonly utilized mechanical task measures temporal summation of mechanical pain. In this task, the participant receives repeated noxious stimuli from a weighted pin prick stimulator which induces pain facilitation or “wind up” (Overstreet et al., 2021; Staud et al., 2001). Temporal summation of mechanical pain can provide evidence of individual and group-based differences in pain facilitatory processes and suggest potential underlying neurobiological

mechanisms for further study. Temporal summation of mechanical pain has been used to measure pain facilitation in various pediatric pain populations including chronic musculoskeletal pain (Li et al., 2023), sickle cell disease (Bakshi et al., 2017), fibromyalgia, joint pain, and headache (Ci et al., 2012). However, thus far, temporal summation of mechanical pain has not been studied in youth with FAP.

Another QST task that is often used in pediatric populations is the cold pressor task. In this task, the participant places their hand in cold water for as they can tolerate and provides a pain rating for the highest pain they felt during the task (von Baeyer et al., 2005). Compared to temporal summation of mechanical pain, the cold pressor task involves a longer duration of pain, allowing C fibers to carry the pain signal to the brain (von Baeyer et al., 2005). Similar to temporal summation of mechanical pain, cold pressor task has been used as a QST method in several pain populations including adolecents with chronic musculoskeletal pain (Tham et al., 2016) and adults with both chronic musculoskeletal and soft-tissue (i.e., visceral) pain (Paccione et al., 2022). Research using a similar QST method, conditioned pain modulation, demonstrated significant impairments in pain modulation abilities in youth with FAPD (Morris et al., 2016). However, no research has used cold pressor task as a QST method for measuring experimental pain tolerance in youth with FAPD.

Although QST has been widely used in adult pain populations, there is significantly less research using QST to characterize pediatric pain experiences (Tham et al., 2016). This represents a gap both in the larger chronic pain literature and our understanding of the neurobiological underpinnings of pediatric FAPD. Some research provides preliminary evidence of psychosocial predictors of abnormal pain processing in

youth with various chronic pain conditions. Bakshi & colleagues (2017) found that anxiety, depressive symptoms, somatization, and pain catastrophizing were associated with increased experimental pain sensitivity in youth with sickle cell disease (Bakshi et al., 2017). Several studies have demonstrated differences in pain tolerance and sensitivity on the basis of race (Ahn et al., 2017). A meta-analysis by Kim & colleagues (2017) demonstrated higher pain sensitivity in minority populations (i.e., Asians, African Americans, and Hispanics) compared to non-Hispanic Whites (Kim et al., 2017). One study found that social support reduced pain severity ratings and distress during a cold pressor task (Roberts et al., 2015). Another study demonstrated that higher rates of childhood adversity, measured as ACEs, predicted greater pain sensitization and decreased decay (i.e., decrease in C fiber activation) during a temporal summation task (You & Meagher, 2016). Taken together, these findings suggest that the effects of psychosocial variables on pain processing, especially central sensitization (i.e., long-term increase in nociception), may reflect an underlying mechanism for various chronic pain disorders. However, more research using QST methods in pediatric FAPD is needed to better understand the biopsychosocial mechanisms that may account for this population's chronic and otherwise unexplainable pain.

Innovation

The present study adds to the current literature on pediatric FAPD by using more objective pain outcomes, including experimental pain sensitivity. Few studies have applied quantitative sensory testing methods to the pediatric FAPD population (Morris et al., 2015a, 2015b). The application of these methods to this population may allow for better understanding of the pain-related mechanisms underlying FAPD symptoms. The current

study will aim to lay a foundation for this work by examining the potential biopsychosocial sources of stress that are related to experimental pain sensitivity in children with FAPDs.

Since the majority of previous FAPD research has involved predominantly NHW samples (Ford et al., 2014), the current study aimed to add to the literature by examining correlates of pain-related outcomes in a racially diverse sample of youth with FAPD. Our current understanding of how FAPD may vary across groups is limited. This study aimed to examine the biopsychosocial stressors (See **Figure 1**) associated with pain in diverse youth with FAPD. Results from the current study may bring awareness to targets for intervention that could refine current treatments for diverse youth with FAPD.

Aims & Hypotheses

Aim 1

Examine the association between allostatic load risk and experimental pain sensitivity (i.e., temporal summation of mechanical pain and cold pain intensity) in youth with FAPDs.

Hypothesis 1. Lower levels of allostatic load risk will be associated with decreased pain sensitivity.

Aim 2

Examine the association between social sources of stress and experimental pain sensitivity in youth with FAPDs.

Hypothesis 2. Higher scores on the peer relationships measure, increased overall social functioning, and increased family relationship scores will be associated with decreased experimental pain sensitivity.

Aim 3

Examine the association between psychological sources of stress and experimental pain sensitivity in youth with FAPDs.

Hypothesis 3. Lower depressive symptoms, anxiety, ACEs, and psychological stress will be associated with decreased experimental pain sensitivity.

Aim 4 (Exploratory Aim)

Examine race-related differences between experimental pain sensitivity, clinical pain severity, and hrQOL in youth with FAPDs.

Hypothesis 4. Non-Hispanic Black youth with FAPDs will exhibit higher rates of clinical pain severity and experimental pain sensitivity and lower rates of hrQOL compared to non-Hispanic white youth.

Methods

Participants

Participants included children aged 8-18 years with a FAPD and at least one caregiver. All children were screened for a FAPD diagnosis using the official Rome IV criteria for functional abdominal pain disorders (Brusaferro et al., 2018). Inclusion criteria included (1) child is ≥ 8 and ≤ 18 years old at the time of assessment, (2) meets Rome IV criteria for at least one FAPD, (3) child and caregiver can read, write, and speak English, and (4) consenting caregiver is the child's legal guardian. Exclusion criteria are (1) diminished cognitive function determined to increase the risk of study participation, (2) current or suspected pregnancy for the child, (3) blood pressure in the hypertensive range, (4) past or present cardiovascular disease, (5) serious psychiatric disorder requiring hospitalization within the past 12 months or characterized by active suicidal ideation. Participants were recruited through the Pediatric Gastroenterology Clinic in the Children's of Alabama Hospital.

Procedures

UAB pediatric gastroenterology providers (i.e., medical doctors and nurse practitioners) identified children with a history of FAP and referred them to the Gastrointestinal Pain Research Clinic which holds appointments every week. See **Figure 2** for a diagram of recruitment procedures. Participants were screened approximately one week prior to their appointment. Eligible patients were scheduled for a 1-hour research visit following their scheduled medical visit and ineligible patients returned to receiving

care from their existing gastroenterology provider. One day prior to their appointment, families received a reminder call, and the child was instructed to fast "between lunchtime until the end of their appointment." Upon arrival at their appointment, participating families were greeted by research staff and triaged by clinic staff. Study staff recorded the child's height (in.), weight (lbs.), and blood pressure (mmHg) measurements taken by medical staff. Study staff evaluated the child's blood pressure using criteria from the National High Blood Pressure Education Program, BP ranges for girls and boys from the National Institutes of Health, and BP ranges for adults from the Centers for Disease Control and Prevention (*High Blood Pressure*, 2022; Riley et al., 2018). If the child or adolescent was determined to have elevated blood pressure for their height and age, the study physician was consulted prior to allowing them to participate in the quantitative sensory testing (QST) and finger prick. Caregivers provided consent for themselves and their children. Children ages 8 to 13 years old provide their assent, while adolescents 14 to 18 years old co-signed the consent form. After finishing the consenting process, children and caregivers each completed a series of digital questionnaires using iPads. Then, children completed QST and blood collection by finger prick. Dyads received a $50 incentive via gift card at the end of their participation in the study.

