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Hypoalgesia Related to Elevated Resting Blood Pressure is Absent in Adolescents and Young Adults with a History of Functional Abdominal Pain

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Abstract

Elevated resting blood pressure (BP) is hypoalgesic in healthy individuals, but this effect is absent in adults with chronic somatic pain. This study tested whether BP-related hypoalgesia is similarly altered in individuals with a history of chronic visceral pain in childhood. Resting BP was assessed in 94 adolescents and young adults with a known history of childhood functional abdominal pain (FAP) and 55 comparable healthy controls. Responses to an acute heat pain stimulus were then evaluated following exposure to two laboratory stressors. A significant Participant Type X Systolic BP (SBP) interaction ($p < .005$) revealed that elevated resting SBP was associated with significantly higher heat pain threshold ($p < .001$) in healthy controls, but was unrelated to pain threshold in the FAP group. A similar pattern was observed for heat pain tolerance, with elevated SBP linked to significantly higher pain tolerance ($p < .05$) in healthy controls, but unrelated to tolerance in the FAP group. Dysfunction in BP-related hypoalgesia associated with FAP was evident regardless of whether childhood FAP had resolved or still persisted at the time of laboratory testing. Subgroup analyses indicated that BP-related hypoalgesia (in healthy controls) and FAP-linked absence of this hypoalgesia was observed only among females. Result suggest that childhood visceral chronic pain may be associated with relatively long-lasting dysfunction in overlapping systems modulating pain and BP that persists even after FAP resolves. Potential implications for later hypertension risk are discussed.

Keywords

blood pressure; pain; chronic pain; hypoalgesia; functional abdominal pain; childhood; pediatric; adolescent

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Introduction

Among healthy normotensive individuals, resting blood pressure (BP) is inversely related to acute pain sensitivity [3,13,27,33,³⁴,36,48,50,52]. This BP-related hypoalgesia reflects functional interactions between overlapping brain circuits modulating both pain and BP which contribute to maintenance of cardiovascular homeostasis in the context of pain [14,19,40,54]. BP-related hypoalgesia is evident not only in adults, but in adolescents [21,27] and possibly infants [37].

Several studies suggest that normally inverse associations between resting BP and acute somatic pain sensitivity are absent or even reversed in individuals with chronic pain [11,12,15,17,25,49]. Prior work has focused on chronic somatic pain patients, and it is unknown whether BP-related hypoalgesia is similarly altered in visceral chronic pain. However, indirect evidence suggests such alterations are likely. Chronic visceral pain appears to be associated not only with visceral hypersensitivity, but also widespread somatic hyperalgesia [10,53,63,64]. Visceral and somatic nociceptive input are both subject to descending modulation at the dorsal horn [45], so co-occurrence of visceral and generalized somatic hyperalgesia in visceral chronic pain conditions might in part reflect dysfunction in descending pain modulatory systems [73]. Similar dysfunction in endogenous pain modulatory systems is believed to contribute to alterations in BP-related hypoalgesia in somatic chronic pain sufferers [14,19], an hypothesis for which there is some experimental support [25]. Chronic pain-related dysfunction in descending pain modulatory systems might similarly alter BP-related hypoalgesia in visceral chronic pain syndromes. This possibility has received little empirical evaluation.

Evidence in animals indicates that early postnatal colon irritation leads to adult hypersensitivity to both visceral and somatic pain stimuli, despite absence of ongoing colon pathology [4]. Moving from animals to humans, such work raises the question of whether chronic abdominal pain in childhood or adolescence might lead to long-term changes in brain regions underlying BP-related hypoalgesia. Prevalence estimates suggest that chronic or recurrent abdominal pain affects 7% to 25% of children [7,9,44,55], and while pain is often episodic rather than daily, it may persist for years [43,51,68]. The population targeted in the current study is adolescents and young adults with a childhood history of functional abdominal pain (FAP), defined as persistent abdominal pain in the absence of significant medical findings [8,60,69]. Examining whether BP-related hypoalgesia is altered in persons with a history of childhood FAP, even after FAP resolves, may be relevant to understanding potential long-term health risks of chronic pain, given that altered cardiovascular/pain regulatory interactions might contribute to increased hypertension risk in somatic chronic pain [15,16,24,25].

In sum, the primary aim of the current study was to test whether BP-related hypoalgesia is altered in adolescents and young adults with a history of FAP. Based on prior work in adult chronic pain populations [11,12,15,17,25,49], we hypothesized that there would be significant inverse associations between resting BP and acute somatic pain sensitivity in participants without a FAP history, but that these associations would be absent in those with a history of FAP.

Method

Design

This study used a between-subjects design to compare BP-related hypoalgesia in adolescents and young adults with a history of FAP and a healthy group of similar age without history of abdominal pain.

Sample

Participants in the current study were all part of a large ongoing prospective study of FAP. The current study is a secondary analysis of this larger FAP dataset. The sample included 95 normotensive adolescents and young adults with a history of childhood FAP and 55 normotensive healthy controls without a history of childhood FAP. Sample sizes across groups were unequal due to planned differences in targeted recruiting focused on achieving the goals of the primary FAP study. While it might have proven interesting to examine BP-related hypoalgesia in adolescents and young adults with other (non-functional) types of chronic pain as well, such comparison samples were unavailable. Participants in the FAP group were recruited for this study from a sample of over 850 former patients who had first presented to the Vanderbilt Pediatric Gastroenterology Clinic for evaluation of abdominal pain when they were 8–16 years old and who had enrolled in one of several studies conducted by Walker and colleagues between 1993 and 2004 [e.g., 66,70,71]. Eligibility criteria for the original studies were abdominal pain of at least 3 months duration and no organic disease diagnosis provided by the referring physician. The healthy control sample for the current study was recruited from the healthy samples in these prior FAP studies, all of whom had had been recruited originally from community schools and who had had no abdominal pain in the previous month and no chronic medical illness at the time of original study participation.

