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Juvenile onset depression alters cardiac autonomic balance in response to psychological and physical challenges

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Abstract

Cardiac autonomic balance (CAB) indexes the ratio of parasympathetic to sympathetic activation (Berntson, Norman, Hawkley, & Cacioppo, 2008), and is believed to reflect overall autonomic flexibility in the face of environmental challenges. However, CAB has not been examined in depression. We examined changes in CAB and other physiological variables in 179 youth with a history of juvenile onset depression (JOD) and 161 healthy controls, in response to two psychological (unsolvable puzzle, sad film) and two physical (handgrip, and forehead cold pressor) challenges. In repeated measures analyses, controls showed expected reductions in CAB for both the handgrip and unsolvable puzzle, reflecting a shift to sympathetic relative to parasympathetic activation. By contrast, JOD youth showed increased CAB from baseline for both tasks (*ps*<.05). No effects were found for the forehead cold pressor or sad film tasks, suggesting that CAB differences may arise under conditions requiring greater attentional control or sustained effort.

Keywords

cardiac autonomic balance; cardiac autonomic regulation; parasympathetic nervous system; sympathetic nervous system; juvenile onset depression; reactivity; self regulation

Abnormalities in autonomic nervous system functioning have been associated with depression. More specifically, there is qualified support for an association between major depression in adults and low resting parasympathetic nervous system (PNS) activity, as indexed by resting levels of respiratory sinus arrhythmia, with mostly positive (RSA;

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Rottenberg, 2007; Udupa et al., 2007; Kemp, Guitana, Gray, Felmingham, Brown & Gatt, 2010; Kikuchi et al., 2009) but some negative results (e.g., Licht et al., 2008; Yeragani et al., 1991; Lehofer et al., 1997). More consistent findings have been observed for RSA reactivity in response to laboratory tasks, with depressed adults exhibiting blunted RSA withdrawal to a laboratory speech stressor (Rottenberg, Clift, Bolden, & Salomon, 2007; Bylsma, Salomon, Taylor-Clift, Morris & Rottenberg, 2014), as well as a handgrip task (Nugent, Bain, Thayer, Sollers, & Drevets, 2011). These patterns are postulated to relate to poorer self regulation. Elsewhere, we have found that atypical patterns of resting RSA and RSA reactivity in youths with a history of juvenile onset depressed predicted deficits in mood repair, where mood repair refers to behaviors that decrease feelings of sadness or dysphoria (e.g., Josephson, Singer, & Salovey, 1996), as assessed by both trait measures and laboratory probes (Yaroslavsky et al., 2015)..). We have also found that atypical patterns of resting RSA and RSA reactivity are more highly concordant in siblings with a history of depression, suggesting that aspects of autonomic functioning may be heritable (Yaroslavsky, Rottenberg & Kovacs, 2014).

To a lesser extent, abnormalities in sympathetic nervous system (SNS) activity have also been observed in depressed adults. For example, Salomon, Clift, Karlsdottir & Rottenberg (2009) and Salomon, Bylsma, White, Panaite, & Rottenberg (2013) found blunted sympathetic nervous system (SNS) reactivity to a laboratory stressor task, as indexed by lengthened pre-ejection period (PEP), although others have found shorter PEP in individuals with depressive symptoms (Light, Kothandapani & Allen, 1998). Overall, research thus far reveals mixed evidence of PNS and SNS deficits in depression.

To date, depression research has focused almost exclusively on individual parasympathetic or sympathetic indices. This exclusive focus is unfortunate in light of recent theory argues arguing for the critical importance of integrating sympathetic and parasympathetic control to provide a comprehensive understanding of behavioral and affective reactivity and regulation (Berntson, Cacioppo, & Quigley, 1991). In fact, the historical views of reciprocally determined activity in both branches of the autonomic nervous system (e.g., activity increases in one branch would be accompanied by invariable decreases in the other) have been largely overturned by new theory and data, which indicate that both autonomic branches can react either independently or together, resulting in complex physiological patterns, including co-activation and co-inhibition (Berntson, et al., 1991; Berntson et al. 2008). Importantly, theory and empirical evidence have indicated that reciprocal sympathetic activation (increases in sympathetic activity in conjunction with decreases in parasympathetic activity) during stress responses are ordinarily adaptive, whereas reciprocal parasympathetic activation would be most adaptive in calm and relaxed states (Berntson et al., 1994; El-Sheikh et al., 2009). Thus, examination of the balance of parasympathetic and sympathetic activity may lead to a more complete picture of regulatory functioning and risk for depression.

Berntson et al. 2008 has previously defined two useful indices for describing complex patterns in autonomic space: Cardiac Autonomic Balance (CAB) and Cardiac Autonomic Regulation (CAR). These indices are derived from a parasympathetic index, RSA, and a sympathetic index, PEP. RSA is a parasympathetically-mediated variation in heart rate that

is germane to individual differences in emotional functioning and regulation capacity in adults and youth (e.g., Beauchaine, 2001; Musser et al., 2011; Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013; Yaroslavsky et al., 2014). PEP is a sympathetically mediated index that reflects the time between left ventricular depolarization and ejection of blood through the aorta, with smaller values indicating greater SNS activity (Berntson et al., 1994). PEP has been viewed as an index of effort mobilization needed to meet environmental demands (with decreases in PEP reflecting increased effort mobilization) required for behavioral approach (Gendolla, 2012; Kelsey, 2012; Richter, Friedrich & Gendolla, 2008; Richter & Gendolla, 2009), and it has been validated as a SNS index in children and adolescents (e.g., Matthews, Salomon, Kenyon, & Allen, 2002; McGrath & O'Brien, 2001; Quigley & Stifter, 2006).

CAB is computed as the difference between standardized values of parasympathetic control (RSA) and sympathetic control (PEP) along a bipolar model of autonomic balance. Therefore, higher CAB values reflect greater parasympathetic relative to sympathetic activation. CAR reflects the coactivation or coinhibition of PNS and SNS activity and is computed as the normalized sum of RSA and PEP. Autonomic dysregulation is often described as overactive SNS and hypoactive PNS (i.e., lower CAB), which has been associated with coronary artery disease, increased mortality (for a review, see Thayer, Yamamoto & Brosschot, 2010), increased risk of metabolic syndrome (Licht, de Geus & Penninx, 2013), diabetes (Berntson & Cacioppo, 2008) and chronic stress states (Lampert, Ickovics, Horwitz & Lee, 2005), and may serve as a link between negative affect and disease states (Thayer et al., 2010). High CAR (high PNS and CNS coactivation) has also been associated with increased risk for metabolic syndrome (Licht, de Geus & Penninx, 2013) and prior occurrence of myocardial infarction (Berntson & Cacioppo, 2008).

