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Effects of stress on pain threshold and tolerance in children with recurrent abdominal pain

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Abstract

Models of stress-induced hyperalgesia state that exposure to stress can exaggerate subsequent pain experiences. Studies using both animal and human subjects have shown evidence for hyperalgesia as a function of stress [e.g., Jorum E. Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. Pain 1988;32:341–48; Peckerman A, Hurwitz BE, Saab PG, Llabre MM, McCabe PM, Schneiderman N. Stimulus dimensions of the cold pressor test and the associated patterns of cardiovascular response. Psychophysiology 1994;31:282–90; Gameiro et al. Nociception and anxiety-like behavior in rats submitted to different periods of restraint stress. Physiol. Behav. 2006;87:643–49; Lucas et al. Visceral pain and public speaking stress: neuroendocrine and immune cell responses in healthy subjects. Brain Behav. Immun. 2006;20:49–56]. However, the role of stress in pediatric pain is not well understood. This study examined stress reactivity and pain tolerance and sensitivity in a population of children with Recurrent abdominal pain (RAP). Forty-nine children meeting criteria for RAP (28 female; mean age 13 years; range 9–17 years) were randomly assigned to either a condition in which they completed an experimental stressor paradigm (stress interview, serial subtraction task) followed by a pain task (cold pressor) or a condition in which they received the pain task prior to the stress tasks. Children who underwent the stress tasks before the pain task exhibited lower levels of pain tolerance than those who received the pain task first ($p < .01$); no differences were found between the two groups in pain threshold or pain intensity ratings. Further, pain tolerance was not related to individual differences in physiological reactivity (heart rate change) to the stressor. The present research demonstrates the first evidence of the occurrence of stress-induced hyperalgesia in a pediatric pain population.

Keywords: Recurrent abdominal pain; Children; Stress reactivity; Cold pressor; Heart rate

1. Introduction

Recurrent abdominal pain (RAP) is the most common type of recurrent pediatric pain, affecting 8–25% of school-aged children (McGrath, 1990; Colletti, 1998). To meet criteria for RAP, pain must occur at least once a month during a period of three months and be associated with significant functional impairment (Apley, 1975). RAP is associated with significant adverse effects on children's functioning, including repeated school problems and absences (Robinson et al., 1990) and frequent pediatrician visits (Starfield et al., 1984). In spite of the prevalence of the condition and its burden on the healthcare system, the mechanisms underlying RAP remain relatively poorly understood.

One promising area of investigation is the role of stress in the course of this disorder (Compas and Boyer, 2001). A plausible mechanism for the link between stress

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and pain may be through increased physiological arousal in response to stress. Evidence from human and rodent studies suggests that exposure to chronic stress and reactivity to stress may increase pain sensitivity and reduce pain threshold (e.g., Geerse et al., 2006; Imbe et al., 2006). However, research on physiological reactivity to stress in children with RAP has produced mixed results (e.g., Rubin et al., 1967; Apley et al., 1971; Battistella et al., 1992). For example, Di Lorenzo et al. (1998) found evidence of both rectal and gastric hyperalgesia in children with RAP. In contrast, Feuerstien et al. (1982) found no differences in autonomic, somatic, subjective, and behavioral reactivity of children with RAP during the cold pressor pain test as compared to controls.

Caceres and Burns (1997) note that one challenge in interpreting results from studies examining pain responses is that stress and pain stimuli are often presented in the same task, causing difficulties in distinguishing physiological reactivity and responses to pain. If physiological reactivity and pain sensitivity are measured in response to the same task, then these two processes are confounded. To address this problem, Caceres and Burns (1997) randomized healthy adults to a stressful task (mental arithmetic) before or after the cold pressor task. Participants exposed to stress before the cold pressor reported lower pain tolerance and decreased pain threshold and there was an interaction of stress exposure by physiological reactivity in predicting pain responses. Only those high in physiological reactivity showed changes in sensitivity to pain, suggesting that individual differences in physiological arousal to a stressor explain a portion of the variability in pain responses. These findings suggest the importance of examining stress-induced responses to pain in children with RAP.

In this study, we examined pain threshold, tolerance, and intensity as a function of exposure to stress in children with RAP. We predicted that children presented with a stressor before a pain task would show lower pain threshold and tolerance, and increased pain ratings as compared to those not exposed to stress prior to the painful stimulus. Consistent with Caceres and Burns (1997), we also expected to find decreased pain threshold and tolerance and increased pain sensitivity in high-reactive participants within the stress–pain group.

