Accepted Manuscript

Underlying Psychophysiology of Dysregulation: Resting Heart Rate and Heart Rate Reactivity in Relation to Childhood Dysregulation

Marike H.F. Deutz, MSc, Steven Woltering, PhD, Helen Vossen, PhD, Maja Deković, PhD, Anneloes L. van Baar, PhD, Peter Prinzie, PhD

PII: S0890-8567(18)31907-5
DOI: https://doi.org/10.1016/j.jaac.2018.09.434
Reference: JAAC 2378

To appear in: Journal of the American Academy of Child & Adolescent Psychiatry

Received Date: 11 March 2018
Revised Date: 22 September 2018
Accepted Date: 28 September 2018


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Underlying Psychophysiology of Dysregulation: Resting Heart Rate and Heart Rate Reactivity in Relation to Childhood Dysregulation
RH = Psychophysiology of Dysregulation

Marike H.F. Deutz, MSc, Steven Woltering, PhD, Helen Vossen, PhD, Maja Deković, PhD, Anneloes L. van Baar, PhD, Peter Prinzie, PhD

Editorial
Supplemental Material
Clinical Guidance

Accepted October 24, 2018

Drs. Vossen, Deković, and van Baar, and Ms. Deutz are with Utrecht University, The Netherlands. Dr. Woltering and Ms. Deutz are with Texas A&M University, College Station, TX. Dr. Prinzie is with Erasmus University Rotterdam, The Netherlands.

For the work reported in this article, the first author Marike Deutz was supported by a Fulbright scholarship and a Young Talent Award from the Prince Bernhard Culture Fund.

Ms. Deutz served as the statistical expert for this research.

Disclosure: Drs. Woltering, Vossen, Deković, van Baar, Prinzie, and Ms. Deutz report no biomedical financial interests or potential conflicts of interest.

*Correspondence to: Marike Deutz, Department of Psychology, Education & Child Studies, Erasmus University Rotterdam, PO Box 1738, 3000 DR, Rotterdam, the Netherlands. E-mail: deutz@essb.eur.nl.
Abstract

Objective: High co-occurrence of externalizing and internalizing problems may underlie inconsistent findings regarding the relation between heart rate and psychopathology. In this study, heart rate measures are examined in relation to a general dysregulation profile, studied from both a variable- and person-centered approach.

Method: The sample ($N = 182$) consisted of 8-12-year-old children referred for externalizing behaviors and typically-developing children ($M_{\text{age}} = 9.70, SD = 1.26, 75.8\% \text{ boys}$). Resting heart rate ($HR_{\text{rest}}$) was assessed during a 3-minute resting period. Heart rate reactivity ($HR_{\text{reactivity}}$) was assessed during an emotionally evoking Go/No-Go task.

Results: From a variable-centered approach, a bifactor model was fitted with a general factor of dysregulation underlying symptoms of anxiety/depression, aggression and attention problems. $HR_{\text{rest}}$ was positively associated with dysregulation and specific aggression. From a person-centered approach, a latent profile analysis was used to identify different psychopathology classes: normative ($n = 92$), predominantly-aggressive ($n = 69$) and dysregulated ($n = 14$). The latter was characterized by co-occurring elevated levels of anxiety/depression, aggression and attention problems. $HR_{\text{rest}}$ was elevated in the predominantly-aggressive class and $HR_{\text{reactivity}}$ was elevated in the dysregulated class.

Conclusions: High $HR_{\text{rest}}$, or (trait-like) overarousal seems to be associated with dysregulation rather than uniquely with low externalizing or high internalizing symptomatology. Additionally, $HR_{\text{rest}}$ predicted higher aggression and $HR_{\text{rest}}$ was elevated in the predominantly-aggressive class. High $HR_{\text{reactivity}}$, or enhanced emotional reactivity, might be characteristic for a clinically relevant dysregulated subgroup. Assessment of heart rate could provide additional knowledge on individual differences that can help refine diagnostics and intervention efforts.
Keywords: autonomic nervous system, comorbidity, stress reactivity, arousal, psychopathology

**Introduction**

The autonomic nervous system (ANS), one of the main human stress regulating systems, indexes physiological reactivity, and is considered a major component of emotion regulation. ANS dysfunction is evident in many psychiatric disorders, but it is unclear to what extent associations are general or specific to certain forms of psychopathology. Such knowledge could however elucidate underlying mechanisms of psychopathology. Two main indices of ANS functioning have been studied in relation to psychopathology: (1) resting heart rate ($HR_{\text{rest}}$), i.e., the amount of heart beats per minute (bpm) when a child is in a relaxed position and without distractions, reflecting relatively stable individual differences in baseline (trait-like) levels of arousal, and (2) heart rate reactivity ($HR_{\text{reactivity}}$), i.e., the amount of change in heart rate in response to a stressor (usually referring to increasing arousal from baseline, indexing individual differences in emotional reactivity, or (state-like) arousal in response to experimental stimuli.

