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Depression and resting state heart rate variability in children and adolescents — A systematic review and meta-analysis

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HIGHLIGHTS

- In adults, depression is associated with reduced resting state high-frequency heart rate variability (HF-HRV).
- We reviewed the evidence on such association in children and adolescents.
- We found lower resting state HF-HRV in clinically depressed adolescents.
- Unlike in adults, depressive symptom severity is not associated with HF-HRV.
- Clinical implications and suggestions for future research are provided.

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ABSTRACT

Among adults, depression is associated with reduced vagal activity, as indexed by high frequency heart rate variability [HF-HRV]), which correlates inversely with depression severity. Available evidence in depressed children and adolescents remains to be reviewed systematically. A search of the literature was performed to identify studies reporting (i) HF-HRV in clinically depressed children/adolescents relative to controls ($k = 4$, $n = 259$) and (ii) the association between HF-HRV and depressive symptoms as measured by standardized psychometric instruments in children and adolescents ($k = 6$, $n = 2625$). Random-effects meta-analysis on group differences revealed significant effects that were associated with a moderate effect size (Hedges' $g = -0.59$; 95% CI [−1.05; −0.13]), indicating lower resting state HF-HRV among clinically depressed children/adolescents ($n = 99$) compared to healthy controls ($n = 160$), consistent with findings among adults. While no correlation between HF-HRV and depressive symptom severity was observed ($r = -.041$ [−0.143; 0.062]), these additional correlational findings are limited to non-clinical samples. Findings have important clinical implications including a potentially increased risk for future physical ill health and also the identification of potential new treatment targets in child and adolescent depression.

Abbreviations: AD, anxiety disorders; BDI, Beck Depression Inventory; CABI, Child Adaptive Behavior Inventory; CBCL, child behavior checklist; CES-D, Center for Epidemiological Studies Depression Scale; COD, childhood-onset depression; CSI, Child Symptom Inventory; DISC, Diagnostic Interview Schedule for Children; HF, high frequency; HRV, heart rate variability; IBI, inter-beat-interval; ISCA, Interview Schedule for Children and Adolescents; LF, low frequency; MDD, major depressive disorder; POMS, Profile of Moods Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCADS, Revised Child Anxiety and Depression Scale; RMSSD, root-mean-square of successive R-R-interval differences; RSA, respiratory sinus arrhythmia; SCID, Structured Clinical Interview; SCL, Symptom Checklist; SCL-90, Symptom Checklist 90 Revised; *SD*, standard deviation; *SEM*, standard error of the mean; SSRI, selective serotonin reuptake inhibitors; TRAILS, Tracking Adolescents' Individual Lives Survey; tVNS, transcutaneous vagus nerve stimulation; VNS, vagus nerve stimulation; YSR, youth self-report.

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Contents

1. Introduction . . . 137
2. Method . . . 138
2.1. Systematic literature research . . . 138
2.2. Meta-analysis on group differences . . . 138
2.3. Meta-analysis on standardized regression coefficients and correlation coefficients . . . 139
3. Results . . . 139
3.1. Group differences in resting state high frequency heart rate variability . . . 139
3.2. Correlation of resting state high frequency heart rate variability and depressive symptoms . . . 139
3.3. Excluded studies . . . 143
4. Discussion . . . 144
4.1. Technical considerations . . . 145
4.2. Comorbidity and medication . . . 145
4.3. Limitations . . . 146
4.3.1. Clinical implications . . . 146
4.4. Conclusion . . . 146
Conflict of interest . . . 147
Acknowledgments . . . 147
References . . . 147

1. Introduction

Depression is the second leading cause of disability worldwide, with at least 20% of people in developed countries experiencing the disorder at some point in their lives, (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Vos et al., 2013). About 2.8% of children under the age of 13, and 5.6% of adolescents between the ages of 13 and 18 fulfill diagnostic criteria for depression, with overall prevalence rates among adolescent girls being slightly higher than among boys (Costello, Foley, & Angold, 2006). Depression among adolescents is a major risk factor for suicide, which is one of the leading causes of death in this age group (Windfuhr et al., 2008). Among adults, depression is associated with reduced vagal activity, indexed by heart rate variability (HRV), and these reductions are inversely correlated with depression severity (Kemp et al., 2010). These findings are important for the field of clinical psychology, because HRV may assist both diagnostic procedures and monitoring of treatment outcome in depressed patients. In addition, altered vagal function, which can be influenced via general lifestyle changes (Buchheit, Platat, Oujaa, & Simon, 2007) as well as specific treatment options (i.e., vagus nerve stimulation [VNS]), may be a promising treatment target for depressive symptoms (Nahas et al., 2005; Rush et al., 2005). Although such options could also support clinical child and adolescent psychology and psychiatry, the relationship between depression and HRV in children and adolescents has not yet been reviewed systematically.

HRV is an index of parasympathetic nervous system function and chronic reductions reflect poor physiological, emotional, cognitive, and behavioral regulation and are associated with numerous risk factors for adverse health outcomes, as well as self-rated heath (Alvares et al., 2013a; Beauchaine & Thayer, 2015; Jarczok et al., 2015; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer & Lane, 2000; Thayer & Lane, 2009). Among other outcomes, a consequence of impairment in the vagus nerve reflected by HRV – and the high-frequency [HF]-HRV component in particular – is a poorly functioning anti-inflammatory reflex (Pavlov & Tracey, 2012), increasing risk for physical ill-health (Thayer, Yamamoto, & Brosschot, 2010; see Kemp & Quintana, 2013 for a review). Time- and frequency-domain measures of HF-HRV reflecting fast parasympathetic modulation of autonomic control of the heart, provide a feasible and readily available index of vagal activity. Both time- and frequency-domain measures of HF-HRV are consistently used in the literature as indices of vagal activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

We consider lower resting state HF-HRV to be a transdiagnostic, psychophysiological marker of general psychopathology (Beauchaine & Thayer, 2015; Caspi et al., 2014). Besides depression, lower resting state HF-HRV is reported among adults with anxiety disorders (Chalmers, Quintana, Abbott, & Kemp, 2014), schizophrenia (Clamor, Lincoln, Thayer, & Koenig, 2016) borderline personality disorder (Koenig, Kemp, Feeling, Thayer, & Kaess, 2015), and several other psychiatric conditions (Beauchaine, 2015; Beauchaine & Thayer, 2015). Among children and adolescents, low resting HF-HRV is observed in autism spectrum disorder (Neuhaus, Bernier, & Beauchaine, 2014), conduct disorder (Beauchaine, Gatzke-Kopp, & Mead, 2007; Beauchaine, Katkin, Strassberg, & Snarr, 2001) and non-suicidal self-injury (Crowell et al., 2005). HF-HRV may be considered a peripheral index of individual differences in perception of emotional stimuli (Park & Thayer, 2014; Park, Van Bavel, Vasey, & Thayer, 2013) which predict affective instability in daily life (Koval et al., 2013). As several authors have noted, HF-HRV is correlated with difficulties in emotion regulation among child, adolescent, and adult samples (see e.g., Beauchaine, 2015; Berna, Ott, & Nandrino, 2014; Williams et al., 2015).

Resting state vagal activity is a biomarker of clinical relevance with respect to diagnosis, monitoring, and treatment of depressed patients. In fact, reduced resting state HF-HRV is both a correlate of depression among adults (e.g., Kemp et al., 2010), and a marker of treatment response (Chambers & Allen, 2002; Chien, Chung, Yeh, & Lee, 2015) such that decreases in depressive symptoms are associated with increases in HRV. Furthermore, stimulation of the vagus nerve, originally developed for the treatment of epilepsy, is a promising approach for addressing treatment refractory depression among adults (Groves & Brown, 2005; O'Reardon, Cristancho, & Peshek, 2006) and may have potential applicability in younger populations. In children and adolescents, only 60% with depression respond to initial treatment with pharmacotherapy or psychotherapy (Bridge et al., 2007; Weisz, McCarty, & Valeri, 2006). If similar to the evidence in adults, vagal activity is altered in children and adolescents with depression, transcutaneous VNS [tVNS], which is considered a safe and well-tolerated alternative treatment option for children with epilepsy (He et al., 2013), may present a promising third-line treatment for depressed children and adolescents who do not respond to pharmacotherapy or psychotherapy.

