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Interacting influences of gender and chronic pain status on parasympathetically-mediated heart rate variability in adolescents and young adults

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1. Introduction

Considerable research links chronic pain to autonomic nervous system (ANS) dysfunction, specifically low heart rate variability (HRV) mediated by reduced parasympathetic cardiac activity [9, 25, 35, 46]. The ANS is the primary pathway in brain-gut communication [21, 45], making it particularly relevant to gastrointestinal disorders, such as irritable bowel syndrome (IBS), characterized by functional abdominal pain (FAP). FAP often begins in childhood and may persist into adulthood [18, 26, 31, 33, 52].

HRV – fluctuation in the interval between consecutive heartbeats – is produced by the interplay between sympathetic (activating) and parasympathetic (inhibitory) influences on the heart. Higher HRV reflects greater autonomic flexibility and more regulated emotional responding to threat; lower HRV reflects autonomic rigidity and heightened emotional reactivity to threat [2, 16, 29, 40, 41, 55]. A recent meta-analysis [24] concluded that the pathogenesis of IBS, the most common FAP condition, may involve low HRV and parasympathetic withdrawal associated with relatively unchecked predominance of sympathetic activity. Evidence to date, however, is based on studies of females.

Two studies of women with FAP found that lower HRV was associated with greater pain severity. Defining severity based on pain duration and intensity, Cain et al [6] found lower HRV in women with more severe IBS. Similarly, Burr, Heitkemper, Jarrett, & Cain [5] reported significantly lower HRV in women with IBS reporting more severe pain. The

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association between HRV and pain severity has not been evaluated in men with FAP. Such research is critical to assess whether sex differences in the relation of ANS function to pain might contribute to the higher incidence of FAP in women.

This study evaluated the relation of sex and pain severity to HRV in adolescents and young adults recruited several years earlier as pediatric patients for a prospective study of the course of FAP [49, 51, 54]. At the follow-up in young adulthood described here, we classified FAP participants into a Pain-Remit group versus a Pain-Persist group based on whether their symptoms were severe enough to meet diagnostic criteria for a pain-related functional gastrointestinal disorder. Youth who were pain-free both at baseline and at follow-up constituted the control group. We expected females with a history of FAP to show lower HRV than female controls and males, and that this difference would be stronger among females with a history of FAP who had persistent pain at follow-up as compared to those with remitted pain at follow-up. Moreover, based on prior literature [24, 46], we hypothesized that spectral analysis of electrocardiogram (ECG) recordings would indicate that the low HRV was largely parasympathetically mediated suggesting deficient parasympathetic braking of the autonomic response to stress.

Because FAP is a stress responsive disorder [7], the relation of pain status and sex to HRV might be most apparent during a stressor. Therefore, we assessed HRV at rest and during exposure to experimentally induced psychosocial stress.

2. Materials and methods

Participants

Participants were older adolescents and young adults (Mean age = 19.46, SD = 3.48, Range: 12–31 years) recruited for a prospective study on the course of FAP. FAP and pain-free control groups were originally recruited and enrolled in studies conducted between 1993 and 2007. The present study presents follow-up evaluations with a subset of these individuals approximately 8 years later.

Baseline psychosocial data collected at the initial pediatric clinical evaluation have been reported previously [49, 51, 54]. At baseline, the FAP group consisted of consecutive new patients, aged 8 to 17 years, evaluated by a pediatric gastroenterology service for abdominal pain of at least 3 month's duration. Patients without evidence of organic disease were eligible for the baseline study. These patients carried diagnoses of irritable bowel syndrome, functional dyspepsia, and non-specific FAP. The Control group consisted of children in the same age range but without abdominal pain who participated in a health survey in local schools during the same time period and subsequently participated in the follow-up study reported here.

The follow-up entailed a comprehensive evaluation of health outcomes (e.g., functional gastrointestinal disorders, chronic pain, psychiatric disorders) reported elsewhere [10, 33, 50, 53] as well as the present laboratory study (for those willing to travel to the laboratory site located at the hospital). FAP and Control participants were eligible for the follow-up evaluation of health outcomes and the laboratory study if they had reached age 12 years or

older, at least 4 years had elapsed since initial evaluation at the pediatric clinic, and they were not pregnant and reported no onset of significant disease (e.g., Crohn's Disease, multiple sclerosis) during the follow-up interval. Of the 491 participants (332 FAP; 159 Controls) who completed health outcome interviews, 382 consented to also participate in the laboratory study presented here. Participants whose laboratory ECG recordings at follow-up indicated arrhythmia (n = 5) or inadequate signal (n = 4) were excluded. Fourteen participants were excluded because of missing data during one or more epochs of ECG recording, one participant was excluded because she was physically too large to be accommodated in our experimental setting, and one participant was not allowed to complete the laboratory stressor activities due to hypertension during baseline. Seven Control participants were excluded because they met symptom criteria for a pain-related functional gastrointestinal disorder at follow-up. The final sample for the laboratory study included 226 previously identified FAP patients and 123 Control participants.

