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Endogenous pain modulation in children with functional abdominal pain disorders

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Introduction

Functional Abdominal Pain Disorders (FAPD) are a major public health concern in children and adolescents, with a worldwide pooled prevalence rate of 13.5% [22]. Children who are diagnosed with FAPD and their parents experience concerns and anxiety that interfere with the child's functioning at school (more absence, less academic performance) and home (less involvement during family activities) [8; 34]. Another potential consequence of chronic pain is the higher risk to develop depressive symptoms and chronic pain into adulthood [44; 46].

The pathogenesis underlying FAPD remains very complex. Firm evidence exists for the "increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input" in adults with functional gastrointestinal disorders, also known as central sensitization (CS) [3; 28]. However, as a result of developmental factors, it is inappropriate to generalize adult findings to pediatric populations. The child's nervous system is still developing and thus more susceptible to plasticity, which possibly leads to faster onset and/or maintenance of CS [17]. A systematic review regarding the presence of CS and its manifestations in children with chronic pain revealed that relatively little is known about the functioning of the descending inhibitory nociceptive pathways in children (6-12 years) with FAPD [32]. A better understanding on how these pathways work in this particular population may reveal their role in the development and maintenance of chronic pain and may lead to the discovery of new treatment modalities [31].

The function of the descending inhibitory nociceptive pathway can be assessed by the conditioned pain modulation (CPM) paradigm [21]. CPM measures the extent of endogenous nociceptive control of a 'test stimulus' during a contralateral 'conditioning stimulus'. A normal CPM response is interpreted as reduced pain intensity or increased pain thresholds in

response to the test stimulus during the administration of a second (conditioning) painful stimulus.

A recent study reported abnormal CPM in youth (aged 10-17 years) with functional abdominal pain [27]. But research has shown that differences in central pain modulation exist between children and adolescents due to, for example, developmental changes in pain cognitions and emotions [40]. Therefore, it might be interesting to assess CPM also in younger children with abdominal pain. The only study investigating CPM in children aged 7-12 years with irritable bowel syndrome included girls with (sub)acute pain solely (i.e., defined as the duration of pain for less than 3 months), which might have influenced the results [45]. Additionally, it is hard to generalize these study results since they are based on a study sample consisting of girls only.

Therefore, the present study assessing central pain modulation (i.e., CPM and pressure algometry) in young children with FAPD of both sexes (6-12 years), will expand the recent evidence on this matter in children and youth. Sex differences for the experimental pain measurements will be studied as well [7]. Since parental pain catastrophizing and child's pain-related fear might have a direct effect on descending pain modulation through activation of the facilitatory pathways, we also assessed these psychological variables in relation to CPM.

Methods

Study Design and Setting

This blinded case-control study has been conducted between February 2017 and September 2018 at the pediatric department of the Antwerp University Hospital (UZA), Edegem,

Belgium. Ethical approval was obtained from the Ethics Committee of the University of Antwerp/Antwerp University Hospital and the study was registered at clinicaltrials.gov (NCT02880332).

Participants

FAPD Group

Participants included boys and girls between 6 and 12 years of age who presented at the pediatric department of the Antwerp University Hospital for abdominal pain. This age cut-off was based on a review article pointing out significant neuroendocrine development as children mature from younger to older ages (> 12 years) [23]. Participants were considered eligible if they (1) were diagnosed with FAPD by the pediatric abdominal pain specialist, based on the Rome III criteria [13]; (2) had a history of pain for at least 3 months; and (3) were able to speak and understand Dutch fluently. Exclusion criteria included (1) the presence of a concomitant chronic disease (e.g., diabetes mellitus), (2) developmental delay that may preclude comprehension of the study procedure, (3) children who previously participated in a study assessing experimental pain, (4) children who were born prematurely [19] or (5) presented with contra-indications to complete the conditioned pain modulation task (e.g. Raynaud's disease, cardiovascular diseases, epilepsia, regular fainting, freezing) [43]. The a priori sample size calculation revealed that a total sample size of at least 66 participants would provide 80% power with an α error probability of .05 to detect a difference in CPM among the children with FAPD and healthy controls (Effect size; d=.71) [45].

Healthy control group

Healthy boys and girls, aged between 6 and 12 years were matched to the FAPD group by means of individual pairing based on age and sex and were recruited through social media,

posters and flyers. Potential subjects were screened on whether they met the inclusion criteria during a telephone interview. The same in- and exclusion criteria as for the FAPD group applied, except for the diagnosis of FAPD and the presence of chronic pain.