Although reduced vagal activity, as indexed by HF-HRV, is associated with depressive symptoms and clinical depression among adults, studies of depressed children and adolescents are less common. However, studies of HF-HRV among younger cohorts are important as we seek to better understand neural and peripheral substrates of early stages

of psychopathology. In this study, we sought to systematically review studies that have assessed associations between resting state HF-HRV and depressive symptoms and between HF-HRV and clinical depression among children and adolescents. We adopted a meta-analytic approach to clarify whether or not (i) HF-HRV is attenuated among clinically depressed children and adolescents and (ii) depression severity is correlated inversely with vagally-mediated HF-HRV among children and adolescents, consistent with research findings among adults.

2. Method

2.1. Systematic literature research

A systematic search of the literature, consistent with the '*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*' (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman,, & PRISMA Group, 2009) was performed in July 2015. Given that this review/meta-analysis was not intended to addressing intervention effects, it was not previously registered and no review protocol exists. Two databases (PubMed and PsycINFO) were searched systematically for the terms ((depress*) AND (((child*) OR adolescen*) AND (((heart rate variability) OR HRV) OR vagal). No filters or limitations were applied. The search in PubMed yielded 175 abstracts and PsycINFO 95. After removing duplicates, abstracts of all articles were screened based on pre-defined inclusion criteria. We aimed to identify (i) studies reporting differences in resting state HRV that compared clinically depressed children/adolescents to healthy controls, and (ii) studies reporting on the association between resting state HRV and depressive symptoms, as measured by established instruments. Abstracts were included if they reported an empirical investigation of HRV conducted among human children or adolescents (<18 years). All titles that met inclusion criteria were retrieved and reviewed in full-text. Excluded studies and reasons for exclusion are presented in Fig. 1. Empirical studies were defined as those that involved active data collection (excluding reviews, meta-analyses, comments, single-case reports, and abstracts from conference proceedings). Studies conducted with infants (<2 years) were excluded. Full-text of studies that remained were reviewed further and screened for inclusion eligibility. To be included, studies had to report (i) a resting state measure of HF-HRV in a (ii-a) clinical sample of depressed children/adolescents who were ascertained using DSM or ICD diagnostic criteria, or (ii-b) an assessment of depressive symptoms using a standardized psychometric instrument.

2.2. Meta-analysis on group differences

Only studies that used time- (root-mean-square of successive R-R-interval differences [RMSSD]) or frequency- (HF-HRV or respiratory sinus arrhythmia [RSA]) domain measures to extract vagally-mediated HF-HRV, according to established guidelines on measurement and interpretation of HRV (Berntson et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), were considered for inclusion. Where citations reported multiple indices of HF-HRV, hierarchical inclusion criteria were implemented to prevent conflation of effect-size estimates: HF-HRV or RSA was selected for analysis if available, followed by RMSSD. Authors who reported HF-HRV but did not provide sufficient quantitative data (e.g., only a graphical display) were contacted to request the necessary information to derive effect size estimates and confidence limits on the selected indices. When only the standard error of the mean [*SEM*] was reported, standard deviation [*SD*] was calculated by multiplying the *SEM* by the square root of the sample size (Higgins & Green, 2011). When descriptive statistics were reported other than the mean, *SD* or *SEM*, data were imputed by established procedures where possible (Glass, McGaw, & Smith, 1981; Wiebe et al., 2006). Descriptive statistics (mean and *SD*) of HF-HRV indices derived from resting baseline recordings were extracted. Where longitudinal or pre-post data were reported, only baseline resting HF-HRV was included to minimize confounding effects by experimental manipulation and conflation of effect size estimates. True effect estimates were computed as adjusted standardized mean differences (Hedge's g). Meta-analyses were performed using random-effect models. Heterogeneity was assessed using the standard I^2 index (Higgins & Thompson, 2002). Substantial heterogeneity was assumed if I^2 was greater than 50%,

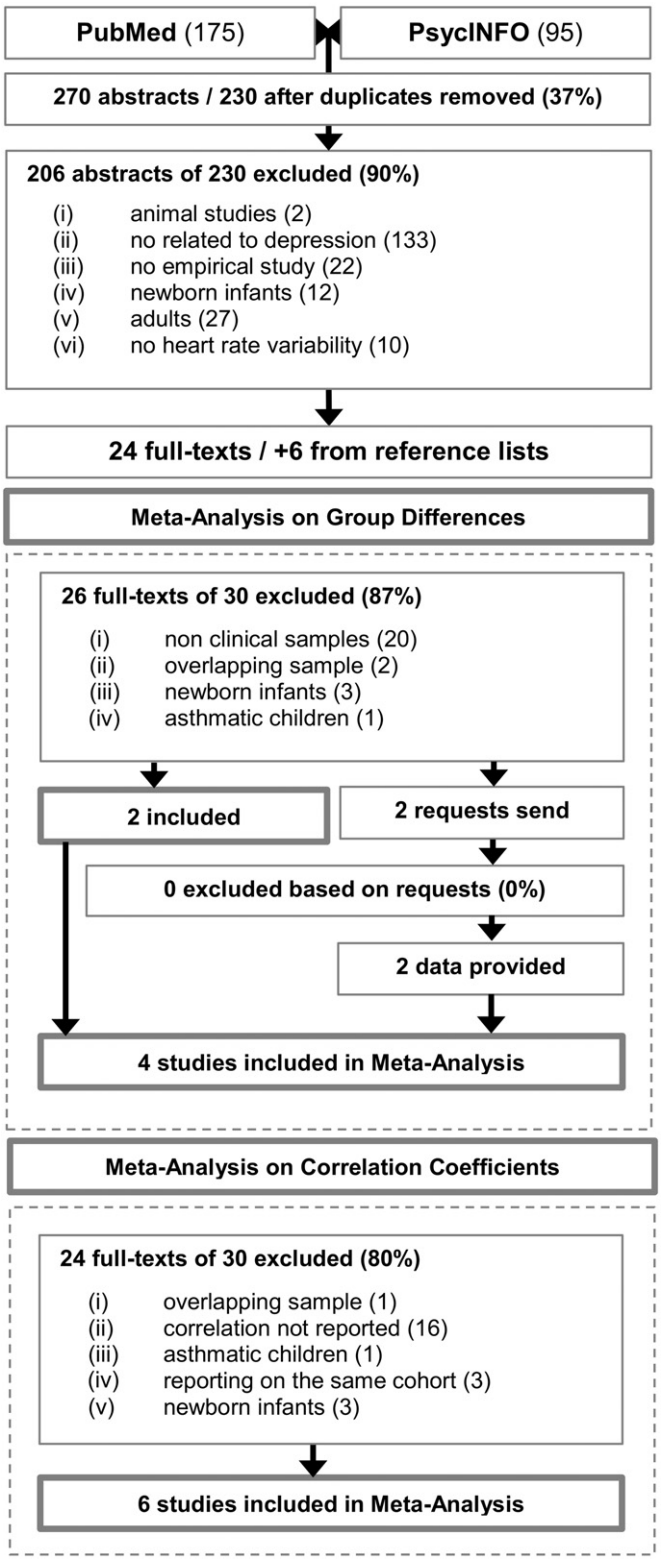

Fig. 1. Systematic search of the literature: PRISMA Flow-Chart.

indicating that 50% of the variability in the outcome cannot be explained by sampling variation.

2.3. Meta-analysis on standardized regression coefficients and correlation coefficients

In a second meta-analysis, we pooled reported measures of association between any given index of resting state HF-HRV (RMSSD, HF-HRV or RSA) and any given continuous measures of depressive symptoms. In order to pool data obtained on the association between resting HF-HRV and depressive symptoms, as derived from correlation and regression analysis using standardized (β) or unstandardized regression (B) coefficients for meta-analysis, we used the simple imputation formula proposed by Peterson and Brown (2005), where $r = \beta + .05\lambda$. In this equation, λ equals 1 when β is nonnegative and 0 when β is negative. Estimated *r* values and the Hedges-Olkin method for calculating the weighted summary correlation coefficient under a random-effects model, using a Fisher *r* to Z transformation of the correlation coefficients were used. We obtained correlation coefficients from unadjusted and adjusted analyses that controlled for potential covariates (i.e., body mass index [BMI]). If possible, we tried to use results from adjusted analysis to provide a more conservative estimate. Similar to the meta-analysis on group differences, heterogeneity was assessed using the standard I^2 index (Higgins & Thompson, 2002). Substantial heterogeneity was assumed if I^2 was greater than 50%, indicating that 50% of the variability in the outcome cannot be explained by sampling variation.

