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Review

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Abstract

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Results: Eight studies reporting on 587 participants met inclusion criteria. Random-effect meta-analysis revealed no significant main effect comparing individuals with ADHD (n=317) and healthy controls (n =270) (Hedges' g=0.06, 95%CI [-0.18:0.29], Z=0.48, *p=0.63*; k=8). Sub-group analysis showed consistent results among studies in adults (k=2) and children (k=6) with ADHD.

Conclusions: Unlike a variety of internalizing psychiatric disorders, ADHD is not associated with altered short-term measures of resting-state vagal tone.

The World Journal of Biological Psychiatry – *Review*

Resting State Vagal Tone in Attention Deficit (Hyperactivity) Disorder: A Meta-Analysis

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Keywords: *Attention Deficit Hyperactivity Disorder; Resting Vagal Tone; Heart Rate Variability; Meta-Analysis; Autonomic Nervous System*

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by inattention, impulsivity, and hyperactivity (Barkley 1997). Related clinical symptoms commonly involve impairment in sustained attention, distractibility and poor task persistence, difficulty in delaying gratification, excessive activity, talking, and fidgeting (Barkley 2001). Children with ADHD can be categorized as primarily inattentive, hyperactive, or a combination of these features (Willcutt 2012). ADHD is diagnosed in approximately 5-7% of children worldwide, but prevalence estimates vary based sex, age, subtype, diagnostic criteria, method of assessment, and incorporation of functional impairment (Polanczyk et al. 2007; Willcutt 2012). For example, ADHD is more prevalent among males and in young children (10-11%) and while the inattentive subtype is predominant in the population, individuals with the combined subtype (i.e., inattentive and hyperactive) are the most likely to be referred for clinical services (Willcutt 2012). Here we investigate whether heart rate variability - a noninvasive marker of vagal function - is reduced in patients with ADHD relative to controls, providing a psychophysiological mechanism that may underpin behavioral impairment in these patients.

In general, psychiatric disorders comorbid with ADHD include oppositional defiant disorder (ODD), conduct disorder (CD), learning disorders, mood disorders, and anxiety disorders (Biederman 2005). Recent conceptualization of ADHD suggests that inattention, impulsivity, and hyperactivity reflect a deficiency in emotion self-regulation, characterized by (1) deficits in regulating physiological arousal caused by emotions, (2) difficulties inhibiting inappropriate behavior to positive and negative emotions, (3) problems refocusing attention following strong emotions, and (4) uncoordinated behavior in response to emotion activation (Barkley 2010). Increasing evidence suggests that psychopathology is associated with altered resting state vagal tone, indexed by high frequency heart rate variability (HF-HRV). Reduced resting state HRV – reflecting impairment in vagal nerve function – is associated with an increased risk for morbidity and mortality (Kemp and Quintana 2013; Thayer et al. 2010). Previously, lower vagal activity has been linked to depression (Kemp et al. 2014a; Kemp et al. 2014b; Kemp et al. 2012; Kemp et al. 2010), anxiety disorders (Kemp et al. 2012; Chalmers et al. 2014; Kemp et al. 2014a), borderline personality disorder (Koenig et al. 2015) and schizophrenia (Clamor et al. In Press). Resting vagal tone reflects physiological flexibility in response to the physical and social environment (Beauchaine et al. 2001). In support of this, higher resting vagal control is associated with less fearful temperament in 9-10 month olds (Braeken et al. 2013),, effortful control of attention among 4-year-olds (Taylor et al. 2015), better performance on a continuous performance task among fourth and fifth grade children (Suess et al. 1994), socio-emotional competence among 2-3-year-old children (Liew et al. 2011), and cognitive performance among 10-year-olds (Staton et al. 2009). Furthermore, greater task-induced withdrawals in vagal tone have been associated with better inhibitory control (Utendale et al. 2014), and fewer externalizing and internalizing problems among children (see Graziano and Derefinko 2013 for a review).

Given that many of the characteristic features of ADHD are associated with vagal activity and existing evidence indicates that alterations of vagal activity are present in other psychiatric disorders, vagal activity might be a potential pathophysiological mechanism underlying ADHD. A systematic review on the topic has previously reported tentative evidence that children with unmedicated ADHD display lower levels of vagal tone (Rash and Aguirre-Camacho 2012). However, conclusions from this study were limited by the number and quality of studies reviewed. Here, we sought to re-examine this evidence and quantify the potential differences in resting state vagal activity in patients with ADHD compared to healthy controls using meta-analysis, providing a more objective review of the previously published evidence.