Participants in the current study were those participants from prior studies who had agreed to undergo the laboratory portion of an ongoing prospective FAP research project, and for whom both resting BP and acute thermal pain response data were available. The FAP group included only those prior study participants whose original medical evaluation at Vanderbilt had been consistent with functional abdominal pain (i.e., no evidence of a recognized pathological basis for pain). The current study was conducted on average ($\pm$ SD) 6.2 ± 1.83 and 9.6 ± 3.69 years after participation in the original study for the Healthy and FAP samples respectively. At the time of the current study, 38% of former FAP study patients met the Rome III symptom-based diagnostic criteria for a current abdominal pain-related Functional Gastrointestinal Disorder [28]. Of the 95 patients recruited for the FAP group, one had since been diagnosed with Crohn's disease (an organic abdominal pain condition) and was excluded from the final sample. Based on information provided by all participants on the Persistent Pain Questionnaire (modified to assess persistent pain in the past 3 months)[18], 41% of the FAP group and 11% of the Healthy group were experiencing daily or near daily pain in at least one body location for the 3 months prior to this study. Mean overall clinical pain intensity in the past month rated on a 0–5 scale (anchored with “none” and “very severe”) was in the “mild” range for both groups, but was significantly higher in FAP group participants than in Healthy participants (see Table 1).

Table 1 summarizes demographic information for the two groups. Both groups were predominately female (FAP: 62.1% female, Healthy: 65.5% female), white, and of non-Hispanic ethnicity, with no significant differences between the groups on these demographic variables ($p > .10$). Significant differences were observed between FAP and Healthy groups in both age and body mass index (BMI), with these two variables significantly correlated ($r = 0.31$, $p < .001$). The FAP group also displayed significantly higher BP. Systolic BP correlated modestly but significantly (given the large sample size) with both age [$r(147) = 0.21$, $p < .01$] and BMI [$r(147) = 0.27$, $p < .01$]. The correlation between diastolic BP and age was much larger [$r(147) = 0.42$, $p < .001$], but the comparable correlation with BMI was small and only marginally significant [$r(147) = 0.16$, $p < .06$]. Only one Healthy participant and four FAP group participants were taking regular medications (esomeprazole, antidepressants, or isotretinoin). FAP participants were significantly ($p < .05$) more likely than Healthy group participants to be experiencing Axis I psychiatric symptomatology at the time of testing. In the interests of space and to maintain focus on the primary findings of the current study, these results are extensively detailed in a separate manuscript (in preparation).

Procedure

All procedures were approved by the university Institutional Review Board. After providing informed consent, participants were interviewed over the phone about their physical and emotional health and functional disability. After completing the phone interview, participants had the option to participate in a laboratory portion of the study that involved taking part in a psychophysiological assessment protocol designed to evaluate stress and pain responsiveness. The laboratory study was conducted at the Vanderbilt University Pediatric Clinical Research Center. Participants remained seated upright in a comfortable chair throughout all laboratory procedures.

During the laboratory session, participants initially completed a 10-minute seated rest period, after which four resting BP determinations were made using an oscillometric blood pressure cuff (Dinamap Compact-T, Johnson & Johnson, Inc.). For both systolic (SBP) and diastolic (DBP) blood pressure, the mean of these four resting baseline BP determinations served as the primary independent variable in the analyses described below.

After this baseline period, participants were exposed to two laboratory stressors (a 10-minute interview about a recent stressful event followed by a two-minute serial subtraction task) prior to assessment of thermal pain sensitivity. The thermal pain task began shortly after the end of the serial subtraction task. This sequence of tasks was designed to enhance physiological arousal prior to the pain task and thereby maximize any group differences in endogenous pain modulatory systems (see Burns et al. [20]). Across groups, mean SBP and DBP during the serial subtraction task occurring prior to the thermal task represented increases of 11.4mmHg and 9.8mmHg respectively from the mean baseline values used in the primary analyses described below, and the magnitude of these BP increases did not differ between groups (p 's $>.10$). Although these increases from baseline were significant for both SBP [$t(148) = 14.48$, $p < .001$] and DBP [$t(148) = 18.51$, $p < .001$], the degree to which BP increased during the stressor was not significantly associated with subsequent thermal pain threshold [SBP: $r(148) = -0.12$, $p > .10$; DBP: $r(148) = -0.07$, $p > .10$] or pain tolerance [SBP: $r(148) = 0.11$, $p > .10$; DBP: $r(148) = 0.10$, $p > .10$]. Associations between these BP increases and pain outcomes did not differ between FAP and Healthy groups (p 's $>.10$).

The thermal pain task in this study employed a Medoc Thermal Sensory Analyzer (TSA-II, Medoc, Inc., Ramat, Israel). This computer-controlled device was used to apply a controlled heat stimulus to the nondominant ventral forearm using a 30×30mm Peltier thermistor probe as reported in prior studies [35], including work in our lab [15,24,25]. A series of four pain threshold trials was conducted, followed by a series of four pain tolerance trials, with the probe applied to a slightly different target site for each trial to avoid local sensitization. For pain threshold trials, the probe started at an adaptation temperature of 32°C, with the temperature increasing at a ramp rate of 0.5°C/sec until the participant indicated that the stimulus had begun to feel "painful." For each tolerance trial, the probe started at an adaptation temperature of 40°C, with the temperature increasing at a ramp rate of 0.5°C/sec until the participant indicated maximum tolerance had been reached. For both thermal pain threshold and tolerance trials, the inter-stimulus interval was 25 seconds. Means of the four thermal pain threshold and tolerance trials were separately derived for use in the analyses below. As in our past work [15,25], participants underwent standardized training to familiarize them with the thermal stimulus device and the concepts of thermal pain threshold and tolerance prior to undergoing the laboratory tasks.