Measures

Caregivers completed a demographic form with child and caregiver sex, age, race/ethnicity, income, insurance status, education, and other variables related to SES.

Allostatic Load.

Participant allostatic load was calculated using high sensitivity C-reactive protein (hsCRP), blood pressure, and body mass index (BMI) percentile. Each indicator was dichotomized using clinical cut-offs (i.e., 0 = "Below Clinical Threshold," 1 = "At or

Above Clinical Threshold"). Hypertension was coded as 0 = < 95th percentile based on height and weight and 1 = ≥ 95th percentile based on systolic and diastolic blood pressure levels taken and evaluated at triage**.** See **Table 1** for all clinical cut-off information. In accordance with previous research on measuring allostatic load (Wiley et al., 2016) and consultation with an expert on allostatic load measurement in pediatric chronic pain samples, indicators were grouped into two allostatic load risk factors. The cardiometabolic risk factor was calculated by summing the dichotomized variables for BMI percentile and hypertension. The inflammatory risk factor served as the dichomotized variable for hsCRP. A total allostatic load risk factor was calculated by summing the cardiometabolic and inflammatory risk factors, resulting in a range of allostatic load risk scores from 0 = lowest allostatic load risk to 3 = highest allostatic load risk. This method of capturing allostatic load by summing allostatic load risk indicators is in accordance with previous research (Duong et al., 2017; Nelson et al., 2017). Height, weight, and blood pressure were recorded at triage. BMI was computed using the height and weight measurements at triage and up-to-date weight status guidelines from the CDC (*About Child and Teen BMI*, 2021).

Trained study staff used a 2.0 mm x 1.5 mm contact-activated lancet to prick the outer edge of the middle finger of the child's non-dominant hand for blood collection. 1-4 large drops of blood were collected using a dried blood spot card. Dried blood spot cards were stored in a - 80 degrees Celsius freezer and sent to ZRT labs for the hsCRP analysis. CRP is a pentameric protein that is synthesized in the liver. Elevated hsCRP is an indicator of chronic inflammation and disease activity in gastrointestinal disorders (Vermeire et al., 2005)

Psychosocial Functioning.

Overall child psychosocial functioning was captured using a series of validated questionnaires. Children completed the following PROMIS measures: Anxiety SF 8a, Depressive Symptoms SF 8a, Psychological Stress SF 8a, and Peer Relationships SF 8a. Caregivers completed the parent proxy for each of the PROMIS measures. The PROMIS measures are reliable pediatric outcome measures that have been validated in several diverse pediatric populations (Bevans et al., 2018; Reeve et al., 2020).

Additionally, caregivers completed the Pediatric ACEs and Related Life Events Screener (PEARLS). The PEARLS is a 17-item parent-report questionnaire that calculates the number of ACEs a child has experienced in their life thus far. The PEARLS has been used in recent pediatric ACEs-related research (Albarran-slovin et al., 2021). Finally, caregivers completed the PedsQL Family Impact Module, a 36-item parent-report measure that captures the impact that a child's illness has on family functioning across social, emotional, and physical domains. The family functioning subscale was used for the purposes of this study (i.e., Aim 2). The PedsQL Family Impact Module has demonstrated excellent reliability and validity in pediatric samples (Medrano et al., 2013). All questionnaires were administered electronically via iPad using the REDCap data management system, and each aspect of psychosocial functioning was analyzed independently.

Experimental Pain Sensitivity.

Youth participated in two experimental pain sensitivity tests. The first test was a temporal summation of mechanical pain test. This test used a weighted (256 mN) pinprick stimulator at the distal middle phalange of the child's non-dominant hand. The

probe was oriented perpendicularly above the point of contact and lowered gently until the filament retracted fully into the metal cylinder holding. Participants first received a single contact from the stimulator and rated their pain on a scale from 0 to 100, where "0 = no pain and 100 = most intense pain imaginable." Participants viewed a visual analog scale to help them conceptualize the 0 to 100 pain rating. Then, the participants were asked to close their eyes as they received ten contacts from the stimulator at a rate of one contact per second. They were then asked to rate their most intense pain resulting from the 10 contacts on the scale from 0 to 100. The full procedure was performed twice on each participant. Temporal summation effects (i.e., Delta change score) were calculated by subtracting the pain intensity ratings following the first contact from the ratings following the series of 10 contacts.

The second experimental pain sensitivity test measured cold pain tolerance and cold pain intensity. Participants were instructed to place their dominant hand in an immersion circulator basin filled with cold water for as long as they could tolerate. Unbeknownst to participants, the maximum allowable immersion time was 180 seconds. The cold pressor was maintained at 7 degrees Celsius using an ARTIC A25 refrigerated bath with an SC150 immersion circulator. 7 degrees Celsius is a safe temperature for the cold pressor task in children that also avoids ceiling effects (Birnie et al., 2016; von Baeyer et al., 2005). Participants spread their fingers wide and placed their hand in the middle of the basin. The display screen of the circulator was covered so that participants could not see the temperature of the water. Study staff used a stopwatch to record the time in seconds from when the participant submerged their hand in the water to when they took it out. When the participant removed their hand, they were asked to provide a

pain rating on a scale from 0 to 100 representing the greatest intensity of pain experienced during the immersion period. Again, participants viewed the visual analog scale to assist in rating their pain. Participants were told to remove their submerged hand after 180 seconds (and provide a cold pain intensity rating) if they had not already done so.

Clinical Pain Severity.

Clinical pain severity was captured using the PROMIS Pain Intensity 1a measure. Participants were asked to rate their abdominal pain on average over the past 7 days using a Likert-type scale ranging from 0 (no pain) to 10 (worst pain you can think of). The PROMIS pain questionnaires are reliable and valid measures for pediatric chronic pain (Jacobson et al., 2015).

Health-Related Quality of Life.