Patient-report measures

We classified FAP participants into a Pain-Remit group versus a Pain-Persist group based on whether their symptoms at follow-up were severe enough to meet diagnostic criteria for a pain-related functional gastrointestinal disorder as assessed by the Rome III Diagnostic Questionnaire for Functional Gastrointestinal Disorders [12]. This measure, administered by a trained interviewer, assesses the symptom criteria for abdominal pain related FGIDs (irritable bowel syndrome, functional dyspepsia, abdominal migraine, functional abdominal pain). Using this assessment, participants were classified as Pain-Persist versus Pain-Remit depending on whether their symptoms at follow-up were severe enough to meet criteria for an FGID with abdominal pain.

Experimental Stressor #1: Social Competence Interview (SCI; [14])

The SCI was designed to measure cardiovascular changes occurring while participants describe a recurring life challenge or problem, re-experience accompanying thoughts and emotions, and identify goals and strategies they have used in a specific instance of the problem. The experimenter introduced the SCI by explaining that its purpose was to determine how people react to personal stress. Each participant was given a deck of six cards listing common sources of stress (e.g., school, work, family, friends, money, neighborhood), asked to sort the cards from most to least stressful, and then interviewed about the problem identified as most stressful. Participants were free to request a different stressor for the interview if they preferred.

During the first 6 to 10 minutes, or the "hot" epoch of the SCI, the interviewer confirmed that the problem selected was a recurring source of emotional distress and asked the participant to describe in detail a specific occasion when the problem occurred, including details of location and setting, who was present, what those involved did and said, their facial expressions, what the participant thought and felt (including bodily sensations), what the participant wanted to say or do, what happened as a result of the situation, and how family, friends, teachers, or others helped or made things worse. The experimenter's goal in this phase was to promote accurate re-experiencing of the moment through use of guided imagery, reflective listening, and empathic remarks.

The final 4 to 6 minutes of the SCI, or "cool" phase, focused on problem solving capabilities. The experimenter asked how the participant would "ideally" like the problem to be resolved (e.g., "Imagine you are a filmmaker and you are making a film about someone like yourself with the same problem. But, there is one very big difference in this film: you can make it end any way you want. How would you make it end for your character?"). Next, the participant was asked what specific actions he/she could take to make that ending happen, and what actions others (e.g., peers) might take in similar circumstances.

The SCI has been documented as a reliable and valid standard laboratory stressor. Cardiovascular responses to the interview match or exceed those typically elicited by stressors such as mental arithmetic, mirror-image tracing, and video games [13]. SCI experimenters for this study attended training sessions conducted by Ewart and colleagues or were trained by an experimenter who had attended those sessions. Audio recordings of the SCI were screened by Ewart and colleagues for consistency in administration and feedback was provided to experimenters.

Experimental Stressor #2: Serial Subtraction Task

Participants were instructed to subtract out loud from 400 by 7's for two minutes [34]. The experimenter told participants to subtract the numbers as quickly as possible without making mistakes. In order to create a sense of urgency, a metronome beeped every three seconds and participants were told to subtract as quick or faster than the beeps. If participants made a mistake, they were told, "That was incorrect. Please go back to 400 and start over."

ANS Measures

Dual-lead ECG was recorded at 1-kHz sampling rate (Biopac Systems, Inc.) throughout the study. R-peak detection in recorded ECG and analysis of R-R intervals and HRV time and frequency variables were performed off-line using a customized MATLAB computer program written by co-author AD (HRV Analyzer, Vanderbilt University Medical Center, Autonomic Dysfunction Center). The program follows guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [37]. Correct identification of the R-peak was visually verified and edited as necessary to remove artifacts.

Beat-to-beat values of R-R intervals were interpolated, low-pass filtered (cutoff 0.5 Hz), and resampled at 4 Hz. Data segments of 300 s were used for spectral analysis. Linear trends were removed and power spectral density was estimated with the FFT-based Welch algorithm using segments of 256 data points with 50% overlapping and Hanning window [38].

The primary dependent variable in the time domain was the standard deviation of R-R intervals (SDRRI), measured in milliseconds. SDRRI reflects the overall variability in the recorded series of inter-beat intervals and served as the measure of heart rate variability for each epoch. SDRRI reflects heart-rate variability from all causes, and thus does not specifically reflect the relative degree of sympathetic versus parasympathetic cardiac input. In addition, we evaluated HR to provide an index of the overall degree of activation that

participants exhibited in response to the laboratory stressors (we expected an increase in HR).

The primary dependent variable for the frequency domain was High Frequency (HF) power, representing a band of the power spectrum that ranges between 0.15 and 0.40 Hz and largely reflects parasympathetic activity [37]. Whereas SDRRI provides a summary of total HRV due to all causes, HF power during an epoch represents an estimate of the variability that is attributable to parasympathetic activity during that epoch.