Methods

Literature Search

A systematic search of the literature, according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (Moher et al. 2009) was conducted. PubMed [212 hits (search performed on 06-01-2015) (no filters)], PsycINFO [90 hits (search performed on 06-01-2015) (no filters; search mode: *find all my search terms*)], and CINAHL Plus [32 hits (search performed on 06-01-2015) (no filters; search mode: *find all my search terms*)] were searched for relevant literature [search term: ((((((Attention Deficit Hyperactivity Disorder) OR hyperkinetic disorder) OR ADHD) OR Attention Deficit Disorder) OR ADD)) AND (((((heart rate variability) OR HRV) OR respiratory sinus arrhythmia) OR vagal) OR vagus)]. Additionally, reference lists of included studies were checked for additional studies eligible for inclusion. After removing duplicates, abstracts of all articles were screened based on pre-defined inclusion criteria independently by the first and last author. Eligible studies included those reporting: (i) an empirical investigation involving active collection of HRV data in (ii) humans (iii) in patients with ADHD. All titles meeting the inclusion criteria were retrieved and reviewed in full-text. Excluded studies and reasons for exclusion are given in *Figure 1*. Reviews, meta-analysis, comments, single-case reports, or abstracts from conference proceedings were excluded. The full-text of studies qualifying for inclusion were further reviewed and screened for inclusion eligibility independently by two authors. To be included, studies had to report (i) any measure of vagally-mediated HRV in (ii) clinical samples of ADHD patients characterized by clinical criteria (e.g. DSM, ICD) and diagnostic procedures, compared to (ii) non-ADHD healthy controls Authors of studies that reported HRV but no data on measures of vagally-mediated HRV were contacted and data on vagally-mediated HRV were requested.

Data Extraction and Meta-Analysis

Parasympathetic modulation of the heart rate is fast (timescale in the order of milliseconds) while sympathetic effects are much slower (Levy 1997). Therefore, HF-HRV, respiratory sinus arrhythmia (RSA), and time-domain measures reflecting these fast changes (i.e., the time-domain root-mean-square of successive R-R-interval differences, RMSSD measure) provide a readily available, surrogate measure of vagal activity. All data on time- and frequency domain measures reflecting vagally-mediated HRV was extracted for meta-analysis. Where citations reported multiple indices of vagally-mediated HRV, hierarchical inclusion criteria were implemented to prevent conflated effect-size estimates: HF power was selected for analysis if available, followed by RSA and RMSSD. Authors who reported vagally-mediated HRV but who did not provide sufficient quantitative data (e.g., only a graphical display) were contacted in order to request the necessary information to derive effect size estimates and confidence limits on the selected indices. When only the standard error of the mean (SEM) was reported, the SD was calculated by multiplying the SEM by the square root of the sample size (Higgins and Green 2008). When descriptive statistics were reported other than the mean, SD or SEM, data were imputed by established procedures where possible (Glass et al. 1984; Wiebe et al. 2006).

Descriptive statistics (mean and SD) of vagally-mediated HRV indices derived from resting baseline recordings were extracted. Where longitudinal or pre-post data were reported, only baseline resting HRV was included to minimize confounding effects by experimental manipulation and conflation of effect size estimates. Indices derived from long-term (e.g. 24 hours) recordings were not considered for inclusion given that only one study reported data from long-term recordings.

True effect estimates were computed as adjusted standardized mean differences (Hedge's g) using random-effect models. Heterogeneity was assessed using the standard I2 index, Chi-Square, and Tau^2 tests (Higgins and Thompson 2002). According to recommendations, substantial heterogeneity was assumed if I^2 was greater than 50%.(Higgins and Thompson 2002) Analytic computations were performed using RevMan (Version 5.3.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Summary of Included Studies

The systematic search of the literature (*Figure 1*) yielded 10 studies (Crowell et al. 2006; de Carvalho et al. 2014; Karalunas et al. 2014; Lackschewitz et al. 2008; Luman et al. 2007; Musser et al. 2011; Musser et al. 2013; Negrao et al. 2011; Oliver et al. 2012; Tonhajzerova et al. 2009) eligible for inclusion in the meta-analysis. Three studies had overlapping samples (Karalunas et al. 2014; Musser et al. 2011; Musser et al. 2013) and the most recent manuscript with the largest sample was retained (Karalunas et al. 2014) resulting in 8 independent samples. Sample characteristics of included studies are summarized in *Table 1*. All technical aspects regarding the recording of HRV in included studies are summarized in *Table 2*.