3. Results

Our search of the literature yielded four studies that compared HF-HRV among clinical samples of depressed children or adolescents ($n = 99$) with healthy controls ($n = 160$), and six studies that addressed the association between a continuous measure of depressive symptoms and HF-HRV among children/adolescents ($n = 2625$).

3.1. Group differences in resting state high frequency heart rate variability

Characteristics of the four studies that compared measures of resting state HF-HRV among children/adolescents who met diagnostic criteria for a depressive disorder vs. healthy controls are summarized in Table 1. Tonhajzerova et al. (2009) compared measures of HF-HRV among 14 girls with major depressive disorder [MDD] compared to aged-matched healthy controls. HF-HRV was significantly lower among depressed girls. The same authors published a similar report one year later on 20 girls with MDD and 20 healthy age-matched controls (Tonhajzerova et al., 2010). RMSSD and HF-HRV during supine rest were again lower among depressed girls. A later report by these authors is not included in our meta-analysis because it included an overlapping sample (Tonhajzerova et al., 2012).

Henje Blom, Olsson, Serlachius, Ericson, and Ingvar (2010) found that HF-HRV was reduced among 69 females with anxiety disorders and/or MDD, compared to 66 sex-matched healthy controls. This group difference was not explained by BMI, blood pressure, or physical activity, but was correlated with selective serotonin reuptake inhibitor (SSRI) use. The same sample is reported in a later study (Henje Blom, Serlachius, Chesney, & Olsson, 2014), which confirmed the original results. Byrne et al. (2010) reported on a mixed sample of 54 male and female adolescents who met diagnostic criteria for unipolar depressive disorder, compared to 73 healthy controls. Analysis showed a higher mean heart rate among depressed adolescents, but no group difference in HF-HRV.

Two of the studies reported sufficient descriptive data on HF-HRV (mean and *SD*) among children/adolescents with depression vs. controls (Byrne et al., 2010; Tonhajzerova et al., 2009). We contacted the other two authors (Henje Blom et al., 2010; Tonhajzerova et al., 2010) to obtain data. Random-effects meta-analysis on these studies yielded a sizeable and significant main effect ($Z = 2.54$, $p = .01$; Hedges' $g = -0.59$; 95% CI [−1.05; −0.13]; $k = 4$, $n = 259$) as illustrated in Fig. 2. Reduced resting state HF-HRV in children and adolescents with depression ($n = 99$) compared to healthy controls ($n = 160$). There was some heterogeneity across studies (Fig. 2), although inspection of the Funnel plot didn't indicate publication bias (Fig. 3), it showed slight asymmetry.

All included studies included children who were similar in mean age (16.4–16.8 years). Although studies found group differences in the expected direction, Byrne et al. (2010) found no group difference. However, these authors applied the peak-to-trough method to estimate RSA rather than using spectral analysis. In a footnote, they indicate that they also applied frequency-domain analysis of RSA for the entire recording but found no group differences. The authors argue that therefore the time-domain measure of RSA would yield similar results as the frequency-domain measure. However, Lewis, Furman, McCool, and Porges (2012) have shown that peak-to-trough and spectral estimates, although correlated highly, are not necessarily equivalent. Thus, methods differences may account for the null finding in the Byrne et al. (2010) study.

3.2. Correlation of resting state high frequency heart rate variability and depressive symptoms

Of the included studies of clinical samples, none reported on the association between depressive symptoms and HF-HRV. Although Henje Blom et al. (2010) reported on the association between depressive symptoms (Beck Depression Inventory [BDI] (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)) and HF-HRV, they did so only for healthy controls. Neither Tonhajzerova et al. (2009) nor Tonhajzerova et al. (2010) presented results from correlational analysis. Similarly, Byrne et al., 2010 did not address the association between symptom severity and HF-HRV.

We identified eight studies that reported on the correlation between HF-HRV and depressive symptoms although these studies were based on non-clinical samples of children and adolescents. Four of these used data from the Tracking Adolescents' Individual Lives Survey ([TRAILS]; Ormel et al., 2012).[1] Bosch, Riese, Dietrich et al. (2009) found no association between HF-HRV and depressive symptoms, as rated by the Youth Self Report [YSR (Achenbach & Rescorla, 2001)] in a large sample of pre-adolescents from the TRAILS study. The authors reported that cognitive-affective symptoms of depression were correlated positively with HF-HRV. Bosch, Riese, Ormel, Verhulst, and Oldehinkel (2009) investigated whether RSA was associated with depressive symptoms in a sample of 1653 adolescents who participated in longitudinal assessments at ages 11 (T1) and 13.5 (T2) years. The Child Behavior Checklist [CBCL (Achenbach, 1991)] and YSR Affective Problems scales were used to assess depressive symptoms. RSA was not associated with depressive symptoms at the first assessment. After adjusting for depressive symptoms at T1, RSA did not significantly predict depressive symptoms at T2. However, the authors reported a significant positive association between RSA and future self-reported depressive symptoms among those who had not used any prescribed medication in the past year, after adjusting for anxiety and somatic symptoms. The authors found several trends for greater resting RSA being associated with concurrent depressive symptoms in a subgroup of clinically depressed participants (those who scored at the 97.5th percentile). In the normal and clinical samples, higher RSA showed a trend of association with future depressive symptoms.[2]

[1] To avoid inflation of correlation coefficient estimates across studies, we only included the earliest report from the TRAILS study, which reported the largest sample sizes.

[2] It should be noted that co-varying symptoms of anxiety from relations between depression and other variables is controversial given shared etiology of anxiety and depressive disorders. When two disorders are related etiologically, using analysis of covariance distorts relations between those disorders and external variables (see (Beauchaine, Hinshaw, & Pang, 2010; Miller & Chapman, 2001)), Thus, it is difficult to interpret. Bosch, Riese, Dietrich et al. (2009) findings.

Table 1
Characteristics and Findings Included Studies in Clinical Samples; AD: anxiety disorder; ALL: exclusion/inclusion criteria related to the entire sample (DEP and HC); BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CDI: Children's Depression Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; DAWBA: standardised assessment of mental health and well-being; DEP: depressive patients; DSM: Diagnostic and Statistical Manual of Mental Disorders; HC: healthy controls; HF: high-frequency; HRV: heart rate variability; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children (diagnostic interview); log: values were natural log-transformed; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; N: number of subject, number of females (f) in brackets; RMSSD: root mean square of successive R-R differences; RSA: respiratory sinus arrhythmia; SDQ: Strengths & Difficulties Questionnaires; SSRI: selective serotonin reuptake inhibitors (+: taking; −: not taking).

Study	N (f)	Age mean years (*SD*)	Diagnostics	Comorbidity/medication	Subgroups	Exclusion	Recording condition	Restrictions	Length	HF-HRV indices	Findings
Byrne et al. (2010)	DEP: 54 (38); HC: 73 (45)	DEP: 16.06 (1.08); HC: 16.17 (1.06)	Unipolar depressive disorder, DSM IV; CES-D; K-SADS	Comorbid psychiatric disorders ($n = 12$ of which $n = 4$ anxiety)	None	ALL: regularly medications with cardiac effects, regular nicotine use; DEP: comorbid externalizing disorders; HC: no current or lifetime history of psychopathology, and no history of mental health treatment	Seated; still and quiet	Abstain from coffee, tea, alcohol, and illicit drugs (2 h); no marijuana use on day of testing	3 min	RSA (log)	No significant group differences
Henje Blom et al. (2010)	DEP: 69 (69); HC: 66 (66)	DEP: 16.8 (14.5–18.4); HC: 16.5 (15.9–17.7)	MDD; DAWBA[a]; BDI; BAI; SDQ	Data on MDD only sample provided	SSRI+/SSRI− reported; comorbid AD/MDD[b]	DEP: severe autism or psychotic symptoms; ALL: diabetes, thyroid dysfunction, pregnancy	Sitting upright; spontaneous breathing; no body movements; preceded by 15 min of rest breathing	Tobacco, tea, coffee, caffeine containing drink, beta stimulant asthma medication (1 h)	2 min × 2 (mean of the two periods used)	HF (log)	Lower HF-HRV in clinical groups; no differences in clinical subgroups (AD, MDD and comorbid AD/MDD)
Tonhajzerova et al. (2009)	DEP: 14 (14); HC: 14 (14)	DEP: 16.4 (0.2); HC: matched for age	MDD, single episode; DSM-IV-TR	n.r.; n.r.	None	ALL: history of cardiovascular, respiratory, endocrinological, neurological, or other disorder known to affect HRV; alcohol or drug abuse; smokers	Lie back comfortably not to speak or move; preceded by 15 min of rest and deep breathing test	n.r.	300 R-R intervals	HF (log)	Lower HF-HRV in depressed
Tonhajzerova et al. (2010)	DEP: 20 (20); HC: 20 (20)	DEP: 16.6 (0.2); HC: 16.5 (0.2)	MDD, DSM-IV-TR; MADRS; CDI	n.r.; n.r.	None	ALL: history of cardiovascular, respiratory, endocrinological, neurological, infectious or other disorders known to affect HRV; obesity, overweight, underweight, alcohol or drug abuse; HC: no history of mental disorders	Supine; preceded by 15 min of rest	Not to use caffeine, alcohol (12 h)	5 min	RMSSD (log), HF (log)	Lower HF-HRV and RMSSD in depressed

[a] Interview by a child and adolescent psychiatrists.
[b] Analysis includes AD, MDD and comorbidity of AD/MDD but no descriptive statistics by group given; authors contacted to request data.