Statistical Analysis

All analyses were conducted using the SPSS for Windows Version 17 statistical package (SPSS, Inc., Chicago, IL). Primary study hypotheses were tested using a series of hierarchical

multiple regressions to examine whether a history of childhood FAP moderated the influence of current resting BP on acute thermal pain responsiveness. Given past work indicating that BP-related hypoalgesia in healthy individuals is generally observed for SBP but not DBP [14], we anticipated that significant effects would be more likely for the SBP measure. Primary analyses consisted of four hierarchical multiple regressions, with the two dependent variables (pain threshold and pain tolerance) examined separately for the independent variables of SBP and DBP. As noted previously, preliminary analyses indicated significant differences between FAP and Healthy groups in both age and BMI. To control statistically for these potential confounds and presence of *current* chronic pain (described above), main effects of age, BMI, and persistent pain in the past three months (dummy coded 1/0 for Yes/No) were entered as control variables in the primary analyses. Additional entry of interactions between BP and control variables did not reveal any significant effects (all p 's $>.19$) nor did this substantially alter the pattern of results reported below. Analyses restricted to the smaller subsample of participants in both groups reporting no chronic pain anywhere in their body for the past 3 months ($n=49$ Healthy, $n=57$ FAP) did not alter the pattern of findings for pain threshold (although findings for pain tolerance no longer approached significance).

The hierarchical regressions entered control variables in step one, main effects of interest in step two (Participant Type, SBP or DBP), and the relevant Participant Type x BP multiplicative interaction term in step three. Follow-up simple effects tests by Participant Type were conducted to determine the source of significant Participant Type x BP interactions. To display significant interactions graphically, simple slopes were calculated separately for FAP and Healthy groups [1]. That is, the regression equations computed for each Participant Type were solved for hypothetical low and high BP values (-1 SD and $+1$ SD from the mean resting BP level). Pain threshold and tolerance were then predicted for these representative low and high BP values and were plotted by Participant Type. All probability values reported are two-tailed with a $p<.05$ criterion for significance, and were not subjected to the Bonferroni adjustment.

Results

Zero-Order Correlations

Zero-order correlations between BP variables and pain outcomes are presented by Participant Type in Table 2. In the Healthy group, higher resting SBP (but not DBP) was associated with significantly higher thermal pain thresholds and greater pain tolerance (i.e., lower sensitivity to the painful stimulus). A somewhat larger magnitude of correlation was noted for effects of SBP on the pain threshold measure compared to the pain tolerance measure. Correlations between BP and acute pain outcomes were not significant in participants with a history of childhood FAP.

Effects of Participant Type

Hierarchical multiple regressions with thermal pain threshold as the dependent variable revealed a significant Participant Type x SBP interaction [R^2 increment = 0.053, F change (1,140) = 8.45, $p<.005$]. This interaction is portrayed graphically in Figure 1. Simple effect analyses indicated that this interaction was due to a significant positive slope between SBP and thermal pain threshold in the Healthy group [$\beta = 0.45$, $t(53) = 3.78$, $p<.001$], with a much smaller and nonsignificant positive slope in the FAP group [$\beta = 0.10$, $t(90) = 0.88$, $p>.10$]. That is, elevated resting SBP was significantly hypoalgesic in individuals *without* a history of childhood FAP, but had no hypoalgesic effects in individuals who had experienced childhood FAP. Similar analyses of the effects of DBP on pain threshold did not reveal any significant main or interaction effects (all F 's <1.0).

Hierarchical multiple regressions with thermal pain tolerance as the dependent variable revealed a similar Participant Type x SBP interaction that just failed to reach the traditional level of statistical significance [R^2 increment = 0.024, F change (1,140) = 3.62, $p < .07$]. Follow-up analyses revealed a statistically significant simple effect contributing to this interaction. Specifically, a significant positive slope was observed between SBP and thermal pain tolerance in the Healthy group [$\beta = 0.31$, $t(53) = 2.39$, $p < .05$], with a much smaller and nonsignificant positive slope in the FAP group [$\beta = 0.09$, $t(90) = 0.74$, $p > .10$]. Figure 2 graphically portrays the source of this interaction, which is similar in character to that noted for pain threshold. Analyses of the effects of DBP on pain tolerance did not reveal any significant main or interaction effects (all F 's < 1.5).

Given the relatively large size of the FAP sample, follow-up analyses were conducted within this group to determine whether FAP that was resolved ($n=60$) versus unresolved ($n=35$) at follow-up might account for the altered relationships between SBP and thermal pain responsiveness observed in the FAP group relative to the Healthy group. Hierarchical regression analysis did not reveal any significant main effects of FAP Resolution on thermal pain threshold outcomes (F change < 0.8), nor was the SBP X FAP Resolution interaction in this analysis significant (R^2 increment < 0.002 , F change < 0.3). Similar results were obtained in analyses of the pain tolerance outcome, again with a nonsignificant SBP X FAP Resolution interaction (R^2 increment < 0.000 , F change = 0.00). In other words, the association between SBP and pain outcomes was not moderated by whether FAP had resolved. These analyses indicate that presence of resolved versus unresolved FAP at the time of acute pain testing was unlikely to explain the differences observed between FAP and Healthy groups with regard to BP-related hypoalgesia.