Six studies evaluated resting-state vagal tone in children with ADHD (Crowell et al. 2006; de Carvalho et al. 2014; Karalunas et al. 2014; Luman et al. 2007; Negrao et al. 2011; Tonhajzerova et al. 2009) and two in adults (Lackschewitz et al. 2008; Oliver et al. 2012). All studies employed DSM-IV criteria for a diagnosis of ADHD, seven studies using structured clinical interviews to gather information about symptoms (Crowell et al. 2006; de Carvalho et al. 2014; Karalunas et al. 2014; Lackschewitz et al. 2008; Luman et al. 2007; Negrao et al. 2011; Tonhajzerova et al. 2009), and one study using a validated, self-report screening measure (Oliver et al. 2012). Two studies did not report on comorbid disorders (de Carvalho et al. 2014; Oliver et al. 2012). Two studies assessed samples with ADHD and without comorbid psychopathology (Negrao et al. 2011; Tonhajzerova et al. 2009), and the remaining studies recruited samples who exhibited ADHD comorbid primarily with externalizing disorders. Five studies reported on ADHD subtypes (Karalunas et al. 2014; Lackschewitz et al. 2008; Luman et al. 2007; Tonhajzerova et al. 2009) with the predominant subtype being combined.

Four studies were designed to evaluate the difference between resting vagal tone among individuals with ADHD and controls. Two studies evaluated differences in resting vagal tone between children with ADHD and matched controls during orthostasis and supine positions (de Carvalho et al. 2014; Tonhajzerova et al. 2009). One study tested the difference in resting vagal tone between individuals with comorbid ODD and ADHD relative to controls (Crowell et al. 2006). One study compared resting vagal tone, with and without the use of methylphenidate, between individuals with ADHD relative to controls (Negrao et al. 2011). This study also included an evoked attention task. The remaining four studies were designed to evaluate vagal-reactivity in response to structured laboratory tasks. One study compared differences in vagal-reactivity between baseline and an emotion task with four conditions among children with ADHD and healthy controls (Karalunas et al. 2014; Musser et al. 2011; Musser et al. 2013). Another study was designed to compare vagal-reactivity from baseline to time-production task among children with ADHD and healthy controls (Luman et al. 2007). One study was designed to compare reactivity of a suite of physiological markers (one of which was vagal-reactivity) from baseline to a social stress task among adults with ADHD and matched controls (Lackschewitz et al. 2008). The final study was designed to compare vagal-reactivity from baseline to a frustration driving simulation task among adults with high and low symptoms of ADHD (Oliver et al. 2012). Details on the baseline recording task, duration of recording, recording equipment, and index of vagal tone used for analysis is provided in *Table 2*. All studies reported HF-HRV and many also reported time-domain measures of resting-state vagal tone. Baseline recording duration ranged between two and twenty minutes with the most commonly reported duration being five minutes. The majority of studies used commercially available software for the calculation of resting-state vagal tone.

Meta-Analysis

Meta-analysis of included studies revealed no significant main effect in random-effect models (Hedges' g = 0.06, 95%CI [-0.18:0.29], Z = 0.48, $p = 0.63$; k = 8; n = 587) as illustrated in *Figure 2*, indicating no significant difference in resting state vagal tone comparing patients with ADHD (n = 317) to healthy controls (n = 270). There was no significant heterogeneity across effect sizes reported by studies, as further reflect by inspection of the funnel plot (*Figure 3*).

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Sub-group analyses were performed on studies in adults (mean age > 18 years) vs. children (mean age < 18 years) patients with ADHD. Effect size estimates across studies in adult samples (Lackschewitz et al. 2008; Oliver et al. 2012) didn't reveal a significant main effect (Hedges' g = -0.06, 95%CI [-0.50:0.38], Z = 0.26, p = 0.79; k = 2, n = 78), comparing ADHD (n = 38) patients and controls (n = 40). Similar, analysis in children with ADHD (n = 279) and controls (n = 230), did not yield a significant effect (Hedges' g = 0.07, 95%CI [-0.23:0.37], Z = 0.45, *p = 0.65*; k = 6, n = 509).

