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DOCTORAL SCHOOL EVIDENCE-BASED PSYCHOLOGICAL

ASSESSMENT AND INTERVENTIONS

Ph.D. THESIS SUMMARY

HEART RATE VARIABILITY A POTENTIAL NEUROPHYSIOLOGICAL MARKER IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

AUTHOR: Ph.D. CANDIDATE ANDREEA ROBE

SCIENTIFIC ADVISOR: PROFESSOR Ph.D. DOBREAN ANCA

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Notes.______________________________

(1) This is to certify by ROBE ANDREEA that:

(a) The thesis includes the original research work of Robe Andreea (author) towards the Ph.D.;

(b) Parts of the thesis have been accepted for publication or submitted for publication; appropriate citations for these publications were included in the thesis. Other co-authors have been included in the publications if they contributed to the exposition of the published text, data interpretation, etc. (their contribution was clearly explained in the footnotes of the thesis);

(c) The thesis was written according to the academic writing standards. All the text of the thesis and its summary was written by Robe Andreea who assumes all the responsibility for the academic writing; also

• A software was used to check for the academic writing (see at http://plagiarism-detector.com); the thesis has passed the critical test;

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The results of the present work have been published or are in the process as follow:

A. Articles

1. Published:
    - **Robe, A.,** Dobrean, A., Cristea, I. A., Păsărelu, C. R., & Predescu, E. (2019). Attention-deficit/hyperactivity disorder and task-related heart rate variability: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 99, 11–22. https://doi.org/10.1016/j.neubiorev.2019.01.022. (IF: 8,33)
    - **Robe, A.,** Păsărelu, C. R., & Dobrean, A. (2021). Exploring autonomic regulation in children with ADHD with and without comorbid anxiety disorder through three systematic levels of cardiac vagal control analysis: Rest, reactivity, and recovery. Psychophysiology, e13850. https://doi.org/10.1111/psyp.13850. (IF: 3,69)
2. In preparation:
    - Robe, A., Dobrean, A., Balazsi, R., Georgescu, R. D., Păsărelu, C. R., Predescu, E. (2020) - Factor structure and measurement invariance across age, gender and clinical status of the Screen for Children Anxiety Related Emotional Disorders, in a Romanian Sample of 9–16-Year-Old (under review EJPA)
    - Robe, A., Dobrean, A. (2021) - The effectiveness of a single session of mindfulness-based cognitive training on cardiac vagal control and core symptoms in children and adolescents with ADHD: a Randomized-Controlled Trial (under review PM)

B. **Conferences**

- **Robe, A.,** Dobrean, A., Cristea, I. A., Păsărelu, C. R., & Predescu, E. (2019). Attention-deficit/hyperactivity disorder and task-related heart rate variability: A systematic review and meta-analysis. Poster presented at the 9th WCBCT Congress, Berlin, Germany, 17-20 July 2019.

- **Robe, A.,** Dobrean, A., Cristea, I. A., Păsărelu, C. R., & Predescu, E. (2019). Tulburarea hiperkinetică cu deficit de atenție și Variabilitatea Ritmului Cardiac legată de o sarcină (task-related HRV): o meta-analiză cantitativă. Oral presentation at the APR Conference, Cluj-Napoca, Romania, 22-24 November, 2019.

- **Robe, A.,** Dobrean, A. (2020) - Factor structure and measurement invariance across age, gender and clinical status of the Screen for Children Anxiety Related Emotional

Disorders, in a Romanian Sample of 9–16-Year-Old. Oral presentation at the 50th EABCT Congress, Athens, Greece, 2-5 September 2020.

- **Robe, A.,** Dobrean, A. (2021)- Exploring autonomic regulation in children with ADHD with and without comorbid anxiety disorder through three systematic levels of cardiac vagal control analysis: rest, reactivity, and recovery. The poster will be presented at the EABCT Congress, Belfast, Northern Ireland, 8-11 September 2021.

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***Keywords*:** children, adolescents, ADHD, biomarker, heart rate variability, cardiac vagal control

1. CHAPTER 1. THEORETICAL BACKGROUND

1.1. Introduction and Research Problem

1.1.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder is one of the most common psychiatric disorders in childhood and adolescence (Polanczyk et al., 2014), characterized by attentional problems, hyperactivity, and impulsivity that are inconsistent with the developmental level and negatively impact social, academic, or occupational functioning (American Psychiatric Association, 2013). The course of the disorder is variable; in up to half of the diagnosed cases the symptoms have been shown to persist into adolescence or adult life (Caye et al., 2016). Children with ADHD also display high comorbidity rates, around 60%-100% have one or more comorbid disorders (Gnanavel et al., 2019), which often continue into adulthood and can complicate the diagnosis and treatment of ADHD (Biederman, 2004).

Autonomic nervous system dysregulation has been associated with ADHD. The ANS is a division of the peripheral nervous system which innervates most of the internal organs and regulates body processes by controlling smooth muscle fibers, cardiac muscle fibers, and glands. Its two branches, the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS), work antagonistically to produce various degrees of physiological arousal. The cardiac vagal control (CVC) reflects the influence of the parasympathetic branch of ANS through the vagus nerve on cardiac activity. Increasing evidence suggests that children with ADHD display impaired autonomic functioning, characterized by low vagal activity during a specific task (Rash & Aguirre-Camacho, 2012; Robe et al., 2019). Moreover, the existing literature suggests that ADHD is associated with ANS hypo-arousal characterized by decreased ANS functioning at rest and impaired adjustments of arousal in response to a task demand (Bellato et al., 2020).

1.1.2. Heart Rate Variability (HRV)

HRV reflects the fluctuation in time between successive heartbeats (Malik, 1996). HRV measures are derived by estimating the physiological variation in successive interbeat intervals (the beat-to-beat interval) on an electrocardiogram (ECG) or recorded by heart rate monitors, or by fingertip pulse photoplethysmography. The analysis of HRV can be performed in time- and frequency-domain. The time-domain analysis assesses the variation of successive RR intervals registered in a continuous span of 5 minutes to 24 hours. Time-domain measures recommended for HRV analysis in the psychophysiological research are: the standard deviation of all NN intervals (SDNN), the root mean square of successive differences (RMSSD), the standard deviation of the averages of NN intervals in all 5 min segments of the entire recording (SDANN) the percentage of successive normal sinus NN intervals more than 50 ms (pNN50) and the HRV triangular index. The RMSSD, NN50, and pNN50 are thought to represent parasympathetically mediated HRV (Malik, 1996). Power spectral density (frequency-domain) analysis separates the ECG signal into distinct frequency bands and quantifies their relative intensity. The main variables are the ultralow frequencies (ULF) band that is located below 0.0033 Hz, the low-frequency (LF) band that ranges between 0.04 and 0.15 Hz, the very-low-frequency (VLF) range that is located between 0.0033 and 0.04 Hz, and the high frequency (HF) band, ranging between 0.15 and 0.40 Hz.

HRV is an easy and non-invasive method used to assess the sympathovagal balance at the sinus node of the heart, therefore, is generally accepted as a physiological marker of ANS activity (Rajendra Acharya et al., 2006). The balancing act of the SNS and PNS branches of the ANS controls the heart rate and reflects the heart's ability to quickly detect and adapt to changing stimuli. More specifically, the enhanced SNS activity or the diminished PNS activity are associated with the acceleration of heart rate. Conversely, a decreased SNS or a high PNS activity is associated with the deceleration of the heart rate and increased HRV. Both time- and frequency-domain measures reflect the activity of the parasympathetic and sympathetic divisions of the ANS on the sinus node and are consistently used as indices of ANS activity (Malik, 1996). HRV components in the LF range are mediated by both vagal and sympathetic systems, while HF components of the HRV reflect the influence of the parasympathetic component. The low to high-frequency ratio (LF/HF) reflects the balance between both ANS divisions according to some investigators or mirrors the sympathetic modulation according to others. Several indices measured in the time domain, such as RMSSD and pNN50, reflect the parasympathetic modulation of the heart.

1.2 Theoretical Foundation and Research Problem

ADHD is one of the most extensively investigated childhood mental illnesses. Nevertheless, no reliable biological marker (biomarker) for the diagnosis of ADHD has been described to date.

A biomarker is described as "a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenetic processes, or pharmacologic responses to a therapeutic intervention", by the National Institutes of Health Biomarkers Definitions Working Group (1998). The task force on biological markers of the World Federation of Societies of Biological Psychiatry (WFSBP) and the World Federation of ADHD has proposed the next criteria for a potential ADHD biomarker: a) a diagnostic sensitivity > 80% for detecting the disorder, and a b) diagnostic specificity of at least 80% to differentiate between ADHD and ADHD-like symptoms. Additionally, the potential biomarker has to be c) non-invasive, reproducible, reliable, inexpensive, and easy to use, and d) to be confirmed by a minimum of two independent studies published in peer-reviewed journals and carried out by qualified investigators (Thome et al., 2012).

The ANS dysregulation has been associated with ADHD, a general state of hypo-arousal characterized by decreased ANS functioning at rest and impaired adjustments of arousal in response to task demand, for a review, see Bellato et al. (2020). Moreover, the biological models of ADHD have proposed the impaired arousal as the underlying mechanism for the behavioral and cognitive symptoms (Geissler et al., 2014). HRV analysis is currently considered a physiological marker of the ANS functioning (Rajendra Acharya et al., 2006); extensive research has focused on HRV due to its value as a transdiagnostic biomarker of psychopathology (Beauchaine & Thayer, 2015). Furthermore, HRV measurements are non-invasive, easy to perform, and have good reproducibility if measured under standardized conditions (Malik, 1996). Finally, HRV is frequently used as a diagnostic and prognostic tool for mortality in different clinical settings (La Rovere et al., 1998, 2001; La Rovere et al., 2007, 2012; Mazzeo et al., 2011). Thus, HRV may serve as a useful biomarker that could help explain the heterogeneous nature of ADHD in symptom profiles, treatment response, and neurobiological mechanisms.

2 CHAPTER II. RESEARCH OBJECTIVES AND OVERVIEW OF THE METHODOLOGY

The main objective of the present thesis was to examine HRV as a potential neurophysiological marker in children and adolescents with ADHD. In this thesis, HRV was used to assess autonomic functioning through cardiac vagal control analysis. CVC represents the influence of the parasympathetic branch of ANS at the sinoatrial level and can be monitored through vagally-mediated HRV(Malik, 1996).

Consequently, the first specific objective of this thesis was to synthesize the differences in CVC, in children with ADHD compared with healthy control, in response to a task demand, based on a meta-analytical approach (Study 1). More specifically, 1) we aggregated and quantified differences in vagally-mediated HRV, across all studies reporting HRV indices, in response to a task demand, in children with ADHD as compared to healthy control and, 2) we examined potential variables that could influence the association between vagally-mediated HRV and ADHD. Additionally, we addressed some of the previous literature limitations, by assessing the quality of the included studies and the publication bias.

The second specific objective of the current thesis was to investigate the psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED), an instrument widely used to screen for anxiety symptoms. Anxiety disorders represent a common comorbid condition in ADHD with the prevalence of anxiety symptoms ranging from 15% to 35% in children with ADHD (Gnanavel et al., 2019). Additionally, recent research suggests that the presence of comorbid anxiety disorder may have a significant impact on the course of the disorder across the lifespan in terms of clinical features and treatment response (Pliszka, 2019; Reimherr et al., 2017). In this context, considerable efforts were made to facilitate the early diagnosis of anxiety symptoms to ensure proper interventions. However, the fulfillment of this aim requires the availability of instruments with sound psychometric properties that can reliably detect anxiety symptoms in youngsters. Therefore, in the second study, we examined the reliability, the construct validity, and the factorial structure, as well as measurement invariance across gender, age, and clinical status of the Romanian version of the SCARED (41 items), both child- and parent reports.

The third specific objective was to assess CVC as a physiological marker of adaptive responses to changes in the environmental demands in children and adolescents with ADHD, with and without a comorbid anxiety disorder. Thus in Study 3, we analyzed the dynamic modulation of CVC on a gradient of challenges: resting, reactivity, and recovery, focusing on the identification of possible differences in ANS pattern of response between children with ADHD with and without a comorbid anxiety disorder. Additionally, we analyzed "vagal flexibility", an indicator of behavioral and autonomic flexibility (Porges, 2009).

