NEW RESEARCH

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 G.M. Vossen, PhD, Maja Deković, PhD, Anneloes L. van Baar, PhD, Peter Prinzie, PhD

Objective: High co-occurrence of externalizing and internalizing problems could underlie inconsistent findings regarding the relation between heart rate (HR) and psychopathology. In this study, HR measures were examined in relation to a general dysregulation profile studied from variable- and person-centered approaches.

Method: The sample (N = 182) consisted of 8- to 12-year-old children referred for externalizing behaviors and typically developing children (mean age 9.70, SD 1.26; 75.8% boys). Resting HR (HR_{rest}) was assessed during a 3-minute resting period. HR reactivity ($HR_{reactivity}$) 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_{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 increased levels of anxiety/depression, aggression, and attention problems. HR_{rest} was increased in the predominantly aggressive class and $HR_{reactivity}$ was increased in the dysregulated class.

Conclusions: High HR_{rest}, or (trait-like) over-arousal, seems to be associated with dysregulation rather than uniquely associated with low externalizing or high internalizing symptomatology. In addition, HR_{rest} predicted greater aggression and HR_{rest} was increased in the predominantly aggressive class. High $HR_{reactivity}$, or enhanced emotional reactivity, might be characteristic for a clinically relevant dysregulated subgroup. Assessment of HR could provide additional knowledge on individual differences that can help refine diagnostics and intervention efforts.

Key words: autonomic nervous system, comorbidity, stress reactivity, arousal, psychopathology

J Am Acad Child Adolesc Psychiatry 2019;■(■):■–■.

The autonomic nervous system (ANS), one of the main human stress-regulating systems, indexes physiologic reactivity and is considered a major component of emotion regulation.[1,2] 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 elucidate underlying mechanisms of psychopathology. Two main indices of ANS functioning have been studied in relation to psychopathology: resting heart rate (HR_{rest}), that is, the number 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 heart rate reactivity ($HR_{reactivity}$), that is, the amount of change in HR 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).[3-6]

Lower HR_{rest} has often been associated with externalizing behaviors (eg, aggressive, antisocial, conduct problems),[4,5,7] and higher HR_{rest} has been associated with internalizing behaviors (eg, anxiety, posttraumatic symptoms).[3,8-11] $HR_{reactivity}$ has been studied far less, with available evidence suggesting that lower $HR_{reactivity}$ is related to aggression and delinquency,[12-17] whereas higher $HR_{reactivity}$ has been linked to internalizing symptoms.[18,19] These findings are often explained in terms of over- and under-arousal. Aggressive children are believed to be under-aroused, which they experience as an unpleasant state, prompting them to seek stimulating activities (sensation-seeking theory),[20] and not fearing the social consequences (eg, punishment, rejection) of their aggressive actions (fearlessness theory).[21] In contrast, disorders from the internalizing spectrum, such as anxiety, are believed to indicate behavioral (over-)inhibition[3,22] or enhanced stress reactivity,[10] which could be expressed as "over-aroused" fear and anxiety.

However, this field of research has shown inconsistencies, with numerous studies failing to find divergent autonomic patterns for externalizing and internalizing behaviors.[16,23-26] One potential explanation for these conflicting findings is that although externalizing and internalizing behaviors are often considered 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.[27,28] These children have recently been described as "dysregulated,"[29] because they are believed to have self-regulatory deficits across multiple domains (ie, affect, attention, and behavior).[29-31] The Child Behavior Checklist–Dysregulation Profile (CBCL-DP)[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 and oppositional defiant disorder as diagnosed using the *DSM*.[32] Therefore, it fits well within recent efforts to describe psychopathology dimensionally in terms of dysregulation and dysfunction (Research Domain Criteria [RDoC]).[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.[34] Although physiologic 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. Because physiological measures might divulge unique insights into children's emotional functioning, it is valuable to examine physiology early in development when early intervention could defer children from chronic problematic developmental trajectories.