Table 2
Sample Characteristics and Findings of Cross-Sectional and Longitudinal Studies; BMI: body mass index; CBCL: Child Behavior Checklist; CDI: Children's Depression Inventory; DISC: Depression Intensity Scale Circles; EATQ-DM: Early Adolescent Temperament Questionnaire Depressive Mood Scale; HF: high-frequency; HRV: heart rate variability; log: values were natural log-transformed; MUSC: medically unexplained somatic complaints; nu: normalized units; RCADS: Revised Child Anxiety and Depression Scale; RSA: respiratory sinus arrhythmia; SBP: systolic blood pressure; YSR: Youth Self Report; Notes/Annotations.

Authors	Design	n (f)	Age	Assessment	Recording condition	Restrictions	Length	HF-HRV indices	Adjustments/covariates	Findings
Bosch, Riese, Dietrich et al. (2009)[a]	Cross-sectional	1781	10–11 years	YSR (child reported)	Supine; spontaneous breathing; after a few minutes of supine rest	Not to move or speak, n.r.	4 min	HF-HRV (log and nu)	All models: sex, age, BMI, physical activity, physical health	ns except for HF-HRV and affective-cognitive symptoms
Bosch, Riese, Ormel et al. (2009)[b]	Longitudinal (T1; T2: 2–3 years afterwards)	1751 (864)	10–11 years	CBCL (parent-reported), YSR (child reported); clinical sub group 97.5th percentile	Supine; spontaneous breathing; after a few minutes of supine rest	Not to move or speak, n.r.	4 min	RSA (log)	Comorbid problems (anxiety and somatic symptoms); sex subgroup; unmedicated subgroup; clinical subgroup at (T1 and T2)	ns except for RSA (T1) predicting depression (T2) in the unmedicated group when adjusting for comrobid symptoms
Blood et al., 2015[c]	Cross-sectional	127 (70)	10–17	Composite score (CDI, EATQ-DM; standardized values, averaged)	Rest	n.r.	7 min	HF-HRV (%)	Sex, age and puberty	Significant negative association
Dietrich et al. (2011)[d]	Cross-sectional	921 (53.1%)	11.0 (0.5)	CBCL (parent-reported), YSR (child reported); clinical sub group 97.5th percentile	Supine; spontaneous breathing; after a few minutes of supine rest	Not to move or speak, n.r.	4 min	HF-HRV (log and nu)	All models: sex, age, physical activity, SBP, externalizing problems, anxiety, MUSC	ns except for HF-HRV and YSR in boys YSR not in girls
Greaves-Lord et al. (2007)[e]	Cross-sectional	1027 (543)	11.0 (0.5)	CBCL; RCADS; YSR	Supine (4 min); standing (2 min); spontaneous breathing; after a few minutes of supine rest	n.r.	4 + 2 min	RSA (log)	Anxiety, sex and comorbid externalizing problems	ns except for RSA (supine) and sex interaction with MDD (RCADS scale)
Kiff, (2012)[f]	Longitudinal (36- (T1), 45- (T2), 54- (T3) and 63-months (T4))	305	36.67 (0.89)	CBCL	Listening to a neutral story	n.r.	2 min	RSA	Zero-Order Correlation	Higher depression at T1 predicted lower RSA, but did not predict depressive symptoms across time
McLaughlin et al. (2014)[g]	Cross-sectional	157 (94)	14.9 (1.36)	CBCL (parent-reported, only externalizing), YSR (child reported)	Sit quietly without moving	n.r.	10 min	RSA	Age, sex and respiration rate	ns
Pang & Beauchaine, (2013)[h]	Longitudinal (T1, T2, T3: each separated by one year)	207	9.9 (1.52)	CBCL, CSI (parent ratings phone interview); DISC (on lab visit)	Seated	n.r.	5 min (final 2 min)	RSA	Zero-Order Correlation	Significant association of baseline RSA at T1 and depression at T2

[a] Bosch, Riese, Dietrich et al. (2009): valid physiological data, n differs for different measures; mean age of the trials sample 11.09 years (0.56); correlations reported for log transformed measures.
[b] Bosch, Riese, Ormel et al. (2009): valid physiological data, n differs for different measures; mean age of the trials sample 11.09 years (0.56).
[c] Blood et al. (2015): three visits typically across three weeks (visit 1: self-report assessments; visit 2: psychophysiological assessment); log of the relative frequency bands resulted in near identical correlations.
[d] Dietrich et al. (2011): correlations reported for log transformed measures.
[e] Greaves-Lord et al. (2007): n refers to valid RSA data during supine recording condition; YSR disruptive behavior scores used as covariates.
[f] Kiff (2012): n at T1; low attrition; sex not reported but used as covariate; age in months at T1 reported.
[g] McLaughlin et al. (2014): n of the final analytic sample; sex ratio based on adolescents initially recruited ($n = 168$); mean age of those initially recruited reported.
[h] Pang and Beauchaine, (2013): diagnosed with depression $n = 28$; diagnosed with depression and comorbid conduct disorder $n = 80$; children were required to score at or above the 85th percentile on the CBCL anxious/depressed subscale; children in the comorbid group had to meet criteria on both the aggression (at or above the 95th percentile) subscale and anxious/depressed subscales.

Table 3
Correlation Coefficients or Estimated Correlation Coefficients used for Meta-Analysis; n: sample size; β/B: standardized or unstandardized beta reported from regression analysis; r/est.: correlation coefficient or estimated correlation coefficient based on beta; Fisher's Z: correlation coefficient after Fisher's Z transformation; 95% CI: 95% confidence interval; BMI: body mass index; CBCL: Child Behavior Check List; CDI: Children's Depression Inventory; DBP: diastolic blood pressure; DISC: Depression Intensity Scale Circles; EATQ-DM: Early Adolescent Temperament Questionnaire Depressive Mood Scale;; HF: high-frequency; HRV: heart rate variability; MUSC: medically unexplained somatic complaints; RCADS MDD: Revised Child Anxiety and Depression Scale; RSA: respiratory sinus arrhythmia; SBP: systolic blood pressure YSR: Youth Self-Report; not included: study not included in meta-analysis (overlapping sample). Notes/Annotations.