Possible Gender Differences

Because primary analyses indicated that Participant Type interacted significantly only with SBP as a predictor of pain outcomes, SBP but not DBP analyses were repeated separately by gender to explore potential gender differences in the impact of FAP on BP-related hypoalgesia. These analyses were conducted to address past findings suggesting that BP-related hypoalgesia may be weaker in females [e.g., 2,36,41] and that the negative impact of chronic pain on cardiovascular risk might be greater in females [16].

In female participants, the Participant Type X SBP interaction was significant for thermal pain threshold [R^2 increment = 0.111, F change (1,85) = 11.10, $p < .001$]. Healthy young women exhibited a significant positive slope between SBP and pain threshold [$\beta = 0.49$, $t(34) = 3.43$, $p < .01$], whereas female participants with a FAP history exhibited a nonsignificant negative slope [$\beta = -0.09$, $t(54) = -0.59$, $p > .10$]. This finding was similar to that observed in the overall sample (of which a large majority were female), indicating that BP-related hypoalgesia was present in females without a history of FAP, but was absent in those who had experienced childhood FAP.

Similar analyses for pain tolerance in the female subsample indicated that the Participant Type X SBP interaction was a nonsignificant trend [R^2 increment = 0.036, F change (1,85) = 3.29, $p < .08$]. Simple effects analyses indicated that healthy young women exhibited a positive slope between SBP and pain tolerance that approached significance [$\beta = 0.31$, $t(34) = 1.95$, $p < .06$], whereas female participants with a FAP history exhibited a slope near zero [$\beta = -0.04$, $t(54) = -0.24$, $p > .10$].

In males participants, main and interactive effects of SBP and FAP status were not significant predictors of either pain threshold (all F 's < 1.7) or pain tolerance (all F 's < 1.4). Diminished power related to the smaller size of the male subsample would not appear to account entirely for the lack of significant findings in males. For example, the effect size for the SBP/pain

threshold relationship expressed in terms of a correlation coefficient was much larger in females (partial $r = 0.52$) than in males (partial $r = 0.08$). Given the small magnitude of effect in males, even a doubling in size of the male sample would not have revealed significant BP-related hypoalgesia in this group.

Discussion

BP-related hypoalgesia is evident in normotensive populations from infancy through adulthood [3,13,27,33,³⁴,36,48,50,52]. This hypoalgesia reflects functional interactions between overlapping brain circuits modulating both pain and BP which contribute to maintenance of cardiovascular homeostasis in the context of painful stimuli [14,19,40,54]. To the extent that baroreceptor and descending pain inhibitory pathways in these interacting homeostatic circuits are disrupted by presence of persistent pain [14,19,25,38], one might anticipate BP-related hypoalgesia to be altered in chronic pain conditions. Past work confirms that in patients with chronic somatic pain (e.g., low back pain), BP-related hypoalgesia is absent [11,15,17,24,25,49].

The current results extend the findings above from somatic to visceral chronic pain conditions, and from older to younger individuals, revealing that BP-related hypoalgesia is absent in adolescents and young adults with a history of FAP. To our knowledge, only one prior study has examined BP-related hypoalgesia in visceral pain patients of any age. Gupta et al. [42] reported weak positive associations between BP and acute pain sensitivity in a small sample of adult IBS patients, like those often observed in somatic chronic pain [11,12,15,17,25,49]. The current study had a substantially larger sample and suggested that BP-related hypoalgesia evident in healthy adolescents and young adults is absent in those who have experienced childhood visceral pain (FAP). In sum, it appears that chronic painful input, whether visceral or somatic, may result in dysfunction in central pathways modulating both pain and cardiovascular function, with changes in BP-related hypoalgesia serving as an index of such dysfunction.

Interestingly, the current findings indicated that cardiovascular/pain regulatory interactions were significantly altered regardless of whether FAP had resolved or was ongoing. This suggests that any dysfunction produced by chronic pain in pathways subserving modulation of both pain and BP can in at least some circumstances persist well after the original pain complaint resolves. However, it remains unknown whether persistence of this dysfunction is due to chronic pain in FAP occurring during developmental periods in which the nervous system is relatively more malleable, or whether such dysfunction might also persist in adults after chronic pain has resolved. This latter issue has yet to be explored.

If the dysfunction in cardiovascular/pain modulatory systems observed in young adults with a history of FAP persists well into later adulthood, this dysfunction might have implications for hypertension risk. For example, past work indicates that altered BP-related hypoalgesia in somatic chronic pain is associated with reduced baroreceptor sensitivity [25,38], which in turn is a prospective predictor of future BP increases [29]. Moreover, chronic somatic pain appears to be associated with significantly increased hypertension risk relative to both non-pain medical populations [16] and general population controls [65].

Mechanisms underlying changes in BP-related hypoalgesia in visceral chronic pain conditions are not known. However, it may be relevant that transmission of visceral sensations occurs in part via afferent vagal pathways synapsing at the nucleus tractus solitarius (NTS; [45]). Vagal pathways and the NTS also are integral components of afferent baroreceptor transmission underlying homeostatic modulation of cardiovascular function [14,54]. Furthermore, healthy individuals show hypoalgesia related to elevated vagally-mediated baroreceptor activity that

parallels the hypoalgesia associated with elevated BP [25]. It is plausible that altered responsivity in these vagal/NTS pathways could both increase perception of visceral stimuli and alter cardiovascular function.