HrQOL was measured using the PedsQL. The PedsQL is a 23-item questionnaire that assesses a child's hrQOL. Specifically, the PedsQL assesses 4 dimensions of functioning: 1) physical functioning, 2) emotional functioning, 3) social functioning, and 4) school functioning (Varni et al., 2001). Scores were calculated for each domain as well as an overall total score for each participant. The child (8-12 years old) and teen (13-18 years old) versions of this measure were utilized for this study. The PedsQL is a reliable measure that has been validated in several pediatric populations (Varni et al., 2001; 2015)

Analytical Plan

Statistical analyses were conducted using SPSS Version 28.0. Aim 1 was evaluated using 2 hierarchical regressions that examined allostatic load as a predictor of experimental pain sensitivity (i.e., cold pain intensity, temporal summation of mechanical

pain) while controlling for the following covariates: cold pain tolerance and child race. In aim 2, 3 linear regressions examined peer relationships, social functioning, and family impact as predictors of experimental pain sensitivity. These social factors were evaluated separately as they represent separate domains of social functioning and have not yet been explored as predictors of experimental pain sensitivity in this population. In aim 3, 1 multiple regression examine anxiety, depressive symptoms, ACEs, and psychological stress as predictors of experimental pain sensitivity. Finally, the exploratory aim involved 4 analyses of variance that examined racial (NHW vs. NHB) differences in clinical pain severity, experimental pain sensitivity, and hrQOL. Effect sizes were provided for all inferential statistical analyses. Cohen's *d* is interpreted such that 0.2 is a small effect, 0.5 is a medium effect, and 0.8 is a large effect. Cohen's f^2 is interpreted such that 0.02 is a small effect, 0.15 is a medium effect, and 0.35 is a large effect. Finally, guidelines for interpretation of η^2 suggest that 0.01 is a small effect, 0.06 is a medium effect, and 0.14 is a large effect (Cohen, 1988).

A Priori Power Analysis

Due to the exploratory nature of these analyses and the lack of current literature, analytic interpretation of results considered the ability to identify signals, effect sizes, and variability in the data, rather than statistical significance alone. At the time of proposal, an initial a priori power analysis was conducted using G*Power 3.1. Estimated effect size was deduced from the adult pain literature (You & Meagher, 2016). A prior calculation for multiple regression (fixed model, R^2 increase) with alpha = .05, power = .80, and total # of predictors = 4 suggested a sample size of $N = 151$ would be necessary for detecting *statistically significant* effects. However, previous research on pediatric pain outcome

research suggests that a sample size of 100 participants should be sufficient for identifying reliable effect sizes and detecting sufficient variability in the data. This includes previous research conducted on topics of race, hrQOL, anxiety, depression, and other variables as they relate to pain-related outcomes in pediatric gastrointestinal and other painful conditions (Campo et al., 2004; Hoff et al., 2006; Lynch et al., 2018, 2021). A sample of 100 participants was also the most logistically (e.g., recruitment opportunities, timeline, effort) and financially feasible option as well. Therefore, a sample size of 100 youth (50 = NHW, 50 = NHB) was initially proposed to feasibly identify preliminary signals of these associations.

An additional power analysis was conducted during data collection to determine progress toward reaching necessary power. A more realistic and appropriate effect size was deduced from a study examining experimental pain sensitivity in youth with FAPDs (Morris et al., 2016). For Aim 1, a calculation for multiple regression (fixed model, R^2 increase) with Cohen's $f^2 = .12$, alpha = .05, power = .80, number of tested predictors, and total # of predictors = 7 suggested a sample size of $N = 68$. Similarly, a calculation for Aim 2 (i.e., Cohen's $f^2 = .12$, alpha = .05, power = .80, and total # of predictors = 1) yielded a sample size of $N = 68$. For Aim 3, the power analysis calculation (i.e., Cohen's $f^2 = .12$, alpha = .05, power = .80, number of tested predictors = 4, and total # of predictors = 4) yielded a sample size of $N = 105$.

The originally proposed sample size of 100 children was not met due to a slower rate of recruitment than expected. This is partially explained by the effects of the Omicron variant of the COVID-19 pandemic in early 2022, families' unwillingness to allow their children to miss part of a school day for participation in the study due to

missing school because of their abdominal pain, and unwillingness to drive to the hospital for a separate appointment dedicated toward participation in research. The third reason listed was mitigated some by offering a transportation supplementary payment of $20.00 to the incentives of families that indicated that the cost of transportation to the hospital was a barrier to participation.

Institutional Review Board Status

Study recruitment and data collection methods were reviewed and approved by the University of Alabama at Birmingham Institutional Review Board (IRB #: 300002719). This was considered to be a low-risk study for all participants. Participants were appropriately screened for any potential health risks (i.e., pregnancy, hypertension). Participants received a small prize following blood collection. All participating families received a $50.00 incentive at the end of participation. As mentioned previously, families demonstrating need received an additional $20.00 for transportation costs.

Timeline

Study recruitment and data collection occurred from April 2021 to December 2022. Total blood data was assayed and received January 2023. Analysis and manuscript preparation occurred from Spring – Summer 2023.

Results

Data Preparation

Data were entered into the REDCap data management system and exported to SPSS (Version 28.0). Data were assessed for outliers. One outlier data point for the social functioning variable was truncated to + 3 standard deviations. Although 4 cold pain tolerance values were approximately 3 standard deviations away from the mean, these values were not truncated due to being within the variable range and representing important data (i.e., participants whose tolerance reached the maximum time allowed). Missing data were analyzed for all variables. 20 out of 75 participants (26.67%) were missing some data. However, most participants were only missing 1 data point. Cases with and without missing data were compared for statistically significant differences across all study variables. All variables with missing data were determined to be either missing at random (i.e., temporal summation, cold pain intensity, cold pain tolerance) or missing completely at random (i.e., hsCRP, family relationships, clinical pain severity). Hotdeck imputation was used to handle missing data in hsCRP [(17.33% of cases (N = 13)], temporal summation of mechanical pain [(6.66% of cases (N = 5)], cold pain intensity [(6.66% of cases (N = 5)], cold pain tolerance [(6.66% of cases (N = 5)], family relationships [(1.33% of cases (N = 1)], and 7-day abdominal pain severity relationships [(1.33% of cases (N = 1)]. Hotdeck imputation is considered an appropriate method for handling missing data when it is < 20% and missing at random or completely at random (Myers et al., 2011). Hotdeck imputation has been utilized in several other studies

examining experimental and clinical pain responses (Penn et al., 2020; Goodin et al., 2018; Thompson et al., 2019). Normality of dependent variables (after imputation) for Aims 1 -3 was assessed using Shapiro-Wilk test of normality and skewness and kurtosis. The temporal summation variable was not normal according to normality testing (Skewness = 1.334, Kurtosis = 1.104, Shapiro-Wilk $p < .001$). BoxCox transformations were considered for the temporal summation variable; however, transformation did not sufficiently improve normality. Thus, transformation was not used in final analyses as it did not provide statistical improvement of normality and would compromise empirically and clinically meaningful interpretation of results for temporal summation effects in the sample. All data were analyzed in their raw (i.e., non-transformed) form.

Assumption testing revealed that all other assumptions, including linearity, homoscedasticity, independence of errors, and multicollinearity, were met for Aims 1 – 3. Assumption testing for the exploratory aim (Aim 4) revealed that the assumption for multivariate normality was not met. Specifically, the Shapiro-Wilk rest revealed a lack of normality in the hrQOL ($p = .033$), clinical pain severity ($p < .001$), and temporal summation ($p < .001$) variables in the sample restricted to only NHW and NHB participants. Furthermore, the dependent variables were not all correlated with each other as is assumed in MANOVA. Thus, adjustments were made to the analytical plan for Aim 4 and additional analyses were explored.