Parents of participants were asked to sign the informed consent form prior to the first study procedure. In case the participant was 12 years old, they were asked to sign the inform consent as well, in addition to parental consent. Both the parents and children were informed that they could withdraw from the study at any time and without any consequences. Participants were asked to refrain from heavy physical activity and analgesics at the day of the pain testing procedure, which was confirmed by the parents before the testing took place.

Study flow

At first, both the participant and their parent were asked to fill out questionnaires. Afterwards, the participant was led to a private room where the pain testing procedures were performed (CPM, being the primary outcome measure and pressure algometry), without the presence of the parent and without visual distraction (watches, posters or flyers).

Questionnaires

Demographic and clinical information

Parents were asked to provide information regarding their child's age, sex, hand dominance, race, length, weight, menarche, duration of the pain problem and number of pain episodes per month. Information retrieved from the parents where age, sex, highest educational level, and presence or history of chronic pain.

Pain intensity

The Faces Pain Scale- Revised (FPS-R) was used to assess the child's abdominal pain intensity. This scale consists of six faces, presented horizontally, which relate to a numeric value from 0 to 10. The endpoints were explained as 'no pain' and 'the worst imaginable pain'. The child was asked to assign the face that best reflected the average abdominal pain intensity of the previous week. This scale has been recommended for research purposes based on its utility and psychometric features in children between 4 and 12 years [38; 39], also in case of chronic pain [25].

Pain-related fear

The Dutch Fear of Pain Questionnaire – parent report (FOPQ-P) is a parent proxy report to assess their child's pain-related fear and avoidance behavior. It is based on the original English version which consists of 23 items that are scored on a 5-point scale and has shown good psychometric properties [36]. Total scores range from 0-92, with a higher score representing more fear [36].

Parental pain catastrophizing

The Dutch Parent version of the Pain Catastrophizing Scale (PCS-P) was used to determine parent's catastrophic thinking about their child's pain [20]. The PCS-P consists of 13 items, describing different thoughts and feelings that they may experience about their child's pain. Each item is scored on a five-point scale (0 = 'not at all', 4 = 'extremely') and total scores range from 0-52. Higher scores indicate more pain catastrophizing about their child's pain. In addition, three subscales can be calculated for (1) rumination, (2) magnification and (3) helplessness. This scale has previously been used to assess parental pain catastrophizing in the pediatric chronic pain population and has been reported to be a valid measurement tool [20].

Functional disability

Finally, the Dutch version of the Functional Disability Inventory – Parent proxy (FDI-P) was used to measure the child's difficulties in physical and psychosocial functioning [10]. This questionnaire consists of 15 items concerning perceptions of activity limitations during the past two weeks. Parents were asked to rate the items on a five-point scale (0= 'no trouble', 4= 'impossible'). Total scores range from 0 to 60, with higher scores indicating greater functional disability. This tool has shown good validity and reliability measures in children with chronic abdominal pain [10].

Pain testing procedures

The two assessors who performed the procedures were trained to perform CPM and algometry in a standardized and reliable manner and were blinded for group allocation (healthy child/ child with FAPD). During the CPM procedure, the researcher sat behind the child to reduce bias.

Pressure Algometry

Pressure pain thresholds (PPT) were measured both at the symptomatic region (umbilical region) [14] as well as at two remote test sites (trapezial [14] and tibial region [26]) (see figure 1) by using the pressure algometer (Force Dial model FDK 40; Wagner Instruments, Greenwich, UK). A small flat rubber disc with a surface area of 1 cm^2 and fixed to a metal plunger attached to a hand-held probe, was held perpendicularly to the test site (dominant body region). Pressure was gradually increased at a rate of 1 kg/s and was recorded by a needle on the manometer scale. The children were instructed to say 'stop' at the moment when the sensation of the mechanical stimulus applied to their body changed from pressure to pain. They were instructed not to bear up with the pain but to communicate the exact moment

when pain started. A total of three measurements were conducted at each testing site, with 30 seconds between each test. The average of the final two values was calculated for further analysis [2]. The sequence of the test sites was randomly determined per patient by a computer-generated allocation schedule.

Conditioned pain modulation (=primary outcome)

The test procedure used in this study to assess CPM in children was based on two studies, both reporting recommendations on how to use the cold pressor task as an experimental pain measurement in children [4; 43]. The CPM paradigm was performed by combining pressure algometry (see above) and the cold pressor task. The PPT at the trapezius (dominant body region) served as the 'test stimulus'. The 'conditioning stimulus' for the CPM procedure was provided by the cold pressor test, consisting of immersion of the non-dominant hand in a water circulator apparatus (Thermo Scientific model Haake A 10B, Haake SC 100). The water was cooled to 12°C ± 1°C by the refrigeration device [45] and had a continuous flow and circulation rate.