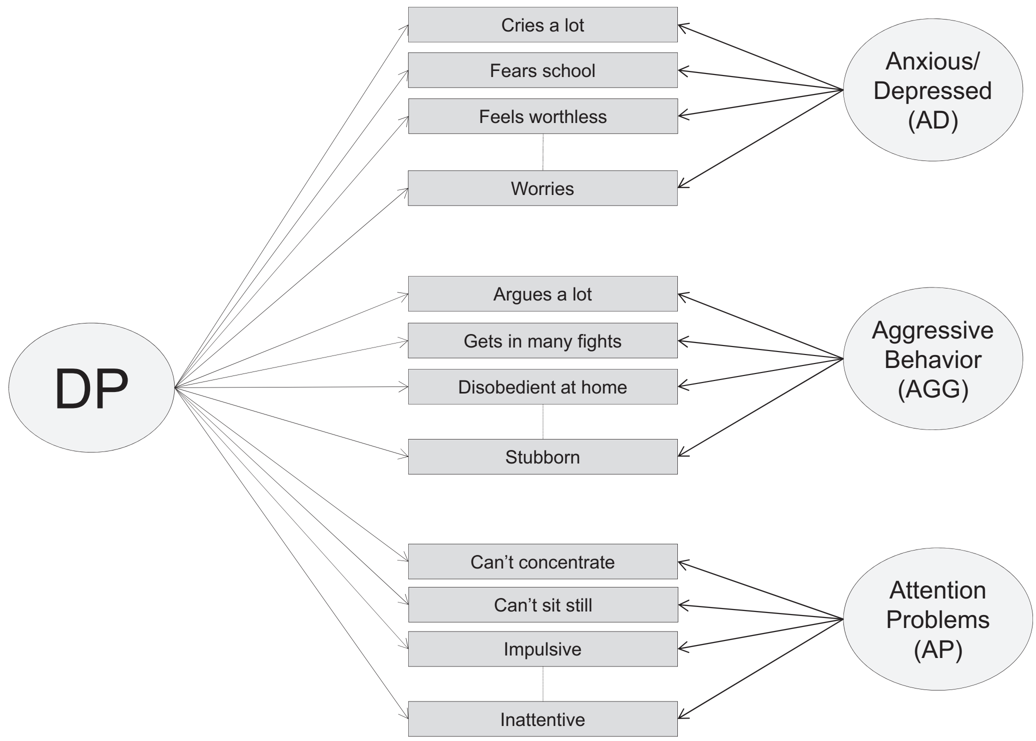
VARIABLE- AND PERSON-CENTERED APPROACHES TO STUDY DYSREGULATION

Dysregulation has been studied from a variable-centered approach and a person-centered approach using mostly 3 key syndrome scales (Anxious/Depressed [AD], Aggressive Behavior [AGG], and Attention Problems [AP]) from the externalizing and internalizing domains of the CBCL.[29-31] Variable-centered analyses focus on relations among variables within a given population. Our previous variable-centered work[35,36] demonstrated that a bifactor model (Figure 1) best described the DP. In this bifactor model, a general factor of dysregulation reflects what is common among symptoms from the externalizing and internalizing spectra. Three additional specific factors of AD, AGG, and AP (representing the 3 DP scales)[35,36] explain the unique coherence among the items within these scales. A bifactor model might be especially useful in determining the specificity of HR_{rest} and $HR_{reactivity}$ in relation to psychopathology, because links with specific anxiety/depression, aggression, and attention problems and 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) of individuals with similar profiles on certain variables are identified. 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 higher scores within the externalizing or internalizing domain only, and youths with co-occurring externalizing and internalizing problems. The latter group is often referred to as "dysregulated,"[30,37] because these children display concurrent disturbances in regulating attention, behavior, and mood.[29,30] 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 because 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 commonalities between different forms of psychopathology, and with a complementary person-centered approach, we look for subgroups of children characterized by similar psychopathology patterns. Applying these two approaches in one study could result in a richer and more comprehensive understanding of ANS dysfunction and dysregulation. In summary, the present study examined two different measures of ANS functioning, HR_{rest} and $HR_{reactivity}$, in relation to dysregulation from a variable-centered approach (DP bifactor model) and a person-centered approach (latent profile analysis) in a predominantly clinically referred sample of children 8 to 12 years of age. Because the DP has been found to be highly stable and heritable,[38,39] examining markers of ANS functioning might help explain the etiology

FIGURE 1 Graphic Representation of the Bifactor Dysregulation Profile (DP) Model



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 associated with specific aggressive behavior and attention problems. For the person-centered approach, we expected to identify a group of dysregulated children who would show increased HR_{rest} and $HR_{reactivity}$ and a group of "predominantly aggressive" children who would show decreased HR_{rest} and $HR_{reactivity}$ (and a normative group with scores between those of the dysregulated and predominantly aggressive groups).

METHOD

Sample

Data were derived from a larger study (2004–2012) on individual differences in neural and psychophysiologic correlates of self-regulation.[40,41] The study was approved by the research ethics board of the University of Toronto. Children 7 to 12 years of age (n = 117) referred for externalizing behavior by mental health professionals, teachers, and/or parents were recruited from 2 community mental health agencies in Canada. In addition, (generally) typically developing children 7 to 18 years of age (n = 103) were recruited through newspaper ads. Parents and children lacking sufficient English-language skills and children with significant cognitive impairment were excluded. Children 7 years or at least 13 years of age were excluded to have a more homogeneous age group of children 8 to 12 years old, representing middle childhood.

The final study sample consisted of 182 children (mean 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 for race, with the majority being Canadian-European (62.3%) and the second largest group being African/Caribbean-Canadian (15.4%). Educational levels for mothers and fathers, respectively, were 33% and 41.9% for high school or less, 33.5% and 26.4% for community college, and 30.7% and 29.5% for university degree or higher. A social adversity index was created (similar to that of Raine *et al.*[42]) with 1 point each for father uneducated (13.7% with no high school diploma; 29.7% missing), mother uneducated (12.1% with no high school diploma; 3.3% missing), low income (38.5% with annual income <40,000 Canadian dollars; 6.6% missing), and child living with both parents versus other (57.1%; 3.3% missing).

All measures reported in this study were taken 2 weeks before the start of treatment (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 laboratory with their mother, where parental consent and child assent were obtained. Children first completed a series of computer tasks (see Woltering *et al.*[43]), while mothers completed questionnaires. Next, children and their mothers discussed neutral and emotional issues (reported in Woltering *et al.*[41]). They were asked to discuss, in this exact order, a randomly assigned positive topic of 2 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?"); a personally relevant negative topic that the parent and child independently listed using a modified version of the Issues Checklist[44] that provoked anger and had not been resolved; and 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 2 minutes left and that they should "try to end on a positive note" (which was explained to participants beforehand). During these discussions, mother and child were connected to the electrocardiographic (ECG) acquisition unit, but HR data collected during these discussions were not used in the present study (see Woltering *et al.*[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. After another short break, ECG measures were continued, and children were fitted with an electroencephalographic net (results not reported in this study) and seated in front of a computer to complete a go/no-go task.[43] From this task, $HR_{reactivity}$ was derived.