2. Methods

2.1. Participants

Fifty-one children and adolescents with RAP participated in the study. Two participants were removed from all analyses due to deviations from the experimental protocol. The remaining sample of 49 participants (28 female; mean age: 13 years, range 9–7 years) was used in all statistical analyses. Participants were recruited through the office of a pediatric gastroenterologist serving patients in northeastern New England and rural northern New York State. The Physician Pain Questionnaire, based on a measure designed by Walker and Greene (1989), was completed and used to verify that all participants met Apley's (1975) criteria for RAP (i.e., three or more episodes of pain within a three-month period accompanied by functional impairment).

2.2. Procedures

Pairs of research assistants, at least one of whom was female, conducted the protocol with each participant. During the consenting process, participants were informed that they would undergo a brief interview about how they cope with stress (Social Competence Interview), a math task (serial subtraction), and a cold-water task (cold pressor). Thus, participants were fully informed about the study protocol before undergoing any of the tasks. Upon arrival, three electrodes used to measure heart rate were placed on the lower left leg, the upper right shoulder, and the upper left shoulder of each participant. Physiological recording instruments were placed on participants by a same sex experimenter and heart rate was recorded continuously throughout the experimental session.

After a 5-minute baseline, subjects in the stress–pain group were presented with two stressful tasks: the Social Competence Interview and a serial subtraction task, lasting a combined total of approximately 10 min. First, the Social Competence Interview (SCI; Ewart and Kolodner, 1991) was administered by a trained experimenter. Participants were asked to describe an interpersonal source of emotional distress and encouraged to discuss their recall of the event and the emotions that they experienced at the time of the event for approximately 8 min. Throughout the discussion of a stressful situation, the experimenter asked questions to promote detailed recall of the event. Following completion of the SCI, a serial subtraction task was administered in which subjects were asked to subtract from 400 by 7 as quickly as possible for 2 min. When an incorrect answer was given, they were told that they had failed and instructed to start the task over from 400. Both the SCI and serial subtraction have been shown to be effective methods of inducing autonomic reactivity (Ewart and Kolodner, 1991; Caceres and Burns, 1997; Hermann and Blanchard, 1998). After completion of the stress tasks, participants in the stress–pain group then underwent the Cold Pressor Test. Participants assigned to the pain–stress condition were administered the Cold Pressor Test before the stress tasks (see Table 1).

2.3. Cold Pressor Test

The Cold Pressor Test (CPT) is a widely used experimental paradigm in stress and pain research (e.g., Zeltzer et al., 1989). It provides an opportunity to study reactions to pain within a controlled setting. Participants are instructed to immerse their hand and arm to a level just above the elbow in water mixed with ice maintained at a constant cold temperature. With the possible exception of patients with advanced coronary heart disease, this procedure, although somewhat painful, can be used without any adverse effects. Since the most frequently

Table 1
Order of procedures

	Baseline	Phase 1	Phase 2
Stress–pain condition	Reading magazines 5 min	Stress task Stress interview approx. 8 min Serial subtraction 2 min	Cold pressor pain task Threshold 40-s Pain report Tolerance
Pain–stress condition	Reading magazines 5 min	Cold pressor pain task Threshold 40-s Pain report Tolerance	Stress task Stress interview approx. 14 min Serial subtraction 2 min

tested outcome using the CPT is duration of pain tolerance, it is particularly well suited for the purposes of the present research.

In the present study, the cold pressor apparatus consisted of an insulated cooler filled with 32 quarts of chilled, circulating water. The water circulated (via a submerged water pump) at a sustained temperature of 5 °C (plus or minus 1°). Data obtained from pilot participants in our laboratory showed that water at a temperature of 5 °C produces substantial variance in pain sensitivity and tolerance ratings in children. A 4-min exposure time limit was used during the CPT. Previous studies have demonstrated that after 4 min the CPT ceases to provide any relevant information, as pain responses become confounded with sensations of numbness (Zeltzer et al., 1989). Previous studies have also shown that children who tolerate 4 min of exposure do not voluntarily discontinue their exposure to the CPT water until instructed (Zeltzer et al., 1989).