The fourth specific objective of the thesis was to evaluate the effectiveness of a single session of mindfulness-based cognitive training for children and adolescents with ADHD, aged 7 -17 years old. This objective was pursued in Study 4, in which we used a randomized double-blind active-controlled design to examine the effects of a mindfulness-based intervention on clinical features of ADHD, cardiac autonomic activity as assessed by vagally-mediated HRV-measures, and mood.

3 CHAPTER III. ORIGINAL RESEARCH

3.1 Study 1: Attention-Deficit/Hyperactivity Disorder and Task-related Heart Rate Variability: A Systematic Review and Meta-analysis[1]

3.1.1 Introduction

Heart rate variability (HRV) reflects the oscillation in time between successive heartbeats, and it can be evaluated by time- and frequency-domain measures (Malik, 1996). The relation between HRV and mental health has been extensively studied due to its value as a trans-diagnostic biomarker of self-regulation and cognitive control (Beauchaine and Thayer, 2015). HRV can be indexed either at tonic- level, as the value at a specific time point measurement, or at phasic-level (reactivity) as the change of values between two-time point measurements (Laborde et al., 2017); both important to consider regarding adaptation abilities of the organism (Laborde et al., 2018).

Numerous studies have reported significant associations between ADHD and autonomic dysregulation, characterized by altered cardiac vagal control (CVC), tracked efficiently through vagally-mediated HRV (Chapleau & Sabharwal, 2011), but the findings were mixed. A first tentative to summarize this evidence was made in a clinical review (Rash & Aguirre-Camacho, 2012), where the authors concluded that children with un-medicated ADHD display lower levels of CVC, at baseline and after a task demand, compared to normal control and that the vagal reactivity depends on the type of employed task. Conclusions from the study were hampered by the number and the quality of the studies reviewed. A recent meta-analysis (Koenig et al., 2017) on resting-state vagal tone in ADHD showed that the disorder is not associated with altered short-term measures of high-frequency HRV (HF-HRV). However, the study was limited by some methodological problems, including the absence of heterogeneity, publication bias, and potential moderator assessment.

Hence, the objectives of the present meta-analysis were twofold: a) to quantify the differences in CVC, across all studies, reporting measures of vagally-mediated HRV, in response to a task demand, in ADHD children compared to healthy control and, b) to examine possible variables that can moderate the relationship between CVC and ADHD. We attempted to address some of the previous literature limitations regarding quality assessment, heterogeneity, potential moderators, and publication bias.

3.1.2 Methods

3.1.2.1 Protocol registration

This systematic review and meta-analysis is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2010) and has a registered protocol (PROSPERO registration: CRD42018091290).

3.1.2.2 Literature search and study selection

[1] Robe, A., Dobrean, A., Cristea, I. A., Păsărelu, C. R., & Predescu, E. (2019). Attention-deficit/hyperactivity disorder and task-related heart rate variability: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 99, 11–22. https://doi.org/10.1016/j.neubiorev.2019.01.022.

A comprehensive search of the literature was performed on January 25, 2018. National Library of Medicine/PubMed, PsycINFO, Web of Science, and Scopus were systematically searched for relevant articles, investigating task-related HRV, among individuals with ADHD compared with control. The keywords used in the search included an ADHD term combined with a search term for heart rate variability.

Eligible studies were: (1) analytical observational studies (case-control or cohort), (2) reporting any given measure of vagally-mediated HRV (HF-HRV, respiratory sinus arrhythmia (RSA) - estimated by the HF-component, Root Mean Square of the Successive Differences (RMSSD), according to established standards of measurement and interpretation of HRV (Malik, 1996b), (3) in response to cognitive, emotional or behavioural tasks (task-related HRV) and (4) computed by frequency- or time-domain methods, in a (3) clinical sample of ADHD compared to a (4) healthy control group, (5) written in English, and (6) published in peer-reviewed journals. No limitations concerning age, medication status, psychiatric comorbid disorders were used. Reviews, meta-analyses, comments, single-case reports, and abstracts from conference proceedings were excluded.

3.1.2.3 Quality Assessment and Data Extraction

The quality of included studies was assessed using the Newcastle Ottawa Scale (NOS; Wells et al., 2014). The NOS evaluates the quality of observational studies according to three quality parameters (selection, comparability, and outcome) divided across eight specific items, which slightly differ when scoring case-control and cohorts. The inter-rater reliability was measured as percentage agreement, and calculated as the number of agreement scores divided by the total number of scores (Zaninotto et al., 2016).

Two independent investigators extracted descriptive and outcome data. We extracted information regarding participants and study characteristics, demographic data, ADHD subtype, the diagnostic criteria used, co-morbid psychiatric illness, medication status, task type, specific details concerning the HRV assessment like recording length, computational methods to derive HRV measures, recording device, the system used to quantify HRV. All data on time- and frequency-domain were extracted. Discrepancies between coding were resolved through discussion with a third reviewer.

The primary outcome of interest was vagally-mediated HRV, computed by a time- (RMSSD) or frequency- (HF-HRV, RSA- estimated by the HF-component) domain measures, after a task demand. Where articles reported multiple indices of parasympathetically-mediated HRV (e.g., HF-HRV, RSA, RMSSD), we extracted separate data for each parameter. If more subgroups were compared in one article (e.g., ADHD, ADHD plus conduct disorder (CD), ADHD plus oppositional defiant disorder (ODD)), data were pooled individually for each subgroup.

3.1.2.4 Statistical analyses

All the statistical analyses were performed using Comprehensive Meta-Analysis software (CMA; 2.2.046 version). The differences in CVC between ADHD and Control were examined using a single effect size of standardized mean difference (SDM). For each comparison, we calculated SDM, as the difference between the mean of the control group and that of the ADHD group at the specific time-point divided by the pooled standard deviation of the two groups. Positive effect sizes indicated ADHD subjects scoring lower than controls on HF-HRV or RSA or RMSSD. Effect estimates were computed as adjusted Hedges' *g* with its 95% confidence interval (CI), which is adjusted for small sample sizes and might be interpreted in the same way as Cohen-*d* as small (d =.2), medium (d =.5) and large (d =.8) (J. Cohen, 1988). When means and SD were not available, we calculated the SMD from other statistics available in the study, such as *t*-values or *p*-values, using the standard formulae in the program (Borenstein et al., 2009).

Individual ESs was aggregated with a random effect model, which assumes that the true effect size can vary from study to study. The homogeneity of effect sizes across studies was assessed using the Q statistic and its *p*-value as a test of significance with a significant *p*-value providing evidence that the true effects vary. We also reported the I^2 statistic, which quantifies heterogeneity: 0% indicates no observed heterogeneity, 25%, 50%, and 75% defining thresholds for low, moderate, and high.

3.1.2.5 Subgroup and sensitivity analyses

We performed sensitivity analyses: (a) by excluding outliers, defined as studies in which the 95% confidence interval was not overlapping with the 95% CI of the pooled ES; (b) by type of subgroup within the study (ADHD only, ADHD plus externalizing disorders (e.g., ADHD/ODD, ADHD/CD, ADHD/ODD/CD); (d) by type of HRV index used (HF-HRV, RMSSD); e) by excluding children that underwent a stimulant washout.

We performed subgroup analyses to assess whether a series of theoretically and exploratory moderators, derived from prior research or related to the selected characteristics of the included studies, were associated with ESs. For categorical moderators, we conducted subgroup analyses using the mixed-effects model, which uses a random-effects model within subgroups and a fixed-effects one across subgroups (Borenstein et al., 2009). For continuous moderators, we employed meta-regression analyses using a restricted maximum likelihood model with the Knapp-Hartung method (Borenstein et al., 2009).

3.1.2.6 Small study effects

We examined small study effects, as an indicator of potential publication bias, through visual inspection of the funnel plot trim and fill procedure (Duval & Tweedie, 2000), which produces an ES estimate after taking publication bias into account and using Egger’s test (Egger et al., 1997) for the funnel plot asymmetry.

3.1.3 Results

3.1.3.1 Selection and inclusion of studies

Of the 2173 records screened, 1730 duplicates were removed, and 1649 articles were excluded based on their title and abstract relevance. Eighty-one full-text articles were retrieved. Figure 1 reports the flowchart of the inclusion process following the PRISMA guidelines (Moher et al., 2010). Twenty-three studies met our inclusion criteria. One had insufficient data for ES calculation (Lackschewitz et al., 2008), and while both the first and the last author were contacted for additional information, they could not provide the missing data and the study was excluded from the final analyses. Two studies were excluded due to the computational methods used to determine HRV that did not imply time- or frequency-domain parameters (Schubiner et al., 2006; Tonhajzerova et al., 2016). Three studies had partially overlapping samples (Buchhorn, 2014; Buchhorn et al., 2012; Buchhorn et al., 2012) and the one with the largest sample was retained (Buchhorn et al., 2012). However, since this was the only study reporting data from long-term recordings, it was excluded, as guidelines for the measurement of HRV suggest strict separation of short- and long-term ECG analyses (Malik, 1996). Only one study reported data in adults with ADHD (Oliver et al., 2012) therefore it was excluded from the final analyses. Finally, three studies were excluded because they did not report any indices of vagally-mediated HRV (Borger et al., 1999; Börger & Van Der Meere, 2000; Luman et al., 2007), thus leaving a total of 13 articles in the meta-analysis.

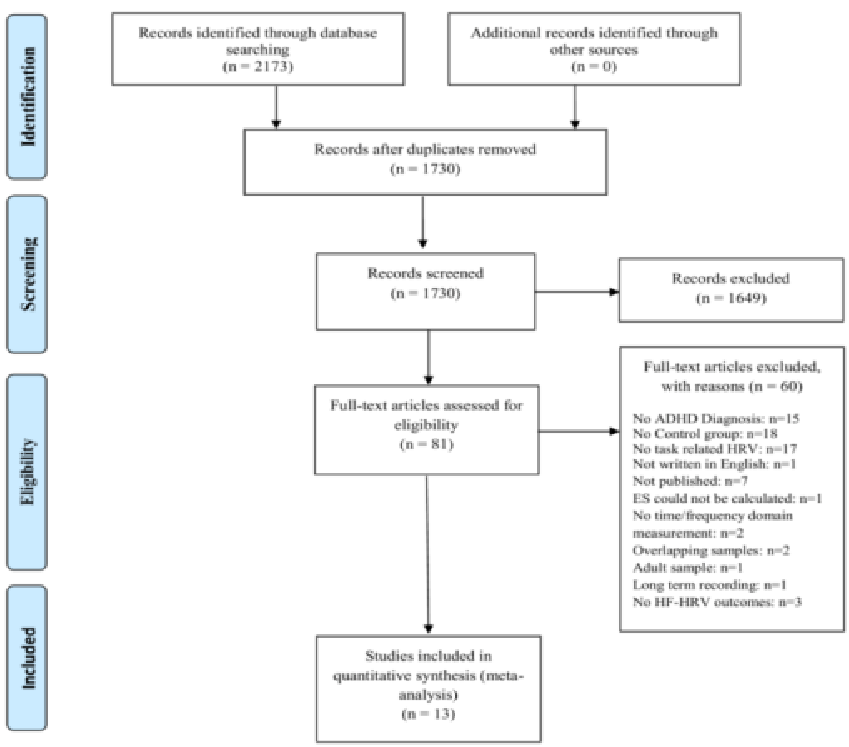

Figure 1. PRISMA flow diagram of the study selection process

3.1.3.2 Characteristics of the selected studies

The studies were published between 1997 and 2017. A total of 1778 participants were included in the analysis: 869 participants with ADHD and 909 with typical development. All studies assessed CVC in children and adolescents after a task demand. Three studies used an attention task to elicit changes in autonomic function, one employed a memory task, seven applied an emotion regulation paradigm, and finally, two were based on a physical activity task implying either a validated postural change or a behavior shaping technique. One study used DSM-III-R (American Psychiatric Association, 1987) criteria for ADHD diagnosis, nine assessed the diagnosis according to DSM-IV (American Psychiatric Association, 2000) and the rest used DSM-5 criteria (American Psychiatric Association, 2013). Most studies targeted mixed samples (e.g., male and female), and the only one used exclusively male population. Four studies assessed ADHD populations without psychiatric co-morbidity, the other nine recruited ADHD populations with psychiatric co-morbidity. Two articles did not report any subtype, the other eleven specified the ADHD subtype using either one or more specific subtypes. All children were medication-free at the time of testing. In 5 studies there were only drug naïve participants, the other studies included variable percentages of patients that underwent a stimulant washout and drug naïve children. The children who were prescribed stimulants were required to have a 24–48 h washout, dependent on the type of stimulant prescribed, before testing.