Lower $HR_{\text{rest}}$ has often been associated with externalizing behaviors (e.g., aggressive, antisocial, conduct problems), and higher $HR_{\text{rest}}$ with internalizing behaviors (e.g., anxiety, posttraumatic symptoms). HR$_{\text{reactivity}}$ has been studied far less, with available evidence suggesting that lower HR$_{\text{reactivity}}$ is related to aggression and delinquency, whereas higher HR$_{\text{reactivity}}$ has been linked to internalizing symptoms. These findings are often explained in terms of over- and under-arousal. Aggressive children are thought to be under-aroused, which they experience as an unpleasant state, prompting them to seek stimulating activities (sensation seeking theory), and not fearing the social consequences (e.g., punishment, rejection) of their aggressive actions (fearlessness theory). In contrast, disorders from the internalizing spectrum,
such as anxiety, are thought to indicate behavioral (over-)inhibition\textsuperscript{3,22} or enhanced stress reactivity,\textsuperscript{10} which could be expressed as ‘over-aroused’ fear and anxiety.

This field of research however has suffered from inconsistencies, with numerous studies failing to find divergent autonomic patterns for externalizing and internalizing behaviors.\textsuperscript{16,23–26} One potential explanation for these conflicting findings is that whereas externalizing and internalizing behaviors are often considered as opposite ends of a spectrum, in reality, they are strongly related. Children who present co-occurring externalizing and internalizing behavioral problems are the norm rather than the exception.\textsuperscript{27,28} These children have recently been described as ‘dysregulated’,\textsuperscript{29} as they are thought to have self-regulatory deficits across multiple domains (i.e. affect, attention, and behavior).\textsuperscript{29–31} The Child Behavior Checklist - Dysregulation Profile (DP)\textsuperscript{31} is increasingly used to describe co-occurring affective, behavioral and cognitive dysregulation. The DP cuts across categorical disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD) as diagnosed using the Diagnostic Statistical Manual (DSM).\textsuperscript{32} Therefore it fits well within recent efforts to describe psychopathology dimensionally in terms of dysregulation and dysfunction (Research Domain Criteria, RDoC).\textsuperscript{33} One of the hallmarks of the RDoC project is examining the underlying physiology of psychopathology to better understand underlying mechanisms and eventually improve children’s outcomes by improving diagnostics and intervention efforts.\textsuperscript{34} While physiological studies are challenging to conduct in childhood samples, let alone in clinically referred samples, such studies are essential for enhancing insights into (neurobiological) mechanisms of childhood psychopathology. As physiological measures might reveal unique insights into children’s emotional functioning, it is valuable to examine physiology early in
development when early intervention could potentially defer children from chronic problematic developmental trajectories.

**Variable- and Person-Centered Approaches to Study Dysregulation**

Dysregulation has been studied from both a variable-centered and a person-centered approach, using mostly three key syndrome scales (Anxious/Depressed, Aggressive Behavior and Attention Problems), from both the externalizing and internalizing domains of the Child Behavior Checklist.\textsuperscript{29–31} Variable-centered analyses focus on relations among variables within a given population. Our previous variable-centered work\textsuperscript{35,36} demonstrated that a bifactor model (see Figure 1) best described the DP. In this bifactor model, a general factor of dysregulation reflects what is common among symptoms from both the externalizing and internalizing spectrum. Three additional specific factors of anxiety/depression, aggression, and attention problems (representing the three DP-scales),\textsuperscript{35,36} explain the unique coherence among the items within these scales. A bifactor model might be especially useful in determining specificity of HR\textsubscript{rest} and HR\textsubscript{reactivity} in relation to psychopathology, as links with specific anxiety/depression, aggression, and attention problems, as well as general underlying dysregulation can be estimated simultaneously. As such, the bifactor model might help clarify previously reported inconsistencies in links between ANS functioning and psychopathology.

In addition to a variable-centered approach, dysregulation has been operationalized from a person-centered approach, in which groups (classes) are revealed of individuals with similar profiles on certain variables. Latent profile analysis has been used to derive homogeneous subgroups (or classes) with different psychopathology profiles, such as youths with normative scores on all scales, youths with elevated scores within the externalizing or internalizing domain only, and youths with co-occurring externalizing and internalizing problems. The latter group is
often being referred to as ‘dysregulated’, since these children display concurrent disturbances in regulating attention, behavior and mood. Latent profile analysis is a person-centered approach that results in empirically derived distinct groups (classes) with similar profiles on several variables. This empirical and holistic person-centered approach is of high clinical and practical use as it acknowledges heterogeneity within the population by identifying clusters of children with similar psychopathology patterns that might show divergent patterns of ANS dysfunction and potentially benefit from different or differentiated treatments.

Thus, variable- and person-centered operationalizations of dysregulation have distinct theoretical bases. The variable-centered approach to psychopathology focuses on communalities between different forms of psychopathology and with a complementary person-centered approach, we look for subgroups of children characterized by similar psychopathology patterns. Applying both approaches in one study to may result in a richer and more comprehensive understanding of ANS dysfunction and dysregulation. Summarizing, the present study examined two different measures of ANS functioning, $HR_{rest}$ and $HR_{reactivity}$ in relation to dysregulation from both a variable-centered approach (DP bifactor model) and a person-centered approach (latent profile analysis) in a predominantly clinically referred sample of children aged 8-12. As the DP has been found to be highly stable and heritable, examining markers of ANS functioning might help explain etiology of dysregulation versus more specific forms of psychopathology. For the variable-centered approach, we expected that $HR_{rest}$ and $HR_{reactivity}$ would be positively associated with general dysregulated psychopathology and specific anxiety/depression, and negatively with specific aggressive behavior and attention problems. For the person-centered approach, we expected to identify a group of dysregulated children that would show elevated $HR_{rest}$ and $HR_{reactivity}$ and a group of ‘predominantly-aggressive’ children
that would show lower $\text{HR}_{\text{rest}}$ and $\text{HR}_{\text{reactivity}}$ (as well as a normative group with scores in between).