When participants were introduced to the CPT apparatus, each was fitted to an adjustable arm hammock to assure that the proportional surface area of exposed arm was consistent between participants (20arm in the cold water, settle their arm in the hammock, and remain as still as possible during the experiment. The instruction to cope (i.e., "do or think about whatever is needed to be able to keep your arm in the water for as long as you can.") was then given (this instruction has been shown to have no effect on laboratory pain responses; Bruenl et al., 1993). Although they were instructed to cope, participants were told that they could remove their arms at any time if it became too uncomfortable to keep their arms in the water. Prior to the experiment, a Visual Analogue Scale (VAS) was explained to the participants (in an age-appropriate format), instructing the participants to report how uncomfortable the cold water was to them. The VAS is a vertical scale, in the shape of a ruler, graduated by increments with a sliding horizontal marker used to represent a continuum from "no pain at all" to "the worst pain imaginable." The VAS has been established as a valid and reliable measure of pain intensity in children and has been shown to correlate positively with parent and physician VAS measures and with independent observations of children's pain behaviors (Zeltzer et al., 1989). Unlike other sources of data, this procedure measures a child's personal experience of pain intensity to determine how participants differ in subjective pain experience. Each subject was asked to report his/her level of pain after 40 s using the VAS. Finally, one behavioral measure of pain responses was used: pain tolerance (in seconds) as indicated by withdrawal of arm from cold pressor.

2.4. Measures

2.4.1. Stress reactivity

Heart rate (HR) change has been shown to be a reliable measure of physiological reactivity to stress tasks (Llabre et al., 1991). In the present study, residualized change scores from Baseline, Task 1 (stress tasks or cold pressor) and Task 2 (stress tasks or cold pressor) were compared. This method incorporates initial baseline differences in heart rate and also allows for differences in direction of heart rate change to be analyzed. Using residualized change scores accounts for potential differences in baseline levels of heart rate.

HR (number of beats per minute) was recorded by electrocardiogram readings using the Biopac system (Biopac Systems, Inc.). HR data were collected continuously throughout the experimental session and were stored in data files on the computer for later scoring. Residualized change scores for HR were calculated in both groups (stress tasks first or CPT first). These residual scores therefore represent change from exposure to the stress tasks before the CPT (in group 1) or from first exposure to the CPT to the stress tasks (in group 2). The use of residualized change scores controls initial (baseline) levels of HR in assessing change.

Because of the wide variability in patterns of heart rate change that was found, additional exploratory analyses examined percent change scores. These scores were derived by subtracting baseline HR scores from Task 1 HR scores, dividing the difference by the baseline scores, and multiplying by 100. Mean beats per minute from the final 2 min of the stress task were used for these calculations, as this segment should be highest following the two stress tasks. The mean beats per minute from the entire pain task were used for those comparisons.

2.5. Overview of data analyses

The following hypotheses were tested. (1) Order of the stress and pain tasks will result in lower pain threshold and tolerance, and higher pain intensity ratings when the stress task was preceded by the pain task as compared with the condition in which the pain task was followed by the stress task. (2) Stress reactivity (as measured by residualized change in heart rate) will interact with exposure to the stress tasks in predicting pain responses (i.e., the interaction of order of stress task first vs. cold pressor first and the residualized change scores).

3. Results

3.1. Identification of outliers

Distributions of the dependent variables were examined for outlying scores. All scores falling greater than two standard deviations from the mean of a specific variable were defined as outliers. Subsequently all scores defined as outliers were removed. No participants were identified as multivariate outliers.

One score was identified as an outlier and removed from the *pain intensity* rating. Because pain intensity ratings were collected after 40 s, these ratings were obtained only for those participants who remained in the cold pressor for at least 40 s; of the 49 participants, 22 removed their arm before 40 s. After removing one outlier, a total of 26 participants' data were included in analyses of the pain intensity rating ($M = 6.4$, $SD = 1.98$). *Pain tolerance* was calculated by total time, in seconds, that the participant left her/his arm in the cold pressor. Three cases were excluded as outliers leaving 46 participants to be included in following analyses ($M = 48.9$ s, $SD = 28.90$). *Pain threshold* was calculated by recording the number of seconds that participants held their arms in the water until they indicated that they first experienced pain. Pain threshold data were not collected for six of the participants because participants did not indicate that they experienced pain; these subjects subsequently reported that they forgot the instruction to indicate when they experienced pain. An additional four participants were excluded as outliers ($n = 39$, $M = 13.8$ s, $SD = 7.23$).

Heart rate data were collected for all 49 participants. Movement artifacts required that several seconds of data be removed from a majority of the data files. Movement artifacts or mechanical complications with the electrocardiogram resulted in five cases that were unable to be used in the analyses.

