Title:

Reactive Heart Rate Variability and Cardiac Entropy in Children With Internalizing Disorder and Healthy Controls

Authors: Charlotte Fiskum [a,b], Tonje G. Andersen[a], Magne A. Flaten[a], Per M. Aslaksen[c], Xavier Bornas[d], Karl Jacobsen[a]

a: Department of Psychology, Norwegian University of Science and Technology, Norway

b: Department of Child and Adolescent Psychiatry, St. Olav's University Hospital, Norway

c: Department of Psychology, the Arctic University, Norway

d: Department of Psychology, The University of the Balearic Islands, Spain

Corresponding author: Charlotte Fiskum, charlotte. fiskum@stolav.no, lottefisk@gmail.com

Acknowledgements

The authors wish to thank the families who participated. The authors also wish to acknowledge professor Birgit Svendsen who contributed to the project before her passing in 2016, as well as Drs. Matthew Long, Julian F. Thayer, Anita L. Hansen and Patrick Vogel for valuable discussions and input on the results. Finally, we wish to thank the reviewers for helpful comments on the manuscript. The authors declare that they have no conflict of interest.

Abstract

Background: Atypical vagal reactivity has been linked to internalizing psychopathology and less adaptive emotion regulation, but reactive cardiac entropy is largely unexplored. Therefore, this study investigated reactive vagally-mediated heart-rate variability (vmHRV) and cardiac entropy in relation to emotion regulation.

Method: Electrocardiograms of 32 children (9-13 years) with internalizing difficulties and 25 healthy controls were recorded during a baseline and a sad film. Reactivity-measures were calculated from root mean square of successive differences (RMSSD) and Sample Entropy (SampEn). Emotion regulation was assessed using the Emotion Regulation Checklist (ERC). Determinants of reactive SampEn and RMSSD were analyzed with marginal and generalized linear models. The study also modeled the relationship between cardiac reactivity and emotion regulation, while controlling for psychopathology.

Results: The two groups differed significantly in vmHRV-reactivity, with seemingly higher vagal-withdrawal in the control group. SampEn increased significantly during the film, but less in subjects with higher psychopathology. Higher reactive entropy was a significant predictor of better emotion regulation as measured by the ERC.

Conclusion: Internalizing subjects and controls showed significantly different vmHRV-reactivity. Higher reactive cardiac entropy was associated with lower internalizing psychopathology and better emotion regulation and may reflect on organizational features of the neurovisceral system relevant for adaptive emotion regulation.

Introduction

The heart-brain connection and the vagus nerve has long been recognized as essential for adaptive self-regulation (Porges, 1995). In the neurovisceral integration model (Thayer & Lane, 2000, 2009) adaptive emotion regulation is seen as dependent on inhibitory neural traffic from prefrontal-subcortical circuits, including the central autonomic network (CAN) (Benarroch, 1993). In particular, the effect of efferent vagal nerve traffic on vagally-mediated heart rate variability (vmHRV) can act as a readout of neural circuits essential for adaptive self-regulation (Beauchaine & Thayer, 2015; Thayer, Åhs, Fredrikson, Sollers Iii, & Wager, 2012).

Cardiac reactivity, which assesses the difference between a resting baseline and a stressor-condition, can serve as an index of the effect of a stimulus on neurocardiac function, and the responsiveness of neural circuits responsible for vagal inhibition (Beauchaine & Thayer, 2015; Porges, Doussard-Roosevelt, & Maiti, 1994). A withdrawal of inhibitory vagal traffic results in a decrease in vmHRV. Studies of cardiac reactivity and vmHRV-withdrawal in response to emotional stimuli, therefore, represents an important source of information that can increase insight into emotion regulation and psychopathology (Beauchaine, 2015; Beauchaine & Thayer, 2015; Porges, 1995).

Several studies on cardiac reactivity have focused on vmHRV related to negative emotions, often fear, anxiety, or sadness (Kreibig, 2010). The literature on vmHRV-reactivity related to negative emotional stimuli in children with, or at risk for, internalizing spectrum psychopathology has shown somewhat conflicting results (Graziano & Derefinko, 2013; Hamilton & Alloy, 2016). For instance, Gentzler and colleagues (Gentzler, Santucci, Kovacs,

& Fox, 2009) found that greater vagal withdrawal during a sad film was associated with more adaptive emotion regulation strategies, prospectively predicting lower depressive symptoms. Conversely, Fortunato and colleagues (2013) found that higher severity of internalizing symptoms was associated with greater vmHRV-withdrawal in response to fearful and sad films. Pang and Beauchaine (2013) found that depressed children showed vmHRV-increases, while children with concurrent depression and conduct disorder showed vmHRV-withdrawal compared to controls when watching a sad film.

In a recent review of the literature, Hamilton and Alloy (2016) concluded that both blunted and increased vmHRV-withdrawal was linked to depression. Finally, a meta-analysis of vmHRV-reactivity in internalizing children found that greater vmHRV-withdrawal was associated with less internalizing symptoms (Graziano & Derefinko, 2013). Interestingly, lower vmHRV-reactivity and withdrawal has also been prospectively linked to higher symptoms of psychopathology after negative life-events and trauma (Mikolajewski & Scheeringa, 2018; Stange, Hamilton, Olino, Fresco, & Alloy, 2017), indicating possible causality.

As the neurocardiac system is a complex adaptive system, there is reason to assume that an analysis of cardiac complexity can provide additional information. Estimates of nonlinear complexity can contribute insight into the underlying flexibility and functionality of a system, and is relevant for the investigation of regulatory and adaptive processes (Bertuglia & Vaio, 2005; Lehrer & Eddie, 2013; Thelen & Smith, 1994; West, 2014). Complexity-based methods may even at times be more sensitive than linear HRV-measures (Kemp et al., 2010; Young & Benton, 2015).

Cardiac entropy-measures are among the most-studied indices of cardiac complexity (Sassi et al., 2015), also for emotional dysregulation and internalizing psychopathology (de la Torre-

Luque, Bornas, Balle, & Fiol-Veny, 2016). Highly predictable low-complexity systems generate little new information, showing low informational entropy. More complex systems show higher rates of information generation, and hence, higher entropy (Bertuglia & Vaio, 2005). Although a high degree of randomness also yields high entropy, in an otherwise healthy system higher entropy is assumed to index a more complex underlying organization (Bertuglia & Vaio, 2005).

Emotional dysregulation and internalizing psychopathology have been associated with lower resting cardiac complexity, or a loss of ordered complexity (de la Torre-Luque et al., 2016). The present authors have linked lower resting cardiac complexity to internalizing psychopathology (Fiskum et al., 2018). This study extends further on this work, also investigating reactive cardiac entropy.