While CAB and CAR represent potentially useful indices of autonomic system functioning that reflect autonomic flexibility, they have not yet been examined in the context of depression or depression risk. Prior depression-related work with joint autonomic indices used metrics that have limited interpretability, such as LF/HF ratio (the ratio of low to high frequency heart rate variability; Malliani, 2005; Malliani & Montano, 2002). While depressed and depression-vulnerable persons have been found to have a higher LF/HF ratio (Nugent et al., 2011; Udupa et al., 2007; Chang et al., 2012), LF is an ambiguous sympathetic index because, as it is currently defined, LF is contaminated by parasympathetic activity (Berntson et al., 1997; Eckberg, 1997; Reyes del Paso, Langewitz, Mulder, van Roon & Duschek, 2013). Further, as Heathers (2014) explains, there is no sound mathematical basis to directly compare LF and HF power, as these measures are only internally consistent (i.e., examining changes over time within an individual), so that comparing their relative proportions is questionable. In addition, possible co-activations in the sympathetic and parasympathetic branches are also not taken into account for the LF/HF ratio (Pagani, 2012).

CAB has been studied once in a depression-relevant sample: Miller, Wood, Lim, Ballow & Hsu (2009) found that children with asthma who were high on depression symptoms showed greater increases in CAB in response to films depicting distressing scenes of loss, death, and dying (greater increases in PNS relative to SNS activity). In contrast, asthmatic children low

on depressive symptoms showed the normative pattern of response to stress (greater decreases in CAB—greater increase in sympathetic relative to parasympathetic activity), which the authors indicated would be most adaptive for airway functioning in these patients. CAR, which reflects the co-activation of sympathetic and parasympathetic activity, has yet to be studied in depression.

The present study focused on Cardiac Autonomic Balance (CAB) in youths with histories of early onset depression and healthy controls with no history of depression. We examined CAB during baseline (viewing a neutral film) and across two physical and two psychological stressor tasks. We expected that the tasks (unsolvable puzzles, handgrip, sad film, and forehead cold pressor) would uncover group differences in psychophysiological reactivity. In studies with healthy individuals, the typical normative response to most laboratory stressors is a decrease in RSA accompanied by an increase in sympathetic relative to parasympathetic activity (Key, Campbell, Bacon, & Gerin, 2008; Lackschewitz, Hüther & Kröner-Herwig, 2008; O'Donnell, Brydon, Wright, & Steptoe, 2008). However, since the forehead cold pressor task elicits a “dive reflex”, which is typically accompanied by activation of the PNS system (Heath and Downey, 1990), we would expect increases in RSA (and likely increases in CAB) in response to this task. Since previous findings have suggested that abnormalities in PNS and SNS activation are associated with depression, we predicted that youth with such a history will fail to show appropriate changes in CAB in response to the stressor tasks. In other words, we expected that healthy controls would show decreases in CAB for the sad film, puzzle, and handgrip tasks or increases in CAB for the forehead cold pressor, while youth with a history of depression would fail to show these changes. As a point of comparison, we also examined effects for the LF/HF ratio, which has been considered another index of autonomic balance. Finally, we included Cardiac Autonomic Regulation (CAR) as a secondary, exploratory measure, given the lack of prior empirical literature.

Method

Subjects

This study included 216 probands whose histories of childhood onset major depressive disorder (MDD) were previously established (e.g., Baji et al, 2009; Kiss et al 2007). The probands are a subset of a larger sample, which were gathered in Hungary from approximately 1997–2006 for a prior genetic and clinical study (e.g., Baji et al., 2009; Dempster et al., 2009; Tamás et al., 2007). Probands for the original study were recruited at 23 child mental health and guidance facilities across Hungary and met several study entry criteria, including having current or recent DSM-IV (American Psychiatric Association, 2000) depressive disorder, being 7–14 years old at initial screen, and not mentally retarded. Six probands who came from families with a history of mania were excluded from analyses. Mean age of the proband sample at the current assessment was 17.0 (SD=1.40, Range=11.6–19.1) and 64.1% were male. Mean age at onset of first MDD episode in the proband youth was 9.07 years (SD= 1.89 years). At the diagnostic assessment for the current study, 58.6 % had one MDD episode, 31.9% had 2 episodes, and 9.5% had 3 or more episodes; 179 subjects were in full remission from their most recent MDD episode, while 31 (14.8%) were

currently in a depressive episode. Rates of comorbid psychiatric disorders of probands were as follows: 18.6 % dysthymic disorder, 39% any anxiety disorder, 37.6% any behavioral disorder (e.g., ADHD, oppositional defiant disorder). Overall, 71% had at least one comorbid psychiatric disorder. Seven probands were taking psychotropic medications at the time of the psychophysiological assessment.

The current study also includes 161 healthy control peers who never had any major psychiatric disorder. Controls were identified in medium size public elementary and secondary schools in the 3 cities in which most of the proband in the current study resided. Controls were recruited to approximate the sex and age distribution of probands. Mean age of the control sample at the current assessment was 16.1 (SD=1.40, Range=11.2–19.0) and 64.1% were male (see Table 1).

Procedure Overview

This study was approved by the institutional review boards of the University of Pittsburgh and the Hungarian clinical research sites. Parents provided written informed consent, and youth provided either assent or consent (depending on their ages) before any data were gathered. Study visits included a psychiatric-psychosocial evaluation, the completion of self- and parent- rated questionnaires, and an experimental protocol with psychophysiological recordings. Following the questionnaires, the adolescent was familiarized with the experimental procedures and equipment. All procedures, schedules, rating scales, and instruments used in this study were first developed in English, were translated into Hungarian, and then back translated by bi-lingual child psychiatrists and clinical psychologists. Original and back-translated versions were compared, with any discrepancies resolved using an iterative procedure.

Diagnostic Assessment

As described previously (e.g., Kiss et al., 2007; Tamás et al., 2007), caseness for each proband was established during the original study via a stringent procedure that included standardized psychiatric diagnostic evaluations (involving the youth and a parent informant) by trained interviewers (child psychiatrists and psychologists), each of whom generated DSM-IV mood-disorder diagnoses, and a final best-estimate diagnosis (Maziade et al., 1992). DSM-IV diagnoses were based on the ISCA-D, a semi-structured interview derived from the ISCA (Sherrill & Kovacs, 2000), which has been described in detail in previous publications (Baji et al., 2009; Kiss et al., 2007). We have previously reported acceptable inter-rater reliability coefficients on the ISCA-D symptom ratings (.63–.92 for current MDD from child interviews and .65-.87 from parent interviews; Kiss et al., 2007).

Physiological Protocol

This study was part of a larger physiological protocol that included a variety of stress reactivity and mood induction tasks. Here we report on a portion of the protocol that included a neutral film (baseline comparison for all tasks), two psychological stressors (sad film, unsolvable puzzle) and two physical stressors (handgrip, forehead cold pressor), described in detail below. In other work with this sample, we examined RSA patterns of resting RSA and RSA reactivity associated trait mood repair and mood repair success in the

lab following the sad film (Yaroslavsky et al., 2014). The order of the stressors (task order) was randomized into four possible orders with buffer periods in between. Participants were asked to avoid any allergy, cold/flue, or asthma medications the morning of the physiological protocol, and to refrain from drinking any caffeinated beverages, smoking or engaging in heavy exercise within 2 hours of beginning the physiological protocol.