3.2. Preliminary analyses

Twenty-four participants were randomly assigned to the stress–pain condition and 25 participants to the pain–stress condition. The two groups did not significantly differ in age (stress–pain, $M = 13.4$, $SD = 2.6$; pain–stress, $M = 12.1$, $SD = 2.7$), gender (the stress–pain condition included 57% girls and 43% boys, and the pain–stress condition included 52% girls and 48% boys), or socioeconomic status (assessed using Hollingshead Occupational Scores) (stress–pain, $M = 61.09$, $SD = 20.34$; pain–stress, $M = 59.80$, $SD = 20.44$, or that of technicians, semi-professionals and small business owners).

Pearson correlations were used to examine the bivariate relations among the dependent and independent variables. Variables included in the correlation matrix were age, pain tolerance, pain threshold, physiological reactivity (i.e., heart rate change), and pain intensity rating taken after 40 s in the cold pressor (see Table 2). Significant associations included a negative correlation ($r = -.64$, $p < .01$) between participants' pain rating at 40 s and pain tolerance scores. This correlation represents a test of the internal validity of these two dependent variables suggesting that the more severe participants rated their pain during the cold pressor pain task, the less time they left their arms in the cold pressor. Pain threshold was not significantly correlated with pain tolerance or pain ratings. Physiological reactivity (change in heart rate) was not significantly correlated with any of the dependent variables (pain tolerance, pain rating, and pain sensitivity).

Table 2
Correlations of pain responses with reactivity and age for total sample

	Pain intensity	Pain tolerance	Age
Pain intensity	–	–	–
Pain tolerance	−.65 **	–	–
Age	.01	.33 *	–

* $p < .05$.
** $p < .01$.

3.3. Hypothesis 1: Between-group tests for order of stress and pain tasks

To test for a main effect for task order, three one-way analyses of variance (ANOVA) were conducted.[1] It was hypothesized that the stress–pain condition would exhibit lower pain threshold and pain tolerance, and higher pain intensity ratings than the pain–stress condition.

Results of the ANOVA indicated a main effect of group on pain tolerance, $F(1, 43) = 3.89$, $p < .05$. Consistent with the hypothesis, participants in the stress–pain condition removed their arms from the cold pressor significantly earlier ($M = 40.4$ s) than did those in the pain–stress condition ($M = 56.7$ s). There were no significant differences between the two conditions on pain intensity ratings or pain threshold.

3.4. Hypothesis 2: Individual differences in reactivity

To test for the effects on stress reactivity on pain responses, the interaction of order (stress tasks followed by cold pressor vs. cold pressor followed by stress tasks) and residualized scores for heart rate from baseline to

[1] Because age was significantly and positively correlated with participants' pain tolerance scores and because there was a trend towards an age difference between conditions, analyses of covariance were conducted using age as a covariate. The results of the ANCOVAs were the same as found with the ANOVAs; a main effect of group on pain tolerance was found, $F(1,43) = 8.34$, $p < .01$. Additionally, age was a significant covariate with tolerance as the dependent variable, $F(1,43) = 9.99$, $p < .01$.

the stress tasks was tested in linear multiple regression analyses predicting pain tolerance, pain intensity, and pain threshold. Regression analyses indicated that the main effect for residualized heart rate change score and the interaction of change with task order were non-significant. Thus, it does not appear that the effects of the stress task on pain tolerance, pain intensity, or pain threshold were moderated by stress reactivity as measured by change in heart rate.

Unexpectedly, examination of the distributions of the heart rate change indicated that only a portion of the participants in the stress–pain condition exhibited the anticipated increase in heart rate. Approximately half of the participants in the stress–pain condition exhibited the expected increase in HR and approximately half exhibited a decrease in heart rate. The median percent HR change for the group was 0.36, with 48% showing increases in HR ($n = 11$, $M = 6.57$, SD = 10.95) and 52% showing decreases in HR ($n = 12$, $M = -4.34$, SD = 4.13).

4. Discussion

Children with RAP represent a population in need of focused research to investigate psychological and biological processes related to recurrent pain. Research has demonstrated a relationship between daily stressors and somatic symptoms, including pain, in this population (Walker et al., 1991). However, the relationship between stress and pain has not been adequately studied in children with RAP under controlled laboratory conditions. Although evidence of stress-induced changes in pain threshold and tolerance has been reported in animal research and more recently in human studies (e.g., Caceres and Burns, 1997), laboratory findings of this phenomenon with children with RAP have been mixed. The present research provided the first experimental evidence of decreased pain tolerance in response to stress in children with RAP. Specifically, we found that participants who experienced two mild stressors (the Social Competence Interview and a serial subtraction task) before a pain task (the cold pressor) showed decreased pain tolerance (i.e., removed their arms from the cold pressor more quickly) than participants who were not exposed to the stressors prior to the pain task.