Measures

Child Behavior Checklist–Dysregulation Profile. Dysregulation was assessed with the CBCL-DP, consisting of items from the AD (13 items; $\alpha = 0.84$), AGG (18 items; $\alpha = 0.94$), and AP (10 items; $\alpha = 0.89$) scales from the CBCL,[45] using the 2007 scale assignments. T scores were computed according to the method of Achenbach.[45]

Early Adolescent Temperament Questionnaire–Revised. To validate the person-centered latent profile solution, mean scale scores derived from the parent-reported Early Adolescent Temperament Questionnaire–Revised (EATQ-R)[46] were used. The EATQ-R consists of 62 items divided into 10 scales: Activation Control (7 items; $\alpha = 0.82$), Affiliation (6 items; $\alpha = 0.70$), Aggression (7 items; $\alpha = 0.82$), Attention (6 items; $\alpha = 0.84$), Depressive Mood (5 items; $\alpha = 0.76$), Fear (6 items; $\alpha = 0.52$), Frustration (6 items; $\alpha = 0.80$), Inhibitory Control (5 items; $\alpha = 0.71$), Shyness (5 items; $\alpha = 0.83$), and Surgency (9 items; $\alpha = 0.62$).

Physiology Measures. A BIOPAC MP150 psychophysiologic recording system (Biopac Systems Inc., Goleta, CA)[47] was used to acquire ECG data at a sampling rate of 1,000 Hz. Electrodes were positioned diagonally across the heart according to a standard lead II configuration. Data were processed with ANSLab software[48] and scored at 1-minute intervals.

Resting Heart Rate. HR_{rest} was measured during a 3-minute resting period after a 14-minute period of mother–child discussions. During these discussions, mother and child were connected to the ECG acquisition unit; HR data collected during these discussions were not used in the present study (see Woltering *et al.*[41]). The protocol for the mother–child discussions was completed by 118 mother–child pairs (64.8%). After 35 participants completed the study, HR_{rest} assessment was added to the study; thus, data were 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_{rest} was assessed. Video recordings were coded for movements, talking, or other behaviors that might affect the HR assessment. The large majority of children sat 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_{rest} data were recoded as missing. Paired-samples t tests indicated that mean HR did not differ significantly between the 1-minute segments and was highly stable ($r > 0.95$ for all comparisons). Mean HR_{rest} was 88.92 bpm (range 65.17–121.81, SD 10.80). HR_{rest} did not significantly differ across sex ($t_{80} = -0.1484$, $p = .142$) or medication status ($t_{71} = -1.220$, $p = .227$).

Heart Rate Reactivity. $HR_{reactivity}$ 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 (go condition) and withhold responding when the same letter appeared twice in a row (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 3 blocks (A, B, C) that each lasted 3 minutes. A dynamic adjustment of stimulus times based on performance was used to make the task challenging for all ages (for more details, see Woltering *et al.*[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 shorter 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, because during block B (when children lost all their points) perceived negative emotions significantly increased and positive emotions decreased (Figure S1, available online).

$HR_{reactivity}$ data were 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 $HR_{reactivity}$, with higher scores indicating a greater increase in HR during block B suggesting greater $HR_{reactivity}$, a procedure in line with a previous study on this sample.[43] $HR_{reactivity}$ did not significantly differ across sex ($t_{144} = 0.965$, $p = .336$) or medication status ($t_{144} = -1.805$, $p = .073$).

RESULTS

Variable-Centered Approach

Bifactor Model. Using confirmatory factor analysis in Mplus 8[51] with the WLSMV estimator for categorical indicators, a bifactor model (see Deutz *et al.*[35]) was estimated using available item-level CBCL data (n = 160, 12.1% missing). Each item loaded on a general DP factor and on 1 orthogonal specific factor of AD, AGG, or AP (Figure 1). Fit indices for this model were good ($\chi^2_{738} = 977.513$, root mean square error of approximation 0.045, comparative fit index 0.966, Tucker-Lewis index 0.963). 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 $\chi^2_{737} = 952.964$, root mean square error of approximation 0.043, comparative fit index 0.970, Tucker-Lewis index 0.966. All factor loadings (Table S1, available online) on the general DP factor were significant (most >0.60). Factor loadings on the specific factors were generally lower, and 10 of 41 loadings (of which 7 were for AGG) were not statistically significant. Factor scores were subsequently saved to use as input for regression analyses.

Regression Analysis. Children with and without HR_{rest} or $HR_{reactivity}$ data did not differ significantly in age, sex, social adversity, factor scores from the bifactor DP model or on CBCL-DP *T* scores. Therefore, regression analyses were conducted in Mplus 8 with saved factor scores using full information maximum likelihood to optimally handle missing data and use the full sample. Bootstrapping (5,000 replications) was used for all analyses because of the relatively small sample. 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). For 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 higher AGG. $HR_{reactivity}$ was not a significant predictor for DP, AD, AGG, or AP. HR_{rest} and $HR_{reactivity}$ were not significantly related ($r = -0.005$, $p = .963$); hence, results did not differ when HR_{rest} and $HR_{reactivity}$ were examined separately. Covariates did not affect patterns of results. R^2 values were 0.298 for DP ($p < .001$) and 0.186 for AGG ($p < .05$). No significant variance was explained in AD (0.062, $p = .267$) or AP (0.085, $p = .096$). Cohen f^2 effect size values (calculated as R^2 divided by $1 - R^2$) were small for AD (0.07) and AP (0.09), medium for AGG (0.23), and large for DP (0.42). As suggested by an anonymous reviewer, post hoc analyses were performed to examine whether sex interacted with HR_{rest} and $HR_{reactivity}$ 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 was performed. Continuous *T* scores for the AD, AGG, and AP scales (n = 175, 3.8% missing) were used rather than item-level data because of sample size limitations. Given high intercorrelations between CBCL *T* scores, covariances among latent profile indicators were allowed. Model fit was evaluated with the Lo-Mendell-Rubin (LMR)