Neutral Film—In order to provide an estimate of physiological functioning at rest (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992), participants viewed a 180s neutral film that depicted fish swimming in an aquarium.

Sad Film—We administered a 164s sad film clip from the movie “The Champ” that depicts a grief-stricken child observing the death of his boxer champion father after a boxing match (Rottenberg, Gross & Gotlib, 2005; Rottenberg et al., 2007).

Unsolvable Puzzle—Subjects completed a task where they tried to re-recreate a pattern on a computer screen. Specifically, subjects had to move pieces (horizontally or vertically) containing letters of the alphabet to duplicate a displayed pattern. A practice puzzle that was easily solvable was first given to ensure that subjects understood the task (15s). Next, two different unsolvable puzzles were given, which were programmed in such a way that the solution was impossible (i.e., mirroring Cole et al., 2007; Nolen-Hoeksema, Wolfson, Mumme & Guskin, 1995). Unsolvable puzzle tasks have been shown to induce negative affect (sadness, frustration) and parasympathetic withdrawal (e.g., Perry, Calkins, Nelson, Leerkes & Marcovitch, 2012). Subjects were given 360s to work on the unsolvable puzzles (180s for each unsolvable puzzle).

Handgrip—Subjects were asked to squeeze a hand dynamometer at 30% Maximum Voluntary Contraction for 120s. This task elicits a reduction in parasympathetic activity (RSA withdrawal), which may also occur in combination with increased sympathetic activity (e.g., Miller, 1994; Freyschuss, 1970; Martin et al., 1974, Nutter, Schlant & Hurst, 1972, Pollak & Obrist, 1988) and has been used successfully in our age group (e.g., Matthews, Woodall, & Stoney, 1990; Kelsey, Patterson, Barnard, Alpert, 2000).

Forehead cold pressor—We administered a 60s forehead cold pressor as follows: While the participant was receiving the instructions for the forehead cold pressor, an ice bag was prepared by filling a plastic bag (25 × 18 cm) with 2 dl of room temperature tap water and 4 ice cubes (approximately 3.5 cm in diameter each). The room air temperature was held at a consistent temperature across study sites, between 22–24°C. The ice bag sat on top of the cooler with the water and ice mixture for approximately 5 minutes before applying it to the participant’s forehead. The temperature of the ice bag at the time of application was approximately 8–10°C. This version of the forehead cold pressor been used successfully with children in previous studies (Matthews, Salomon, Kenyon, & Allen, 2002). This task evokes parasympathetically-mediated heart rate deceleration and is an effective means to stimulate the “dive reflex” (e.g., Heath & Downey, 1990; Reyners et al., 2000).

Psychophysiological recording

Physiological data were recorded continuously throughout the protocol. The ECG signal was acquired according to published guidelines (Jennings et al., 1981) using Cleartrace LT disposable Ag/AgCL electrodes (Conmed Andover Medical, Haverhill, MA) placed in a modified Lead II configuration on the chest. We collected impedance cardiography using spot electrodes according to the guidelines outlined by Sherwood et al. (1990). All ECG and dZ/dt signals were sampled online at 1000Hz using a Mindware BioNex system with associated BioLab software. The dZ/dt signals were ensemble-averaged over the length of the experimental epochs defined for each task. The data were screened for artifact by visual inspection. Psychophysiological data were processed and analyzed as a single epoch for each task.

Measures

Body mass index (BMI)—Since BMI is known to impact SNS reactivity and CAB, we measured it to include as a covariate in analyses. Subjects' height and weight were obtained at the beginning of the physiological assessment. BMI was calculated as weight in kg/(height in m^2). BMI raw scores were Z-transformed for analyses. See Table 1 for descriptive information.

Respiratory Sinus Arrhythmia (RSA) and LF/HF Ratio—RSA was calculated using MindWare HRV 3.0.21 software (MindWare Technologies, Ltd., Gahanna, OH). R-wave markers in the ECG signal were processed with the MAD/MED artifact detection algorithm (Berntson, Quigley, Jang & Boysen, 1990) implemented by the MindWare software. The signals were manually inspected and suspected artifacts were corrected. Our approach accords with current guidelines for frequency domain methods to determine heart rate variability and is well suited for short-term recordings (Berntson et al., 2008; Lombardi & Malliani, 1996). To estimate heart rate and RSA during baselines and tasks (using the entire task epoch for each task), a time series of interbeat intervals (IBIs: the time in milliseconds between sequential ECG R-spikes) was created from an interpolation algorithm. This IBI time series was (a) linearly-detrended, (b) mean-centered, and (c) tapered using a Hanning window. Spectral-power values were determined (in ms^2/Hz) with fast Fourier transformations, and the power values in the 0.15–0.50 Hz spectral bandwidth were integrated (ms^2). These spectral-power values were natural-log transformed prior to statistical analyses because of distributional violations. Our indicator of RSA was defined as the Natural-logged (ln) spectral-power value in the high frequency (HF) 0.15–0.50 Hz bandwidth, and LF was defined by the spectral power in the low frequency .04-.15Hz bandwidth (see Berntson et al., 1997). For purposes of comparison, LF/HF ratio was computed using the ratio of the raw LF and HF values.

Pre-Ejection Period (PEP)—The impedance-derived measure of PEP was derived using MindWare IMP 3.0.1 software (MindWare Technologies, Ltd., Gahanna, OH) based on the dZ/dt signal. Specifically, PEP was quantified as the time interval (in milliseconds) from the onset of the ECG Q wave to the B point (corresponding to the opening of the aortic value) of the dZ/dt wave (Sherwood et al., 1990). The max slope method was used to place the B point, which was adjusted manually based upon visual inspection.

Cardiac Autonomic Balance (CAB) and Cardiac Autonomic Regulation (CAR)—CAB and CAR were computed based on Berntson et al. (2008). Following Berntson's procedure, we first normalized RSA and PEP by transforming these values to z-scores, due to the differences in scaling of these measures. Because greater sympathetic activity is associated with shortened (lower) PEP values, PEP was multiplied by −1 in order to invert the relationship to a positive association (where greater PEP values indicate greater sympathetic activity, just as greater RSA values indicate greater parasympathetic activity). Since CAB provides a measure of the balance of parasympathetic to sympathetic activation, CAB was computed using the formula: **CAB = RSAz - (− PEPz)**. Consequently, greater CAB values indicate greater parasympathetic relative to sympathetic activation, and lower CAB values indicate greater sympathetic relative to parasympathetic activation. Since CAR reflects the co-activation of the parasympathetic and sympathetic systems, CAR was computed as: **CAR = RSAz + (− PEPz)**. As a result, greater CAR values indicate greater co-activation.