According to previously established guidelines, participants had to wash their hands with soap and consume a fruit juice prior to hand immersion to avoid vasovagal reactions [4]. The participants were given 5 minutes to adapt to the environment before the hand immersion took place. Afterwards, they were asked to hold their non-dominant hand in an unclenched palm-up position, while submerged to 5 cm above the wrist in the immersion tank. Following initial immersion of 20 seconds, the PPT at the trapezial region was reassessed three times, with an inter-stimulus duration of 30 seconds. Immediately after the last PPT measurement, the child was instructed to withdraw its hand out of the water and was offered a towel to dry and warm the hand. At the end of the CPM procedure, the participant was asked to rate the experienced

pain during hand immersion on the Faces Pain Scale- Revised (FPS-R). Previous research has shown good inter-rater reliability for the use of the cold pressor task in children [5].

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software version 25.0. The CPM effect (i.e. absolute difference) was calculated by subtracting the PPT (trapezius region) during the cold pressor task from the PPT (trapezius region) during baseline algometry. A negative change score was interpreted as an increased PPT, thus representing increased activity of descending pain inhibitory pathways. On the other hand, a positive change score reflected a decreased PPT, thus indicating altered endogenous pain processing, namely pain facilitation. The CPM percent change score was calculated by the following formula [(PPT preCPM- PPT postCPM)/ PPT pre-CPM]*100.

Normality assumptions were checked using the Shapiro-Wilk test, checking normality Q-Q plots and histograms. Differences between the FAPD and healthy control group regarding the demographical data, for all questionnaires and pain testing procedures were examined by using the parametric independent samples T-test and non-parametric Mann-Whitney U test for numerical data and Chi-square or Fisher's exact test for categorical data. To assess the magnitude of the group differences for the questionnaires and pain testing procedures, the effect size (ES) was calculated. Because data distribution violated the general assumptions of Cohen's formula, the formula of Rosenthal $r = Z/\sqrt{N}$. The r-value represents a correlational effect and has different interpretation thresholds compared to its parametric counterpart Cohens-d. Hence interpretation intervals for the r-value are 0.10-0.29 small, 0.30-0.49 medium, 0.50-0.69 large and above 0.70 as a very large effect size [35]. Since the r-value is a correlation effect, effect sizes can be both positive and negative.

Sex-differences within the pain testing procedures were assessed using a Mann-Whitney U test. A Spearman's correlation was run to determine the relationship between the child -and parent reported questionnaires and the CPM-effect within each group separately.

Results

Demographic characteristics

Descriptive statistics regarding the demographic data are presented in Table 1. Between February 2017 and September 2018, 39 children met the criteria for a FAPD and were eligible to participate, as well as 36 healthy children. No group differences regarding childrens' age, sex and race, or parental age and sex differences were identified between the groups. Significantly more parents of children with FAPD had a history of chronic pain (p=0.002). Children within the FAPD group reported a median pain duration of 24 months, with a median of 18 pain episodes each month. Of the FAPD group, 25.6% reported the use of pharmacological treatment for their abdominal pain (Paracetamol, Omeprazol and Esomeprazol).

Pressure algometry and conditioned pain modulation

Detailed information regarding the pain testing procedures can be found in Table 2. PPTs at the trapezial (p=0.011), tibial (p<0.001) and umbilical region (p<0.001) were significantly lower in children with FAPD compared to healthy controls. Figure 2 shows the changes in mean PPTs at the trapezial region over time; both children with FAPD (p=0.035), as well as the healthy control group (p<0.001) showed a significant increase in PPT from before to during the cold pressure task. Regarding the CPM effect, a significantly less negative score for both CPM absolute difference (-0.11 vs -0.36; p=0.003) and CPM percentage change (9%

vs -25%; p=0.023) was found in children with FAPD, indicating less efficient endogenous analgesia. No sex differences were found for the PPT measurements, nor for CPM. For detailed information, see Table 3.