Procedure

Gastrointestinal symptoms were assessed by telephone interview prior to participants' laboratory visit. The laboratory protocol was conducted for all participants using the same equipment and lighting in the same room with a temperature averaging 74.7° F (SD = 2.6). Participants were instructed to refrain from eating and drinking (other than water) for one hour before their scheduled laboratory appointment. Informed consent was obtained from participants older than age 18; for those under age 18, consent was obtained from parents and assent was obtained from the youth.

Upon their arrival at the laboratory, an experimenter collected measurements of participants' height, weight, and body temperature. Next, participants were seated in a comfortable chair and ECG leads were placed. Participants remained seated throughout the protocol and were asked to minimize bodily movements. The experimental protocol was approximately 26 minutes in duration and consisted of five epochs: (1) baseline; (2) SCI experimental stressor, hot phase; (3) SCI experimental stressor, cool phase; (4) recovery; (5) serial subtraction experimental stressor. ECG was assessed continuously.

For the baseline epoch, participants were instructed to sit with their feet flat on the floor, legs uncrossed, and to remain silent while they watched a slideshow of nature pictures on a computer screen. During this baseline period, resting ECG activity was recorded for 5 minutes. Next, the first experimental stressor – the Social Competence Interview [13] – was administered. The SCI-Hot epoch represented the first phase of the SCI when participants were guided in re-experiencing the stressful event (mean completion time for the epoch = 7.03 minutes, SD = 2.20 minutes). The SCI-Cool epoch represented the second phase when participants were asked to reflect on possible solutions for the identified stressor (mean completion time for the epoch = 4.75 minutes, SD = 1.40 minutes). A 5-minute recovery period followed the SCI-Cool epoch. During this period participants once again sat quietly while watching a slideshow of nature pictures. Finally, participants completed the second experimental stressor – the 2-minute Serial Subtraction Task [34]. (Experimental pain testing and several questionnaires were administered following the Serial Subtraction Task; results are reported elsewhere [53]).

Two female experimenters were present in the room during the protocol and were unaware of participants' health status. Procedures were approved by the Vanderbilt Institutional Review Board.

Statistical analyses

ANS measures were assessed in each epoch of the experiment: Baseline (BL), SCI-Hot, SCI-Cool, Recovery (RC), and Serial Subtraction (SS). Mean values were calculated for each individual for each epoch. SDRRI and HF data were logarithmically transformed to approximate normal distributions, and statistical tests were conducted using transformed variables (observed means are illustrated in the figures for ease of interpretation).

Participants were categorized into six groups based on sex and pain status (Pain-Persist Females [$n = 68$], Pain-Remit Females [$n = 76$], Control Females [$n = 66$], Pain-Persist Males [$n = 28$], Pain-Remit Males [$n = 54$], Control Males [$n = 57$]). To capture our a priori predictions, we partitioned the between-subjects variance using five a priori orthogonal contrasts [30]. The first two contrasts captured our a priori expectation that HRV would be lowest in females with a history of FAP, but especially for those with persistent pain: (1) females with a history of FAP (both Pain-Remit and Pain-Persist) versus Control females and all three male groups combined; (2) Pain-Persist Females vs. Pain-Remit Females. The remaining three contrasts tested for possible differences among the other groups, which we did not expect to differ: (3) Control Females vs. all three male groups combined; (4) Control Males vs. males with a history of FAP (both Pain-Persist and Pain-Remit; (5) Pain-Persist Males vs Pain-Remit Males.

Using the multivariate approach to repeated measures [47], the effect of stress – a within-subjects repeated measure factor – was also analyzed using a priori contrasts. The experimental pain protocol had two non-stress epochs (BL, RC) and three stress epochs (SCI-Hot, SCI-Cool, SS). Among the stress epochs, two (SCI-Hot, SS) were expected to be significantly more stressful than the third (SCI-Cool). We partitioned the within-subjects variance using orthogonal contrasts to test these hypothesized differences. The first contrast pitted the three stress epochs (SCI-Hot, SCI-Cool, SS) against the two non-stress epochs (BL, RC). The remaining contrasts tested for differences between the two non-stress epochs (BL vs. RC) and across the three stress epochs, testing both for differences between the two hot epochs v. the one cool epoch (SCI-Hot and SS vs. SCI-Cool), and for possible differences between the two hot ones; (SCI-Hot vs. SS).

To analyze the data, the sets of between- and within-subjects contrasts were crossed in a mixed-model MANCOVA with both BMI and age as covariates,[1] as both influence HRV [19], although BMI is not usually related to HRV in normal-weight samples [1]. These analyses were conducted separately for the two dependent variables: SDRRI, and HF. In addition, we also conducted this analysis for HR, to test whether the high stress epochs of the experimental protocol were in fact activating, as intended. Analyses were conducted using IBM SPSS version 19.0. Effect sizes are reported as eta squared (η^2) statistics when appropriate. Eta squared can be interpreted as the proportion of variance accounted for in the dependent variable. Guidelines generally suggest interpreting η^2 similar to r^2 (small: 0.01, medium: 0.06, large: 0.14; [15]).