**Methods**

**Sample**

Data were derived from a larger study (2004-2012) on individual differences in neural and psychophysiological correlates of self-regulation. The study was approved by the Research Ethics board of the University of Toronto. Children aged 7-12 ($n = 117$) referred for externalizing behavior by mental health professionals, teachers and/or parents were recruited from two community mental health agencies in Canada. Additionally, (generally) typically-developing children aged 7-18 ($n = 103$) were recruited through newspaper ads. Parents and children lacking sufficient English language skills, and children with significant cognitive impairment were excluded. Children aged 7 years or 13 or older were excluded to have a more homogenous age group of children aged 8-12, representing middle childhood.

The final study sample consisted of 182 children ($M_{\text{age}} = 9.70, SD = 1.26, 75.8\%$ boys), of whom 115 were clinically referred (63.2%) and 67 were recruited through newspaper ads (36.8%). Children lived mostly with both biological parents (40.9%) or with their mother only (35.2%). The sample was relatively diverse in terms of race, with the majority being Canadian-European (62.3%), and African/Caribbean-Canadian being the second largest group (15.4%). Educational levels for mothers and fathers respectively were 33%/41.9% high school or less, 33.5%/26.4% community college, and 30.7%/29.5% university degree or higher. A social adversity index was created (similar to) with one point each for father uneducated (no high school diploma, 13.7%, with 29.7% missing), mother uneducated (no high school diploma,
12.1%, with 3.3% missing), low income (annual income <40,000 Canadian dollars, 38.5%, with 6.6% missing), and child living with both parents vs other (57.1%, with 3.3% missing).

All measures reported in this study were taken 2 weeks before the start of treatment (a combined parent management and child-focused cognitive behavioral therapy). At this time, 44 of the clinically referred children (24.2% of all children, data were missing for 10 participants) received psychopharmacotherapy, mostly stimulants (n = 31).

Procedure

Children visited the university research lab with their mother where parental consent and child assent were obtained. Children first completed a series of computer tasks (see 43), while mothers completed questionnaires. Next, children and their mothers discussed neutral and emotional issues (reported in 41). They were asked to discuss, in the exact order: i) a randomly assigned - positive topic out of two topics (“You will be taken to live on an island paradise that has nothing on it - you can take anything you want with you - use your imagination to talk about what you would take”; “you have won the lottery, what are you both planning to do with the money?”); ii) a personally relevant negative topic that both the parent and child independently listed using a modified version of the Issues Checklist 44 that was anger-provoking and had not been resolved, and lastly, iii) another positive topic. Two minutes before the end of the discussions, a research assistant knocked on the door and reminded the subjects that there were two minutes left and that they should “try to end on a positive note” (which was also explained to participants beforehand). During these discussions both mother and child were connected to the ECG acquisition unit, but heart rate data collected during these discussions was not used in the present study (see 41 for more details). After a brief break of several minutes, the researcher would ensure good connectivity of the equipment and explain the HR rest procedure. Following
another short break, ECG measures were continued, and children were fitted with an
electroencephalography (EEG) net (results not reported in this study) and seated in front of a
computer to complete a Go/No-Go-task. From this task, HR_{reactivity} was derived.

**Measures**

**Child Behavior Checklist - Dysregulation Profile.**

Dysregulation was assessed with the Child Behavior Checklist - Dysregulation Profile
(CBCL-DP), consisting of items from the Anxious/Depressed (13 items, \( \alpha = .84 \)), Aggressive
Behavior (18 items, \( \alpha = .94 \)), and Attention Problems (10 items, \( \alpha = .89 \)) scales from the Child
Behavior Checklist, using the 2007 scale assignments. T-scores were computed following.

**Early Adolescent Temperament Questionnaire – Revised**

To validate the person-centered latent profile solution, mean scale scores derived from
parent-reported the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) were
used. The EATQ-R consists of 62 items divided into 10 scales: Activation Control (7 items, \( \alpha = .82 \)), Affiliation (6 items, \( \alpha = .70 \)), Aggression (7 items, \( \alpha = .82 \)), Attention (6 items, \( \alpha = .84 \)),
Depressive Mood (5 items, \( \alpha = .76 \)), Fear (6 items, \( \alpha = .52 \)), Frustration (6 items, \( \alpha = .80 \)),
Inhibitory Control (5 items, \( \alpha = .71 \)), Shyness (5 items, \( \alpha = .83 \)), and Surgency (9 items, \( \alpha = .62 \)).