TABLE 1 Regression Coefficients (SEs; STDYX Standardized) of Resting Heart Rate (HR_{rest}) and Heart Rate Reactivity ($HR_{reactivity}$) Predicting Factors in the Dysregulation Profile (DP) Bifactor Model

	DP	AD	AGG	AP
Sex	−0.157* (0.079)	0.089 (0.076)	−0.199* (0.085)	−0.167 (0.087)
Age	−0.036 (0.075)	−0.003 (0.083)	−0.072 (0.080)	−0.116 (0.070)
Social adversity index	0.257** (0.076)	0.092 (0.080)	−0.037 (0.084)	0.108 (0.088)
Medication status	0.310*** (0.083)	0.061 (0.095)	0.108 (0.104)	0.148 (0.086)
HR_{rest}	0.285* (0.119)	−0.217 (0.136)	0.342** (0.115)	0.060 (0.125)
$HR_{reactivity}$	−0.011 (0.089)	0.044 (0.109)	0.081 (0.103)	−0.022 (0.093)

***Note**: Anxious/depressed (AD), aggressive behavior (AGG), and attention problems (AP) refer to factor scores derived from the bifactor DP model.*
**p < .05; **p < .01; ***p < .001.*

test, with significant values indicating better fit compared with a model with $k - 1$ profiles,[52] lower values on the sample size adjusted Bayesian information criterion (AdjBIC), and entropy levels of at least 0.80. LMR results indicated that a 3-class solution fit best statistically and had good entropy (0.90) and lower AdjBIC values (3,751.323) than a 1-class solution (3,807.037) and a 2-class solution (3,783.682). Although the 4-class solution showed lower AdjBIC (3,746.611), results of the LMR test indicated that the 4-class solution fit significantly worse ($p = .108$ by LMR test). Because the 4-class solution also consisted of 2 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 because the average probabilities for the most likely class were high enough (>0.924) and probabilities for the other 2 classes were low enough (<0.076).

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, the subclinical range for AP, and the normative range 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 3 classes were compared on means on 10 temperament dimensions (Figure 3). The 3 classes did not differ significantly on affiliation, shyness, and surgency. For 5 scales, the 3 classes differed significantly from one another, 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 confirmed the validity of the profile solution because the degree of adjustment of the 3 classes was normative > predominantly aggressive > dysregulated.

Profile Comparisons. To compare the latent profiles on means (ie, HR_{rest}, $HR_{reactivity}$, and covariates), the BCH procedure in Mplus was used for continuous variables and the DCATEGORICAL option was used 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 (0.982) compared with those in 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 (0.033 probability) compared with the predominantly aggressive class (0.495 probability; $\chi^2 = 38.690$, $p < .001$) and the dysregulated class (0.527 probability; $\chi^2 = 9.020$, $p < .01$).

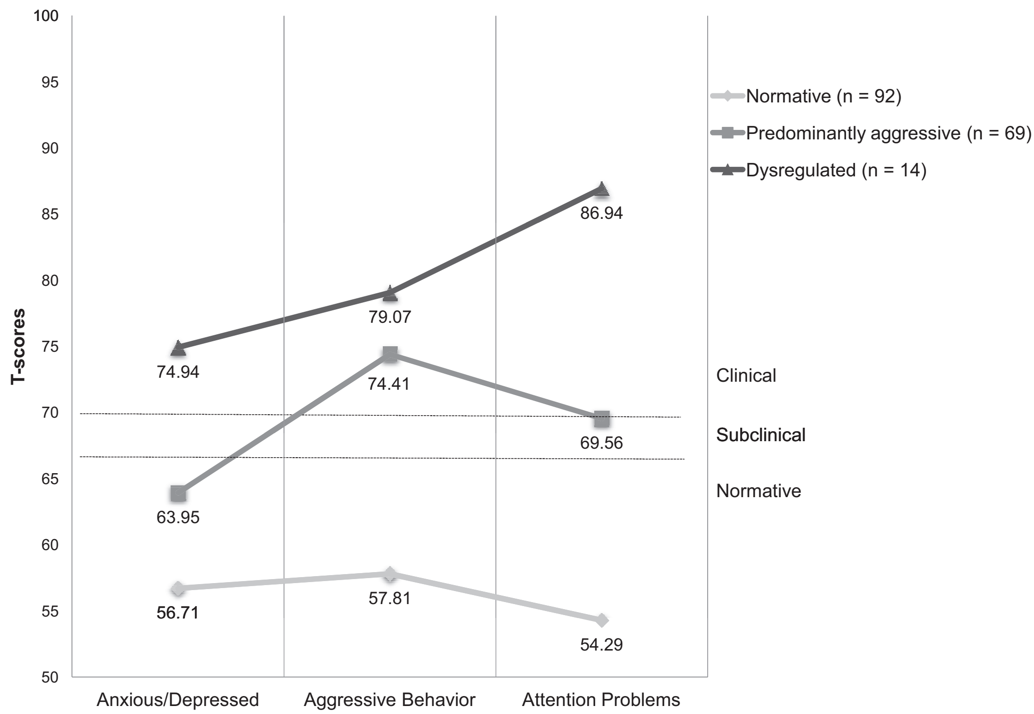
Next, the 3 psychopathology classes (normative, predominantly aggressive, and dysregulated) were compared on mean levels of HR_{rest} and $HR_{reactivity}$. The predominantly aggressive group had significantly higher HR_{rest} (93.30, SE 2.12) compared with the normative group ($HR_{rest} = 86.07$, SE 1.61; $\chi^2 = 6.917$, $p < .01$), whereas the dysregulated group ($HR_{rest} = 88.03$, SE 1.86) did not differ significantly from either group.