Excluded Studies

Two studies by Musser and colleagues (Musser et al. 2011; Musser et al. 2013) were excluded after correspondence with the authors. The authors declared, that there was an overlap among each of the samples reported, such that each of the participants described in the earlier manuscripts were included in the later manuscripts. Thus, we decided to include the most recent study (Karalunas et al. 2014) reporting on the largest sample of ADHD patients. One dissertation (Karalunas 2011) was excluded because RSA was only measured in study 2 which did not include a sample with ADHD and controls. The study by Buchhorn and colleagues (Buchhorn et al. 2012) was excluded, because it was the only study reporting on 24-hour recordings of HRV. The guidelines for the measurement of HRV (Task Force 1996) suggest that "*because of the important differences in the interpretation of the results, the spectral analyses of short- and long-term electrocardiograms should always be strictly distinguished*". We initially aimed to perform meta-analysis for short- and long-term recordings separately, however, given that only one manuscript reported on long-term recordings of HRV (Buchhorn et al. 2012), there was sufficient data available for meta-analysis. Two studies by Börger and colleagues (Börger and van der Meere 2000; Börger et al. 1999) and one study by Kelly and colleagues (Kelly et al. 2014) was excluded, because the authors did not respond to our request and there was insufficient data to estimate effects sizes. Unfortunately, data reported by two studies was no longer available for analysis (Ashman et al. 2008; Beauchaine et al. 2001).

Discussion

The present meta-analysis quantified differences in resting state vagal tone between children with ADHD and healthy controls. The systematic search of three bibliographic databases yielded 8 studies eligible for inclusion. Meta-analysis was based on 317 patients with ADHD and 270 controls and no evidence was obtained for altered resting state vagal tone in ADHD. Except for one study (Tonhajzerova et al. 2009), none of the included studies reported differences on short-term measures of baseline HRV. While findings across existing studies on resting state vagal activity in ADHD are consistent, several aspects need to be discussed.

Medication Status

Methylphenidate (MPH) is frequently prescribed and effective in reducing ADHD symptoms in children (Van der Oord et al. 2008) and both stimulant (short- and long-acting) and non-stimulant medications are effective for treating ADHD in adults (Faraone and Glatt 2010), with greater effect-sizes reported for stimulant medication (Faraone and Glatt 2010; Mészáros et al. 2009). Psychotropic medication can have significant effects on HRV (Ikawa et al. 2001) that need to be accounted for. Evidence on the effect of MPH on HRV is limited. However, a meta-analysis has reported that treatment with stimulants is associated with increased mean heart rate in adults with ADHD (Mick et al. 2013). While heart rate and HRV are two distinct measures of autonomic function, increased heart rate in response to MPH points to a possible decrease in cardiac vagal-tone (HRV); thus, future studies need to address this issue in children with ADHD treated with MPH or other stimulants. Most samples included in the present meta-analysis were free of medication or underwent a medication washout prior to participating in the study (*Table 1*). One of the included studies allows for the analysis of the effect of medication status (Negrao et al. 2011). In that study, all children were taking MPH (1 long-acting, all others, short-acting) and were also measured after they refrained from MPH for 3 weeks. The authors reported no significant differences on time- or frequency-domain measures of vagally-mediated HRV comparing the same children while medicated and medication free.