Studies reported data collected from short-term recordings. Inter-rater reliability for the overall quality scoring, based on NOS was 85%. Eleven studies were included in the category of "high" methodological quality (NOS score > 6) and 2 as low quality (NOS score ≤ 5). Seven studies were rated as having high quality at all three domains. For the selection component, the inter-rater reliability was 85%. Ten studies had a maximum score of 4. The comparability domain registered the highest inter-rater reliability score (100 %). One study was assessed as being of very low quality because none of the confounding variables influencing HRV was controlled for, 9 studies had a maximum score of 2. For the outcome component, the inter-rater reliability was 92% and 8 studies had a maximum score of 3.

3.1.3.3 Meta-analysis of CVC in ADHD compared to healthy control

3.1.3.5.1 ***Main effects.***

The pooled ES of the 13 eligible articles (19 comparisons), reporting measures of vagally-mediated HRV, derived from short-term recordings, was g= 0.209 (95% CI .01 to .40, p = .040), indicating reduced vagally-mediated HRV in children and adolescents with ADHD compared to control. Heterogeneity was high (Q (18) = 76.59, $p < .001$; $I^2 = 77\%$). The visual inspection of the forest plot revealed three outliers. Their exclusion resulted in a small change in the ESs (g = 0.24; 95% CI .04 to .44) and a substantial reduction of heterogeneity (Q (15) = 48.04, $p < .001$; $I^2 = 69\%$). Of the thirteen studies that investigated CVC in response to a cognitive, emotional, or physical task in ADHD, five reported reduced vagally-mediated HRV relative to control; seven studies reported no group differences, while one study reported highly HF-HRV.

Sensitivity analyses, limited to subgroups with ADHD with no comorbid conditions (15) showed a slightly smaller and non-significant ES, g = .12; 95% CI -.08 to .34, with large heterogeneity, Q (14) = 62.58, p < .001; I^2 = 78%. For the subgroup with ADHD plus externalizing disorders (4), the ESs was larger, g = .59, 95% CI .30 to .88, with reduced evidence of heterogeneity, Q (3) = 2.02, p = 0.07; I^2 = 0 %. Analyses restricted to the medication naïve children, 6 studies (9 contrasts), showed a slightly larger and non-significant ES, g = .28; 95% CI -.05 to .063, with large heterogeneity, Q (8) = 45.56, p < .001; I^2 = 82%. One study (Ward et al., 2015), which also happened to be the study with the largest weight in the meta-analysis, contained a mixed sample of participants: the majority were drug naïve, but roughly a third (35 %) of children underwent a stimulant washout. The authors just reported pooled results (i.e. no separate results for these two subgroups). The exclusion of the study led to a slightly larger and significant ES, g = .37; 95% CI .02 to .72, with slightly reduces but still large heterogeneity, Q (7) = 30.04, p < .001; I^2 = 77%. However, these results should be interpreted with caution as this was the study with the biggest weight. For measures of vagally-mediated HRV derived from short-term recordings, 19 comparisons were pooled for HF-HRV and 3 contrasts were pooled for RMSSD. We found a significant main effect for HF-HRV (g = .209, 95% CI .01 to .40), with large heterogeneity, Q (18) = 76.59, p < .001; I^2 = 77%. For RMSSD, the ES was non-significant (g = .55, 95% CI -.19; 1.30) and heterogeneity was high, Q (2) = 10.42, p = .005; I^2 = 81%.

3.1.3.5.2 ***Subgroup analyses*** *(Table 1).*

Moderator analysis revealed evidence for the moderator effect of the psychiatric co-morbidity: the ES was larger in the absence of comorbidities (g=.78, 95% CI .48 to 1.09). Also, task type was a significant moderator, the largest pooled ESs were registered in studies that used a physical activity task (g=1.16, 95% CI 0.61 to 1.72), followed by studies based on a reactivity/negativity/lability (ERNL) task (g=.70, 95% CI .38 to 1.01), an attention task (g=.70, 95% CI .38 to 1.01) and lastly an emotion regulation (EREG) task (g= .04, 95% CI -.20 to .30). This result needs to be interpreted with caution due to the small number of studies from one subgroup that could increase the risk for spurious findings (Higgins & Thompson, 2002). The assessment of respiration rate (RR) was a significant moderator showing different ESs across studies that didn't assess the RR (g=.30, 95% CI -.05 to .54) compared to those that did (g=-.12, 95% CI -.44 to .19). However, the reduced power for the moderator analysis, due to the small number of studies, should be mention.

Table 1

Differences in Vagally-mediated HRV in ADHD compared to Control and moderator analysis

		N[a]	*g*[b]	95% CI	*I²*	*p*[c]
Vagally-mediated HRV						
All studies		19	*0.209*	0.01 to 0.40	77	
Outliers excluded [d]		16	*0.24*	0.04 to 0.44	69	
ADHD only		15	0.12	-0.08 to 0.34	78	
ADHD plus ED		4	0.59	0.30 to 0.88	0	
HF-HRV		19	*0.209*	0.01 to 0.40	77	
RMSSD-HRV		3	*0.55*	-0.19 to 1.30	81	
Medication naïve		9	0.28	-.05 to .63	82	
Medication naïve*		8	0.37	.02 to 0.72	77	
Subgroup analysis [e]						
ADHD subtype	More subtypes	11	0.22	-0.01 to 0.47	79	0.92
	One subtype	6	0.20	-0.25 to 0.66	80	
Comorbidities	Absent	5	0.78	0.48 to 1.09	0	*<0.001*
	Present	14	0.05	-0.14 to 0.25	75	
Medication status	Never been medicated	9	0.28	-0.05 to 0.63	82	
	Medication washout	10	0.15	-0.09 to 0.40	71	0.54
Task type	Attention task	3	0.12	-0.14 to 0.40	26	*<0.001*
	ER/N/L task	3	0.70	0.38 to 1.01	0	
	EREG task	10	0.04	-0.20 to 0.30	73	
	Physical activity task	2	1.16	0.61 to 1.72	0	
Recording device	ECG	16	0.14	-0.06 to 0.35	77	0.08
	HRM	3	0.61	0.12 to 1.11	42	
Respiration assessment	Yes	3	-0.12	-0.44 to 0.19	74	*0.03*
	No	16	0.30	-0.05 to 0.54	75	

3.1.3.5.3 **Meta-regression analyses.**

The meta-regression analyses revealed a statistically significant positive association between ESs and the percentage of male participants from the ADHD sample (slope= .01, 95% CI .00 to .02, p =.005); larger ESs were registered in studies that had a sample containing a high percentage of males with ADHD. The results were maintained when outliers were excluded. No other significant moderators were identified (e.g., publication year, mean age of the ADHD sample, the number of participants in the ADHD sample, the NOS total score).

3.1.3.6 Publication Bias

The visual inspection of the funnel plot revealed some evidence of publication bias (Figure 5). Egger’s intercept test was non-significant (intercept: 1.95; 95% CI - .30 to 4.23; p = .080), but its reliability was probably affected by the small number of studies. Duval & Tweedie's (2000) trim and fill procedure indicated significant publication bias (Figure 4):

adjusting for missing studies (n = 6), the ES decreased from a g of .20 to a non-significant *g* of -.02 (95% CI -.23 to .19).

3.1.4 Discussion

In this meta-analysis of 13 published studies, we demonstrate reduced vagally-mediated HRV after a task demand, derived from short-term, time- and frequency-domain measures, in medication-free at the time of testing children and adolescents with ADHD compared to control. Though the pooled ES was small, it's worth noting it represents the first quantitative synthesis of a broad range of inconsistent findings regarding autonomic dysregulation in ADHD patients, see (Rash & Aguirre-Camacho, (2012) for a review.

The only other meta-analysis (Koenig et al., 2017) that examined CVC in ADHD, found no overall difference in HF-HRV between ADHD and controls, but heterogeneity and possible sources of heterogeneity were not evaluated. Whereas the authors of this meta-analysis focused on resting-state HRV, we selected studies reporting measures of CVC after a task demand. Even though both meta-analyses targeted CVC indexed at a tonic level, investigating HRV in response to a task demand is important as novel research in the area suggests taking into account the specific circumstances in which it is measured and the importance of this specific time point, related to a specific event (Laborde et al., 2017), to better understand the psychophysiological mechanisms underlying the pathology. Investigating HRV in response to a task demand could better surprise a dysfunction of ANS associated with the disorder as this might be more pronounced after a challenging task.

Sensitivity analyses limited to the subgroups with ADHD plus ED showed a moderate ES, which is not surprising as conduct disorders are themselves associated with lower resting HF-HRV (Beauchaine et al., 2008)**.** While the overall analyses of HF-HRV and RMSSD revealed reduced vagal activity in ADHD, the non-significant ES for RMSSD, when the analysis was performed separately for each parameter, might be due to the measurement techniques. Even though RMSSD and HF-HRV are highly correlated, frequency-domain methods are recommended over time-domain methods when investigating short-term recordings (Malik, 1996). Sensitivity analysis limited to medication naïve children showed a slightly larger and non-significant ES. The fact that the analyses were restricted to a small number of studies and the high heterogeneity between studies could explain the lack of significance. As there is evidence that stimulant medication might lead to a normalization of the HRV parameters (Buchhorn et al., 2012) it is difficult to ascertain if the differences in HRV are due to ADHD and not to medication.

Possible moderators were examined to determine the sources of heterogeneity. Contrary to individual studies, we found larger effect sizes in the absence of comorbidities. Among a variety of mental disorders associated with ADHD, the typical externalizing disorder: CD/ODD (Beauchaine et al., 2013, 2000; Beauchaine et al., 2008) and typical internalizing disorders: depression (Koenig et al., 2016), anxiety (Chalmers et al., 2014) and bipolar disorder (Faurholt-Jepsen et al., 2017) are associated with reduced vagal tone. In line with previous work (Rash &

Aguirre-Camacho, 2012), task type was a statistically significant moderator. Not surprisingly, the largest pooled effect size was registered in studies that used a task based on physical activity. Given that HRV reflects the activity of the sympathetic and parasympathetic nervous systems, the movement affects immediately HRV, as both systems are involved in meeting physical demands (Laborde et al., 2017). Diverging ESs were registered across studies that used an attention task design or an emotion regulation paradigm; not surprisingly as a high resting, CVC has been positively associated with optimal attention (Suess et al., 1994) and positive output at the level of emotion (Appelhans & Luecken, 2006). However, this result is based on a small number of studies and many covariates were unbalanced, so it should be interpreted with caution. Studies that did not assess respiration rate resulted in significantly higher ESs than studies that did. As respiratory parameters may modify the relationship between HF-HRV and CVC, respiratory monitoring and respiration control have been proposed (Grossman & Taylor, 2007); however, the importance of monitoring respiration is still contentious. None of the included studies controlled for respiration. There was a positive association between the proportion of males in the ADHD sample and ESs, which could be explained by sex differences in vagal activity (Koenig & Thayer, 2016), as girls display lower vagally mediated-HRV compared to boys, during adolescence (Koenig et al., 2017). As the percentage of males was higher in most of the samples, the results should be interpreted with great caution.

To conclude, the current meta-analysis is the first to assess measures of CVC in ADHD, after a task demand, and has important implications for understanding the complex mix of cognitive, affective, behavioral, and physiological features associated with the disorder. The available evidence is not sufficient to establish the value of task-related HRV as a physiological biomarker of the disorder: reduced vagally-mediated HRV after a task demand was shown in children and adolescents with ADHD compared to control but the ESs was small and the confounding role of medication could not be fully ruled out.