[1]BMI and age were significant covariates for SDRRI and HF. However, they only accounted for small amounts of variance in SDRRI and HF. The patterns of means across groups were not appreciably changed by including the covariates. For heart rate, BMI and age were not significant covariates.

3. Results

Sample characteristics

Table 1 presents demographic characteristics for each group. The Pain-Persist and Pain-Remit groups did not differ on any demographic characteristics. The proportion of females was lower in the Control group (53.7%) than in the Pain-Persist group (70.8%). Control participants were somewhat younger and had lower BMI compared to Pain-Persist and Pain-Remit participants. The interaction of group by sex was not significant for age or BMI.

Table 2 shows means and standard deviations for heart rate, SDRRI, and HF power by group and sex for each epoch.

Baseline ANS Measures at Rest

During the resting baseline an overall significant effect was seen between groups for SDRRI and HF. Pain-Persist females had significantly lower SDRRI and HF power compared to all male groups and to Control females (p's < .05), but did not differ significantly from Pain-Remit Females on SDRRI or HF.

Effect of stress manipulation

As expected, we observed significantly higher HR and SDRRI for the total sample in the three stress epochs combined as compared to the two non-stress epochs combined (BL, RC), (HR: $F[1,343] = 598.95$; $p < .001$, $\eta^2 = .64$; SDRRI: $F[1,343] = 77.86$; $p < .001$, $\eta^2 = .19$). Additionally, the two higher stress epochs (SCI-Hot, SS) had significantly higher HR and SDRRI compared to the moderate stress (SCI-Cool) epoch (HR: $F[1,343] = 398.22$, $p < .001$, $\eta^2 = .54$; SDRRI: $F[1,343] = 9.63$, $p = .002$, $\eta^2 = .03$). HF did not differ significantly between stress and non-stress epochs. Thus, both HR and SDRRI indicated that our manipulation of stress produced increased levels of autonomic activity as anticipated.

In addition, the contrast between the two high stress epochs (SCI-Hot versus SS) suggested that the SS epoch may have been somewhat more stressful than the SCI-Hot epoch, resulting in higher HR ($F[1,343] = 67.94$, $p < .001$, $\eta^2 = .17$), lower SDRRI (i.e., less variability; $F[1,343] = 5.18$, $p = .023$, $\eta^2 = .01$), and lower HF (i.e., more parasympathetic withdrawal; $F[1,343] = 15.95$, $p < .001$, $\eta^2 = .04$) during the SS epoch as compared to the SCI-Hot epoch.

Effect of group across stressor and non-stressor epochs

As our main hypotheses involved SDRRI and HF we focus on these in the remaining analyses. Collapsing across the five epochs, significant between-subject (group) effects were found for our primary dependent variables, SDRRI ($F[5,341] = 4.68$, $p < .001$, $\eta^2 = .06$), and HF ($F[5,341] = 2.85$, $p = .015$, $\eta^2 = .04$). Planned post hoc comparisons showed that both Pain-Persist Females and Pain-Remit Females had significantly lower SDRRI and HF compared to Control Females and all male groups (SDRRI: $F[1,341] = 16.30$, $p < .001$; HF: $F[1,341] = 8.72$, $p = .003$). Moreover, Pain-Persist Females had significantly lower SDRRI and HF than Pain-Remit Females (HR: $F[1,341] = 4.80$, $p = .029$; SDRRI: $F[1,341] = 5.16$,

p = .024; HF: F[1,341] = 5.29, p = .022). Across male participant groups, SDRRI, and HF did not differ. These group differences are illustrated in Figure 1.

Interaction Effect of Group by Epoch

Figure 2 shows SDRRI for each of the six groups across epochs. Results of the mixed-model MANOVA indicated a significant participant group by epoch interaction effect for SDRRI (Pillai's Trace = .11, p = .007). Specifically, the difference in SDRRI between the combined groups of Pain-Persist Females and Pain-Remit Females versus the other groups varied by epoch (Pillai's Trace = .05, p = .001). Pain-Persist and Pain-Remit females demonstrated lower SDRRI than other groups throughout the procedure, but this difference was significantly greater during the two non-stress epochs (BL, RC) compared to the three stress epochs (SCI-Hot, SCI-Cool, SS), F(1,343) = 11.56, p = .001, η^2 = .03. Thus, although Pain-Persist females and Pain-Remit females had lower levels of HRV compared to other groups throughout the procedure, these differences were smallest, in terms of total HRV, under conditions of stress as compared to conditions of rest.

Differences in SDRRI between Pain-Persist Males and Pain-Remit Males varied by epoch (Pillai's = .035, p = .016). Specifically, Pain-Persist Males differed from Pain-Remit Males in their response to two stressor epochs (SCI-Hot epoch versus SS epoch, F(1,343) = 7.45, p = .006, η^2 = .02. Pain-Persist males had significantly higher SDRRI than Pain-Remit males during the SCI-Hot epoch; this difference between Pain-Persist males and Pain-Remit males was not present during the other epoch contrasts.