Preliminary Analyses

Participant Characteristics

Participants (*N*=75) were 80.0% female, 77.3% Caucasian/White, 16.0% Black/African American, and 6.7% Multiracial, and 93.3% Non-Hispanic. Mean age was 13.97 years (range 8 – 18 years old). Regarding functional abdominal pain diagnosis; 46.7% of participants were diagnosed with functional dyspepsia, 34.7% were diagnosed with IBS, 2.7% were diagnosed with abdominal migraine, and 24.0% were diagnosed with functional abdominal pain – not otherwise specified. A paired-samples t-test revealed evidence of significant temporal summation effects across the sample ($t = 7.812$, $p < .001$) such that, on average, participants' pain rating in response to 10 contacts from the pinprick stimulator was higher than their pain rating in response to 1 contact from the pinprick stimulator. This indicates that the intended facilitatory pain effect was achieved by the temporal summation task. See **Table 2** for additional demographic characteristics of child-caregiver dyads. See **Table 3** for descriptive statistics for allostatic load, psychosocial functioning, experimental pain sensitivity, clinical pain severity, and covariates. Finally, see **Table 4** for relationships between biological, social, and psychological sources of stress, experimental and clinical pain responses, and demographic variables.

Biological Sources of Stress in Relation to Experimental Pain Sensitivity (Aim 1)

Proposed covariates were evaluated for statistically significant associations with the experimental pain sensitivity variables, temporal summation of mechanical pain and cold pain intensity (see **Table 5**). One hierarchical regression was used to examine

allostatic load risk in relation to temporal summation of mechanical pain while controlling for child race. A separate hierarchical regression was used to examine allostatic load risk in relation to cold pain intensity (i.e., pain rating from 0 to 100) after controlling for cold pain tolerance (i.e., time in seconds with hand in cold water) and child race.

There was no significant relationship between allostatic load risk and temporal summation of mechanical pain after controlling for child race (B = .408, $t(72) = .128$, $p = .898$, $R^2 = .022$, Cohen's $f^2 = .022$). Similarly, there was no significant relationship between allostatic load risk and cold pain intensity after controlling for cold pain tolerance and child race (β = .126, $t(71) = .354$, $p = .689$, $R^2 = .086$, Cohen's $f^2 = .094$). See **Table 6** for additional information.

Social Sources of Stress in Relation to Experimental Pain Sensitivity (Aim 2)

As a covariate, cold pain tolerance was significantly associated with cold pain intensity such that decreased tolerance was associated with increased pain severity ratings (β = -.310, $t(72) = -2.786$, $p = .007$, $R^2 = .096$, Cohen's $f^2 = .326$) (see **Table 7**). See **Table 8 and 9** for initial correlations among social sources of stress and experimental pain variables.

Social Functioning in Relation to Experimental Pain Sensitivity

There was no significant relationship between social functioning and temporal summation of mechanical pain (β = -.059, $t(73) = -.504$, $p = .616$, $R^2 = .003$, Cohen's $f^2 = .054$) (see **Table 10**). Similarly, social functioning was not significantly related to cold

pain intensity (β = .075, $t(72) = .655$, $p = .514$, $R^2 = .073$, Cohen's $f^2 = .281$) after controlling for cold pain tolerance (see **Table 7**).

Peer Relationships in Relation to Experimental Pain Sensitivity

Peer relationships were not significantly related to temporal summation of mechanical pain (β = -.148, $t(73) = -.1.276$, $p = .206$, $R^2 = .022$, Cohen's $f^2 = .150$). Furthermore, peer relationships were also not significantly related to cold pain intensity after controlling for cold pain tolerance, (β = -.065, $t(72) = -.581$, $p = .563$, $R^2 = .100$, Cohen's $f^2 = .333$).

Family Relationships in Relation to Experimental Pain Sensitivity

Family relationships were not significantly related to temporal summation of mechanical pain (β = .150, $t(73) = 1.285$, $p = .203$, $R^2 = .022$, Cohen's $f^2 = .150$) (see **Table 10**). Additionally, family relationships were not significantly related to cold pain intensity after controlling for cold pain tolerance (β = .051, $t(72) = .445$, $p = .657$, $R^2 = .072$, Cohen's $f^2 = .279$) (see **Table 7**).

Psychological Sources of Stress in Relation to Experimental Pain Sensitivity (Aim 3)

See **Tables 11 and 12** for initial correlations among psychological sources of stress and experimental pain variables.

Anxiety, Depressive Symptoms, Psychological Stress, and ACEs in Relation to Temporal Summation of Mechanical Pain

The total regression model examining anxiety, depressive symptoms, psychological stress, and ACEs in relation to temporal summation of mechanical pain

was not significant (R^2 = .077, F(4, 70) = 1.465, p = .222, Cohen's f^2 = .279). Anxiety (β = .112, t(70) = .595, p = .554), depressive symptoms (β = .364, t(70) = 1.497, p = .139), and ACEs (β = -.066, t(70) = -.567, p = .573) were each not uniquely related to temporal summation of mechanical pain. Psychological stress was the only statistically significant psychological variable in the model (β = -.550, t(70) = -2.345, p = .022). Increased psychological stress levels were associated with decreased temporal summation of mechanical pain. See **Table 13** for additional statistical information.

Anxiety, Depressive Symptoms, Psychological Stress, and ACEs in Relation to Cold Pain Intensity, Controlling for Cold Pain Tolerance.

The total regression model examining anxiety, depressive symptoms, psychological stress, and ACEs in relation to cold pain intensity controlling for cold pain tolerance reached statistical significance (R^2 = .165, F(5, 69) = 2.733, p = .026, Cohen's f^2 = .445). However, none of the psychological variables in this model were uniquely and significantly related to cold pain intensity after controlling for cold pain tolerance. However, correlations among psychological variables demonstrated a significant positive relationship between greater anxiety and greater cold pain tolerance (r (73) = .192, p = .050). See **Table 14**.

Racial Differences in Experimental and Clinical Pain Responses and Health-Related Quality of Life (Exploratory Aim)

See **Table 15** for relationships among the clinical and experimental pain response dependent variables. Four one-way ANOVAs examined differences in experimental (i.e., temporal summation of mechanical pain and cold pain intensity) and clinical (i.e., 7-day

abdominal pain severity) responses and hrQOL between NHW and NHB participants. Analyses revealed no significant differences between NHW and NHB participants on temporal summation (F (1, 64) = .473, p = .494, Cohen's d = .220), cold pain intensity (F (1, 64) = .752, p = .389, Cohen's d = .277), clinical pain severity (F (1, 64) = 1.973, p = .165, Cohen's d = .445), and hrQOL (F (1, 64) = .128, p = .722, Cohen's d = .115). See **Tables 16 and 17** for additional statistical information. A non-parametric comparison of means using the Mann-Whitney two-sample rank-sum test was conducted for the non-normal dependent variables: hrQOL, temporal summation of mechanical pain, and clinical pain severity. Mann-Whitney U tests demonstrated no significant differences in hrQOL (U = 306, p = .765, η^2 = .001) or clinical pain severity (U = 237, p = .143, η^2 = .033) between NHW and NHB participants. However, one analysis did reveal statistically significant differences in temporal summation of mechanical pain between NHW and NHB participants such that NHW participants exhibited greater temporal summation effects compared to NHB participants (U = 191, p = .027, η^2 = .075). See **Table 18** for additional statistical information.