$HR_{reactivity}$ did not differ between the predominantly aggressive ($HR_{reactivity} = 2.31$, SE 0.42) and the normative ($HR_{reactivity} = 1.65$, SE 0.46) group but was significantly higher in the dysregulated group ($HR_{reactivity} = 4.39$, SE 92) compared with the normative group ($\chi^2 = 7.147$, $p < .01$) and the predominantly aggressive group ($\chi^2 = 4.117$, $p < .05$).

DISCUSSION

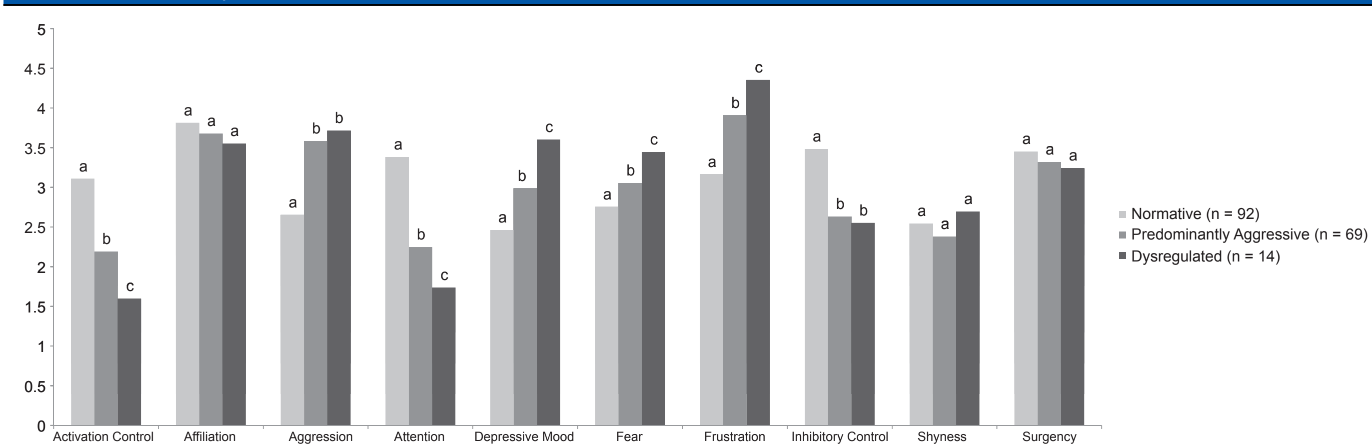
In this study, we examined HR_{rest} and $HR_{reactivity}$, 2 different markers of ANS (dys-)function, in relation to

FIGURE 2 Graphic Representation of Average *T* scores of the Anxious/Depressed, Aggressive Behavior, and Attention Problems Syndrome Scales of the Child Behavior Checklist, Graphed for the 3 Latent Profile Groups



psychopathology in a sample of 8- to 12-year-old children, predominantly clinically referred for externalizing problem behavior. We used 2 approaches of considering commonalities between internalizing and externalizing behavior problems: a variable-centered approach and a person-centered approach. For the variable-centered approach, we estimated a bifactor model with a general psychopathology factor of dysregulation underlying externalizing and internalizing symptomatology that exists next to specific factors of AD, AGG, and AP. For the person-centered approach, we used latent profile analysis to derive groups with different psychopathology profiles. The person-centered

FIGURE 3 Means on the Subscales of the Early Adolescent Temperament Questionnaire–Revised Across the 3 Psychopathology Latent Profile Groups (Normative, n = 92; Predominantly Aggressive, n = 69; and Dysregulated, n = 14)



Note: *Means that do not share identical letters (a, b, or c) were significantly different from one another as indicated by* χ^2 *equality tests of means across classes using the BCH procedure in Mplus 8.*

latent profile analyses showed 3 distinct groups of children with different psychopathology profiles: normative, predominantly aggressive, and dysregulated (characterized by co-occurring anxiety/depression, aggression, and attention problems). These psychopathology profiles differed significantly on temperament dimensions, which confirmed that the normative group was well adapted, whereas 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), decreased 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]

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

Resting Heart Rate

Results from the variable-centered analyses showed 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 because 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 increased emotional arousal that might affect a broad expression of psychopathologic symptoms going beyond the internalizing spectrum. HR_{rest} was not significantly increased in the dysregulated class, but the relatively large coefficient size suggests that the small group ($n = 14$) could have affected the non-significance of this result.

Unexpectedly, HR_{rest} also was positively associated with specific aggression and it was increased in a subgroup of children characterized as predominantly aggressive. Although low HR_{rest} is often described as a biomarker for antisocial behavior,[4,7] several studies have failed to demonstrate links between low HR_{rest} and externalizing behaviors.[16,23-26] There are several possible explanations for our findings. First, the AGG scale from the CBCL consists of a heterogeneous set of behaviors, and it has been proposed that low HR_{rest} is an autonomic risk factor for proactive (goal-directed, intentional) psychopathic-like aggression rather than for reactive (or impulsive, emotional) aggression.[42,56,57] Autonomic over-arousal has been associated with internalizing subtypes of conduct disorder[58] and has been suggested to explain the co-occurrence between reactive aggression and anxiety.[59] 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_{rest} compared with controls.[56,60,61] Our convergent findings from 2 different approaches to examine (comorbid) psychopathology substantiate a previous notion that the link between low HR_{rest} and externalizing behavior link might be primarily encountered in community samples.[8]