The current results highlight an important consideration in childhood FAP. By definition, there is no evidence of recognized gastrointestinal pathology to account for the abdominal pain complaints in FAP. Given this circumstance, investigators have examined a variety of potential etiological factors including psychopathology [23,30,39], stress [31,61,71], social reinforcement of symptom complaints [46,47,67,72], and altered gut function and sensation [26,56,62]. Although potential FAP mechanisms previously considered have emphasized either psychological factors or alterations in the gut itself, results of the current study suggest that FAP is associated with objective physiological changes in the central nervous system, that is, alterations in interacting systems modulating pain and cardiovascular function. Such changes are consistent with apparent changes in endogenous pain modulatory systems noted in brain imaging studies of adult IBS patients [58]. Thus, the current study further highlights the potential role of central nervous system changes in childhood FAP.

Another issue addressed by this study is the impact of gender. Nearly two-thirds of the study participants were female. Previous reports suggested that BP-related hypoalgesia is somewhat weaker in females [e.g., 2,36,41], possibly influenced by hormonally-induced variability in pain responses across the menstrual cycle [36,57,59]. In the current study, results confirmed the presence of a significant inverse relationship between SBP and acute thermal pain sensitivity in healthy young adult females, a relationship which was absent in similar females with a history of FAP. In contrast to expectations based on the adult literature, significant BP-related hypoalgesia was not noted in young adult male participants, whether in the healthy or FAP group. The relationship between resting BP and acute pain in males was much weaker than in females, and therefore, statistical power issues related to the smaller male subsample would not account entirely for these differences. Prior work in healthy male adolescents has confirmed presence of significant BP-related hypoalgesia [21,27], so reasons for its absence in healthy males in the present study remain unclear. In contrast to the thermal pain stimulus used in the current study, work by Ditto et al. [27] and Campbell et al. [21] employed pressure pain stimuli, and it is conceivable that stimulus-related differences might have impacted on the differing pattern of results. Although the current gender effects must be interpreted cautiously until replicated, the finding that BP-related hypoalgesia was altered in FAP specifically in females is intriguing given past work suggesting that somatic chronic pain had a much larger impact on occurrence of hypertension in females than in males [16].

Several potential limitations with the current study must be addressed. First, 41% of FAP participants and 11% of healthy participants reported experiencing daily or near daily pain in the 3 months prior to the study procedures. This latter finding is not surprising given results of studies regarding the relatively common occurrence of persistent pain in the general population [e.g., 5,6,18]. Although ongoing chronic pain at the time of the study would not seriously confound general conclusions regarding the effects of chronic pain on BP-related hypoalgesia, it would potentially influence conclusions regarding whether such changes persist once FAP is resolved. In the current study, this potential confound was handled in two ways, with similar results for each. Whether analyses included presence/absence of ongoing pain as a statistical control or whether analyses were restricted only to the smaller subset of participants without any recent chronic pain, results in either case supported the pattern of findings described above. It should be noted that the pattern of findings was also unchanged by statistical control of significant differences between Healthy and FAP groups in age and BMI, suggesting that these differences were unlikely to have confounded the study results.

A second potential interpretive limitation was the fact that an interview about a recent stressful event and a serial subtraction task were carried out before thermal pain evaluation was conducted. Although resting BP was obtained before the stress tasks, these tasks might have influenced subsequent pain responses. This was not considered a design weakness. It was hoped that the sequence of tasks would maximize any differences between FAP and Healthy groups with regards to endogenous pain inhibitory function. For example, our recent work demonstrated that an emotionally arousing stress task elicits endogenous opioid-mediated analgesia in a subsequent pain task [20]. The fact that the stressors preceded the thermal pain task in the current study was unlikely to have confounded the findings given that BP increases during the last stress task were not correlated with subsequent thermal pain responses.

A third potential study limitation was the fact that the FAP and Healthy groups differed significantly in mean resting BP levels. This difference between groups in absolute BP levels would be unlikely to confound the results because the analyses focused on differences in rank-ordering of BP relative to pain responses within each participant type, rather than focusing on absolute levels of BP.

Finally, because the study sample was not highly diverse in terms of race/ethnicity, impact of these variables on the pattern of current findings could not be evaluated. This issue may be important to consider given past findings that both pain responsiveness [32] and endogenous pain modulatory systems like those contributing to BP-related hypoalgesia may differ between non-Hispanic whites and African-Americans [22].

In summary, this study found evidence for BP-related hypoalgesia in healthy adolescents and young adults, but not in those with a history of childhood FAP. These effects were restricted to female participants. The current results extend previous findings that chronic pain alters functional interactions between the cardiovascular and pain regulatory systems from somatic to visceral chronic pain conditions. These alterations may persist in individuals with a history of childhood FAP even after this original pain condition has resolved. Changes in BP-related hypoalgesia associated with chronic pain, whether visceral or somatic in origin, may have implications for hypertension risk.