A study of reactive entropy in electroencephalograms (EEGs) in healthy adults found an increase in brain-pattern-complexity during both positive and negative emotion compared to a neutral condition (Aftanas et al., 1997), indicating that emotion elicitation is associated with higher complexity of underlying brain activity. Few studies have been conducted on cardiac entropy related to sad emotional material. Köbele and colleagues (2010) found no differences in cardiac complexity in healthy adult females exposed to either a neutral or a sad mood induction. Studies looking at stressful or anxiety-creating situations in adolescents or adults have shown a decrease in cardiac entropy during stress (Bornas et al., 2006; de la Torre-Luque, Fiol-Veny, Bornas, Balle, & Llabres, 2017; Mateo, Blasco-Lafarga, Martinez-Navarro, Guzman, & Zabala, 2012).

As far as the authors know, no studies have yet investigated the link between reactive complexity and adaptive emotion regulation in children, nor has anyone investigated the discriminative power of reactive cardiac entropy relative to reactive vmHRV. Therefore, this

study investigates cardiac entropy and vmHRV during exposure to a sad film in children with, and without, internalizing difficulties focusing on three main hypotheses.

H1: During the film we expect a decrease in vmHRV due to a withdrawal of vagal inhibitory efferent traffic and an increase in cardiac entropy due to the active recruitment of areas involved in emotional processing and self-regulation.

H2: We expect individuals with higher psychopathology scores to present with lower vmHRV reactivity and lower cardiac reactivity compared to the controls.

H3: Higher reactive cardiac entropy will be associated with more adaptive emotion regulation, also when controlling for internalizing psychopathology.

Methods

The project was conducted in agreement with the Helsinki Declaration (World Medical Association, 2013) and received approval from the Norwegian Regional Committees for Medical and Health Research Ethics. All participants received a written and oral explanation of the procedures and background for the project, and parents gave written consent.

Design

The study was a between-groups repeated measures design, with a clinical group presenting with internalizing problems and an age-matched healthy control group. A 5-min resting baseline was followed by a sad film. The participants have been described previously (Fiskum et al., 2017).

Subjects

Forty children aged nine to thirteen years were referred to the clinical group by parents and health- and social services. The children were assessed with the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001), which gives an age- and gender-adjusted assessment of symptom severity for internalizing and externalizing childhood disorders. Inclusion in the

clinical group called for clinical or borderline clinical internalizing symptoms. Four children were excluded due to normal CBCL scores. Further exclusion criteria were severe learning difficulties, major somatic or psychiatric disorders in the thought-disorder or externalizing spectrums or medicine use. Two children were excluded due to medicine use, one due to psychotic symptoms, and one because of a congenital heart condition. A total of 16 boys and 16 girls were included in the clinical group (mean age 10.9 years, SD 1.3).

For the control group 28 children were recruited through local schools (20 children) and convenience sampling (8 children). Inclusion in the control group called for healthy children with no previous referral to mental health services and CBCL scores within the normal range. The same exclusion criteria as for the clinical group applied. One child was excluded due to an elevated CBCL score, one child due to an earlier referral for developmental delay, and one child because of combined medicine use and an elevated CBCL. A total of 14 girls were included in the control group (mean age 10.3 years, SD 1.2).

The children were recruited from two Norwegian urban areas in Trondheim (47 children) and Oslo (10 children). There were no statistical differences for the groups on income or parental education.

Assessment of Psychological Variables

Emotion regulation was assessed through the Emotion Regulation Checklist (Shields & Cicchetti, 1997). The Emotion Regulation subscale (Cronbach's $\alpha = .88$) consists of 8 items assessing processes linked to adaptive emotion regulation and responding, like the ability to adequately express positive and negative emotions, and give appropriate affective responses in social settings. A higher score indicates more adaptive emotion regulation.

Internalizing psychopathology was assessed through the CBCL (Child Behavior Checklist) 6-18 parent rating form Internalizing Problems scale ($\alpha = .90$) reflecting the dimensional load on internalizing disorders, mainly anxiety and depression.

Experimental Protocol

On the day of the experiment children and parents were given a 15-min explanation of the protocol and their right to withdraw. Parents were then escorted to a private waiting area and instructed to fill out the study forms. Most recordings took place in Trondheim, but 10 subjects were assessed in Oslo. To minimize confounding effects the locations were configured similarly visually and were run by the same female experimenters, using the same equipment and protocol. All recordings were conducted between 9 am and 6 pm, except for one recording that started at 8.30 am. A preliminary analysis of the data showed no significant influence of time of day or location on the psychophysiological variables.

Wearing light clothing the children were weighed (Coline scale) and their height was measured to calculate body mass index (BMI). Children received a hearing screening using a Micromate 304 audiometer (Madsen Electronics), ensuring normal hearing thresholds. Afterward, standard disposable Ag/AgCl electrodes were attached in a lead-II configuration on the clavicle and lower rib. The last 10 minutes before the experiment began the children sat quietly in the experimental chair.

First, the children were instructed to sit as quietly as possible for a 5-min baseline recording. The children were not instructed to breathe in a paced manner. After the resting baseline the children were exposed to a sad film. The children were instructed to sit quietly and watch, and “try to engage emotionally”.

The children were randomly assigned to watch one of two animated film clips from either *The Lion King* (LK) (Walt Disney Pictures, 1994) or *The Land Before Time* (LBT) (Universal Pictures, 1988). Both films have been used to induce negative emotion previously (Davis, Quiñones-Camacho, & Buss, 2016; Leupoldt et al., 2007), and the selected segments follow a highly similar story with similar pacing. The length of the film-clips were slightly different at 460 s (LK) and 496 s (LBT) to make sure the semantic and emotional content was similar. A 5-min segment was chosen a priori from both films containing the same story- elements. The use of two film clips depicting the same emotional content is thought to increase the likelihood that ANS-reactivity during induction is related to the emotion rather than the films themselves (Rottenberg, Ray, & Gross, 2007).

Self-Assessment Manikins (SAM) (Bradley & Lang, 1994) were administered after the films, to assess categorization and valence of the children's emotional reaction. Emotional response was assessed with the question: “This movie made me feel… happy, scared/anxious, sad, angry, surprised, disgusted, no feeling”. Eighty-four percent of the children reported feeling sad, 15 percent reported feeling scared/anxious. The SAMs also assessed the valence of the main emotion with a 9-point Likert scale ranging from “very negative” to “very positive”.