Statistical Analyses—First, in preliminary analyses to determine whether there were any group baseline differences, we used one-way ANCOVAs for each physiological variable (RSA, PEP, CAB, CAR, and LF/HF) during the neutral film, with group and sex as between subjects factors and age and BMI as continuous covariates (see Table 1). The effects of age, sex, and BMI were statistically controlled in all analyses based on previous literature showing that PNS and SNS activity are significantly influenced by these individual characteristics (Berntson et al., 2008). Age and BMI were entered as continuous covariates, while sex was added as a between-subjects categorical factor in all models. Next, we conducted a series of repeated measures 2 (proband vs. control) x 4 (sad film, forehead cold pressor, handgrip, unsolvable puzzles). ANCOVAS were used for each task for each physiological dependent variable. First we examined RSA, LF/HF Ratio, and PEP as the dependent physiological variables. Then we examined CAB and CAR as the dependent variables (as these are computed using RSA and PEP). In these analyses, we also included means of the physiological variables during the baseline neutral film to adjust for baseline effects, as well as task order (4 possible task orders) to account for potential confounding by task order effects. Subjects lacking analyzable data for all tasks included in the analyses for a particular physiological variable (i.e., due to data acquisition issues or noisy data) were dropped from analyses as follows: RSA=4 missing, PEP=8 missing, LF/HF=8 missing). CAB and CAR analyses only included subjects with complete RSA and PEP data.

Results

Physiological variable means and standard deviations are reported in Table 2 by group and task. Preliminary analyses revealed no statistically differences between probands and controls for any of the physiological variables during the neutral film baseline: (PEP: $F(1,394)=.96$, $p=.32$; RSA: $F(1,397)=1.89$, $p=.17$; LF/HF Ratio: $F(1,397)=2.67$, $p=.10$; CAB: $F(1,394)=.06$, $p=.81$; CAR: $F(1,394=1.29$, $p=.26$), although there was a trend effect for LF/HF Ratio with probands having slightly higher values relative to controls.

Next, we used repeated measures ANCOVA (described in detail above) to examine whether group status predicted changes in RSA and PEP. For RSA (Figure 1), the linear group by

time interaction did not reach significance (F(1.385)=2.24, p=.135), indicating that the groups did not differ in their change in RSA across the tasks. Similarly, for LF/HF Ratio (Figure 2), the linear group by time interaction did not reach significance (F(1,385)=.029, p=.87). There were also no quadratic or cubic effects for RSA or LF/HF. By contrast, for PEP (Figure 3), analyses yield significant group by time linear (F(1,373)=7.51, p=.006) and cubic (F(1,373)=8.01, p=.005) effects. Follow-up LSD pairwise comparisons revealed that controls exhibited greater decreases in PEP relative to probands to the handgrip (mean difference=3.10, 95% CI: 1.30–4.9, p=.001), indicating that controls had greater increases in SNS in response to the handgrip task.

We then conducted repeated measures ANCOVA to examine whether group status predicted changes in CAB and CAR. The analysis for CAB (Figure 4), yielded a significant linear group by time interaction (F(1,373)=8.71, p=.003). Follow-up LSD pairwise comparisons revealed significant group differences for both the unsolvable puzzles (mean difference=0.217, 95% CI: 0.039–0.395, p=.017) and handgrip tasks (mean difference=0.428, 95% CI: 0.048–0.428, p=.014), such that probands exhibited increased CAB relative to controls. Specifically, for both unsolvable puzzle and handgrip tasks, controls showed task-appropriate decreases in CAB, while probands showed unexpected increases (greater PNS relative to SNS activation. For CAR (Figure 5), there was a marginally significant quadratic group by time interaction (F(1, 373)=3.50, p=.062). Follow-up LSD pairwise comparisons revealed a significant group difference for the handgrip task only (mean difference=-.197, 95%CI: -.379 - -.014, p=.034), such that probands exhibited reduced CAR to the handgrip relative to controls. More specifically, controls showed an increase in CAR to the handgrip (reflection greater SNS and PNS coactivation), while probands showed a reduction in CAR (reflecting less SNS and PNS coactivation). There were no significant group differences on CAR for any of the other tasks.

Because some probands were currently in a depressive episode, we conducted follow-up analyses of CAB and CAR to examine the impact of current depression by modeling it as a dummy coded variable (0=no current depression, 1=current depression). Current depression status was significantly related to changes in CAR (F(1,372)=6.61, p=.011). Although the follow up pairwise comparisons did not reach significance, the pattern of results suggests that probands with current depression showed greater differences in their changes in CAR in comparison to controls relative to probands without current depression. Further, the quadratic group by time interaction lost significance with current depression status in the model (F=2.05, p=.15). In contrast, current depression status was not related to changes in CAB (F(1,372)=.168, p=.682), and the linear group by time interaction remained significant (F(1,372)=8.65, p=.003), as well as the follow-up pairwise comparisons for handgrip (p=.024) and unsolvable puzzles (p=.003), with results showing the same pattern of findings. In additional follow-up ANCOVA comparing currently depressed and remitted probands on changes in CAB and CAR, there was also no significant group by time interaction for CAB (F(1,202)=.20, p=.66). However, current and remitted probands did significantly differ on CAR (F=5.04, p=.026), although follow-up pairwise comparisons did not reach significance, which may have been due to lack of power to detect effects in the smaller sample subset.

Discussion

Depression has been related to abnormal autonomic nervous system functioning and deficits in self-regulation. An adaptive, flexible autonomic nervous system should allow for rapid modulation of physiological and emotional states, including deployment of attention and effortful processes that are critical for effective emotion regulation. It has been proposed that examination of the balance of PNS and SNS activity may lead to a more complete picture of regulatory functioning (Berntson et al., 1991, 2008). Cardiac Autonomic Balance (CAB; Berntson et al., 2008) has been proposed as a useful index to capture the relative balance of PNS to SNS activation that may reflect autonomic control better than individual measures of PNS and SNS. In this study, we examined changes in CAB in response to a series of stressful laboratory tasks in youths with a history of juvenile onset depression and control peers. In exploratory analyses, we also examined Cardiac Autonomic Regulation (CAR; Berntson et al., 2008), another autonomic index that reflects the mutual co-activation of the PNS and SNS.

Partially consistent with predictions, we found that probands with a history of juvenile onset depression exhibited abnormalities in CAB relative to controls, when facing selected stressors. Specifically, probands exhibited *increases* in CAB to the handgrip and unsolvable puzzle tasks relative to baseline (reflecting relative parasympathetic activation and sympathetic withdrawal). In contrast, controls showed the expected normative pattern of decreases in CAB (reflecting relative parasympathetic withdrawal and sympathetic activation) to these tasks. Our findings are generally consistent with Miller et al. (2009), who reported a similarly atypical response pattern to a laboratory stressor among asthmatic youth with depressive symptoms, while nondepressed asthmatic youth showed the normative response. However, since Miller et al. (2009) observed the effect with emotional films, it is unclear why we did not also observe this effect to our sad film. Notably, Miller et al., (2009) also focused on children with asthma, a condition that may lead to vagal overactivity. Importantly, we also found that our group differences between probands and controls were not explained by current depression, suggesting that CAB may reflect an underlying vulnerability rather than a mood state dependent phenomenon.