Elevated resting blood pressure (BP) is hypoalgesic in healthy individuals, but this effect is absent in adults with chronic somatic pain. This study tested whether BP-related hypoalgesia is similarly altered in individuals with a history of chronic visceral pain in childhood. Resting BP was assessed in 94 adolescents and young adults with a known history of childhood functional abdominal pain (FAP) and 55 comparable healthy controls. Responses to an acute heat pain stimulus were then evaluated following exposure to two laboratory stressors. A significant Participant Type X Systolic BP (SBP) interaction ($p < .005$) revealed that elevated resting SBP was associated with significantly higher heat pain threshold ($p < .001$) in healthy controls, but was unrelated to pain threshold in the FAP group. A similar pattern was observed for heat pain tolerance, with elevated SBP linked to significantly higher pain tolerance ($p < .05$) in healthy controls, but unrelated to tolerance in the FAP group. Dysfunction in BP-related hypoalgesia associated with FAP was evident regardless of whether childhood FAP had resolved or still persisted at the time of laboratory testing. Subgroup analyses indicated that BP-related hypoalgesia (in healthy controls) and FAP-linked absence of this hypoalgesia was observed only among females. Results suggest that childhood visceral chronic pain may be associated with relatively long-lasting dysfunction in overlapping systems modulating pain and BP that persists even after FAP resolves. Potential implications for later hypertension risk are discussed.

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References

1. Aiken, LS.; West, SG. Multiple regression: Testing and interpreting interactions. Thousand Oaks, CA: Sage; 1991.
2. al'Absi M, Buchanan TW, Marrero A, Lovallo WR. Sex differences in pain perception and cardiovascular responses in persons with parental history of hypertension. *Pain* 1999;83:331–338. [PubMed: 10534606]
3. al'Absi M, Petersen KL, Wittmers LE. Blood pressure but not parental history for hypertension predicts pain perception in women. *Pain* 2000;88:61–68. [PubMed: 11098100]
4. al Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 2000;119:1276–1285. [PubMed: 11054385]
5. Andersen S, Worm-Pedersen J. The prevalence of persistent pain in a Danish population. *Pain* 1987;S332.
6. Andersson HI. The epidemiology of chronic pain in a Swedish rural area. *Qual Life Res* 1994;3:s19–s26. [PubMed: 7866366]
7. Apley J, Naish N. Recurrent abdominal pains: a field study of 1,000 school children. *Arch Dis Child* 1958;33:165–170. [PubMed: 13534750]
8. Baber KF, Anderson J, Puzanovova M, Walker LS. Rome II versus Rome III classification of functional gastrointestinal disorders in pediatric chronic abdominal pain. *J Pediatr Gastroenterol Nutr* 2008;47:299–302. [PubMed: 18728525]
9. Borge A, Nordhagen R, Moe B, Botten B, Bakkevig L. Prevalence and persistence of stomach ache and headache among children. Follow-up of a cohort of Norwegian children from 4 to 10 years of age. *Acta Paediatr* 1994;83:433–437. [PubMed: 8025405]
10. Bouin M, Meunier P, Riberdy-Poitras M, Poitras P. Pain hypersensitivity in patients with functional gastrointestinal disorders: a gastrointestinal-specific defect or a general systemic condition? *Dig Dis Sci* 2001;46:2542–2548. [PubMed: 11713967]
11. Bragdon EE, Light KC, Costello NL, Sigurdsson A, Bunting S, Bhalang K, Maixner W. Group differences in pain modulation: pain-free women compared to pain-free men and to women with TMD. *Pain* 2002;96:227–237. [PubMed: 11972994]
12. Brody S, Angrilli A, Weiss U, Birbaumer N, Mini A, Veit R, Rau H. Somatosensory evoked potentials during baroreceptor stimulation in chronic low back pain patients and normal controls. *Int J Psychophys* 1997;25:201–210.
13. Bruehl S, Carlson CR, McCubbin JA. The relationship between pain sensitivity and blood pressure in normotensives. *Pain* 1992;48:463–467. [PubMed: 1594268]
14. Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neurosci Biobehav Rev* 2004;28:395–414. [PubMed: 15341037]
15. Bruehl S, Chung OY, Diedrich L, Diedrich A, Robertson D. The relationship between resting blood pressure and acute pain sensitivity: effects of chronic pain and alpha-2 adrenergic blockade. *J Behav Med* 2008;31:71–80. [PubMed: 17940860]
16. Bruehl S, Chung OY, Jirjis JN, Biridepalli S. Prevalence of clinical hypertension in chronic pain patients compared to non-pain general medical patients. *Clin J Pain* 2005;21:147–153. [PubMed: 15722808]
17. Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: The effects of opioid blockade. *Pain* 2002;100:191–201. [PubMed: 12435472]