Equipment and Psychophysiological Measurements

The films were presented on a 21.5 in. monitor placed at a 1 m distance. Electrocardiograms (ECG) were recorded using a Biopac MP150 system, ECG100C amplifier and AcqKnowledge (ver. 4.4) data-acquisition software. The sampling rate was 1000 Hz. Three 35 Hz low pass, 1.0 Hz high pass, and 50 Hz notch filters were applied on acquisition.

Biometric Analysis

The ECG-signal was exported from AqcKnowledge and subsequently analyzed using Kubios premium version 3.0.1. (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).

A smoothing prior filter (500 lambda) was applied to correct for slow drift and non-stationarity. The signal was visually inspected for artifacts using both the raw ECG waveform and the R-R tachogram. Artifacts were manually corrected following the Kubios manual. Misidentified points in the RR-tachogram were placed correctly using the ECG-waveform. For ectopic beats, the corrupt RR-values were replaced with interpolated values using the automatic correction option. No beats beyond those identified as ectopic were corrected using this procedure.

Root mean square of successive differences.

The root mean square of successive differences in the inter-beat interval (RMSSD) is a much-used measure of vmHRV that presents with acceptable reliability in child/adolescent populations (Weiner & McGrath, 2017).

Sample entropy.

Sample Entropy (SampEn) (Richman & Moorman, 2000) is a measure of cardiac entropy. SampEn was defined as the negative natural log of the estimated conditional probability that template vector epochs of length *m* (the embedding dimension) that match pointwise within a tolerance (*r*) also match at the next point (*m+1*) through the time series (the number of R-R intervals, *N*). Sample entropy is then given as $SampEn\ (m, r, N) = -\log A/B$, where *A* is the number of vector pairs $< r$ of length $m+1$, and *B* is the number of vector pairs $<r$ of length *m*. A higher value of SampEn indicates a less regular, more complex signal. SampEn was calculated with an *m* of 2 and *r* set to 0.2 standard deviations of the R-R interval.

Calculation of reactive RMSSD and reactive SampEn.

Reactive RMSSD (rRMSSD) and reactive SampEn (rSampEn) were calculated by subtracting the baseline-values from the values obtained during the induction (film - baseline). A negative value indicates a reduction in entropy or RMSSD, with a more negative value

indicating a greater decrease. A positive value indicates an increase, with a larger value indicating a greater increase.

Statistical Analysis

For statistical analysis SPSS version 25 (IBM) was used. Before analysis all outliers ± 3.29 SD) were removed from the psychological and physiological data to limit the impact of outliers. This resulted in the removal of 3 datapoints. Analysis were run with and without outliers to check that the results were not altered significantly with the removals.

Relationships between the cardiac variables were assessed with Spearman ranked order correlations rho (ρ) due to the small sample size. Mann-Whitney U-tests were used for statistical analysis of between-group differences for the same reasons. Effect sizes are given as Cohen's *d*.

A marginal linear model was used to investigate differences in RMSSD and SampEn across the baseline and induction. Experimental condition (baseline versus induction), film (LK versus LBT), and sex were treated as fixed factors, and BMI, age and internalizing psychopathology scores were treated as fixed continuous variables. Baseline HR and HR during the film were included in all models as fixed continuous variables, to control for the physiological and mathematical relationship between HR and HRV (Sacha, 2013). Restricted maximum likelihood (REML) was chosen as estimation method, and a heterogeneous compound symmetry (CSH) covariance structure provided the best fit for the models as assessed by lower Schwarz's Bayesian (Schwarz, 1978) and Akaike's information criterion (Akaike, 1974). Residuals were assessed for normality. For between-group comparison of the grand means t-tests of the estimated marginal means were used. Spotlight analysis (Spiller, Fitzsimons, Lynch, & McClelland, 2013) in the marginal linear models tested the slopes of the dependent variables (RMSSD or SampEn) from the baseline to the film at fixed values of internalizing psychopathology as measured by the CBCL. A spotlight analysis of chosen

values of a scale provides more power than treating each value as a discrete categorical factor in an ANOVA, because the spotlight analysis is a regression parameter estimate using all data points and not just those at a fixed value. For this analysis the values 40 (low normal), 60 (borderline clinical) and 65 (clinical) on the CBCL were chosen to reflect no psychopathology, borderline psychopathology and clinical psychopathology respectively.

As reactive entropy in psychopathology is largely unexplored, a generalized linear model using maximum likelihood estimate further investigated the relationship between internalizing psychopathology and rSampEn, while controlling for group, sex, age, film, BMI, HR and baseline SampEn.

Finally, a generalized linear model was used to investigate the relationship between rRMSSD, rSampEn and emotion regulation while controlling for film, sex, age, BMI, HR and internalizing psychopathology. For easier interpretation of the parameter estimates, the continuous predictor- and co-variables in both generalized models were normalized through Z-score transformation before the linear modeling.

Model fit for the full generalized models was evaluated using information criteria (Aikaike's and Bayesian information criteria) and the models were inspected for influential cases through Cook's D and residual plots. Effect sizes for both generalized models are given with odds-ratio (Exp-B), which indicates the likelihood of an increase/decrease in the dependent variable given an increase in the independent variable. A positive odds-ratio indicates a likely increase, while a negative odds-ratio indicates a likely decrease.

Results

Descriptive Statistics and Between-Group Differences

Mann-Whitney U-tests showed that there were no significant differences between the films with respect to emotional valence for neither the clinical (LK: M 3.8, (SD 1.2), LBT: M 4.4

(SD 1.9), U = 96.5, p = .27), nor the control group (LK: M 4.2 (SD 2.0), LBT: M 5.2 (SD 1.3), U = 49, p = .13).

The control group showed a higher score on the Emotion Regulation scale than the clinical group. Baseline data for RMSSD and SampEn were not significantly different. There was a significant difference between the groups in rRMSSD, but not rSampEn. See Table 1 for descriptive data and between-group differences.

Correlations

A non-parametric Spearman's ranked order correlation showed no significant relationship between the values of RMSSD and SampEn during the film (clinical group: ρ = .05, p = .80, control group: ρ = .18, p = .39). Similarly, there was no significant relationship between the reactive scores for rRMSSD and rSampEn in either the clinical (ρ = -.23, p = .21) or the control group (ρ = .13, p = .53).