Authors/sub-sample	Adjusted correlation coefficient					HRV measure	Depression measure	Statistics & adjustments	Comment
	n	β/B	r/est. r	Fisher's Z	95% CI				
*Bosch, Riese, Dietrich et al. (2009)	1765	.00	.05	0.05	0.033; 0.097	HF-HRV	YSR Affective Problems Scale (self-report)	Regression (standardized β) adjusted for sex, age, BMI, physical health, and physical activity	Lowest n (self-reports of depressive symptoms)
Bosch, Riese, Ormel et al. (2009)	1645	.01	Not included	Not included	Not included	HF-HRV	YSR Affective Problems Scale (self-report)	Regression (unstandardized B) adjusted for anxiety and somatic symptoms	RSA and depressive symptoms at T1; lowest n (completed self-reports)
Bosch, Riese, Ormel et al. (2009)	1453	.03	Not included	Not included	Not included	HF-HRV	CBCL (parent-report)	Regression (unstandardized B) adjusted for anxiety and somatic symptoms	RSA and depressive symptoms at T1; lowest n (completed parent-reports)
*Beauchaine & Thayer (2015)	127	−.233	−.233	−0.237	−0.413; −0.061	HF-HRV	Composite score (CDI, EATQ-DM)	Regression (standardized β) adjusted for age, sex and puberty	
Dietrich et al. (2011)	921	.01	Not included	Not included	Not included	HF-HRV	YSR Affective Problems Scale (self-report)	Regression (unstandardized B) adjusted for sex, age, physical activity, SBP, externalizing problems, anxiety symptoms, MUSC	
-Boys only	432	.15	Not included	Not included	Not included	HF-HRV	YSR Affective Problems Scale (self-report)	See above	
- Girls only	489	−.05	Not included	Not included	Not included	HF-HRV	YSR Affective Problems Scale (self-report)	See above	
Dietrich et al. (2011)	921	−.03	Not included	Not included	Not included	HF-HRV	CBCL (parent-report)	Regression (unstandardized B) adjusted for sex, age, physical activity, SBP, externalizing problems, anxiety symptoms, MUSC	
Greaves-Lord et al. (2007)	1027	.21	Not included	Not included	Not included	HF-HRV	RCADS MDD (self-report)	Regression (standardized β) adjusted for sex (see below)	
-Boys only	478	.15	Not included	Not included	Not included	HF-HRV	RCADS MDD (self-report)	See above	Smallest n (RCADS self-reports)
-Girls only	542	−.05	Not included	Not included	Not included	HF-HRV	RCADS MDD (self-report)	See above	Smallest n (RCADS self-reports)
*Henje Blom et al. (2010)	53		−.26	−0.266	−0.543; 0.011	HF-HRV	BDI	Correlation (r) adjusted BMI, SBP; DBP, p-glucose, physical activity	
*Kiff (2012)	305		−.10	−0.100	−0.213; 0.012	HF-HRV	CBCL (parent report)	Zero-Order Correlation	HF-HRV and depression at T1
*McLaughlin et al. (2015)	168	.07	.12	0.121	−0.032; 0.273	HF-HRV	YSR depression/ withdrawal (self-report)	Regression (standardized β) unadjusted	
*Pang & Beauchaine (2013)	207		.03	0.03	−0.107; 0.167	HF-HRV	DISC (self-report)	Zero-Order Correlation	HF-HRV and depression at T1

* Study included in meta-analysis.

Using data from the same study, Greaves-Lord et al. (2007) evaluated the association between RSA and depressive symptom, as assessed by the CBCL and the Revised Children's Anxiety and Depression Scale [RCADS (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000)] among 1027 boys and girls. Depression was not associated with RSA. However, the authors reported a positive association between RSA in the supine

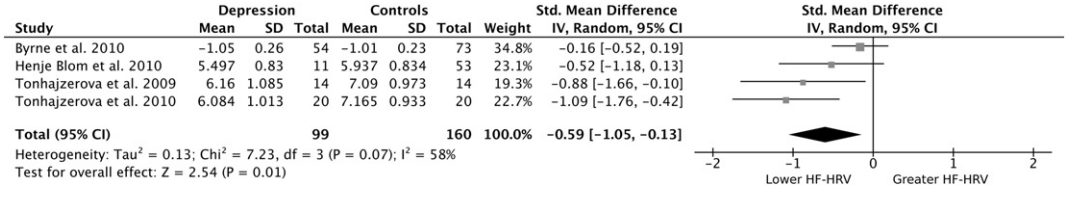

Fig. 2. Meta-Analysis Forrest Plot comparing Resting State HF-HRV in Clinically Depressed Adolescents and Healthy Controls; Data from Tonhajzerova et al., 2010 and Henje Blom et al., 2010 provided by the authors.

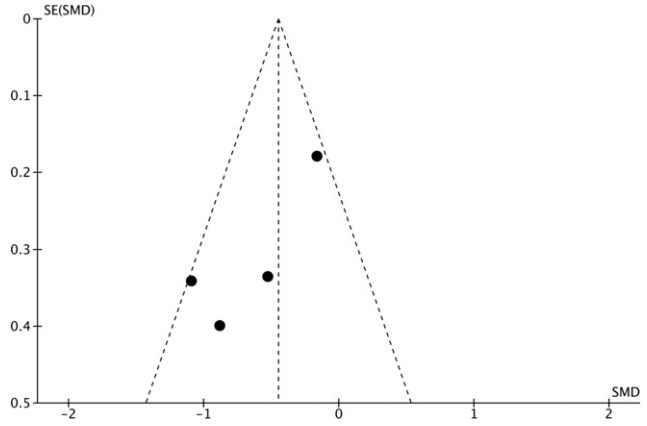

Fig. 3. Meta-Analysis Funnel-Plot comparing Resting State HF-HRV in Clinically Depressed Adolescents and Healthy Controls.

posture and MDD among boys only. Furthermore, a letter to the editor regarding the TRIALS study reported findings from 921 adolescents for whom depressive symptoms (YSR) were associated with higher HF-HRV among boys (Dietrich et al., 2011).

In two papers, McLaughlin, Alves, and Sheridan (2014) and McLaughlin, Rith-Najarian, Dirks, and Sheridan (2015) evaluate associations between resting RSA and internalizing symptoms. Here the later report is described in detail, as associations between RSA and the depression subscales of the YSR are given. Using data from a diverse community sample of 168 adolescents, the authors investigated whether a variety of psychosocial stressors (e.g., childhood trauma, peer victimization etc.) are associated more strongly with internalizing and externalizing psychopathology (CBCL, YSR) among adolescents with lower HF-HRV. RSA was not associated with self-reported symptoms of anxiety/depression or depression/withdrawal when adjusting for age, sex, and respiration. However, RSA interacted with stressors (i.e., child abuse, community violence exposure, peer victimization and traumatic events) in predicting anxiety/depression. The authors conclude, that "*adolescents with low vagal tone are particularly likely to exhibit internalizing problems following exposure to stressors and that high vagal tone may serve as a buffer against the negative mental health consequences of multiple types of stressors*" (McLaughlin et al., 2015; *p. 10*).

Pang and Beauchaine (2013) explored longitudinal associations (three time points separated by one year each) between RSA and depression in a sample of 207 children, of whom 28 at ages 8–12 were diagnosed with MDD (preliminary diagnosis via telephone interview

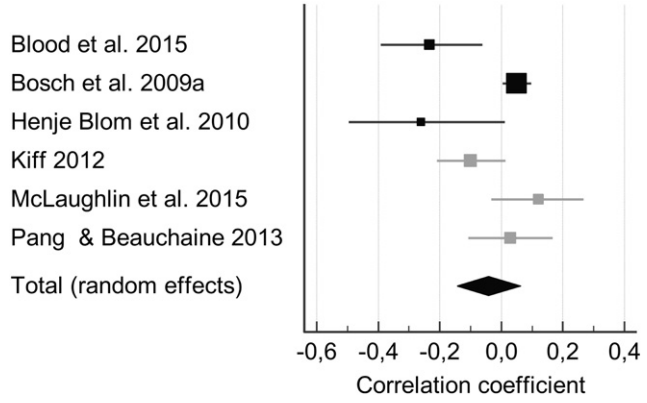

Fig. 4. Meta-Analysis Forrest Plot on Correlation Coefficients between Resting State HF-HRV and Measures of Depressive Symptom Severity; details of the measures applied are given in Tables 2 and 3; correlation coefficients from unadjusted analysis are lighter in color.

using the CBCL and Child Symptom Inventory [CSI (Gadow & Sprafkin, 1997)], which was later confirmed using the Diagnostic Interview Schedule for Children; [DISC (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000)], or conduct disorder with comorbid depression ($n = 80$). While depression scores showed no bivariate correlation with RSA at T1 they were inversely and significantly associated with intercepts in resting RSA.

In her dissertation, Kiff (2012) evaluated HF-HRV as a predictor of depressive symptoms (CBCL mother reports) among 305, 3-year-old children over four time-points at 36- (T1), 45- (T2), 54- (T3) and 63-months (T4) of age. Depressive symptoms at T1 were not associated with RSA at T1, T2, or T3. Initial levels and changes in RSA over time did not predict depressive symptoms at the end of the study. However, higher depressive symptoms (which remained stable across the study) at 36-months of age predicted lower initial basal RSA ($b = -.05$, $p = .02$), but did not predict depressive symptoms across time. Kiff concluded, that "*RSA does not predict increases in internalizing or externalizing symptoms across the preschool period*" ((Kiff, 2012); *p. 62*).