Child and parent reported questionnaires

Results of the child- and parent-reported questionnaires are shown in Table 4. Children with FAPD reported significantly higher abdominal pain intensity ($p<0.001$) compared with healthy children. Parents of the children with FAPD reported significantly more pain-related fear ($p<0.001$) than parents of healthy controls. All three subscales (i.e. school $p<0.001$, fear $p=0.003$ and avoidance $p<0.001$) of the FOPQ-P were significantly different between both groups, showing higher scores in children with FAPD. Parents of children with FAPD catastrophized significantly more about their child's pain than parents of healthy children according to the PCS-P overall score ($p<0.001$). For all three subscales of the PCS-P a significant difference was found between the groups, with parents of children with FAPD indicating more helplessness ($p<0.001$), rumination ($p<0.001$) and magnification ($p=0.012$). Compared with the healthy control group, parents of children with FAPD reported more disability than healthy controls ($p<0.001$). No significant correlations were found between the child-and parent reported questionnaires and the CPM-effect neither within the FAPD group, nor the control group.

Discussion

This study examined endogenous analgesia, primary and secondary hyperalgesia in children with FAPD by measuring CPM and pressure pain thresholds respectively. Psychological variables such as parental pain catastrophizing and children's pain-related fear (parent-proxy report) were also taken into account.

Our study, indicating less efficient CPM in children with FAPD of both sexes (6-12 years), expands recent evidence of less efficient CPM in youth with functional abdominal pain (11-17 years) [27], girls with irritable bowel syndrome (7-12 years) [45] and complements with the evidence in adults (>18 years) with functional gastrointestinal disorders [3; 28]. The median CPM percentage change score of -25% in the healthy control group (indicating pain inhibition) is comparable with two other studies, reporting respectively -23% and -19% percentage change in a sample of healthy children (age range 8-17) [27; 40]. Strikingly, in comparison with another study investigating CPM in a younger, comparable age group, we found a much stronger CPM effect (-25% vs. -9%) [40]. This discrepancy in findings could be explained by many factors (related to the population or CPM procedure) that have received attention as potential moderators of CPM effect [41]. The study sample of Tsao et al. (2013) had a different sex -and race distribution compared to our healthy control group. The socio-economic status and symptoms of anxiety or depression might have varied as well, however these data are missing in our study and thus cannot be compared. In addition, the use of a different test site could explain the stronger CPM effect found in the present study.

Previous studies emphasized the fact that the CPM assessment paradigm is only able to quantify the balance between the descending inhibitory and facilitatory nociceptive pathways and not to distinguish between both pathways [30]. Consequently, when patients have a less efficient CPM response it is not obvious whether inhibition has reduced or facilitation has increased. A recent study in adults with fibromyalgia however, suggested that patients may be classified as CPM reducers (inhibition) or CPM increasers (facilitation) [33]. In our study, 40% of the children with FAPD showed a pro-nociceptive pattern –or pain facilitation- reflected in reduced PPTs from baseline algometry to PPT during the cold pressure task,

which is similar to the 43% reported by Morris et al. (2016) in youth with functional abdominal pain [27].

Medium effect sizes regarding the presence of primary and secondary hyperalgesia in children with FAPDs were found. Our findings showing reduced PPTs in children with FAPD both at the symptomatic and remote test sites are in line with two other studies previously assessing somatic pain sensitivity in response to pressure stimulation in children with FAPD and healthy controls [1; 14]. Compared with the results of Duarte et al. (2000), we found similar median differences in PPTs between children with FAPD and healthy controls at the umbilical (0.44 vs. 0.40 kg/cm^2), trapezial (0.28 vs. 0.40 kg/cm^2) and tibial region (0.85 vs. 1.20 kg/cm^2) [14]. A more recent study found no evidence for primary or secondary hyperalgesia in children with FAPD in response to heat and mechanical stimuli [48]. Findings on the presence of primary and secondary hyperalgesia may vary upon the type of somatic stimulation that is used [3]. Children with FAPD may present with primary and secondary hyperalgesia but only when deeper tissues (e.g. pressure stimuli) rather than superficial tissues (e.g. mechanical pinprick or thermal stimuli) are examined. Secondly, the relative small sample sizes used in the study of Zohsel et al. (2008) (FAPD group n= 20) might be another explanation why this study did not find differences in pain perception [48].

Sex differences in pain perception are commonly reported in adults, with women demonstrating greater sensitivity to experimental pain tasks [18]. Previous studies exploring sex differences in healthy children in response to experimental pain measurements found no significant differences in younger children (aged < 12 years) [7; 40]. Although our study sample might be underpowered to check for sex differences in pain thresholds and CPM, statistical analyses support these findings in both the FAPD and healthy control group. Sex

differences in pain perception might emerge around the time of pubertal development, which could explain our findings in children aged 6-12 years.