18. Bruehl S, France CR, France J, Harju A, al'Absi M. How accurate are parental chronic pain histories provided by offspring? *Pain* 2005;115:390–397. [PubMed: 15911166]
19. Bruehl S, McCubbin JA, Harden RN. Theoretical review: altered pain regulatory systems in chronic pain. *Neurosci Biobehav Rev* 1999;23:877–890. [PubMed: 10541062]
20. Burns JW, Bruehl S, Chung OY, Magid E, Chont M, Goodlad JK, Gilliam W, Matsuura J, Somar K. Endogenous opioids may buffer effects of anger arousal on sensitivity to subsequent pain. *Pain*. 2009 Aug 12; [Epub ahead of print] PMID: 19682793.
21. Campbell TS, Ditto B, Séguin JR, Assaad JM, Pihl RO, Nagin D, Tremblay RE. A longitudinal study of pain sensitivity and blood pressure in adolescent boys: results from a 5-year follow-up. *Health Psychol* 2002;21:594–600. [PubMed: 12433012]
22. Campbell CM, France CR, Robinson ME, Logan HL, Geffken GR, Fillingim RB. Ethnic differences in diffuse noxious inhibitory controls. *J Pain* 2008;9:759–766. [PubMed: 18482870]
23. Campo JV, Bridge J, Ehmann M, Altman S, Lucas A, Birmaher B, Di Lorenzo C, Iyengar S, Brent DA. Recurrent abdominal pain, anxiety, and depression in primary care. *Pediatrics* 2004;113:817–824. [PubMed: 15060233]
24. Chung OY, Bruehl S, Diedrich L, Diedrich A. The impact of blood pressure and baroreflex sensitivity on wind-up. *Anesth Analg* 2008;107:1018–1025. [PubMed: 18713923]
25. Chung OY, Bruehl S, Diedrich L, Diedrich A, Chont M, Robertson D. Baroreflex sensitivity associated hypoalgesia in healthy states is altered by chronic pain. *Pain* 2008;138:87–97. [PubMed: 18164819]
26. Di Lorenzo C, Youssef N, Sigurdsson, Scharff L, Griffiths J, Wald A. Visceral hyperalgesia in children with functional abdominal pain. *J Pediatr* 2001;139:838–843. [PubMed: 11743510]
27. Ditto B, Séguin JR, Boulerice B, Pihl RO, Tremblay RE. Risk for hypertension and pain sensitivity in adolescent boys. *Health Psychol* 1998;17:249–254. [PubMed: 9619474]
28. Drossman, DA.; Rome, III. The functional gastrointestinal disorders. 3rd edition. McLean VA: Degnon Associates; 2006.
29. Ducher M, Fauvel JP, Cerutti C. Risk profile in hypertension genesis: a five-year follow-up study. *Am J Hyper* 2006;19:775–780.
30. Dufton LM, Dunn MJ, Compas BE. Anxiety and somatic complaints in children with recurrent abdominal pain and anxiety disorders. *J Ped Psychol* 2009;34:176–186.
31. Dufton LM, Konik B, Colletti R, Stanger C, Boyer M, Morrow S, Compas BE. Effects of stress on pain threshold and tolerance in children with recurrent abdominal pain. *Pain* 2008;136:38–43. [PubMed: 17716818]
32. Edwards RR, Fillingim RB. Ethnic differences in thermal pain responses. *Psychosom Med* 1999;61:346–354. [PubMed: 10367615]
33. Edwards RR, Fillingim RB. Age-associated differences in responses to noxious stimuli. *J Gerontol A Biol Sci Med Sci* 2001;56:M18–M185.
34. Edwards L, McIntyre D, Carroll D, Ring C, Martin U. The human nociceptive flexion reflex threshold is higher during systole than diastole. *Psychophysiology* 2002;39:678–681. [PubMed: 12236336]
35. Fillingim RB, Edwards RR. Is self-reported childhood abuse history associated with pain perception among healthy young men and women? *Clin J Pain* 2005;21:387–397. [PubMed: 16093744]
36. Fillingim RB, Maixner W. The influence of resting blood pressure and gender on pain responses. *Psychosom Med* 1996;58:326–332. [PubMed: 8827795]
37. France CR, Taddio A, Shah VS, Pagé MG, Katz J. Maternal family history of hypertension attenuates neonatal pain response. *Pain* 2009;142:189–193. [PubMed: 19157710]
38. Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, Porta A, Pace F, Malliani A, Sarzi-Puttini P. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *J Rheumatol* 2005;32:1787–1793. [PubMed: 16142879]
39. Garber J, Zeman JL, Walker LS. Recurrent abdominal pain in children: psychiatric diagnoses and maternal psychopathology. *J Am Acad Child Adol Psychiatry* 1990;29:648–656.
40. Ghione S. Hypertension-associated hypalgesia: Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. *Hypertension* 1996;28:494–504. [PubMed: 8794839]

41. Girdler SS, Koo-Loeb J, Pedersen CA, Brown HJ, Maixner W. Blood pressure-related hypoalgesia in bulimia nervosa. *Psychosom Med* 1998;62:517–523.
42. Gupta V, Sheffield D, Verne GN. Evidence for autonomic dysregulation in the irritable bowel syndrome. *Dig Dis Sci* 2002;47:1716–1722. [PubMed: 12184520]
43. Hotopf M, Carr S, Mayou R, Wadsworth M, Wessely S. Why do children have chronic abdominal pain and what happens to them when they grow up? Population based cohort study. *BMJ* 1998;316:1196–1200. [PubMed: 9552994]
44. Hyams J, Burke G, Davis P, Rzepski B, Andrulonis P. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. *J Pediatr* 1996;129:220–226. [PubMed: 8765619]
45. Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. *Pain* 2009;141:191–209. [PubMed: 19155134]
46. Langer SL, Romano JM, Levy RL, Walker LS, Whitehead WE. Catastrophizing and parental response to child symptom complaints. *Child Health Care* 2009;38:1–16.
47. Levy RL, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, Christie D. Increased somatic complaints and health care utilization in children: Effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterology* 2004;99:1–10.
48. Lewkowski MD, Young SN, Ghosh S, Ditto B. Effects of opioid blockade on the modulation of pain and mood by sweet taste and blood pressure in young adults. *Pain* 2008;135:75–81. [PubMed: 17560720]
49. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. *Psychosom Med* 1997;59:503–511. [PubMed: 9316183]
50. McCubbin JA, Bruehl S. Do endogenous opioids mediate the relationship between blood pressure and pain sensitivity in normotensives? *Pain* 1994;57:63–67. [PubMed: 8065798]
51. Mulvaney S, Lambert W, Garber J, Walker LS. Trajectories of symptoms and impairment for pediatric patients with functional abdominal pain: A 5-year longitudinal study. *J Am Acad Child Adolesc Psychiatry* 2006;45:737–744. [PubMed: 16721324]
52. Page GD, France CR. Objective evidence of decreased pain perception in normotensives at risk for hypertension. *Pain* 1997;73:173–180. [PubMed: 9415503]
53. Price DD, Zhou Q, Moshiree B, Robinson ME, Verne GN. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. *J Pain* 2006;7:529–535. [PubMed: 16885007]
54. Randich A, Maixner W. Interactions between cardiovascular and pain regulatory systems. *Neurosci Biobeh Rev* 1984;8:343–367.
55. Saps M, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C. A prospective school-based study of abdominal pain and other common somatic complaints in children. *J Pediatr* 2009;154:322–326. [PubMed: 19038403]
56. Shulman RJ, Eakin MN, Czyzewski DI, Jarrett M, Ching-Nan O. Increased gastrointestinal permeability and gut inflammation in children with functional abdominal pain and irritable bowel syndrome. *J Pediatr* 2008;153:646–650. [PubMed: 18538790]
57. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *J Neurosci* 2006;26:5777–5785. [PubMed: 16723535]
58. Song GH, Venkatraman V, Ho KY, Chee MW, Yeoh KG, Wilder-Smith CH. Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls. *Pain* 2006;126:79–90. [PubMed: 16846694]
59. Straneva PA, Maixner W, Light KC, Pedersen CA, Costello NL, Girdler SS. Menstrual cycle, beta-endorphins, and pain sensitivity in premenstrual dysphoric disorder. *Health Psychol* 2002;21:358–367. [PubMed: 12090678]
60. Subcommittee of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Chronic abdominal pain in children: A technical review. *J Ped Gastroent Nutrit* 2005;40:249–254.
61. Thomsen AH, Compas BBE, Colletti RB, Stanger C, Boyer MC, Konik BS. Parent reports of coping and stress responses in children with recurrent abdominal pain. *J Ped Psychol* 2002;27:215–226.