Group differences were task specific, as our proband and control groups responded similarly to the sad film and cold face tasks. One possible explanation of this finding is that the sad film and cold face were passive tasks, while the handgrip and unsolvable puzzles required sustained effort and focused attention. Indeed, other researchers have interpreted blunted physiological reactivity in depression in term of deficient “effort mobilization” during performance of cognitive tasks, which may reflect deficits in the self-regulation of behavior (e.g., Brinkmann & Gendolla, 2008; Brinkmann & Franzen, 2015). Friedman and Thayer (1998) have suggested links between parasympathetic nervous system activity and enhanced attention and effective emotion regulation. Successful attention deployment is an important component of effective emotion regulation that involves selecting meaningful information from the environment and linking it with appropriate emotional responses (Gross, 1998; Appelhans & Luecken, 2006). Indeed, both the neurovisceral integration model (Thayer & Lane, 2000) and Porges’ Polyvagal theory (Porges, 1992) suggest that strong PNS activity at rest provides increased flexibility to rapidly adjust parasympathetic influence on the

autonomic nervous system as called for by task demands (i.e., to effectively deploy attentional engagement or disengagement). Sustained attention has been associated with PNS withdrawal and SNS activation, as well as task performance in tests of attention and working memory (Backs & Seljos, 1994; Hansen, Johnsen, Sollers, Stenvik & Thayer, 2004; Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; Luft, Takase, & Darby, 2009; Hansen, Johnsen & Thayer 2003). Therefore, it is possible that tasks involving sustained effort or focused attention elicit larger normative reductions in CAB, and therefore more readily distinguish proband and control cases. Future research should examine the impact of effort and attention on changes in CAB among depressed and nondepressed individuals. However, given that Miller et al. (2009) reported group differences in CAB changes to emotional films as a function of depression, it also may be that our sad film stimulus was insufficiently potent. Importantly, although CAB reflects the balance of parasympathetic (RSA) and sympathetic (PEP) indices, there were no group differences in RSA changes to either task, and PEP abnormalities in probands were only exhibited in response to the handgrip task, but not the unsolvable puzzle. Finally, we also did not find any effects for the LF/HF ratio, another index of the balance of SNS and PNS activity. It should be noted that the LF/HF ratio and may reflect a blend of PNS and SNS activity, limiting its interpretability (Berntson et al., 1997, Eckberg, 1997 and Goldstein, Bentho, Park, & Sharabi 2011).

Given that CAB incorporates both parasympathetic and sympathetic activation, it provides a more comprehensive index of autonomic functioning that is more sensitive to autonomic changes that may reflect aspects of self regulation. Indeed, researchers have suggested that composite measures may be more reliable and sensitive metrics of autonomic functioning than individual indices (Kreibig, Gendolla, & Scherer, 2012). For example, Norman, Berntson & Cacioppo (2014) have observed that while averaged cardiovascular responses to orthostatic stress and standard psychological stressors tend to be very similar when analyzed at the group level, examination of SNS and PNS influences separately reveals a much more complex picture, particularly for psychological stressors.

These findings may also have relevance for physical health, as CAB has been associated with a number of poor health outcomes (Thayer et al., 2010; Berntson & Cacioppo, 2008; Licht et al., 2013). Our findings may be germane to the large literature documents relationships between depression and cardiovascular disease (Barth, Schumacher & Herrmann-Lingen, 2004; Nicholson, Kuper & Hemingway, 2006; Rugulies, 2002). Thus, elucidating the relationship between CAB and self regulation may also lead to a better understanding of the links between depression and poor health.

Given the lack of empirical literature on the relationship between CAR and depression, we did not have specific predictions about group performance. Notably, although CAR also incorporates sympathetic and parasympathetic indices, the only group difference we observed for this measure was for the handgrip task, which seemed to be driven by changes in PEP, rather than coactivation of both PNS and SNS measures. Further, the group difference in CAR for the handgrip task results did not withstand control for current depression status, suggesting the possibility that this variable may index mood state rather than trait vulnerability. The stronger results for CAB suggest that the balance of PNS and SNS activation is more relevant for self regulation and depression vulnerability than their

coactivation or coinhibition, which is consistent with prior literature (e.g., Nugent et al., 2011; Udupa et al., 2007; Chang et al., 2012).

Strengths of our study include use of multiple psychological and physical stress tasks, a large well-characterized sample of high risk youth and healthy control peers, and a comprehensive assessment of autonomic functioning. At the same time, we were limited in our ability to assess aspects of effort mobilization or attention that may be relevant to group differences in CAB. In addition, while CAB and CAR may have interpretable advantages over prior indices, such as the LF/HF ratio, we are nevertheless limited by the assumption that CAB and CAR assume integrated control of chronotropic (i.e., related to heart rate) and inotropic (i.e., related to force of contraction of the heart) function and are assessing joint sympathetic and parasympathetic control (see Thayer & Uijtdehaag, 2001). In sum, the results from this study suggest that CAB may be a useful index that reflects the balance and flexibility of the autonomic nervous system to respond to aspects of the environment that may be sensitive to psychophysiological abnormalities reflecting depression vulnerability.

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Highlights

- We examine cardiac autonomic balance in youth with a history of depression.
- Changes in cardiac autonomic balance were measured using four laboratory tasks.
- Youth with a history of depression showed abnormalities in autonomic balance.
- Results may have implications for depression risk and self regulation.