The effect of the experimental condition on RMSSD

The marginal linear model showed there was no significant main effect of internalizing psychopathology (F (1, 46.47) = 2.07, p = .157), but there was a significant main effect of condition (F (1,53) = 6.86, p = .011) indicating withdrawal (estimate of fixed effects time 1 versus time 2: 27.13 SE ±10.36 [CI 6.35 to 47.89]). There was also a significant condition - psychopathology interaction in the prediction of RMSSD (F (1, 53) = 7.30, p = .009). With degree of psychopathology fixed at 40 (no psychopathology) in the estimated marginal means there was a near significant reduction from baseline to induction (-7.11 SE ±3.58 [CI -14.3 to 0.07] p = .052). Fixed at 60 (borderline clinical) there was no significant change from baseline to induction (3.0 SE ±2.6 [-2.32, 8.11] p = .270), and fixed at 65 (clinical) there was a non-significant trend towards an increase in RMSSD from baseline to induction (5.4 SE

±3.1 [CI -0.80 to 11.60], p = .086). See Figure 1a for a visual presentation of the response pattern for different levels of psychopathology.

There was also a significant effect of age on RMSSD (F (1, 47) = 7.35, p = .009), where higher age was associated with lower RMSSD (estimate of fixed effects = -10.11, SE ±3.73, p = .009).

HR during the film also had a significant effect on RMSSD (F (1, 47) = 12.07, p = .001), higher HR was associated with lower RMSSD (estimate of fixed effects = -25.44, SE ±7.32, p = .001). Film (p = .79), sex (p = .85), BMI (p = .69) and baseline HR (p = .83) were not significantly associated with RMSSD in the marginal linear model.

The effect of the experimental condition on SampEn

The marginal linear model showed that SampEn was significantly affected by the factor condition (F (1,53.82) = 4.79, p = .033). Estimated marginal means revealed that there was a significant increase in SampEn from baseline to induction (.073 SE ±0.028, CI [0.016 to 0.130], p = .013).

There was no significant interaction effect between degree of psychopathology and experimental condition (F (1, 53.95) = 2.69, p = .107), so the model did not detect a significant distinction in the response pattern (increase versus decrease) dependent on psychopathology, but there was a trend towards a lower increase in subjects with higher psychopathology. See Figure 1b for a visual presentation of the response pattern for different levels of psychopathology.

The grand mean of the conditions combined (grand mean of entropy across baseline and film combined) was significantly different depending on degree of psychopathology. When

psychopathology was fixed at 40 (no psychopathology), the SampEn grand mean was 1.79 (SE ±0.03), at 60 (borderline) it was 1.70 (SE ±0.02) and at 65 (clinical) it was 1.68 (SE ±0.03). T-tests indicated that the grand means were significantly different between normal and borderline clinical psychopathology (p = .014) and normal and clinical psychopathology subjects (p =.011), but not between borderline clinical and clinical subjects (p =.58).

Degree of internalizing psychopathology was a significant predictor of SampEn in the marginal model (F (1, 49.46) = 9.16, p = .004). Higher internalizing psychopathology was associated with lower SampEn (estimate of fixed effects = -.006, SE ±.002, p = .005). BMI was also a significant predictor of SampEn (F (1, 48.26) = 4.06, p = .050). Higher BMI was associated with lower SampEn (estimate of fixed effects = -.04, SE ±.02, p = .050).

Finally, SampEn was significantly affected by sex (F (1, 48.11) = 4.69, p = .035). Male gender was associated with higher SampEn (estimated marginal mean of SampEn for males = 1.77 (SE ±.03), females = 1.69 (SE ±.03)).

Neither HR during baseline (F (1, 51.03) = 0.02, p = .89) nor film (F (1, 51.07) = 1.21, p = .28) were significantly associated with SampEn across the two conditions in the marginal model.

Further exploration of determinants of rSampEn: **generalized model**

The full model was significant (likelihood ratio X_2 (8) = 19.57, p = .012). Inspection of model effects and parameter estimates showed that higher baseline SampEn was associated with a lower rSampEn (Wald X_2 = 13.52, p ≤ .001, B = -1.0, 95 percent CI [-1.52 to -0.46], Exp(B) = 0.37, p ≤ .001). A higher degree of internalizing psychopathology was also associated with a lower rSampEn (Wald X_2 = 11.09, p = .001, B = -0.78, 95 percent CI [-1.23 to -0.32] Exp(B) = 0.46). Sex (p = .70), film (p = .47), age (p = .64), BMI (p = .26), baseline HR (p = .20) and HR during the film (p = .11) were non-significant.

Reactive RMSSD and reactive SampEn as Determinants of Emotion Regulation

The full generalized linear model was significant (likelihood ratio X_2 (9) = 32.45, $p \leq .001$). A higher BMI was related to lower emotion regulation (Wald X_2 = 5.68, p = .017, B = -0.10, 95 percent CI [-0.19 to -0.02], Exp(B) = .90), as was a higher degree of internalizing psychopathology (Wald X_2 = 16.12, p ≤ .001, B = -0.18, 95 percent CI [-0.27 to -0.09], Exp(B) = 0.84). A higher rSampEn was associated with a higher Emotion Regulation Score (Wald X_2 = 4.35, p = .037, B = 0.09, 95 percent CI [0.01, 0.17], Exp(B) = 1.09). There were no significant effects of rRMSSD (p = .115), sex (p = .72), film (p = .95), age (p = .17) or baseline HR (p = .33), but HR during the film was significant (Wald X_2 = 3.93, p = .047, B = -0.22, 95 percent CI [-0.43 to -0.002], Exp(B) = 0.81) showing that a higher HR during the film was associated with a lower Emotion Regulation score.

Discussion

The Impact of the Film on RMSSD and SampEn

The first part of the study investigated the impact of the emotional condition on the cardiac measures. Hypothesis 1 predicted that RMSSD would decrease and SampEn would increase.

Consistent with the first hypothesis the marginal linear model showed a decrease in RMSSD from the baseline to the film, indicating vagal withdrawal. There was also a significant interaction with condition (baseline vs induction) and internalizing psychopathology in the development of RMSSD, indicating different patterns of reactivity across the groups, which we will return to in the discussion of Hypothesis 2.

Cardiac entropy, as indexed by SampEn, increased significantly during the film compared to the baseline, indicating increased information in the cardiac signal. Complex systems generate more information than less complex systems, and an increase in informational output in an otherwise healthy system is most often a sign of increased complexity (Bertuglia & Vaio, 2005). Therefore, we propose that the increase in SampEn indexed a shift in

processing in underlying brain-areas relevant for both HR-control and emotional processing, from a less complex state during the resting baseline, to a more complex state during the film.

It is unclear whether an increase in complexity during processing of emotional material would always be expected, as few similar studies have been conducted. Valenza and colleagues (2012) found a decrease in entropy in healthy subjects when viewing arousing versus neutral pictures. Köbele et al. (2010) found no effects of a sad mood induction while de la Torre-Luque and colleagues (de la Torre-Luque, Caparros-Gonzalez, Bastard, Vico, & Buela-Casal, 2017) found higher levels of cardiac entropy during recovery from stress when listening to relaxing music, compared to silence. Finally, several studies looking at stressful or anxiety-triggering material have shown decreases in cardiac entropy when exposed to a stressor (Bornas et al., 2006; de la Torre-Luque, Fiol-Veny, et al., 2017; Mateo et al., 2012).