3.2 Study 2: Factor Structure and Measurement Invariance across Age, Gender and Clinical Status of the Screen for Children Anxiety Related Emotional Disorders, in a Romanian Sample of 9–16-Year-Old

3.2.1 Introduction

With a lifetime prevalence of up to 33.7% according to large population-based surveys (Bandelow & Michaelis, 2015), anxiety disorders are one of the most impairing psychopathological conditions in young people. The low rates of diagnostics combined with a high prevalence of anxiety problems led to a stringent need to detect anxiety in the early stages so that appropriate intervention can be provided. However, the realization of this aim is based on the availability of instruments with sound psychometric properties. The Screen for Child Anxiety Related Emotional Disorders (SCARED-C/P; Birmaher et al., 1997), child- and parent-ratings, is an instrument widely used to assess anxiety symptoms in youngsters.

Exploratory factor analysis from the initial validation studies (Birmaher et al., 1997; Birmaher et al., 1999), revealed a five factors structure that mirrors the DSM-IV classification of anxiety disorders: generalized anxiety (GA), panic/somatic (PD), social phobia (SocP), separation anxiety (SepA), and school phobia (SchP). The five-factor structure has been largely replicated (e.g., Hale et al., 2005; Su et al., 2008); but the existing literature suggests that the factor structure may vary across different countries, cultures, and ethnicities (Hale et al., 2011).

The initial version of SCARED, proved to be a reliable instrument to detect specific anxiety disorders in youths with good psychometric properties for children and adolescents coming from multiple cultures (Hale et al., 2011). Meta-analyses on coefficient alphas with data coming from culturally diverse samples revealed that the internal consistency of the SCARED total score was found to be excellent, for the 38-item ($\alpha = .91$) as well as for the 41-item ($\alpha = .91$) version of the scale (Hale et al., 2011). However, the existing studies on the psychometric properties of the SCARED have been carried out with samples coming from individualistic cultures (e.g., USA, Germany) and, to a lesser degree on samples coming from collectivist cultures (e.g., China).

Although the SCARED has been widely used over the last two decades in a variety of cultures and populations (e.g., community, clinical, males, females), it tends to be implicitly assumed that the instrument function in the same manner across groups. The construct of anxiety may differ across groups, with each group conceptualizing it differently and using different symptoms to describe it (Dirks et al., 2014). Despite the possibility of measurement noninvariance, little research has systematically tested whether this is the case through formal tests of measurement invariance; if MI is not proved, there is evidence that the construct has a different structure or meaning to different groups, therefore it would be unwise to compare latent factors mean across groups (Skriner & Chu, 2014).

Hence, this study has jointly examined the reliability, construct validity, and the underlying factor structure, as well as measurement invariance across different groups, for both parent-and child-reports, the 41-item Romanian version of the SCARED (Birmaher et al., 1999).

3.2.2 Methods

The study sample included 1106 adolescents (44.9 % boys and 55.1 % girls) and their parents (mothers = 91.5%). Children' age ranged from 9 to 16 years (M =13; SD =1.51). Two age groups were represented in the sample: younger children (9–13 years, N = 203) and older participants (14–18 years, N=820). The exclusion criteria were minimal and included the presence of an intellectual disability, parents, or youth who were able to communicate and write in Romanian. The sample consisted of non-clinical (90.1%) and clinical youths. A community sample (n = 1007) was recruited from several Romanian schools. The clinical sample consisted of 99 consecutive referrals to a Romanian Child and Adolescent Psychiatric Facility.

The SCARED, parent and child reports (Birmaher et al., 1999); is a 41-item instrument designed to screen for anxiety disorders. Responders are required to grade the frequency of each symptom on a three-point scale: 0 (almost never), 1(sometimes), or 2 (often). The total score is obtained by summing the values of all items. Additionally, five subscales scores can also be computed: PD (13 items; score range, 0–26), GAD (nine items; score range, 0–18), SeA (eight items; score range, 0–16), SocP (seven items; score range, 0–14), and SchP (four items; score range, 0–8). In the present study, Cronbach's alpha was .92 for SCARED-P and .89 for SCARED-C.

3.2.2.1 Statistical analysis

The descriptive statistics were done using IBM SPSS Statistics 23 (IBM Corp., Chicago, IL). Mplus software (Muthen & Muthen, 1998; version 8.11) was used to implement the confirmatory factor analyses (CFAs). All CFA used a weighted least squares mean and variance-adjusted estimator (WLSMV), as recommended for ordered-categorical items distributed asymmetrically (Finney & DiStefano, 2013). Model fit was evaluated using: chi-square ($\chi 2$), Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), according to the standard interpretation of the fit indices, including a statistically non-significant $\chi 2$ (Carmines & McIver, 1983), CFI and TLI values acceptable if $\geq .90$ and an RMSEA $\leq .06$ (Hu & Bentler, 1999).

Multi-group CFA (MG-CFA) was used to investigate measurement invariance across gender, age, and clinical status. Following the recommendations of (Meredith, 1993) invariance testing was addressed at four levels (configural, weak, strong, and strict factorial invariance) using increasingly stringent nested models. The forward (sequential constraint imposition) approach was used (Dimitrov, 2010); the invariance analysis started with a model without invariance constraints and then a set of equality constraints were added for model parameters. Based on recommendations of (Chen, 2007) measurement invariance across gender, age, and clinical status was based on the examination of relative changes (Δ) in the sample-size-independent fit indices (e.g., CFI and RMSEA) and chi-square difference tests. Specifically, a non-significant result of the chi-square difference test, a decrease in CFI lesser than -.010

(Cheung & Rensvold, 2002), and an increase in RMSEA lower than .015 (Chen, 2007) were used as cut off criterion for invariance, at each step. If the stepwise tests indicated invariance, then factor means across groups were compared. To assess latent mean differences we used the value of the critical ratio (CR).

The correlations between SCARED, PSWQ-C/P, SAS-A, SPAI-C, CATS, PANAS, YSR, and CBCL were computed using Pearson's correlation. The Cronbach's alpha coefficients were computed to assess the reliability of each factor as well as for the total scale.

3.2.3 Results

3.2.3.1 Descriptive statistics and internal consistency

Cronbach's alpha for the total scores was .92 for the child- and .89 for parent-version. In general, the Cronbach's alpha for all SCARED-C subscales ranged from .64 to .83. Cronbach'α for parents' ratings of anxiety symptoms ranged from .57 to .78.

3.2.3.2 Parent-child correlations

The child and parent total anxiety scores were moderately correlated (Cohen, 1988; 1992), with $r = .40$, $p < .001$. For each factor, the interrater correlation was moderate, ranging from 0.32 for the social phobia to .40 for separation anxiety, all significant at $p < .001$.

3.2.3.3 Factor structure

The original model, proposed by Birmaher (1999), in which all items load onto five latent variables (i.e., (1) generalized anxiety; (2) panic/somatic; (3) separation anxiety; (4) school phobia; and (5) social phobia, was examined. The 5-factor model revealed a good approximation of the data for the child version of the SCARED, as indicated by CFI, TLI $\geq .90$, and an RMSEA $\leq .06$. The model yielded a sub-optimal fit to the data, for the parent version of the scale. The original 5-factor model displayed adequate fit only according to RMSEA (< .06); the CFI and TLI fit indices were below recommended cut-off values.

The factor loadings were acceptable for all of the items; with values of at least .40 (Osborne, 2008), except for item 29 (.34 respectively 0.30). Item loadings onto the five factors were consistent with those identified in the original version.

3.2.3.4 Measurement invariance

To examine the invariance of the model's configuration across age, gender, and clinical status we used MG-CFA. First, the 5-factor model was assessed separately, on child and parent data. For the child-version, the model was an acceptable fit. Next, we verified the extent to which the five-factor model replicated across population types (males and females; ≤13 years and >13 years; non-clinical and clinical population). The goodness-of-fit indices indicated an acceptable fit of the model across all groups: CFI and TLI ranged from .90 to .95, and RMSEA were all under .06. The model with no invariance constraints provided a good fit to the data, suggesting that a similar factor structure was present across groups (male vs. female; ≤13 years vs >13 years; non-clinical vs clinical population) and supporting configural invariance. Imposing constraints on the factor loadings did not markedly diminish model fit. Although some $\Delta\chi 2$ values were statistically significant, values of ΔRMSEA and Δ CFI clearly pointed to metric invariance across age ($\Delta\chi 2$ (36) = 66.38; $p <.05$, $\Delta RMSEA \leq .015$, $\Delta CFI \leq .010$), gender ($\Delta\chi 2$

(36) = 49.81; p>.05, ΔRMSEA ≤ .015, ΔCFI ≤ .010) and clinical status (Δχ2 (36) = 45.84; p <.05, ΔRMSEA ≤ .015, ΔCFI ≤ .010). The subsequent model assumed the invariance of item thresholds. The comparison of the models suggested evidence for scalar invariance across age (Δχ2 (77) = 263.03; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010), gender (Δχ2 (77) = 114.76; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010) and clinical status (Δχ2 (77) = 208.39; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010). We next proceeded with the inclusion of invariance constraints on item residuals (model 4). Strict measurement invariance across age (Δχ2 (41) = 81.52; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010), gender (Δχ2 (41) = 60.012; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010) and clinical status (Δχ2 (41) = 66.71; p < .05, ΔRMSEA ≤ .015, ΔCFI ≤ .010) was found, as evidenced by changes in fit from the scalar to the strict invariance model.

Results of the examination of MI across age and sex, on parent data, revealed similar results. Four sequential levels of MI were tested, corresponding to the four invariance conditions of configural, metric, scalar, and residual invariance. Goodness-of-fit indexes associated with the unconstrained model across population types (males and females; ≤13 years and >13 years old). The changes in fit from the configural to the metric invariance model provided evidence for metric invariance across age and gender. We also found evidence for scalar and strict invariance; as confirmed by the changes in CFI and RMSEA values at each level of invariance.

3.2.3.5 Differences in latent factors mean

As measurement invariance at scalar level was supported latent factors mean differences across age and gender for both versions of the questionnaire and across clinical-status on child-version were tested. For SCARED-C, latent mean comparison yielded significant differences across gender for the following factors: PD (.28 ± .07, CR = 4.07, p < .001, d =.423); GA (.33 ± .07, CR = 4.63, p < .001, d=.43); SeA (.28 ± .07, CR = 3.88, p <.001, d =.377), SocP (.20 ± .07, CR = 2.79, p = .005, d =.371). As boys' latent mean was fixed to 0 (used as reference), the obtained results indicated that girls showed a higher level of PD, GA, SeA, and SocP. Concerning the age differences, we found significant latent mean differences for the following factors: SchP (.50 ±.14, CR = 3.42, p = .001, d =.614), GA (.25 ± .09, CR = 2.72, p = .006, d =.31), and SeA (-0.35 ± .11, CR = -3.00, p = .003, d =.429). The 13-16 year children showed a higher level of SchP and GA, whereas 9-12 year children showed a higher level of SeA. The comparison of latent factor mean differences across clinical status, with latent mean used as reference (set to zero) for nonclinical sample, indicated significant latent mean differences for the following factors: PD (.94±.13, CR = 6.86, p < .001, d =1.428), GA (.89 ± .12, CR = 6.99, p < .001, d = 1.177), SeA (1.04 ± .15, CR = 6.75, p < .001, d =1.569), SocP (.90 ± .11, CR = 7.56, p < .001, d =), SchP (.92 ± .16, CR = 5.65, p < .001, d =1.265). The clinical sample showed a higher level of PD, GA, SeA, SocP, and SchP compared with nonclinical sample.

For SCARED-P, compared to boys, girls had higher scores on GA (.19 ± .09, CR = 2.02, p = .043, d =.245) and SeA (30 ± .12, CR = 2.43, p = .015, d =.509) subscales. Additionally, the 9-12 year children had lower scores than 13-16 year children on the following latent factors: GA (-.38 ±.14, CR = -2.57, p = .010, d =.431), SeA (-.49 ± .17, CR = -2.78, p = .005, d =.824).

3.2.3.6 Convergent and divergent validity

Convergent validity was established as the SCARED-C's total score, significantly positively correlated with YSR syndrome scales for anxious-depressed ($r = .63$, $p < .001$) and withdrawn/depressed ($r = .53$, $p < .001$); as expected, lower correlation were registered with YSR syndrome scale for rule-breaking behavior ($r = .11$, $p < .001$), and aggressive behavior ($r = .29$, $p < .001$). Significant positive correlations emerged between the SCARED-C total score and PSWQ-C ($r = 57$, $p < .001$), SAS-A ($r = .62$, $p < .001$), CATS-Negative self-statements scale ($r = .51$, $p < .001$), supporting its convergent validity. Conversely, negative correlations were registered with the CATS-Positive self-statements scale ($r = -.15$, $p < .001$).