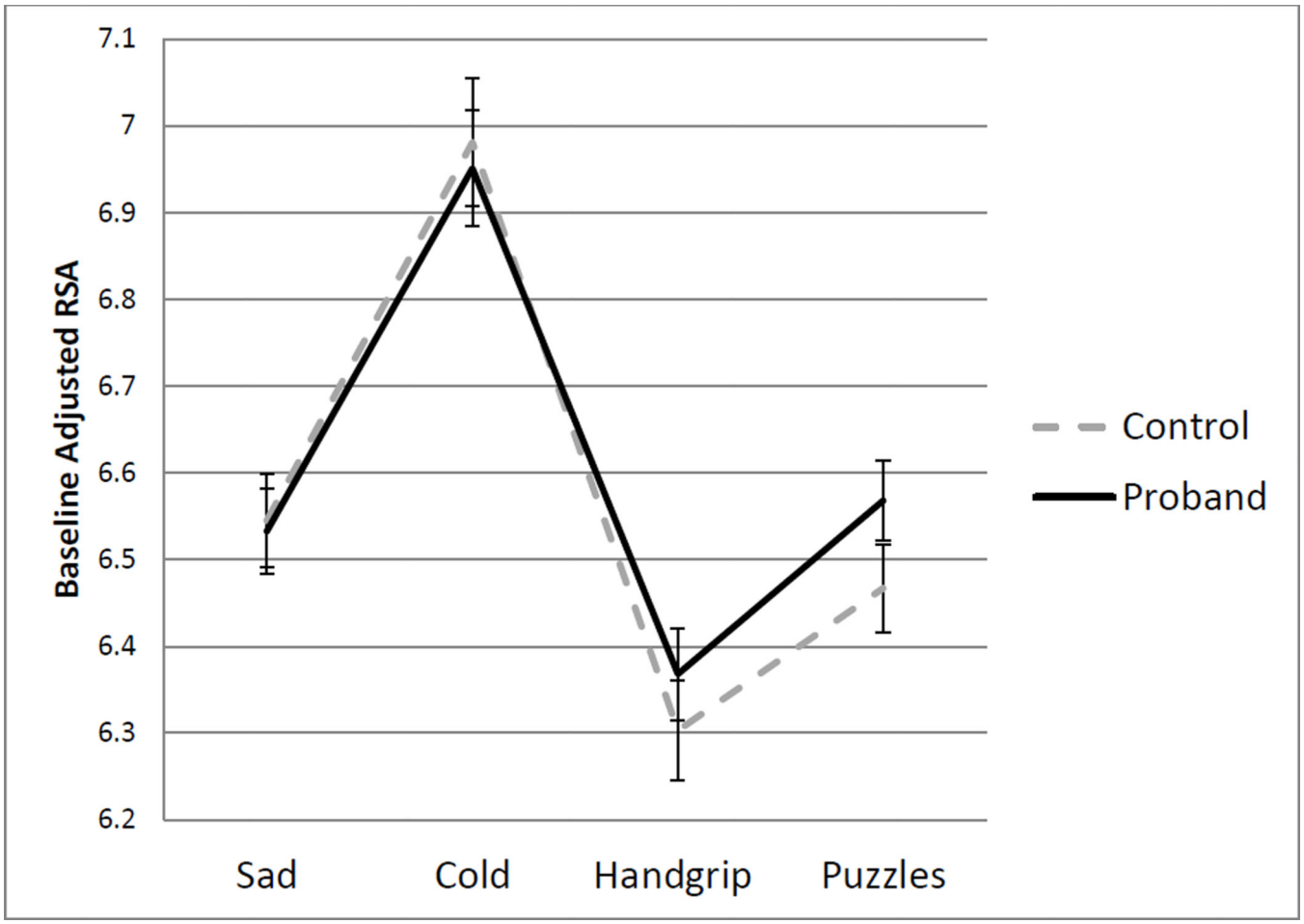

Figure 1. RSA changes from baseline across tasks by group

Note: Covariates appearing in the model are evaluated at the following values: Body Mass Z-Score = −.0790, Age Years = 16.6057, RSA Baseline = 6.6305.

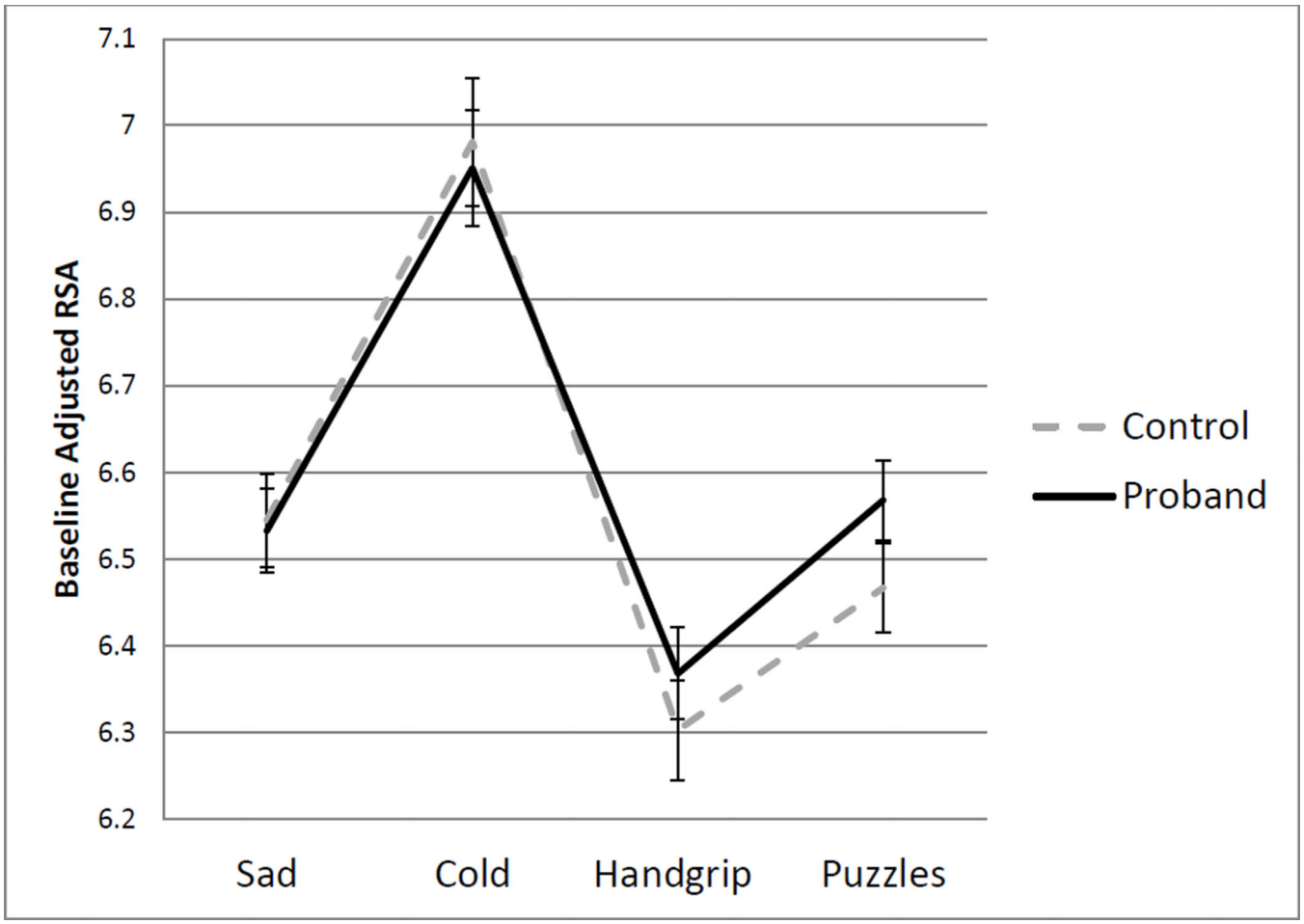

Figure 2. LF/HF Ratio changes from baseline across tasks by group

Note: Covariates appearing in the model are evaluated at the following values: Body Mass Z-Score = −.0790, Age Years = 16.6057, LF/HF Ratio Baseline = 1.3858.