Discussion

The present study examined the relationships among biopsychosocial sources of stress and experimental pain sensitivity in diverse youth with FAPDs. As an exploratory aim, this study also examined racial differences in experimental and clinical pain responses in NHW and NHB youth with FAPDs. Overall, findings suggested that the chosen biopsychosocial sources of stress, including allostatic load risk, peer relationships, social functioning, family relationships, anxiety, depressive symptoms, psychological stress, and ACEs, were not significant predictors of experimental pain sensitivity based on evaluation of temporal summation and cold pain tolerance and intensity. However, one finding suggested that psychological stress may be a significant predictor of decreased temporal summation of mechanical pain. Further, a significant relationship was observed between greater anxiety and greater cold pain tolerance. Overall, racial differences were not observed between NHW and NHB participants aside from one finding suggesting significant differences in temporal summation of mechanical pain. This study was limited by reduced power across several findings which may, in part, explain some of the non-significant findings. Many analyses produced medium and medium to large effect sizes. Thus, this study provides some initial evidence of relationships between biopsychosocial sources of stress and pain in diverse youth with FAPDs that should be evaluated in future studies.

Regarding Aim 1, allostatic load risk did not significantly predict either temporal summation of mechanical pain or cold pain intensity after controlling for cold pain tolerance as hypothesized. However, the analysis between allostatic load and cold pain intensity did produce a small to medium effect size which provides a signal of a potentially meaningful association between these two variables. Although the literature suggests a relationship between allostatic load and pain severity (Sibille et al., 2017; Slade et al., 2012), less is understood about the mechanistic relationship between allostatic load and endogenous pain processing (Wallden & Nijhs, 2019). Research on allostatic load in pediatric pain populations suggests that it is the increased activation of the hypothalamic-pituitary-adrenal axis and increased release of cortisol that may be driving the relationship between allostatic load and pain in children (Nelson et al., 2017). It is proposed that markers of neuroendocrine functioning, and specifically cortisol, leads to greater overall sensitization across body systems, including those that are responsible for regulating pain signals (Kendall-Tackett, 2000). It is possible that there was not a significant relationship between allostatic load risk and experimental pain sensitivity in the current study because our allostatic load risk variable was limited by the data available and did not include these key indicators of chronic hyperarousal. See the limitations section for additional details.

However, allostatic load risk was significantly related to anxiety such that greater anxiety predicted greater allostatic load risk. This finding aligns with literature that suggests consistent relationships between anxiety and other mood disorders and allostatic load (D'Alessio et al., 2020; Guidi et al., 2021). Although the neurobiological mechanisms driving this relationship are not well established, recent literature using

animal models suggests that allostasis may be an adaptive mechanism that buffers against the negative effects of chronic stress and anxiety (Ullmann et al., 2019). This positive association between anxiety and allostatic load risk suggests sufficient construct validity and indicates that the allostatic load risk variable is clinically relevant. Furthermore, since allostatic load is meant to capture the cumulative effects of chronic stress on one's physical body over time (Guidi et al., 2021; Nelson et al., 2021), it might be less likely to observe relationships between allostatic load and pain in a pediatric sample. This is because youth are likely to have only experienced chronic psychological/social stress for a few consecutive years thus far. Finally, it is also possible that there are resilience factors that may buffer youth from the harmful effects of allostatic load which were not accounted for in the present study. For example, research suggests that parent-child bonding and social support may be protective factors against allostatic overload in adults (Juster et al., 2010). Future research should assess the protective roles of these and other variables in pediatric samples.

Regarding Aim 2, none of the social sources of stress (i.e., social functioning, peer relationships, and family relationships) predicted experimental pain sensitivity as hypothesized. However, several analyses revealed medium effect sizes which may suggest that these associations would have been statistically significant with a greater sample size. Although research supports significant associations between family and social functioning on a child's self-reported pain severity and disability (Feldman et al., 2010; Peterson & Palermo, 2004; Walker et al., 2006), there is little research which has examined the contribution of social deficits to endogenous pain processing in pediatric chronic pain populations. Although research suggests that social pain shares the same

neural activation patterns as physical pain (Eisenberger, 2012), this finding applies more to acute experiences of social attachment and rejection and may not translate to markers of long-standing social and family functioning. This research has also only been conducted in adults thus far, and the impacts of social deficits on pain in children is less understood at this time.

It is also possible that these social factors have an impact on one's cognitive appraisal of their pain experience but do not necessarily correlate with psychophysiological differences in experimental pain sensitivity. One study found that negative cognitive appraisal was a significant mediator between social support and social undermining and clinical pain severity in adult women with acute pain (Gaffey et al., 2020). In this study, social undermining was defined as one's perception of experiencing "aggressive or threatening behavior" from another person as a result of one or more stressful interpersonal social interactions and/or relationships (Gaffey et al., 2020). Women who experienced greater social undermining experienced a more negative cognitive appraisal of their pain which was associated with higher self-reported pain severity (Gaffey et al., 2020). Studies of experimental pain sensitivity in the laboratory setting suggest that greater social support is associated with higher pain thresholds (i.e., reduced pain sensitivity) during quantitative sensory tests including the cold pressor task (Roberts et al., 2015). Taken together, these findings suggest that social support, or lack thereof, might be a more salient predictor of either clinical or experimental pain responses compared to global measures of social or family functioning. Of note, the majority of this research has been conducted in adult populations, and thus, more

investigation is needed to determine if these associations translate to children and adolescents with chronic pain.

There were some significant relationships among the social sources of stress and other variables in the present study. Social functioning was negatively associated with anxiety, depressive symptoms, and psychological stress, and positively associated with peer relationships. Thus, in the current sample, it appears that greater social functioning was related to better psychological functioning due to decreased amounts of anxiety, depression, and perceived stress. This finding is well supported in the literature, which largely demonstrates positive associations between social and psychological functioning in children and adolescents (Bell-Dolan et al., 1993; Motoca et al., 2012; Lau, 2002). For this particular sample, these relationships may be, in part, explained by social stigma that is often experienced by children and adolescents living with chronically painful conditions. Literature suggests that youth with chronic pain conditions often spend considerable energy concealing their pain symptoms to avoid negative social experiences (Wakefield et al., 2021). Furthermore, this constant effort to conceal has been associated with greater cognitive burden and related emotional difficulties (Wakefield et al., 2021). Thus, our findings point to the possibility that youth with FAPDs may experience stigma and other social stressors that can have deleterious effects on their emotional wellness.

Regarding Aim 3, anxiety, depressive symptoms, and ACEs did not predict either experimental pain sensitivity variable. For the relationship between these variables and cold pain intensity, it is possible that the variance in cold pain intensity was largely accounted for by cold pain tolerance given the strong relationship between these two variables. However, psychological stress was associated with temporal summation such

that greater psychological stress predicted reduced temporal summation. This finding may be partially explained by stress-induced analgesia. Stress-induced analgesia refers to a phenomenon in which acute stress is associated with reduced pain sensitivity in experimental tests of ascending pain pathways (e.g., wind-up) (Bruehl et al., 2022). Findings on the role of stress-induced analgesia in reducing temporal summation are mixed; some studies suggest that greater acute stress leads to reduced summation, suggesting less excitatory pain (Coppieters et al., 2016) while other studies demonstrate the opposite effect (Mertens et al., 2020). Nevertheless, it is possible that the participants in the present study could have experienced stress-induced analgesia resulting from the mild but acutely stressful experience of undergoing painful quantitative sensory testing procedures at a young age. This study would be improved by measuring momentary stress levels in participants prior to administering the pain testing protocol so that this could be factored into the analytical model.