The SCARED-P total scores were significantly correlated with PSWQ-C ($r = .25$, $p < .001$), and SAS-P ($r = .49$, $p < .001$). As expected, the correlation between SCARED-P total score and CBCL syndrome scale for rule-breaking behavior ($r = .23$, $p < .001$) and aggressive behavior ($r = .42$, $p < .001$) were lower compared with CBCL syndrome scale for anxious-depressed ($r = .47$, $p < .001$) and withdrawn/depressed ($r = .43$, $p < .001$).

3.2.4 Discussions and conclusion

Our result supports the original five-factor solution of the SCARED proposed by Birmaher (1999). The model provided an excellent fit to the data on child-version and sub-optimal fit to the data for the parent version of the SCARED; suggesting that the parents of children with anxiety, from collectivist oriented cultures, such as Romania, may respond differently to scale's items compared to those from individualistic countries, in which the scale was originally developed.

Both SCARED-C/P had moderate to high internal consistency with most subscales reaching acceptable levels; except SeA and SchP. Similar issues with SeA and SchP factors have been reported before (Hariz et al., 2013; Su et al., 2008); suggesting that their items need to be further refined in future studies. The SCARED-C/P versions showed appropriate convergent validity with both parent measure (CBCL anxious-depressed and withdrawn/depressed syndromes scales) and with child measure (YSR anxious-depressed and withdrawn/depressed syndromes scales) of anxiety symptoms, consistent with prior research (Essau et al., 2002; Monga et al., 2000; Su et al., 2008). Divergent validity was supported by a weak statistically significant relationship with scores on the CATS- Positive self-statements scale for SCARED-C and with YSR and CBCL syndrome scale for rule-breaking and aggressive behavior factor for SCARED-C/P.

The current results support strict MI across age for the SCARED-C/P, 41-item version, in a large sample of youths. This age equivalence means that children and adolescents used this instrument in similar ways and between-group differences on the latent factors mean can be unambiguously interpreted. Second, strict MI across gender was demonstrated; boys do not appear to interpret SCARED' items any differently than girls suggesting the means of the five latent factors (panic/somatic, separation anxiety, generalized anxiety, social phobia, and school phobia) may be accurately compared across gender. Regarding MI across clinical status, our results showed that the community and the clinical sample presented similar interpretations of the SCARED-C items, regardless of the clinical status. These findings largely support and expand on an extant body of literature documenting the SCARED-C/P measurement equivalence across age (Behrens et al., 2019), informants (Dirks et al., 2014), and with multi-ethnic youth samples (Skriner & Chu, 2014). Additionally, strict MI across gender and clinical status was established.

In summary, the current research provides supports for the construct validity and reliability of SCARED scores, arguing for its utility as a screening instrument for anxiety symptoms. Overall, our results support the five-factor solution for the Romanian youth and measurement invariance of the instrument across gender, age, and clinical status.

3.3 Study 3: Exploring autonomic regulation in children with ADHD with and without comorbid anxiety disorder through three systematic levels of cardiac vagal control analysis: rest, reactivity, and recovery[2]

3.3.1 Introduction

ADHD is one of the most common neurodevelopmental disorders with risks extending into adulthood (Abecassis et al., 2017), thus representing a significant public health issue (Mahone & Denckla, 2017). Approximately 25% of children with ADHD also have one or more comorbid anxiety disorders (Tannock et al., 1995), and according to recent research, the comorbidity between ADHD and anxiety disorders changes the clinical presentation and the treatment response across lifespan (Pliszka, 2019; Reimherr et al., 2017). Therefore, it has been suggested that ADHD with comorbid anxiety may represent a distinct "subtype" of ADHD (Pliszka, 1989; Pliszka, 2019) but few studies are investigating the biological processes involved. Up to date studies have focused primarily on variation in behavioral phenotypes, usually quantified as differences in clinical characteristics, laboratory task performance, or treatment response.

Recent research showed that ADHD is associated with autonomic dysregulation, a general state of ANS hypo-arousal characterized by reduced functioning of the ANS at rest and impaired adaptation of arousal in response to task demands, for a review, see Bellato et al., (2020). The evidence of hypo-activation of the ANS during cognitive tasks is consistent with previous findings from a meta-analysis showing that children with ADHD display low vagal activity and reduced vagally mediated-HRV in response to a task demand (Robe et al., 2019). Anxiety disorders are also associated with impaired vagal regulation and reduced HRV (Chalmers et al., 2014). The biological models of anxiety have linked anxiety with excessive autonomic lability and ANS hyperactivity (Friedman & Thayer, 1998); this view posits that an unstable and over-reactive ANS promotes episodic bursts of spontaneous anxiety (e.g., panic attacks), or hypersensitivity to anxiety-provoking stimuli.

This study's main objective was to analyze the dynamic modulation of cardiac vagal control on a gradient of challenges: resting, reactivity and recovery, in children and adolescents with ADHD.

The second aim of the study focused on identifying possible differences in ANS functioning in children with ADHD with and without a comorbid anxiety disorder. Past research had suggested that children with externalizing behavior problems, such as aggression, hyperactivity, and inattention, display a pattern of autonomic dysregulation characterized by low baseline sympathetic arousal and lower levels of vagal withdrawal in response to a challenge (Graziano & Derefinko, 2013). According to the biological model, anxiety in its phasic, tonic,

[2] This study has been published: Robe, A., Păsărelu, C. R., & Dobrean, A. (2021). Exploring autonomic regulation in children with ADHD with and without comorbid anxiety disorder through three systematic levels of cardiac vagal control analysis: Rest, reactivity, and recovery. Psychophysiology, e13850. https://doi.org/10.1111/psyp.13850

and pathologic forms is marked by aberrant ANS cardiac control characterized by sympathetic hyperactivation and parasympathetic (vagal) withdrawal (van Lang et al., 2007).

The last aim was to analyze "vagal flexibility" while controlling for potential confounding variables influencing HRV (e.g., age, gender, BMI, WHR). We operationalized the term as the difference between vagal activation in two types of mental states (rest vs. challenge), that is, higher vagal tone at rest and greater vagal withdrawal during the cognitive task: a higher vagal tone at rest and greater vagal withdrawal during a cognitive task (Muhtadie et al., 2015).

In summary, we hypothesized:

H1: a lower HF-HRV during the sustained attention task than HF-HRV at baseline and a higher HF-HRV during post-task recovery period compared to HF-HRV during task execution. Specifically, we expected a significant main effect of condition for HF-HRV measures following an ANS normative pattern of response to experimental conditions (hypothesis 1);

H2: a negative phasic HRV reactivity score (task– baseline), which would reflect a diminished parasympathetic activity of the ANS under the cognitive challenging task and a positive recovery score (post-task), which would reflect the parasympathetic restoration when the challenge is over (hypothesis 2);

H3: a higher tonic HF-HRV level at baseline would be associated with a greater magnitude of HRV change (reactivity) from rest to task (hypothesis 3), and

H4: children with ADHD and comorbid anxiety would exhibit a greater decline in parasympathetic activity followed by difficulties in reengaging the vagal brake when the challenge is over (hypothesis 4a), relative to (e) children with ADHD only, which will display a lower but significant decline in parasympathetic activity in response to the cognitive challenge followed by a healthy recovery process afterward (hypothesis 4b).

3.3.2 Method

3.3.2.1 Participants

Participants aged 6-15 years old were recruited from an outpatient Child and Adolescent Psychiatric Unit. The outpatient mental institution provides psychiatric services to children and adolescents, including diagnostic evaluations, medication management, and individual and group therapies. Fifty youth (M_{age} = 9.38, SD = 2.31, 78 % boys) were included in the final sample. Participant eligibility criteria were: confirmed clinical diagnosis of ADHD with or without a comorbid anxiety disorder, the ability to complete the measures, and normal intellectual ability. Participants did not receive any compensation for participating in the study.

3.3.2.2 Measures

3.3.2.2.1 Behavioral Measures.

The Screen for Child Anxiety Related Emotional Disorders (SCARED-P; Birmaher et al., 1999) was used to obtain parent ratings of anxiety symptoms.

The ADHD-Rating Scale-IV, Home version (ADHD-RS; DuPaul et al., 1998) was used to determine symptomatic frequencies of a child's daily behavior related to inattention or hyperactivity-impulsivity over the previous 6 months.

The Child Behavioral Checklist for Ages 6-18 (CBCL; Achenbach & Rescorla, 2004) was used to assess childhood behavioral and emotional problems in the past 6 months. Two of the six DSM-Oriented scales were of particular interest for the current study's purpose, namely Anxiety Problems (6 items) and ADHD Problems (7 items) scales.

3.3.2.2.2 Neurocognitive assessment.

Participants underwent standardized neurocognitive testing of sustained and selective attention with the d2 Test (Oswald et al., 1997). The concentration performance parameter was used in the statistical analysis as it is not affected by tendencies such as marking all letters or skipping random test sections.

3.3.2.2.3 Physiological measures.

HRV was continuously measured across the experimental protocol, which included three successive periods: at rest (baseline), during the cognitive challenge (sustained attention task), and post-task (recovery) period in a sitting position. The subjects were asked to remain in the same position without speaking during the recording time to minimize movement artifacts in measurement. Subjects were instructed to breathe spontaneously, given that breathing at a specific rate could mask true variations in vagal tone (Thayer et al., 2011).

HF-HRV values were averaged across each of the 5-minutes conditions: Vanilla baseline (baseline), during task execution, and post-task recovery period, thus leading to three tonic HRV measures. In addition, two phasic HRV indexes were calculated: reactivity (Δ HF-HRV1) and recovery (Δ HF-HRV2). Reactivity was assessed as the difference between baseline and HRV measured during cognitive stressor, estimated as (task – baseline). Recovery was the difference in HRV measured during the task and post-task recovery period, estimated as (post-task).

3.3.2.3 Procedure

The experimental test procedure took approximately half an hour and consisted of three successive periods: a baseline recording followed by a sustained attention task, and finally a post-task recovery period. In line with the Task Force recommendations (Malik, 1996) we chose a 5-minute time frame for each recording phase as it is considered the gold standard for short-term recordings.

3.3.2.4 Data analysis

Statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corp., Chicago, IL). Mixed within-between repeated measures analyses of covariance (ANCOVA), with one between-subjects (e.g., comorbidity: with and without a comorbid anxiety disorder and one within-subject factor (e.g., condition: baseline, task, and post-task) while controlling for gender, were conducted to investigate the participants' ANS pattern of response across the experimental conditions. We conducted bivariate Pearson correlations to test the hypothesized relationships between HF-HRV baseline and reactivity.

3.3.3 Results

3.3.3.1 Demographic and background characteristics

A total of 50 patients with ADHD were included in the present study. Of the included participants, 29 had a primary diagnosis of ADHD, while 21 had a diagnosis of ADHD with a comorbid anxiety disorder. Children's age ranged from 6 to 15 years (M =9.38; SD =2.31). Thirty-seven children were drug naïve at the time of the testing, 8 took specific psychotropic medication, and five were on a stimulant washout. The children who were prescribed stimulants were required to have a 24 h washout before testing.

3.3.3.2 Differences in HRV measures

The 2 (Comorbidity) X 3 (Condition) repeated measures ANCOVA, with Comorbidity (Anxiety absent vs present) as between-subjects factor and Condition (experimental condition: baseline, task, post-task) as the within-subject factor assessed the effect of comorbid anxiety on autonomic functioning while controlling for gender. The analysis yielded no significant main effect of Comorbidity, F (1, 43) = .01, p = .896, $\eta2$ < .001 on HF-HRV; nor a significant main effect of gender, F (1, 43) = .82, p = .370, $\eta2$ = .019 on HF-HRV measures. Nor did we find any significant interaction effect of Condition by Gender, V = .01, F (2, 42) = .24, p = .786, $\eta2$ = .001 on physiological measures. Also, results showed a significant and large main effect of Condition on HF-HRV while controlling for gender, V = .24, F (2, 42) = 6.73, p = .003, $\eta2$ = .243, indicating a significant change in HF-HRV across the experimental conditions, consistent with our hypothesis (H1). Post hoc within-group comparisons revealed that there was a significant decrease in HF-HRV from baseline to the sustained attention task: M (task-baseline) = -5.97, p = .004; thus, a negative reactivity score. The HF-HRV continued to decrease thereafter, M (post-task) = -1.07, p = 1, offering again a negative reactivity score, partially confirming our hypothesis (H2). The HF-HRV during post-task recovery period was significantly different from HF-HRV during baseline, M (post-baseline) = -7.05, p = .002.