A recent study, Blood et al. (2015) examined the association between HF-HRV and depression in a sample of 127 healthy adolescents (10–17 years; 66 boys, 70 girls). The authors found a significant negative association between depressive symptoms (composite score) and HF-HRV — even while controlling for sex, age, and pubertal status. The authors state, "*children and adolescents with greater depressive tendencies may have less relative parasympathetic influence on their HRV*" (Blood et al., 2015; *p. 123*).

The meta-analysis of selected correlation coefficients (Table 3), not including overlapping samples, revealed no significant association between HF- HRV and depressive symptoms, measured at the same time-point, among adolescents and children in random-effect models ($Z = -0.775$, $p = .438$; $r = -.041$ [−0.143; 0.062], $k = 6$, $n = 2625$), as illustrated in Fig. 4. Significant heterogeneity across correlation coefficients was observed ($Q = 19.913$; $df = 5$; $p = .0013$; $I^2 = 74.89\%$).

3.3. Excluded studies

Several studies were not included in this review, but deserve to be mentioned. Most of the excluded studies reported on overall internalizing problems (including anxiety), or reported on samples with comorbid depression and anxiety. Although anxiety and depression are highly comorbid in children and adolescents (Garber & Weersing, 2010), we aimed to only examine evidence for a relation between HF-HRV and depression in children and adolescents. Similar to depression, anxiety is associated with reduced resting state HF-HRV in adults (e.g., Chalmers et al., 2014), and a selective review of the existing literature among children and adolescents (Srinivasan, 2006) yielded similar findings.

Pine et al. (1998) assessed the association between different measures of HF-HRV and both internalizing and externalizing symptoms in a sample of 69, 7–11-year-old boys. They found a significant negative correlation for RMSSD ($r = -.29$), and a similarly-sized but non-significant negative correlation for HF-HRV ($r = -.28$), with the internalizing subscale of the CBCL. However, they did not have an exclusive measure of depression. Shenk, Noll, Putnam, and Trickett (2010) assessed the correspondence between HF-HRV and depressive symptoms (YSR, BDI-II) in a longitudinal sample of females, ages 6–16 years, with a history of childhood sexual abuse ($n = 52$) and a non-abused comparison group ($n = 77$). Although they found group differences in physiological responses to stress in late adolescence, no data on the correlation of depressive symptoms and HF-HRV were reported. Shannon, Beauchaine, Brenner, Neuhaus, and Gatzke-Kopp (2007) recruited 8- to 12-year-old children, 117 of whom suffered from clinical levels of conduct problems and/or depression (CSI, CBCL), and 63 who reported no significant symptoms. The relation

between maternal melancholia and child depression was moderated by children's RSA. However, no analysis on the correlation of RSA and depression is reported. Ashman (2004) and Ashman, Dawson, and Panagiotides (2008) collected RSA and assessments on psychopathology among children (CBCL, DISC, Child Adaptive Behavior Inventory [CABI (Cowan, Cowan, Schulz, & Heming, 1994)]) but did not report a correlation between depressive symptoms and RSA.

Forbes, Fox, Cohn, Galles, and Kovacs (2006) evaluated the relation between depressive symptoms and HF-HRV among 57 children, ages 3–9 years, 41 of whom had a parent history of childhood-onset depression [COD] (Interview Schedule for Children and Adolescents [ISCA] (Sherrill & Kovacs, 2000), Structured Clinical Interview for DSM-IV [SCID] (First, Spitzer, Gibbon, & Williams, 2002)). Again, no data on the correlation between depressive symptoms and RSA were reported. Huang and Wan (2013) evaluated the association between HF-HRV and depression (Tung's questionnaire[3]) in a sample of 333 seventh grade students from Taiwan. The authors found no differences in HF-HRV among students with high vs. low depression scores.

Gentzler, Rottenberg, Kovacs, George, and Morey (2012), in a sample of 163, 5–14-year-old children who were either at high risk for depression (parent with a childhood-onset mood disorder) or low-risk for depression, found that those at high-risk had lower RSA compared to those at low-risk. However, no data on the association of RSA and child depressive symptoms is reported.

Hsu (2014) evaluated the association between depression and RSA among asthmatic children. Given the underlying somatic illness, we did not include this study. Blandon, Calkins, Keane, and O'Brien (2008) examined children's RSA in relation to maternal depressive symptoms (Symptom Checklist 90 Revised [SCL-90 (Derogatis, 1986)] in a community sample of 269 children (4–7 years). No data on depressive symptoms in the children were provided.

In another study, Gentzler, Santucci, Kovacs, and Fox (2009) assessed RSA among 65, 5–13-year-old children who were reared by a parent with a childhood-onset mood disorder, vs. controls. All children underwent a psychiatric assessment after an initial visit at which psychophysiological measures were recorded. However, the time between the recording of RSA and the assessment of depressive symptoms was up to 2 years. Thus, the study was not included.

DiPietro, Novak, Costigan, Atella, and Reusing (2006) assessed depressive symptoms in a sample of healthy women during mid-pregnancy and at 6 weeks and 2 years after birth. HF-HRV was recorded among 94 children at age 2. Again children's depressive symptoms were not assessed.

Jovanovic et al. (2011) recruited 36 highly traumatized mother–child dyads. Depressive symptoms were assessed (SCID, BDI) and HF-HRV was recorded in children. However, the authors only report the low-frequency [LF]/HF ratio. Field et al. (1996) followed infants from 3 months following birth to preschool and reported HF-HRV as well as psychopathology in children and mothers (CBCL, BDI). However, there is no information given on the measure of HF-HRV.

Waldron, Wilson, Patriquin, and Scarpa (2015) recruited a small sample of 14 young adult women (mean age 19.15 years) who reported child sexual abuse. Depressive symptoms (Center for Epidemiological Studies of Depression Scale [CES-D Radloff, 1977]) were correlated inversely with baseline RMSSD ($r = -.51$). Although this effect size is large, it was not significant given low power. Given the older age in this sample, we excluded this study.

[3] No further information on the instrument is provided. It is assumed that this is the Taiwanese Depression Questionnaire (TDQ) published by the John Tung Foundation (Lee, Yang, Lai, Chiu, & Chau, 2000). According to Lee et al. (2008) the TDQ shows sensitivity, specificity, positive predictive, and negative predictive values similar to the BDI and better validity.

4. Discussion

In the present review, we sought to clarify the association between resting state HF-HRV and depression in children and adolescents. Following a systematic search of the literature, we identified (i) studies reporting on HF-HRV in clinical samples of depressed children and adolescents compared to controls, and (ii) studies that evaluated the correlation between resting state HF-HRV and depressive symptom severity, as assessed by standardized psychometric instruments in this age group. Consistent with research among adults, adolescents who met clinical criteria for depressive disorders exhibited lower resting state HF-HRV. However, no correlation between HF-HRV and depressive symptom severity was observed, although these latter findings were restricted to non-clinical samples.

Of the four studies that evaluated group differences in resting state HF-HRV, three found significant differences in the expected direction, whereas one found no difference. Across studies, there was a significant and sizeable effect such that depression was associated with lower HF-HRV. Thus, consistent with findings among depressed adults (Brunoni et al., 2013; Kemp, Quintana, Quinn, Hopkinson, & Harris, 2014; Kemp et al., 2010), depressed adolescents show reduced resting state HF-HRV. Also consistent with research conducted among adults in which effect sizes range from about −.30 (Kemp et al., 2010) up to −.50 (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012), we found a medium effect size (−.45 to −.59).

In contrast to our group-based finding, we found no significant correlation between depressive symptoms and HF-HRV, although this finding was obtained from non-clinical samples. Significant heterogeneity across studies was found, and studies used a host of different measures to assess depressive symptoms. Of the eight studies reviewed reporting a correlation between depressive symptoms and HF-HRV, only one (Blood et al., 2015) yielded a true significant (negative) correlation consistent with findings from adult samples. The studies by Kiff (2012) and Henje Blom et al. (2010) also reported a negative, but non-significant, correlation between vagally-mediated HF-HRV and depressive symptoms. Similarly, Dietrich et al. (2011) reported a non-significant negative correlation between children's HF-HRV and depressive symptoms, but only when using parent reports. Self-reports by children on depressive symptoms tended to report positive associations with-HRV recorded at rest. Such non-significant trends toward a positive correlation between resting HF-HRV and depressive symptoms in children and adolescents were reported by Bosch, Riese, Dietrich et al. (2009), Greaves-Lord et al. (2007), McLaughlin et al. (2015), and Pang and Beauchaine (2013).