The fact that our results showed an increase in entropy from the baseline to the sad film is in contrast to the aforementioned studies showing a decrease in cardiac entropy associated with stress/anxiety. The contrasting results are interesting, and may indicate a potential difference in the complexity of the cardiac signal in sadness versus anxiety. A comparison of cardiac entropy during a sad versus an anxious/stressed state in the same participants would have helped elaborate on whether this could indeed be the case, and should be investigated further in future studies.

There was no apparent relationship between vagal withdrawal and increase in cardiac complexity, as seen in non-significant correlations between RMSSD and SampEn across conditions.

The Impact of Internalizing Psychopathology

Hypothesis 2 predicted that internalizing psychopathology would have an effect on reactive vmHRV and cardiac entropy. There were no significant group differences in baseline or film

SampEn or RMSSD, but rRMSSD was significantly lower in the control group, indicating a larger vagal-withdrawal in the controls compared to the clinical group.

The marginal linear model showed that RMSSD was significantly affected by an interaction between condition (film vs baseline) and degree of internalizing psychopathology. The spotlight analysis showed a nearly significant decrease in RMSSD when psychopathology was fixed at a low level. Results were more uncertain for subjects with elevated psychopathology but indicated a possible trend towards either no change or an increase in RMSSD. The different patterns of HRV-response in the two groups could perhaps indicate that the clinical versus control children spontaneously engaged in differential coping strategies (Davis, Levine, Lench, & Quas, 2010; White, Kross, & Duckworth, 2015) with HRV-reactivity indexing different strategies or success of regulation. However, the use of different coping-strategies may also result in similar HRV-responses, dependent on context, (Davis et al., 2016) meaning that no strong inferences can be made. Overall, the results are largely consistent with previous studies showing atypical vmHRV-reactivity in subjects presenting with psychopathology compared to controls (Graziano & Derefinko, 2013; Hamilton & Alloy, 2016).

Across the baseline and film-conditions combined (the grand mean) the marginal linear model also showed that higher psychopathology was linked to lower SampEn. This is consistent with other studies linking internalizing psychopathology with lower complexity (see for instance de la Torre-Luque et al., 2016), and expands on results presented previously (Fiskum et al., 2018) looking at the baseline only. The association between psychopathology and complexity in several studies, and across conditions is indicative of a common underlying factor influencing both cardiac complexity and psychopathology.

Interestingly, sex was also a significant determinant of SampEn across the two conditions, with males exhibiting higher SampEn across the two conditions than females. While some studies have failed to show sex-differences in entropy in children aged 1 to 15 (Pikkujämsä et al., 1999) and 6-8 (Seppala et al., 2014), a study recently showed lower entropy in adolescent girls (12-15 years), suggestive of an association between lower cardiac complexity and increased risk of anxiety in girls (Fiol-Veny, De la Torre-Luque, Balle, & Bornas, 2018b). These results are clinically interesting, given the higher risk of internalizing disorder in females (Hayward & Sanborn, 2002; McLean, Asnaani, Litz, & Hofmann, 2011), and the high risk of debut in adolescence (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2007).

In line with the Fiol-Veny study (2018b), our results suggest a possible common underlying factor between higher risk of internalizing problems and lower cardiac complexity in adolescent girls. Lower informational cardiac complexity is suggestive of less flexibility in the underlying neurovisceral system. This lower flexibility may in turn be related to differences in brain areas such as the limbic system, that has shown developmental differences between the sexes in adolescence, while also being implicated in internalizing psychopathology (Lenroot & Giedd, 2010). It is important to note that the results do not mean that girls are less capable of complex regulation. Lower entropy in a complex system can be a sign of a less complex state, but may also sometimes index more synchronized activity across large areas of the system (Bertuglia & Vaio, 2005). In such an example a high degree of synchronized (or coherent) activity across different brain-areas providing input to for instance the cardiac signal (see for instance McCraty & Zayas, 2014 for a discussion on coherence and synchronization in regulation of the cardiac rhythm) could present as a more uniform and regular aggregate signal, while not necessarily indicating lower complexity as such (Bertuglia & Vaio, 2005). Further analysis looking at coherence and synchrony across ECG, as well as electroencephalograms, could perhaps help elucidate this distinction further. Nonetheless, our

results, along with those of Fiol-veny and colleagues (2018a; 2018b) point to the potential role of reduced cardiac complexity as a biomarker of increased vulnerability to internalizing problems in adolescent girls.

As very little is known about reactive complexity, we also investigated possible determinants of rSampEn. This part of the study revealed no significant effects of sex, or any of the other co-variables apart from baseline complexity and psychopathology. Subjects with higher initial complexity exhibited a smaller increase in complexity compared to subjects with lower baseline complexity. This could be a display of the law of initial values, where subjects with a higher baseline will show statistically smaller changes in a manipulation raising the value in question, compared to subjects with lower initial values (Wilder, 1962). The smaller reactivity in high-complexity baseline-individuals could also mean that children exhibiting a high degree of resting complexity may function closer to a hypothetical optimal level of complexity. Both very low and very high levels of complexity can lead to reduced functionality, with optimal organization residing in-between, in a curvilinear function (Bertuglia & Vaio, 2005; Guastello, 2015).

Importantly, internalizing psychopathology also affected the degree of reactivity negatively, and rSampEn was lower in subjects with higher psychopathology scores. The lower reactive increase in cardiac entropy in subjects with higher psychopathology gives further support to the idea of cardiac entropy as an index of neurovisceral flexibility and adaptability. To test this idea further, we wanted to see whether rSampEn would be associated with adaptive emotion regulation.

The Association Between rRMSSD, rSampEn and Emotion Regulation

The next part of our study investigated the relationship between rRMSSD, rSampEn and emotion regulation. Hypothesis 3 predicted that higher rSampEn would be related to better emotion regulation capabilities. The results were in line with Hypothesis 3 and showed that a

higher rSampEn was associated with more adaptive emotion regulation as measured by the ERC. There was also a nonsignificant trend towards a more negative rRMSSD (indicating more vagal withdrawal) being associated with better emotion regulation. Higher psychopathology, higher BMI and higher HR during the film were linked to lower emotion regulation. Interestingly, higher BMI was also related to lower cardiac complexity in the marginal linear model.

Implications of the Results

Cardiac entropy as a marker of flexibility and adaptability.