Results showed that only in the ADHD without anxiety group the HF-HRV values were significantly different across experimental conditions (baseline, during the sustained attention task and post-task), V= .21, F (2, 42) = 5.73, p = .006, η2 = .21 with HF-HRV values decreasing from baseline to the sustained attention task and continuing to decrease thereafter (Figure 2). Post-hoc within-group comparisons indicated that HF-HRV significantly decreased during the sustained attention task, M (task-baseline) = -6.55, p = .036; also results showed a non-significant decrease in HF-HRV during post-task recovery period, M (post-task) = -2.01, p = 1; which was significantly different from HF-HRV during baseline, M (post-baseline) = -8.56, p = .011, partially confirming our hypothesis (H4b). Contrary to our hypothesis (H4a), no significant differences in HF-HRV values across conditions were found in the ADHD/Anxiety group, V= .10, F (2, 42) = 2.46, p = .097, η2 = .11. However, to analyze the ANS functioning as a response to various experimental demands, in children with ADHD and comorbid anxiety disorder, we assessed the condition effect by looking at the trend in the descriptive statistics. The cardiac pattern followed a decrease of HF-HRV from baseline (M = 46.60, SE = 4.04) to exposure to cognitive challenging task (M = 41.20, SE = 4.17) and continued to decrease (M = 41.05, SE = 4.28), during post-task recovery period (Figure 2).

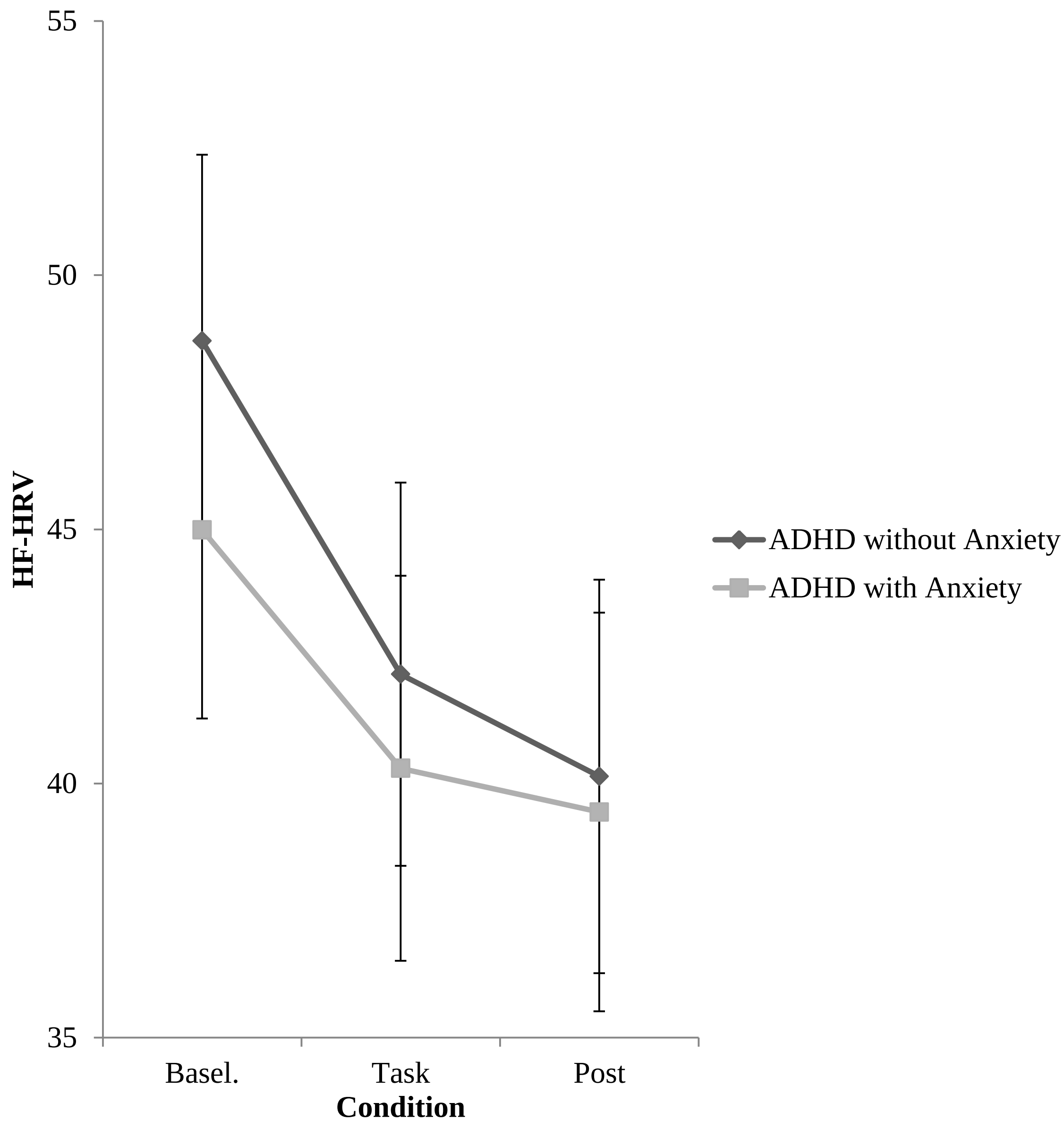

Figure 2. *HF-HRV means by Condition and Comorbidity*

3.3.3.3 Vagal flexibility (H3)

HF-HRV resting baseline predicted HF-HRV reactivity, when controlling for age r (43) = .31, *p* = .036; gender, r (43) = .29, *p* = .047; BMI, r (43) = .31, *p* = .037 and WHR, r (43) = .31, *p* =.034.

3.3.4 Discussions and conclusion

Our data indicate that, as a group, children and adolescents with ADHD displayed an autonomic activity pattern characterized by adaptive reactivity in response to a challenging cognitive task and maladaptive recovery immediately after the task. Consistent with expectations, the HF-HRV values decreased during d2 test execution, indicating that parasympathetic withdrawal occurred in response to perceived stress (mental effort). These results are in line with prior studies showing that tasks requiring increased cognitive effort or attentional control reliably elicit vagal withdrawal (Althaus et al., 1998; Duschek et al., 2009; Muhtadie et al., 2015; Van Roon et al., 2004). Furthermore, we predicted a return to the initial baseline or higher levels of HF-HRV during the post-task condition, but this was not the case; the HF-HRV values continued to decrease thereafter. The Polyvagal model posits the ANS's ability to return to a previous or higher degree of parasympathetic control once the stressor has disappeared (Porges, 2009). Up to date, no other studies have examined the ANS functioning in children with ADHD focusing on the process of parasympathetic restoration following a cognitive challenge. These results partially confirmed the second hypothesis. Importantly, this only happened during reactivity; consistent with expectations, the mean HF-HRV reactivity was negative. The participants did not display an adaptive process of restoration following the cognitive challenge, the HRV suppression was prolonged during the post-task recovery period, contrary to our hypothesis. According to the polyvagal theory, this pattern of cardiac reactivity and recovery is believed to facilitate effective coping with stressful situations (Porges, 2007, 2009). Such a delay in ANS adjustment response during recovery would suggest the individual is less capable of tracking rapid changes in environmental demands and is less able to organize appropriate responses. These anomalies in physiological response may explain why children with ADHD have difficulties supporting flexible regulation of behavior, emotion, and cognition (Bellato et al., 2020).

The data indicated considerable heterogeneity in parasympathetic autonomic functioning among children and adolescents with ADHD as a comorbidity function (depending on the presence or absence of the anxiety). Only the ADHD without comorbid anxiety disorder group displayed significantly different HF-HRV values across experimental conditions, with a normative cardiac vagal control pattern (reduced HF-HRV) in response to a challenging cognitive task. In the ADHD/Anxiety group, the HF-HRV slightly decreased during task execution but did not reach a significance level. Then, during the post-task recovery period, the HF-HRV values continued to decrease in both groups; indicating that participants did not display an adaptive restoration process following the cognitive challenge. The HRV suppression was prolonged during the post-task recovery period, suggesting that ANS responded as if the cognitive stressor was still present. Our study showed that the two groups differed in the amplitude of the ANS response to a challenging cognitive task; in the ADHD/Anxiety subgroup, there were no significant differences in HF-HRV across experimental conditions. Results suggest that the presence of comorbid anxiety tended to attenuate the ANS' ability to track rapid changes in environmental demands and to organize appropriate responses. This result is consistent with

Schmitz et al.'s (2011) findings, showing that children with social phobia exhibited restricted RSA reactivity in response to a stressful speech task (Schmitz et al., 2011). Monk et al. (2001) also showed deficient vagal modulation during stress among children and adolescents with anxiety disorders as compared to control (Monk et al., 2001).

Finally, significant associations between HF-HRV resting baseline and HF-HRV reactivity while controlling for age, gender, WHR, and BMI were observed. These findings support and extend prior work on the association between resting cardiac vagal tone and the extent of cardiovascular reactivity (Duschek et al., 2009; Porges, 2007). According to Porges' model, high resting vagal control is an indicator of the behavioral and vagal flexibility tone needed to modulate adaptive responses to changing situational demands (Porges, 1991, 1992); moreover, a higher resting vagal tone has been positively associated with better performance on tasks involving executive function (Hansen et al., 2003; Suess et al., 1994).

To conclude, the current study is the first to assess CVC as a psychophysiological index of adaptive responses to changing situational demands in children and adolescents with ADHD, through three systematic levels of CVC analysis: rest, reactivity, and recovery and has important implications for understanding how different processes might contribute interactively to the complex behavioral symptoms of the disorder. These findings showed a pattern of group differences in ANS functioning in children with ADHD, with and without a comorbid anxiety disorder. The HF-HRV decreased during task execution in both groups suggesting that the vagal influence was withdrawn in response to a cognitive challenge. However, the amplitude of the autonomic response displayed during the reactivity phase was different in the two groups; only the ADHD without comorbid anxiety group displayed a significant decrease in HF-HRV during the cognitive challenging task. The HF-HRV showed a nonsignificant decrease during the sustained attention task in the ADHD/Anxiety group, supporting the idea that ADHD with comorbid anxiety may represent a distinct "subtype" of ADHD. The participants did not display an adaptive process of restoration following the cognitive challenge; the HRV suppression was prolonged during the recovery period, suggesting that ANS responded as if the cognitive stressor was still present.

3.4 Study 4: The Effectiveness of a Single Session of Mindfulness-based Cognitive Training on Cardiac Vagal Control and Core Symptoms in Children and Adolescents with ADHD: A Randomized-Controlled Trial

3.4.1 Introduction

Over the years, research has cumulated for supporting the effectiveness of mindfulness for a wide range of mental health conditions, such as depression, pain conditions, smoking, and addictive disorders (Goldberg et al., 2018). There is evidence that mindfulness-based interventions (MBIs) could significantly reduce ADHD core symptoms (Xue et al., 2019) and may enhance HRV through increased parasympathetic modulation (Zou et al., 2018). Additionally, research has also demonstrated that brief mindfulness training programs can improve cognitive functions including attention and memory, after a single session with brief interventions of 5 minutes or longer (Howarth et al., 2019). Although emerging research has demonstrated MBIs to be an effective treatment for ADHD symptoms (Cairncross & Miller, 2020; Xue et al., 2019), most of the research in this area involves extensive multi-week training; there is limited research evaluating brief mindfulness programs in the context.

The aim of this randomized controlled trial (RCT), was to examine the effectiveness of a single session of mindfulness-based cognitive training for children and adolescents with ADHD, aged 7 y-17y. We hypothesized that children and adolescents receiving MBI would have a significant improvement in ADHD symptoms as well as vagally mediated-HRV, relative to the control group. As an exploratory secondary aim, we also wanted to determine whether improvement of symptoms and CVC may be sustained for 4 weeks after the intervention.