Measures of HF did not vary significantly by epoch across the six groups.

4. Discussion

This study demonstrated ANS dysregulation – low overall HRV and, more specifically, reduced parasympathetic cardiac activity – in young women with persistent FAP as compared to young women with FAP in remission, young women with no history of FAP, and young adult males regardless of abdominal pain status. Specifically, young women with a childhood history of FAP and continuing abdominal pain in adulthood exhibited low overall HRV (SDRRI) several years following their pediatric medical evaluation for FAP. Moreover, spectral analysis of ECG recordings in these young women demonstrated reduced cardiac ANS activity specifically in the HF domain, i.e., reduced parasympathetic "braking" of sympathetic activity. This pattern of low HRV and reduced parasympathetic activity matches that observed in combined samples of men and women with various chronic pain conditions [46]. Our study yielded two important new findings: (1) reduced HRV and HF power was particular to women with more severe, persistent pain and, (2) occurred both at rest and during experimental stress. These findings underscore autonomic dysregulation as a unique mechanism in females which may contribute to gender differences in the prevalence of FAP.

At present, mechanisms that may link ANS function to FAP are unknown. A close association exists between cardiac and gastric autonomic processes [4], but the relation of cardiac vagal tone to gut function is not clear. It is possible that parasympathetically

mediated low HRV affects the gut directly, for example by influencing gut motility. Alternatively, this pattern of ANS dysfunction may affect the gut indirectly by means of a CNS mechanism associated with pain amplification or poor emotion self-regulation. HRV is considered an index of the ability to self-regulate emotions in order to effectively confront threat [2]. Low HRV is associated with poor fear inhibition [55], failure to recognize safety cues [41], and hypervigilance [39] manifest in worry and rumination [3, 27]. These psychological characteristics of low HRV are consistent with the fear-avoidance model of chronic pain [48]. To the extent that low HRV reflects a general hypervigilance to threat and poor emotion-regulation by young women with FAP, it could give rise to catastrophizing reactions to pain, avoidance of situations associated with pain and, over time, exacerbation of symptoms and disability. Indeed, emotional reactivity to pain in the form of catastrophizing has been linked to low HRV [22] and is significantly higher in females than males [36]. Moreover, the association between female sex and poor pain outcomes may be mediated by pain catastrophizing [20]. Thus, reduced parasympathetic activity could reflect a biological mechanism underlying the relation between pain catastrophizing and poor pain outcomes in women.

We expected exposure to laboratory stressors might exaggerate autonomic differences between groups. However, women with persistent FAP maintained relatively low HRV both at rest and during exposure to stress in the laboratory. All participants showed significant increases in HRV during the laboratory stressors, and the magnitude of the increase in HRV was similar in females with persistent FAP and other participants. Nonetheless, because of their very low resting baseline HRV, even the highest HRV attained by females with persistent FAP did not reach the level of resting baseline HRV observed in females with no history of FAP or in males regardless of pain status.

Although increases in HRV were evident in the measure of SDRRI, which picks up HRV from all sources, they were not reflected in changes in estimated parasympathetic activity reflected in HF power. Instead, HF power was low and stable throughout the task in women with persistent FAP. In fact, the greatest differences between females with persistent FAP and other participants were during the experimental epochs without stress, i.e., pre-stressor baseline rest and post-stressor recovery. Perhaps these periods of rest and recovery created situations of ambiguity that produced greater stress in females with persistent FAP as compared to the universally stressful experimental situations. If so, these young women may experience physiological correlates of high threat appraisal throughout the day, even when others do not perceive threat or experience stress.

Interestingly, recent studies have found that resting HRV, rather than HRV during challenge, may be the most relevant predictor of the capacity for adaptation to threat. Wendt, Neubert, Koenig, Thayer & Hamm [55] (p. 1161) postulated that resting HRV "may reflect the capacity of the prefrontal cortex to inhibit subcortical fear response in the presence of safety or when former threat cues are presented in the absence of threat," and Pappens et al [28] (p. 9) speculated that low resting HRV might reflect subcortical "hard-wired defensive responding." Thus, low resting HRV among the young women with persistent pain may reflect continuous difficulty adapting to routine changes in internal and external demands. The parasympathetic branch of the ANS is a "rest and digest" system that plays a restorative

role during states of safety [31]; that is, application of the parasympathetic action puts a break on heart rate whereas withdrawal acts like an accelerator. Future research will need to address the question of whether ANS dysfunction, in the form of dominant sympathetic activation in the context of reduced parasympathetic activation, was present in childhood before symptoms of FAP occurred, and might even have contributed to the development and persistence of FAP or, alternatively, emerged subsequent to years of chronic pain.