Our results showed that cardiac entropy contained information that was seemingly unconnected to vagal withdrawal, and was a more sensitive determinant of individual differences in emotion regulation than vagally-mediated HRV-reactivity.

Based on these results, and a theoretical understanding of entropy as an index of system complexity, we propose that reactive cardiac entropy has potential as an index of emergent complexity in the neurocardiac system during processing of emotional material. Further, we propose that reactive cardiac entropy can provide clinically relevant information about the systemic potential for flexible and adaptive emotion regulation and behavior in the face of emotional stimuli.

As previously suggested by Young and Benton (2015), we believe that cardiac entropy may be related to integration of information. Specifically, we speculate that future research may connect cardiac entropy to functional and structural connectivity in brain networks relevant for both HR-control and adaptive self-regulation. Particularly small-world-connectivity (Watts & Strogatz, 1998), combining high local clustering and short path length through sparser long-range connections is a promising candidate, due to the connection between small-worldness and integrative capacity in the brain (Bassett & Bullmore, 2016).

Limitations

The small sample size means that the results should be considered preliminary, and several limitations should be taken into consideration. The lack of a baseline SAM meant that we could not estimate the effect of the film on the childrens' emotional states relative to initial emotional states. Another limitation was the lack of a neutral film, making it impossible to distinguish increases in cardiac entropy from emotional versus perceptual, attentional or cognitive processes. The age diversity also meant that the children may have been at different stages of puberty. Finally, it is a limitation that the study used only one parent rating scale to measure emotion regulation and that we did not record which, if any, emotion regulation strategies the children may have spontaneously engaged in. Further exploration across larger samples including neutral content and other measures of emotion regulation should be conducted to help verify and expand on the results. The possibility of a curvilinear relationship between cardiac complexity, psychopathology and self-regulation should also be further explored, as health and adaptive regulation may be found to reside in an area characterized by neither too much, nor too little complexity (Bornas & de la Torre-Luque, 2016; Guastello, 2015).

Conclusion

Children with higher symptoms of internalizing psychopathology presented with lower emotion regulation, lower reactive cardiac entropy and different levels of vmHRV-reactivity compared to low-psychopathology subjects. Higher reactive cardiac entropy was in turn linked to more adaptive emotion regulation. The results show that cardiac entropy holds methodological promise as a marker of flexibility that can provide clinically relevant information in addition to vmHRV-reactivity. Future studies should investigate cardiac

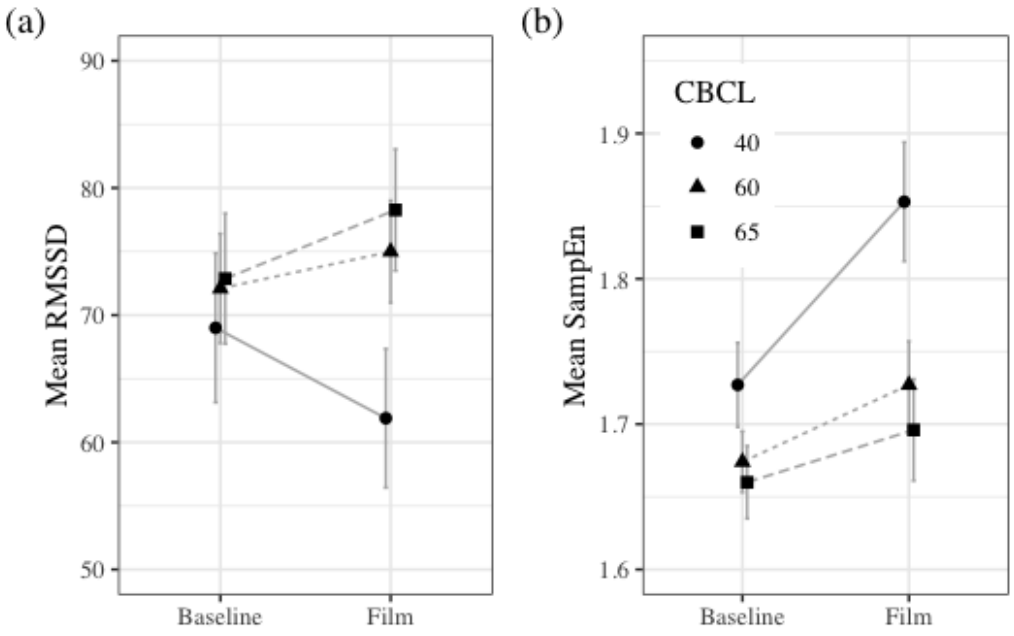
entropy related to underlying properties and processes of the neurocardiac system, across tasks. One line of research that may hold promise is the analysis of functional brain network connectivity related to entropy in the cardiac time-series.

Table 1: Descriptive statistics and between-group differences

	Clinical Group			Control Group					
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*U*	*p*	*d*
Emotion Regulation	31	3.16	0.50	25	3.56	0.36	169.0	.001**	-0.92
SampEn Baseline	31	1.690	0.180	25	1.673	0.146	348.0	.52	
SampEn Film	31	1.741	0.205	25	1.782	0.241	330.0	.35	
SampEn Reactive score	31	0.066	0.210	25	0.109	0.257	304.0	.169	
RMSSD Baseline	31	73.80	39.41	25	67.88	35.88	353.0	.57	
RMSSD Film	30	80.19	46.41	25	60.82	26.81	281.0	.112	
RMSSD Reactive score	30	6.06	17.03	25	-7.06	18.37	220.0	.009*	0.74

Note: RMSSD, root mean square of successive differences in ms; SampEn, sample entropy; U, Mann Whitney U-test; d, Cohen's d. Parts of this table related to baseline RMSSD and SampEn have been presented earlier. * $p \leq .05$, ** $p \leq .001$

Figure 1: Visualization of the spotlight analysis for RMSSD (a) and SampEn (b) at different levels of psychopathology



References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT.

Aftanas, L. I., Lotova, N. V., Koshkarov, V. I., Pokrovskaja, V. L., Popov, S. A., & Makhnev, V. P. (1997). Non-linear analysis of emotion EEG: calculation of Kolmogorov entropy and the principal Lyapunov exponent. *Neuroscience Letters, 226*(1), 13-16. doi:10.1016/S0304-3940(97)00232-2

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control, 19*(6), 716-723. doi:10.1109/TAC.1974.1100705

Bassett, D. S., & Bullmore, E. T. (2016). Small-World Brain Networks Revisited. *Neuroscientist*. doi:10.1177/1073858416667720

Beauchaine, T. P. (2015). Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current Opinion in Psychology, 3*, 43-47. doi:10.1016/j.copsyc.2015.01.017

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology, 98*(2, Part 2), 338-350. doi:10.1016/j.ijpsycho.2015.08.004

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. *The Psychiatric clinics of North America, 32*(3), 483-524. doi:10.1016/j.psc.2009.06.002

Benarroch, E. E. (1993). The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings, 68*(10), 988-1001. doi:10.1016/S0025-6196(12)62272-1

Bertuglia, C. S., & Vaio, F. (2005). *Nonlinearity, Chaos, and Complexity: The Dynamics of Natural and Social Systems*. Oxford: OUP Oxford.