Although Bosch, Riese, Dietrich et al. (2009) found no significant association between depressive symptoms and HF-HRV, they reported a significant positive correlation between HF-HRV and cognitive-affective symptoms of depression after controlling for a host of covariates (i.e., sex, age, physical activity, physical health, and BMI). In their later report (Bosch, Riese, Ormel, Verhulst & Oldehinkel, 2009) they found a trend for a positive correlation between RSA and depressive symptoms within a clinical subgroup using parent-reported depressive symptoms. Interestingly, later analyses of the TRIALS cohort uncovered a significant positive correlation between HF-HRV and self-reported depressive symptoms among boys, but not in girls (Dietrich et al., 2011; Greaves-Lord et al., 2007). Here we show that depressive symptoms are not correlated with HF-HRV in non-clinical samples of children and adolescents.

It is important to note that although our meta-analysis on group differences used homogenous samples of adolescents, data on correlations between HF-HRV and depressive symptoms are reported in heterogeneous samples with a wide age range including children as young as 36 months (Kiff, 2012), and adolescents up to a mean age of 14.9 years (McLaughlin et al., 2014). Age differences might account for the fact that vagally-mediated HF-HRV and depressive symptom severity were not related in our meta-analysis. Furthermore, it is possible that

the relationship between HF-HRV and depressive symptoms is not linear, at least in the lower range (with low levels of depressive symptoms) among non-clinical subjects. Non-linear effects have been reported in links between externalizing symptoms and HF-HRV among children and adolescents (see Beauchaine, 2009; Zisner & Beauchaine, in press). Future longitudinal studies that follow adolescents with subthreshold symptoms as they develop depressive disorders may be necessary to disentangle underlying mechanisms. It is also possible that ANS function is simply not associated with non-clinical depression.

Finally, it is possible that sex – a potential moderating variable not considered here – may influence correlations between HRV and depressive symptoms. Two studies that used the same data set reported differences in the correlation between HF-HRV and depressive symptoms between boys and girls (Dietrich et al., 2011; Greaves-Lord et al., 2007), and another study found that sex interacted with self-reports of depressive symptoms in predicting HF-HRV (Dietrich et al., 2011). Among adults, there are marked sex differences in HF-HRV (Koenig & Thayer, 2016). Relative to men, the autonomic control of the women's heart is characterized by greater relative parasympathetic autonomic control. Thus, despite higher mean heart rates, women show higher parasympathetic activity relative to men. Of particular relevance to this meta-analysis, we and others have noted that females who report more depressive symptoms show greater vagally-mediated HF-HRV than females who report fewer depressive symptoms (Thayer, Smith, Rossy, Sollers, & Friedman, 1998), that depressed females have greater vagally-mediated HF-HRV than depressed males (Chambers & Allen, 2007), and that daily sadness correlates positively with HRV among women, but not men (Verkuil et al., 2015). Thus, future research is needed to evaluate sex differences in associations between depressive symptoms and HF-HRV among children and adolescents.

4.1. Technical considerations

Measures of HF-HRV are not directly comparable in adults and children/adolescents. It is important to note that respiratory rate decreases with increasing age (see Fleming et al., 2011), so adjustments to the frequency windows used for HF-HRV analysis must be made accordingly for children and adolescents of younger age (Zisner & Beauchaine, in press). The HF-band represents rapid, beat-to-beat changes in heart rate reflecting respiratory-gated parasympathetic outflow (Stein & Kleiger, 1999). The studies by Tonhajzerova et al. (2009); Tonhajzerova et al. (2010); Henje Blom et al. (2010), and Bosch, Riese, Dietrich et al. (2009), all defined a HF window between 0.15–0.4 Hz. Only Byrne et al. "*calculated a 'time-domain' RSA variable by measuring the difference in milliseconds between the maximum inter-beat interval (IBI, or R-R interval) during expiration and the minimum IBI during inspiration*", the so called peak-to-trough method (Byrne et al., 2010; *p. 1053*).

Some studies adjusted frequency bands to extract power in the HF spectrum. The study by Kiff (2012) was the only one to use a age adjusted HF band between 0.24 Hz and 1.04 Hz. McLaughlin et al. (2015) used a frequency band between 0.12–0.40 Hz but controlled for respiration. Although they discuss age related differences in breathing patterns, they assume that spontaneous breathing without adjusting the frequency bands "*provides sufficiently reliable HF-HRV measurements*" (Bosch, Riese, Dietrich, et al., 2009; *p. 42*). Pang and Beauchaine (2013) indexed RSA by extracting the HF component >.15 Hz. It has been shown repeatedly that time-domain measures of vagally-mediated HRV (i.e., RMSSD) are affected less by respiration than other indices, including spectrally derived HF-HRV (Hill, Siebenbrock, Sollers, & Thayer, 2009; Penttilä et al., 2001). HRV indices derived from frequency domain analysis provide information of different quality and detail compared to time domain analysis (Sinnreich, Kark, Friedlander, Sapoznikov, & Luria, 1998). Although RMSSD and HF-HRV are correlated highly (Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007), time domain parameters may be estimated with less bias and considerably smaller variability compared with frequency-domain parameters (Kuss, Schumann, Kluttig, Greiser, & Haerting, 2008). To our surprise, only one study reported time-domain measures of vagally-mediated HRV (Ingrid Tonhajzerova et al., 2010). Therefore, we were not able to conduct meta-analysis on time-domain measures of HF-HRV. Given that frequency-domain measures of HRV and RSA are most likely to be affected by respiration, which varies by age (Fleming et al., 2011) future studies of HRV should either adjust frequency-bands for spectral analysis (see Zisner & Beauchaine, in press), use time-domain measures of that are less affected by respiration, or adjust measures to be less affected by respiration (Lewis et al., 2012).

4.2. Comorbidity and medication

Lower vagal activity, indexed by HF-HRV, has been linked to a variety of adverse health (Kemp & Quintana, 2013) and psychiatric conditions (see Beauchaine & Thayer, 2015; Malik & Camm, 2007), including depression (Brunoni et al., 2013; Kemp, Brunoni, Santos, Nunes, Dantas, Carvalho de Figueiredo, et al., 2014; Kemp, Quintana, et al., 2014; Kemp et al., 2010; Kemp et al., 2012) and anxiety disorders (Chalmers et al., 2014; Kemp, Brunoni, et al., 2014), including social anxiety disorder (Alvares et al., 2013b), generalized anxiety disorder, and panic disorder (Cohen et al., 2000; Friedman & Thayer, 1998). Generalized anxiety disorder is frequently comorbid with depression and such comorbidity is associated with the greatest and most robust reductions in HF-HRV.

Here, we addressed the specific link between depression and HF-HRV among children and adolescents, excluding studies that reported on internalizing disorders in general. Some of the studies in our analysis included participants with comorbid anxiety. For instance, in the study by Byrne et al. (2010), four participants met criteria for an anxiety disorder in addition to MDD, whereas the studies by Tonhajzerova and colleagues (Tonhajzerova et al., 2009; Tonhajzerova et al., 2010) did not report comorbid disorders. Henje Blom kindly provided data from their study (Henje Blom et al., 2010) that related to the sample of depressive patients without comorbid anxiety disorders. The analysis we conducted in the present study indicates that – as with existing evidence among adults (Kemp, Brunoni, et al., 2014; Kemp, Quintana, et al., 2014; Kemp et al., 2012) – depression without comorbid disorders in children and adolescents is associated with reduced HF-HRV.

A variety of medications including antihypertensives (Pavithran, Prakash, Dutta, & Madanmohan, 2010), antidepressants (Kemp, Brunoni, et al., 2014; Kemp et al., 2010), analgesics (Koenig, Jarczok, Fischer, & Thayer, 2015) and anti-cholinergics (Penttilä, Kuusela, & Scheinin, 2005) have significant effects on vagal activity as measured by HF-HRV. Serotonin selective reuptake inhibitors (SSRIs), which are commonly used to treat depression among adults and adolescents, lead to small decreases in HF-HRV (Kemp, 2011; Kemp, Quintana, & Malhi, 2011). Although some believe that SSRIs should not be a first-line treatment for mild to moderate depression in children and adolescents, severe depression may require medication (Kemp, Brunoni, & Machado-Vieira, 2015; Kemp, Gordon, Rush, & Williams, 2008; Wong, Besag, Santosh, & Murray, 2004).