Previous studies found children with FAPD to have greater levels of psychological distress compared to healthy children [45]. This pattern was replicated in our study, finding greater parent-reported pain-related fear in children with FAPD compared to healthy children. In addition, this study shows that parents of children with FAPD catastrophize significantly more about their child's pain. Given the known bidirectional relationship between parent and child on the experience of pain, as demonstrated by the interpersonal fear-avoidance model [37], children with catastrophizing parents are more likely to experience more pain-related disability and increased pain perception [9; 20]. Although this study did not account for the presence of other psychological variables, it has been clear from previous studies that many children with FAPD suffer from anxiety disorders (prevalence rates of 42%-85%) [15]. Moreover, the co-occurrence of FAPD and anxiety in children implies increased pain-related impairments [11] and a higher risk of long-term problems including persistent pain and pain-related disability [12]. Further studies should account for anxiety disorders in children with FAPD, given the understanding that psychological symptoms may exacerbate or contribute to pain symptoms, also in the context of CPM [16] [29].

A recent meta-analysis provided evidence for the relation between modality-specific CPM responses and psychological factors in healthy individuals, showing a correlation between pressure-based CPM responses and anxiety, heat-based CPM and depression and electrical-based CPM and pain catastrophizing [29]. However, conflicting evidence exists regarding the relation between CPM responses and fear of pain [29], with one study supporting our findings of no relation in children with FAPD and healthy controls [6]. Yet, the most important explanation why our study found no association between psychological factors and CPM is

probably the use of parent-proxy questionnaires, which may have led to parental over- or under-estimation of their child's psychological constructs.

The present study has some limitations. The inclusion of 6 -and 7-year-old children made it impossible to use child-reported questionnaires to assess the child's pain-related fear and functional disability. Although child self-reported questionnaires are preferred above parent-proxy questionnaires, previous research reported the ability of parents to offer a clinically valid, single clinical perspective about functional disability and pain-related fear [36; 42]. The present study was underpowered to conduct covariate analyses, looking for the influence of the child's functional disability, fear of pain and parental history of pain, educational level and parental pain catastrophizing on the CPM effect. Yet, a subsequent correlation analysis, looking for a relation between parental history of chronic pain and the experimental pain responding in children with FAPD was not significant (X^2=0.106; df=1; p=0.744).

In order not to overburden the children, our pain testing procedure did not include visceral pain thresholds which are more directly relevant for the clinical presentation of FAPD in children. Further research should explore the possibility to use a visceral stimulus within the CPM testing procedure. We used age and the presence of menarche as a proxy for pubertal status, however, certain hormonal changes may occur before the age of 12 years [23].

The large heterogeneity regarding experimental pain measurements used in studies in children made it difficult to set up the pain testing procedure for this study. Recent guidelines suggest a water temperature of 10°C ± 1°C to perform the cold pressor task in children and adolescents [5; 43]. However, most studies using this water temperature included 8-year-old children, whilst studies in younger children (5-6 year olds) used slightly warmer water temperatures

(12- 15 °C) [24; 47]. After the first pilot testing of the CPM procedure in a 6-year-old child, the water temperature was raised from 10°C ± 1°C to 12°C ± 1°C, because the child was not able to complete the whole testing procedure. Prior to administering the test stimulus (PPT at trapezial region) the assessor should have rated the participants' pain intensity to make sure the water temperature was painful enough (i.e. 8/10 of the FPS-R or VAS) [4]. Nonetheless, overall the test protocol was able to elicit CPM.

The findings obtained by this study expand previous research regarding the presence of CS in children with FAPD and have implications for clinical practice [32]. Results of this study indicate that centrally-driven changes may be present in children with FAPD, possibly leading to a more intense or more painful reaction to nociceptive input signals. Studies in the future should investigate how procedures such as pain neuroscience education, physical exercise and cognitive-behavioral therapy can influence this state of CS observed in children with FAPD.

Conclusion

In summary, this study was the first to investigate and report that young children of both sexes with FAPD have less efficient endogenous analgesia compared with healthy controls. Furthermore, we replicated previous findings of primary and secondary hyperalgesia in young children with FAPD. No sex differences were found for the experimental pain measurements, nor did we found a relation between the psychological variables and the CPM-effect.

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Figure legends

Figure 1. Symptomatic and remote test sites for the PPT measurements

Figure 2. Changes in mean Pressure Pain Thresholds (PPTs) over the CPM procedure