Bornas, X., & de la Torre-Luque, A. (2016). The thin line between health and disease: A matter of dynamical variability. *Fractal geometry and nonlinear analysis in medicine and biology*. doi:DOI: 10.15761/FGNAMB.1000128

Bornas, X., Llabrés, J., Noguera, M., López, A. M., Gelabert, J. M., & Vila, I. (2006). Fear induced complexity loss in the electrocardiogram of flight phobics: A multiscale entropy analysis. *Biological Psychology, 73*(3), 272-279. doi:doi:10.1016/j.biopsycho.2006.05.004

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *Journal of Behavior Therapy and Experimental Psychiatry, 25*(1), 49-59.

Davis, E. L., Levine, L. J., Lench, H. C., & Quas, J. A. (2010). Metacognitive emotion regulation: children's awareness that changing thoughts and goals can alleviate negative emotions. *Emotion, 10*(4), 498-510. doi:10.1037/a0018428

Davis, E. L., Quiñones-Camacho, L. E., & Buss, K. A. (2016). The effects of distraction and reappraisal on children's parasympathetic regulation of sadness and fear. *Journal of Experimental Child Psychology, 142*, 344-358. doi:10.1016/j.jecp.2015.09.020

de la Torre-Luque, A., Bornas, X., Balle, M., & Fiol-Veny, A. (2016). Complexity and nonlinear biomarkers in emotional disorders: A meta-analytic study. *Neuroscience and Biobehavioral Reviews, 68*, 410-422. doi:10.1016/j.neubiorev.2016.05.023

de la Torre-Luque, A., Caparros-Gonzalez, R. A., Bastard, T., Vico, F. J., & Buela-Casal, G. (2017). Acute stress recovery through listening to Melomics relaxing music: A randomized controlled trial. *Nordic Journal of Music Therapy, 26*(2), 124-141. doi:10.1080/08098131.2015.1131186

de la Torre-Luque, A., Fiol-Veny, A., Bornas, X., Balle, M., & Llabres, J. (2017). Impaired cardiac profile in adolescents with an increasing trajectory of anxiety when confronting an acute stressor. *European Child and Adolescent Psychiatry, 26*(12), 1501-1510. doi:10.1007/s00787-017-1009-8

Fiol-Veny, A., De La Torre-Luque, A., Balle, M., & Bornas, X. (2018a). Altered Heart Rate Regulation in Adolescent Girls and the Vulnerability for Internalizing Disorders. *Frontiers in Physiology, 9*(852). doi:10.3389/fphys.2018.00852

Fiol-Veny, A., De la Torre-Luque, A., Balle, M., & Bornas, X. (2018b). Diminished heart rate complexity in adolescent girls: a sign of vulnerability to anxiety disorders? *Anxiety, Stress, & Coping*, 1-12. doi:10.1080/10615806.2018.1475004

Fiskum, C., Andersen, T. G., Aslaksen, P. M., Svendsen, B., Flaten, M. A., & Jacobsen, K. (2017). Cardiac complexity and emotional dysregulation in children. *International Journal of Psychophysiology, 121*, 38-45. doi:10.1016/j.ijpsycho.2017.08.005

Fiskum, C., Andersen, T. G., Bornas, X., Aslaksen, P. M., Flaten, M. A., & Jacobsen, K. (2018). Non-linear Heart Rate Variability as a Discriminator of Internalizing Psychopathology and Negative Affect in Children With Internalizing Problems and Healthy Controls. *Frontiers in Physiology, 9*(561). doi:10.3389/fphys.2018.00561

Fortunato, C. K., Gatzke-Kopp, L. M., & Ram, N. (2013). Associations between respiratory sinus arrhythmia reactivity and internalizing and externalizing symptoms are emotion specific. *Cognitive, Affective & Behavioral Neuroscience, 13*(2), 238-251. doi:10.3758/s13415-012-0136-4

Gentzler, A. L., Santucci, A. K., Kovacs, M., & Fox, N. A. (2009). Respiratory sinus arrhythmia reactivity predicts emotion regulation and depressive symptoms in at-risk and control children. *Biological Psychology, 82*(2), 156-163. doi:10.1016/j.biopsycho.2009.07.002

Graziano, P., & Derefinko, K. (2013). Cardiac vagal control and children's adaptive functioning: a meta-analysis. *Biological Psychology, 94*(1), 22-37. doi:10.1016/j.biopsycho.2013.04.011

Guastello, S. J. (2015). The Complexity of the Psychological Self and the Principle of Optimum Variability. *Nonlinear Dynamics, Psychology, and Life Sciences, 19*(4), 511-527.

Hamilton, J. L., & Alloy, L. B. (2016). Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research. *Clinical Psychology Review, 50*, 67-79. doi:10.1016/j.cpr.2016.09.003

Hayward, C., & Sanborn, K. (2002). Puberty and the emergence of gender differences in psychopathology. *Journal of Adolescent Health, 30*(4), 49-58. doi:10.1016/S1054-139X(02)00336-1

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biological Psychiatry, 67*(11), 1067-1074. doi:10.1016/j.biopsych.2009.12.012

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry, 20*(4), 359-364. doi:10.1097/YCO.0b013e32816ebc8c

Kreibig, S. D. (2010). Autonomic nervous system activity in emotion: a review. *Biological Psychology, 84*(3), 394-421. doi:10.1016/j.biopsycho.2010.03.010

Köbele, R., Koschke, M., Schulz, S., Wagner, G., Yeragani, S., Ramachandraiah, C. T., . . . Bär, K. J. (2010). The influence of negative mood on heart rate complexity measures and baroreflex sensitivity in healthy subjects. *Indian Journal of Psychiatry, 52*(1), 42-47. doi:10.4103/0019-5545.58894

Lehrer, P. M., & Eddie, D. (2013). Dynamic Processes in Regulation and Some Implications for Biofeedback and Biobehavioral Interventions. *Applied Psychophysiology and Biofeedback, 38*(2), 143-155. doi:10.1007/s10484-013-9217-6

Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain and Cognition, 72*(1), 46-55. doi:10.1016/j.bandc.2009.10.008

Leupoldt, A., Rohde, J., Beregova, A., Thordsen-Sörensen, I., Nieden, J., & Dahme, B. (2007). Films for eliciting emotional states in children. *Behavior Research Methods, 39*(3), 606-609.