Although most psychosocial sources of stress were not significantly related to experimental pain variables, findings demonstrated positive associations between clinical pain severity and anxiety, depressive symptoms, and psychological stress. This finding is supported by the literature demonstrating robust associations between pain and mental health outcomes (Campo et al., 2004; Mahrer et al., 2012). These results suggest that psychological symptoms may be a more salient driver of the pain experiences of children living with FAPDs compared to the social or biological predictors utilized in the present study. Literature suggests that the effect of emotional functioning on pain is unique to the individual but that the general tendency is for negative affect to precede pain symptoms (Frumkin & Rodebaugh, 2021). It is possible that the differential findings between the

biological and psychological stressors are due to a greater amount of time required for biological mechanisms to affect physiological pain processes (e.g., central sensitization) that can be detected by quantitative sensory testing (Guidi et al., 2021; Nelson et al., 2021).

Overall, exploratory analyses did not reveal significant differences between NHW and NHB participants on clinical and experimental pain responses as was hypothesized. Although one analysis revealed significantly greater temporal summation of mechanical pain in NHW participants compared to NHB participants, this finding should be interpreted with caution given that it was not replicated across other analyses. Although research suggests race-based differences across clinical and experimental pain responses in adult populations (Ahn et al., 2017; Vaughn et al., 2019), less is known about the role of race in subjective and objective experiences of pain in youth. It is possible that racial differences in pain do not manifest until adulthood, but more research is needed. In an examination of temporal summation of heat pain in healthy youth, Morris and colleagues (2015a) found that NHW participants exhibited temporal summation effects, but African American participants did not. The same study also study found higher evoked pain responses in African American participants compared to NHW which potentially suggests higher initial pain sensitivity but no significant race-based differences in excitatory pain processes (Morris et al., 2015a). Taken together, the findings from this study and the present study suggest that race-based differences in experimental pain sensitivity may not be consistent in pediatric populations and that more research, particularly using longitudinal designs, is needed to answer this question. Additionally, it is also possible that racial differences in pediatric pain populations may be less dependent

on differences in skin color and racial identity but are rather influenced by social determinants of health such as socioeconomic status and discrimination. Similar to allostatic load, research suggests these social stressors have a cumulative effect on health over the lifetime (Braveman et al., 2011). Thus, race-based differences in pain may not manifest until later adolescence or adulthood due to a greater accumulative effect of stress on physical health over time.

Almost all analyses examining race-based differences in this sample were limited by power. A few analyses examining racial differences in clinical pain severity and temporal summation produced small to medium effect sizes, suggesting that, with a larger sample size, race-based differences across these variables might reach statistical significance. Along with issues related to power, the exploratory analyses for the present study were likely affected by unequal sample sizes across the two racial groups (NHW = 54, NHB = 12). These analyses would be more robust if the NHW and NHB sample sizes were more equal, and this should be prioritized in future replications of the present study.

Limitations

The following limitations should be considered for the present study. Several analyses suffered from a lack of statistical power due to reduced sample size. However, a few analyses still demonstrated medium effect sizes and, as such, provide signals for potentially meaningful findings. Nevertheless, findings should be interpreted with caution as replication with a larger sample size is needed. Furthermore, our measure of allostatic load was limited by the biomarker data available for use. Thus, our allostatic load measure was one of allostatic load “risk,” combining measures of cardiometabolic risk and inflammatory risk. Although this is in accordance with research guidelines on

allostatic load measurement (Wiley et al., 2016), the present study would benefit from a more robust measure of allostatic load involving the following variables; hypothalamic-pituitary-adrenal axis activation, cortisol, waist-to-hip ratio, and lipid and glucose levels. The more limited measurement of allostatic load may not be as salient for physiological mechanisms implicated in pain, which may partially explain our lack of significant findings related to this variable. Finally, the present study failed to account for a few important variables that may help explain some important associations. As discussed previously, this study did not capture some of the known pain-related protective factors that may buffer youth with FAPDs from the harmful effects of biopsychosocial sources of stress on pain sensitivity. This study would be improved by measuring such factors as cognitive appraisal of pain, social support, pain catastrophizing, and pain coping. Regarding the exploratory examination of race-based differences in pain, the present study would be improved by assessing social determinants of health associated with racial health disparities such as socioeconomic status and discrimination.

Implications and Future Directions

The present study contributes to the literature by examining comprehensive biopsychosocial sources of stress in youth with FAPDs. Little attention has been given to the neurobiological underpinnings of pain in pediatric FAPDs. This study addressed this gap in the literature by using a protocolized quantitative sensory testing battery to assess ascending pain processing in this population. The findings from this study suggest that many of these biopsychosocial sources of stress may not have the same direct impact on pain processing in children as is evidenced in the adult pain literature. However, findings from this study suggest that psychological stress and anxiety, in particular, may be related

to physiological differences in youth with FAPDs (i.e., pain processing, allostatic load) that may contribute to their pain experience. Additionally, the significant relationships between psychological functioning variables and clinical pain severity suggest that providers should regularly screen pediatric FAPD patients for comorbid psychological symptoms such as anxiety and depression. Detection of such symptoms in the clinical setting may present greater opportunities to provide diagnostic education and referral to psychological treatment, which in turn could improve the child's clinical course and reduce pain severity over time.

More research in this population is needed to better understand how various types of stress may impact clinical and experimental responses in youth with FAPDs. In particular, there is a need for research using longitudinal designs to understand the developmental timeline of the relationships between chronic stress and pain that is represented in the adult pain literature. There is still a great need for research in racially minoritized youth with FAPDs. Thus, longitudinal models using racially diverse samples would help to specifically understand the developmental trajectory of racial differences in self-reported and quantitative measures of pain which are observed in the adult pain literature.

Conclusions

To our knowledge, this was the first study to examine the relationships between biopsychosocial sources of stress and experimental pain sensitivity in youth with FAPDs. The results of this study largely did not support overall hypotheses suggesting that greater evidence of stress across these areas would be associated with greater pain sensitivity. However, the lack of statistically significant findings may be due, in part, to study

limitations. This study provides a foundation for additional research that will elucidate the factors that contribute most to pain in youth with FAPDs. Research that builds upon the current study could help better understand the mechanisms underlying pain sensitivity in youth with FAPDs. Furthermore, these findings could prompt research examining important targets for clinical interventions aimed at reducing pain severity and improving health-related quality of life in this population.