**Physiology Measures**

A BIOPAC MP150 psychophysiological recording system was used to acquire ECG
data at a sampling rate of 1000 Hz. Electrodes were positioned diagonally across the heart
according to a standard Lead II configuration. Data were processed with ANSLab software and scored in 1-minute intervals.

**Resting heart rate.** HR_{rest} was measured during a three-minute resting period following a 14-
minute period of mother-child discussions. During these discussions both mother and child were
connected to the ECG acquisition unit; heart rate data collected during these discussions was not used in the present study (see \(^{41}\)). The protocol for the mother-child discussions was completed by 118 mother-child pairs (64.8%). After 35 participants completed the study, HR\(_{\text{rest}}\) assessment was added to the study, data thus being available for 83 participants (45.6%). After a small break, children were told to relax and sit still in a chair in an observation room with the parent present during which HR\(_{\text{rest}}\) was assessed. Video recordings were coded for movements, talking or other behaviors that might affect the HR assessment. The large majority of children were sitting quietly and calmly during the 3 minutes. One child was reluctant to participate and kicked feet and yelled, after which the assessment was stopped. For this child, available HR\(_{\text{rest}}\) was recoded into missing. Paired-samples t-tests indicated that mean HR did not differ significantly between the one-minute segments and were highly stable (\(rs > .95\)). Mean bpm for HR\(_{\text{rest}}\) was 88.92 (Range = 65.17 – 121.81, \(SD = 10.80\)). HR\(_{\text{rest}}\) did not significantly differ across sex (\(t(80) = -.1484, p = .142\)) or medication status (\(t(71) = -1.220, p = .227\)).

**Heart rate reactivity.** HR\(_{\text{reactivity}}\) was assessed during an adapted version of a previously developed emotion induction Go/No-Go task. \(^{49}\) The task was programmed using E-Prime software. \(^{50}\) Children were shown a series of letters and were instructed to press a button on a response pad with their index finger as fast as possible whenever a letter appeared on the screen (the Go condition) and withhold responding when the same letter appeared twice in a row (the No-Go condition). To ensure engagement and motivation, children received performance feedback periodically on-screen, and were told beforehand that if they accumulated enough points they could pick a prize (such as large action figures). A practice block was followed by three blocks (A, B, C), that each lasted three minutes. A dynamic adjustment of stimulus times based on performance was used in order to make the task challenging for all ages (for more
details, see \(^\text{43}\). In block A (200 trials, 66 No-Go trials) children steadily gained points, in block B (150 trials, 40 No-Go trials) they immediately began losing all or almost all their points (intended to induce negative emotion) because of a change in the point-adjustment algorithm and reduced stimulus times (as such, the task deviated from the typical Go/No-Go task in which generally no manipulation takes place). In block C (200 trials, 66 No-Go trials), the algorithms went back to normal and children were awarded their prize (see Supplement 1, available online, for more details). Analysis of manipulation checks confirmed that the Go/No-Go task was emotionally evoking as Block B (when children lost all their points) perceived negative emotions significantly increased and positive emotions decreased (see Figure S1, available online).

HR\text{reactivity} data was available for 149 participants (81.9\%). HR increased significantly from 87.91 bpm in block A to 88.68 bpm in block B (\(t(146) = -2.980, p = .003\)) and then to 91.11 bpm in block C (\(t(145) = -9.468, p < .001\)). The difference between HR in the first minute of block B (the emotion induction block) and the last minute of block B (when participants were typically losing all their points and were most upset) was taken as an indication of HR\text{reactivity}, with higher scores indicating a greater increase in HR during Block B suggesting greater HR\text{reactivity}, a procedure in line with a previous study on this sample. \(^\text{43}\) HR\text{reactivity} did not significantly differ across sex (\(t(144) = .965, p = .336\)) or medication status (\(t(144) = -1.805, p = .073\)).

**Results**

**Variable-Centered Approach**

**Bifactor Model.** Using confirmatory factor analysis in Mplus 8 \(^\text{51}\) with the WLSMV estimator for categorical indicators, a bifactor model (see \(^\text{35}\)) was estimated using available item-level CBCL data (\(n = 160, 12.1\%\) missing). Each item loaded on a general Dysregulation Profile
factor (DP) and on one orthogonal specific factor of Anxious/Depressed (AD), Aggressive Behavior (AGG), or Attention Problems (AP), see Figure 1. Fit indices for this model were good ($\chi^2(738) = 977.513$, RMSEA = .045, CFI = .966, TLI = .963). Based on inspection of modification indices, item 41 ‘Impulsive or acts without thinking’ (part of AP) was allowed to cross-load on AGG, which significantly improved model fit, $\Delta \chi^2(1) = 22.482$, $p < .001$. Model fit indices for the final model were: $\chi^2(737) = 952.964$, RMSEA = .043, CFI = .970, TLI = .966. Factor loadings (see Table S1, available online) on the general DP-factor were all significant (most > .60). Factor loadings on the specific factors were generally lower, and 10 out of 41 loadings (of which 7 for AGG) were not statistically significant. Factor scores were subsequently saved to use as input for regression analyses.