Mateo, M., Blasco-Lafarga, C., Martinez-Navarro, I., Guzman, J. F., & Zabala, M. (2012). Heart rate variability and pre-competitive anxiety in BMX discipline. *European Journal of Applied Physiology, 112*(1), 113-123. doi:10.1007/s00421-011-1962-8

McCraty, R., & Zayas, M. A. (2014). Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. *Frontiers in Psychology, 5*, 1090. doi:10.3389/fpsyg.2014.01090

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research, 45*(8), 1027-1035. doi:10.1016/j.jpsychires.2011.03.006

Mikolajewski, A. J., & Scheeringa, M. S. (2018). Examining the Prospective Relationship between Pre-Disaster Respiratory Sinus Arrhythmia and Post-Disaster Posttraumatic Stress Disorder Symptoms in Children. *Journal of Abnormal Child Psychology, 46*(7), 1535-1545. doi:10.1007/s10802-017-0396-0

Pang, K. C., & Beauchaine, T. P. (2013). Longitudinal patterns of autonomic nervous system responding to emotion evocation among children with conduct problems and/or depression. *Developmental Psychobiology, 55*(7), 698-706. doi:10.1002/dev.21065

Pikkujämsä, S. M., Mäkikallio, T. H., Sourander, L. B., Räihä, I. J., Puukka, P., Skyttä, J., . . . Huikuri, H. V. (1999). Cardiac interbeat interval dynamics from childhood to senescence: Comparison of conventional and new measures based on fractals and chaos theory. *Circulation, 100*(4), 393-399. doi:10.1161/01.CIR.100.4.393

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage: A Polyvagal Theory. *Psychophysiology, 32*(4), 301-318. doi:10.1111/j.1469-8986.1995.tb01213.x

Porges, S. W., Doussard-Roosevelt, J. A., & Maiti, A. K. (1994). Vagal tone and the physiological regulation of emotion. *Monographs of the Society for Research in Child Development, 59*(2-3), 167-186. doi:10.2307/1166144

Richman, J. S., & Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology - Heart and Circulatory Physiology, 278*(6), H2039-H2049. doi:10.1152/ajpheart.2000.278.6.H2039

Rottenberg, J., Ray, R. D., & Gross, J. J. (2007). Emotion elicitation using films. In *Handbook of emotion elicitation and assessment.* (pp. 9-28). New York, NY, US: Oxford University Press.

Sacha, J. (2013). Why should one normalize heart rate variability with respect to average heart rate. *Frontiers in Physiology, 4*(306). doi:10.3389/fphys.2013.00306

Sassi, R., Cerutti, S., Lombardi, F., Malik, M., Huikuri, H. V., Peng, C. K., . . . Yamamoto, Y. (2015). Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology, 17*(9), 1341-1353. doi:10.1093/europace/euv015

Schwarz, G. (1978). Estimating the Dimension of a Model. *The Annals of Statistics, 6*(2), 461-464.

Seppala, S., Laitinen, T., Tarvainen, M. P., Tompuri, T., Veijalainen, A., Savonen, K., & Lakka, T. (2014). Normal values for heart rate variability parameters in children 6-8 years of age: the PANIC Study. *Clinical Physiology and Functional Imaging, 34*(4), 290-296. doi:10.1111/cpf.12096

Shields, A., & Cicchetti, D. (1997). Emotion regulation among school-age children: The development and validation of a new criterion Q-sort scale. *Developmental Psychology, 33*(6), 906-917. doi:10.1037//0012-1649.33.6.906

Spiller, S. A., Fitzsimons, G. J., Lynch, J. G., & McClelland, G. (2013). Spotlights, Floodlights, and the Magic Number Zero: Simple Effects Tests in Moderated Regression *Journal of Marketing Research, 50*(2), 277-288. doi:10.1509/jmr.12.0420

Stange, J. P., Hamilton, J. L., Olino, T. M., Fresco, D. M., & Alloy, L. B. (2017). Autonomic reactivity and vulnerability to depression: A multi-wave study. *Emotion, 17*(4), 602-615. doi:10.1037/emo0000254

Tarvainen, M. P., Niskanen, J. P., Lipponen, J. A., Ranta-Aho, P. O., & Karjalainen, P. A. (2014). Kubios HRV--heart rate variability analysis software. *Computer Methods and Programs in Biomedicine, 113*(1), 210-220. doi:10.1016/j.cmpb.2013.07.024

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders, 61*(3), 201-216. doi:10.1016/S0165-0327(00)00338-4

Thayer, J. F., & Lane, R. D. (2009). Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience and Biobehavioral Reviews, 33*(2), 81-88. doi:10.1016/j.neubiorev.2008.08.004

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers Iii, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews, 36*(2), 747-756. doi:10.1016/j.neubiorev.2011.11.009

Thelen, E., & Smith, L. (1994). *A dynamic systems approach to the development of perception and action*. Cambridge, MA: MIT Press.

Valenza, G., Allegrini, P., Lanatà, A., & Scilingo, E. P. (2012). Dominant Lyapunov exponent and approximate entropy in heart rate variability during emotional visual elicitation. *Frontiers in Neuroengineering, 5*(3). doi:10.3389/fneng.2012.00003

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature, 393*, 440. doi:10.1038/30918

Weiner, O. M., & McGrath, J. J. (2017). Test-Retest Reliability of Pediatric Heart Rate Variability: A Meta-Analysis. *J Psychophysiol, 31*(1), 6-28. doi:10.1027/0269-8803/a000161

West, B. J. (2014). *Where Medicine Went Wrong : Rediscovering the Path to Complexity*. Singapore, SINGAPORE: World Scientific Publishing Co Pte Ltd.

White, R. E., Kross, E., & Duckworth, A. L. (2015). Spontaneous Self-Distancing and Adaptive Self-Reflection Across Adolescence. *Child Development, 86*(4), 1272-1281. doi:10.1111/cdev.12370

Wilder, J. (1962). Basimetric approach (law of initial value) to biological rhythms. *Annals of the New York Academy of Sciences, 98*(4), 1211-1220. doi:10.1111/j.1749-6632.1962.tb30629.x

World Medical Association. (2013). World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. *The Journal of the American Medical Association, 310*(20), 2191-2194. doi:10.1001/jama.2013.281053

Young, H., & Benton, D. (2015). We should be using nonlinear indices when relating heart-rate dynamics to cognition and mood. *Scientific Reports, 5*, 16619. doi:10.1038/srep16619