Because comorbidity of internalizing problems in children with disruptive behavior disorders is generally high,[62] comorbid anxiety might drive increased HR_{rest}, which shows the usefulness of measures such as the DP that cut across spectra. Our findings corroborate previous reports of neural hypervigilance in externalizing disorders,[22,63] 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.[64] 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 under-reactivity is associated with externalizing behaviors[12-17] and over-reactivity is associated with internalizing behaviors.[18,19] 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 increased $HR_{reactivity}$ in response to emotional induction (losing points during a game in the present study). 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.[65] Our predominantly aggressive group did not show the previously reported blunted $HR_{reactivity}$,[12-17] possibly because of their increased levels of anxiety/depression and subclinical levels of attention problems. Attenuated $HR_{reactivity}$ could be specific for proactive aggression,[66] but a subtype of children displaying only proactive aggression is quite rare. Another explanation might lie in task characteristics. A wide range of stimulus types has been used to measure $HR_{reactivity}$ 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 relation between $HR_{reactivity}$ and psychopathology.[67] In our study, $HR_{reactivity}$ 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 $HR_{reactivity}$ 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_{rest} and $HR_{reactivity}$ proved to be unrelated independent measures and including them simultaneously exposed unique insights into autonomic dysfunction of dysregulation. By using variable- and person-centered approaches to operationalize dysregulation, this study showed differentiated associations with autonomic functioning depending on operationalization. This finding has important implications because variable-centered and person-centered approaches have been used in previous research, often without acknowledging how such approaches differ. 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_{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 relation between HR_{rest} and aggression was highly generalizable across different study designs and samples. This relation also was not affected by method of HR assessment and a range of other potential covariates such as age,[4,7] body mass index, pubertal stage and physical health status,[8] and crying and muscle tone of the child during the HR_{rest} assessment.[68] Regarding the role of medication use in ANS functioning, in our study HR_{rest} and $HR_{reactivity}$ were not significantly different for children with and without medication (similarly to Schoorl *et al.*[56] and De Wied *et al.*[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. However, this was ethically not feasible in this clinical sample. Another limitation is the relatively small sample overall, which prohibited formal comparisons of the results from the variable-centered and person-centered approaches. In addition, especially the small size of the dysregulated subgroup (which consisted of only 14 children) weakened power to detect group differences. Nonetheless, very few studies have examined ANS functioning in clinical samples, especially in children, and we look forward to future research to complement our findings. Causality cannot be determined from this study. However, it seems that altered ANS functioning predicts subsequent psychiatric problems rather than vice versa[9] because it is generally stated that HR_{rest} not only co-occurs with psychopathology but also precedes it.[7]

It must be noted that associations between HR_{rest} and psychopathology were relatively modest. Future research should focus further on elucidating underlying mechanisms of ANS dysfunction in dysregulation, because these are still poorly understood. For example, it is unclear whether HR_{rest} might be a marker of other processes that are implicated in dysregulated behavior such as prefrontal cortex dysfunction,[6] or whether HR_{rest} and dysregulation are influenced by the same genetic factors because they are (at least in part) genetically determined. Because our study shows that ANS dysfunction is especially related to dysregulated behavior, early patterns of disrupted ANS functioning could 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 than considering higher HR_{rest}, or (trait-like) over-arousal, as a unique risk factor for low externalizing and high internalizing symptomatology, we might better conceptualize such HR characteristics 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.

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. Dr. Prinzie is with Erasmus University Rotterdam, The Netherlands.

For the work reported in this article, the first author (Ms. 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 H.F. Deutz, MSc, Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, PO Box 1738, 3000 DR, Rotterdam, the Netherlands; e-mail: deutz@essb.eur.nl