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Tables

Table 1

Clinical Cut-Off Scores for Allostatic Load Risk Variables

Variable	Below Clinical Threshold	At or Above Clinical Threshold
Allostatic Load		
BMI Percentile	< 85th percentile	≥ 85th percentile
Hypertension	< 95th percentile	≥ 95th percentile
hsCRP (mg/L)	< 1 mg/L	≥ 1 mg/L

Table 2

Demographic Characteristics of Participant Dyads

Characteristics	*N*	% or Mean ± SD
Child		
Age (years)	75	13.97 ± 2.80
Sex		
Female	60	80.0%
Male	15	20.0%
Race		
White/Caucasian	58	77.3%
Black/African American	12	16.0%
Multiracial	5	6.7%
Ethnicity		
Hispanic	4	5.3%
Non-Hispanic	71	94.7%
FAPD Diagnosis		
Functional Dyspepsia	35	46.7%
Irritable Bowel Syndrome	26	34.7%
Abdominal Migraine	2	2.7%
FAPD - NOS	18	24.0%
Caregiver		
Age (years)	75	43.86 ± 8.10
Sex		
Female	69	92%
Male	6	8%
Race		
White/Caucasian	64	85.3%
Black/African American	9	12.0%
Multiracial	2	2.7%
Ethnicity		
Hispanic	3	4.0%
Non-Hispanic	72	96.0%
Annual Family Income		
$0 – 19,999	7	9.9%
$20,000 – 39,999	21	25.3%
$40,000 – 74,999	20	28.1%
$75,000 – 99,999	6	8.5%
$100,000 or greater	20	26.7%
Caregiver-Child Relationship		
Mother	67	89.3%
Father	3	4.0%
Grandmother	3	4.0%
Other	2	2.7%

Note. FAPD – NOS = Functional Abdominal Pain - Not Otherwise Specified

Table 3

Descriptive Statistics of Allostatic Load, Psychosocial Functioning, Experimental Pain Sensitivity, Clinical Pain Severity, and Covariates

Variable	*N*	Mean (SD)
Allostatic Load Risk		
Cardiometabolic Risk Factor	75	0.60 (0.62)
Body Mass Index Percentile	75	69.39 (31.23)
Systolic Blood Pressure (mm/HG)	75	118.99 (9.17)
Diastolic Blood Pressure (mm/Hg)	75	67.49 (9.48)
Hypertension, n (% hypertensive)	75	8 (10.70)
Inflammatory Risk Factor	75	0.44 (0.50)
hsCRP (mg/L)	75	2.35 (3.29)
Allostatic Load Risk Factor	75	1.04 (0.95)
Psychosocial Functioning		
Anxiety Symptoms (T score) [c]	75	54.95 (11.94)
Depressive Symptoms (T score) [c]	75	54.26 (12.87)
Psychological Stress (T score) [c]	75	58.77 (12.20)
Adverse Childhood Experiences	75	3.79 (3.21)
Social Functioning	75	75.43 (23.09)
Peer Relationships (T score) [c]	75	44.30 (10.86)
Family Relationships	75	48.46 (34.82)
Health-Related Quality of Life (raw)	75	62.45 (16.23)
Experimental Pain Sensitivity		
Temporal Summation of Mechanical Pain	75	24.67 (25.65)
Cold Pain Tolerance Pain Intensity[a]	75	52.47 (27.25)
Cold Pain Tolerance Time (in seconds)	75	40.44 (41.10)
Clinical Pain Severity		
7-day Abdominal Pain Severity[b]	75	5.00 (2.56)
Additional Covariates		
Analgesic Medication Use, n (% use)	75	54 (72%)

Note. Data are presented post-imputation using the Hot Deck Imputation method for hsCRP, temporal summation of mechanical pain, cold pain tolerance, cold pain intensity, family relationships, and 7-day pain severity.

[a] Measured as 0 – 100 with 0 representing "no pain" and 100 representing the "most pain imaginable."

[b] Measured as 0 – 10 with 0 representing "no pain" and 10 representing the "most pain imaginable."

[c] T scores based on U.S. population norms

Table 4

Correlations Amongst Key Variables of Interest

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. AL Risk														
2. Anxiety Sx	.267*													
3. Dep. Sx	.140	.773**												
4. Psych Stress	.013	.756**	.860**											
5. ACEs	.040	.110	.156	.124										
6. Social Fx	-.054	-.258*	-.330**	-.254*	-.227									
7. Peer Rel.	-.060	-.381**	-.386**	-.282*	-.218	.431**								
8. Family Rel.	-.076	.090	.175	.226	.116	-.234*	-.114							
9. TSMP	.025	-.029	-.032	-.160	-.065	-.059	-.219	.148						
10. CP Intensity	.049	-.050	-.147	-.208	-.026	.056	-.166	-.007	.459**					
11. CPT	-.002	.192*	.150	.164	-.008	.069	.018	.067	-.130	-.261*				
12. Pain Severity	.164	.437**	.366**	.423**	.192	-.178	-.137	.223	.006	.087	.077			
13. Child Age	-.162	-.018	.146	.143	.043	.031	-.007	.064	.047	-.078	-.070	.072		
14. Child Sex	.169	.340**	.406**	.360**	.047	-.135	-.097	.050	-.028	-.088	-.007	-.042	-.042	

Note. Spearman's correlations conducted for correlations involving variable 14. All other correlations conducted using Pearson product-moment correlation test.
$N = 75$ for all analyses
$^{*} = p < .05$, $^{**} = p < .01$
Abbreviations: AL = allostatic load, Sx = symptoms, Dep. = depressive, ACEs = adverse childhood experiences, Fx = functioning, Rel. = relationships, TSMP = temporal summation of mechanical pain, CP = cold pain, CPT = cold pain tolerance

Table 5

Correlations Amongst Allostatic Load Risk, Temporal Summation, Cold Pain Intensity, and Covariates

Variable	1	2	3	4	5	6	7	8
1. AL Risk								
2. TSMP	.025							
3. CP Intensity	.049	.459**						
4. Child Age	-.173	.119	-.022					
5. Child Sex	.169	-.028	-.088	-.042				
6. Analgesic Medication Use	-.089	-.028	-.010	-.114	-.015			
7. Child Race (Black vs. White)	.073	.246*	.071	.034	.057	.199		
8. Child Race (Multiracial vs. White)	.068	.254*	.055	.073	.007	-.164		
9. Income ($40,000-74,999 vs. $0-39,999)	-.181	-.198	-.240	.184	.111	.075	-.241	-.101
10. Income ($75,000+ vs. $0-39,999)	.087	-.021	-.174	.140	.359**	-.012	-.227	-.129

Note. Spearman's correlations conducted for correlations involving variables 5-10. All other correlations conducted using Pearson product-moment correlation test.
*= $p < .05$, ** = $p < .001$
$N = 75$ for all correlations except those involving income (variables 9 & 10). $N = 71$ for correlations involving income.
Abbreviations: AL = allostatic load, TSMP = temporal summation of mechanical pain, CP = cold pain

Table 6

Hierarchical Regressions Predicting Experimental Pain Sensitivity from Allostatic Load Risk

Dependent Variable	Predictors	*B* (SE)	β	R^2
Temporal Summation				
	Constant	17.179 (6.859)		
	Allostatic Load Risk	.408 (3.177)	.015	.022
	Child Race	8.937 (7.149)	.146	
Cold Pain Intensity				
	Constant	51.647 (7.669)		
	Allostatic Load Risk	1.193 (3.369)	.040	.086
	Cold Pain Tolerance	-.186 (.077)	-.275	
	Child Race	-2.529 (2.54)	.126	