The present study represents the first experimental laboratory findings that demonstrate a link between stress and pain experience in children and adolescents with RAP. These results complement findings of Walker et al. (1991), who demonstrated that daily diary records of stress in children with RAP were predictive of abdominal complaints. Combined with results from Walker et al. (1991), these findings suggest that stress may play a role in the ways that children with RAP experience and respond to pain.

Although results from this study provide the first evidence for stress-induced decreased pain tolerance in children with RAP, differences on pain threshold and pain intensity ratings were not found as a function of exposure to stress. A potential source of this discrepancy may be because pain threshold and pain sensitivity scores were not collected for all participants. A portion of the participants did not tolerate the cold water the minimum length of time (40 s) required to give an intensity rating. Thus, future studies using this paradigm should consider reducing the time at which this measurement of pain sensitivity is taken or simply measure pain sensitivity after the cold pressor task. In addition, several participants did not provide pain threshold data because they reported that they forgot this aspect of the instructions and failed to supply this rating during the task. The reduction in sample size, particularly a reduction in those who provided information about pain intensity, may have reduced power to levels that would make it difficult to detect effects on these variables. Finally, pain tolerance is a behavioral measure and as such may be a different indicator of participants' response to the cold pressor than self-reported measures of pain sensitivity.

Physiological reactivity to stress, as measured by residualized heart rate change, was not associated with pain threshold in participants; that is, there was not an interaction between the order of the tasks and changes in heart rate across the two tasks. Thus, Caceres and Burns (1997) finding that stress reactivity was a moderator of pain responses to stress in adults was not replicated in this sample of children with RAP. Several differences between the present study and the Caceres and Burns' study may account for this difference. Caceres and Burns used an adult sample without a history of pain and assessed stress reactivity by examining changes in mean arterial pressure. Additionally, individual differences between participants, such as an increase in heart rate before the stress tasks that left little room to increase once the stress tasks commenced, may have confounded the results. Thus, further research is needed to clarify the possible role of physiological reactivity to stress as a moderator of the effects of stress on pain responses in children with RAP.

Future research investigating differences between children with chronic pain, particularly RAP and non-pain samples, should consider the potential of stress as a precipitant of pain episodes. Previous research investigating differences between children with RAP and no-pain controls has produced mixed results (Feuerstien et al., 1982; Battistella et al., 1992; Alfven, 1993; Di Lorenzo et al., 1998). However, the present findings suggest that differences in the magnitude of stress-induced hyperalgesia between children with RAP and non-pain children would be easier to detect if the groups are primed with a stressor.

There are limitations to the present study that will be important to address in future research. First, this study focused on within group differences among children with RAP and as a result did not include a comparison sample

of children without a history of chronic or recurrent pain. Future research is needed to determine if the pattern of responses to stress is unique to children with RAP. Second, the lack of ethnic or racial diversity in the study sample creates a diminished ability to generalize findings. Third, a peripheral pain paradigm was used to examine pain responses in a population that is characterized by recurrent visceral pain symptoms. The use of a peripheral pain paradigm might not accurately simulate the true pain responses encountered by children with RAP. However, several studies examining pain sensitivity in adults with irritable bowel syndrome (IBS) have found both visceral and cutaneous hyperalgesia (e.g., Verne et al., 2001). That is, IBS patients demonstrated hyperalgesia not only in response to rectal distension (visceral pain), but also in response to nociceptive heat stimulation of the foot and hand. Therefore, like IBS patients, children with RAP may also have widespread pattern of referred cutaneous hyperalgesia. The use of an experimental stressor may not appropriately simulate a real world stressful situation, thus impairing the ability to infer conclusions of these results. In addition, physiological reactivity analyzed as HR-only does not allow for the analysis of other important variables such as respiration and mean arterial pressure.

In spite of these limitations, the results of this study suggest that the use of laboratory paradigms may be a productive avenue for investigating the relation between stress and pain in children with RAP. It appears that stress may decrease pain tolerance in children with RAP and that a subgroup of this population may react to stress with increased physiological arousal which in turn is related to increased sensitivity to pain. Most importantly, these findings suggest that stress may play a role in precipitating pain episodes in children with RAP.

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