**Regression Analysis.** Children with and without either HR$_{rest}$ or HR$_{reactivity}$ data did not differ significantly on age, sex, social adversity or factor scores from the bifactor DP, CBCL T-scores. Therefore, regression analyses were conducted in Mplus 8 with saved factor scores using full information maximum likelihood (fiml), to optimally handle missing data and utilize the full sample. Bootstrapping (5000 replications) was used for all analyses because of relatively low sample size. HR$_{rest}$ and HR$_{reactivity}$ were examined as predictors of DP, AD, AGG, and AP factor scores from the DP bifactor model (simultaneously) (Table 1). Regarding the covariates, sex negatively predicted DP and AGG, meaning that boys had higher (factor) scores on these variables. Higher social adversity predicted higher DP only. Medication use predicted higher DP. Controlling for covariates, higher HR$_{rest}$ predicted higher DP, and, also higher AGG. HR$_{reactivity}$ was not a significant predictor for DP, AD, AGG, or AP. HR$_{rest}$ and HR$_{reactivity}$ were not significantly related ($r = -.005$, $p = .963$), and consequently results did not differ when HR$_{rest}$ and HR$_{reactivity}$ were examined separately. Covariates did not affect patterns of results. R-square
values were .298 for DP ($p < .001$) and .186 for AGG ($p < .05$). No significant variance was explained in AD (.062, $p = .267$) or AP (.085, $p = .096$). Cohen's $f^2$ effect size values (calculated as $R^2$ divided by 1- $R^2$) were small for AD (.07) and AP (.09), medium for AGG (.23) and large for DP (.42). As suggested by an anonymous reviewer, we did post-hoc analyses to examine whether sex interacted with $HR_{\text{rest}}$ and $HR_{\text{reactivity}}$ in predicting psychopathology in the variable-centered approach. No significant interactions with sex emerged.

**Person-Centered approach.**

**Latent Profile Analysis.** To examine whether, and how many, homogeneous latent subgroups with different psychopathology profiles could be distinguished, latent profile analysis (LPA) was performed. Continuous T-scores for the Anxious/Depressed, Aggressive Behavior and Attention Problems scales ($n = 175, 3.8\%$ missing) were used rather than item-level data because of sample size limitations. Given high intercorrelations between the CBCL T-scores, covariances among latent profile indicators were allowed. Model fit was evaluated with the Lo-Mendell-Rubin (LMR) test, with significant values indicated better fit compared to a model with k-1 profiles, lower values on the sample size adjusted Bayesian Information Criterion (adjBIC), and entropy levels of .80 or higher. LMR-results indicated that a 3-class solution fit best statistically, and had good entropy (.90), and lower AdjBIC values (3751.323) than a 1-class (3807.037) and 2-class solution (3783.682). Although the 4-class solution showed lower AdjBIC (3746.611), results of the LMR-test indicated that the 4-class solution fits significantly worse ($p$-value of the LMR-test was .108). As the 4-class solution also consisted of two very small classes (of 9 and 4 participants), the 3-class solution was chosen as the final solution. The classification of individuals in the 3-class solution was good as the average probabilities for the most likely
class were high enough (> .924) and probabilities for the other two classes were low enough (<.076).

A graphic representation of the classes is presented in Figure 2. The largest class (n = 92), with mean T-scores in the normative range on AD, AGG and AP, was referred to as the normative class. The second largest class (n = 69), had mean T-scores in the clinical range for AGG, subclinical for AP, and normative for AD, and was labeled the predominantly-aggressive class. The third class (n = 14), had mean T-scores in the clinical range for AD, AGG, and AP, and was labeled the dysregulated class, in line with previous studies.37,53

To examine the validity of the latent profile solution, the three classes were compared on means on 10 temperament dimensions (see Figure 3). The three classes did not differ significantly on affiliation, shyness and surgency. For five scales, the three classes all differed significantly from each other: with dysregulated children scoring highest on depressive mood, fear and frustration and lowest on activation control and attention. The predominantly-aggressive and dysregulated classes did not differ significantly on aggression and inhibitory control. These results confirm the validity of the profile solution since the degree of adjustment of the three classes was normative > predominantly-aggressive > dysregulated.

Profile Comparisons. To compare the latent profiles on means (i.e., HRrest, HRreactivity and covariates) the BCH procedure in Mplus was used for continuous variables and the DCATEGORICAL option for categorical variables.51 Mean T-scores of AD, AGG and AP differed significantly between classes, except levels of AGG that did not significantly differ between the predominantly-aggressive and dysregulated classes. There were no sex and age differences between classes. Children in the normative class had lower social adversity scores (.982) compared to the predominantly-aggressive class (1.491), $\chi^2 = 7.778$, $p < .01$ and the
dysregulated class (1.887), $\chi^2 = 13.791, p < .001$) and they were less likely to use medication (.033 probability) compared to the predominantly-aggressive class (.495 probability), $\chi^2 = 38.690, p < .001$ and the dysregulated class (.527 probability), $\chi^2 = 9.020, p < .01$).

Next, the three psychopathology classes (normative, predominantly-aggressive, and dysregulated) were compared on mean levels of $HR_{rest}$ and $HR_{reactivity}$. The predominantly-aggressive group had significantly higher $HR_{rest}$ (93.30, S.E. = 2.12) compared to the normative ($HR_{rest} = 86.07, S.E. = 1.61$) group ($\chi^2 = 6.917, p < .01$), whereas the dysregulated group ($HR_{rest} = 88.03, S.E. = 1.86$) did not differ significantly from either group.