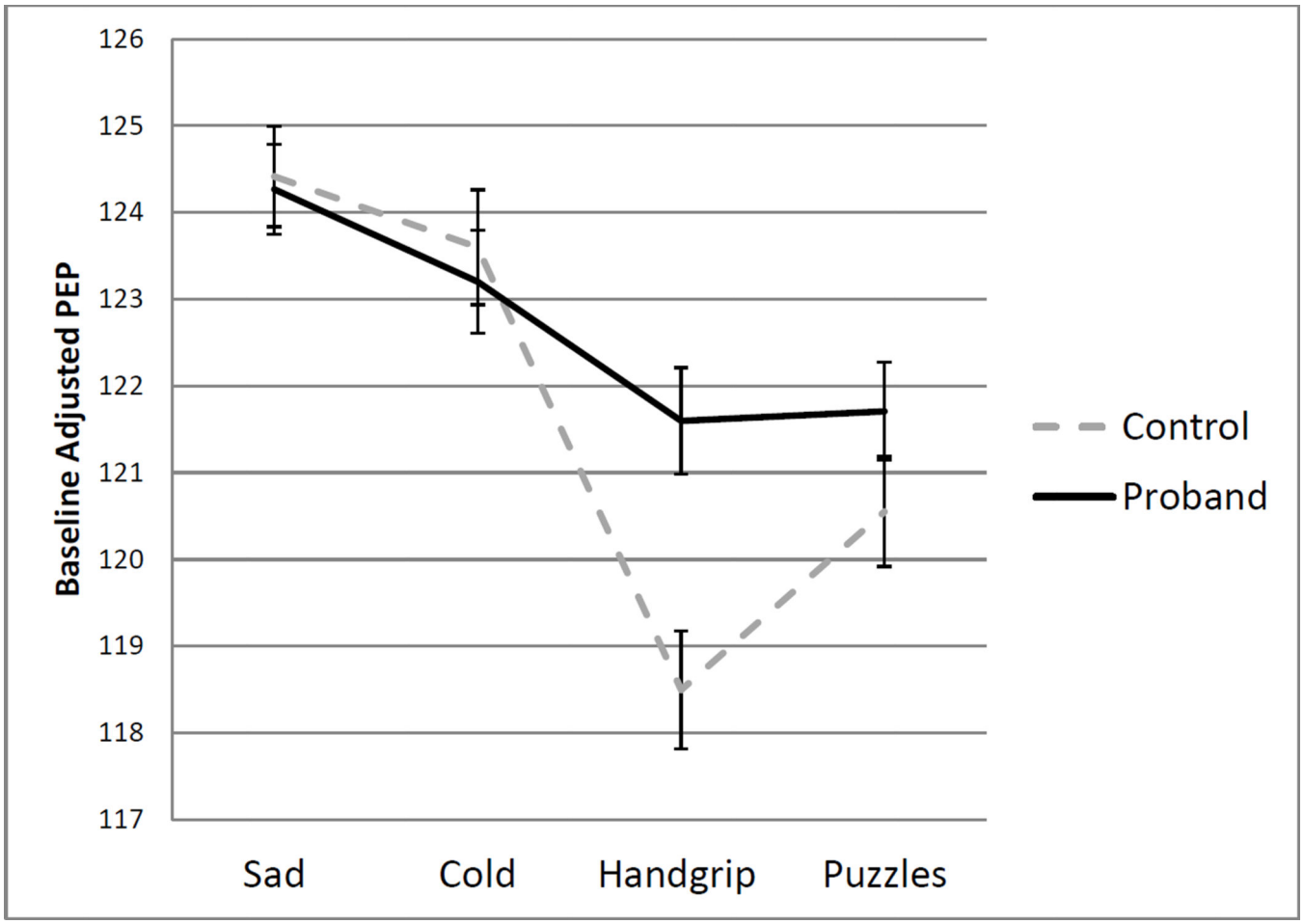

Figure 3. PEP changes from baseline across tasks by group

Note: Covariates appearing in the model are evaluated at the following values: Body Mass Z-Score = −.0781, Age Years = 16.5987, PEP Baseline = 124.8564.

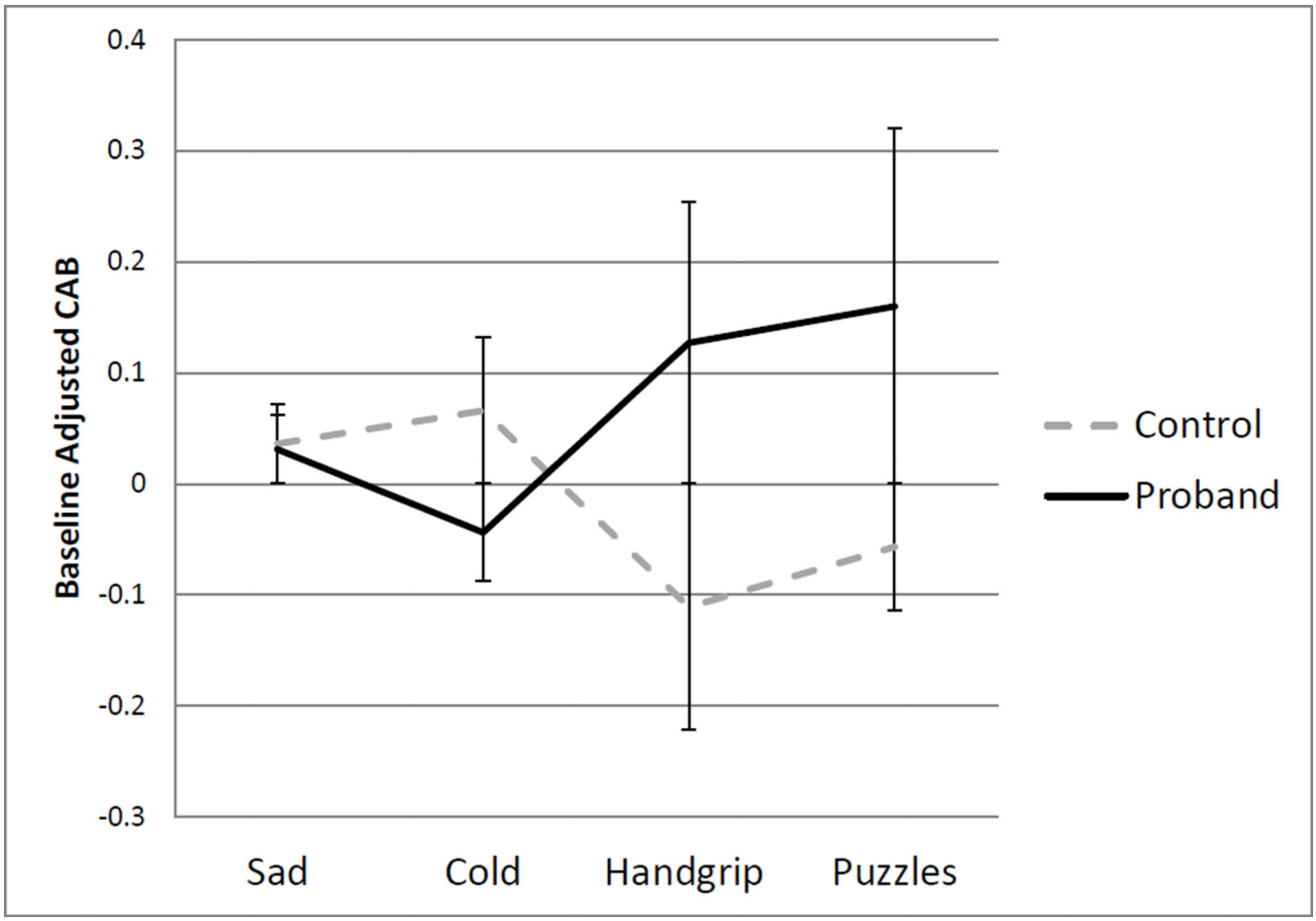

Figure 4. CAB changes from baseline across tasks by group

Note: Covariates appearing in the model are evaluated at the following values: Body Mass Z-Score = −.0781, Age Years = 16.5987, CAB Baseline = .0619.