https://doi.org/10.1016/j.jaac.2018.09.434

REFERENCES

1. Appelhans BM, Luecken LJ. Heart rate variability as an index of regulated emotional responding. Rev Gen Psychol. 2006;10:229-240.
2. Kreibig SD. Autonomic nervous system activity in emotion: a review. Biol Psychol. 2010; 84:394-421.
3. Kagan J, Reznick JS, Snidman N. The physiology and psychology of behavioral inhibition in children. Child Dev. 1987;58:1459-1473.
4. Ortiz J, Raine A. Heart rate level and antisocial behavior in children and adolescents: a meta-analysis. J Am Acad Child Adolesc Psychiatry. 2004;43:154-162.
5. Lorber MF. Psychophysiology of aggression, psychopathy, and conduct problems: a meta-analysis. Psychol Bull. 2004;130:531-552.
6. Raine A. Annotation: the role of prefrontal deficits, low autonomic arousal, and early health factors in the development of antisocial and aggressive behavior in children. J Child Psychol Psychiatry. 2002;43:417-434.
7. Portnoy J, Farrington DP. Resting heart rate and antisocial behavior: an updated systematic review and meta-analysis. Aggress Violent Behav. 2015; 22:33-45.
8. Dietrich A, Riese H, Sondeijker FEPL, *et al*. Externalizing and internalizing problems in relation to autonomic function: a population-based study in preadolescents. J Am Acad Child Adolesc Psychiatry. 2007;46:378-386.
9. Latvala A, Kuja-Halkola R, Rück C, *et al*. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: a longitudinal population study of more than 1 million men in Sweden. JAMA Psychiatry. 2016; 73:1268-1275.
10. Monk C, Kovelenko P, Ellman LM, *et al*. Enhanced stress reactivity in paediatric anxiety disorders: implications for future cardiovascular health. Int J Neuropsychopharmacol. 2001;4:199-206.
11. Rogeness GA, Cepeda C, Macedo CA, Fischer C, Harris WR. Differences in heart rate and blood pressure in children with conduct disorder, major depression, and separation anxiety. Psychiatry Res. 1990;33:199-206.
12. Sijtsema JJ, Nederhof E, Veenstra R, Ormel J, Oldehinkel AJ, Ellis BJ. Effects of family cohesion and heart rate reactivity on aggressive/rule-breaking behavior and prosocial behavior in adolescence: the Tracking Adolescents' Individual Lives Survey study. Dev Psychopathol. 2013;25:699-712.
13. Popma A, Jansen LMC, Vermeiren R, *et al*. Hypothalamus pituitary adrenal axis and autonomic activity during stress in delinquent male adolescents and controls. Psychoneuroendocrinology. 2006;31:948-957.
14. Fairchild G, van Goozen SHM, Stollery SJ, *et al*. Cortisol diurnal rhythm and stress reactivity in male adolescents with early-onset or adolescence-onset conduct disorder. Biol Psychiatry. 2008;64:599-606.
15. Williams SC, Lochman JE, Phillips NC, Barry TD. Aggressive and nonaggressive boys' physiological and cognitive processes in response to peer provocations. J Clin Child Adolesc Psychol. 2003;32:568-576.
16. Bimmel N, van IJzendoorn MH, Bakermans-Kranenburg MJ, Juffer F, De Geus EJC. Problem behavior and heart rate reactivity in adopted adolescents: longitudinal and concurrent relations. J Res Adolesc. 2008;18:201-214.
17. Herpertz SC, Mueller B, Qunaibi M, Lichterfeld C, Konrad K, Herpertz-Dahlmann B. Response to emotional stimuli in boys with conduct disorder. Am J Psychiatry. 2005; 162:1100-1107.
18. Matthews KA, Manuck SB, Saab PG. Cardiovascular responses of adolescents during a naturally occurring stressor and their behavioral and psychophysiological predictors. Psychophysiology. 1986;23:198-209.
19. Rozenman M, Sturm A, McCracken JT, Piacentini J. Autonomic arousal in anxious and typically developing youth during a stressor involving error feedback. Eur Child Adolesc Psychiatry. 2017;26:1423-1432.
20. Zuckerman M. Sensation Seeking: Beyond the Optimal Level of Arousal. Hillsdale, NJ: L. Erlbaum Associates; 1979.
21. Raine A. The Psychopathology of Crime: Criminal Behavior as a Clinical Disorder. San Diego: American Press; 1997.
22. Woltering S, Shi Q. On the neuroscience of self-regulation in children with disruptive behavior problems: implications for education. Rev Educ Res. 2016;86:1085-1110.
23. Dierckx B, Kok R, Tulen JH, *et al*. A prospective study of heart rate and externalising behaviours in young children. J Child Psychol Psychiatry. 2014;55:402-410.
24. Van Hulle CA, Corley R, Zahn-Waxler C, Kagan J, Hewitt JK. Early childhood heart rate does not predict externalizing behavior problems at age 7 years. J Am Acad Child Adolesc Psychiatry. 2000;39:1238-1244.
25. Posthumus JA, Böcker KBE, Raaijmakers MAJ, Van Engeland H, Matthys W. Heart rate and skin conductance in four-year-old children with aggressive behavior. Biol Psychol. 2009;82:164-168.
26. Scarpa A, Haden SC, Tanaka A. Being hot-tempered: autonomic, emotional, and behavioral distinctions between childhood reactive and proactive aggression. Biol Psychol. 2010;84:488-496.
27. Rhee SH, Lahey BB, Waldman ID. Comorbidity among dimensions of childhood psychopathology: converging evidence from behavior genetics. Child Dev Perspect. 2015;9:26-31.
28. Achenbach TM, Ivanova MY, Rescorla LA, Turner LV, Althoff RR. Internalizing/externalizing problems: review and recommendations for clinical and research applications. J Am Acad Child Adolesc Psychiatry. 2016;55:647-656.
29. Althoff RR. Dysregulated children reconsidered. J Am Acad Child Adolesc Psychiatry. 2010;49:302-305.
30. Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. Adult outcomes of childhood dysregulation: a 14-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2010;49:1105-1116.
31. Ayer L, Althoff R, Ivanova M, *et al*. Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. J Child Psychol Psychiatry. 2009;50: 1291-1300.
32. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
33. Yee CM, Javitt DC, Miller GA. Replacing DSM categorical analyses with dimensional analyses in psychiatry research: the Research Domain Criteria initiative. JAMA Psychiatry. 2015;72:1159-1160.
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 Child Psychol Psychiatry. 2014;55:849-851.
35. Deutz MHF, Geeraerts SB, van Baar AL, Deković M, Prinzie P. The Dysregulation Profile in middle childhood and adolescence across reporters: factor structure,