$HR_{reactivity}$ did not differ between the predominantly-aggressive ($HR_{reactivity} = 2.31, S.E. = .42$) and normative ($HR_{reactivity} = 1.65, S.E. = .46$) group, but was significantly higher in the dysregulated group ($HR_{reactivity} = 4.39, S.E. = 92$) compared to the normative group ($\chi^2 = 7.147, p < .01$) and the predominantly-aggressive group ($\chi^2 = 4.117, p < .05$).

**Discussion**

In this study, we examined $HR_{rest}$ and $HR_{reactivity}$, two different markers of ANS (dys-)function in relation to psychopathology in a sample of 8 to 12-year old children, predominantly clinically referred for externalizing problem behavior. We used two approaches of considering communalities between internalizing and externalizing behavior problems: a variable-centered and person-centered approach. For the variable-centered approach, we estimated a bifactor model with a general psychopathology factor of dysregulation underlying both externalizing and internalizing symptomatology that exists next to specific factors of anxiety/depression, aggression, and attention problems. For the person-centered approach, we used latent profile analysis to derive groups with different psychopathology profiles. The person-centered latent profile analyses revealed three distinct groups of children with different psychopathology
profiles: (a) normative, (b) predominantly-aggressive, and (c) dysregulated (characterized by co-occuring anxiety/depression, aggression, and attention problems). These psychopathology profiles differed significantly on temperament dimensions, which confirmed that the normative group was well-adapted, while the dysregulated group was the least well-adapted (more so than the predominantly-aggressive group). The dysregulated group showed an overall temperamental pattern of increased negative affect (aggression, depressive mood, frustration), reduced effortful control (attention, activation control) and increased fear. This is in line with previously reported patterns of personality pathology predicted in late adolescence by early childhood DP. 39

As our relatively low sample size in relation to model complexity prohibited formal statistical comparisons of the variable- and person-centered approach, only convergent findings across the approaches can be interpreted with some degree of certainty, while differences must be interpreted with caution as they could result from model differences.

**Resting Heart Rate**

Results from the variable-centered analyses revealed that, as expected, $HR_{rest}$ was positively related to dysregulation, suggesting that high(er) $HR_{rest}$ might reflect a more general predisposition for developing psychopathology rather than being a precise marker for specific internalizing symptomatology. Bifactor models, in which a general factor of dysregulation or psychopathology explains common interrelatedness between externalizing and internalizing symptomatology, have been recognized as highly useful in variable-centered psychopathology research, especially since they offer a refined way to disentangle shared versus specific associations with etiologies and outcomes.54,55 Using this approach our study demonstrated shared biopsychological mechanisms and showed that higher $HR_{rest}$ indicates elevated emotional arousal that might affect a broad expression of psychopathological symptoms going beyond the
internalizing spectrum. $HR_{\text{rest}}$ was not significantly elevated in the dysregulated class, but the relatively large coefficient size suggests that the small group size ($n = 14$) could have affected the non-significance of this result.

Unexpectedly, $HR_{\text{rest}}$ was also positively associated with specific aggression and it was elevated in a subgroup of children characterized as predominantly-aggressive. Although low $HR_{\text{rest}}$ is often described as a biomarker for antisocial behavior, several studies have failed to demonstrate links between low $HR_{\text{rest}}$ and externalizing behaviors. There are several possible explanations for our findings. First, the Aggressive Behavior scale from the CBCL consists of a heterogeneous set of behaviors, and it has been proposed that low $HR_{\text{rest}}$ is an autonomic risk factor for proactive (goal-directed, intentional) psychopathic-like aggression rather than for reactive (or impulsive, emotional) aggression. Autonomic overarousal has been associated with internalizing subtypes of conduct disorder and has been suggested to explain the co-occurrence between reactive aggression and anxiety. In our study, given the high degree of comorbid internalizing problems in children referred for externalizing behaviors, this implies that the aggressive behaviors reported might have been primarily reactive. Another explanation can be found in sample characteristics, with several other clinical studies also reporting that children with disruptive behavior disorders had higher $HR_{\text{rest}}$ compared to controls. Our convergent findings from two different approaches to examine (comorbid) psychopathology substantiate a previous notion that the link between low $HR_{\text{rest}}$ and externalizing behavior link might be primarily encountered in community samples.

As comorbidity of internalizing problems in children with disruptive behavior disorders is generally high, comorbid anxiety might drive elevated $HR_{\text{rest}}$, which shows the usefulness of measures such as the DP that cut across spectra. Our findings corroborate earlier reports of
neural hypervigilance in externalizing disorders, in line with a theoretical model proposing that anxiety, typically associated with too much inhibitory control, is not merely an auxiliary phenomenon, but rather drives and maintains aggression. Larger clinical samples would offer the opportunity to identify additional subtypes of externalizing behavior with different neurobiological correlates, potentially identifying a subgroup of ‘aggressive-only’ children, for whom fearlessness would be a key differentiating symptom. Including children with internalizing disorders in such studies could further refine results.