Comorbidity and Subtypes of ADHD

In addition to medication intake, co-morbid psychiatric conditions might serve as important covariates altering vagal activity. While we consider lower resting state vagal tone to represent a common non-specific physiological mechanism associated with psychopathology (Caspi et al. 2014), the present analysis showed that resting state vagal tone is not altered in patients with ADHD. Resting state vagal tone is lower in adults (Kemp et al. 2014; Kemp et al. 2012; Kemp et al. 2010; Kemp et al. 2014b) and adolescents (Koenig et al. Under Review) with depression, anxiety disorders (Kemp et al. 2012; Chalmers et al. 2014; Kemp et al. 2014a), borderline personality disorder (Clamor et al. In Press) and schizophrenia (Koenig et al. 2015). Interest into vagal activity in psychiatric disorders arises, given the association of vagal activity and emotion regulation. Vagally mediated HRV is strongly associated with emotion regulation (Appelhans and Luecken 2006; Butler et al. 2006; Hanson et al. 2013), and underpins individual differences in the perception of emotional stimuli (Park et al. 2013). It predicts affective instability in daily life (Koval et al. 2013) and is inversely correlated to greater reports of difficulties in emotion regulation (Berna et al. 2014; Williams et al. 2015). ADHD itself might not be strongly related to emotion dysregulation (Barkley 2010) if not accompanied by internalizing disorders, such as comorbid depression or anxiety.

ADHD is a heterogeneous disorder consisting of different subtypes (APA 2013) associated with different clusters and patterns of comorbidity. Empirical evidence supports distinct clinical entities of ADHD with differential patterns of socio-emotional and cognitive impairment (Gadow et al. 2004; Graetz et al. 2001). Children with a combined subtype display greater comorbidity and externalizing behavior problems, while children with the hyperactive-impulsive subtype display greater social problems, and children with the inattentive subtype evidence greater cognitive and academic problems (Gadow et al. 2004; Graetz et al. 2001). Most interestingly, recent evidence suggests that subtypes of children with ADHD can even be distinguished by measures of vagal activity and vagal reactivity (Karalunas et al. 2014). Thus, not all ADHD subtypes might be associated with alterations of resting vagal tone, based on unique profiles of comorbid conditions. While the inattentive ADHD subtype is associated with greater comorbid internalizing behavior problems (Nigg 2000; Weiss et al. 2003), the hyperactive-impulsive and combined subtype, is associated with externalizing behavior problems (Liu 2004) and may not be associated with resting-state vagal tone due to hyperactvity in the absence of hyperarousal (Lackschewitz et al. 2008). Supported by evidence on difference in vagal activity between ADHD subtypes (Karalunas et al. 2014), we hypothesize that comorbidity, which distinguishes the different subtypes of ADHD, may partly explain the results observed. An insufficient number of studies have examined children with subtypes of ADHD making it difficult to test this hypothesis here; this is clearly one potential avenue for future research. In general there were relatively few studies eligible for inclusion in the meta-analysis, prohibiting examination of other confounds and covariates, such as gender (*Table 1*), age (continuous), the length of HRV recording or condition at recording (*Table 2*).

Vagal Reactivity and Circadian Variation

While measures of resting state vagal tone show good trait specificity (Bertsch et al. 2012), and are therefore of great interest for research into neurobiological mechanisms underlying psychopathology, the influence of these disorders might extend beyond short-term measures obtained during resting conditions. Relative to controls, children with ADHD may exhibit differences in task-related vagal reactivity in the absence of differences in resting-state vagal tone. In support of this hypothesis, an augmented pattern of vagal-reactivity in response to positive and negative emotion induction and inhibition tasks was reported in children with ADHD compared to healthy controls (Musser et al. 2011). Similarly, vagal-reactivity from baseline to short-term memory storage and rehearsal tasks moderated the association between short-term memory performance and ADHD (defined categorically or dimensionally) independent of comorbidity in a sample of children with ADHD and healthy controls (Ward et al. 2015). The results supported a compensatory cascading risk model where deficits in cognition (evidenced in short-term memory performance) predicted ADHD in the presence of atypical vagal-reactivity (evidenced by excessive vagal withdrawal). Taken together, these results suggests that task-related vagal-reactivity may be one important pathophysiological mechanisms underlying ADHD symptomatology when considered in the context of other neurocognitive factors.

In addition, Buchhorn and colleagues (Buchhorn et al. 2012) provided first evidence for alterations of long-term vagal activity in children with ADHD. High levels of nocturnal activity have been reported in children with ADHD (Konofal et al. 2001) and evidence points to disturbed sleep in ADHD (Konofal et al. 2010), and the presence of circadian rhythm sleep disorders among children with ADHD combined subtype (Chiang et al. 2010), that might affect long-term vagal activity, as it is well known, that lower vagal activity during the night is associated with poor rest and sleep problems (Hall et al. 2004; Stein and Pu 2012; Tobaldini et al. 2013). These long-term alterations might not be captured by measures of resting-state vagal tone in children with a short symptom history in particular. Furthermore, recent studies using chaotic global techniques – addressing the irregularity of amplitude and frequency of the HRV power spectrum - reported significant group differences comparing children with ADHD and controls (Wajnsztejn et al. 2015). Taken together, this suggests that the involvement of parasympathetic activity in ADHD might be more complex and is not adequately captured by short-term measures of resting-state.