Note. Child race was coded as 0 = Black or Multiracial, 1 = White

Table 7

Hierarchical Linear Regression Model Predicting Cold Pain Intensity from Social Sources of Stress, Controlling for Cold Pain Tolerance

Predictors	*B* (SE)	β	R^2
Cold Pain Tolerance	-.206	-.310	.096
Social Functioning	.092 (.140)	.075	.073
Cold Pain Tolerance	-.180 (.077)	-.266	.068
Peer Relationships	-.140 (.241)	-.065	.100
Cold Pain Tolerance	-.204 (.074)	-.308	.096
Family Relationships	.041 (.092)	-.268	.072
Cold Pain Tolerance	-.181 (.077)	-.268	.070

Note. Cold pain tolerance was added as a covariate in all analyses

Table 8

Correlations Between Social Sources of Stress and Temporal Summation of Mechanical Pain

Variable	*r*	*p*
Social Functioning	-.059	.616
Peer Relationships	-.219	.059
Family Relationships	.148	.206

Note. Dependent variable is temporal summation of mechanical pain for all correlations.

Table 9

Correlations Amongst Social Sources of Stress and Cold Pain Intensity

Predictor	*r*	*p*
Social Functioning	.056	.632
Peer Relationships	-.166	.153
Family Relationships	-.007	.950

Note. Cold pain intensity is dependent variable for all correlations.

Table 10

Linear Regression Models Predicting Temporal Summation of Mechanical Pain from Social Sources of Stress

Predictor	*B* (SE)	β	R^2
Social Functioning	-.067 (.132)	-.059	.003
Peer Relationships	-.299 (.235)	-.148	.022
Family Relationships	.111 (.086)	.150	.022

Table 11

Correlations Amongst Psychological Sources of Stress and Temporal Summation of Mechanical Pain

Variable	1	2	3	4	5
1. Anxiety					
2. Depressive Symptoms	.773**				
3. Psychological Stress	.756**	.860**			
4. Adverse Childhood Experiences	.110	.156	.124		
5. Temporal Summation of Mechanical Pain	-.029	-.032	-.160	-.065	

** = $p < .01$

Table 12

Multiple Regression Model Predicting Temporal Summation of Mechanical Pain from Psychological Sources of Stress

Predictor	*B* (SE)	β	*p*
Constant	41.882 (15.351)		
Anxiety	.242 (.408)	.112	.554
Depressive Symptoms	.730 (.487)	.364	.139
Psychological Stress	-1.162 (.495)	-.550	.022
Adverse Childhood Experiences	-.530 (.935)	-.066	.573

Table 13

Correlations Amongst Psychological Sources of Stress and Cold Pain Intensity and Tolerance

Variable	1	2	3	4	5	6
1. Anxiety						
2. Depressive Symptoms	.773**					
3. Psychological Stress	.756**	.860**				
4. Adverse Childhood Experiences	.110	.156	.124			
5. Cold Pain Tolerance	.192	.150	.164	-.008		
6. Cold Pain Intensity	-.050	-.147	-.208	-.026	-.261*	

* = $p < .05$

** = $p < .01$

Table 14

Multiple Regression Model Predicting Cold Pain Intensity from Psychological Sources of Stress, Controlling for Cold Pain Tolerance

Predictor	*B* (SE)	β	*p*
Constant	73.269 (15.910)		
Cold Pain Tolerance	-.179 (.076)	-.265	.021
Anxiety	.539 (.436)	.229	.221
Depressive Symptoms	.034 (.507)	.015	.947
Psychological Stress	-.709 (.527)	-.308	.183
Adverse Childhood Experiences	-3.249 (1.937)	-.194	.098

Table 15

Correlations Amongst Clinical and Experimental Pain Responses and Health-Related Quality of Life

Variable	1	2	3	4
1. Temporal Summation				
2. Cold Pain Intensity	.437**			
3. Clinical Pain Severity	-.004	.139		
4. Health-Related Quality of Life	-.085	-.258*	-.258*	

* = $p < .05$

** = $p < .01$

$N = 66$

Table 16

Descriptive Statistics for Race-Based Differences in Clinical and Experimental Pain Responses and Health-Related Quality of Life

Variable	Group	Mean	*SD*
Temporal Summation	NHW	27.528	23.974
	NHB	21.667	37.141
Cold Pain Intensity	NHW	55.037	26.001
	NHB	47.417	33.932
Clinical Pain Severity	NHW	4.796	2.528
	NHB	5.917	2.353
Health-Related Quality of Life	NHW	62.666	16.911
	NHB	64.493	10.572

Note. NHW $N = 54$, NHB $N = 12$

Table 17

One-Way Analyses of Variance Examining Differences in Clinical and Experimental Pain Responses and Health-Related Quality of Life Between Non-Hispanic White and Non-Hispanic Black Participants

Dependent Variable	Sum of Squares	df	Mean Square	*F*	*p*
Temporal Summation	337.280	1, 64	337.280	.473	.494
Cold Pain Intensity	570.142	1, 64	570.142	.752	.389
Clinical Pain Severity	12.324	1, 64	12.324	1.973	.165
HrQOL	32.779	1, 64	32.779	.128	.722

Table 18

Non-Parametric Comparison of Clinical and Experimental Pain Responses and Health-Related Quality of Life Between Non-Hispanic White and Non-Hispanic Black Participants

Dependent Variable	Mann-Whitney U	Wilcoxon W	*Z*	*p*
Temporal Summation	191.000	1269.000	-2.212	.027*
Clinical Pain Severity	237.000	1,722.00	-1.463	.143
HrQOL	306.000	384.000	-.299	.765

* = $p < .05$

Figures

Figure 1. *Conceptual Model of the Biopsychosocial Sources of Stress in Pediatric FAPD*

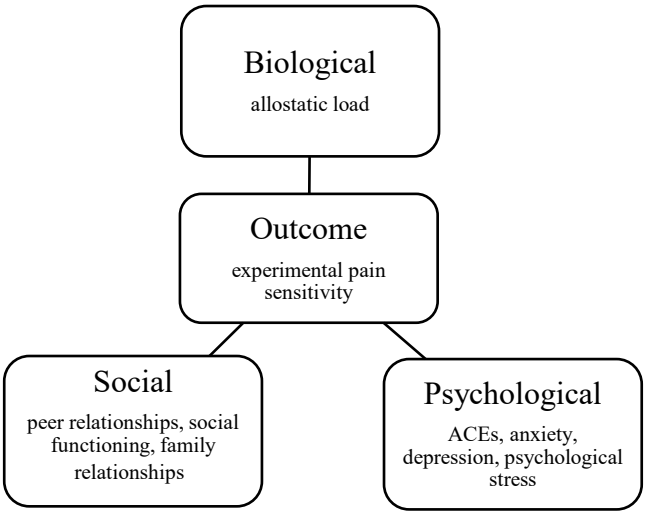

Figure 2. *Flow Diagram of Study Recruitment Procedures*