By contrast, tricyclic medication is associated with large reductions in HRV in children/adolescents (Mezzacappa, Steingard, Kindlon, Saul, & Earls, 1998) and these findings are associated with reduced vagal modulation at the level of the heart. The sample reported by Henje Blom et al. (2010), included 23 patients taking antidepressants, of whom 22 used SRRIs (citalopram, fluoxetine, sertralin), and 1 used a tricyclic (tryptizol). The authors found significant differences in HF-HRV between clinical patients and controls only among those who were taking SSRIs. Unfortunately, we could not control for SSRI intake given the small sample size of this subgroup ($n = 11$). Moreover, the studies by Tonhajzerova et al. (2009); Tonhajzerova et al. (2010) did not report on medication status. Curiously, Byrne et al. (2010) excluded participants who were taking antidepressants regularly, and found no

significant group differences in resting state HF-HRV. Although group differences among adolescents may be moderated by medication effects, the general consensus is that HF-HRV reductions are not solely attributable to antidepressant medications (Kemp, 2011; Kemp, Brunoni, et al., 2014; Kemp, Quintana & Gray, 2011; Kemp, Quintana & Malhi, 2011; Kemp, Quintana, et al. 2014).

4.3. Limitations

The present review and meta-analysis faces several limitations that deserve mention. First, data were limited to relatively few studies and participants, and correlational analysis could only be conducted on non-clinical samples. Studies comparing resting state, vagally-mediated HRV in depressed children and controls of younger age are missing. Furthermore, only one study (Byrne et al., 2010) reported on a mixed sample of boys and girls. Second, our review focused only on HF-HRV, RSA, or time-domain measures reflecting vagal activity. Some studies have reported interesting associations between depression or its symptoms with other measures of HF-HRV, such as the LF/HF ratio. LF power reflects slower changes in heart rate (0.03–0.15 Hz), however, this component has been the subject of much debate in the literature. Although some have claimed that LF power expressed in normalized units is an index of the relative contribution of sympathetic activity to HRV, contradictory evidence exists. For example, beta-adrenergic blockade does not always reduce LF power (Stein & Kleiger, 1999). Thus, most researchers have concluded that LF power reflects a combination of sympathetic and parasympathetic influences (Stein & Kleiger, 1999; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Other data indicate that LF power indexes short-term baroreceptor-mediated changes in blood pressure control (Friedman et al., 1993; Goldstein, Bentho, Park, & Sharabi, 2011; Stein & Kleiger, 1999). The earlier meta-analysis on LF in adult depressed patients found no-significant differences (Kemp et al., 2010) and consistent with the existing research conducted with adults, we only focused on indices reflecting predominately vagal activity. Potential age-related differences reflecting early alterations of other measures of HRV remain to be addressed. Finally, the present review only focused on baseline measures of resting state HF-HRV. It is notable that some of the included studies reported findings for measures of vagal reactivity during a stressor or an experimental condition, which were not reviewed in the present study.

4.3.1. Clinical implications

Reductions in HF-HRV precede development of depression in adults (Jandackova, Britton, Malik, & Steptoe, in press). Interestingly, reduced HF-HRV also precedes the development of externalizing disorders (Beauchaine et al., 2007). We have also demonstrated that the offspring of unmedicated women with a past anxiety disorder display reduced HRV (Braeken et al., 2013), and that these reductions in HRV correlated with measures of fearfulness in children, suggesting that reductions in HRV may precede future child psychopathology. Unfortunately, little is known about the early developmental trajectories of depression and general psychopathology in children and adolescents. Future research in younger samples is needed to explore these developmental pathways in greater detail. If supported by empirical evidence, early alterations in vagally-mediated HF-HRV might indicate children and adolescents at risk for the development of psychopathology, and could be used as a simple biological marker of early risk.

Furthermore, clinical studies addressing the feasibility of HF-HRV to track outcome of therapeutic interventions in children and adolescents with depression are needed. Studies on treatment of depressed adults with anti-depressant medication (Agelink et al., 2001; Davidson et al., 2005; Khaykin et al., 1998; Lederbogen et al., 2001; Tulen et al., 1996; Udupa et al., 2007) show that such pharmacological treatment (except for tricyclic medication) has minimal impact on HF-HRV over and above a reduction in symptom severity (Kemp, Quintana, & Malhi, 2011; Kemp et al., 2010) — findings that need to be replicated in children and adolescents. Others have shown that HRV may be a useful marker of treatment response (Chambers & Allen, 2002; Chien et al., 2015) in depression, such that decreases in depressive symptoms are associated with increases in HRV. If proven in the younger age group addressed in this review, HRV could serve as a valuable (bio) marker to monitor treatment outcome in depressed children and adolescents, in addition to self- and parent-reports — in particular in children struggling to report on their symptomatic distress.

In addition, potential treatment options designed to increase vagal activity might themselves lead to symptom improvement in depressed children and adolescents. It is well known that physical activity can increase HRV (Buchheit et al., 2007; Rennie et al., 2003) and changes in diet and nutrition can increase HRV and lead to reduced anxiety (Hansen et al., 2014). Given that nutrition (O'Neil et al., 2014) and physical activity (Biddle & Asare, 2011) are both related to mental health in children and adolescents, future research on the impact of life-style changes on HRV and symptom severity seems fruitful — identifying those at-risk and to develop or monitor treatment for those with clinical symptoms.

The present findings also have implications for the treatment of depression in children and adolescents. VNS was originally developed for the treatment of epilepsy (Ben-Menachem, 2002) and is now a promising treatment option for adult patients with chronic or recurrent, treatment-resistant depression (Nahas et al., 2005; Rush et al., 2005). Invasive VNS is reported to be a safe and feasible procedure, although its concrete mechanism of action and cost-effectiveness are not yet well evaluated for the treatment of affective disorders (Daban, Martinez-Aran, Cruz, & Vieta, 2008). Recent technological developments allow for noninvasive transcutaneous tVNS, that is considered a safe and well-tolerated method and alternative treatment option in epilepsy (Stefan et al., 2012), including in pediatric patients (He et al., 2013). tVNS modulates functional connectivity of the default mode network in MDD (Fang et al., 2015) and may lead to increases in well-being by decreasing activity in limbic brain areas, including the amygdala (Kraus et al., 2007). Preliminary case studies on tVNS in treatment of MDD are promising (Trevizol et al., 2015) and clinical trials among adults are ongoing (Rong et al., 2012) Animal studies suggest that tVNS may act as an antidepressant by triggering melatonin secretion (Li et al., 2014). Although the potential for tVNS in the treatment of psychiatric patients is subject to further research, this meta-analysis provides support for its use in children and adolescents with depression. In the present study we report that HRV is reduced in children and adolescents with clinical depression and tVNS may lead to increases in HF-HRV (Clancy et al., 2014).

4.4. Conclusion

Here we show that adolescents with depression show decreased resting state HF-HRV, a finding that is consistent with the adult literature. Although vagal activity – indexed by measures of HF-HRV – is related to depressive severity in adults, such a relationship was not observed in children and adolescents. However, existing studies examining the correlation between vagal activity and depressive symptoms in children and adolescents are based on non-clinical samples only. Studies are also characterized by methodological differences in the assessment of depressive symptoms and age group studied. Future studies are necessary to extend the existing literature in several important directions; studies on potential age and sex related differences in particular will likely bear fruit. Furthermore, longitudinal studies need to address the causal pathways linking depression and HF-HRV in children and adolescents. Resting state, vagally-mediated HF-HRV is of great interest to researchers focusing on potential mechanisms underlying depressive psychopathology and its application to the study of developmental psychopathology may help to facilitate psychiatric assessment and treatment outcome. The present findings support the

use of HF-HRV to assist the diagnosis and monitoring of treatment outcome in clinically depressed children and adolescents. Targeting reduced vagal activity in depressed children and adolescents (i.e. by increasing physical activity) may add to current treatment options. In addition, the use of tVNS may offer a promising third-line treatment for depressed children and adolescents not responding to pharmacotherapy or psychotherapy. Proof-of-concept studies on the use of tVNS in this age group are encouraged.

Conflict of interest

The authors have no conflict of interest to declare.

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