Clinical Implications

The measurement of resting-state HRV to quantify vagal tone in psychiatric populations is of great interest for research as well as routine clinical care. Measures of HRV are easy to obtain by affordable equipment with little effort. Measures of resting state vagal tone are physiologically grounded, theoretically explicated, and empirically supported within the context of psychiatry. While we found no evidence for alterations of vagal tone in patients with ADHD compared to controls, the measurement of HRV may still be useful for (1) monitoring medication status; (2) assessing comorbid psychopathology and internalizing behaviors in particular, (3) distinguishing different clinical entities of ADHD, and (4) obtaining biologically informed differential diagnostics.

Beyond techniques to assess resting state vagal-tone by short-term measures of HRV, long-term measurements, measures of vagal reactivity (to standardized tasks or stressors) and more complex methods to analyze the power spectral density of derived data may better help to distinguish clinical patients from healthy controls.

5. Conclusion

Unlike other psychiatric disorders, ADHD is not associated with altered resting state vagal tone. While there is some evidence on differences in the circadian variation of vagal activity and task-related vagal reactivity in children with ADHD, we found no differences on short-term measures of vagally-mediated HRV. These findings suggest that altered vagal tone might be specific to disorders associated with internalizing behaviors (i.e. depression and anxiety disorders). Future research into alterations of vagal tone in different subtypes of ADHD, characterized by differences in internalizing and externalizing behaviors is needed. Such research might help to elucidate the unique association of vagal tone and internalizing behavior, and to evaluate the use of resting state vagal tone as a biomarker for distinguishing different clinical entities within pediatric psychiatry.

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Author	Year	Study Location	ADHD criteria	Comorbidities & Subtypes	Exclusions	Medications	ADHD Condition (Combined) N(Female)	Age(M)	Age(SD)	Control Condition N(Female)	Age(M)	Age(SD)
de Carvalho et al	2014	Brazil	DSM-IV	Not reported	Congenital abnormalities, CNS malformities, metabolic disorder, cardiac medications	Medication free	28(6)	9,96	1,93	28(12)	9,85	1,84
Crowell et al	2006	United States	DSM-IV criteria; phone interview (CBCL)	ODD (100%) Hyperactive (n=4) Combined (n=14)	Elevated internalizing behaviors (e.g., anxiety/depression)	Medication free	18(7)	4,78	0,73	20(9)	4,55	0,6
Karalunas et al. (see also Musser et al. 2011; 2013)	2014	United States	DSM-IV; structured telephone interview/clinical interview	Internalizing (38.4%); Externalizing (78.5%) Inattentive (26.4%); Combined (73.6%)	Non-stimulant and long-lasting medications, neurological impairments, seizures, TBI, mental retardation, MDD, learning disability, mania	Medication free/5 half-life washout	178 (51)	8,5	1,14	128 (69)	8,32	1,04
Lackschewitz et al	2008	Germany	DSM-IV; structured telephone interview (SCID)	Inattentive (n=7); Hyperacti	Neurological disorder, psychotic symptoms, PTSD, medication (including stimulants), somatic disorder, psychotherapy	Medication free	18(10)	36	10,62	18(10)	35,34	11,3

				ve (n=1) Combined (n=10)								
Luman et al.	2007	Amsterdam	DSM-IV (DISC-IV)	Externalizing (n=13) Internalizing (n=0) Inattentive (n=2) Combined (n=16)	IQ < 70, neurological disorders, learning disabilities, sensory-motor impairments, psychopathology other than ODD.	36-hour medication washout	18(3)	10,17	1,225	18(2)	10,33	1,3
Negrao et al	2011	South Africa	DSM-IV (SCID)	No comorbidities; Subtypes not reported	Comorbidities, medications other than methylphenidate, mental retardation	Medication free	19(6)	9,53	2,12	18(6)	9,17	1,42
Oliver et al.	2012	United States	DSM-IV based self-report ADHD symptoms (CSS)	Not Reported	NR	2 children on medications	20(15)	20,5	1,5	22(17)	20,5	1,5
Tonhajzerova et al.	2009	Slovak Republic	DSM-IV (DISC)	No comorbidities Combined (100%	Comorbid disorder, psychopharmacological treatment, hypertension, diabetes, obesity	Medication free	18(3)	10,8	0,4	18(3)	10,9	0,5