3.4.2 Methods

This trial was approved by the Research Ethics Board of Babeş-Bolyai University (approval number: 4171/04.03.2020) and was registered at ClinicalTrials.gov under the identifier: NCT04316832. A copy of the trial protocol can be found in Appendix 3.

3.4.2.1 Study design

The study is a two-arm randomized controlled trial exploring whether a single session of MBI could improve task-related scores of attention and hyperactivity/impulsivity, CVC, and mood in children and adolescents with ADHD referred to a Romanian Child and Adolescent Psychiatric Unit. The data were collected at baseline, immediately after the session of training (T1) and 4 weeks after the intervention (T2). Assessments commenced in October 2020 and were completed in May 2021.

3.4.2.2 Participants

Participants aged between 7 to 17 years were recruited from an outpatient Child and Adolescent Psychiatric Unit and surrounding clinics. Participants were eligible if they had a primary diagnosis of ADHD according to DSM 5 criteria. Additional inclusion criteria included the ability to verbally communicate and write in Romanian, normal intellectual ability, and no medication/agree to no medication changes (dose or type) within 3 months of trial onset. Exclusion criteria were as follows: comorbidities of conduct disorder or oppositional defiant disorder, the presence of a chronic disorder and, previous participation in mindfulness-based training.

3.4.2.3 Procedure

The principal investigator, a well-trained child, and adolescent psychiatrist examined the children and made the clinical diagnosis of ADHD, according to the DSM 5 criteria. For all children, the written informed consent for the evaluation and intervention was obtained from parents. Each participant was tested separately in a quiet room; the evaluation included HRV monitoring and a computer-based task of attention.

3.4.2.4 Randomization, blinding, and allocation concealment

Immediately after baseline assessments, participants were randomized to either one session of Mindfulness-based Intervention (MBI), or to control conditions, to keep the assessors blinded.

3.4.2.5 Intervention

The mindfulness-based intervention was delivered in one session and included three short mindfulness exercises: a) a *breathing exercise* that encourages the participant to focus on a slow and deliberate breath, b) a *body scan exercise* that promotes the awareness of body sensations while maintaining an accepting attitude towards these sensations and helps children to relieve tension, and c) a *mindfulness attention exercise* to increase moment-by-moment awareness.

3.4.2.6 Control

Participants allocated to the control condition listened to the first chapter of the audiobook The Hobbit, JRR Tolkien (Shaw, 2005).

3.4.2.7 Outcome Measures

3.4.1.1.1 Primary outcomes.

The primary outcome was the change from pre- to post-treatment, pre-treatment to follow-up, and post-treatment to follow-up in Conners' Continuous Performance Test (CPTs) scores (Lee & Park, 2006). The test provides several performance measures; four of which were analyzed in this study: omission errors (OMI), commission errors (COM), hit reaction time (Hit RT) and, detectability (d'). Omission errors (missed responses), and reaction times (RT; latency response), are related to sustained attention deficits; commission errors (responding when the target is not present), are indicative of impulsive and hyperactive symptoms. d' reflects the subject's ability to distinguish and detect targets and non-targets.

3.4.1.1.2 Secondary outcomes.

The secondary outcomes of this trial were changes from pre- to post-treatment, pre-treatment to follow-up, and post-treatment to follow-up in a) cardiac vagal control and b) mood. CVC was tracked through vagally-mediated HRV indexed by frequency- (HF-HRV) and time-domain measures (RMSSD). The mood was assessed through a Visual Analogue Scale (VAS) for four basic emotions (e.g., anxiety, sadness, anger, worry as experienced at the moment), derived from the Present Functioning Visual Analogue Scale (Sherman et al., 2006). An Emotional Distress Summary Score (EDSS) was computed by summing the scores of the worry, sadness, anxiety, and anger items, similar to the PedsQL™ Emotional Functioning Scale (Varni et al., 2001).

3.4.1.1.3 Additional clinical outcomes.

The Romanian version of the Child Behavioral Checklist for Ages 6-18 (CBCL; Achenbach & Rescorla, 2019) is a parent questionnaire that assesses the behavioral and emotional problems of the children over the past 6 months.

The ADHD-Rating Scale-IV, Home version (ADHD-RS; (DuPaul et al., 1998) is an 18-item questionnaire, that requires the parents to rate the frequency of occurrence of ADHD symptoms as defined by the DSM-IV-TR over the previous 6 months.

All participants provided demographic information, such as age, and gender, urban or rural residency, and education level, and had their weight and height checked. The psychiatric comorbidities and current medication were documented.

3.4.2.8 Data analysis

All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corp., Chicago, IL). Linear mixed models (LMM), were used to compare the MBI and Control groups' change scores from pre- to post-treatment, pre-treatment to follow-up, and post-treatment to follow-up on CPT scores (primary outcomes), and HF-HRV and EDSS scores (secondary outcomes). The data were structured in a two-level hierarchical model, with time at Level 1 nested within individuals at Level 2. All participants with at least one measurement were included in the analyses. All models were fitted using the maximum likelihood (ML) estimation, with a random intercept per subject for all outcomes, with variance components matrix for the random intercept and an autoregressive structure (AR1) of the within-subject variance-covariance matrix for the repeated measure of time. The Akaike's information criterion (AIC) was selected to determine the appropriate statistical model.

3.4.2.9 Missing data, dropout

Overall, the percentage of missing values ranged between 0-10.6 %; the Little's Missing Completely at Random test (MCAR) was non-significant indicating that data were missing completely at random (Little & Rubin, 1987). Missing data were handled through the LMM analyses, which account for all available data, under the missing-at-random assumption. In terms of dropout, none of the participants dropped out of the treatment, 7 participants were unavailable at 4-week follow-up, 6 in the active control condition, and one in the intervention group.

3.4.3 Results

Figure 3 presents the Consolidated Standards of Reporting Trials flow diagram of participants through the study. A total of 66 participants were enrolled in the trial and assigned to the MBI (N= 33) or Control (N=33) groups.

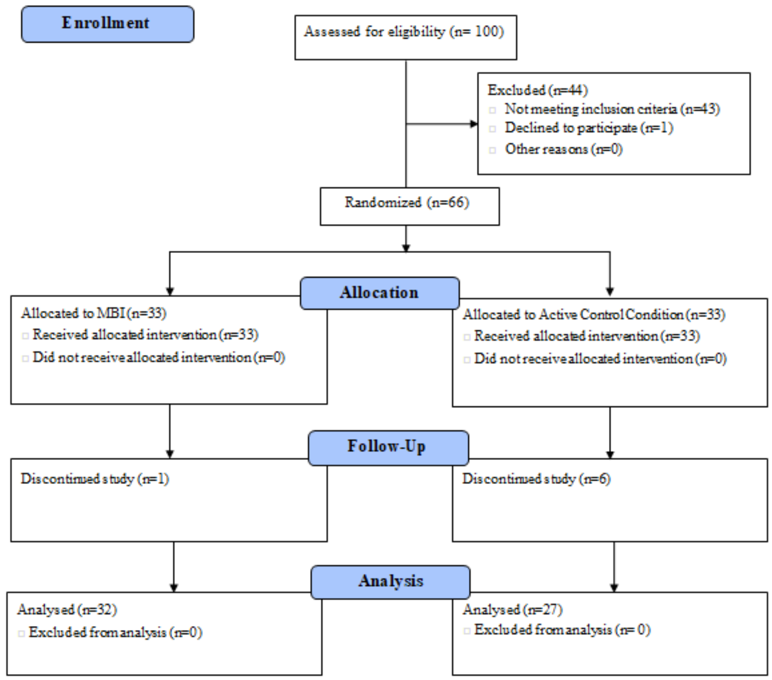

Figure 3. CONSORT diagram showing participant enrolment, allocation, and analysis

For the primary outcome, change in CPT scores (COM, OMI, hit RT, d') there was a significant main effect for time on COM, OMI, and hit RT. However, time-by-group interaction did not achieve statistical significance for any of the outcomes, indicating that the decrease in these outcomes over time was not significantly different between the MBI and Control group. There were significant between-group differences in hit RT; the Control group presented a higher mean hit RT as compared to the intervention group. Furthermore, there were no significant differences in detectability.

Secondary outcomes, including changes in CVC, assessed by vagally mediated HRV (HF-HRV and RMSSD), from pre- to post-treatment, pre-treatment to follow-up, and post-treatment to follow-up had similar results, with no significant differences between the two conditions and a significant main effect of time on RMSSD values. Furthermore, no significant differences were found for HF-HRV. The LMM analysis of change in mood, assessed by EDSS, revealed a significant main effect of time on EDSS scores. The EDSS baseline score was included as a control for pretreatment levels of emotional distress in all subsequent analyses, given the baseline differences between conditions. However, the time-by-group interaction and the main effect of the group were non-significant indicating that the decrease in this outcome over time was not significantly different between conditions.

3.4.4 Discussions and conclusion

Contrary to our expectation, the results suggest that the brief MBI was not effective for improving children's attention, nor cardiac vagal control nor mood. Although, several main effects of time were found; more specifically pre-post reduction in scores of commission errors, omission errors, and emotional distress, pre-post improvements in vagally mediated HRV, the change over time of these outcomes was not significantly different between conditions. This may be explained by the fact that the duration of the mindfulness exercises was too short to induce change.

In our study, mindfulness training was not effective at increasing the participants' performance on the CPT task. These results are consistent with Eisenbeck et al.'s (2018) findings, showing the lack of effect of focused breathing mindfulness exercise on a simple sustained attention task, the attention task of the Toulouse-Pierron factorial battery (Eisenbeck et al., 2018). One possible explanation for the lack of effect would be that one short mindfulness session may not have been strong enough to affect the participants' performance on the cognitive task or that the task lack the complexity to capture minor behavioral changes induced by a short mindfulness session.

Regarding the CVC, the MBI did not increase vagally mediated HRV. There could be several reasons why MBI did not significantly improve any of the HRV measures in our study. First, the power calculation was based on the primary outcome, ADHD symptoms, therefore the analyses for the secondary outcomes were underpowered. Another possible explanation for the lack of change in CVC is that mindfulness may improve HRV when delivered to specific psychiatric disorders; mindfulness practice has been associated with improved HRV in people with high levels of generalized anxiety (Mankus et al., 2013).

As for the mood outcomes, our study has shown that a single session of MBI did not improve mood in children and adolescents with ADHD. Previous studies have shown that MBIs improve anxiety and mood symptoms, especially among patients with anxiety disorders and depression and even when these symptoms are associated with chronic medical conditions, such as cancer (Hofmann et al., 2010). Moreover, brief mindfulness training interventions have been shown to be efficacious in reducing measures of negative affectivity, a dimension of subjective distress (Schumer et al., 2018). In our study, the mood was operationalized similarly, as an aversive, negative, uncomfortable, or unpleasant emotional state, such as anxiety, worry, depression, or anger. Despite the nonsignificant findings, results appear promising with a larger sample that could detect small effects. A recent meta-analysis indicated that brief MBIs have an immediate and significant (albeit small) effect on decreasing negative affectivity in both nonclinical and clinical samples (Schumer et al., 2018).

In conclusion, this is one of the first trials that systematically examined the potential benefits of a brief mindfulness intervention in children and adolescents with ADHD. This study represents an initial attempt to deliver a more accessible and flexible mindfulness intervention for children and adolescents with ADHD. Despite the nonsignificant findings, the positive evaluation of the program and the high rate of adherence suggest that this type of intervention could be easily implemented in different settings, such as the classroom. A larger, adequately powered trial should be conducted to determine the potential therapeutic benefits of this novel intervention.

4 CHAPTER IV. GENERAL CONCLUSIONS AND IMPLICATIONS

4.1 General Conclusions

ADHD is one of the most common neurodevelopmental disorders of childhood (*Centers for Disease Control and Prevention [CDC]*, 2014). Nevertheless, it still lacks specific biomarkers and remains underspecified (Tannock et al., 2008).