**Heart Rate Reactivity**

$HR_{reactivity}$ as a marker of ANS dysfunction has received much less attention in research, with the few available studies suggesting underreactivity being associated with externalizing behaviors and overreactivity with internalizing behaviors. Our findings showed that $HR_{rest}$ and $HR_{reactivity}$ were not related. Relations with $HR_{reactivity}$ and psychopathology did not converge across the variable- and person-centered analyses, and therefore findings should be interpreted cautiously. No associations emerged between $HR_{reactivity}$ and psychopathology in the variable-centered approach. For the person-centered approach, a distinct group of dysregulated children appeared to have slight elevated $HR_{reactivity}$ in response to emotional induction (in our study: losing points during a game). This could point to greater emotional reactivity, especially downregulating negative emotions such as anger and frustration, in dysregulated children, in line with studies demonstrating greater ANS reactivity in children with comorbid disorders. Our predominantly-externalizing group did not show the previously reported blunted $HR_{reactivity}$, possibly because of their elevated levels of anxiety/depression and sub-clinical levels of attention problems. Attenuated $HR_{reactivity}$ could be specific for proactive aggression, but a subtype of children displaying proactive aggression only, is quite rare. Another explanation might lie in task
characteristics. A wide range of stimulus types has been used to measure $HR_{\text{reactivity}}$ in previous research, such as psychosocial stress tasks in which participants need to deliver a speech, $^{12,13}$ or games aimed to elicit stress or frustration $^{14,16}$ and peer provocations, $^{15}$ which could influence the relationship between $HR_{\text{reactivity}}$ and psychopathology. $^{68}$ In our study, $HR_{\text{reactivity}}$ was measured during an emotionally evoking Go/No-Go task, in which children were led to believe they would not receive a desirable gift. Future studies with preferably a more extensive $HR_{\text{reactivity}}$ protocol with different tasks or stimuli are needed. $^3$

Strengths of this study concern examination of autonomic dysfunction in relation to dysregulation, rather than with externalizing and internalizing problems separately. $HR_{\text{rest}}$ and $HR_{\text{reactivity}}$ proved to be unrelated independent measures and including them simultaneously revealed unique insights into autonomic dysfunction of dysregulation. By using both a variable- and person-centered approach to operationalize dysregulation, this study revealed differentiated associations with autonomic functioning depending on operationalization. This finding has important implications as both variable-centered and person-centered approaches have been used in previous research, often without acknowledging how such approaches are different. This presents a drawback in current research and limits the ability to draw comparisons among studies. $^{35}$ Research into formal comparisons of person- and variable-centered approaches to dysregulation is required to determine the impact of the different approaches.

Limitations of our study also need to be considered. Ideally $HR_{\text{rest}}$ reflects autonomic activity in the absence of any affecting external stimuli. In our study we cannot rule out that the presence of the parent affected the child. However, meta-analytic evidence showed that the relationship between $HR_{\text{rest}}$ and aggression was highly generalizable across different study designs and samples. This relationship was also not affected by method of HR assessment as
well as a range of other potential covariates such as age, \(^4\,7\) BMI, pubertal stage and physical health status \(^8\), and crying and muscle tone of the child during the \(HR_{\text{rest}}\) assessment. \(^6\,7\)

Regarding the role of medication use in ANS functioning: in our study \(HR_{\text{rest}}\) and \(HR_{\text{reactivity}}\) were not significantly different for children with and without medication (similarly to \(^56,61\)). Furthermore, adding medication status as a covariate in the regression analyses did not affect the results. However, to rule out effects of medication completely, participants would need to refrain from medication use before assessment. This was however ethically not feasible in this clinical sample. Another limitation is the relatively low sample size overall, which prohibited formal comparisons of the results from the variable-centered and person-centered approach.

Additionally, especially the low size of the dysregulated subgroup (which consisted of only 14 children), lowered power to detect group differences. Nonetheless, very few studies have examined ANS functioning in clinical samples, especially in children, and we look forward for future research to complement our findings. Finally, causality cannot be determined from this study. However, it seems that altered ANS functioning predicts subsequent psychiatric problems rather than vice versa \(^9\) as it is generally stated that \(HR_{\text{rest}}\) not only co-occurs with psychopathology but also precedes it. \(^7\)

It must be noted that associations between \(HR_{\text{rest}}\) and psychopathology were relatively modest. Future research should focus further on elucidating underlying mechanisms of ANS dysfunction in dysregulation, as these are still poorly understood. For example, it is unclear whether \(HR_{\text{rest}}\) might be a marker of other processes that are implicated in dysregulated behavior such as prefrontal cortex dysfunction, \(^6\) or whether \(HR_{\text{rest}}\) and dysregulation are influenced by the same genetic factors since both are (at least in part) genetically determined. As our study shows that ANS dysfunction is especially related to dysregulated behavior, early patterns of disrupted...
ANS functioning may constrain the acquisition of self-regulatory abilities. More research is needed, especially in younger samples given their higher neural plasticity. Future research in larger samples could further examine potential differences between boys and girls.