One clinical implication of this study is that women with a childhood history of FAP that persists into adulthood may be at elevated long-term risk for a host of physical and psychiatric disorders associated with low HRV. The documented association between low HRV and all-cause morbidity [42, 43] suggests that ANS dysfunction may play a role in the extra-intestinal symptoms and co-morbid pain conditions common in FAP [10, 11, 56] and other chronic pain conditions [17]. Indeed, female pain patients with low HRV may constitute a clinically meaningful phenotype of chronic pain that has more similarities than differences across sites of chronic pain.

Young women whose childhood FAP had remitted at follow-up exhibited levels of autonomic imbalance intermediate between those of females with persistent FAP and all other participants. Across the experimental protocol, they exhibited significantly lower SDRRI and HF as compared to control females without pain and all males. It is possible that these findings reflect an ongoing vulnerability for recurrence of abdominal pain among women with a childhood history of FAP that remitted in adulthood.

Sex differences in autonomic function were striking. Among males, autonomic function in those with persistent or remitted FAP did not reliably differ from that in males with no history of FAP. Others have suggested the possibility of sex differences in the mechanisms underlying the etiology or maintenance of FAP [8, 23]. Tillisch et al [44] found low HRV in males but not females with IBS; the sample, however, was middle aged. Thus, the question of autonomic imbalance in males with childhood-onset FAP remains open for further study.

The current study has important strengths. The large sample allowed us to evaluate separate and interactive effects of pain severity, sex, and laboratory stress exposure on HRV. Data analyses employed statistical controls for variables known to influence HRV including BMI and age. We extracted measures of both time and frequency domains of cardiac activity from ECG recordings. Our measure of pain persistence at follow-up was clinically meaningful as it was based on the standard symptom diagnostic criteria for pain-related FGIDs. Experimenters were unaware of the health status of research participants. Finally, the relative youth of our sample meant that participants had not yet experienced decades of lifestyle factors (e.g., smoking, sedentary habits) known to influence HRV, and which may confound research with older populations.

Limitations of the study suggest directions for future research. First, our clinical sample consisted of adolescents and young adults, whereas most studies of FAP, particularly IBS, have focused on individuals who are middle-aged or older. Replication of our work with younger children and older adults will reveal the extent to which our findings generalize across the lifespan. Second, we employed psychological stressors in the laboratory to assess

the effect of stress on HRV. These stressors were relevant to the population but do not necessarily reflect ANS response to naturally occurring stressors. Future research might use 24-hour ambulatory recording of ECG in conjunction with patient-reported daily stressors. Evaluation of ANS responses to visceral stressors is also an important focus for future research, as ANS reactivity to visceral stressors may differ from that for psychological stressors. Third, we did not assess ANS function in childhood when participants enrolled in the study and do not know whether low HRV observed in women with persistent pain at follow-up had decreased over time from childhood to young adulthood or was already low in childhood. Longitudinal studies are critical to understand the nature of the relation between HRV and chronic pain, including whether the trajectories of each are parallel over time, and the extent to which they influence each other. Assessment of HRV in RCTs also will be important to evaluate whether HRV predicts responses to treatment and whether successful treatment of chronic pain is associated with increased HRV and greater parasympathetic braking of cardiac sympathetic activity.

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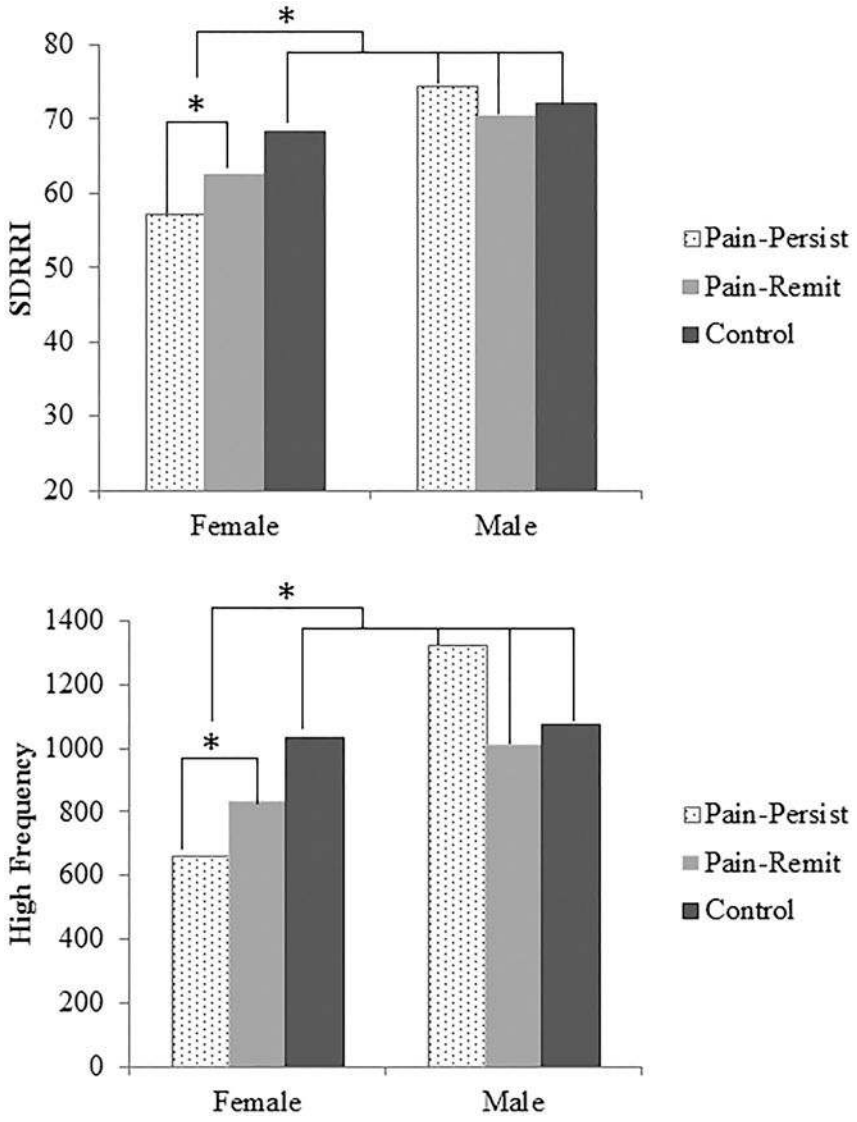