62. Van Ginkel R, Voskuijl WP, Benninga MA, Taminiau JA, Boeckxstaens GE. Alterations in rectal sensitivity and motility in childhood irritable bowel syndrome. *Gastroenterology* 2001;12:31–38. [PubMed: 11208711]
63. Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, Price DD. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. *Pain* 2003;103:99–110. [PubMed: 12749964]
64. Verne GN, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. *Pain* 2001;93:7–14. [PubMed: 11406333]
65. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain* 2005;113:331–339. [PubMed: 15661441]
66. Walker LS, Baber KF, Garber J, Smith CA. A typology of pain coping strategies in pediatric patients with chronic abdominal pain. *Pain* 2008;137:266–275. [PubMed: 17928144]
67. Walker LS, Claar RL, Garber J. Social consequences of children's pain: When do they encourage symptom maintenance? *J Ped Psychol* 2002;27:689–698.
68. Walker LS, Guite JW, Duke M, Barnard JA, Greene JW. Recurrent abdominal pain: a potential precursor of irritable bowel syndrome in adolescents and young adults. *J Pediatr* 1998;132:1010–1015. [PubMed: 9627595]
69. Walker LS, Lipani TA, Greene JW, Caines K, Stutts J, Polk DB, Caplan A, Rasquin-Weber A. Recurrent abdominal pain: symptom subtypes based on the Rome II criteria for pediatric functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2004;38:187–191. [PubMed: 14734882]
70. Walker LS, Smith CA, Garber J, Claar RL. Testing a model of pain appraisal and coping in children with chronic abdominal pain. *Health Psychol* 2005;24:364–374. [PubMed: 16045372]
71. Walker LS, Smith CA, Garber J, Van Slyke DA, Claar RL. The relation of daily stressors to somatic and emotional symptoms in children with recurrent abdominal pain. *J Consult Clin Psychol* 2001;69:85–91. [PubMed: 11302281]
72. Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: impact on symptom complaints by children with and without chronic functional abdominal pain. *Pain* 2006;122:43–52. [PubMed: 16495006]
73. Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World J Gastroenterol* 2007;13:3699–3704. [PubMed: 17659729]

Figure 1.

Effects of resting SBP on thermal pain threshold across participant types. SBP values plotted are hypothetical values representing one standard deviation (SD) below and above the sample mean.

Figure 2.

Effects of resting SBP on thermal pain tolerance across participant types. SBP values plotted are hypothetical values representing one standard deviation (SD) below and above the sample mean.

Table 1

Participant Characteristics.

Variable	Participant Type	
	Healthy (<i>n</i> =55)	FAP (<i>n</i> = 94)
Age (years) ***	17.1±0.35	21.0±0.45
Gender (% Female)	65.5	62.1
Race (%):		
White	94.5	87.4
African-American	0.0	7.4
Mixed	5.5	5.2
Ethnicity (%):		
Non-Hispanic	98.0	97.8
Overall Pain Intensity in Past 4 Weeks (0–5) *	2.0±0.14	2.4±0.13
BMI ***	22.6±0.52	26.7±0.77
Resting SBP *	108.9±1.16	113.4±1.23
Resting DBP *	60.3±0.82	62.9±0.77
Thermal Pain Threshold (°C)	41.4±0.45	42.0±0.33
Thermal Pain Tolerance (°C)	46.7±0.26	46.9±0.19

*
p<.05***
p<.001

Note: All means are presented as mean ± SE. FAP = history of chronic functional abdominal pain, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table 2

Zero-order correlations between resting blood pressure and acute pain outcomes by participant type.

Pain Outcome	Participant Type			
	Healthy		FAP	
	SBP	DBP	SBP	DBP
Thermal Pain Threshold	0.48***	0.02	0.11	-0.02
Thermal Pain Tolerance	0.35**	0.02	0.12	-0.14

**
p<.01***
p<.001