)

Table 1: Sample Characteristics of Included Studies; CBCL: Child Behavior Check List; CNS: Central Nervous System: CSS: Current Symptoms Scale; DISC: Diagnostic Inventory for Screening Children; DSM: Diagnostic and Statistical Manual of Mental Disorders; IQ: Intelligence quotient; NR: not reported; ODD: Oppositional Defiant Disorder; PTSD: Post Traumatic Stress Disorder; SCID: Structured Clinical Interview for DSM Disorders

Author	Year	Baseline task	Recording Length	vmHRV indices	Equipment Specs	System used to quantify HRV	Group differences reported	Note
de Carvalho et al	2014	Rest in supine position without talking	20-minutes	HF-HRV using FFT (.15-.40Hz) (Time domain was also measured)	Polar RS800 CX monitor (1000Hz sampling frequency)	Kubios software	Not significant	Data provided by authors;
Crowell et al	2006	Not explicitly described	5-minutes (final minute used)	HF-HRV using FFT (.15-.40Hz)	AIM-8-V3 ambulatory impedance cardiography (Bio-Impedance Technologies)	Software developed by Dr. Richard Sloan	Not significant	
Karalunas et al. (see also Musser et al. 2011; 2013)	2014	Resting baseline	2-min	HF-HRV using FFT (> .15Hz)	Mindware Biolab Acquisition Software (1000Hz)	Mindware HRV	Not reported	Data provided by authors
Lackschewitz et al	2008	Not explicitly described	15-min	HF-HRV using FFT (.15-.40Hz) (Time domain was also measured)	Polar S810i (1000Hz)	HRV Analysis 1.1	Not significant	
Luman et al.	2007	Asked to press a button 1-second after hearing an auditory sound and provided feedback.	The last 340 seconds of recording	HF-HRV using FFT (.15-.60Hz) (Time domain was also measured)	Two Ag/AgCL electrodes sampled at 500Hz. Equipment not otherwise listed	reported as "custom software program"	Not reported	Data provided by authors
Negrao et al	201	Seated in a quiet room	5-minutes	HF-HRV using FFT (.15-.40Hz) (Time domain was also	Polar NV	HRV Analysis 1.1	Not sig	Dat

	1			measured)			nificant (subgroups)	a provided by authors; Data pooled
Oliver et al.	2012	Baseline driving condition	Not reported	HF-HRV using FFT (.15-.40Hz)	Bionex impedance cardiography (1000Hz)	Mindware HRV	Not significant	
Tonhajzerova et al.	2009	Supine	5-min	HF-HRV using FFT (.15-.50Hz) (Time domain was also measured)	Telemetric diagnostic system VarCor PF6 chest belt (Dimea, Olomouc, Czech Republic)	Not specified	Significantly lower in ADHD	SD imputed

Table 2: Specifications on HRV Recordings; Ag/AgCl: silver/ silver chloride; FFT: Fast Fourier Transform; HF-HRV: high frequency heart rate variability; HRV: heart rate variability; *Note: based on a reviewers comment we requested log-transformed data on HF-HRV from Negrao et al., Luman et al., and de Carvalho et al.; Negrao et al.and de Carvalho et al. provided log-transformed data that was used for analysis. Dr. Luman evaluated kurtosis and skewness of her data and informed us, that "data was not skewed for any of these [frequency] bands" [personal communication]*