Figure 1.
SDRRI and HF by group and sex across all epochs combined
Note. * $p < .05$

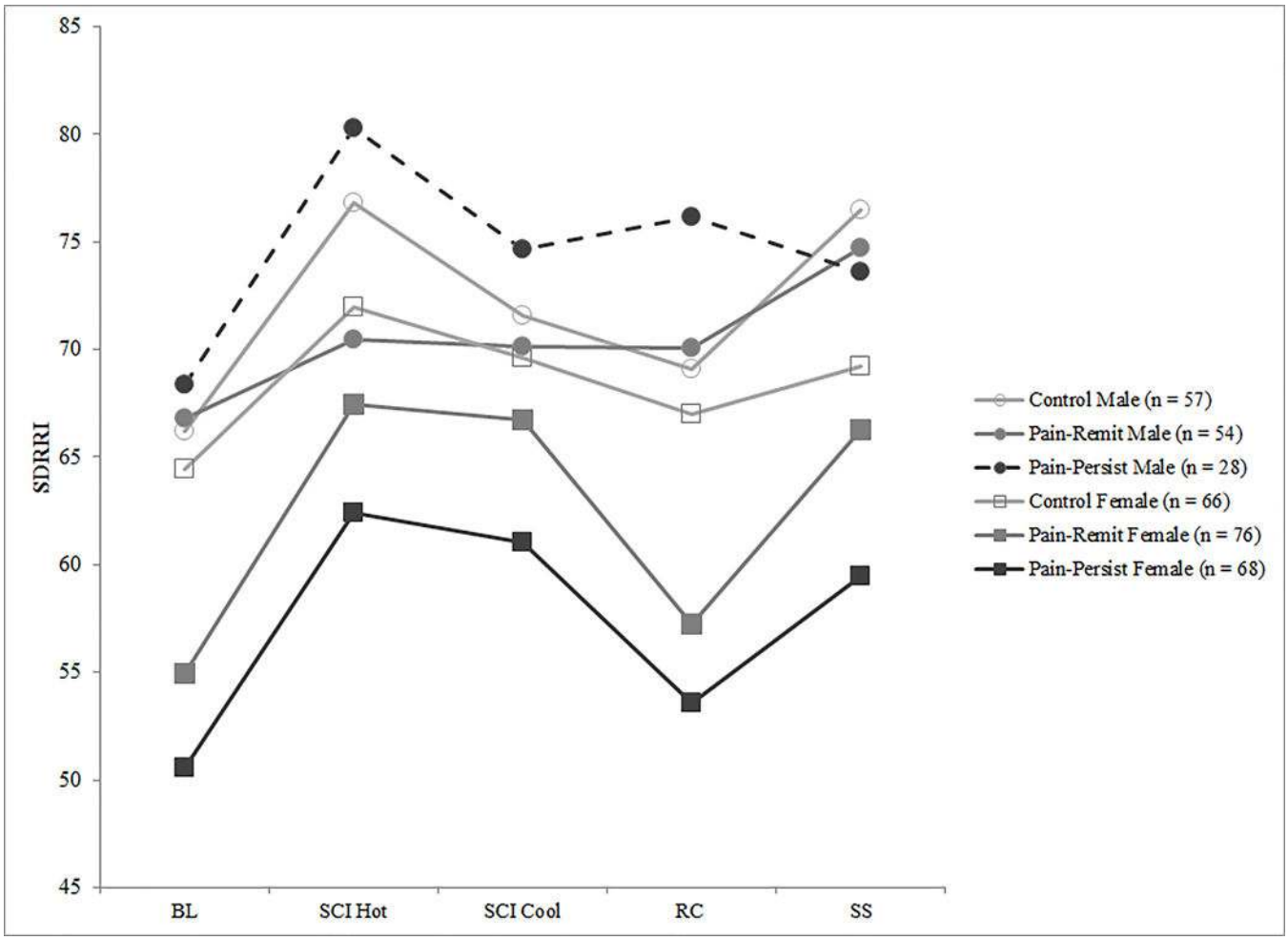

Figure 2.