To conclude, this study offers new insights into links between ANS (dys-)function and externalizing, internalizing, and underlying dysregulated symptomatology. Rather seeing higher HR_{rest}, or (trait-like) overarousal as a unique risk factor for low externalizing and high internalizing symptomatology, we might conceptualize such heart rate characteristics better as a general risk factor for the development of psychopathology. In addition, high HR_{reactivity}, or enhanced emotional reactivity, might be characteristic for a clinically relevant subgroup of dysregulated children. Our findings are exploratory rather than explanatory, and replication in different samples is needed. HR can be assessed with relatively inexpensive and easy-to-use equipment and could provide incremental knowledge on individual differences that can help refine diagnostic assessments and intervention efforts.
References:


34. Sonuga-Barke EJS. ‘What’s up, (R)DoC?’--can identifying core dimensions of early functioning help us understand, and then reduce, developmental risk for mental disorders? J


42. Raine A, Fung ALC, Portnoy J, Choy O, Spring VL. Low heart rate as a risk factor for child and adolescent proactive aggressive and impulsive psychopathic behavior. Aggress Behav.


Table 1. Regression Coefficients and Standard Errors (STDYX standardized) of HR\textsubscript{rest} and HR\textsubscript{reactivity} Predicting Factors in the Dysregulation Profile (DP) Bifactor Model

<table>
<thead>
<tr>
<th></th>
<th>DP</th>
<th>AD</th>
<th>AGG</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-.157*</td>
<td>.089</td>
<td>-.199*</td>
<td>-.167</td>
</tr>
<tr>
<td>Age</td>
<td>-.036</td>
<td>-.003</td>
<td>.072</td>
<td>-.116</td>
</tr>
<tr>
<td>Social Adversity Index</td>
<td>.257**</td>
<td>.092</td>
<td>.037</td>
<td>.108</td>
</tr>
<tr>
<td>Medication Status</td>
<td>.310***</td>
<td>.061</td>
<td>.108</td>
<td>.148</td>
</tr>
<tr>
<td>HR\textsubscript{rest}</td>
<td>.285*</td>
<td>-.217</td>
<td>.342**</td>
<td>.060</td>
</tr>
<tr>
<td>HR\textsubscript{reactivity}</td>
<td>-.011</td>
<td>.044</td>
<td>.081</td>
<td>-.022</td>
</tr>
</tbody>
</table>

Note. AD = Anxious/Depressed, AGG = Aggressive Behavior, AP = Attention Problems (these all refer to factor scores derived from the bifactor DP model)

*\(p < .05\), **\(p < .01\), ***\(p < .001\)
**Figure 1.** Graphical Representation of the Bifactor Dysregulation Profile (DP) Model.

**Figure 2.** Graphical Representation of Average T-scores of the Anxious/Depressed, Aggressive Behavior and Attention Problems Syndrome Scales of the Child Behavior Checklist, Graphed for the Three Latent Profile Groups.

**Figure 3.** Means on the Subscales of the Early Adolescent Temperament Questionnaire – Revised across the Three Psychopathology Latent Profile Groups (Normative, $n = 92$, Predominantly Aggressive, $n = 69$, and Dysregulated, $n = 14$).

*Note:* Means that do not share identical subscripts (a, b or c) were significantly different from one another as indicated by Chi-Square equality tests of means across classes using the BCH procedure in Mplus 8.
Anxious/Depressed (AD)
- Cries a lot
- Fears school
- Feels worthless
- Worries

Aggressive Behavior (AGG)
- Argues a lot
- Gets in many fights
- Disobedient at home
- Stubborn

Attention Problems (AP)
- Can’t concentrate
- Can’t sit still
- Impulsive
- Inattentive

DP
<table>
<thead>
<tr>
<th>Class</th>
<th>Anxious/Depressed</th>
<th>Aggressive Behavior</th>
<th>Attention Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normative (n = 92)</td>
<td>56.71</td>
<td>57.81</td>
<td>54.29</td>
</tr>
<tr>
<td>Predominantly aggressive (n = 69)</td>
<td>63.95</td>
<td>74.41</td>
<td>69.56</td>
</tr>
<tr>
<td>Dysregulated (n = 14)</td>
<td>74.94</td>
<td>79.07</td>
<td>86.94</td>
</tr>
</tbody>
</table>

![Graph showing T-scores for different classes](image_url)
Aggressive Behavior

- Normative (n = 92)
- Predominantly aggressive (n = 63)
- Dysregulated (n = 14)

Attention Problems

Normative

Clinical

Subclinical

57.81

79.07

74.41

69.56

86.94

54.29
3) Predominantly aggressive (n = 69)
Surgency

- Normative (n = 92)
- Predominantly Aggressive (n = 69)
- Dysregulated (n = 14)
JAACAP-D-18-00125R2, entitled "Underlying Psychophysiology of Dysregulation: Resting Heart Rate and Heart Rate Reactivity in Relation to Childhood Dysregulation"

Section 3: On an attached page, please list the funding, acknowledgments, and financial disclosures of all authors.

Funding:
For the work reported in this article, the first author (Marike Deutz) was supported by a Fulbright scholarship and a Young Talent Award from the Prince Bernhard Culture Fund.

Financial disclosures:
All authors report no biomedical financial interests or potential conflicts of interest.