Figure Legends

Figure 1. PRISMA search flow chart

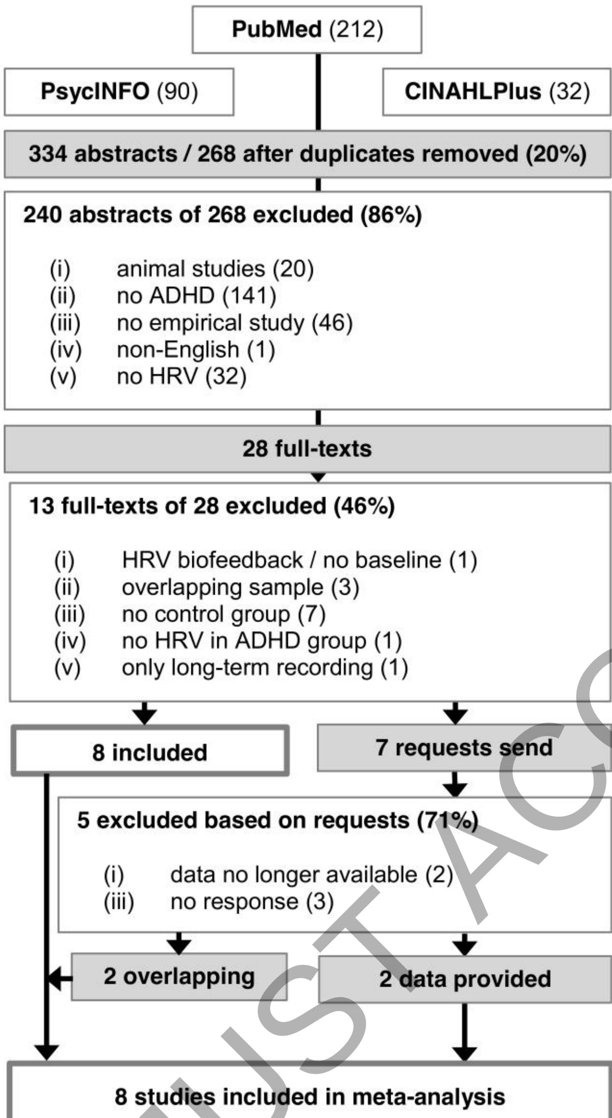
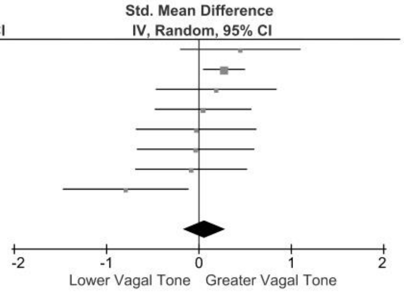


Figure 2. Random Effect Meta-Analysis on Resting State Vagal Tone in Attention Deficit (Hyperactivity) Disorder Compared to Healthy Controls; 95%CI: 95% Confidence Interval; SD: Standard Deviation; grey shaded values: data imputed; de Carvalho et al 2014: data provided by the authors; Karalunas et al. 2014: data provided by the authors; Luman et al. 2007: data provided by the authors; Negrao et al 2011: data provided by the authors; data pooled across patients on and off medication;

	ADHD			Controls				Std. Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Negrao et al. 2011 (1)	5.93	1.04	19	5.42	1.19	18	9.6%	0.45 [-0.21, 1.10]
Karalunas et al. 2014	7.49	1	178	7.21	1.07	128	28.6%	0.27 [0.04, 0.50]
Luman et al. 2007	4,249.24	4,293.46	18	3,505.92	3,472.28	18	9.5%	0.19 [-0.47, 0.84]
de Carvalho et al. 2014	9.09	1.34	28	9.03	1.33	28	13.1%	0.04 [-0.48, 0.57]
Lackschewitz et al. 2008	30.78	18.24	18	31.23	8.59	18	9.6%	-0.03 [-0.68, 0.62]
Crowell et al. 2006	6.68	1.26	18	6.73	1.36	20	9.9%	-0.04 [-0.67, 0.60]
Oliver et al. 2012	6.54	0.96	20	6.62	0.89	22	10.7%	-0.08 [-0.69, 0.52]
Tonhajzerova et al. 2009	6.49	0.89	18	7.25	0.98	18	9.0%	-0.79 [-1.48, -0.11]
Total (95% CI)			**317**			**270**	**100.0%**	**0.06 [-0.18, 0.29]**

Heterogeneity: Tau² = 0.04; Chi² = 10.55, df = 7 (P = 0.16); I² = 34%
Test for overall effect: Z = 0.48 (P = 0.63)



Footnotes
(1) pooled data

Figure 3. Funnel-Plot from Meta-Analysis on Resting State Vagal Tone in Attention Deficit (Hyperactivity) Disorder Compared to Healthy Controls