Consequently, the current thesis sought to investigate HRV measures as a potential neurophysiological marker in children and adolescents with ADHD, according to the criteria proposed by the World Federation of ADHD, for potential biomarker candidates evaluation (Thome et al., 2012). HRV analysis is currently accepted as a simple, non-invasive measurement of the ANS influences on the sinus node, thus representing one of the most promising quantitative markers of autonomic functioning (Rajendra Acharya et al., 2006) in healthy individuals (Malik, 1996), athletes (Aubert et al., 2003) and various conditions, such as myocardial infarction (La Rovere et al., 1998), sudden death (La Rovere et al., 2001), heart failure (Hoyer et al., 2008), diabetes (May & Arildsen, 2000). Among psychiatric conditions, HRV is considered a transdiagnostic biomarker of psychopathology (Beauchaine & Thayer, 2015).

The first step was to quantify CVC differences, after a task demand, in ADHD compared to healthy control, through a systematic review and meta-analysis of analytical observational studies (Study 1). The results of the 13 studies, published between 1997 to 2017, indicated lower vagally-mediated HRV in response to a task demand, indexed by time- and frequency-domain measures, in medication-free children and adolescents with ADHD as compared to control. Although the effect sizes were small, this represents the first synthesis of a wide range of inconsistent results related to the association of autonomic impairment with ADHD. Furthermore, it is noteworthy that investigating HRV in response to a task demand could better surprise the ANS impairment associated with the disorder; no overall differences in ANS functioning were found between ADHD and controls when the vagal tone was indexed by resting-state HRV measures (Koenig, Rash, Kemp, et al., 2017). When sensitivity analyses were performed for time- (RMSSD) and frequency-domain (HF-HRV) measures, only the ES of HF-HRV remained significant, suggesting that frequency-domain analysis might better capture the ANS impairment when investigating short-term recordings. Additionally, the type of the task, the assessment of the respiration rate, and the presence of the psychiatric comorbidities moderated the association between CVC and ADHD.

Next, a methodological study (Study 2) was conducted to assess the psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED), an instrument widely used to screen for anxiety disorders in youth (Birmaher et al., 1997); a high prevalent comorbid condition in ADHD. SCARED has been adapted to several cultures and languages, with good psychometric properties (Hale et al., 2011). However, previous research focusing on the investigation of the psychometric properties of the SCARED has been conducted with samples coming from individualistic cultures (e.g., USA, Germany) and, to a lesser degree on samples coming from collectivist cultures (e.g., China), such as Romania**.** Additionally, it has been suggested that the factor structure may vary across different countries, cultures, and ethnicities (Hale et al., 2005) thus, it is important to evaluate the factorial structure for the Romanian version as well. Moreover, little research had systematically addressed measurement invariance testing, an essential prerequisite, before testing latent factors mean differences across groups or measurement occasions (Putnick & Bornstein, 2016).

The results of the confirmatory factor analyses support the initial five-factor solution proposed by the authors of the scale in a Romanian sample of youths, for both child- and parent ratings. Furthermore, correlations with a wide range of anxiety symptoms measures demonstrated similar construct validity for the Romanian version when compared to the original version of the scale. Additionally, the results of measurement invariance testing indicated configural (structural), weak (metric), scalar (strong), and strict (residual) across age, gender, and clinical status for the child ratings respectively across age and gender for the parent-ratings suggesting that SCARED had the same factor structure, factor loadings, item thresholds and item residuals across groups (≤ 13 years vs. > 13 years, male vs. female, clinical vs. non-clinical). These results are particularly important given the comorbidity between ADHD and anxiety, having a scale with strong psychometric proprieties could facilitate early diagnosis of individuals with ADHD and comorbid anxiety disorder, which may represent a distinct “subtype” of ADHD (Pliszka, 1989; Pliszka, 2019).

In the third study, through an experimental design, we examined the specificity of CVC as a physiological marker of adaptive response to changing environmental demands in children and adolescents with ADHD, with and without a comorbid anxiety disorder. Thus in Study 3, we analyzed the dynamic modulation of CVC over successive changing situational demands: resting, reactivity, and recovery, by focusing on the identification of possible differences in ANS functioning between children with ADHD with and without comorbid anxiety disorder. The results indicated significant group differences in ANS pattern of response in children with ADHD, depending on the presence or absence of the comorbid anxiety disorder. The ANS response to the cognitive challenge followed a normative pattern only for the participant with ADHD without a comorbid anxiety disorder. None of the participants displayed an adaptive process of restoration following stress with prolonged vagal suppression during the post-task recovery period.

In the last study, we aimed to investigate the effectiveness of a single session of mindfulness-based cognitive training for children and adolescents with ADHD, through a randomized double-blind active-controlled design. More specifically, we conducted an RCT, to assess the effects of a mindfulness-based intervention on the core symptoms of ADHD, CVC as assessed by vagally-mediated HRV-measures, and mood. In addition, to identify possible markers for assessing treatment response we tested for the influence of several potential predictors (such as children's gender and age, psychiatric comorbidity, and medication status). The results indicated that the brief MBI was not effective for improving children’s attention, nor cardiac vagal control, or mood. Further, results also showed that psychiatric comorbid conditions and medication predicted the change in RMSSD over time.

4.2 Implications of the Thesis

4.2.1. Theoretical Implications

The theoretical implications of the present thesis primarily emerged from Study 1; in this study, we sought to respond to the following research question: is the ANS functioning impaired in ADHD? Therefore, in Study 1 the literature investigating the relationship between CVC and ADHD was systematically reviewed. This is the first meta-analytical approach of a body of literature reporting mixed results on the association between ADHD and autonomic dysregulation. Results indicated that children and adolescents with ADHD, displayed lower levels of CVC, as compared to healthy controls, in response to a task demand. However, the effect sizes were small and the confounding role of medication could not be fully excluded. This finding is consistent with the smaller effects sizes (often small to moderate-sized) for impaired vagal function, indicated by reductions in HRV, associated with psychiatric conditions (Chalmers et al., 2014; Koenig et al., 2016). These results support and extend prior psychophysiological research integrating HRV as an index of cardiac vagal tone (Rajendra Acharya et al., 2006). Furthermore, it also adds to the existing literature on the association between measures of HF-HRV and mental illnesses, namely HRV as a transdiagnostic biomarker of psychopathology (Beauchaine & Thayer, 2015), by investigating the value of HRV as a potential biomarker for ADHD.

The theoretical implications of the present work also emerged from Study 3, as a secondary output. Study 3 was the first attempt to analyze CVC as a physiological index of adaptive responses to different situational demands in children and adolescents with ADHD, through a newly proposed experimental design including three levels of control: rest, reactivity, and recovery, based on vagal tank theory (Laborde et al., 2018). The vagal tank theory is a relatively new research framework that aims to extend our understanding of adaptative physiological functioning through the systematic investigation of the three Rs (resting, reactivity, and recovery) of CVC functioning.

4.2.2. Methodological Implications

Several methodological features were refined by the studies of this thesis. In Study 1 we aggregated and quantified previous research on the association between autonomic dysregulation characterized by deficient control of the heart by parasympathetic influences, and ADHD through a systematic review and meta-analysis. The meta-analysis had a pre-registered protocol and addressed some of the existing literature limitations such as quality assessment, potential moderators, heterogeneity, and publication bias.

Next, in Study 2, we validated in the Romanian language an instrument widely used to screen for anxiety in youths, SCARED. More specifically, we examined the reliability, construct validity, and factor structure, as well as measurement invariance across age, gender, and clinical status to ensure sound psychometric properties for the Romanian version of the scale. Consequently, the result of this research contributes to the field of evidence-based assessment tools for anxiety symptoms and creates the premises for meaningful comparisons in terms of anxiety symptoms (panic/somatic, generalized anxiety, separation anxiety, social phobia, and school phobia) across different populations.

Finally, in the fourth study, we used a strong RCT design to assess the effectiveness of a brief mindfulness intervention in children with ADHD; the study was registered in an online database (i.e., ClinicalTrials.gov, NCT04316832), the patients were recruited from regular mental health services, rigorous methods for randomization and well-validated measures of ADHD were used, along with a longitudinal assessment of treatment response, thus increasing the generalisability of the results.

4.2.3. Practical Implications

First of all, these findings are particularly important because HRV is a simple, cost-effective, non-invasive quantitative biomarker of ANS functioning, thus, task-related HRV could be used as a biomarker of clinical relevance, for early detection of the autonomic impairment associated with the disorder. Second of all, ANS dysregulation, characterized by reduced vagal control, is considered a risk factor for cardiovascular pathology (Malik, 1996) and has also been linked to a variety of psychiatric coexisting conditions, including conduct disorder (Beauchaine, 2011; Beauchaine et al., 2008, 2013), anxiety (Chalmers et al., 2014) and depression (Koenig et al., 2016). Moreover, individuals with low parasympathetic activity display an increased risk for sudden cardiac death (Singer et al., 1988), thus, HRV measures could play an important role in risk stratification for sudden death in ADHD patients. In third place, because the normalizing effects of stimulant medication on ANS functioning (Bellato et al., 2020) and HRV parameters (Buchhorn, Conzelmann, et al., 2012; Buchhorn, Muller, et al., 2012) has been described, task-related HRV might be used to ascertain the autonomic impairment and to assist treatment response in ADHD patients. In the fourth place, the reduced cardiac vagal tone, which can be influenced through specific non-pharmacological interventions such as mindfulness-based interventions (Zou et al., 2018) may be a promising option for children that insufficiently respond to current best practices in ADHD’s treatment.

4.3 Limitations and Further Lines of Research

The current thesis has several limitations, which should be taken into account when interpreting the main findings. Thus, although the results of the first study support the association between autonomic dysregulation and ADHD, these findings should be interpreted with caution as the potential confounding role of medication could not be fully ruled out. However, given the fact children taking stimulant medication were asked to refrain from medication and the analyses were controlled for the prescription status which was treated as a covariate, in each of the individual studies, is less likely that the results were entirely confounded by medication. Therefore, future studies must establish if the effect of stimulant medication on CVC could persist after a stimulant washout and for how long. Furthermore, the effects were associated with high heterogeneity which persisted even after sensitivity analyses (e.g., excluding children who underwent a stimulant washout) were conducted, or potential moderators were explored.

Another major limitation of this thesis is the lack of a direct comparison to a typical development control group (Study 3), which limits the strength of conclusions about “anomalies” in ANS functioning in children with ADHD, with and without comorbid anxiety disorder. However, we do note that all the participants underwent the same experimental protocol and the within-subject designs are highly recommended given the high variations across individuals and the various interactions influencing HRV (Quintana & Heathers, 2014). This type of experimental design offers several advantages, including a) an optimal experimental control, b) contributes to the elimination of individual differences in respiratory rates, c) requires fewer participants, and d) reduces the impact of external factors on HRV, such as medication, alcohol, smoking, etc. Furthermore, the experimental protocol consisted of three successive periods: a baseline recording followed by a sustained attention task, and finally, a post-task recovery period; each of the three conditions was carefully chosen to elicit a typical pattern of ANS response, based on the existing literature (Porges, 2001, 2007, 2009). In addition, the lack of a control group, as well as well-established optimal levels of task-induced changes in HRV for children and adolescents, we cannot conclude that the ADHD without comorbid anxiety subgroup displayed an adaptive reactivity pattern (indexed by vagal withdrawal) in response to the cognitive challenging task. Future studies should focus on establishing optimal levels of task-induced changes in HRV for children and adolescents.

Finally, HRVanalyses relied on a relatively small number of participants (Study 4) because the trial was powered to detect changes in ADHD symptoms. The sample size of approximately 30 individuals per group was small, thus, is possible that the beneficial effect of one session of mindfulness-based training on HRV measures would be apparent with a larger sample size and more statistical power. Also, this study only allocated approximately 12 minutes for participants to engage in mindfulness training, thus future research should take into consideration extending the time frames utilized in the present study.

To summarize, the current findings point to the value of HRV as a simple, non-invasive, cost-effective biomarker of the autonomic dysfunction associated with ADHD. HRV holds the potential to become a clinically useful tool to define more homogenous subgroups (based on ANS pattern of response to environmental demands) that might benefit from alternative forms of interventions that tackle the altered vagal activity such as mindfulness interventions. Additionally, it could help enhance risk stratification for sudden cardiac death and to assist treatment response (e.g., stimulant medication) in ADHD patients. However, new research is needed to unequivocally ascertain task-related HRV as a biomarker able to capture the whole complex of behavioral, affective, cognitive, and physiological features associated with the disorder.

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