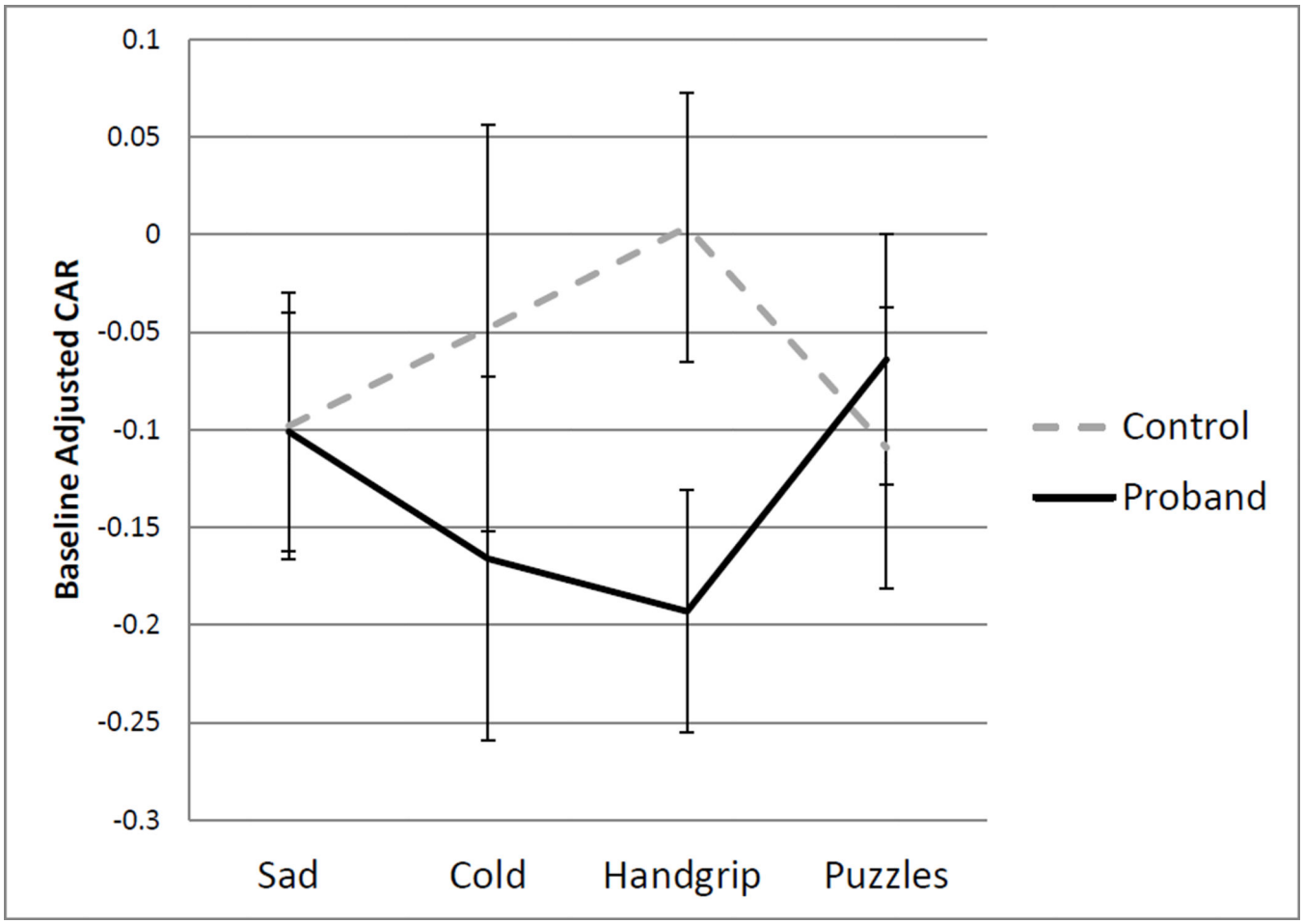

Figure 5. CAR changes from baseline across tasks by group

Note: Covariates appearing in the model are evaluated at the following values: Body Mass Z-Score = −.0781, Age Years = 16.5987, CAR Baseline = −.1337.

Table 1

Characteristics of Sample

	% Male	Age (SD)	BMI (SD)
Probands	64.1	17.0 (1.40)	22.12 (4.77)
Controls	64.1	16.1 (2.13)	21.57 (4.29)

Note: BMI=Body Mass Index in kg/m^2, SD=Standard Deviation. Age and BMI are presented as means in each group.

Table 2

Characteristics of the Unadjusted Psychophysiological Variables (Means; Standard Deviations) by Group and Task

	Probands					Controls				
	Baseline	**Cold**	**Sad**	**Handgrip**	**Unsolvable**	**Baseline**	**Cold**	**Sad**	**Handgrip**	**Unsolvable**
HR	72.16(10.32)	65.52(9.11)	68.78(9.52)	77.91(10.67)	73.96(9.93)	75.12(11.49)	67.94(10.98)	70.88(11.17)	81.07(11.69)	77.03(11.63)
RSA	6.58(1.06)	6.89(1.17)	6.47(1.08)	6.31(1.02)	6.53(1.00)	6.71(1.01)	7.03(1.16)	6.55(1.07)	6.33(1.05)	6.48(0.91)
PEP	126.21(14.01)	124.52(14.61)	125.58(13.56)	122.77(14.60)	122.85(14.61)	123.53(14.09)	122.27(15.03)	123.42(14.09)	117.12(14.74)	119.48(14.90)
CAB	.13(1.32)	.02(1.18)	.09(1.30)	.18(1.38)	.20(1.35)	−.00(1.19)	.04(1.79)	−.05(1.32)	−.17(1.33)	−.15(1.33)
CAR	−.25(1.42)	.03(1.18)	.09(1.30)	.18(1.38)	.20(1.35)	−.01(1.37)	.07(1.89)	−.05(1.30)	.12(1.32)	−.06(1.30)
LF/HF	1.53(1.71)	.85(1.15)	1.38(1.50)	1.31(1.26)	1.67(1.29)	1.21(1.27)	.71(1.00)	1.08(1.09)	1.11(1.11)	1.42(.97)

Note: HR=Heart Rate, RSA=Respiratory Sinus Arrhythmia, Pep=Pre-ejection Period, CAB=Cardiac Autonomic Balance, CAR=Cardiac Autonomic Regulation, LF/HF=Low Frequency to High Frequency Ratio