Heart rate variability (standard deviation of R-R intervals, SDRRI) across epochs by group and sex

Note. BL = Baseline, RC = Recovery, SCI = Social Competence Interview, and SS = Serial Subtraction

Table 1

Demographic characteristics by group

	Participant Group		
Demographics	**Controls (n = 123)**	**Pain-Remit (n = 130)**	**Pain-Persist (n = 96)**
Sex (% Female)	53.7[a]	58.5[a,b]	71.6[b]
Race (% Caucasian)	96.7[a]	88.7[b]	95.8[a,b]
Age	18.15 (2.72)[a]	20.50 (3.33)[b]	19.73 (3.68)[b]
Body Mass Index (BMI)	23.83 (4.57)[a]	26.57 (7.43)[b]	26.57 (7.69)[b]

Note. Within rows, means with different superscripts differ significantly at $p < .05$.

Table 2

Means and standard deviations on heart rate, SDRRI, and high frequency power by group and sex for each epoch

Heart rate (BPM)					
Males	**Baseline M (sd)**	**SCI HOT M (sd)**	**SCI COOL M (sd)**	**Recovery M (sd)**	**Serial Subtraction M (sd)**
Control	70.92 (11.54)	77.31 (12.72)	74.56 (12.14)	70.38 (11.64)	81.87 (14.34)
Pain-Remit	70.00 (9.51)	76.20 (9.84)	73.99 (8.86)	70.19 (7.68)	80.24 (11.64)
Pain-Persist	70.89 (10.27)	76.09 (11.37)	73.93 (11.03)	71.48 (9.79)	80.25 (10.83)
Females					
Control	74.40 (10.26)	81.56 (10.09)	77.92 (9.03)	74.22 (9.70)	84.21 (11.24)
Pain-Remit	74.74 (9.84)	81.66 (9.91)	78.45 (9.64)	74.41 (9.30)	83.93 (11.35)
Pain-Persist	78.45 (11.48)	85.65 (12.63)	82.15 (11.36)	78.44 (10.81)	87.42 (12.34)
Heart rate variability (SDRRI)					
Males	**Baseline M (sd)**	**SCI HOT M (sd)**	**SCI COOL M (sd)**	**Recovery M(sd)**	**Serial Subtraction M (sd)**
Control	66.22 (25.40)	76.8 (26.21)	71.57 (26.23)	69.1 (24.96)	76.49 (28.96)
Pain-Remit	66.78 (25.07)	70.47 (22.86)	70.11 (21.57)	70.08 (29.00)	74.75 (24.32)
Pain-Persist	68.39 (33.79)	80.29 (39.93)	74.66 (38.84)	76.16 (43.09)	73.63 (31.84)
Females					
Control	64.41 (25.61)	71.99 (19.33)	69.6 (21.97)	67.01 (23.83)	69.24 (17.76)
Pain-Remit	54.92 (18.04)	67.46 (19.85)	66.72 (21.62)	57.22 (18.78)	66.27 (22.04)
Pain-Persist	50.53 (21.62)	62.44 (22.64)	61.02 (23.34)	53.6 (23.12)	59.47 (21.97)
High frequency power (HF)					
Males	**Baseline M(sd)**	**SCI HOT M (sd)**	**SCI COOL M (sd)**	**Recovery M (sd)**	**Serial Subtraction M (sd)**
Controls	1130.18 (1151.11	1187.94 (1063.95	1089.24 (1098.14)	1058.13 (1524.75)	944.17 (1099.03
Pain-Remit	1293.48 (2098.34)	911.58 (990.43)	905.75 (977.55)	1058.13 (1524.75)	789.78 (600.92)
Pain-Persist	1314.76 (1985.79)	1467.64 (2592.12)	1478.49 (2510.35)	1223.51 (1854.08)	1151.92 (1790.08)
Females					

Heart rate (BPM)					
Males	**Baseline M (sd)**	**SCI HOT M (sd)**	**SCI COOL M (sd)**	**Recovery M (sd)**	**Serial Subtraction M (sd)**
Control	1232.77 (1382.52)	952.6 (852.24)	970.42 (1055.35)	1169.52 (1343.91)	847.39 (982.81)
Pain-Remit	888.73 (1070.67)	809.24 (881.37)	875.22 (1145.61)	758.79 (874.95)	840.49 (1126.9)
Pain-Persist	729.52 (835.23)	639.75 (690.43)	649.89 (759.62)	641.4 (755.55)	658.33 (944.16)