measurement invariance, and links with self-harm and suicidal ideation. Eur Child Adolesc Psychiatry. 2016;25:431-442.
36. Geeraerts SB, Deutz MHF, Deković M, *et al*. The Child Behavior Checklist Dysregulation Profile in preschool children: a broad dysregulation syndrome. J Am Acad Child Adolesc Psychiatry. 2015;54:595-602.e2.
37. De Caluwé E, Decuyper M, De Clercq B. The child behavior checklist dysregulation profile predicts adolescent DSM-5 pathological personality traits 4 years later. Eur Child Adolesc Psychiatry. 2013;22:401-411.
38. Boomsma DI, Rebollo I, Derks EM, *et al*. Longitudinal stability of the CBCL-juvenile bipolar disorder phenotype: a study in Dutch twins. Biol Psychiatry. 2006;60:912-920.
39. Deutz MHF, Vossen HGM, De Haan AD, Deković M, Van Baar AL, Prinzie P. Normative development of the Child Behavior Checklist Dysregulation Profile from early childhood to adolescence: associations with personality pathology. Dev Psychopathol. 2018;30:437-447.
40. Woltering S, Granic I, Lamm C, Lewis MD. Neural changes associated with treatment outcome in children with externalizing problems. Biol Psychiatry. 2011;70:873-879.
41. Woltering S, Lishak V, Elliott B, Ferraro L, Granic I. Dyadic attunement and physiological synchrony during mother-child interactions: an exploratory study in children with and without externalizing behavior problems. J Psychopathol Behav Assess. 2015;37:624-633.
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. 2014;40:290-299.
43. Woltering S, Lishak V, Hodgson N, Granic I, Zelazo PD. Executive function in children with externalizing and comorbid internalizing behavior problems. J Child Psychol Psychiatry. 2015;57:30-38.
44. Robin AL, Weis JG. Criterion-related validity of behavioral and self-report measures of problem-solving communication skills in distressed and nondistressed parent-adolescent dyads. Behav Assess. 1980;3:339-352.
45. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profiles. Burlington: Department of Psychiatry, University of Vermont; 1991.
46. Capaldi DM, Rothbart MK. Development and validation of an early adolescent temperament measure. J Early Adolesc. 1992;12:153-173.
47. *BIOPAC Systems Inc.* [computer program]. Goleta, CA
48. Wilhelm FH, Grossman P, Roth WT. Analysis of cardiovascular regulation. Biomed Sci Instrum. 1999;35:135-140.
49. Stieben J, Lewis MD, Granic I, Zelazo PD, Segalowitz S, Pepler D. Neurophysiological mechanisms of emotion regulation for subtypes of externalizing children. Dev Psychopathol. 2007;19:455-480.
50. Taylor PJ, Marsh JE. E-Prime (Software). In: The International Encyclopedia of Communication Research Methods. Hoboken, NJ: John Wiley & Sons; 2017:1-3.
51. Muthén LK, Muthén BO. Mplus User's Guide. 8th ed. Los Angeles, CA: Muthén & Muthén; 1998-2017.
52. Lo Y; NRM and DBR. Testing the number of components in a normal mixture. Biometrika. 2001;88:767-778.
53. Althoff RR, Ayer LA, Rettew DC, Hudziak JJ. Assessment of dysregulated children using the Child Behavior Checklist: a receiver operating characteristic curve analysis. Psychol Assess. 2010;22:609-617.
54. Reise SP. The rediscovery of bifactor measurement models. Multivariate Behav Res. 2012;47:667-696.
55. Snyder HR, Hankin BL. All models are wrong, but the p factor model is useful: reply to Widiger and Oltmanns (2017) and Bonifay, Lane, and Reise (2017). Clin Psychol Sci. 2017;5:187-189.
56. Schoorl J, Van Rijn S, De Wied M, Van Goozen SHM, Swaab H. Variability in emotional/behavioral problems in boys with oppositional defiant disorder or conduct disorder: the role of arousal. Eur Child Adolesc Psychiatry. 2016;25:821-830.
57. Scarpa A, Tanaka A, Chiara Haden S. Biosocial bases of reactive and proactive aggression: the roles of community violence exposure and heart rate. J Community Psychol. 2008; 36:969-988.
58. Fanti KA. Understanding heterogeneity in conduct disorder: a review of psychophysiological studies. Neurosci Biobehav Rev. 2018;91:4-20.
59. Bubier JL, Drabick DAG. Co-occurring anxiety and disruptive behavior disorders: the roles of anxious symptoms, reactive aggression, and shared risk processes. Clin Psychol Rev. 2009;29:658-669.
60. Zahn TP, Kruesi MJ. Autonomic activity in boys with disruptive behavior disorders. Psychophysiology. 1993;30:605-614.
61. De Wied M, Boxtel AV, Posthumus JA, Goudena PP, Matthys W. Facial EMG and heart rate responses to emotion-inducing film clips in boys with disruptive behavior disorders. Psychophysiology. 2009;46:996-1004.
62. Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct disorder and oppositional defiant disorder in a national sample: developmental epidemiology. J Child Psychol Psychiatry. 2004;45:609-621.
63. Woltering S, Liao V, Liu Z-X, Granic I. Neural rhythms of change: long-term improvement after successful treatment in children with disruptive behavior problems. Neural Plast. 2015;2015:873197.
64. Granic I. The role of anxiety in the development, maintenance, and treatment of childhood aggression. Dev Psychopathol. 2014;26:1515-1530.
65. Waschbusch DA, Pelham WE, Jennings JR, Greiner AR, Tarter RE, Moss HB. Reactive aggression in boys with disruptive behavior disorders: behavior, physiology, and affect. J Abnorm child Psychol. 2002;30:641-656.
66. Hubbard JA, McAuliffe MD, Morrow MT, Romano LJ. Reactive and proactive aggression in childhood and adolescence: precursors, outcomes, processes, experiences, and measurement. J Pers. 2010;78:95-118.
67. Obradović J, Bush NR, Boyce WT. The interactive effect of marital conflict and stress reactivity on externalizing and internalizing symptoms: the role of laboratory stressors. Dev Psychopathol. 2011;23:101-114.
68. Raine A, Venables PH, Mednick SA. Low resting heart rate at age 3 years predisposes to aggression at age 11 years: evidence from the Mauritius Child Health Project. J Am Acad Child Adolesc Psychiatry. 1997;36:1457-1464.